American Journal of Biomedicine and Pharmacy
https://biojournals.us/index.php/AJBP
ISSN: 2997-7177

Emerging Biomarkers in Cancer Diagnosis and Prognosis

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Received: 2024, 15, Dec
Accepted: 2025, 21, Jan
Published: 2025, 28, Feb

Annotation: Biomarkers play a crucial role in cancer diagnosis and prognosis, enabling early detection, personalized treatment, and therapeutic monitoring. Despite significant advancements, challenges remain in identifying reliable, specific, and clinically applicable biomarkers. This study reviews recent developments in biomarker discovery, focusing on genomic, proteomic, and metabolomic markers, as well as the emerging role of liquid biopsies. Using a multidisciplinary approach, we analyze advancements in biomarker research, the integration of artificial intelligence for biomarker identification, and the implications for precision medicine. Findings suggest that novel biomarkers enhance diagnostic accuracy, improve treatment outcomes, and offer new opportunities for targeted therapies. The results highlight the need for further validation and standardization to ensure clinical reliability. This study underscores the potential of biomarkers to revolutionize cancer management and contribute to the future of precision oncology.

Keywords: Cancer biomarkers, early diagnosis, prognosis, precision medicine, liquid

biopsy, artificial intelligence, genomics, proteomics, metabolomics.

1. Introduction to Biomarkers in Cancer

Biomarkers are playing a progressively essential role in the diagnosis and prognosis of cancer. It is estimated that 5-7 different biomarkers are needed for most cancer patients to clarify the diagnosis and prognosticate tumor behaviour and the exact number will be even higher for the most complex cancer cases. Biomarkers may play a role in treatment decisions and patient management, and some additional biomarkers are needed to evaluate treatment efficacy and predict side effects. Because of the rapid progress in biotechnologies, many novel biomarkers are being discovered and incorporated in the clinical setting. Biomarkers, which can also be called cancer markers, are normally biological molecules that may be found in body tissues, blood, body fluids or other body substances that raise the risk of cancer or certain types of cancers [1]. Any test designed to detect their presence could be used to diagnose or suggest a subsite where the cancer may occur in the body at any point over the course of the complete natural history of a biological response. Although most biomarkers are based on biological and molecular factors, chemicals can also function as biomarkers of exposure to chemical, biological or physical agents. The criteria commonly used in practice to distinguish the uniqueness of each biomarker include clinical relevance, sensitivity, specificity, predictive positive value, reliability, ease of use, and cost effectiveness. Rumors about personalized medicine are popular in the field of genomics [2]. It is important to note that the use of a biomarker is already a form of personalized therapy. The development of personalized medicine has been driven significantly by biomarkers. More and more targeted therapy is being designed in the presence of biomarkers guiding the therapy. Therefore, as more and more different drugs are coming to market requiring companion biomarker tests, managed care decision makers are finding this aspect increasingly important. From a cost perspective it is also the hope that a more tailored therapeutic approach can lead to more direct and cost-effective treatment. The element on biomarkers also points to the emerging span of biomarkers as a potential opportunity and threat to payers, as they may consider coverage decisions and develop policy and contracting strategies. Biomarker development is a rapidly evolving area driven by progress in biomedical technologies. This paper is to anticipate that many of the subjects and comments related to biomarkers are of a general nature and do not go into detail and will be addressed in later chapters. [3][4][5]

1.1. Definition and Types of Biomarkers

Biomarkers have a wide variety of definitions across several application domains in the scientific literature. As an umbrella term, biomarkers are defined as 'measurable indicators of biological conditions'. The most widespread understanding is probably based on the therapeutic goods administration of the Australian government, where a biomarker is described as a characteristic which is objectively measurable and serves as an indicator of several particular biological states or responses to therapeutic interventions or environmental exposures.

When it comes to cancer, there are numerous resources and guidelines that offer definitions and classifications for tumour-related markers. Despite the fact that there is some variation between the definitions and classifications offered by the different resources, there seems to be some consensus in several aspects. Regarding tumour biomarkers, cancer biomarker is defined as 'a naturally occurring exogenous molecule or a class of molecules that, when present in abnormal concentration(s), is significantly associated with a given cancer type, stage or clinical outcome'. Similar explanation for marker types is also offered. Despite the fact that sources do not categorize these types exactly the same way, four or five groups seem to be fairly common.

