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Biochemical alterations in cancer: A clinical chemistry perspective on tumor pathogenesis

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Abstract
Cancer is a complex and heterogeneous disease characterized by uncontrolled cell proliferation, evasion of apoptosis, and abnormal tissue invasion. Biochemical alterations play a central role in tumor pathogenesis and progression, serving as both markers of disease and potential therapeutic targets. This review provides a clinical chemistry perspective on the biochemical changes associated with cancer, focusing on the molecular and metabolic alterations that underpin tumorigenesis. Key alterations in cellular signaling pathways, including those related to cell cycle regulation, apoptosis, and metastasis, are discussed in the context of their biochemical implications. Metabolic reprogramming in cancer cells, such as the Warburg effect, altered amino acid metabolism, and dysregulated lipid metabolism, is explored in detail, highlighting how these changes support the rapid growth and survival of tumors. Additionally, we examine the role of serum biomarkers, enzymes, and other molecular profiles that are increasingly used in clinical diagnostics and prognosis. This review emphasizes the importance of understanding these biochemical alterations for early detection, personalized treatment strategies, and the development of novel biomarkers for cancer diagnosis and monitoring. By integrating clinical chemistry with molecular oncology, we aim to provide insights into the biochemical foundation of cancer and its potential for improving clinical outcomes in cancer management.

Keywords: Cancer pathogenesis, biochemical alterations, metabolic reprogramming, tumor biomarkers, cellular signaling, clinical chemistry

1. Introduction

Introduction to Cancer and Tumor Pathogenesis

Introduction: Cancer is a global health issue and a complex disease caused by uncontrolled cell growth and division. A thorough understanding of cancer cell biology is required for the development of successful therapeutic strategies. Tumor pathogenesis can be defined as the molecular research of the mechanisms that control normal cells and tissues and the molecular changes that take place in the cancerous condition, leading to the initiation, maintenance, and metastasis of tumors. Tumorigenesis refers to the complex orchestration linking numerous processes that occur when tumors continue to develop and advance. Tumor development involves a series of acquisitions of different capabilities by cells and emerging tumorigenesis abilities. Furthermore, these new skills are not merely a result of any single mutation, but may arise from a finely balanced network of various genetic and epigenetic changes. Tumor pathogenesis can be incredibly challenging, as it requires a vast array of cellular changes and alterations in the microenvironment that fosters tumor development. An individual's hereditary predisposition and the pathogenic conditions are crucial and impact the natural behavior of each malignancy (Fares *et al*., 2020; De Visser & Joyce., 2023; Malki *et al*., 2020) [18, 15, 11]. Understanding these systems makes it significantly feasible to develop more effective early detection tests and reduce patients' entry into a specific regular monitoring system to prevent any possible progression of the disease. Our goal is to present a scientific and at the same time easily accessible overview of cancer, to better understand its pathophysiology. This assessment will address different biomedical advancements made towards a better understanding of tumor suppressor genetics and their function in controlling many biochemical and physiological processes, using clinical chemistry techniques. Clinical practice and the underlying research are increasingly moving toward developing methods for the early detection of a developing cancer, aiming to increase the number of cancer survivors and thus control the incidence and impact of cancer (Fares *et al*., 2020; De Visser & Joyce., 2023; Malki *et al*., 2020) [18, 15, 11].

In this context, the role of clinical chemistry in research on cancer – from pathophysiology to therapy – has seen increasing interest in diagnostics. This is due to the need for a permanent exchange of information from clinical practice with fundamental research for the purpose of continuously developing new diagnostic methods that are urgently needed for such a highly prevalent disease. This assessment will address different biomedical advancements made towards a better understanding of tumor suppressor genetics and their function in controlling many biochemical and physiological processes, using clinical chemistry techniques. Furthermore, utilizing proteomic, metabolomic, transcriptomic, image-based, and other central molecular approaches, efforts to measure tumor-related biochemical alterations are intensified. In addition, processing any related data to further advance the research and development of new cancer-diagnosing clinical chemistry will likewise be addressed (Hibino *et al*., 2021; Fares *et al*., 2020; De Visser & Joyce., 2023; Malki *et al*., 2020) [22, 18, 15, 11].

2. The Role of Clinical Chemistry in Cancer Research

Clinical chemistry traditionally deals with the routine analysis of biological samples such as plasma, serum, urine, and others to diagnose disease, monitor therapy, and assay toxins. There are several methods and techniques for detecting tumor markers and cancer-related metabolites in serum, urine, and other body fluids (Tonry *et al*., 2020; Tayanloo-Beik *et al*., 2020) [71, 70]. In addition to the standard tests carried out in every hospital or laboratory, research laboratories in clinical chemistry, universities, and hospitals are engaged in proteomic and metabolic investigation to develop new tumor markers with possible applications in diagnosis, prognosis, and therapy. The advanced methodologies used in clinical chemistry are permitting an advanced understanding of tumor pathogenesis and aiding in defining tumor subclasses suitable for selecting targeted therapeutic protocols, thus contributing substantially to the development of assertive oncology care. The pathologist and the oncologist directly apply the concepts of biochemical alterations to diagnosis and therapy, and clinical chemists are part of the health care team involved in the management of cancer patients, monitoring disease progression and the outcome of the therapy. To do this, clinical chemists must have a thorough understanding of each technique to advise the clinician regarding their utilization (Tonry *et al*., 2020; Tayanloo-Beik *et al*., 2020) [71, 70]. A biochemical test is certainly reliable if properly assayed in a reproducible manner, but it is not necessarily relevant for the diagnosis, prognosis, follow-up, or best therapeutic choice. It is on the basis of careful clinical chemistry laboratory merge that biochemical data can provide help to the clinician involved in cancer patients. In this work, we present two short reviews and ten original papers related to clinical chemistry and cancer. The authors are clinical chemists, pathologists, and researchers involved in both basic and clinical aspects of cancer management. Each paper or review uses the advanced knowledge of clinical chemistry laboratory practices to give valuable suggestions for cancer diagnosis and therapy evolution (Macklin *et al*., 2020; Schmidt *et al*., 2021; Tonry *et al*., 2020; Tayanloo-Beik *et al*. 2020) [39, 64, 71, 70,].

3. Biochemical Alterations in Tumor Cells

Biochemical changes are ubiquitous in tumor cells and play a central role in tumor progression. Metabolism and signaling are the two aspects where the changes are commonly investigated in terms of cellular signaling and signaling pathways. The concentration change of biochemical substances is another area that has clinical significance. The main pathways known to be changed in tumors elucidate the biological significance of these changes in tumorigenesis. The details are shown in the next section (Metabolic Reprogramming: Adapting to Biomechanical Requirements for Proliferation; Omic-Scale Signaling Hallmarks; Persistent DNA Damage and Mechanisms).

Metabolic reprogramming is an essential hallmark of cancer and a potential target for therapy. It was a former assumption that unregulated growth of tumors required an increased energy supply, and thus developed the hypothesis that cancer cells grow in a predominantly glycolytic environment even in the presence of O2 due to mitochondrial impairment. It is paradoxically true that grown cancer cells require a different nutrient chain, partly contrary to the assumption, and have created an environment where it is possible to gain insight by considering the combination of both metabolic pathways. Tumor tissues harvest O2 by recruiting blood vessels to keep intratumoral hypoxia, which is the deepest environment, and associated enzymes unique to overcome the limitation, while also synthesizing a building material for tumor cells to grow and vitalize even in the rapid growth environment of high-pressure time, under both non-hypoxic and environmental factors. Since these are performed on the condition of proliferation, DNA replication is also rapidly progressing and leading to genomic instability, which triggers mutations and variation in tumor percentages (Tang *et al*., 2024; Faubert *et al*., 2020; Yu *et al*., 2020) [69, 19, 78]. Several of these enzymes could be considered therapeutic targets, and imaging can be used to visualize the cancer-specific metabolism. The key question is: What benefits would occur if the glycolytic and oxidative phosphorylation pathways were monitored in combination with imaging of the pentose phosphate pathway to diagnose tumors at an early stage or to monitor the effectiveness of anticancer therapy based on tumor reprogramming, Warburg effect, and preferentially metabolic compensatory changes in more than 95% of cancer tissue (Tang *et al*., 2024; Faubert *et al*., 2020; Yu *et al*., 2020) [69, 19, 78].

