Biomarkers for Cancer: A Detail Review

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When aberrant cells multiply uncontrolled, transcend their normal borders, invade nearby tissues, or spread to other organs, a wide spectrum of illnesses collectively referred to as "cancer" can arise in practically every organ or tissue of the body. The second-leading cause of death globally in 2018, cancer was expected to be responsible for 9.6 million deaths, or one in every six fatalities. A cancer biomarker is a characteristic that can be used to gauge a patient's likelihood of developing cancer or its outcome. Various biomarkers can be used at molecular and cellular level. It is crucial that biomarkers undergo thorough review, including analytical validation, clinical validation, and appraisal of clinical value, prior to being included into normal clinical treatment because of the crucial role they play at all stages of disease. We discuss important steps in the creation of biomarkers in this review, including how to prevent introducing bias and standards to adhere to when presenting the findings of biomarker research.

Introduction

One of the major public health issues associated with high mortality and cross-group migration is cancer. Current therapy modalities have been demonstrated to have a number of limitations. For instance, a sizable proportion of people experience a disease-related relapse and do not get better after chemotherapy. The way that cancer is controlled is significantly influenced by a variety of internal and environmental factors. [1] According to estimates, cancer killed 530,000 people in the US in 1993, accounting for 23% of all avoidable deaths. (3). 55% Of all cancer-related deaths are caused by deaths from the colon, stomach, breast, and prostate cancers based on the National Cancer Institute's 1993 SEER report. [2] Breast cancer is the second most common cancer in women in the US and the primary cause of cancer death in this population. The word "breast

cancer" refers to cancers that originate in the breast tissue, most commonly in the lobules or milk ducts that produce milk. Breast cancer, which accounts for 10.4% of all cancer cases in women, is the second most common non-skin cancer worldwide (behind lung cancer) and the sixth most common cause of cancer mortality. Globally, 519,000 persons (7% of all cancer fatalities; more than 1% of all deaths) perished from breast cancer in 2004. Men often receive a diagnosis of breast cancer later than women, but they frequently have worse prognoses. [3] The second most common cancer found in both men and women, lung cancer is responsible for 30% of cancer-related deaths in the United States each year. Men lose their lives to lung cancer more than three times as often as they do to prostate cancer, and women lose their lives to lung cancer almost twice as often as they do to breast cancer. [4] 33% Of newly diagnosed male malignancies in the US are prostate cancers. 220,900 Men are anticipated to be diagnosed with prostate cancer in 2003. According to the American Cancer Society, 28,900 males are anticipated to pass away from the disease. [5] The development of new throughput technologies, particularly -omic technologies like genomics (the study of a cell's genome complement) and proteomics (the study or analysis of a cell's protein profile), has led to a better understanding of a number of complex mechanisms relating to uncontrolled cell division. The molecular mechanisms that control healthy cell division, proliferation, and death have been extensively studied through the study of cancer biology. [6]

Biomarkers for cancer

A cancer biomarker is a trait that can be used to estimate a patient's risk of getting cancer or how it will turn out. These traits might exist based on molecular, cellular, physiological, or imaging evidence. The focus of the current work is on cellular and molecular cancer biomarkers. These biomolecules are created by or present in both cancer cells and healthy cells in response to cancer, and they can be discovered in tissues or bodily fluids. Performing a DNA, RNA, or protein profile on tumours or bodily fluids can be one method of finding cancer indicators. [7] In addition to information on cancer risk, germ line genetic markers can offer significant information on treatments that are now available. [8] The identification of these biomarkers should increase our understanding of the mechanisms behind the therapeutic effects of immunotherapy and support the development of innovative combination medicines. Additionally, it would help individuals avoid the treatment's negative effects and related expenditures who are unlikely to benefit from it. [9] A biomarker could be thought of as a tool for making informed choices about the least expensive cancer treatment options. Biomarker testing, particularly for cancer, can help crucial decisions made during the medication development process. But when it comes to making therapeutic decisions, rigour

ought to be the basis of ideal performance traits. To help explain test performance, receiver operating characteristic (ROC) plots should be made whenever it is feasible. [10] Two investigations used plasma, the part of blood that contains clotting factors, to examine biomarkers in sALS patients. RT-qPCR was employed by Takahashi et al. after microarray analysis. [11] The Biomarkers of Nutrition for Development (BOND) initiative should provide evidence-based advice to anybody interested in the relationship between nutrition and health. In terms of selection, the BOND programme specifically provides modern knowledge and services. [12] Research on the diagnosis of oral and periodontal disease is increasingly adopting methods that allow the detection and quantification of periodontal risk using biomarkers and other objective metrics.

Radiogenetics and radiogenomics in Cancer biomarkers:

Molecular biomarkers: The use of biological markers or biomarkers evaluated at the molecular and cellular level is of utmost significance as sensitive 'early warning' instruments for measuring biological effects in environmental quality assessment. The idea behind radiogenomics is the potential to examine the connection between imaging, genomics, and clinical knowledge purely through data analysis, devoid of any qualitative interpretation; to put it another way, by letting the facts speak for themselves [13]. When compared to radiogenomics, radiogenetics biomarkers are used as expensive integration biomarkers. The histological analysis of bioptic tissues has historically served as the foundation for cancer diagnosis and categorization. However, this method has drawbacks such as invasive tissue collection, inability to differentiate between clinically important cancer subtypes, and inter- and intra-observer variability [14]. Due to these limitations, new high-throughput technologies have been developed in an effort to characterise cancer at the molecular level better than histological methods, enabling earlier diagnosis, better stratification, and a more accurate prognosis for targeted therapies. In this scenario, advances in molecular biology and imaging technology have produced "radiogenomics" or "imaging genomics." [15]. Literally speaking, radiogenomics refers to the analytical procedures used to correlate genomic information with cancer imaging findings. The idea behind radiogenomics is the potential to examine the connection between imaging, genomics, and clinical knowledge purely through data analysis, regardless of any qualitative interpretation; to put it another way, by letting the facts speak for themselves [16-17]. In order to maintain and analyse a very high number of variables for each sample and modality, radiogenomic approaches heavily rely on tools from numerical calculus and computer science. This unique analytical technique has been widely adopted not only in

cancer but also in neurology, where morpho-functional traits or the connectivity of brain regions can replace textural markers associated with oncological lesions. [18] Despite the fact that the fundamental ideas of radiogenomics are essentially straightforward, the definition of their breadth is very debatable. [19] There are two main explanations for ambiguity. The term radiogenomics which is meant to be radiation genomics—comes from the prefix radio, which can be used to allude to radiation. The goal should be to identify genes with single nucleotide polymorphisms (SNPs) as potential biomarkers of radiation-induced adverse effects and to develop an assay that can predict which cancer patients would experience toxicity as a result of radiotherapy treatment. The second rationale comes from the suffix "omics," which suggests that each biological and imaging sample will provide complex, high-dimensional, mineable data. [20]

Classification of biomarkers

Cancer biomarkers have been defined and categorized using a variety of techniques, but no universal consensus has been achieved (**Figure 1**). Any biologically derived item or procedure is potentially qualified to be used as a cancer biomarker for the purposes of prediction, screening, and risk assessment, as well as during and after a cancer diagnosis (in the therapy and treatment module)[21-28].