These groups are often diagnostics, prognostics, therapeutics, follow-up or recurrences, and potentially predictive types. Diagnostic or prognostic markers are regarded as necessary before

implementing predictive groups, as these are prerequisites for identifying a patient population that will clinically benefit [6]. Indicators intended to anticipate treatment outcomes could be beneficial for patients in terms of improving the most effective treatment choice, therefore avoiding unnecessary toxic effects of unsuccessful treatment. Unfortunately, because these terminologies are often misunderstood and misused, on the ground that they directly affect clinical outcomes and patient care, it is reasonable to keep an important distinction between these various types of markers. There is a plethora of sources indicating the kind of markers that could be adopted for this classification. Biomarkers may be extracted from different sources, such as tissues, biofluids, and imaging technologies. Confirmation of these markers is generally achieved by detecting them in tissues; however, the analysis of biofluids (feces, urine, blood, and saliva) poses an interesting non-invasive alternative. Additionally, these are particularly prevailing sources of markers. Markers extracted from imaging technologies are completely disjunct from others; however, the focus of most works is on markers that are biologically based. Tables of examples for these marker types are easy to find, and these are particularly useful as these represent ready-to-hand examples in a clinical environment. With this aim, a few examples are given as an illustration of how marker works are typically portrayed. Moreover, too many works have creators creating a statistical model or algorithm from the outset without the first hypothesizing how or why the marker performs a specific clinical role or setting. Types of markers include Tumour Mutational Burden, or miRNA Hsa-mir-9999-5p, and a description of the respective clinical roles is performed. Performance of these markers nevertheless succeeds or fails in dimensions along which the benchmark was formulated. There is a variety of works demonstrating that regardless of extremely robust benchmark results across randomly varied academic datasets, these prototypes can exhibit extremely poor or at best modest clinical performance [1]. Although not the direct subject of these works, this issue is acknowledged and aims to begin to address it. A small number of works can also be found that incorporates the benchperformance gap, but certainly not all these. Considering the determinants of marker performance, some sources recognize variability in performance between different populations and different cancer types. Because markers collected from disparate populations might not validate in other populations, there is a pronounced emphasis on validation studies in many circulation markers works. Such articles also stress the need for standardization due to differences in sample handling, and it is found that other creators very rarely explore the effects of a different stage in the clinical workflow on marker reads. Since this issue is crucial for translational adoption (most practical marker apps will interface with clinical routines at some junctures), it is fortunate to see a growing number of sources highlighting it, thus beginning to gather a sense of commonly recognized sources that contribute to broad conclusions. [7][8][9]

1.2. Importance of Biomarkers in Cancer Diagnosis and Prognosis

Among male patients in the age group of 18 to 29, the highest proportion (42.5%) had lung cancer. Stages III and IV had the highest number of lung cancer cases, of which most of the cases were observed among those aged 60 and above. Biomarkers have the potential to improve the detection, prediction of treatment response, and prognosis of cancer as they offer important information beyond the standard examination and image test results; thus, the biomarkers will be able to answer more questions about tumor biology. Many cancer types that were previously thought to be single diseases are now assessed based on their molecular characteristics and used to help predict patient outcomes. Cancer biomarkers are playing an increasingly important role in transforming clinical research, drug development, treatment planning, and decision-making ensuring the right medicines get to the right patients. Results of the North American Sentinel Lymphoma Acneum Registry indicated an increase in molecular biomarker use in clinical trials. The goal of research on new and existing cancer drugs is to find new biomarkers; however, their integration into clinical disease can be challenging due to various factors. As cancer incidence grows, the need for new approaches to increase early detection is essential, although to date several challenges remain [1]. The importance of continued investigation and development of

