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

**Samuel, P\***., Sudarmani, D.N.P1., Prabakaran, D.S2., Prince, L3

\*Corresponding author: Assistant Professor, Department of Biotechnology, Bishop Heber College (Autonomous), Trichy, Tamilnadu, India.

1Assistant Professor, Department of Zoology (PG), Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi, Tamilnadu, India.

2Department of Radiation Oncology, College of Medicine, Chungbuk National University, Republic of South Korea / Visiting Faculty, Department of Biotechnology, Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi, Tamilnadu, India.

3Head, Department of Microbiology, Maruthu Pandiyar College, Trichy Main Road, Vallam, post, Thanjavur, Tamil Nadu, India.

**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" can be used to determine if a patient has a specific disease subtype or to identify, confirm, or detect the presence of a disease or condition of interest. As we go towards the era of precision medicine, this type of biomarker will develop significantly. When a biomarker may be serially evaluated to examine the state of a disease or medical condition for symptoms of exposure to a medical product or environmental agent, or to identify an influence of a medical product or biological agent, the term "monitoring biomarker" is used. The levels of "Pharmacodynamic/response biomarkers" change in response to exposure to a drug or an environmental factor. This sort of biomarker is extremely useful for both clinical practice and the 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**

As of right now, there are no definitive biomarkers for confirming the presence of Parkinson's disease (PD). Alpha α-synuclein was found in cerebrospinal fluid (CSF) in Parkinson's disease (PD) patients, which is positive yet leaves room for skepticism. To figure out how effectively CSF α-synuclein works 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 into repeatable CSF α-synuclein quantification methods was conducted in electronic databases. In an in-depth investigation and meta-analysis that was spearheaded by [41] a total of 17 experiments with 3311 patients were included. The mean CSF α-synuclein concentration was substantially reduced in PD patients [weighted mean difference (WMD) 0.31; 95% CI, 0.45, 0.16; p 0.0001] as well as in patients with Alzheimer's disease (AD) [WMD 0.15; 95% CI, 0.26, 0.04; p 0.0001] compared with normal/neurological controls. Patients experiencing Parkinson's disease (PD), dementia with Lewy bodies (DLB), or those with multiple system atrophy (MSA) were not significantly distinct from each other [WMD 0.05; 95% CI, 0.04, 0.13; p = 0.25]. CSF α-synuclein exhibited sensitivity and specificity for the identification of Parkinson's disease (PD) of 0.88 (95% CI, 0.84-0.91) and 0.40 (95% CI, 0.35-0.45), respectively. Based on CSF concentrations of α-synuclein, the probability 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 detection 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 employed to identify interferon (IFN)-treated patients. There is not much proof 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 examined in serum samples using authorized assays. 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 research REFLEXION, 302 people with CIS or individuals who later developed multiple sclerosis (MS) had their blood levels for neopterin, IP-10, and TRAIL measured every six months. The pharmacodynamic impact of each biomarker adhering to scIFN-1a treatment was assessed 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. 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 an outcome, metabolome profiling can be an effective method for identifying reliable diagnostic markers to investigate into unknown clinical disorders. A highly effective method for illuminating metabolic pathways that could ultimately contribute to better treatments and diagnostics is metabolomics. It includes linking phenotype and a metabolic signature, two things that are crucial for 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.

**REFERENCES**

1. Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet‐Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, *65*(2), 87-108.
2. Guo, Y., Warren Andersen, S., Shu, X. O., Michailidou, K., Bolla, M. K., Wang, Q., & Zheng, W. (2016). Genetically predicted body mass index and breast cancer risk: Mendelian randomization analyses of data from 145,000 women of European descent. PLoS medicine, 13(8), e1002105.
3. Lambertini, M., Santoro, L., Del Mastro, L., Nguyen, B., Livraghi, L., Ugolini, D., & Azim Jr, H. A. (2016). Reproductive behaviors and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis of epidemiological studies. Cancer treatment reviews, 49, 65-76.
4. Chlebowski, R. T., Manson, J. E., Anderson, G. L., Cauley, J. A., Aragaki, A. K., Stefanick, M. L., & Prentice, R. L. (2013). Estrogen plus progestin and breast cancer incidence and mortality in the Women’s Health Initiative Observational Study. Journal of the National Cancer Institute, 105(8), 526-535.
5. Rice, M. S., Eliassen, A. H., Hankinson, S. E., Lenart, E. B., Willett, W. C., & Tamimi, R. M. (2016). Breast cancer research in the nurses’ health studies: exposures across the life course. American journal of public health, 106(9), 1592-1598.
6. Zeng, C., Guo, X., Long, J., Kuchenbaecker, K. B., Droit, A., Michailidou, K., & Mannermaa, A. (2016). Identification of independent association signals and putative functional variants for breast cancer risk through fine-scale mapping of the 12p11 locus. Breast cancer research, 18, 1-21.
7. Zhang, B., Beeghly-Fadiel, A., Long, J., & Zheng, W. (2011). Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. The lancet oncology, 12(5), 477-488.
8. De Mattos-Arruda, L., Cortes, J., Santarpia, L., Vivancos, A., Tabernero, J., Reis-Filho, J. S., & Seoane, J. (2013). Circulating tumour cells and cell-free DNA as tools for managing breast cancer. Nature reviews Clinical oncology, 10(7), 377-389.
9. Gracia-Aznarez, F. J., Fernandez, V., Pita, G., Peterlongo, P., Dominguez, O., de la Hoya, M., & Benitez, J. (2013). Whole exome sequencing suggests much of non-BRCA1/BRCA2 familial breast cancer is due to moderate and low penetrance susceptibility alleles. PloS one, 8(2), e55681.
10. Konishi, H., Mohseni, M., Tamaki, A., Garay, J. P., Croessmann, S., Karnan, S., & Park, B. H. (2011). Mutation of a single allele of the cancer susceptibility gene BRCA1 leads to genomic instability in human breast epithelial cells. Proceedings of the National Academy of Sciences, 108(43), 17773-17778.
11. Rasheed, P. A., & Sandhyarani, N. (2014). Graphene-DNA electrochemical sensor for the sensitive detection of BRCA1 gene. Sensors and Actuators B: Chemical, 204, 777-782.
12. Kabat, G. C., Kandel, R. A., Glass, A. G., Jones, J. G., Olson, N., Duggan, C., & Rohan, T. E. (2011). A cohort study of p53 mutations and protein accumulation in benign breast tissue and subsequent breast cancer risk. Journal of Oncology, 2011.
13. Yang, L., Tao, Y., Yue, G., Li, R., Qiu, B., Guo, L., & Yang, H. H. (2016). Highly selective and sensitive electrochemiluminescence biosensor for p53 DNA sequence based on nicking endonuclease assisted target recycling and hyperbranched rolling circle amplification. Analytical chemistry, 88(10), 5097-5103.
14. Chase, J. W., L'italien, J. J., Murphy, J. B., Spicer, E. K., & Williams, K. R. (1984). Characterization of the Escherichia coli SSB-113 mutant single-stranded DNA-binding protein. Cloning of the gene, DNA and protein sequence analysis, high pressure liquid chromatography peptide mapping, and DNA-binding studies. Journal of Biological Chemistry, 259(2), 805-814.
15. Singh, B., Chatterjee, A., Ronghe, A. M., Bhat, N. K., & Bhat, H. K. (2013). Antioxidant-mediated up-regulation of OGG1 via NRF2 induction is associated with inhibition of oxidative DNA damage in estrogen-induced breast cancer. BMC cancer, 13(1), 1-9.
16. Yan, W., Zhang, A., & Powell, M. J. (2016). Genetic alteration and mutation profiling of circulating cell-free tumor DNA (cfDNA) for diagnosis and targeted therapy of gastrointestinal stromal tumors. Chinese journal of cancer, 35(1), 1-8.
17. Schwarzenbach, H., & Pantel, K. (2015). Circulating DNA as biomarker in breast cancer. Breast Cancer Research, 17(1), 1-9.
18. Bertoli, G., Cava, C., & Castiglioni, I. (2015). MicroRNAs: new biomarkers for diagnosis, prognosis, therapy prediction and therapeutic tools for breast cancer. Theranostics, 5(10), 1122.
19. Matamala, N., Vargas, M. T., Gonzalez-Campora, R., Minambres, R., Arias, J. I., Menendez, P., & Benitez, J. (2015). Tumor microRNA expression profiling identifies circulating microRNAs for early breast cancer detection. Clinical chemistry, 61(8), 1098-1106.
20. Li, S., Yang, X., Yang, J., Zhen, J., & Zhang, D. (2016). Serum microRNA-21 as a potential diagnostic biomarker for breast cancer: a systematic review and meta-analysis. Clinical and experimental medicine, 16, 29-35.
21. Lee, J. S., Park, S., Park, J. M., Cho, J. H., Kim, S. I., & Park, B. W. (2013). Elevated levels of serum tumor markers CA 15-3 and CEA are prognostic factors for diagnosis of metastatic breast cancers. Breast cancer research and treatment, 141, 477-484.
22. Jung, J. H., Park, H. Y., & Lee, Y. H. (2001). Clinical value of CEA, CA15-3 and TPS in breast cancer. Journal of Korean Breast Cancer Society, 4(2), 136-143.
23. Duffy, M. J. (1999). CA 15-3 and related mucins as circulating markers in breast cancer. Annals of clinical biochemistry, 36(5), 579-586.
24. Orlandi, A., Di Dio, C., Calegari, M. A., & Barone, C. (2016). Paradox CA 15–3 increase in metastatic breast cancer patients treated with everolimus: a change of paradigm in a case series. Biomarkers in Medicine, 10(11), 1191-1195.
25. Cui, J. W., Li, W. H., Wang, J., Li, A. L., Li, H. Y., Wang, H. X., & Zhang, X. M. (2005). Proteomics-based identification of human acute leukemia antigens that induce humoral immune response. Molecular & Cellular Proteomics, 4(11), 1718-1724.
26. Asif, H. M., Sultana, S., Ahmed, S., Akhtar, N., & Tariq, M. (2016). HER-2 positive breast cancer-a mini-review. Asian Pacific Journal of Cancer Prevention, 17(4), 1609-1615.
27. Sorensen, P. D., Jakobsen, E. H., Madsen, J. S., Petersen, E. B., Andersen, R. F., Ostergaard, B., & Brandslund, I. (2013). Serum HER-2: sensitivity, specificity, and predictive values for detecting metastatic recurrence in breast cancer patients. Journal of cancer research and clinical oncology, 139, 1005-1013.
28. Molina, R., Escudero, J. M., Muñoz, M., Augé, J. M., & Filella, X. (2012). Circulating levels of HER-2/neu oncoprotein in breast cancer. Clinical chemistry and laboratory medicine, 50(1), 5-21.
29. Hunter, T. (2000). Signaling—2000 and beyond. Cell, 100(1), 113-127.
30. Kabuyama, Y., Resing, K. A., & Ahn, N. G. (2004). Applying proteomics to signaling networks. Current opinion in genetics & development, 14(5), 492-498.
31. Iliuk, A. B., Arrington, J. V., & Tao, W. A. (2014). Analytical challenges translating mass spectrometry‐based phosphoproteomics from discovery to clinical applications. Electrophoresis, 35(24), 3430-3440.
32. Melo, S. A., Luecke, L. B., Kahlert, C., Fernandez, A. F., Gammon, S. T., Kaye, J., & Kalluri, R. (2015). Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature, 523(7559), 177-182.
33. Gonzales, P. A., Pisitkun, T., Hoffert, J. D., Tchapyjnikov, D., Star, R. A., Kleta, R., & Knepper, M. A. (2009). Large-scale proteomics and phosphoproteomics of urinary exosomes. Journal of the American Society of Nephrology: JASN, 20(2), 363.
34. Boukouris, S., & Mathivanan, S. (2015). Exosomes in bodily fluids are a highly stable resource of disease biomarkers. PROTEOMICS–Clinical Applications, 9(3-4), 358-367.
35. Zhang, Y., & Wang, X. F. (2015). A niche role for cancer exosomes in metastasis. Nature cell biology, 17(6), 709-711.
36. Costa-Silva, B., Aiello, N. M., Ocean, A. J., Singh, S., Zhang, H., Thakur, B. K., & Lyden, D. (2015). Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nature cell biology, 17(6), 816-826.
37. Saraswat, M., Joenvaara, S., Musante, L., Peltoniemi, H., Holthofer, H., & Renkonen, R. (2015). N-linked (N-) glycoproteomics of urimary exosomes. Molecular & cellular proteomics, 14(2), 263-276.
38. Sokolova, V., Ludwig, A. K., Hornung, S., Rotan, O., Horn, P. A., Epple, M., & Giebel, B. (2011). Characterisation of exosomes derived from human cells by nanoparticle tracking analysis and scanning electron microscopy. Colloids and Surfaces B: Biointerfaces, 87(1), 146-150.
39. Palmisano, G., Jensen, S. S., Le Bihan, M. C., Laine, J., McGuire, J. N., Pociot, F., & Larsen, M. R. (2012). Characterization of membrane-shed microvesicles from cytokine-stimulated β-cells using proteomics strategies. Molecular & cellular proteomics, 11(8), 230-243.
40. Cocucci, E., & Meldolesi, J. (2015). Ectosomes and exosomes: shedding the confusion between extracellular vesicles. Trends in cell biology, 25(6), 364-372.
41. Gao, L., Tang, H., Nie, K., Wang, L., Zhao, J., Gan, R., & Wang, L. (2015). Cerebrospinal fluid alpha-synuclein as a biomarker for Parkinson's disease diagnosis: a systematic review and meta-analysis. International journal of neuroscience, 125(9), 645-654.
42. Schmitter, D., Cotter, G., & Voors, A. A. (2014). Clinical use of novel biomarkers in heart failure: towards personalized medicine. Heart failure reviews, 19, 369-381.
43. McMurray, J. J., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., & Ponikowski, P. (2012). Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail, 14(8), 803-869.
44. Akat, K. M., Moore-McGriff, D. V., Morozov, P., Brown, M., Gogakos, T., Correa Da Rosa, J., & Schulze, P. C. (2014). Comparative RNA-sequencing analysis of myocardial and circulating small RNAs in human heart failure and their utility as biomarkers. Proceedings of the National Academy of Sciences, 111(30), 11151-11156.
45. Goren, Y., Kushnir, M., Zafrir, B., Tabak, S., Lewis, B. S., & Amir, O. (2012). Serum levels of microRNAs in patients with heart failure. European journal of heart failure, 14(2), 147-154.
46. Voellenkle, C., Van Rooij, J., Cappuzzello, C., Greco, S., Arcelli, D., Di Vito, L., & Martelli, F. (2010). MicroRNA signatures in peripheral blood mononuclear cells of chronic heart failure patients. Physiological genomics, 42(3), 420-426.
47. Vogel, B., Keller, A., Frese, K. S., Leidinger, P., Sedaghat-Hamedani, F., Kayvanpour, E., & Meder, B. (2013). Multivariate miRNA signatures as biomarkers for non-ischaemic systolic heart failure. European heart journal, 34(36), 2812-2823.
48. Tijsen, A. J., Creemers, E. E., Moerland, P. D., de Windt, L. J., van der Wal, A. C., Kok, W. E., & Pinto, Y. M. (2010). MiR423-5p as a circulating biomarker for heart failure. Circulation research, 106(6), 1035-1039.
49. Ellis, K. L., Cameron, V. A., Troughton, R. W., Frampton, C. M., Ellmers, L. J., & Richards, A. M. (2013). Circulating microRNAs as candidate markers to distinguish heart failure in breathless patients. European journal of heart failure, 15(10), 1138-1147.
50. Corsten, M. F., Dennert, R., Jochems, S., Kuznetsova, T., Devaux, Y., Hofstra, L., & Schroen, B. (2010). Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. Circulation: Cardiovascular Genetics, 3(6), 499-506.
51. Ovchinnikova, E. S., Schmitter, D., Vegter, E. L., Ter Maaten, J. M., Valente, M. A., Liu, L. C., & Berezikov, E. (2016). Signature of circulating microRNAs in patients with acute heart failure. European journal of heart failure, 18(4), 414-423.
52. Roncarati, R., Viviani Anselmi, C., Losi, M. A., Papa, L., Cavarretta, E., Da Costa Martins, P., & Condorelli, G. (2014). Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. Journal of the American College of Cardiology, 63(9), 920-927.
53. Derda, A. A., Thum, S., Lorenzen, J. M., Bavendiek, U., Heineke, J., Keyser, B., & Thum, T. (2015). Blood-based microRNA signatures differentiate various forms of cardiac hypertrophy. International journal of cardiology, 196, 115-122.
54. Watson, C. J., Gupta, S. K., O'Connell, E., Thum, S., Glezeva, N., Fendrich, J., & Thum, T. (2015). MicroRNA signatures differentiate preserved from reduced ejection fraction heart failure. European journal of heart failure, 17(4), 405-415.
55. Wong, L. L., Armugam, A., Sepramaniam, S., Karolina, D. S., Lim, K. Y., Lim, J. Y., & Richards, A. M. (2015). Circulating microRNAs in heart failure with reduced and preserved left ventricular ejection fraction. European journal of heart failure, 17(4), 393-404.
56. Akinyemiju, T., Abera, S., Ahmed, M., Alam, N., Alemayohu, M. A., Allen, C., & Global Burden of Disease Liver Cancer Collaboration. (2017). The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA oncology, 3(12), 1683-1691.
57. Marrero, J. A., Kulik, L. M., Sirlin, C. B., Zhu, A. X., Finn, R. S., Abecassis, M. M., & Heimbach, J. K. (2018). Diagnosis, S taging, and M anagement of H epatocellular C arcinoma: 2018 P ractice G uidance by the A merican A ssociation for the S tudy of L iver D iseases. Hepatology, 68(2), 723-750.
58. Omata, M., Cheng, A. L., Kokudo, N., Kudo, M., Lee, J. M., Jia, J., & Sarin, S. K. (2017). Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatology international, 11, 317-370.
59. European Association For The Study Of The Liver. (2018). EASL clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology, 69(1), 182-236.
60. Lou, J., Zhang, L., Lv, S., Zhang, C., & Jiang, S. (2017). Biomarkers for hepatocellular carcinoma. Biomarkers in cancer, 9, 1179299X16684640.
61. Agopian, V. G., Harlander-Locke, M. P., Markovic, D., Zarrinpar, A., Kaldas, F. M., Cheng, E. Y., & Busuttil, R. W. (2017). Evaluation of patients with hepatocellular carcinomas that do not produce α-fetoprotein. JAMA surgery, 152(1), 55-64.
62. Yang, J. D., Kim, W. R., Park, K. W., Chaiteerakij, R., Kim, B., Sanderson, S. O., & Park, J. W. (2012). Model to estimate survival in ambulatory patients with hepatocellular carcinoma. Hepatology, 56(2), 614-621.
63. Mehta, N., Heimbach, J., Harnois, D. M., Sapisochin, G., Dodge, J. L., Lee, D., & Yao, F. Y. (2017). Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA oncology, 3(4), 493-500.
64. Johnson, P. J., Pirrie, S. J., Cox, T. F., Berhane, S., Teng, M., Palmer, D., & Satomura, S. (2014). The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiology, Biomarkers & Prevention, 23(1), 144-153.
65. Hippo, Y., Watanabe, K., Watanabe, A., Midorikawa, Y., Yamamoto, S., Ihara, S., & Aburatani, H. (2004). Identification of soluble NH2-terminal fragment of glypican-3 as a serological marker for early-stage hepatocellular carcinoma. Cancer research, 64(7), 2418-2423.
66. Feng, J., Zhu, R., Chang, C., Yu, L., Cao, F., Zhu, G., & Sun, L. (2016). CK19 and glypican 3 expression profiling in the prognostic indication for patients with HCC after surgical resection. PLoS One, 11(3), e0151501.
67. Marrero, J. A., Romano, P. R., Nikolaeva, O., Steel, L., Mehta, A., Fimmel, C. J., ... & Block, T. M. (2005). GP73, a resident Golgi glycoprotein, is a novel serum marker for hepatocellular carcinoma. Journal of hepatology, 43(6), 1007-1012.
68. Zhu, W. W., Guo, J. J., Guo, L., Jia, H. L., Zhu, M., Zhang, J. B., & Ye, Q. H. (2013). Evaluation of midkine as a diagnostic serum biomarker in hepatocellular carcinoma. Clinical Cancer Research, 19(14), 3944-3954.
69. Wan, H. G., Xu, H., Gu, Y. M., Wang, H., Xu, W., & Zu, M. H. (2014). Comparison osteopontin vs AFP for the diagnosis of HCC: a meta-analysis. Clinics and research in hepatology and gastroenterology, 38(6), 706-714.
70. Pozzan, C., Cardin, R., Piciocchi, M., Cazzagon, N., Maddalo, G., Vanin, V., & Farinati, F. (2014). Diagnostic and prognostic role of SCCA‐IgM serum levels in hepatocellular carcinoma (HCC). Journal of gastroenterology and hepatology, 29(8), 1637-1644.
71. Zhang, H., Yao, M., Wu, W., Qiu, L., Sai, W., Yang, J., & Yao, D. (2015). Up-regulation of annexin A2 expression predicates advanced clinicopathological features and poor prognosis in hepatocellular carcinoma. Tumor Biology, 36, 9373-9383.
72. Zhu, S., & Hoshida, Y. (2018). Molecular heterogeneity in hepatocellular carcinoma. Hepatic oncology, 5(01), HEP10.
73. Ye, Q., Ling, S., Zheng, S., & Xu, X. (2019). Liquid biopsy in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. Molecular cancer, 18, 1-13.
74. Parkinson, D. R., Dracopoli, N., Petty, B. G., Compton, C., Cristofanilli, M., Deisseroth, A., & Kelloff, G. J. (2012). Considerations in the development of circulating tumor cell technology for clinical use. Journal of translational medicine, 10, 1-20.
75. Mego, M. (2014). Emerging role of circulating tumor cells in cancer management. Indian Journal of Medical and Paediatric Oncology, 35(04), 237-238.
76. Jennett, B. (1996). Epidemiology of head injury. Journal of neurology, neurosurgery, and psychiatry, 60(4), 362.
77. Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. J. A. N. (2006). A systematic review of brain injury epidemiology in Europe. Acta neurochirurgica, 148, 255-268.
78. Roozenbeek, B., Maas, A. I., & Menon, D. K. (2013). Changing patterns in the epidemiology of traumatic brain injury. Nature Reviews Neurology, 9(4), 231-236.
79. Maas, A. I., Stocchetti, N., & Bullock, R. (2008). Moderate and severe traumatic brain injury in adults. The Lancet Neurology, 7(8), 728-741.
80. Masel, B. E., & DeWitt, D. S. (2010). Traumatic brain injury: a disease process, not an event. Journal of neurotrauma, 27(8), 1529-1540.
81. Hinkle, D. A., Baldwin, S. A., Scheff, S. W., & Wise, P. M. (1997). GFAP and S100β expression in the cortex and hippocampus in response to mild cortical contusion. Journal of neurotrauma, 14(10), 729-738.
82. Raabe, A., Kopetsch, O., Woszczyk, A., Lang, J., Gerlach, R., Zimmermann, M., & Seifert, V. (2004). S-100B protein as a serum marker of secondary neurological complications in neurocritical care patients. Neurological research, 26(4), 440-445.
83. Thelin, E. P., Nelson, D. W., & Bellander, B. M. (2014). Secondary peaks of S100B in serum relate to subsequent radiological pathology in traumatic brain injury. Neurocritical care, 20, 217-229.
84. Thelin, E. P., Johannesson, L., Nelson, D., & Bellander, B. M. (2013). S100B is an important outcome predictor in traumatic brain injury. Journal of neurotrauma, 30(7), 519-528.
85. Donato, R., Sorci, G., Riuzzi, F., Arcuri, C., Bianchi, R., Brozzi, F., & Giambanco, I. (2009). S100B's double life: intracellular regulator and extracellular signal. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1793(6), 1008-1022.
86. Thelin, E. P., Jeppsson, E., Frostell, A., Svensson, M., Mondello, S., Bellander, B. M., & Nelson, D. W. (2016). Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels, outcome, and extracranial injury severity. Critical care, 20(1), 1-15.
87. Mondello, S., Papa, L., Buki, A., Bullock, M. R., Czeiter, E., Tortella, F. C., & Hayes, R. L. (2011). Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. Critical Care, 15(3), 1-10.
88. Al Nimer, F., Thelin, E., Nyström, H., Dring, A. M., Svenningsson, A., Piehl, F., ... & Bellander, B. M. (2015). Comparative assessment of the prognostic value of biomarkers in traumatic brain injury reveals an independent role for serum levels of neurofilament light. PloS one, 10(7), e0132177.
89. Undén, J., Ingebrigtsen, T., Romner, B., & Scandinavian Neurotrauma Committee (SNC). (2013). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC medicine, 11, 1-14.
90. Jönsson, H., Johnsson, P., Höglund, P., Alling, C., & Blomquist, S. (2000). Elimination of S100B and renal function after cardiac surgery. Journal of cardiothoracic and vascular anesthesia, 14(6), 698-701.
91. Undén, J., & Romner, B. (2010). Can low serum levels of S100B predict normal CT findings after minor head injury in adults?: an evidence-based review and meta-analysis. The Journal of head trauma rehabilitation, 25(4), 228-240.
92. Kanner, A. A., Marchi, N., Fazio, V., Mayberg, M. R., Koltz, M. T., Siomin, V., ... & Janigro, D. (2003). Serum S100β: A noninvasive marker of blood‐brain barrier function and brain lesions. Cancer: Interdisciplinary International Journal of the American Cancer Society, 97(11), 2806-2813.
93. Kleindienst, A., Schmidt, C., Parsch, H., Emtmann, I., Xu, Y., & Buchfelder, M. (2010). The passage of S100B from brain to blood is not specifically related to the blood-brain barrier integrity. Cardiovascular psychiatry and neurology, 2010.
94. Plog, B. A., Dashnaw, M. L., Hitomi, E., Peng, W., Liao, Y., Lou, N., ... & Nedergaard, M. (2015). Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. Journal of Neuroscience, 35(2), 518-526.
95. Thelin, E. P., Carpenter, K. L., Hutchinson, P. J., & Helmy, A. (2017). Microdialysis monitoring in clinical traumatic brain injury and its role in neuroprotective drug development. The AAPS Journal, 19, 367-376.
96. Goyal, A., Failla, M. D., Niyonkuru, C., Amin, K., Fabio, A., Berger, R. P., & Wagner, A. K. (2013). S100b as a prognostic biomarker in outcome prediction for patients with severe traumatic brain injury. Journal of neurotrauma, 30(11), 946-957.
97. Dadas, A., Washington, J., Marchi, N., & Janigro, D. (2016). Improving the clinical management of traumatic brain injury through the pharmacokinetic modeling of peripheral blood biomarkers. Fluids and Barriers of the CNS, 13(1), 1-12.
98. Usui, A., Kato, K., Abe, T., Murase, M., Tanaka, M., & Takeuchi, E. (1989). S-100ao protein in blood and urine during open-heart surgery. Clinical chemistry, 35(9), 1942-1944.
99. Molina, R., Navarro, J., Filella, X., Castel, T., & Ballesta, A. M. (2002). S-100 protein serum levels in patients with benign and malignant diseases: false-positive results related to liver and renal function. Tumor biology, 23(1), 39-44.
100. Gross, S., van der Heide, J. J. H., van Son, W. J., Gans, R. O., Foell, D., Navis, G., & Bakker, S. J. (2010). Body mass index and creatinine clearance are associated with steady-state serum concentrations of the cell damage marker S100B in renal transplant recipients. Medical Science Monitor, 16(7), CR318-CR324.
101. Johnsson, P., Blomquist, S., Lührs, C., Malmkvist, G., Alling, C., Solem, J. O., & Ståhl, E. (2000). Neuron-specific enolase increases in plasma during and immediately after extracorporeal circulation. The Annals of thoracic surgery, 69(3), 750-754.
102. Freedman, M. S., Wojcik, J., Holmberg, K. H., Fluck, M., D'Antonio, M., Hyvert, Y., & Dangond, F. (2021). Pharmacodynamic biomarkers of long-term interferon beta-1a therapy in REFLEX and REFLEXION. Journal of Neuroimmunology, 360, 577715.
103. Zhang, A., Sun, H., Wu, X., & Wang, X. (2012). Urine metabolomics. Clinica Chimica Acta, 414, 65-69.
104. Arakaki, A. K., Skolnick, J., & McDonald, J. F. (2008). Marker metabolites can be therapeutic targets as well. Nature, 456(7221), 443-443.
105. Zhang, T., Wu, X., Yin, M., Fan, L., Zhang, H., Zhao, F., & Li, K. (2012). Discrimination between malignant and benign ovarian tumors by plasma metabolomic profiling using ultra performance liquid chromatography/mass spectrometry. Clinica Chimica Acta, 413(9-10), 861-868.
106. Zhang, A., Sun, H., Han, Y., Yuan, Y., Wang, P., Song, G., & Wang, X. (2012). Exploratory urinary metabolic biomarkers and pathways using UPLC-Q-TOF-HDMS coupled with pattern recognition approach. Analyst, 137(18), 4200-4208.
107. Yuan, M., Breitkopf, S. B., Yang, X., & Asara, J. M. (2012). A positive/negative ion–switching, targeted mass spectrometry–based metabolomics platform for bodily fluids, cells, and fresh and fixed tissue. Nature protocols, 7(5), 872-881.
108. Nicholson, J. K., & Wilson, I. D. (2003). Understanding'global'systems biology: metabonomics and the continuum of metabolism. Nature Reviews Drug Discovery, 2(8), 668-676.
109. Chen, F., Xue, J., Zhou, L., