**A DEEP DIVE IN TO BIOMARKERS, TYPES, ROLE IN THE DIAGNOSIS OF DISEASES AND IMPACT OF SAMPLE KIND ON SELECTION OF BIOMARKER**

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**ABSTRACT**

Biomarkers, also known as biological markers, are biological indicators of the state of a person's biological system. Biomarkers can be used alone or in combination to assess an individual's state of health or disease. A "diagnostic biomarker" can be used to determine whether a patient has a particular disease subtype or to identify, confirm, or detect the presence of a disease or condition of interest. As we move into the era of precision medicine, these types of biomarkers will grow significantly. When a biomarker is serially evaluated for symptoms of exposure to a medical product or environmental agent, or to test the status of a disease or medical condition to identify the effect of a medical product or biological agent, the term "monitoring biomarker" is used. Levels of “pharmacodynamic/response biomarkers” change in response to exposure to a drug or environmental factor. This type of biomarker is extremely useful for both clinical practice and early development of therapeutics.

**Keywords:** Biomarkers, diagnostic biomarker, monitoring biomarker, Pharmacodynamic/response biomarkers, medication, environmental factor.

1. **DIAGNOSTIC BIOMARKERS**

With an estimated 1.7 million incident cases and 521,900 deaths in 2012 [1], breast cancer is the most common malignancy and the main cause of cancer-related mortality in women globally. According to epidemiological investigation, an increased probability of breast cancer in women is associated with obesity, advanced maternal age at the time of the first birth, the use of estrogen and progestin, lack of physical activity, and consumption of alcohol [2–5]. Some of these elements have an impact on patients' post-treatment prognoses as well. Genetic variables are crucial to the genesis of breast cancer since individuals with the same circumstances and family aggregation have varying lifetime risks [6, 7]. Gene markers for breast cancer susceptibility, such as BRCA1 and BRCA2, are often employed [8, 9]. Breast cancer is caused by DNA double-strand breaks, which are repaired by tumour suppressor genes. The human genome became unstable as a result of gene mutations, which also elevated the risk of breast cancer by about 21–40% in cases of hereditary breast cancer [10]. A graphene-based electrochemical DNA sensor for the detection of BRCA1 was created by [11] on a glassy carbon electrode modified with graphene, target probe DNA and reporter probe DNA hybridized in a sandwich configuration. This sensor was reliable, repeatable, and sensitive; it could identify the BRCA1 gene down to 1 femtomolar levels. About 30–35% of breast tumors have p53 mutations [12]. A DNA biosensor has been constructed for studying the p53 gene [13]. The affinity traits of response elements (REs) and the p53 gene are shown by serially injecting REs above the active oligonucleotide probes. These experiments demonstrate that the ligands varied in their affinities for the REs. For the purpose of locating p53 mutations in breast cancers, a single strand binding protein biosensor was developed [14]. Breast cancer is associated with excessive DNA damage, which is generated by necrotic and apoptotic cells [15]. Breast cancer treatment information is provided by cell-free tumor DNA (cfDNA) precise quantification, a novel non-invasive approach to diagnosis. cfDNA has been investigated as a breast cancer biomarker to demonstrate the correlation between cancer development and cfDNA concentration, despite the fact that the technology is not especially advanced. [16, 17]. MicroRNAs (miRNAs) are transforming into reliable biological markers based on the hybridization principle and guanine oxidation [18]. For the purpose of investigating the target miRNAs, a variety of electrochemical nanobiosensors have been employed [19]. Although MiR-21 offers the best sensitivity and specificity of all miRNA markers, it also has substantial shortcomings, notably sequence similarity with related RNAs, occurrence in other malignancies, and low serum levels. [20]. Carbohydrate antigen 15-3 (CA15-3), an established biomarker for advanced breast cancer, has a relatively low sensitivity for early-stage breast cancer. CA15-3, which has been extensively used to detect recurrences and track therapy in metastatic breast cancer detects the mucin MUC1 [21,22,23,24,25]. The typical secretory epithelium's apical membrane contains MUC1, which may be located anywhere along the membrane's outside surface. The clinical value of MUC1 measures is limited to measurements of CA15-3, which is liberated from the cell surface by proteolytic cleavage, despite the fact that MUC1 is expressed in both normal and malignant breast epithelium. About 30% of breast cancer patients had HER2 levels that were much higher than in healthy individuals. Human blood samples can be used to identify HER2, which has been utilized as a breast tumor related antigen [26]. Breast cancer patients often have HER2 levels of 15–75 ng/mL whereas healthy persons typically have values of 2–15 ng/mL [27]. Circulating HER2 levels have been proven to be useful for monitoring disease recurrence, cancer progression, and choosing the most suitable treatment, such as giving Herceptin to patients with HER2 positive breast malignancies [28]. HER2 serum levels, tumor dimensions, nodal involvement, and tumor indicators are dependent prognostic factors for both disease-free survival and overall survival.