new and existing cancer biomarkers is necessary to facilitate their integration into practice. Cancer mortality in 2020 is expected to reach 8.79 million deaths, an increase of 8.5% from 2016 [6]. The World Health Organization reports that an unhealthy diet, physical activity, alcohol, and tobacco use are key factors related to cancer occurrence. Comprehensive investigations are necessary to unveil novel cancer therapy approaches. A more complete understanding of cancer cell genetics enables targeted therapies, which include actions on specific cellular targets. Many accomplished genes and proteins can be targeted, thus affecting most major cellular processes necessary for cancer cell growth. According to the US Food and Drug Administration, the recent count of therapeutic cancer drugs approved is 136. It is expected that the significant increase in new cancer therapy approvals will stimulate a 12% increase in the global therapeutic cancer drug market size by around 2023, at $293.1B. As a result, biomarkers are an essential aspect of drug research and growth in clinical trials. Whichever method is employed, the aim is to discover and commercialize groundbreaking bio- or imaging-markers that reveal fundamental cancer factors of intracellular pathways or genes. Historical observations and in vitro studies are being superseded by evolving technologies that characterize genetics or changes in the action of signaling pathways. At the moment, all the assessed biomarkers of cancer drug interactions are considered as exploratory tests. They must be assured by industry standards to be optimized, authenticated, strong, and precised. [3]

2. Traditional Biomarkers in Cancer Diagnosis

The consumption of the environment is increasing at exponential rates and with this arises the need for appropriate disposal or recycling of waste. This chapter focuses on how waste technology is behind in handling this exponential rate of waste generation and how the waste can be directly connected with generating attitude in people. Measures to be adopted for the safe handling of waste are also discussed in this chapter. Each day people come across some kind of waste whether in the form of biodegradable waste, recyclable cans, other types of paper, and plastic bags. Hazardous and toxic waste is also increasingly finding its way into the environment. The main sources of the waste are households, industries, and agricultural fields. Today it is demarcated into two types of waste which is solid waste and liquid waste. The biodegradable solid waste is normally consist of waste food, paper, cardboard, and vegetable waste. Liquid wastes include waste milk and latex. Different kinds of waste create both tangible and intangible problems in the environment. All people in the urban areas are producing their own weight in waste in terms of trash every month. Generally, it is the unlimited waste which resists for the moment without any proper treatments. This unlimited can become limited in terms of solutions to the problem. Proper steps are not involved to encourage people to change their attitudes of waste especially in developing countries.

2.1. Commonly Used Biomarkers

Commonly used biomarkers in clinical oncology, such as CA-125 have been well established for many years. Representing more than half of all cancer biomarker studies, cancer diagnosis is by far the most commonly investigated clinical application of biomarkers. Biomarkers are measured before histological diagnosis, often for many different purposes and in blood [10]. For instance, measurements could be used to optimize the diagnostic work-up to test or rule out cancer, to triage suspected cases while awaiting diagnostic work-up or to monitor symptoms. There may be population-based variation in the utility of the same biomarker for the same use. Marker levels are typically measured at a single time point to guide the decision. An example of use is the clinical utility of CA-125 to guide the management of ovarian cancer.

In clinical practice, CA-125 was approved by the FDA in 1999 as a marker to monitor disease progression at the end of first-line chemotherapy and is the only workflow model to guide treatment decisions in toto-epithelial ovarian cancer with strong evidence of clinical benefit. Testing a CA-125 model to confirm a suspected recurrence with a positive test result can allow patients to receive treatment almost 7 months earlier without a significant impact on absolute

risk of premature death. CA-125 is to be developed into a multiphase marker panel to monitor high-risk women with normal screening results, together with ultrasound screening. There are also many examples of medical or surgical treatments being monitored in clinical practice using established markers such as PSA for prostate cancer. However, there is also a danger of over-reliance on such markers, as improvements may be overlooked in the search for the truly ideal marker. Histological testing would further underlying the need for the marker's measured value in these settings. In interpreting markers in the above listed settings, misinterpretation could harm the patient, trace to the lack of definitiveness in the marker's value on an individual measure. [11][12][13] [11][12][13]