3.1. Metabolic Reprogramming

The shift of cancer cells to use certain metabolic pathways is an adaptive response of cell populations to increased proliferation, oxygen concentrations, lack of nutrients, or other metabolic situations. Hence, cancer cells only rarely depend on one metabolic route. Instead, some key pathways can be upregulated in a majority of tumors, even if the relation may vary within them. Glucose, as the main energy precursor in a supposedly nutrient-restricted environment, is metabolized to extract fewer ATP molecules in a process called glycolysis, through which glucose is metabolized to pyruvate. Unlike normal cells, though, pyruvate is then reduced to lactate even when oxygen is abundant in a process called aerobic glycolysis, as described by Otto Warburg. Although mitochondrial oxidative phosphorylation would produce more ATP, the glycolytic pathway leads to the generation of metabolic intermediates, such as amino acids; hence, cancer cells use this step as a feeder to other metabolic pathways including the tricarboxylic acid cycle and fatty acid metabolism (Sevrin *et al*., 2023; D'Aniello *et al*., 2020) [65, 13].

Indeed, cancer cells sustain a high degree of plasticity in their metabolic routes; however, gene expression studies have revealed in various tumor types an increased proliferation-associated metabolic gene signature, indicating that under the selective pressure of rapid growth, cells shift from using ATP-directed glycolysis to using glycolysis to generate metabolic precursors for biomass synthesis to be used in tumor growth. These pathways, required for cellular transformation, are also essential for the existence of fully developed tumors. Consequently, both *in vivo* and *in vitro* approaches highlighted that cancer cells can show an increased plasticity to oxidative phosphorylation while retaining some

dependency on glycolysis. This preference for aerobic glycolysis has provided for more than a century a valuable tool in oncologic clinical chemistry for tumor positron emission tomography imaging diagnosis due to the Warburg effect. Additionally, metabolites and intracellular pathways directly linked to the Warburg effect can be targeted by medication; this encourages the beginning of personalized oncologic chemotherapy, often combining a metabolic PET staging with further tumor type-specific burgeoning metabolite imaging (Sevrin *et al*., 2023; D'Aniello *et al*., 2020) [65, 13].

3.2. Oncogenic Signaling Pathways

The molecular biology of eukaryotic cells is regulated by specific signaling pathways following the reception of signals by transmembrane or intracellular receptors. If these pathways are dysregulated, normal cell processes can be altered due to an accumulated load of genetic mutations. The influence of altered genes in humans has been studied for many years. Over time, it has become clear that some essential pathways lie at the heart of proliferation, survival, motility, cell fate, and stem cell ability, and are involved in tumor growth, establishment, and metastasis. For now, when routine pathology contributes to classifying tumor disease, this information is often not taken into account. Other than that, the enumeration of specific altered genes will not readily suggest the potential success of the targeted therapy if colorectal disease therapy offers all potentially effective therapies from the known confounded gene alterations in a by-domain analysis (Bergers & Fendt., 2021; Massague & Ganesh., 2021) [5, 42].

Oncogenic signaling pathways usually regulate the homeostasis and normal physiology of cells. The initial transduction of the signal involves heterotrophic trimeric G-proteins, the non-receptor tyrosine kinase family of transmembrane receptors, the integrin family of transmembrane receptors, the cytokine family of transmembrane receptors, the transmembrane receptor-related tyrosine kinases, the non-receptor tyrosine kinase, the intracellular protein kinases, the transcription factors, and GTPase. The signal can then be escalated or transduced to essential physiological responses such as enzyme activation, gene expression, and cell change. Any genetic modification can lead to an overabundance of signal transduction in an unregulated connection to the growth or survival or motility-related gene expression activity. It could result in wild-type oncogene conversion or even loss of function. Organic changes will drive tumor technology. The most frequently involved signaling pathways in cancer will be taken up below. Genes including these pathways have been identified as potential clinical indicators for use. Oncogenic signaling pathways as targets for cancer therapy will be analyzed separately (Majidpoor & Mortezaee., 2021; Neophytou *et al*., 2021; Bergers & Fendt., 2021; Massague & Ganesh., 2021) [40, 49, 5, 42].

3.3. Alterations in DNA Repair Mechanisms

DNA repair pathways are responsible for maintaining genomic stability through the elimination of DNA lesions that cause mutations and genomic rearrangements. Stage mutations in several DNA repair pathways result in the accumulation of damages that activate repair genes, but those that mediate cell cycle arrest or apoptosis may not adequately activate. Lack of activation of these DNA repair genes leads to a further increase in the number of mutations and may result in additional inactivating mutations in the same or other pathways. Most human tumors, particularly those with p53 inactivation, demonstrate a deficiency in at least one of these DNA repair mechanisms. BRCA1 and BRCA2 are proteins that play key roles in homologous recombination repair of double-strand breaks. Women carrying germline mutations in the BRCA1 or BRCA2 gene have a 65% and 45% chance of developing breast cancer, and a 39% and 12% chance of developing ovarian epithelial cancer, respectively, during their lifetime (Jin & Sinicrope., 2022; Jiang *et al*., 2021) [29, 28].

The role of DNA repair in cancer is not limited to specific familial syndromes, and several examples of somatic mutations in DNA repair genes have also been observed. For instance, a germline mutation in an activating gene for base excision repair was associated with an increased risk of colorectal cancer. In childhood acute lymphoblastic leukemia with 9q deletions, the deletion of the mismatch repair gene was observed. Tumors deficient in MGMT have a greater response to alkylating agents. Founder mutations in have been associated with the acquisition of both clonal and subclonal mutations in patients with chronic lymphocytic leukemia. Mutations in the DNA polymerase B gene have been associated with an indolent form of mantle cell lymphoma, and polymorphisms in MMR protein have been associated with the development of tubular and villous adenomas. In general, DNA repair variability will affect the mutation rate and the response to genotoxic therapy. In addition, when one of the repair systems is lacking, the cancer will 'mutate or perish' due to increased numbers of mutations or to apoptosis. The choice of therapy may depend on the DNA repair system that is mutated. Furthermore, the determination of DNA repair capacity of tumors is moving into clinical practice because exonuclease-antioncogene-dependent strains are more resistant to radiotherapy (Lu *et al*., 2021; Oaknin *et al*., 2020; Jin & Sinicrope., 2022; Jiang *et al*. 2021) [37, 50, 29, 28].