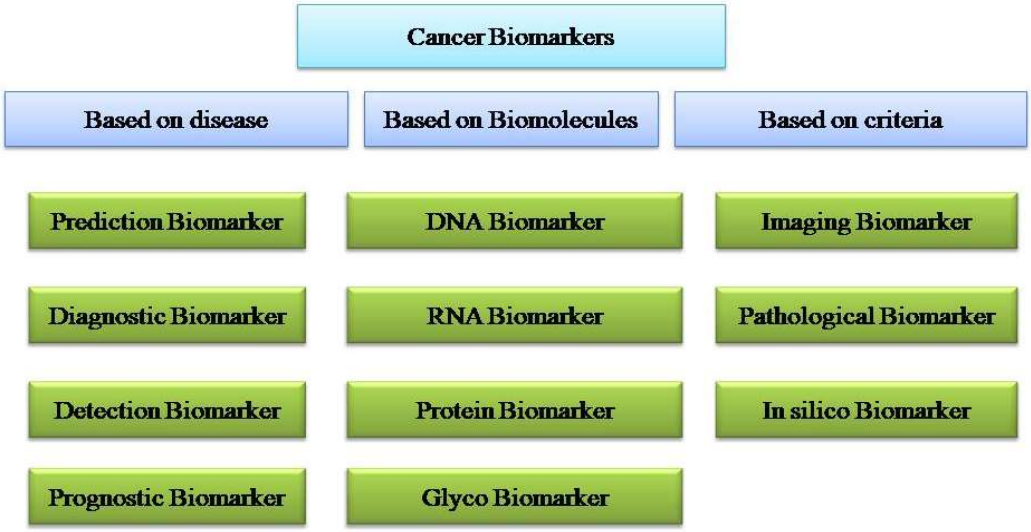

Figure 1. Classification of Biomarkers

Prediction, Detection, Diagnostic, Prognostic, and Pharmacodynamics Cancer Biomarkers

Prognostic biomarkers are built on the characteristics that differentiate benign from malignant tumours. The differentiation state of tumours may also be taken into account when choosing these biomarkers, as this can influence doctors' decisions regarding the best course of action. For instance, oral cancers linked to the human papillomavirus (HPV) have a reasonable chance of survival because they first appear in a condition that is relatively well differentiated.

[20] Only the effects of administering a specific medication are considered when using predictive biomarkers, also referred to as response indicators. By using these biomarkers, physicians can select the most effective chemotherapy drug combination for a particular patient. While Herceptin is successful in breast cancer lesions that only show Her2/Neu over expression, Tamoxifen is advised for the treatment of all other breast cancer lesions. Her-2/Neu is a cancer biomarker as a consequence because it can predict how well a particular subset of breast cancer treatments will work. [21] The treatment outcomes of individuals with HER2-positive breast cancer (BC) have significantly improved with the use of targeted treatments against the human epidermal growth factor receptor 2 (HER2). [29] Patients with HER2 amplification or overexpression benefit from these HER2-targeted medicines, but those without this change do not. In order to standardise the identification of BC patients with HER2-positive status who might benefit from HER2-blockade, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations were created in 2007. They were reviewed and modified in 2013 and 2018 and were last updated in 2018. [30] New therapeutic possibilities, such as antibody-drug conjugates (ADCs), have been created. One of these medications, trastuzumab-deruxtecan (T-DXd), is already advised for HER2-low metastatic BC in NCCN guidelines. It targets cancer cells with low levels of HER2 (HER2-low). [31] T-DXd is used in several therapeutic trials for individuals with metastatic BC with HER2-low that progressed while receiving endocrine therapy or that had received chemotherapeutic treatment in the past [32]. Similar to this, drugs like erlotinib or gefitinib are only effective in treating lung cancer patients who have specific EGFR gene abnormalities. Confined to particular types of Philadelphia-positive leukemia [22], there is also the Gleevec gene mentioned. [23] In a particular collection of tumor-patient circumstances, the suitable chemotherapeutic agent doses are selected using cancer pharmacodynamic indicators. These markers assist in optimizing cancer treatment doses below their cytotoxicity level and phasing clinical trials to the following stage. Any time along the course of cancer development, diagnostic indicators may be present. [24-30]

1.0 Cancer Biomarkers on the Basis of Biomolecules.

1.1.1 DNA:

The epigenetic alteration of CpG methylation-induced gene silencing has so far attracted a lot of attention. [31-38] Strong correlations exist between the level of methylation in prostate cancer tissue, lung cancer patients' sputum and serum, and oral cancer patients' saliva and the severity of the lesions. Repetitive DNA sequences, such as those in the Alu family, are often found in the pericentric heterochromatic area of metaphase chromosomes, which is

located adjacent to the centromere and at the centromere/juxtacentromeric and centromeric regions. Furthermore, "satellite" DNA is frequently present in these areas. 5-Methylcytosine (m5 C) is disproportionately prevalent in repeated regions of the genome in healthy postnatal somatic tissue cells. Sperm cells have lesser levels of DNA than most somatic cells, but they lack the characteristic methylation pattern of these repetitive regions. Hypomethylation of repetitive sequences is a sign of malignancy in practically all other circumstances. The hypomethylation of satellite DNA, for instance, has been seen in ovarian tumours, and according to histological criteria, the level of hypomethylation is correlated with the tumour's predisposition for malignancy. [38-45] Though the term "personalized medicine" is frequently used to refer to finding the best medication and dosage for a specific group of patients, its current applications are much broader and may also include situations where treatment is withheld, preventive measures, or customized treatment plans for specific patients. For example, DNA biomarker tests may be used to determine whether prostate cancer therapy can be safely delayed for a time of watchful waiting. If the tumour is discovered to remain stable for decades as a result of the lack of genes generating an aggressive variant of the disease, the requirement for severe surgical resection followed by radiotherapy or chemotherapy may be avoided. [46-51] However, in other circumstances, the selection of preventive steps may be based on genetic profiles. This approach is already used in the treatment of a number of hereditary cancers, where exact, occasionally extremely severe interventions like preventive surgery are chosen using the results of individual genetic testing as the basis. [52-54] Beyond the term "stratified medicine," which some authors have used explicitly to refer to treatment plans that are provided uniformly to various patient groupings, other uses of personalized medicine [55-60] offer people individualised treatment options. Medications that block TNF, IL-6, or IL-1b, for example, are thought to be effective in managing inflammatory diseases like Crohn's disease. [61] [62]. Several drugs appear to be effective as anti-inflammatory medications as well. The doctor may first utilise genetic sequencing to identify the patient's genetic profile before deciding which anti-inflammatory medications to use alone or in combination. The doctor may choose from among the various anti-inflammatory combo drugs available depending on the patient's Genetic profile. Biological markers are the cornerstone of customised treatment, despite the fact that there are several interpretations of them in the literature. A biomarker is any material or biological component that may be identified in the human body that has the capacity to affect, explain, or predict how an illness will progress. Remember a few of the meanings and note that this is the category that is utilised the most. However,