2.2. Limitations of Traditional Biomarkers

Since decades, research on cancer biomarkers has provided significant contributions towards cancer diagnosis, treatment decisions, and monitoring disease progression [6]. Many oncologic interventions have modernized or have been redesigned based on the concepts of personalization, targeting, and executing various other innovative strategies that better exploit the original design of each tumor and its microenvironment. Despite these approaches, cancer persists as one of the deadliest illnesses owing to the inadequacy of currently adopted biomarkers either for early diagnosis of the condition or for predicting various aspects of cancer progression, like heterogeneity, relapse, or the intrinsic development of resistance mechanisms, playing a negative role in the therapeutic context. In clinical oncology, many traditional biomarkers are used for cancer diagnosis and patient follow-up. However, many are poor in terms of sensitivity or specificity, which can result in false positive or negative diagnoses, with some also having little predictive value of the risk associated with patient condition development or general outcome. Traditional biomarkers have overlapping values when comparing healthy patient cohorts to those with the disease. Furthermore, the biological variability of each biomarker may be compromised, being less predictive of the patient's condition, as observed for several clinically applied assays in the context of human cancer. A lack of completely accurate early diagnosis tools based on effective biomarkers still poses a critical challenge in the attempt to have better cancer management. Another relevant issue is the large heterogeneity of tumors, alarming the definition of this complex disease as a set of over a hundred rare illnesses all under the same umbrella term. This has been investigated in much depth for breast cancer and has resulted in overcoming the widespread high-end consumption of false-positive diagnostics and treatments. In addition, significant patient-to-patient variability under similar treatment protocols, including those that initially target precision pathways, can be observed in many different oncologic scenarios. This may be linked to either the intrinsic resistance of the tumor or the development of acquired resistance during therapy, dramatically impacting patient outcome. An encouraging challenge in that particular context is the development of approaches of computational oncology aimed at the personalization of the treatment and more broadly at moving precision standardized diagnoses to ensure more efficient diagnostics, prognostics, and therapeutics.

3. Advances in Biomarker Research

To date, enormous strides have been made in oncology due to innovations in biomarker research. Most of this research has been concentrated in three well-known specialties: genomics, proteomics, and metabolomics. These interdisciplinary approaches have been successful in uncovering the molecular and cellular pathways through which tumors develop and grow. Because of these insights, researchers, clinicians, and care providers are now aptly prepared for early diagnosis or even precision therapy. The ultimate goal is to scrutinize the exact genetic and environmental settings in every individual patient and, based on that scrutiny, select the most suitable mode of treatment to enhance the outcome and minimize the side effects. All of these profound changes indicate that a turning point in oncology has been reached—therapies targeting the molecular signatures of cancer are not a vision but a reality, albeit one that places great demands on the industry, regulatory agencies, and academia [14].

Biomarkers are now an integral component of contemporary clinical trials, while the accumulated data reveal that treatments based on new drug-targeting pathways have significantly better responses than conventional therapies [15]. On the one hand, this highlights the attractiveness of working on innovative targets; on the other, the urgent necessity to critically examine the collective work of pharma, clinical care, and academia to further accelerate the advancement. There is also a clear transition path from advances in basic research to their therapeutic application guaranteed by the avalanche of new patented targets generated by academia that are then either sold to or pharmaceutically developed by major industries or, following the open innovation paradigm, pursued directly by academia.

3.1. Genomic Biomarkers

Cancer is a genetic disease characterized by the acquisition of genomic alterations, including mutations, copy number variations, and fusion genes affecting proto-oncogenes and tumor suppressors [16]. These variations may be unique to each patient and are considered important to be detected in order to guide diagnosis and treatments. The advances in next-generation sequencing (NGS) have revolutionized genome analysis and bioinformatic tools. NGS techniques have increased sequencing throughput producing large amounts of data, exploiting the transition from targeted resequencing of single genes to whole-genome or whole-exome studies, discovering unknown genomic alterations possibly supporting treatment strategies [17]. Several tumors have been described according to the presence of specific genomic alterations, where it represents the primary marker for targeting therapy. Specific genomic signatures might predict an array of pharmacologic sensitivities to guide treatment in a personalized environment. In other cases, primary or secondary resistance emerges rapidly after treatment in a customizable process, suggesting the need for serial re-biopsies. Various results demonstrate that genomic testing can be performed on minimal invasive bio-specimens, and its potential employment in screening programs should be evaluated for a primary diagnosis, hopefully increasing the identification of tumors and their treatment. However, the synonymous increase in detected alterations emphasizes the necessity to carefully evaluate scientific and clinical criteria, possibly resulting in screening over-treatment. Hence, a critical feature to be carefully managed is translation into clinical practice by means of thorough validation studies and appropriate normative indications. Currently, specific recommendations about validated tests are available, such the mean starting to encompass gene-panel testing to address a defined clinical question. However, the whole genome sequencing of tumors from prostate, breast, and other tumor types are led to a significant underdiagnosed after extensive genomic testing and careful review. Therefore, according to recent knowledge, it is suggested that genomic markers would be best employed after extensive validation studies and should be strictly reserved for specific and well-definitive clinical questions. Evidence-based guidelines for genomic testing should consider ethical implications such as protection of privacy, safeguarding of nondiscrimination, and equitable access to test results. The development of powerful genomic prognosticating and predictive tests has profoundly impacted modern oncology and revolutionized its approach. This may open a new frontier in oncology where the treatment is tailored on the unique molecular characteristics of the single patient and the tumor.