4. Biomarkers of Cancer and Tumor Progression

Interest in developing candidate biomarkers for diagnosis, prognosis, and treatment monitoring of cancer dates back to the late 1800s with the initial discovery of the Philadelphia chromosome in leukemia. Developments in molecular genetics in the twentieth century enhanced the rate of biomarker discovery, notably the use of serological assays to test for preselected candidate angiogenic proteins and cancer antigens postulated to be chromosomally derived tumor-specific antigens. In the early 2000s, however, primitive understanding of the transcriptome and limited ability to algorithmically discern combinations of multiple RNA and protein biomarkers confounded scientific advances, stifling heightened translation to clinical utility of biomarker research. The overarching objective of this review is to consolidate multifaceted research endeavors and perspectives spanning a single-century timeframe such that modern researchers and physicians recognize historical complexities in the route to the clinic of biomarkers, appreciate the more than a century-long clinical significance of a tumor phenotype, and more likely brace for the next memory stretch from 2020 to 2120 (Kim *et al*., 2024; Ouni *et al*., 2022) [32, 52]. The first line of evidence of a tumor phenotype stems from gross patient symptoms such as anemia, weight loss, and fatigue. To survey the presence and progression of tumors, many classically operating divisions of clinical labor are monitoring endogenous substances associated with energy metabolism, tumor-derived protein byproducts, and cytokines promoting immune evasion. Many of these molecular biomarkers include constituent tumor nucleic acids ranging from tissue-resident DNA, exosomal RNA, and noteworthy DNA methylation. For a few such biomarkers, therapeutic stromal response to chemotherapy may lead to more circulating biomarkers being observed at steady state. Given patient stratification and companion diagnostics have both risen in prominence these past ten years, personalization of diagnosis, staging, and

treatment are undergoing ethical discussions—particularly regarding predictive diagnostic value that should be revealed by rigorous scrutiny. Panels of biomarkers that were independently validated for the most secure disease stratification offer augmented diagnostic value due to diminished diagnostic false positives and false negatives. Of late, simultaneous messages from many biomarkers are undergoing formal study for added benefit in certain settings (Durgalakshmi *et al*., 2021; Hicks & Turner., 2024; Kim *et al*., 2024; Ouni *et al*., 2022) [17, 23, 32, 52].

4.1. Serum Markers

Serum markers are extensively used in cancer detection and follow-up. Such markers can be related to the level of a constituent present in diseased tissue or biomarkers associated with the tumor microenvironment or patient immune response. The former can serve as indicators of tumor burden or the risk of developing symptomatic disease. Whether the latter are useful in patient follow-up should be established for each marker. The current subsection will give a general insight into the current knowledge and challenges with serum marker selection and the perspective of what can be expected in an era when serum parameters will be characterized in a high-throughput manner. Serum markers can be specific proteins, such as tumoral enzymes or oncoproteins, which reflect the host response to underlying neoplasm. In general, such markers are not sufficiently sensitive to detect early cancers with adequate confidence except for a few examples. Population screening of cancer patients using serum markers will only be useful if they also reflect the net tumor load in patients. Proteomic investigations have shown that there are very few serum proteins that correlate with primary tumor size, but several others can stage the extent of metastatic spread (Middleton *et al*., 2020; Albakova *et al*., 2021) [46, 2]. Serum markers correlate with a number of established prognostic indicators such as histologic grade and nodal status. Research is now needed to identify the serum protein markers that reflect the genetic changes which pertain to clinical behavior. So far, a smaller number of studies of serum markers in cancer patients have investigated their role in treatment response and pathogenesis as evaluated by functional imaging. In the era of targeted therapies, the serum proteins that can reflect their molecular targets, especially at the early stages of treatment, are being investigated. The most extensively studied are angiogenic factors in patients undergoing treatment in the hope of their short-term predictive value in the evaluation of anti-angiogenic effects. Finally, serum, in contrast to tissue samples, is affected by a variety of non-cancer comorbidities in the host, and their level does depend on normal tissue function and metabolism, which can be affected by various reasons. Thus, the elevation of a serum marker does not necessarily mean cancer (Park *et al*. 2022; Ravindranathan *et al*., 2021; Wang *et al*. 2022; Middleton *et al*. 2020; Albakova *et al*. 2021) [56, 60, 75, 46, 2].

4.2. Tissue Markers

The histopathological analyses of samples are still considered the gold standard for the final diagnosis and prognosis. Biopsy can provide information on the tumor microenvironment and metabolic activity not only for the tumor cells. Both molecular tumor entities have full clinical validation to guide patients to targeted treatments. Surgical samples are usually recommended to show response trajectories to specific treatments and to identify new potential therapy-coupling biomarkers. Resection specimens, such as thyroid and breast carcinomas, are macroscopically driven by the pathologist to ensure more reliable sampling. The immunohistochemistry for the metabolite efflux transporters, such as P-glycoprotein, and in situ techniques to determine the pathways affected are now of high interest in therapeutic monitoring of patients with other malignant diseases (Jahn *et al*., 2020; Melo *et al*., 2020; Cifci *et al*., 2022) [27, 45, 10].

Despite the above mentioned, the use of tissue as a biomarker has obstacles from an analytical point of view. A big part of interpathologist agreement in the studies published does not often surpass 85%, which can pose a problem when guiding patient management. The biggest concern is due to sampling bias, tumor heterogeneity, and site of biopsy. Limitations to their use can be caused by an invasive procedure required, the risk of tumor progression induced by biopsy or re-biopsy, fluid risk at the biopsy site, and cost-ineffectiveness related to non-availability of clinical tissue samples. In the future, to elucidate tumor heterogeneity, other efforts in the tissue on healthy-adjacent tissues, immune cells, and ECM will be necessary to pave the way to a more holistic view for patient management. These are examples where an interesting study at the proteome, metabolome, or lipidome level on tissues could help in patient stratification and management (Sonni *et al*., 2022; Hoque *et al*., 2024; Jahn *et al*., 2020; Melo *et al*., 2020; Cifci *et al*., 2022; Mohsein, O. A *et al*., 2023) [68, 24, 27, 45, 10, 43].

4.3. Liquid Biopsies

The concept of liquid biopsy involves the non-invasive analysis of circulating tumor cells, cell-free DNA, and exosomes in bodily fluids, such as blood. It entails the potential to serve as surrogates for solid-tumor biopsies. There is currently an ongoing quest to standardize the best approaches for the various technologies available or under development in the field of liquid biopsies. The characterization of these components of a liquid biopsy is both qualitative and quantitative. Indeed, they provide real-time information on the ability of a tumor to spread. Most of the technological approaches were first applied to cell-free DNA, the most soluble and small component of a liquid biopsy. These technologies face several interrelated technical challenges, such as the identification of somatic alterations in the blood. For example, asking the right question and making a correct interpretation necessitate pre-analytic considerations, the use of well-characterized assays with validated performances that can distinguish healthy subjects, and the gene panels of interest. Post-analytic and output considerations include the monitoring of disease progression and treatment responses. Currently, only a few technologies have the required sensitivity and specificity for the early detection of cancer based on the utilization of these components of a liquid biopsy. Numerous research studies and clinical trials are ongoing to assess whether liquid biopsy analyses can be effective in the field of cancer medicine. At a minimum, in the future, liquid biopsy may offer means for early detection in patients at high risk with preneoplastic conditions (Keup *et al*., 2021; Zhao *et al*., 2022; Salvianti *et al*., 2020; Pang *et al*., 2020) [31, 80, 62, 54].

Circulating cell-free DNA shed by tumors constitutes a potential surrogate for tumor biopsies. Cell-free DNA from tumors in the blood was first described in 1977, but it could not be specific and detectable in patients with cancer, especially in the early stages of disease. Indeed, being a by-product of cellular death, analysis of cell-free DNA requires high sensitivity methods to discern the characteristic alterations found only in the patients' tumors. Over time, sensitivity limits have improved, and this issue is critical in the decision-making process when applied to early detection. Furthermore, in the proportion of less than 1% of tumor DNA in a background of wild-type DNA, these tools are also suitable for the detection of minimal residual disease (Casanova-Salas *et al*., 2021; Keup *et al*. 2021; Zhao *et al*. 2022; Salvianti *et al*. 2020; Pang *et al*. 2020) [8, 31, 80, 62, 54].