1. **PHOSPHOPROTEINS AS BIOMARKERS – BREAST CANCER**

Medical diagnostics has long sought to identify and track illnesses like cancer early through blood testing. One of the most noteworthy and widespread molecular regulatory mechanisms, protein phosphorylation governs almost every facet of cellular activity [29, 30]. Thus, the status of phosphorylation processes may provide a window onto the progression of a disease [31]. Few phosphoproteins, nevertheless, have been created as disease indicators. However, only few phosphoproteins have been established as disease markers. Assays of phosphoproteins from tissues confront substantial obstacles due to the invasive nature of tissue biopsy and the very unpredictable nature of protein phosphorylation throughout the occasionally difficult and drawn-out procedure of tissue biopsy. Furthermore, it is not feasible to evaluate the patient's response to therapy using tumor sample tissue. Developing phosphoproteins into biomarkers of disease from biofluids is made much more complicated by the elevated levels of active phosphatases seen in blood. Despite certain highly abundant proteins making up over ninety-five percent of the mass in blood, very few phosphorylated proteins may be found in steady and measurable levels in plasma/serum. Due to their potential importance in tumor biology and metastasis, extracellular vesicles (EVs), such as microvesicles and exosomes, are currently being investigated to be attractive sources for the development of biomarkers for identifying signs of sickness [32, 33, 34]. A few of the particular features of the cargo derived from cancer cells comprise mutations, active miRNAs, and signaling molecules with metastatic qualities [35, 36]. These properties make EVs essential to immune system regulation and intercellular communication. Since the rising body of functional research has shown substantial proof that they may be noticed far before the onset of symptoms or physiological detection of a tumor, these EV-based indicators of disease are an actual possibility for early-stage cancer and other illnesses [34, 37]. The fact that EVs are membrane-encapsulated nano- or microparticles that shield their own internal contents from exogenous proteases and other enzymes is captivating [38, 39, 40]. These features make phosphoproteins in EVs exceptionally stable in a biofluid for a longer period of time and permit us to synthesize them for use in medical diagnostics. Having the ability to detect the genome output (active proteins, and in particular phosphoproteins), one may be possible to acquire more precise real-time information on the biological functions of the organism and the advancement of disease, particularly in malignancies.