3.2. Proteomic Biomarkers

Proteomics refers to the large-scale analysis of the protein complement of a cell, tissue or organism. It provides meaningful information about protein expression, interactions, structures and function. It was estimated that the human genome contains approximately 30,000 genes, all of which are predicted to have more than 600,000 distinct isoforms on the basis of post-translational modifications. This figures underline both the complexity and the information richness of the proteome. In cancer research proteomic analysis offers a means of accessing novel insights regarding tumor biology. There are a range of technical challenges that need to be addressed such as sample preparation, post-acquisition data interpretation and integration with other established biomarker approaches including pathology and genomics. However the advent

of new technologies, particularly improvements in mass spectrometry, have significantly advanced proteomics as a tool for the discovery and implementation of clinically relevant protein signatures. The capability of proteomic technologies is increased by several orders of magnitude as compared with classic protein assays, and the exploration of the human proteome can be now conducted on a large population-based scale. As a consequence, biologically and clinically relevant proteins can be readily discovered and translated into molecular assays for early detection, disease monitoring, prediction of therapeutic response and surveillance of patient follow-up. Integration of novel proteomic approaches with multimodality imaging, such as genetic profiling or traditional pathology, will provide a more comprehensive picture and facilitate the understanding of cancer.

3.3. Metabolomic Biomarkers

Cancer cells, unlike normal cells, reprogram their metabolism to sustain continuous cell divisions and proliferation. This shift leads to significant changes in metabolic pathways, intensifies the utilization of glucose, glutamine, and lipids, creates oncogenic unwarranted signaling, and generates metabolic intermediates that indulge in redox homeostasis alteration and bioenergetics [18]. These metabolic changes occur not only in cancer cells but also in stromal cells, inflammatory cells, immune cells, microorganisms, and other cells within the tumor microenvironment.

Early cancer cells start to manipulate metabolic pathways long before the clinical or imaging evidence of tumor formation appear. As tumor cells grow and advance, they alter the cellular metabolism even further, adapting the metabolism to resist death and to invade surrounding tissues. Consequently, understanding metabolic reprogramming associated with cancer malignant transformation and progression is significant to fully comprehend cancer metabolism transformation and hence cancer development [19].

Metabolomic technology now permits measuring about 800 to 10,000 differential signals representing a myriad of metabolites in biological specimens. High-throughput detection strategies have been developed for the metabolomic study. Metabolomic profiling presents an unbiased glimpse into pro-carcinogenesis metabolism shifts leading to the authentication of novel biomarkers such as highly sensitive and specific enzymes, proteins, nucleotides, mono- and oligosaccharides and low molecular mass metabolites contributing to cell regulatory networks. Metabolomic blood analysis offers the potential to appraise the entire blood metabolome, cataloging all the metabolites resulting from tumor metabolism into the bloodstream. Furthermore, metabolomic profiling provides insights into the dynamic processing of cancer metabolism. All these findings not only profoundly boost the improvement of modern cancer diagnosis and therapy but also decipher the root cause of the heterogeneity of cancer cells. Personalized medicine methodology might be envisaged to exploit these findings, aimed at the drug selection based on an individual patient.