whether the rule that those biomarkers be tested in human tissue is a reasonable restriction is up for debate. [63-65] The genetic information encoded in DNA needs stability because it regulates the production of the proteins required for a cell's structure and function over the course of its lifespan. Some writers claim that a person's DNA doesn't change over their lifetime. In the discussion that follows, "DNA biomarkers" refers to biomarkers that specifically reflect this stability.[66] This group of DNA sequence variations includes single nucleotide polymorphisms (SNPs), short tandem repeats (STRs), deletions, and insertions. SNPs are the most widely used kind of DNA variation because high-throughput molecular biology abilities are so accessible. [67-70] The majority of SNP applications are diallelic, resulting in three distinct genotypes. Cancer is a condition that modifies a cell's genome; the tumour manifests these modifications. We shall refer to DNA biomarkers that are particular to malignant tumours as "DNA tumour biomarkers" in contrast to the DNA biomarkers that were previously described. Usually, the only thing that is known is whether a DNA mutation exists or not. Last but not least, we refer to all other categories of biomarkers as "generic biomarkers," including readings of RNA, protein, or metabolites in biofluid, tissue, or even cell lines. [71-73] Despite the fact that DNA biomarkers and DNA tumour markers have different characteristics, most general biomarkers have the quality of being quantitative with successful assessment outcomes. Thresholds need to be established for all types of biomarkers when they are used in the diagnostic process in order to link biomarker readings to clinical decision-making. DNA biomarkers differ significantly from DNA tumour or general biomarkers because DNA is stable over the length of a person's lifetime.[74-77] When clinical data have already been collected for studies or when using biobanks, it is possible to prospectively validate DNA biomarkers. The authors stress that a research of this kind would not be regarded as prospective. DNA biomarkers are typically more difficult to evaluate than general or tumor DNA biomarkers. [78-82] Aside from being simpler to gather, process, and store samples, DNA biomarkers are also usually quicker and less expensive to measure in the lab. However, DNA indicators do have some disadvantages. They do not alter throughout a person's lifetime, so they cannot be used for therapeutic tracking, pharmacodynamics, or as replacement markers. Durability is a second problem that frequently arises because novel DNA biomarker development is frequently more rapid than their product cycle times. [83]

1.1.2 RNA and Micro RNA (miRNA):

RNA and Micro RNA are the examples of emerging techniques used in cancer biomarker studies. [84] Small non-coding RNAs, or miRNAs, are micro RNAs. Leukaemia, breast, prostate, colorectal, hepatic, lung, and pancreatic

tumours are just a few cancer types with specific miRNA populations that are tissue- and time-dependently expressed. [85-87] In prostate cancer, myeloma, and chronic lymphocytic leukaemia (CLL), miR15a reduces Bcl-2 expression. Let-7 inhibits RAS in the lung and -RII, whereas mir17 and mir21 groups alter PTEN, TGF, lymphomas, blastomas, prostate, breast, and lung cancers in addition to many other gastric cancers and lungs. These results demonstrate the potential of miRNAs as biomarkers for the diagnosis, prognosis, stage, risk stratification and prediction, and therapeutic response of cancer patients. The first RNA type that has been thoroughly studied as a biomarker is mRNA. Differential gene expression might either correlate with disease pathology favourably or unfavourably. A number of cancer study investigations have thus far used various gene expression profiles as a diagnostic for clinical outcome. [88] For instance, the 50-gene panel PAM50 has been successfully used to classify breast cancer [89]. Here, we have reanalyzed TCGA breast cancer data using the PAM50 group [90]. With the help of a panel of 31 indicators related to cell cycle progression, similar to another expression, the likelihood of prostate cancer recurrence and risk variables were identified [91]. Recently, a significant number of functionally significant non-mRNA RNAs that do not encode proteins have been found. They can all be used as indicators for several of them. A good example of this is the short, evolutionary conserved non-coding RNAs (ncRNAs) known as microRNAs (miRNAs), which are frequently engaged in RNA silencing and other post-transcriptional controls. Because they are necessary for cell proliferation, differentiation, and death, some miRNAs function as oncogenes or tumour suppressors. [92] MiRNA expression patterns have been found to classify various varieties of poorly differentiated tumours. [93] A low expression of miR-21 after adjuvant treatment has also been shown to indicate a low chance of hazard for people with pancreatic ductile adenocarcinoma. MiR-21 was also suggested as a potential therapeutic target. [94] Piwi-interacting RNA (piRNA), a new family of short non-coding RNA, interacts with the Piwi subclass Argonaute proteins, which are involved in DNA methylation-mediated transposon silencing. PiRNAs have been linked to cell invasion and growth. [95]

