**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 a condition of biological system of an individual. To evaluate a person's health or illness condition, biomarkers may be utilized singly or in combination. A “diagnostic biomarker” identifies a person who has a particular disease subtype or detects or verifies the existence of a disease or condition of interest. This kind of biomarker will develop significantly as we enter the era of precision medicine. A biomarker is referred to as a "monitoring biomarker" when it may be serially assessed to evaluate the state of a disease or medical condition for signs of exposure to a medical product or environmental agent, or to identify an impact of a medical product or biological agent. “Pharmacodynamic/response biomarkers” are those whose levels alter as a result of exposure to a medication or an environmental factor. This kind of biomarker is incredibly helpful in early treatment development as well as clinical practice.

**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. Obesity, advanced maternal age at first birth, estrogen and progestin usage, physical inactivity, and alcohol intake have all been linked to an increased risk of breast cancer in women, according to epidemiological research [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]. To analyze the p53 gene, a DNA biosensor has been created [13]. By serially injecting response elements (REs) above the active oligonucleotide probes, the affinity characteristics of REs and the p53 gene are demonstrated. These tests show that each ligand has a different affinity for the REs. A single strand binding protein biosensor was created [14] to identify p53 mutations in breast tumors. Excessive DNA damage, which is generated by necrotic and apoptotic cells, is linked to breast cancer [15]. Cell-free tumor DNA (cfDNA) quantitative quantification offers a new non-invasive tool for diagnosing breast cancer and delivers treatment information. Although the technique is not particularly developed, cfDNA has been investigated as a breast cancer biomarker to show the association between cancer development and cfDNA concentration [16, 17]. Based on the hybridization principle and guanine oxidation, microRNAs (miRNAs) are emerging as trustworthy biological indicators [18]. Several electrochemical nanobiosensors have been used to study the target miRNAs [19]. MiR-21 is the most stable of these miRNA indicators, with the highest sensitivity and specificity, but it also has significant limitations, such as sequence similarity with related RNAs, prevalence in other malignancies, and low serum levels [20]. The classic biomarker for advanced breast cancer, carbohydrate antigen 15-3 (CA15-3), has a low sensitivity for early-stage breast cancer. The mucin MUC1 is detected by CA15-3, which has been widely used to detect recurrences and track treatment in metastatic breast cancer [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]. Both disease-free survival and overall survival are dependent prognostic variables for HER2 serum levels, tumor size, nodal involvement, and tumor markers.

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

Medical diagnostics has long sought to identify and track illnesses like cancer early through blood testing. Protein phosphorylation is one of the most significant and prevalent molecular regulatory processes, controlling practically every aspect of cellular function [29, 30]. As a result, the status of phosphorylation events may offer information about the state of a disease [31]. Few phosphoproteins, nevertheless, have been created as disease indicators. Few phosphoproteins, nevertheless, have been created as disease indicators. Due to the intrusive nature of tissue biopsy and the very dynamic nature of protein phosphorylation throughout the sometimes lengthy and challenging process of tissue biopsy, assays of phosphoproteins from tissues encounter enormous obstacles. Additionally, tumor biopsy tissue is not accessible for assessing patient response to therapy. The presence of active phosphatases at large concentrations in blood makes it even more difficult to develop phosphoproteins as disease biomarkers from biofluids. Few phosphorylated proteins in plasma/serum can be identified at stable and detectable amounts, despite some extremely abundant proteins accounting for more than 95% of the mass in blood. Extracellular vesicles (EVs), such as microvesicles and exosomes, have recently been identified as attractive sources for the development of biomarkers for the diagnosis of illness due to their potential significance in tumor biology and metastasis [32, 33, 34]. Mutations, active miRNAs, and signaling molecules with metastatic properties are only a few of the distinctive traits of cancer cell-derived cargo that make EVs important for immune modulation and intercellular communication [35, 36]. These EV-based disease indicators are a viable possibility for early-stage cancer and other disorders since the expanding corpus of functional research has demonstrated compelling evidence that they may be detected much before the onset of symptoms or physiological detection of a tumor [34, 37]. It's interesting to note that EVs are membrane-encapsulated nano- or microparticles, shielding the contents of their interiors from external proteases and other enzymes [38, 39, 40]. These characteristics allow us to construct phosphoproteins in EVs for medical diagnosis and also make them very stable in a biofluid for long periods of time. More direct real-time information on the physiological processes of the organism and the development of illness, particularly in malignancies, may be obtained by having the capacity to detect the genome output (active proteins, and in particular phosphoproteins).