5. Technological Advances in Clinical Chemistry for Cancer Diagnosis and Monitoring

Over the past decades, clinical chemistry and laboratory medicine have experienced rapid technological advancement. This section summarizes the most relevant developments in cancer research and disease monitoring that are primarily driven by these cutting-edge methodologies. Techniques like mass spectrometry, next-generation sequencing, or advanced imaging techniques have significantly contributed to a major improvement in cancer diagnostics. Recent technological advancements have allowed the detection of novel and sensitive cancer biomarkers for risk assessment, early diagnosis, and therapy response monitoring. The list of these biomarkers or tumor-related genetic alterations also expands rapidly. It is now clear that even very small nonfunctioning tumors produce several proteins or genetic variants that can be readily detected by ultra-high sensitivity methods at very early time points (Qayyum *et al*., 2023; Koopman *et al*., 2021; Cree *et al*., 2021) [58, 34, 12].

In cancer research, panel sequencing or whole-genome sequencing has also been reported to show that very small tumors already contain all the typical tumor-associated genetic alterations of cancer but at a very low level. Many of the detected genetic alterations or neoantigens are also unique to an individual patient and have never been seen before, emphasizing the heterogeneity of cancer development. The detection of these genetic alterations in blood or any other body fluids may therefore facilitate the implementation of personalized medicine. However, switching from the detection of known tumor markers to the interpretation of the numerous genetic alterations requires unique education for doctors and facilities and the exchange of patient information between different centers (Qayyum *et al*., 2023; Koopman *et al*., 2021; Cree *et al*., 2021) [58, 34, 12]..

Importantly, clinical testing and future implementation must also be performed with in-hospital accredited assays or facilities. Although many of these technological developments have yet to result in translation to clinical medicine, each new technological advancement provides a unique instrument for enhancing patient outcomes. Ongoing collaboration among oncologists, clinical chemists, pathologists, and their professional societies will be a crucial factor in our progress toward providing the evidence to facilitate these translations. In the future, massive collaboration among different disciplines is required to analyze all the data, brainstorm, and support the implementation of safe and efficient cancer patient management (Melas *et al*. 2020; Panwar & Gupta., 2024; Qayyum *et al*., 2023; Koopman *et al*., 2021; Cree *et al*., 2021) [44, 55, 58, 34, 12].

5.1. Mass Spectrometry

Mass spectrometry is an advanced biochemical separation and detection technology that is found ever more often in clinical laboratories, particularly for detecting low-molecular-weight metabolites and drugs. This technology is highly suitable for exploring the molecular complexity of cancer. Mass spectrometry can be used to identify and quantify various biomolecules in complex biological samples, either directly when coupled to an appropriate chromatography method or via mass-based separation itself, in the case of techniques such as matrix-assisted laser desorption/ionization. One application that has proved increasingly important is for studying the content of biological fluids and tissue, for example, in proteomic and metabolomic analyses, which have been used to detect potential cancer molecular markers such as single proteins, metabolites, or lipid species (Ma & Fernández., 2024; Richards *et al*., 2021) [38, 61].

The use of mass spectrometry in combination with chromatography methods as a tool to identify and quantify signatures for disease has allowed the development of assays that reveal differential expression and translation of proteins in large cohorts of healthy controls and patients. In samples obtained directly from the site of the disease, it has permitted profiling of tumor-specific metabolic changes and detection of tumor-agnostic/marker-driven genetic changes. The resulting big data have been mined for potential markers and therapeutic targets as well as for a refined definition of cancer taxonomy. This approach has been particularly successful for blood cancers, since the disease is more easily accessible. Already, candidate proteins, however, have been translated into diagnostic assays that are sensitive for detecting minimal residual disease with a previously unattainable sensitivity and specificity. Mass spectrometry also provides details about post-translation modification of proteins in different tissues and cells, furthering insights into tumor biology (Macklin *et al*., 2020; Ma & Fernández., 2024; Richards *et al*., 2021) [39, 38, 61].

5.2. Next-Generation Sequencing

The emerging NGS technologies have already revolutionized cancer genomics. With comprehensive analysis of the cancer genome, point mutations, copy number variations, fusions, gene expression levels, and DNA or histone methylation patterns can now be analyzed. This prompted the search for genetic mutations in individual cancer samples but also across different cancer types, deepening knowledge of the landscape of the cancer genome, beginning with complete genome sequences of cancer cells and their healthy controls. The resulting large-scale studies identified prognostically relevant genetic alterations, as well as mutations of genes with potential for targeted therapy resulting from cell-based studies. Lymphomas, solid tumors, hematological malignancies, and many other cancers have been sequenced using NGS technologies (Satam *et al*., 2023; Kazim *et al*., 2024) [63, 30].

The identification of actionable mutations includes predictions based on primary protein structure analysis. Genomic approaches enable molecular tumor phenotyping that goes beyond the detection and classification of clinical symptoms. They hold the promise to address the key factor to achieve lifelong survival in cancer patients: early diagnosis of tumor formation, indicating the necessity of multimodal tumor intervention as early as possible prior to resistant cancer phenotypes becoming predominant, also referred to as minimal residual disease. This also requires identifying resistant cancer phenotypes early by combining diagnostic evidence with predictive evidence and gene-protein interactions working together. Although NGS technologies are highly robust and further large projects, including pan-cancer studies, are currently underway, in many cases, the application of NGS in clinical practice is still hampered by challenges such as data management, secure and ethical reuse of the molecular data, and interpretation in the context of tissue damage. Moreover, the cost-effectiveness across a broad range of diseases associated with molecular patterns must be proven for routine application. Ultimately, due to the variable course of disease and insufficient tumor biopsies, NGS and analysis should be integrated to understand spatiotemporal heterogeneity from a systems pathology perspective. Although mainly applied in tumor biopsies, NGS has already been successfully used for individualized treatment of cancer and represents a cornerstone technology of precision medicine. The continuous and significant evolution of the technology might even lead to a molecular-phenotype-driven approach for designing individualized cancer therapy combinations, potentially predictive of treatment efficacy. Ongoing research efforts on technological

development include the improvement of sequencing speed, sensitivity, and cost. (Krubaa *et al*., 2024; Hussen *et al*., 2022; Satam *et al*., 2023; Kazim *et al*., 2024) [35, 25, 63, 30].

5.3. Imaging Techniques

Today, cancer is almost invariably diagnosed by imaging, primarily supplemented by histological diagnosis. However, imaging is not just involved in detection, but also in staging, treatment planning, monitoring, and follow-up. Advanced imaging techniques have been developed to visualize anatomy and physiology, as well as metabolism using positron emission tomography, anatomy using magnetic resonance imaging, and a combination of both using software-based techniques, such as diffusion-weighted MRI, dynamic contrast-enhanced MRI, and computed tomography, magnetic resonance spectroscopy, and hybrid techniques, such as PET-CT. The basis of most of these techniques is the Warburg effect, which states that cancer cells generate energy with a higher ATP yield by the glycolytic degradation of glucose even in the presence of adequate oxygen supply. Based on their limitations, controversies, and costs, the role of these tests in the diagnosis of tumors has been emphasized in evidence-based guidelines. These imaging methods have not eliminated the need for tumor biopsy because, for example, abscesses and tumors have similar appearances in CT and MRI. They are valuable in "guided" biopsy or in treatment planning, for example, in radiation therapy. Imaging offers a non-invasive means of measuring treatment response with a resolution superior to that afforded by tumor histopathology. Molecular imaging modalities are highly attractive for this application (Wang & Patti., 2023; Liu *et al*., 2021) [76, 36].