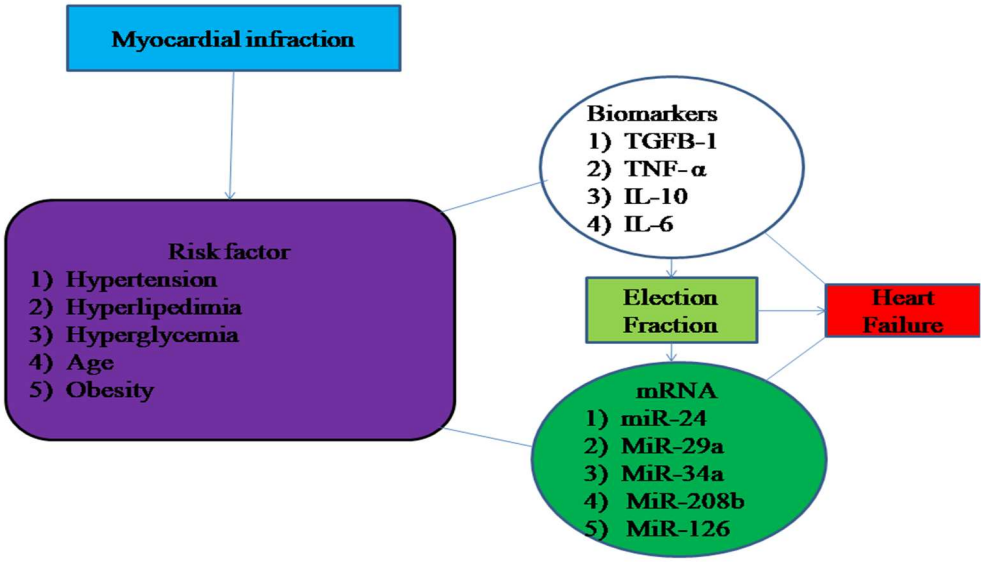

Figure 2: mRNA Biomarker

1.1.3 Protein biomarkers:

Protein-based markers are more significant indicators than DNA- or RNA-based markers since proteins are the primary macromolecules that cells employ for execution. [35] Recently, one of the approaches available to evaluate the potential of protein molecules as cancer biomarkers was the use of quantum dots and nanoparticles [49]. In order to find cancer biomarkers in various organ locations, quantitative proteomics has been utilised, for example, Stable Isotope Labeling with Amino Acids in Cell Culture (SILAC) for prostate cancer. [37] Aptamer arrays for breast, lung, and colorectal malignancies; bead suspension arrays for ovarian and cervical tumours. [38] One of the most useful categories of biological markers is proteins [39]. Many protein biomarkers have been identified and examined for a wide range of illnesses with applications in clinical diagnosis, prognosis of disease progression, and specialised therapy. There is usually no need for costly treatments to get such samples (from blood, plasma, urine, etc.), as these markers may often be retrieved and identified utilising noninvasive approaches. [96]

At various illness phases, proteins are produced and processed in a number of ways, revealing a plethora of information about the specific ailment. When a person is sick, different protein processing, such as adjustments to protein folding or glycosylation, might diverge from typical posttranslational changes. For instance, a frequent posttranslational protein modification in both healthy circumstances and inflammation is the loss of membrane differentiation molecules from immune cell membranes. Thus, histocompatibility and soluble differentiation molecules are more prevalent in body fluids. [97-99]. IgE and IgG antibodies, which are specific for the allergens that cause the sickness, cytokines, enzymes, and other proteins,

such as soluble differentiation molecules of the immune cells or membrane protein indicators, are the most well-known soluble protein biomarkers for allergies. The progress of molecular cloning techniques over the past few decades has sparked a real revolution in biological research and clinical allergy diagnosis. By employing recombinant molecules based on the sequences of allergens, it is now possible to establish the 3-dimensional structure and molecular features of disease-causing allergens or specific IgE against them and use these recombinant allergens for exceptionally accurate allergy diagnosis (i.e., molecular allergy diagnosis and component-resolved diagnosis) [100], [101], [102], [103] Medical professionals can now comprehend allergies at the molecular level thanks to these cutting-edge procedures that have made molecular allergology a part of normal clinical practise. [104] Moreover, it has been discovered that the N-terminal peptide of the VP1 coat is a target of the natural immune response to rhinovirus, the most prevalent respiratory virus that causes protein asthma. [106-108].

1.1.4 Carbohydrate Biomarkers:

The expression of certain N-linked and O-linked glycans varies as various cancers grow. These modified glycoforms might be used as cancer markers. [40] The most widely used method for locating disease-related carbohydrate markers is mass spectrometry. The detection of tumours in the breast, colon, ovary, pancreas, lung, and colon can be done using tissue samples and biofluids (serum, cerebrospinal fluid, pancreatic fluid, and lavage). [43] [44] Glycomarkers, such as glycoproteins, proteoglycans, and glycolipids, are more stable than RNA and proteins, making them more suited for biological applications. A crucial method for identifying glycan-based cancer biomarkers is the profiling of O- and N-linked glycosylation of protein molecules at serine and threonine residues in human sera, tissues, and cell lines using MALDI-TOF and Electro spray Ionization (ESI). Glycans have different terminal structures and spread out more as a result of the altered expression of glysyltransferases (sialyl and fucosyl-transferases). According to the study, sialyl Lewis x (sLex), sialyl Tn (sTn), Globo H, Lewis y (Ley), and polysialic acid are some of the most prevalent terminal glycan moieties discovered in cancer cells. [45]

1.1 Cancer biomarkers on the basis of criteria

1.2.1 Pathogenic Cancer Markers :

Viral markers:

Since viruses are linked to specific tumour types, they are very desirable biomarkers because infectious agents in general and viral infection in particular cause 15-20% of all human malignancies. [46] The RNA viruses human T-cell lymphotropic virus type 1 (HTLV-1) and Kaposi's sarcoma associated herpes virus (KSHV/HHV-8) are responsible for some kinds of leukaemia, respectively. These two viruses have both been linked to cancer. [47]

Antigen and Antibody Detection

Hepatitis B surface antigen (HBsAg), originally known as Australia antigen, was the first HBV infection marker discovered. The discovery of it by Blumberg marked the biggest sea change in the treatment, prevention, and diagnosis of hepatitis B [109]. The primary method for determining if a person has HBV infection is the detection of HBsAg. Due to the fact that it is overproduced by HBV-infected hepatocytes and circulates in substantial concentrations in the blood, HBsAg is a highly sensitive and specific biomarker for HBV infection. [110]. The patient's profile is sufficient for the diagnosis of acute and for the screening of chronic HBV infection based on the results of the detection of HBsAg combined with the measurement of the pertinent anti-HBs antibodies as well as the detection of anti-HBc antibodies (total and IgM). Testing for HBeAg and the related anti-HBe antibody is required following the confirmation of chronic HBV infection. The methods used for this testing is typically the same as for the serological markers outlined above. HBV serology is currently performed using automated analyzers with very sensitive immunoassays based on chemiluminescence (CLIA) and electrochemiluminescence technology (ECLIA) [110-112]. Yet, rarely, the HBsAg tests' enhanced sensitivity might result in erroneously positive results. It is recommended to utilise a confirmatory test to confirm HBsAg positive in patients with HBsAg index values that are close to the threshold and inconsistent other serological markers. HBeAg and HBV antibodies may also be detected using these automated immunoassay techniques [113-116]. The classic enzyme-linked immunoassay (ELISA), which is inexpensive and simply needs a microplate reader as an equipment, is still used by many laboratories for HBV serology (photometer). Commercial ELISAs offer great sensitivity (>99%) and adequate specificity (>95%) for HBsAg, albeit it is still crucial to verify positive results in the context of low absorbance [117]. Moreover, these tests may experience either positive or negative interference in the context of rheumatoid factor positivity. [118]. According to reports, there is a 97.05% agreement between ECLIA and ELISA for HBsAg, 92.62% for anti-HBs, 100% for HBeAg, 76.75% for anti-HBe, and 58.67% for anti-HBc. The concordance for HBeAg detection was reported to be 45.83% and for anti-HBe to be 79.17% in patients with coexisting HBeAg and anti-HBe. The major reason for the tests' inconsistencies was variations in their sensitivity. [119]

Quick tests that are available at the point of service make HBV screening practicable (POC). A number of serological markers, such as those for syphilis, the human immunodeficiency virus (HIV), hepatitis B, and hepatitis C, may be found using point-of-care serology [120]. It may also be used as an HBsAg single test. Rapid HBsAg tests

are straightforward to perform and have a sensitivity of over 90% and a specificity of over 99.5%. They employ capillary blood samples taken by fingerstick. Fast tests for anti-HBs, however, fall short of their promise due to a sensitivity issue, which is their main shortcoming. Furthermore unavailable are anti-HBc POC tests. [121].