1. **CEREBROSPINAL FLUID ALPHA-SYNUCLEIN AS A BIOMARKER - PARKINSON'S DISEASE DIAGNOSIS**

There are currently no conclusive biomarkers for the diagnosis of Parkinson's disease (PD). The identification of alpha (α)-synuclein in cerebrospinal fluid (CSF) in Parkinson's disease (PD) patients has shown encouraging but ambiguous results. A systematic search of all pertinent studies looking into reproducible CSF α-synuclein quantification methods was done in electronic databases to find out how well CSF α-synuclein performs as a diagnostic biomarker of PD and whether it can distinguish PD from other neurodegenerative diseases. In a comprehensive review and meta-analysis led by [41] comprised a total of 17 studies with 3311 patients. In comparison to normal/neurological controls, the mean CSF α-synuclein concentration was considerably lower in PD patients [weighted mean difference (WMD) 0.31; 95% CI, 0.45, 0.16; p 0.0001] and in patients with Alzheimer's disease (AD) [WMD 0.15; 95% CI, 0.26, 0.04; p 0.0001]. There was no discernible difference between patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), or individuals with multiple system atrophy (MSA) [WMD 0.05; 95% CI, 0.04, 0.13; p = 0.25]. In order to diagnose Parkinson's disease (PD), CSF α-synuclein had sensitivity and specificity of 0.88 (95% CI, 0.84-0.91) and 0.40 (95% CI, 0.35-0.45), respectively. The likelihood ratios for the diagnosis of Parkinson's disease based on CSF α-synuclein 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 detection of Parkinson's disease may be the amount of CSF α-synuclein [41].

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

There are various uses for biomarkers in heart failure. They are used to identify the etiology of heart failure and are crucial in the diagnosis of the condition. Numerous biomarkers can also be utilized to predict outcomes and, in certain cases, to direct the selection, potency, and outcome of therapy. Finally, biomarkers could shed further light on certain pathophysiological processes underlying heart failure [42]. MiRNAs are intriguing potential new biomarkers in heart failure because there is compelling evidence that they are involved in the development and progression of heart failure and because of their stability in plasma. Circulating miRNAs have been widely investigated as prospective diagnostic biomarkers, even though B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are now employed as the gold standard in excluding and confirming the diagnosis of heart failure, respectively [43]. However, they must either outperform natriuretic peptides or have an additive value in order to be employed as biomarkers for the diagnosis of heart failure. The sensitivity of natriuretic peptides for the diagnosis of heart failure is high, but there is space for improvement in their specificity. Numerous miRNAs have been suggested as potential candidates for heart failure diagnostic biomarkers in the future [44, 45, 46, 47]. A few studies have described the use of circulating miRNAs to discriminate between individuals with heart failure-related breathlessness and those with dyspnea from other causes. A research performed by [48] discovered that patients with heart failure, healthy controls, and patients with various causes of dyspnea had varied expression levels of the gene miR-423-5p. Acute heart failure is also associated with differently expressed circulating miRNAs, such as high levels of miR-499 and low levels of miR-103, miR-142-3p, miR-30b, and miR-342-3p [49, 50]. In a recent research, our team found a panel of miRNAs that are unique to acute heart failure. When compared to healthy controls and patients who had recently had an acute exacerbation of chronic obstructive pulmonary disease, patients with acute heart failure had lower levels of these miRNAs [51]. MiR-29a was one of many miRNAs that were discovered to be highly increased in the plasma of patients with HCM who had no symptoms of heart failure, and it was the only miRNA to be correlated with both LV hypertrophy and fibrosis [52]. These findings imply that this miRNA could serve as a biomarker for HCM remodelling processes. The ability of miR-29a to distinguish between hypertrophic obstructive cardiomyopathy (HOCM), hypertrophic non-obstructive cardiomyopathy (HNCM), senile amyloidosis, and aortic stenosis [53] provided further evidence of the specificity of miR-29a to HCM. The interventricular septum size, a measure for remodelling processes including hypertrophy and fibrosis, was positively linked with miR-29a. MiRNAs may be able to distinguish between heart failure with a preserved ejection fraction (HFpEF) and heart failure with a decreased ejection fraction (HFrEF), according to recent research. Only a few circulating miRNAs have been shown to have differing levels in HFrEF and HFpEF by three investigations to far [49, 54, 55]. In addition to being important for diagnosis, differentially expressed miRNAs between HFpEF and HFrEF may also shed light on their unique pathogenesis.