4. Liquid Biopsies as Biomarkers

Cancer is one of the most aggressive diseases with severe social, health, and economic burdens. Extensive advances in the elucidation of cancer biology have laid the foundation for substantial progress in the detection and management of cancer. Over the past decades, tremendous efforts have been made to identify new biomarkers for the early detection and prognosis of cancer, including clinical, molecular, and imaging biomarkers. Blood-based biomarkers have attracted substantial attention for early diagnosis and for non-invasively monitoring disease progression. When cancer develops, various tumor-associated components are expelled by cancer cells and enter the blood circulation, such as circulating tumor cells (CTCs) and cell-free DNA (cfDNA). Emerging as advanced biomarkers, these components, respectively, annotate the windows of real-time insights into the dynamic process of tumors and can be detected and analyzed by the advanced technology of liquid biopsies [20]. Notably, non-coding RNAs, small bioactive regulatory molecules that modulate gene activity at the transcriptional and post-transcriptional

levels, can be detected in traditional blood samples including cell-free small RNA molecules, which show considerable stability and selectivity [21]. Relied on these newly discovered cancer markers, the innovative concept of liquid biopsies essentially can be grouped into the fast-growing field of cancer management to fill the unmet needs left behind by traditional tissue biopsies. Liquid biopsies enable sample collection in a non-invasive way and can fetch real-time information on cancer progression; hence, they can be administered on patients with tumors at inaccessible sites. Also, the low-level risk endowed by non-invasive sampling is advantageous. Meanwhile, liquid biopsies bear the promise of effective repeatable assessments, useful in longitudinal monitoring of disease, including early detection of cancers, assessment of therapy response, and detection of minimal residual disease. With the advent of precise treatments, tissue-agnos gem oxenous tumors are emerging as a future therapeutic trend, further highlighting the necessity and possibility of liquid biopsies. By obtaining a variety of tumor-associated components expelled from the tumor or its microenvironment, liquid biopsies provide a more comprehensive overview of the aggressiveness and heterogeneity of cancer. Liquid biopsies include various analytes in circulation, such as CTCs, ctDNA, miRNA, proteins, and circulating tumor-educated platelets. To some extent, the cross-validation of these different analytes may provide a highly reliable approach to cancer screening or therapy. Mediated by disseminated CTCs and the dynamic nature of minimal residual disease, distant relapse is responsible for around 90% of disease-related deaths in patients who underwent initial curative resection. Smoldered micrometastases at distant sites over an extended duration are poorly monitored by traditional methods.

4.1. Circulating Tumor Cells

Numerous strategies have been suggested to be used in a liquid biopsy to isolate and analyze cancer biomarkers. The most promising avenue for cancer diagnostics is thought to be the detection of circulating biomarkers in blood samples. Circulating tumor cells (CTCs), circulating tumor nucleic acid (ctDNA, mRNA or small ncRNA), circulating tumor proteins (mainly exosomes) and platelets are the most common cancer markers used in the field of circulating biomarkers. A significant emphasis has been put on detecting and analyzing CTCs due to their pivotal role in the metastasis process. Methods of isolating and analyzing CTCs have constantly been advancing to improve their sensitivity and specificity for better use in a clinical setting, which is regularly demanded so the determination of an appropriate treatment strategy can be initiated quicker and more efficiently [22]. First evidence on CTCs goes back to the 19th Century, but their true clinical significance in predicting metastasis and response of the patient to the treatment was not evaluated until 2004. Nevertheless, the importance of CTCs in cancer research has only been recognized during the past few years. The idea of using CTCs to individualize treatment decisions is considered the next big step towards the “personalized medicine dream”. This is because CTCs are the only “liquid biopsies” that can provide direct information about true intra-patient tumor heterogeneity and since CTCs are the ones responsible for forming metastasis, which are the cause of 90% of death in cancer patients. However, there are still substantial experimental problems associated with CTC detection: CTCs are very rare in blood, ranging from 1 in 106 to 104 cells which makes it hard to be distinguished from the surrounding normal blood cells, and not all patients with the same cancer of the same stage have CTCs.