1. **BIOMARKER CEREBROSPINAL FLUID ALPHA-SYNUCLEIN IN THE DIAGNOSIS OF PARKINSON'S DISEASE**

Currently, there are no specific biomarkers to confirm the presence of Parkinson's disease (PD). Alpha α-synuclein was found in the cerebrospinal fluid (CSF) of Parkinson's disease (PD) patients, which is positive but leaves room for doubt. To explore how effectively CSF α-synuclein serves as a diagnostic biomarker of PD and if it can help differentiate PD from other neurodegenerative disorders, an extensive search of all relevant publications looking for repeated CSF α-synuclein quantification methods in electronic databases was performed. was carried out. An in-depth review and meta-analysis that was conducted by [41] included a total of 17 trials with 3311 patients. Mean CSF α-synuclein concentrations were significantly decreased in PD patients [weighted mean difference (WMD) 0.31; 95% CI, 0.45, 0.16; p 0.0001] as well as Alzheimer's disease (AD) [WMD 0.15; 95% CI, 0.26, 0.04; p 0.0001] compared with normal/neurological controls. Patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA) were not significantly different from each other [WMD 0.05; 95% CI, 0.04, 0.13; p = 0.25]. CSF α-synuclein showed a sensitivity and specificity of 0.88 (95% CI, 0.84-0.91) and 0.40 (95% CI, 0.35-0.45) for the detection of Parkinson's disease (PD), respectively. Based on the CSF concentration of α-synuclein, the odds ratios for the diagnosis of Parkinson's disease were 1.41 (95% CI: 1.24-1.60) and 0.29 (95% CI: 0.15-0.56), respectively. The area under the curve (AUC) for the associated summary receiver operating characteristic (SROC) curve was 0.73. A biomarker for the diagnosis of Parkinson's disease may be the amount of CSF α-synuclein [41].

1. **microRNAs AS BIOMARKERS IN HEART FAILURE**

Biomarkers offer an array application in heart failure. They play a role in the diagnosis of the ailment and are utilized to figure out the root cause of heart failure. Multiple biomarkers may additionally be employed for foreseeing results and, in specific situations, to guide the choice, effectiveness, and outcome of medication. Finally, biomarkers could assist shed light on some pathophysiological mechanisms that explain heart failure [42]. Because there is strong evidence linking miRNAs to the beginning and development of heart failure in addition to their stability in plasma, miRNAs are fascinating potential emerging biomarkers in heart failure. Even though B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have become regarded as the gold standard in excluding and confirming the diagnosis of heart failure, respectively, circulating miRNAs have been thoroughly investigated as potential diagnostic biomarkers [43]. However, in order to be employed as biomarkers for determining the presence of heart failure, they must either work better than natriuretic peptides or have an additional benefit. Natriuretic peptides have a high degree of sensitivity for the identification of heart failure, although there is still time for improvement. There have been a number of miRNAs suggested as prospective alternatives for heart failure diagnostic biomarkers [44, 45, 46, 47]. Circulating miRNAs were recently used in a few studies to help differentiate between those who encounter dyspnea from other reasons and those who have it because of heart failure. In accordance with an investigation conducted by [48], the level of expression of the gene miR-423-5p differed across those suffering from heart failure, healthy individuals, and patients with various kinds of dyspnea. Acute heart failure is also linked to circulating miRNAs that are unevenly expressed, such as miR-499, which is highly expressed, and miR-103, miR-142-3p, miR-30b, and miR-342-3p, which is weakly expressed [49, 50]. Patients with acute heart failure demonstrated lower levels of these miRNAs when compared with normal control subjects and patients who recently underwent a sudden flare-up of chronic obstructive pulmonary disease [51]. One of numerous miRNAs that were demonstrated to be substantially higher in the plasma of HCM individuals who did not exhibit heart failure symptoms was miR-29a, and it was the only miRNA to be associated with both LV hypertrophy and fibrosis [52]. The results obtained demonstrate that this miRNA may act as a diagnostic tool for the mechanisms involved in HCM remodeling. Additional evidence of miR-29a's specificity to HCM was provided by its ability to discriminate between hypertrophic obstructive cardiomyopathy (HOCM), hypertrophic non-obstructive cardiomyopathy (HNCM), senile amyloidosis, and aortic stenosis [53]. The size of the interventricular septum, a marker for processes like fibrosis and hypertrophy, had a positive correlation with miR-29a. Recent investigations indicate that miRNAs may be able to tell the difference between heart failure with a preserved ejection fraction (HFpEF) and heart failure with a decreasing ejection fraction (HFrEF). By three studies so far [49, 54, 55], just a handful of circulating miRNAs have been showed to have different levels in HFrEF and HFpEF. Differentially expressed miRNAs between HFpEF and HFrEF are critical for diagnosis and can offer insight into the distinctive etiology of each condition.

1. **MONITORING BIOMARKER**

Hepatocellular carcinoma (HCC) is an aggressive primary liver cancer that generally develops in conjunction with cirrhosis and chronic liver disease. It is the fourth cause of cancer-related mortality worldwide and the sixth greatest cause of cancer incidence [56]. Those with significant tumor burden, vascular invasion, or metastasis have a poor prognosis and are handled with systemic therapy and supportive care, whereas a limited number of patients with tiny, localized HCC may receive curative treatments. HCC biomarkers are required for early identification, prognostication, as well as prediction and therapy response monitoring. Alpha-fetoprotein (AFP) is now the most frequently utilized HCC biomarker. The primary HCC screening method advised by leading societies [57, 58, 59] is biannual hepatic ultrasonography with or without serum AFP. In patients with HCC, AFP is employed as a prognostic and predictive biomarker. Increased tumor growth, portal vein thrombosis, waitlist abandonment for liver transplants, and post transplant recurrence have all been linked to elevated levels of AFP [60, 61]. Serum After a liver transplant and ramucirumab therapy, AFP is also a predictor of therapeutic response in HCC patients [62, 63]. However, because to its low sensitivity, AFP has limited utility as a biomarker for the early diagnosis of HCC. When combined with AFP, other protein-based blood tumor indicators including the AFP lectin fraction (AFP-L3) and des-y-carboxy prothrombin (DCP) have been demonstrated to enhance diagnostic efficacy [64]. Despite having been demonstrated to play diagnostic and prognostic roles in HCC, glipican-3 (GPC3) [65], cytokeratin 19 (CK19) [66], golgi protein 73 (GP73) [67], midkine [68], osteopontin [69], squamous cell carcinoma antigen (SCCA) [70], and annexin A2 [71] have not yet been widely incorporated into clinical practice. A liver biopsy enables molecular analysis of the tumor and direct sampling of the tumor tissue. It is an intrusive test, though, and there is a chance of bleeding as well as a worry about potential tumor seeding. Moreover, a single biopsy specimen containing a limited quantity of tumor tissue would not be indicative of the entire HCC tumor since HCCs demonstrate high inter- or intra-tumoral heterogeneity due to genetic abnormalities, transcriptional dysregulation, and epigenetic dysregulation [72]. Many "liquid biopsy" approaches have gained substantial traction in recent years as cutting-edge HCC indicators. Body fluid samples are taken during a liquid biopsy in order to gather crucial phenotypic, genomic, and transcriptomic data on the underlying tumor [73]. Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), microRNA (miRNA), and extracellular vesicles (EVs) are the four main components of liquid biopsies. CTCs are cancerous cells that move into the systemic circulation, either as metastases or from the original tumor, and were first identified in 1869 [74]. Due to the fact that they are a sample of the patient's living tumor cells, CTCs stand out from all other cancer biomarkers [75]. By detecting particular target gene alterations and predicting a patient's response to or resistance to a certain medication, analysis of CTCs can assist direct treatment strategies.