The current progress of cancer research has generated many promising biomarkers, each providing information that assists with clinical management, genomic profiling, risk assessment, stratification, treatment delivery, and response and survival prediction. While many of these new biomarkers are molecular markers, another completely different approach is to use advanced imaging as a biomarker using personalized diagnostics. An increasing number of imaging facilities are integrating advanced imaging with other molecular techniques within existing prospective, prospective/retrospective, or retrospective programs and employing computerized and probabilistic interpretation systems to mine these image data. Nevertheless, widely accepted imaging techniques for personalized diagnostics do not yet exist, and comprehensive standards need to be established for image acquisition that can be performed using different imaging modalities. "Radiomics" is an emerging field based on the idea of applying computerized and probabilistic techniques to medical image data to extract large amounts of data, which is used during biological and clinical research. Despite phenomenal advances in imaging technologies, immediately available, reproducible, and reliable analysis still poses considerable practical barriers before the techniques may be exploited clinically. It is for this reason that new approaches such as artificial intelligence are now being used to provide a more accurate, consistent, and reproducible interpretation of reflected tumor biology and image-measured data. (Pascale *et al*., 2020; Bose *et al*., 2021; Wang & Patti., 2023; Liu *et al*., 2021) [57, 7, 76, 36].

6. Therapeutic Implications of Biochemical Alterations in Cancer

6.3. Targeted therapies

In recent years, novel compounds have been developed that target and bind to specific mutations. Impoverished in the associated formal characteristics, such an adaptation is based on a technology called high-throughput screening. Among others, imatinib is a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia patients characterized by the BCR-ABL gene rearrangement. Another example is bevacizumab, an antibody against the ligand for vascular endothelial growth factor. Currently, a favorable feature of these specific drugs is the patient subpopulation mosaically presenting the indicated molecular change that benefits from using them. Consequently, the molecular heterogeneity of tumors is indirectly partially diminishing. Many other examples are already accessible in a vast proprietary database of clinical trials. Regarding the aforementioned aspect, they also offer the perspective of partially progressively evolving our research paradigm, successively moving from the disease site to a disease genotype-oriented topic (Alves *et al*., 2021; Cha *et al*., 2023; Ratajczak *et al*., 2023) [3, 9, 59].

6.4. Immunotherapies

In the last decade, dynamic research efforts have started to focus on immunotherapies, which have been asserted in treatment paradigms across different tumor types. Approved options are the immune checkpoint inhibitors for use in metastatic melanoma. Phase III results have demonstrated substantial clinical benefit for a GM-CSF-secreting vaccine in metastatic castration-resistant prostate cancer. Furthermore, combinations of multiple compounds can be seen in several ongoing clinical trials. Immunotherapy disrupts the balance between negative immune regulation and stimulation. Many tumor types recruit myeloid-derived suppressor cells and regulatory T cells as well as special immune-inhibitory T cells. Blockades maintain cytotoxic T lymphocyte functionality. In addition to these drugs, patients can experience long-term tumor regression. Subsequently, these compounds were improved and have become more selective with less toxicity (Oliveira & Wu., 2023; Agur *et al*., 2020; Zhang & Zhang., 2020) [51, 1, 79].

6.5. Targeted and personalized treatment through serum albumin analysis

The abovementioned properties of alterations might be exploited therapeutically by focusing on the molecular changes occurring within complex tumor development. Any nanochanges might have potential relevant clinical features. For example, only in breast cancer might be useful in the context of therapy. In addition to the use of early imaging after an initial diagnosis, the addition of ER/HER2 was significant in terms of the therapeutic focus and prognosis. In comparison, patients with isolated ER+/HER2- breast tumors are candidates for endocrine therapy, and HER2+ cases can receive targeted therapy using a humanized antibody against the extracellular domain of the ERBB2 receptor, in addition to a chemotherapy regimen including taxane. For example, a 24-month extension of overall survival was observed when a combined EGFR/ERBB2 inhibitor was added to hormonal treatment. In the realm of breast cancer, neutrophils and lymphocytes in absolute terms and in the neutrophil-lymphocyte ratio at pretreatment were studied (Corbeau *et al*., 2020; Van *et al*., 2020; Grassadonia *et al*., 2021) [11, 73, 20].

6.1. Targeted Therapies

The concept of targeted therapies is based on the principle that cancer cells bear molecular characteristics that distinguish them from normal cells. These unique properties enable cancer cells to grow uncontrollably, avoid apoptosis, evade the immune system, metastasize, and resist conventional anticancer therapies. Thus, the hope is to attack the cancer selectively by inhibiting some of these unique cellular pathways that go wrong. The premise of targeted therapies is that by targeting deleterious pathways caused by specific mutations, the cancer cells will be more sensitive to the treatment while leaving the healthy cells unaffected. The

two principal types of targeted therapies are tyrosine kinase inhibitors and monoclonal antibodies. The former targets the enzyme that conveys the signaling message, whereas the latter targets the ligand or cell receptor protein. By blocking this pathway, targeted therapies can effectively interfere with different oncogenic mechanisms and exert their cytostatic or cytotoxic effects. In spite of these impressive advances, targeted therapies also have limitations. One of the most important is that the tumor might develop resistance to a drug, which in turn leads to cancer progression. To curtail this potential surmount, new strategies have been developed, including combination with other therapies such as conventional chemotherapeutic agents, radiation, or other targeted agents. Another limitation is that not all tumors express the specific altered molecule, which means that only one slice of the cancer population can be targeted. Developments in genomic analysis now allow the identification of mutations in each sample, thus selecting potentially responsive cases. Furthermore, elucidation of different cellular pathways has expanded the molecular targets of anti-tumor drugs, thus permitting the development of new agents for the treatment of different neoplasms (Min & Lee., 2022; Shyam *et al*., 2023; Iancu *et al*., 2022; Adnan *et al*., 2024) [47, 67, 26].

6.2. Immunotherapies

Since the initiation of the immune system is one of the most effective ways to fight cancer, the field of immunotherapies has grown rapidly over the last decade. One of the most potent immunotherapies is the use of checkpoint inhibitors. Checkpoint inhibitors are agents that alter "immunological brakes" such as CTLA-4 or PD-1 to restore the function of T cells in different cancers by blocking the ligand-receptor interaction. Another innovative approach to immunotherapy is the genetic reprogramming of T cells to express a chimeric antigen receptor (CAR) specific for a tumor-associated antigen. After ex vivo expansion and transduction, CAR-modified T cells are infused back into the patients where they can efficiently kill targeted cancer cells expressing the respective antigen. Other approaches include the use of therapeutic vaccines to boost immune responses. All of this resulted in durable responses even in late-stage patients for whom no other treatment was effective **(**Wojtukiewicz *et al*., 2021; Deshmukh., 2020; Bewersdorf *et al*., 2021) [77, 16, 6].

Currently, checkpoint inhibitors for CTLA-4, PD-1, or PD-L1 therapy are approved for more than 10 different tumor entities. The efficiency differs between the tumor entities as well as for multiple patients within one tumor entity. One main reason for this is that many patients already develop resistance or are refractory to immunotherapy. One part of the solution is to develop combinatory approaches to increase response rates to immunotherapies. Trials are ongoing that look at combinational checkpoint inhibition, adding immunostimulatory antibodies, vaccination, oncolytic viruses, chemotherapy, molecular targeted therapies, or radiation. An important basis for this is the development of response-predicting biomarkers. Efforts on one hand focus on kidney tumors, where a high total number of neoantigens seems to correlate with therapeutic response, as well as on research that demonstrates that a "hot" immune environment shows a better response to immunotherapies. The importance of the tumor immune environment and escape mechanisms from the immune system is often seen and influenced by localized radiotherapy. On the other hand, studies are ongoing to demonstrate that the number of anti-tumor T cells in the tumor reduces due to Treg cells with upregulated checkpoints, which could be performed by immunohistochemical staining of Treg cells. This approach needs to be further evaluated in larger cohorts and should be tested under immunotherapy conditions for predictive purposesv (Wojtukiewicz *et al*., 2021; Deshmukh., 2020; Bewersdorf *et al*., 2021) [77, 16, 6].