4.2. Cell-Free DNA and RNA

A growing number of studies on cell-free DNA (cfDNA) and cell-free RNA (cfRNA) illustrate the strong potential for these long and stable nucleic acids to become non-invasive clinical liquid biopsy biomarkers for the early detection and monitoring of diseases, monitoring treatment efficacy or disease reoccurrence after treatment. These molecular biomarkers may assist in immediate treatment and may even show mutations that are inaccessible to solid biopsies since they are released from very few tumor cells in a large size heterogeneity. Consumption of rigorous quality control samples mirror closely the actual biopsy samples. Concerns about

robustness and reproducibility in the fast-developing field of cfDNA pre-analytical and analytical methods include the choice of sample type, preservation method, cfDNA extraction protocol, assay setup, etc. Suggestions for best practice are then offered to guide harmonized development and validation of cfDNA-based diagnostic tests, reduce duplicative effort, and accelerate the translation of promising discoveries to high-quality liquid biopsy commercial tests.

Cell-free DNA (cfDNA) as a form of circulating nucleic acids has garnered a great deal of attention from researchers in the biomedicine field. In the past years, many cfDNA-focused studies have been conducted exploring their potential use and disease relevance, particularly where cancers are concerned. As an accurate reflection of the genetic material of the corresponding tumor, cfDNA can be utilized to detect the a priori presence of cancerous tissue at the onset of the disease. In contrast, current methods for the pathological confirmation of cancers are costly and laborious and become accessible only in the advanced stages of the disease. Furthermore, the use of cfDNA can provide invaluable information about the disease progression, guiding therapy selection and reevaluation, evaluating residual disease post-therapy, among others, which, in turn, may improve patient outcomes. Other types of malignancies like hematological and pediatric oncology diseases, in which tissue biopsy is particularly challenging, still stand to benefit from the non-invasive approach of cfDNA analysis. Another exciting proposal is the use of cfDNA to analyze the entire body of the genetic material in the plasma of the patient and liken human beings to a book that, once read, reveals essential secrets of health and disease.

5. Artificial Intelligence in Biomarker Discovery

Biomarkers are hailed as the cornerstone of personalized medicine. Particularly in oncology, discovering the right biomarkers can enhance the accuracy of diagnostics as well as patient stratification. The transformative impact of artificial intelligence in biomarker discovery has been studied. Exploited in the form of machine and deep learning, AI approaches can effectively navigate overwhelming datasets to reveal previously unsuspected markers. The potential of AI-assisted automated approaches to circumvent laboratory experimentation has also been analyzed. The amalgamation of AI and multi-omics analyses significantly streamlines the wet lab validation process, highlighting how technological advancements can overhaul the classic routines of biomarker discovery. Generally, it is demonstrated that AI fosters a significant breakthrough in unveiling clinically relevant, innovative biomarkers.

The key objectives of this section are: to provide an overview of how AI methods—particularly machine learning and deep learning—facilitate the discovery of novel biomarkers; present case studies showcasing successfully implemented AI techniques in oncology research, including predictive modeling and patient stratification; to explore the challenges and ethical dilemmas associated with the integration of AI in classical methodologies of biomarker research.

6. Challenges and Ethical Considerations in Biomarker Research

Biomarkers are critical in both cancer diagnosis and in support of early phase trials. The identification and adoption of new cancer biomarkers have been limited by scientific hurdles relating to the reliability and reproducibility of the tests. From discovery to validation to regulatory approval, biomarker tests are complex in terms of the characteristics of the test, the type of specimen analyzed, the clinical comparisons made, and the number of variables assessed. The complexity and the large number of potential sources of variation have meant only a handful of new tests have been validated and received regulatory approval in the past few years.

In biomarker research and, more broadly, biomedical research, the invention of breakthrough technologies will always precede a deep understanding of the technologies and their results. The advent of whole genome and transcriptome technologies has generated a tsunami of data, revealing much that was known, affirming much that is suspected, and hinting at much more to

be explored. Moreover, the convergence of the -omics with Systems Biology and personal genome initiatives promises a quantum leap in our knowledge, akin to the shift from geocentrism to heliocentrism.

Significant challenges for biomarker discovery, validation, and use in a clinical setting are delineated. Given the many complexities in analytical, pre-analytical, and regulatory validity as well as generalizability, renewals of statistical guidance are suggested. Such an approach may lead to the establishment of a broad variety of boundaries and the development of a consistent system of guidelines, useful for study design, quality control and assurance. These guidelines could then be subjected to a continual testing-validation-refinement process of best practices. Overall, biomarker research offers clinical, biospecimen, and database science an emerging area with potential benefits for billions of human beings yet to be fully realized. The wide adoption of biomarkers will depend not only on the innovation of those working in the wet lab, but on the commitment of all participants to the highest possible standards in the design and execution of research plans and clinical care. Ultimately, it will be developed in a way that is consistent with the best medical practices, rather than the desire of those initially using the procedures.