Bacterial Markers:

Helicobacter pylori cause a persistent, mild inflammation of the stomach lining (H. pylori). The H. pylori infection, which is also a recognised biomarker for gastric cancer, is closely linked to duodenal and stomach ulcers. [48] [49] The upper digestive tracts of more than 50% of individuals on the planet are infected with H. pylori. Infected people are more prevalent in developing countries. The bacterium affects more than 80% of people without any symptoms. Detecting H. pylori in individuals can be done either through DNA polymorphisms or antibody-based techniques. This bacteria is susceptible to antibiotic treatment, and eliminating the infection would alleviate a person's dyspepsia, gastritis, and peptic ulcer symptoms as well as perhaps prevent stomach cancer.

Imaging Markers:

Cancer imaging biomarkers are essential for the early identification, diagnosis, staging, and follow-up of cancer. These biomarkers entail the visualisation and quantification of certain traits of tumours and adjacent tissues using a variety of imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound.

Imaging biomarkers give quantifiable, objective measurements of tumour features, enabling more precise and consistent evaluations of cancer-related alterations. They can help with early diagnosis, separating benign from malignant lesions, measuring the size of tumours, gauging therapy effectiveness, and tracking the development of the illness. [122-125]

1.3.0 Bioinformatics and Cancer Biomarkers

Technology that integrate clustering algorithms and visualisation tools into a Web-based application and those that analyse high-throughput gene expression data using a variety of case-control models have both been used to identify cancer subtypes and biomarkers. Among the typical analytical tools are the following: Interwoven Loop, also known as ILOOP, is used to create arrays. Gene Expression Profile Analysis Suite, also known as GEPAS, and CARMAweb, also known as CARMAweb.genome.tugraz.at, are used to analyse microarray data. MAGMA is used to do statistical analysis. Several tools are available for gene ontology research, including AmiGO (http://amigo.geneontology.org/cgi-bin/amigo), GOS tat, and Discover (http://discover.nci.nih.gov/gominer), bin/ amigo /go. cgi) BiNGO (http://www.psb.ugent.be/cbd/papers/B These

techniques are used as in silico or bioinformatics tools in the search for cancer indicators. Using RMA Express (http://rmaexpress.bmbolstad.com/RMAExpress), dChip (http://www.dchip.org/automate.htm), and ca CORRECT (http://cacorrect.bme.gatech.edu), data from expression arrays are normalised, quality-checked, and analysed. Omni Biomarker is used for building biomarkers in oncology. [51]

1.4.0 Cancer Biomarkers for Selected Organ Sites

Lung:

The largest cause of cancer-related deaths worldwide is lung cancer. Among blood tests for lung cancer, CA-125, NSE, squamous cell carcinoma antigen, and carcino embryonic antigen (CEA) are the most frequently utilised tests [52]. Following early validation, certain promising circulating blood biomarker candidates for lung cancer diagnosis, prognosis, or prediction have advanced to clinical trials. By focusing on high-risk participants, several studies have validated these biomarkers in the context of LDCT lung cancer screening trials. They have also demonstrated how useful these biomarkers are for estimating the risk of developing lung cancer in asymptomatic individuals. In people with end-stage NSCLC, circulating microparticles (MPs) may be valuable indicators for predicting 1-year death. In a prospective trial where the level of four MPs was assessed by flow cytometry, the circulating level of endothelial-derived activated MPs (EDAc-MPs) was one of several indicators that were substantially and independently predictive of 1-year mortality of NSCLC patients. [122] Circulating prosurfactant protein B was studied as a potential lung cancer risk biomarker in participants of the lengthy Physicians' Health Study. Plasma levels of prosurfactant protein B were shown to have a nonlinear, J-shaped connection with lung cancer risk (OR1=45.88), and it was proposed that this protein could assist identify the high-risk population who should undergo LDCT screening. IDH1 had considerably greater diagnostic value in ADC over a clinical trial period (AUC: 0.858; sensitivity: 77%; specificity: 82%) than CA125, CYFRA21-1, or CEA. IDH1 plasma levels were significantly higher in NSCLC patients compared to healthy people. [124]

Uterine and Cervical Cancers:

The most significant risk factors for uterine and cervical cancer in women are the HPV virus and expression of the oncogenes E6 and E7. In severe dysplastic lesions, micro chromosome maintenance (MCM) proteins are overexpressed. [54] The cell division cycle protein 6 is overexpressed in malignant cervical carcinoma as well (CDC6). [55]

Despite the fact that this method is susceptible to intra-observational subjectivity, microscopic examination of biopsied samples has long served as the foundation of screening and diagnostic procedures. Therefore, many

malignancies are sadly discovered at the microscopic level when it is frequently too late for effective intervention, despite the technological breakthroughs made to identify cancer in its earliest stages of development. [125-126]. Vaginal discharge, itching, or burning is not usually early signs of cervical cancer, in contrast to many genitourinary diseases. Some cervical cells may go through early modifications, but these variations are not cancerous. Nevertheless, these precancerous cells result in dysplasia or squamous intraepithelial lesions within the epithelium, or exterior layer of cells (SIL). [127]

Breast Cancers:

The American Society for Clinical Oncology (ASCO) proposed eight distinct protein-related tumour markers for breast cancer, including urokinase plasminogen activator (uPA), CA 15-13, CA 27-29, carcinoembryonic antigen, oestrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2), and plasminogen activator inhibitor (PAI)-1. Monitoring biomarkers include carcinoembryonic antigen, CA 15-13, CA 27-29, oestrogen receptor (ER), progesterone receptor (PR), and HER2. Recurrence risk prediction biomarkers include uPA and PAI-1, and treatment planning biomarkers include uPA and PAI-1. [56] While the MapQuant DxTM Genomic Grade platform is based on the mRNA expression of about 100 genes to identify breast cancer, BCtectTM is an RT-PCR-based assay with many genes for early detection. Studies have demonstrated that the dysregulation of the miRNA markers (mir-125b, mir-145, mir-21, and mir-155) in breast cancer [57]