6.3. Personalized Medicine

Personalized medicine is an approach that tailors disease treatment regimens to the patient based on genetic and biochemical profiles. With the advent of new technologies to detect mutations and a growing list of clinical biomarkers, personalized cancer care, in which tumor treatment is selected based on the genetics of the patient, is becoming a reality. Advances in genomic analysis and biological marker discovery have paved the way for personalized oncology. As each cancer contains a unique set of genetic mutations, there is an expanding potential list of targets for drug therapy. In addition, tumor mutations are believed to provide a specific biological makeup, which is important to identify to generate signaling pathways that promote growth or resistance to drug therapy. From a clinical perspective, personalized medicine results in a cost-effective treatment regimen, either by looking for specific driver mutations in oncogenes or clinicopathologic factors that may predict response to certain drugs. In the long term, personalized oncology holds the promise of a paradigm shift in treatment approaches to cancer. This refashioned paradigm of treatment based on individual tumor genetic makeup has sparked the need for infrastructure and research to move forward with its clinical implementation. A major need involves comprehensive genomic testing, as well as subsequent treatment recommendations and clinical trials to validate the strategies. There needs to be a close collaboration between the disciplines of pathology, molecular diagnostics, clinicians, and surgeons to bring this into a clinical reality. Several related clinical trials in this domain of personalized medicine are currently ongoing. Successful examples of personalized medicine in practice are seen with the use of trastuzumab in breast cancer. A subset of patients' tumors contains a primary defect in the HER2/neu gene. It is hoped that by further linking biological information with treatment response strategies, a more comprehensive reconstructed paradigm for cancer decision-making, emphasizing primary treatment, can be realized (Tsimberidou *et al*. 2020; Wang *et al*., 2021; Kiyotani *et al*. 2021; Sherani *et al*. 2024) [72, 74, 33, 66].

7. Challenges and Future Directions in Clinical Chemistry Research on Tumor Pathogenesis

The biggest problem in the current biomarker literature is the lack of standardization. Especially in the beginning of the biomarker discovery process, total freedom from preconceived notions and from current methods would be best, but experimental design and execution are usually designed to fit into methods already available and well-practiced. Another challenge is to integrate the vast amount of new knowledge from genomics, tissue proteomics, and other new technologies in clinical management. Large-scale sequencing studies also provide important information, but individual amino acid changes with known clinical effects should be more informative in a clinical setting. Individual sequencing can also verify the RNA sequencing results directly in a certain specimen. Tumor tissue also contains other RNA species that can complement the data analysis (Gromova *et al*., 2020; Nakayasu *et al*., 2021; Davis *et al*., 2020) [21, 48, 14].

The most important and fundamental research gaps in the pathogenesis of tumors are the poor knowledge of the biology behind them and the genetic changes they elicit in the surrounding tumor stroma. Ongoing efforts in this direction take place on a limited scale and often by small businesses, while big pharma bypasses this type of pathway-driven molecular preclinical development. Also, in cancer

diagnostics, improvement in accuracy and reproducibility is ongoing. Civilized countries have large-scale healthcare screening programs and robust diagnostic tools, not just by CT but also other diagnostic modalities in the acute diagnostic sequence, like clinical chemistry. Many blood biomarkers can be relevant; at least they are for prognostication as earlier discussed. The methods for robustly measuring the blood analytes are also the focus for technical development. Still, most of these changes are not high-profile papers in top-tier journals. Different areas for cancer research for these persons are quality control, improvement of disease classification, treatment monitoring, and the use of AI and big data analytics. The last two are also difficult to implement. One solution is to make collaborations in this direction to enable this to take effect. To enable the major cancer organizations to afford these investments, interest has been called for involving the diagnostic companies in more direct talks with the technology researchers. Clinical chemists seldom engage in preclinical efforts in diagnostic innovation and studies, so further education and strengthening the practical impact are required. Also, an interdisciplinary approach is important: new knowledge in medicine can offer new questions in biochemistry and vice versa (Gromova *et al*., 2020; Nakayasu *et al*., 2021; Davis *et al*., 2020) [21, 48, 14].

8. Conclusion

Biochemical alterations are central to the development and progression of cancer, playing a crucial role in the pathogenesis of tumors. From changes in metabolic pathways to alterations in cellular signaling, these biochemical shifts not only support tumor growth and survival but also present opportunities for early diagnosis and targeted therapies. The reprogramming of metabolism in cancer cells, including the Warburg effect, altered amino acid metabolism, and deregulated lipid metabolism, highlights the complex biochemical landscape of cancer. Additionally, the identification of specific serum biomarkers and molecular signatures has improved diagnostic accuracy and provides valuable insights into prognosis and treatment response. Understanding these biochemical changes from a clinical chemistry perspective is essential for advancing precision medicine in oncology, enabling more effective, personalized treatment strategies. As research continues to uncover the underlying molecular mechanisms, the integration of clinical chemistry with oncology promises to drive innovations in cancer detection, management, and therapeutic development.

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11. References

1. Agur Z, Elishmereni M, Foryś U, Kogan Y. Accelerating the development of personalized cancer immunotherapy by integrating molecular patients' profiles with dynamic mathematical models. Clinical Pharmacology & Therapeutics. 2020;108(3):515-527. Available from: imbm.org.
2. Albakova Z, Siam MKS, Sacitharan PK, Ziganshin RH, Ryazantsev DY, Sapozhnikov AM. Extracellular heat shock proteins and cancer: New perspectives. Translational Oncology. 2021;14(2):100995. Available from: sciencedirect.com.
3. Alves R, Gonçalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, *et al*. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia—from molecular mechanisms to clinical relevance. Cancers. 2021;13(19):4820. Available from: mdpi.com.
4. Adnan ZA, Farhan ZM, Mohsein OA. Understanding the link between diabetes mellitus and fatty liver disease: A narrative review. Int J Chem Stud. 2024;12(4):40-48.
5. Bergers G, Fendt SM. The metabolism of cancer cells during metastasis. Nature Reviews Cancer. 2021. Available from: nih.gov.
6. Bewersdorf JP, Shallis RM, Zeidan AM. Immune checkpoint inhibition in myeloid malignancies: Moving beyond the PD-1/PD-L1 and CTLA-4 pathways. Blood Reviews. 2021. [HTML].
7. Bose S, Zhang C, Le A. Glucose metabolism in cancer: The Warburg effect and beyond. Adv Exp Med Biol. 2021. Available from: oapen.org.
8. Casanova-Salas I, Athie A, Boutros PC, Del Re M. Quantitative and qualitative analysis of blood-based liquid biopsies to inform clinical decision-making in prostate cancer. European Urology. 2021. Available from: sciencedirect.com.
9. Cha SH, Kim K, Song YK. Comparison of cutaneous adverse events between second-generation tyrosine kinase inhibitors and imatinib for chronic myeloid leukemia: A systematic review and …. Acta Oncologica. 2023. Available from: tandfonline.com.
10. Cifci D, Foersch S, Kather JN. Artificial intelligence to identify genetic alterations in conventional histopathology. The Journal of Pathology. 2022. Available from: wiley.com.
11. Corbeau I, Jacot W, Guiu S. Neutrophil to lymphocyte ratio as prognostic and predictive factor in breast cancer patients: A systematic review. Cancers. 2020;mdpi.com.
12. Cree IA, Indave Ruiz BI, Zavadil J, McKay J, Olivier M, Kozlakidis Z, *et al*. The international collaboration for cancer classification and research. International Journal of Cancer. 2021;148(3):560-571. Available from: wiley.com.
13. D'Aniello C, Patriarca EJ, Phang JM, Minchiotti G. Proline metabolism in tumor growth and metastatic progression. Frontiers in Oncology. 2020;10:776. Available from: frontiersin.org.
14. Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, *et al*. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: Challenges and opportunities. Nature Reviews Neurology. 2020;16(7):381-400. Available from: nature.com.
15. De Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023. Available from: cell.com.
16. Deshmukh SK. CTLA-4 and PD-L1 or PD-1 pathways: Immune checkpoint inhibitors and cancer immunotherapy. Journal of Cancer Immunology. 2020. Available from: scientificarchives.com.
17. Durgalakshmi D, Rishvanth R, Mohanraj J, Aruna P, Ganesan S. A roadmap of cancer: From the historical evidence to recent salivary metabolites-based nanobiosensor diagnostic devices. Current Metabolomics and Systems Biology. 2021;8(1):27-52. [HTML].
18. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: A hallmark of cancer revisited. Signal Transduction and Targeted Therapy. 2020;5(1):28. Available from: nature.com.
19. Faubert B, Solmonson A, DeBerardinis RJ. Metabolic reprogramming and cancer progression. Science. 2020. Available from: nih.gov.
20. Grassadonia A, Graziano V, Iezzi L, Vici P, Barba M, Pizzuti L, *et al*. Prognostic relevance of neutrophil to