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 that results in primary damage to the cerebral parenchyma and blood vessels, which may be followed by the onset of harmful secondary insults [79], which are characterized by progressive cell death due to inflammation, impaired cerebral blood flow, and impaired metabolic function [80]. Injured, damaged, or dying central nervous system cells either produce, release, or leak proteins, some of which are particularly concentrated in the CNS [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]. The glycolytic enzyme neuron-specific enolase [86], the astrocytic cytoskeleton component glial fibrillary acidic protein [87], the ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) involved in the neuronal production of ubiquitin [88], and neurofilament light (NF-L) are additional brain-specific proteins that have been extensively studied in TBI. S100B is currently employed locally as an early screening tool in the Scandinavian Guidelines for mild and moderate TBI [89], where low serum levels have been demonstrated to be capable of safely ruling out intracranial injury in patients with mild TBI and eliminating the need for head computed tomography in these circumstances. 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]. These proteins are likely first produced in the cerebral extracellular space, a location that is challenging to sample repeatedly [95], before being transferred to the cerebral spinal fluid (CSF) [96] and/or serum, where samples are most convenient. However, a number of variables, including as clearance, redistribution, protein stability, and continuing release from the injured brain, may affect this transport and, consequently, the availability in serum [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**

Patients receiving interferon (IFNβ) have been characterized with a number of pharmacodynamic biomarkers. While some biomarkers, such as neopterin, 2′5′-oligoadenylate synthetase, and Myxovirus protein A (MxA), are well established, there is little evidence to support the use of soluble TRAIL, IP-10, and IL-1RA as pharmacodynamic markers following subcutaneous (sc) IFNβ-1a administration on long-term treatment. Using approved assays, biomarkers (neopterin, 2′5′OAS, TRAIL, IP-10, IL-1RA) were evaluated in serum samples. Serum samples from 448 REFLEX trial participants with clinically isolated syndrome (CIS) who received scIFNβ-1a 44g delivered once (ow), three times weekly (tiw), or placebo were taken at baseline (month [M] 0), M6, M12, M18, and M24. At M0 and M24, the expression of the whole-blood MxA gene was assessed. In the extension experiment REFLEXION, blood levels for neopterin, IP-10, and TRAIL were assessed every six months in 302 individuals with CIS or who later developed multiple sclerosis (MS). Using linear mixed effect models with biomarker expression as the independent variable, biomarker expression at M0, treatment arm, gender, and time as fixed variables, and subject as a random effect, the pharmacodynamic effect of each biomarker was examined after scIFNβ-1a delivery. In comparison to M0, all examined biomarkers significantly increased 1.5–4 fold in response to scIFN-1a therapy. Over the course of the 5-year monitoring period, upregulation *vs* M0 for each biomarker was sustained and dose-dependent. Patients who received placebo showed no changes, whereas those who received scIFN-1a 44μg showed intermediate or greater alterations. The following pharmacodynamic indicators connected 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 even prophylactic medicines will depend heavily on the identification of biomarkers of preclinical illness. The key to effective patient treatment and management is early illness identification. The recent development of new technologies has led to a flurry of study and activity surrounding the identification of biomarkers. Metabolite changes in biofluids are signs of physiologic or pathological changes. Assessment of metabolites in biological systems, both quantitatively and qualitatively, is the focus of the well-established and rapidly growing scientific subject of metabolomics [103, 104, 105, 106]. The metabolome serves as both the omics cascade's endpoint and its closest point to the phenotype. As a result, metabolome analysis can be a practical method for identifying reliable diagnostic indicators and investigating unidentified clinical diseases. Metabolomics is a potent method for elucidating biochemical pathways to better diagnosis and therapy. It entails the creation of links between phenotype and a metabolic signature, which are essential components of biological function [107, 108]. It offers the ability to identify diagnostic markers for therapeutic targets and shed light on the pathophysiology of disease conditions. Metabolomics' prediction ability, which was a benefit of this strategy, performed better in terms of sensitivity and specificity and might be useful for the identification of biomarkers in the future [109]. Furthermore, metabolic profiling is very straightforward, precise, and particular and should be similarly useful in metabolomic research applications.