7. Clinical Applications of Emerging Biomarkers

Biomarkers of generalized inflammatory responses are frequently used in the clinical context to provide rapid, cost-effective, and minimally invasive information about the disease burden in cancer patients. Higher circulating levels of inflammatory cytokines, for instance, might prevent treatment responses by driving cancer resistance to chemotherapy [23]. Similarly, a large number of research findings suggest that chronic systemic inflammation is part of the cancer's immune evasion and promotion by altering leukocyte profiles. Therefore, it makes sense to explore anti-inflammatory therapies in chemotherapy. When translating research findings from bench to bedside, actionable biomarkers that can be measured simply and non-invasively are desirable. The clinical application and validation of biomarkers in conjunction with other experimental therapeutics, radiation, and surgery have a complex timing and are performed in heterogeneous patient populations, making it challenging to extend the findings. Consequently, over the years, research has focused on the identification of circulating proteins, nucleic acids, or cells that might act as surrogate markers of therapeutic success in the clinical setting. By measuring the changes in these analytes during treatment, it may be possible to anticipate the likely therapeutic outcomes. Given the advantages of blood-based biofluids in cancer patients, these act as promising sources of potential circulating biomarkers of early therapeutic responses. Blood samples can be quickly obtained and evaluated and are believed to reflect the physiological state of the cancer, as well as off-target effects of treatment incurred on normal tissues and blood cells.

8. Future Directions and Potential Impact of Emerging Biomarkers in Cancer Diagnosis and Prognosis

The latest and massively informative data are being generated from multi-omics-based studies, enabling to understand molecular status in greater depth than ever before and to design new therapeutic strategies. Recently, topic evolution and clinical transformations have set off upsurges of research activities on novel diagnostics, therapeutic and biomarker discovery, integrating with multiple omics or other complementary data sets. The continued investigations ahead will more rigorously review the approaches, theories, and data utilization of omics data integration to boost the discovery of novel biomarkers for better cancer treatment outcome on the basis of big data analysis [24]. Combined with the current development, there are wide comments focusing on the challenges and subsequent resolutions, conventional approaches, and newer technologies, ideas, potential collaboration, and research directions still in pursuit.

Research highlights the usefulness of incorporating multi-omics-based patient-specific in-silico platforms in planning and evaluating the effectiveness of combination therapies. In order to convert CRC cancer management to more successful personalized therapies, in-silico platforms

should be used more frequently for creating comprehensive multi-omics-based biomarker signatures, as well as for conducting drug-repurposing simulations [14]. The public health issue was resolved that suggested feasible multi-omic deregulation of in-silico modeling paradigms and their implementation for the discovery of novel patient-specific therapeutic and prognostic strategies with the available therapies, minimizing the necessity of novel drug introduction.

9. Conclusion

Personalized medicine has expanded the utility of complex biomarkers in diagnosis and therapies. The 20-year-long millennium post-genome era has seen human genomes and proteomes reaching over 90% completion, based on the most stringent criteria. These complete human proteomes are poised to enhance our understanding of human health and diseases, including their underlying mechanisms; in particular, they have revealed a significant compact number of proteins that are translated from vast majority of alternatively spliced exonic regions.

Evidence-based new knowledge and new technologies could be used for further cancer biomarker discovery and synthesis, and also for cancer-stage-based new therapeutic strategy design. It has been anticipated that through the intensive lab-based and clinical research efforts, higher percentages of proteins encoded by the human genome should be detected in the near future. Such discoveries are likely to contribute to early diagnosis, personalized therapy and screening for cancer monitoring. As a result, a significant decline would be expected in cancer-related death. A decade ago, it was proposed that the combined efforts of lab-to-lab and lab-to-clinics would accelerate the current slow progress toward the discovery of most of the proteins encoded by the human genome. Bioinformatic and other advanced omics knowledge-based strategies could be applied to accelerate this process.

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