1. **BIOMARKERS OF TRAUMATIC BRAIN INJURY (TBI)**

Traumatic brain injury (TBI) is one of the major causes of mortality and disability worldwide, and it is becoming more common among the elderly due to sociodemographic changes [76, 77, 78]. TBI is made up of two processes: the initial traumatic impact at the scene, leading to primary damage to the cerebral parenchyma and blood vessels, and the development of detrimental secondary insults [79], which have been defined by advancing cell death due to inflammation, impaired cerebral blood flow, and impaired metabolic function [80]. Proteins, some of which are extremely concentrated in the CNS, are either produced, released, or leaked by injured, damaged, or dying central nervous system cells [81]. These proteins can be measured in order to determine the degree of cellular damage. The purpose of specialist neurointensive care units (NICUs) that treat TBI patients who are unconscious is to identify, prevent, and treat these secondary insults in order to maximize brain recovery. In clinical practice, measuring these tissue-specific proteins (referred to as "biomarkers") may aid in the early diagnosis of secondary damage [82, 83]. S100B, a calcium-binding protein that is largely intracellular and found in mature, perivascular astrocytes, is the TBI biomarker that has been researched the most [84, 85]. Further brain-specific proteins that have been extensively investigated in TBI include the glycolytic enzyme neuron-specific enolase [86], the astrocytic cytoskeleton component glial fibrillary acidic protein [87], the ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) connected in the neuronal production of ubiquitin [88], and neurofilament light (NF-L). Low serum levels of S100B have been experimentally shown to effectively rule out intracranial injury in patients with mild TBI and reduce the need for head computed tomography in these circumstances. S100B is currently employed locally as an early screening tool in the Scandinavian Guidelines for minor and moderate TBI [89]. The protein's extremely brief serum elimination half-life, however, has been mentioned as one of its drawbacks [90]. Therefore, delayed sampling may be unnecessarily comforting in patients with mild to moderate TBI who lack pathophysiological mechanisms to induce a sustained release in S100B, and this is reflected in the recommendations, which recommend a cutoff of 6 hours after trauma [91]. It is becoming more and more obvious that, in the absence of kinetic factors, a particular serum level is not very significant. How these proteins leave the damaged brain and enter the circulation is not entirely understood. Possible pathways include rupture of the blood-brain barrier (BBB) [92], release independent of BBB integrity [93], and travel through the recently identified glymphatic system [94]. Before being transported to the cerebral spinal fluid (CSF) [96] and/or serum, where samples are easiest to get, these proteins are presumably at first synthesized in the cerebral extracellular space, a site that is challenging to obtain frequently [95]. The availability in serum may be influenced by a number of variables such as clearance, redistribution, protein stability, and ongoing release from the seriously injured brain [97]. Since the protein S100B has been demonstrated to be completely cleared by the kidneys [98], individuals with renal insufficiency may be impacted [90, 99, 100]. Although there are few studies on serum clearance for the other indicators, given their larger samples, it is likely that liver metabolism is involved [101].

1. **PHARMACODYNAMIC BIOMARKERS**

Multiple pharmacodynamic signals have been used to identify patients with interferon (IFN) treatment. There is not much evidence to support the use of soluble TRAIL, IP-10, and IL-1RA as pharmacodynamic markers following subcutaneous (sc) IFN-1a administration on long-term therapy, despite the fact that some biomarkers, such as neopterin, 2′5 ′-oligoadenylate synthetase, and Myxovirus protein A (MxA), are widely recognized. Biomarkers (neopterin, 2′5′OAS, TRAIL, IP-10, IL-1RA) have been investigated in serum samples using validated assays. Serum samples from 448 REFLEX trial participants with clinically isolated syndrome (CIS) who received scIFNβ-1a 44g once (ow), three times weekly (tiw), or placebo were taken at baseline (month [M] 0), M6, M12 they came. , M18 and M24. At M0 and M24, whole blood MxA gene expression was assessed. In an extension research reflection, 302 people with CIS or individuals who later developed multiple sclerosis (MS) had their blood levels measured every six months for neopterin, IP-10, and TRAIL. The pharmacodynamic effect of each biomarker on adherence to scIFN-1a treatment was assessed using a linear mixed effects model with biomarker expression as the independent variable, biomarker expression at M0, treatment arm, sex, and time as fixed variables and subject as a random effect. Compared to M0, all examined biomarkers significantly increased 1.5–4-fold in response to scIFN-1a treatment. Over the 5-year monitoring period, upregulation vs M0 for each biomarker was sustained and dose-dependent. Patients who received placebo showed no changes, while those who received scIFN-1a 44μg showed intermediate or greater changes. The following pharmacodynamic indicators linked to scIFN-1a therapy were confirmed: neopterin, 2′5′OAS, MxA, IL-1RA, and – on long-term treatment – ​​TRAIL and IP-10 [102].

1. **ROLE OF METABOLOMICS IN BIOMARKER DISCOVERY**

The development of disease-modifying or prophylactic drugs relies heavily on the identification of pre-clinical disease biomarkers. The key to effective patient treatment and management is early recognition of the illness. Recent developments in new technologies have led to a surge in studies and activity around the identification of biomarkers. Metabolite changes in biofluids are indicators of physiological or pathological changes. Assessing metabolism in biological systems, both quantitatively and qualitatively, is central to the well-established and rapidly growing scientific topic of metabolomics [ 103 , 104 , 105 , 106 ]. The metabolome serves as both the endpoint of the omics cascade and the closest point to the phenotype. As a result, metabolome profiling can be an effective method to identify reliable diagnostic markers to investigate unknown clinical disorders. Metabolomics is a highly effective method for elucidating metabolic pathways that can ultimately contribute to better treatment and diagnosis. It combines phenotype and metabolic signatures, two things that are crucial for biological function [107, 108]. It offers the potential to identify diagnostic markers for therapeutic targets and shed light on the pathophysiology of disease states. The predictive ability of metabolites, which was an advantage of this strategy, performed better in terms of sensitivity and specificity and may be useful for the identification of biomarkers in the future [109]. Moreover, metabolic profiling is very direct, precise and specific and should be equally useful in metabolic research programs.

1. **METABOLOMICS IN DIAGNOSIS**

Effective treatment of the disease depends on early diagnosis. Identification of disease biomarkers is crucial for early diagnosis, classification, disease progression, prognostic assessment and therapy response. Monitoring the status of living organisms now relies heavily on the analysis of essential metabolites. To understand biochemical changes in linked disorders, metabolomics is a new analytical tool to determine metabolite profiles throughout the body [110]. It is more often used to identify biomarkers for disease diagnosis and risk assessment [111]. Metabolomics is a relatively young topic in bioinformatics that uses the measurement of metabolite abundance for disease diagnosis and other medical reasons according to recent advances [112]. It shows promise for early diagnosis, expands treatment options, and identifies new metabolic pathways that can be targeted for disorders [113]. Pattern recognition techniques have dominated medical science due to the complexity and volume of data produced by state-of-the-art metabolomics, and may be suitable for some diagnostic medical applications. It is envisioned that the data obtained from metabolite profiling will enable the prescription of personalized drugs that treat the disease more effectively. Metabolome analysis has been used in a number of clinical researches as advances in analytical technology have made it possible to rapidly measure the amount of thousands of metabolites in any biological sample. These objectives are in focus with the introduction of state-of-the-art metabolomics technology and related bioinformatics research. The still-evolving field of metabolomics holds great promise for elucidating biological processes and identifying clinical biomarkers, supporting efforts to improve disease prevention and treatment.

1. **SAMPLE KIND IMPACTS ON BIOMARKER SELECTION**

Most diseases can be identified using different sample types and sampling circumstances. For example, urine or swabs can be used to sample various sexually transmitted diseases. However obtaining an adequate swab-based sample from male patients may be difficult or uncomfortable for STIs [114, 115]. Therefore, if swab sampling is not feasible for a particular demographic, a well-characterized biomarker may not be effective. In contrast, it is easy to collect urine from all patients in different contexts [116]. It is possible that biomarkers with great clinical sensitivity and specificity, but insufficient concentration to be detected by an efficient analytical approach, will not be helpful in all circumstances. For instance, when urine contains nucleic acid indicators for Chlamydia infection, the clinical concentration of Chlamydia gDNA is only 101 to 106 copies/ml [117]. The amount of Chlamydia gDNA will often be too low to detect if an assay can handle only 100 μl of sample, making gDNA an unreliable biomarker for that test. Despite the fact that gDNA can be amplified, the amount of accessible biomarkers may be limited, which may hinder or restrict biomarker discovery. Collection of high sample volumes would be one way to get around this restriction, but there are limits to how much volume can be obtained without negatively impacting the patient, increasing the signal background, or making the detection assay significantly more difficult. . Moreover, certain situations call for invasive specimens, including tissue biopsies, which are unsuitable for non-trained users to collect. The biomarker of choice can be significantly affected by the type of sample used.

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