lymphocyte ratio (NLR) in luminal breast cancer: A retrospective analysis in the neoadjuvant setting. Cells. 2021;10(7):1685. Available from: mdpi.com.
21. Gromova M, Vaggelas A, Dallmann G, Seimetz D. Biomarkers: Opportunities and challenges for drug development in the current regulatory landscape. Biomarker Insights. 2020;15:1177271920974652. Available from: sagepub.com.
22. Hibino S, Kawazoe T, Kasahara H, Itoh S, Ishimoto T, Sakata-Yanagimoto M, *et al*. Inflammation-induced tumorigenesis and metastasis. International Journal of Molecular Sciences. 2021;22(11):5421. Available from: mdpi.com.
23. Hicks DG, Turner BM. Optimized biomarker evaluation and molecular testing in the era of breast cancer precision medicine. Biotechnic & Histochemistry. 2024. Available from: tandfonline.com.
24. Hoque MZ, Keskinarkaus A, Nyberg P, Seppänen T. Stain normalization methods for histopathology image analysis: A comprehensive review and experimental comparison. Information Fusion. 2024. Available from: sciencedirect.com.
25. Hussen BM, Abdullah ST, Salihi A, Sabir DK, Sidiq KR, Rasul MF, *et al*. The emerging roles of NGS in clinical oncology and personalized medicine. Pathology-Research and Practice. 2022;230:153760. [HTML].
26. Iancu G, Serban D, Badiu CD, Tanasescu C, Tudosie MS, Tudor C, *et al*. Tyrosine kinase inhibitors in breast cancer. Experimental and Therapeutic Medicine. 2022;23(2):1-10. Available from: spandidos-publications.com.
27. Jahn SW, Plass M, Moinfar F. Digital pathology: Advantages, limitations, and emerging perspectives. Journal of Clinical Medicine. 2020. Available from: mdpi.com.
28. Jiang M, Jia K, Wang L, Li W, Chen B, Liu Y, *et al*. Alterations of DNA damage response pathway: Biomarker and therapeutic strategy for cancer immunotherapy. Acta Pharmaceutica Sinica B. 2021;11(10):2983-2994. Available from: sciencedirect.com.
29. Jin Z, Sinicrope FA. Mismatch repair-deficient colorectal cancer: Building on checkpoint blockade. Journal of Clinical Oncology. 2022. Available from: nih.gov.
30. Kazim I, Gande T, Reyher E, Bhutia KG, Dhingra K, Verma S. Advancements in sequencing technologies: From genomic revolution to single-cell insights in precision medicine. Journal of Knowledge Learning and Science Technology. 2024;3(4):108-124. Available from: jklst.org.
31. Keup C, Suryaprakash V, Hauch S, Storbeck M, Hahn P, Sprenger-Haussels M, *et al*. Integrative statistical analyses of multiple liquid biopsy analytes in metastatic breast cancer. Genome Medicine. 2021;13(1):85. Available from: springer.com
32. Kim SM, Park N, Park HB, Lee J, Chun C, Kim KH, *et al*. Exploring novel immunotherapy biomarker candidates induced by cancer deformation. PLOS One. 2024;19(5):e0303433. Available from: plos.org
33. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. Cancer Biology & Medicine. 2021;18(4):955. Available from: nih.gov
34. Koopman B, Groen HJ, Ligtenberg MJ, Grünberg K, Monkhorst K, Langen AJ, *et al*. Multicenter comparison of molecular tumor boards in the Netherlands: definition, composition, methods, and targeted therapy recommendations. The Oncologist. 2021;26(8):e1347-e1358. Available from: oup.com
35. Krubaa P, Jha AM, Mahmood AAR, Kumar A, Abraham J. Next-generation sequencing technology in cancer. International Journal of Trends in OncoScience. 2024;23-31. Available from: ijtos.com
36. Liu C, Jin Y, Fan Z. The mechanism of Warburg effect-induced chemoresistance in cancer. Frontiers in Oncology. 2021;11:693-695. Available from: frontiersin.org
37. Lu C, Guan J, Lu S, Jin Q, Rousseau B, Lu T, *et al*. DNA sensing in mismatch repair-deficient tumor cells is essential for anti-tumor immunity. Cancer Cell. 2021;39(1):96-108. Available from: cell.com
38. Ma X, Fernández FM. Advances in mass spectrometry imaging for spatial cancer metabolomics. Mass Spectrometry Reviews. 2024;43(3):203-225. Available from: nih.gov
39. Macklin A, Khan S, Kislinger T. Recent advances in mass spectrometry based clinical proteomics: applications to cancer research. Clinical Proteomics. 2020;17(1):22-34. Available from: springer.com
40. Majidpoor J, Mortezaee K. Steps in metastasis: an updated review. Medical Oncology. 2021;38(2):23-30. Available from: [HTML]
41. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa AE. Molecular mechanisms of colon cancer progression and metastasis: recent insights and advancements. International Journal of Molecular Sciences. 2020;22(1):130. Available from: mdpi.com
42. Massague J, Ganesh K. Metastasis-initiating cells and ecosystems. Cancer Discovery. 2021;11(5):885-892. Available from: nih.gov
43. Mohsein OA, Thuwaini MM, Salman HK. The relationship between leptin, thyroid hormone and insulin resistance in obese diabetic patients. Central Asian Journal of Medical Natural Sciences. 2023;4(3):518-523. Available from: https://doi.org/10.17605/cajmns.v4i3.1560
44. Melas M, Subbiah S, Saadat S, Rajurkar S, McDonnell KJ. The community oncology and academic medical center alliance in the age of precision medicine: cancer genetics and genomics considerations. Journal of Clinical Medicine. 2020;9(7):2125. Available from: mdpi.com
45. Melo RC, Raas MW, Palazzi C, Neves VH, Malta KK, Silva TP. Whole slide imaging and its applications to histopathological studies of liver disorders. Frontiers in Medicine. 2020;6:310. Available from: frontiersin.org
46. Middleton MR, McAlpine C, Woodcock VK, Corrie P, Infante JR, Steven NM, *et al*. Tebentafusp, a TCR/anti-CD3 bispecific fusion protein targeting gp100, potently activated antitumor immune responses in patients with metastatic melanoma. Clinical Cancer Research. 2020;26(22):5869-5878. Available from: aacrjournals.org
47. Min HY, Lee HY. Molecular targeted therapy for anticancer treatment. Experimental & Molecular Medicine. 2022;54(3):215-229. Available from: nature.com
48. Nakayasu ES, Gritsenko M, Piehowski PD, Gao Y, Orton DJ, Schepmoes AA, *et al*. Tutorial: best practices and considerations for mass-spectrometry-based protein biomarker discovery and validation. Nature Protocols. 2021;16(8):3737-3760. Available from: nature.com
49. Neophytou CM, Panagi M, Stylianopoulos T, Papageorgis P. The role of tumor microenvironment in cancer metastasis: molecular mechanisms and therapeutic opportunities. Cancers. 2021;13(9):2053. Available from: mdpi.com
50. Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, *et al*. Clinical activity and safety of the anti–programmed death 1 monoclonal antibody

dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncology. 2020;6(11):1766-1772. Available from: jamanetwork.com
51. Oliveira G, Wu CJ. Dynamics and specificities of T cells in cancer immunotherapy. Nature Reviews Cancer. 2023;23(6):315-330. Available from: nih.gov
52. Ouni E, Nedbal V, Da Pian M, Cao H, Haas KT, Peaucelle A, *et al*. Proteome-wide and matrisome-specific atlas of the human ovary computes fertility biomarker candidates and opens the way for precision oncofertility. Matrix Biology. 2022;109:91-120. Available from: uclouvain.be
53. Nasser NA, Sadek AH, Mahmeed BA, Mohsein OA. The levels of prostate specific antigen and leptin hormone in patients with prostate cancer. South Asian Journal of Life Sciences. 2025;13:1-7. Available from: [HTML]
54. Pang B, Zhu Y, Ni J, Thompson J, Malouf D, Bucci J, *et al*. Extracellular vesicles: the next generation of biomarkers for liquid biopsy-based prostate cancer diagnosis. Theranostics. 2020;10(5):2309-2321. Available from: nih.gov
55. Panwar P, Gupta S. A review: Exploring the role of ChatGPT in the diagnosis and treatment of oral pathologies. Oral Oncology Reports. 2024;4:52-61. Available from: sciencedirect.com
56. Park Y, Kim MJ, Choi Y, Kim NH, Kim L, Hong SPD, *et al*. Role of mass spectrometry-based serum proteomics signatures in predicting clinical outcomes and toxicity in patients with cancer treated with immunotherapy. Journal for ImmunoTherapy of Cancer. 2022;10(3):e00463. Available from: nih.gov
57. Pascale RM, Calvisi DF, Simile MM, Feo CF, Feo F. The Warburg effect 97 years after its discovery. Cancers. 2020;12(6):1494. Available from: mdpi.com
58. Qayyum MU, Sherani AMK, Khan M, Hussain HK. Revolutionizing healthcare: The transformative impact of artificial intelligence in medicine. Bulletin of Informatics. 2023;1(2):71-83. Available from: jurnalmahasiswa.com
59. Ratajczak B, Przybyłowicz-Chalecka A, Czerwińska-Rybak J, Kanduła Z, Ustaszewski A, Gil L, *et al*. The presence of additional cytogenetic aberrations in chronic myeloid leukemia cells at the time of diagnosis or their appearance on tyrosine kinase inhibitor therapy predicts the imatinib treatment failure. Leukemia Research. 2023;132:107349. Available from: sciencedirect.com
60. Ravindranathan D, Master VA, Bilen MA. Inflammatory markers in cancer immunotherapy. Biology. 2021;10(8):587-602. Available from: mdpi.com
61. Richards AL, Eckhardt M, Krogan NJ. Mass spectrometry-based protein–protein interaction networks for the study of human diseases. Molecular Systems Biology. 2021. Available from: embopress.org
62. Salvianti F, Gelmini S, Costanza F, Mancini I, Sonnati G, Simi L, *et al*. The pre-analytical phase of the liquid biopsy. New Biotechnology. 2020;55:19-29. Available from: unifi.it
63. Satam H, Joshi K, Mangrolia U, Waghoo S, Zaidi G, Rawool S, *et al*. Next-generation sequencing technology: current trends and advancements. Biology. 2023;12(7):997. Available from: mdpi.com
64. Schmidt DR, Patel R, Kirsch DG, Lewis CA, Vander Heiden MG, Locasale JW. Metabolomics in cancer research and emerging applications in clinical oncology. CA: A Cancer Journal for Clinicians. 2021;71(4):333-58. Available from: wiley.com
65. Sevrin T, Strasser L, Ternet C, Junk P, Caffarini M, Prins S, *et al*. Whole-cell energy modeling reveals quantitative changes of predicted energy flows in RAS mutant cancer cell lines. iScience. 2023;26(2). Available from: cell.com
66. Sherani AMK, Khan M, Qayyum MU, Hussain HK. Synergizing AI and Healthcare: Pioneering Advances in Cancer Medicine for Personalized Treatment. International Journal of Multidisciplinary Sciences and Arts. 2024;3(1):270-7. Available from: itscience.org
67. Shyam Sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. Signal Transduction and Targeted Therapy. 2023;8(1):262. Available from: nature.com
68. Sonni I, Felker ER, Lenis AT, Sisk AE, Bahri S, Allen-Auerbach M, *et al*. Head-to-head comparison of 68Ga-PSMA-11 PET/CT and mpMRI with a histopathology gold standard in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer: results from a prospective single-center imaging trial. Journal of Nuclear Medicine. 2022;63(6):847-54. Available from: snmjournals.org
69. Tang Q, Wu S, Zhao B, Li Z, Zhou Q, Yu Y, *et al*. Reprogramming of glucose metabolism: the hallmark of malignant transformation and target for advanced diagnostics and treatments. Biomedicine & Pharmacotherapy. 2024;178:117257. Available from: sciencedirect.com
70. Tayanloo-Beik A, Sarvari M, Payab M, Gilany K, Alavi-Moghadam S, Gholami M, *et al*. OMICS insights into cancer histology; Metabolomics and proteomics approach. Clinical Biochemistry. 2020;84:13-20. Available from: [HTML]
71. Tonry C, Finn S, Armstrong J, Pennington SR. Clinical proteomics for prostate cancer: understanding prostate cancer pathology and protein biomarkers for improved disease management. Clinical Proteomics. 2020. Available from: springer.com
72. Tsimberidou AM, Fountzilas E, Nikanjam M, Kurzrock R. Review of precision cancer medicine: Evolution of the treatment paradigm. Cancer Treatment Reviews. 2020;86:102019. Available from: sciencedirect.com
73. Van Berckelaer C, Van Geyt M, Linders S, Rypens C, Trinh XB, Tjalma WAA, *et al*. A high neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are associated with a worse outcome in inflammatory breast cancer. The Breast. 2020;53:212-20. Available from: sciencedirect.com
74. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. Nature Medicine. 2021. Available from: [HTML]
75. Wang X, Huang J, Chen W, Li G, Li Z, Lei J. The updated role of exosomal proteins in the diagnosis, prognosis, and treatment of cancer. Experimental & Molecular Medicine. 2022;54(9):1390-400. Available from: nature.com
76. Wang Y, Patti GJ. The Warburg effect: a signature of mitochondrial overload. Trends in Cell Biology. 2023. Available from: [HTML]
77. Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, *et al*. Inhibitors of immune checkpoints—PD-1, PD-L1, CTLA-4—new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer and Metastasis Reviews. 2021;40:949-82. Available from: springer.com
78. Yu Y, Gong L, Ye J. The role of aberrant metabolism in cancer: insights into the interplay between cell metabolic reprogramming, metabolic syndrome, and cancer. Frontiers in Oncology. 2020. Available from: frontiersin.org

79. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cellular & Molecular Immunology. 2020. Available from: nature.com
80. Zhao M, Mi D, Ferdows BE, Li Y, Wang R, Li J, *et al*. State-of-the-art nanotechnologies for the detection, recovery, analysis and elimination of liquid biopsy components in cancer. Nano Today. 2022;42:101361. Available from: [HTML]