1. **METABOLOMICS IN DIAGNOSIS**

Effective illness treatment depends on early diagnosis. The identification of disease biomarkers is crucial for early illness diagnosis, categorization, disease progression, prognosis evaluation, and therapy response. Monitoring the condition of biological organisms now heavily relies on the analysis of essential metabolites. In order to comprehend the biochemical alterations in linked disorders, metabolomics is a new analytical tool for determining metabolite profiles throughout the body [110]. It is being used more often to identify biomarkers for illness diagnosis and risk assessment [111]. Metabolomics is a relatively young topic in bioinformatics that employs measurements of metabolite abundance as a tool for illness detection and other medical reasons, according to recent advancements [112]. It shows promise for early diagnosis, expands treatment options, and identifies new metabolic pathways that may be targeted for disorders [113]. Pattern recognition techniques have dominated the medical sciences due to the complexity and volume of data produced by metabolomics' sophisticated technology, and they may be appropriate for some diagnostic medical applications. It is envisaged that the data obtained from metabolite profiling would enable the suggestion of personalized medicines that cure illness more effectively. Metabolome analysis has been used in a number of clinical research since advancements in analytical technology have made it feasible to quickly quantify the quantities of thousands of metabolites in any biological sample. These objectives are coming into focus with the introduction of cutting-edge metabolomics technology and related bioinformatics research. The still-evolving field of metabolomics has great promise for illuminating biological processes and identifying clinical biomarkers, supporting efforts to improve illness prevention and treatment.

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

Most illnesses may be identified using a variety of sample types and sampling circumstances. For instance, urine or swabs can be used to sample a variety of sexually transmitted illnesses. Although it might be difficult or uncomfortable to acquire an adequate swab-based sample from male patients for STIs [114, 115]. Therefore, if taking a sample from a swab is not feasible for a certain demographic, a biomarker that exhibits well may not be effective. Contrarily, it is easy to collect urine from all patients in a variety of contexts [116]. It's possible that biomarkers with great clinical sensitivity and specificity but insufficient concentration to be detected by a workable analytical approach won't be helpful in all circumstances. For instance, whereas urine contains nucleic acid indicators for *Chlamydia* infection, the clinical concentration of *Chlamydia* gDNA is only 101 to106 copies/ml [117]. The quantity of *Chlamydia* gDNA would frequently be too little to detect if an assay could only handle a 100 μl sample, making gDNA an unreliable biomarker for that test. Despite the fact that gDNA may be amplified, the amount of accessible biomarker might be restricted, which can hinder or prohibit the detection of the biomarker. The collection of a higher sample volume would be one way to get around this restriction, but there are limits to how much volume can be obtained without having a negative influence on the patient, raising the signal background, or making the detection assay substantially more difficult. Furthermore, certain conditions call for intrusive samples, including tissue biopsies, which are inappropriate for non-trained users to collect. The biomarker of choice may be significantly impacted by the sample type used.

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