Cancer biomarkers without specificity

Cell development involves the basic fibroblast growth factor (bFGF), a protein. Sadly, it has been shown to be highly active in tumours, which raised the concern that it might encourage the growth of cancerous cells. A number of causes of cancer have been shown to respond favourably to anti-bFGF antibodies. [59] A number of causes of cancer have been shown to respond favourably to anti-bFGF antibodies. [72] A further component in cell growth and proliferation is insulin-like growth factor (IGF-R). It might play a part in averting apoptosis, or the deliberate cell death brought on by a flaw. [60] As a consequence, IGF-R levels may increase in the presence of cancers such as breast, prostate, lung, and colorectum. As a result, when cancers including breast, prostate, lung, and colorectum are present, IGF-R levels may rise. [61]

2. Techniques Used to Detect Molecular Cancer Biomarkers

Fish:

The method uses a fluorescently tagged probe that hybridises with DNA in order to find gene fusions or changes in gene copy number in tumour cells or tissue sections. Multiplex FISH, spectral karyotyping, and comparative genomic hybridization are a few FISH variations. Spectral

karyotyping is a 24-color chromosome painting technique with a high sensitivity for detecting chromosomal abnormalities. It can be utilised to find chromosomal biomarkers for cancer diagnosis and prognosis, especially for brain tumours, sarcomas, and haematological malignancies. [66]

PCR/Real-Time PCR/Digital PCR:

The method most often employed in cancer diagnosis for both DNA- and RNA-based purposes is PCR-based targeted genomic profiling. This method may be used to identify gene fusions, minor DNA changes (such as EGFR mutations), and DNA methylation utilising methylation-specific PCR (e.g., MGMT promoter methylation in glioblastoma or Septin9 gene methylation in CRC). This fundamental approach is continually being improved in a variety of ways to improve the sensitivity of identifying biomarkers from trace sources.

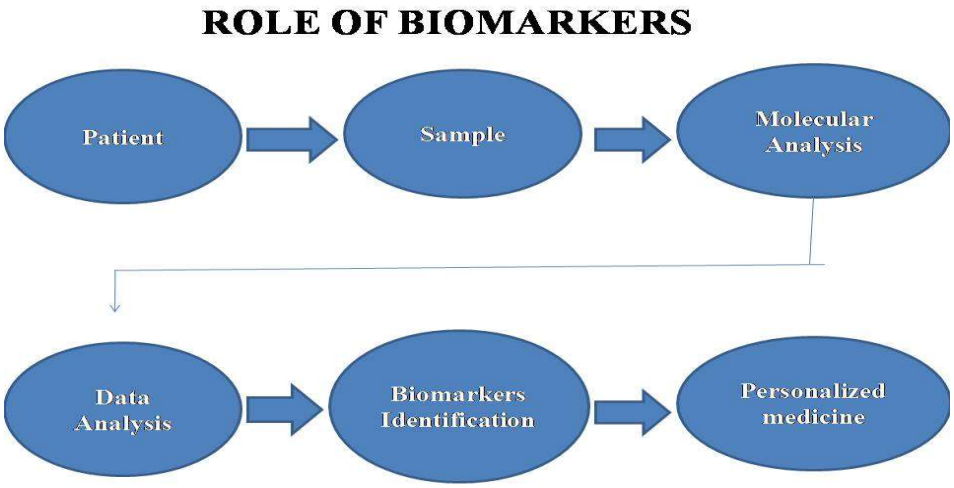

Figure 3. General role of Biomarkers

NGS:

Genetic testing for somatic mutations such SNVs, indels, and CNAs as well as germ line variations is done using NGS. Two more RNA-based indicators that are utilised in combination with it are gene fusions and RNA sequencing. The techniques employ targeted capture and hybridization to select specific segments of interest for sequencing as well as amplicon-based screening using primer panels to amplify areas of interest with driver gene mutations. Both of these methods make use of capture probes. NGS gene panels can be cancer-specific (for instance, for breast, lung, and CRC cancers), generic pan-cancer panels for solid tumours, haematological malignancies, or panels aimed to discover genomic changes for targeted therapy. [67]

Flow Cytometry:

In leukaemia and lymphoma diagnosis, a panel of fluorescently tagged antibodies is frequently employed to identify and count cells.

Using DNA-binding, light-sensitive pigments on cancer cells allows for the measurement of their DNA content. Breast, prostate, or bladder cancer might recur at any time as indicated by changes in DNA amount. Moreover, it can be used in CTC-based indicators.

Gene Expression Microarrays:

In order to predict prognosis or treatment response, they are utilised in the analysis of differentially expressed genes in tumour samples and the molecular subtyping of tumours. For instance, Mamma Print, a microarray-based predictive diagnosis, uses a 70-gene expression profile from FFPE tissue to identify early-stage breast cancer patients with a high/low likelihood of recurrence. The utilisation of these microarray-based molecular classifications of breast cancer by Mamma Print, Target Print, or Blueprint has shown the efficacy of these tests for enhancing the management of this condition. [128-131]

IHC:

In order to detect the proteins that cancer cells produce in tumour tissues, IHC is a technique that is often employed in the pathology and diagnosis of cancer. There have been advancements in this area, including the use of fluorescent quantum dot nanocrystals, tyramide signal amplification, and MultiOmyxTM, which has a greater sensitivity for identifying low-abundance proteins and a higher signal-to-noise ratio. Another one is multiplex IHC, which repeats the steps of antibody staining, imaging, and quenching using several antibodies on the same tissue segment. [132-135]

ELISA:

The protein analysis method is most often applied in clinical contexts, particularly for bodily fluids. Newer innovations include electrochemical ELISA tests boost signal, enhancing ELISA's sensitivity to protein biomarkers in physiological fluids at low concentrations. They are less expensive and easier to use. [136]

Lectin Microarrays:

Lectin microarrays are used for high-throughput glycan profiling, particularly to investigate variations in glycomic profiles between cancer and healthy tissue or to discover novel markers in plasma or EVs. [137]

Proteomic Tools:

Mass spectrometry (MS) and reverse-phase protein arrays (RPPA) are two additional proteomic techniques that can be used to detect numerous proteins in cancer samples. When looking for cancer biomarkers, MS can be used as a targeted approach or as a tool for wide profiling. [71] as opposed to RPPA, a targeted proteomics platform built on antibodies? Sometimes, possible protein biomarkers identified by MS profiling are confirmed by RPPA. Both can recognise and quantify proteins in tumour cells or bodily fluids as well as their post-translational modifications. In comparison to MS, RPPA performs better in terms of throughput, expense, limit of detection, and

sensitivity. 240 verified antibodies were investigated by a vastly improved RPPA platform, which discovered significant cancer-related proteins. [138-141]

Biosensors/Nanotechnology

The main challenge in the development of cancer biomarkers is the extremely low quantity of analytes in samples of non-tumor tissue, such as blood or other bodily fluids. Biosensors and nanotechnology are being investigated in an effort to increase the sensitivity and precision of detection. A transducer transforms a chemical process into an electronic signal, which a biosensor then processes and amplifies to identify a biomarker. [142]

Micro fluidics

For usage in clinical applications, micro fluidic chips are being developed in combination with various biomarker detection methods. [74] With the use of micro fluidic chips, it is now possible to recognise proteins that are connected to cancer in cases of oral cancer. In order to detect miRNA at the attomole level, [75] created a nonmaterial micro fluidic chip that is employed in the diagnosis of cancer. In addition, digital PCR and microfluidic chips have been developed for analysing ncRNA or DNA methylation from liquid biopsies. [143]

Synthetic Biomarker Technology

Synthetic biomarker technology A novel class of synthetic biomarkers is being created to overcome some of the issues with cancer biomarkers, such as inadequate sensitivity or specificity and technological restrictions. [144]. Activity-based synthetic biomarkers work by combining a bioengineered sensing component with an exogenous drug. This chemical causes the production of artificial biomarkers from the tumour, producing a detectable indication. It focuses on specific physiologic and behavioural characteristics of cancer cells. Examples include small-molecule probes and synthetic indicators that are triggered by proteases. [145-147]

3. Steps in the search new biomarkers:

Despite the fact that much success has been made, the field of cancer urgently needs to identify and develop more effective biomarkers. The process of developing a cancer biomarker involves the finding, development of an assay and analytical validation, clinical validation, clinical utility, and finally clinical implementation. [148-151]

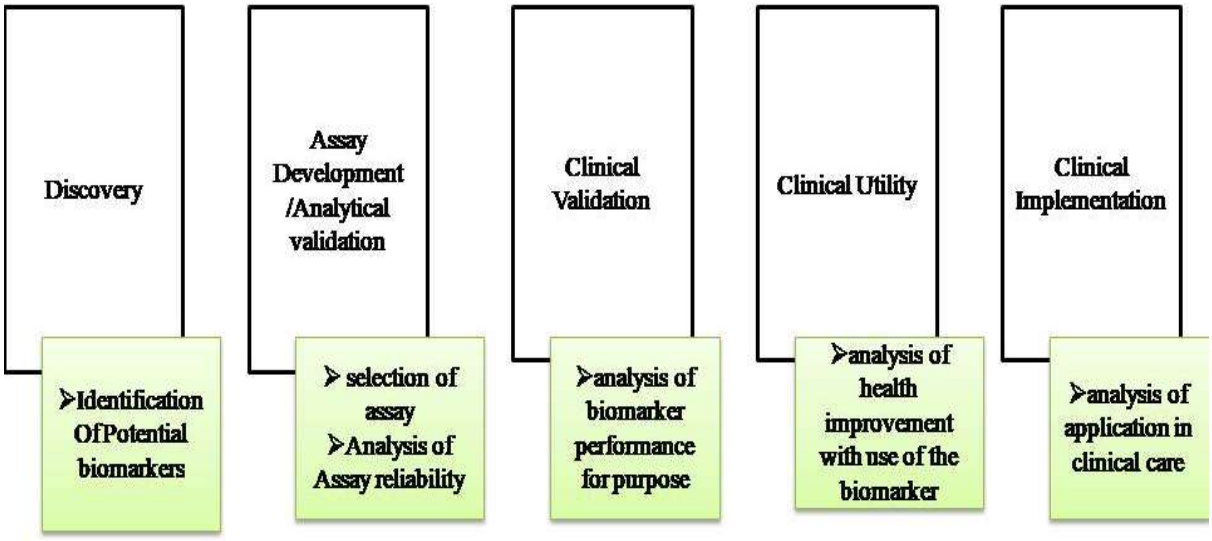

Figure 4. Discovery of new biomarker

4. Detection of cancer cell by Biomarker

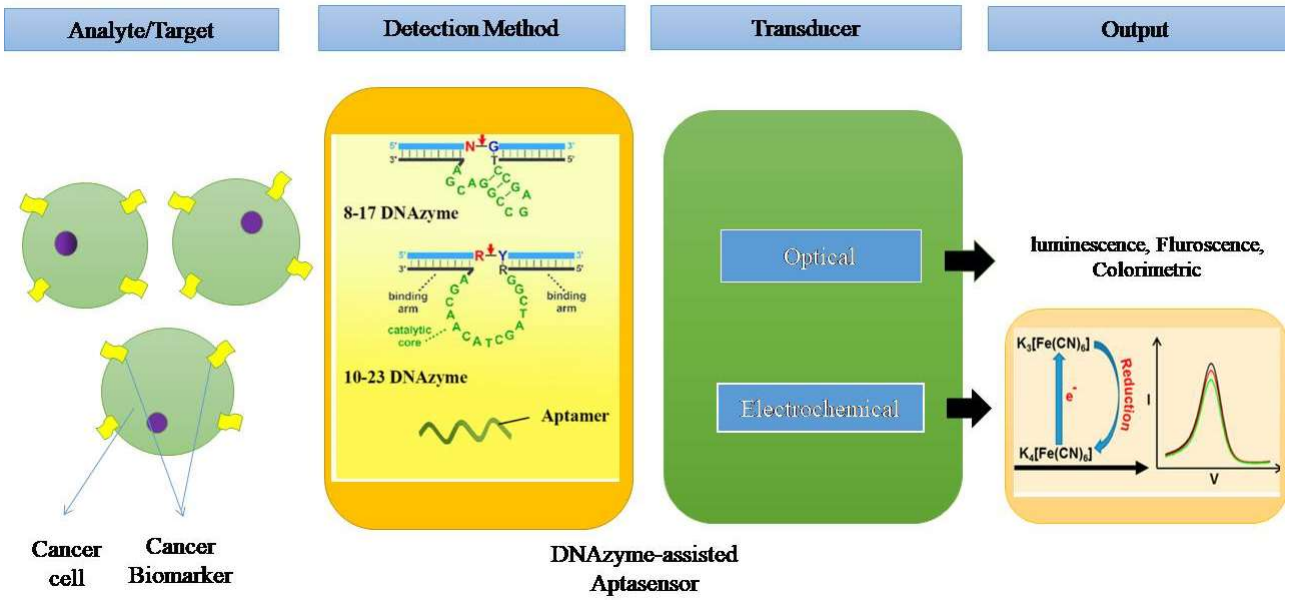

Figure 5. Detection process of cancer cell by biomarker

DNAzyme

It has been shown that DNAzymes, also known as catalytic DNA, have the ability to specifically carry out processes like target mRNA ligation, DNA phosphorylation, and target mRNA destruction. [128] Numerous distinct DNAzyme forms have been discovered using in vitro screening technology. According to Kamali et al. in the Journal of Nanobiotechnology, there is a significant possibility for structural recognition. [129] The possibility for using three of them—RNA-cleaving DNAzymes, DNA-cleaving DNAzymes, and Hemin/G-quadruplex (G4) DNAzymes—in techniques for identifying cancer biomarkers is considerable. [130],[131]

Nearly any phosphodiester link between paired pyrimidines and unpaired purines can be broken by the two most common varieties of DNAzyme, 8-17 and 10-23. [132],[132] By catalyzing the hydrolysis of the target RNA's phosphodiester, DNAzyme can effectively cut the target mRNA in the presence of particular metal ions, including Mg2+, Pb2+, Mn2+, Cu2+, and Na+. [133], [152] As a result, DNAzyme has the potential to become a powerful instrument for building biosensing platforms for cancer diagnostics as well as an innovative and promising gene therapy method.

Aptamer and aptasensors:

Aptamers, which are RNA or DNA strands that may be selectively attached to chemicals, proteins, and biological components, are created using the SELEX (Systematic evolution of ligands by exponential enrichment) method. [135] Over antibodies, aptamers offer various advantages, including a simpler production, easier storage, and improved stability and resilience to environmental variables. [136], [137] The flexibility of aptamers allows them to precisely bind to their target. They are widely employed in biosensing technologies to find biomarkers, illnesses, and other biological elements. [138], [139] Instruments that assess the quantity or presence of a chemical or biological component while giving both quantitative and qualitative data are known as aptamer-based biosensors (aptasensors). [140]. A display system, a signal transduction device that is commonly optical or electrochemical, and an aptamer that functions as a bioreceptor and recognises a target and produces a signal are all components of an aptasensor. As they are inexpensive, very sensitive, dependable, and quick to detect, aptasensors have become more and more common. Moreover, [142] the incorporation of NPs into aptasensors results in nanoaptasensors, which have contributed to the development of novel, incredibly sensitive detection techniques in a range of diverse domains. [143] The most advanced biosensors for prognostics, diagnostics, and monitoring include DNAzyme (also known as aptazyme) and therapeutic disease screening, which are based on nanomaterials. This article [144] discusses the possibility of DNAzyme-based aptasensors for the identification of cancer-specific biomarkers. Innovations in aptazyme manufacturing using NPs for the detection of cancer biomarkers are also explored.

DNAzymes-assisted aptasensors for cancer detection

DNAzyme-assisted aptasensors are made up of an aptamer structure and a catalytically active nucleic acid molecule, which may be a ribozyme or a DNAzyme. [145] In these designs, the aptamer domain serves as a molecular switch to regulate the catalytic activity of the DNAzyme component. The aptamer-target binding causes a substantial physical change in the full aptazyme. As a result, aptazymes function similarly to

allosteric enzymes, whose catalytic activity is controlled by the attachment of ligands (efectors) to allosteric sites brought on by modifications in the 3D structure of the enzyme's active site. [146] The allosteric location of aptazymes is made up of aptamers. The production of aptazymes allows for a wide range of applications, including the regulation of gene expression and the execution of scientific procedures. [134]

5.4 Optical based DNAzymes-assisted aptasensors Luminescence based DNAzymes-assisted aptasensors

Recently, several optical-based DNAzyme-assisted aptasensors for cancer detection were reported. Platforms built on luminescence are one of them. A substance is said to be luminescent when it produces light without being heated. In a variety of light emission processes, the luminescence-based approaches are categorised according to the energy source that generates the luminescence. Chemical reactions provide the energy for chemiluminescence (CL). Electrochemiluminescence (ECL) is a byproduct of electrochemical processes in solutions. Luminescence-based methods are regarded as a common platform for the creation of ultrasensitive biosensors due to their numerous advantages, including high sensitivity, excellent selectivity, and a wide linear range (LR). Some academics are interested in luminescence-based DNAzyme aptasensing platforms for the biomarker-based diagnosis of cancer. [147]

Tissue agnostic biomarkers

A particular kind of biomarker called tissue agonistic biomarkers for cancer provides light on the function or activity of certain molecules in tumor tissue. Tissue agonistic biomarkers concentrate on the molecular interactions and signaling pathways taking place inside the tumour microenvironment, as opposed to conventional biomarkers, which are focused on the detection of certain chemicals in blood or other physiological fluids.

In cancer research and clinical practise, tissue agonistic biomarkers are especially helpful because they give researchers and clinicians a better knowledge of the molecular processes behind tumour development, progression, and therapeutic response. Researchers and physicians can learn more about the biological behaviour of the tumour and create more tailored treatment plans by analysing the activation or inhibition of certain molecules inside the tumour tissue.

These biomarkers may involve a variety of molecules, including receptors, enzymes, or signalling proteins linked to important processes implicated in the initiation and spread of cancer. For instance, the presence or activation of certain receptor tyrosine kinases in the tumour tissue, such as the EGFR or HER2 (human epidermal growth factor receptor 2), might point to certain therapeutic choices that target these receptors. [153-155]

The results in drug development driven by biomarkers rather than histological cancer

type that have been highlighted above show the possibility of a new oncology paradigm. Future advances in our knowledge of the scope and character of recurrent, genetic, and immunological abnormalities that develop in malignancies in diverse tissues of origin will make it possible to further improve patient subclassification schemes, which will become more complex, similarly to how rare subtypes within histologically defined cancers have been established. This intricacy highlights the need for creative research designs and regulatory flexibility and creates challenges for conducting large phase III clinical trials involving patient populations with uncommon abnormalities. For instance, if 0.1% of NSCLC patients had NTRK fusions, the number of patients presenting with metastatic disease per year in the USA would be 200, underscoring the challenge of pursuing a clinical trial for a particular histology. [156]

Conclusion

In conclusion, cancer biomarkers are essential for the detection, assessment, and management of cancer. The existence of cancer, its subtype, stage, and possible response to therapy are all revealed by these molecular signs. Significant progress has been achieved in the identification and validation of numerous biomarkers over time, allowing physicians to make better judgements and provide patients with individualised therapy.

The discovery of cancer biomarkers has transformed the management of cancer by enhancing early detection, enabling more accurate diagnoses, and assisting in the choice of treatment. Specific gene mutations, protein expression levels, circulating tumour cells, and circulating tumour DNA have all demonstrated significant promise for improving the precision of cancer detection and tracking the course of the illness. Moreover, biomarkers can shed light on the biological behaviour of tumours, assisting in the prediction of patient outcomes and directing treatment choices.

However, the future of cancer biomarker research seems hopeful given the continual advances in genomics, proteomics, and other molecular methods. Biomarkers will continue to be essential in directing therapeutic decisions, evaluating therapy response, and enhancing patient outcomes, especially with the development of precision medicine and personalized cancer treatment techniques.

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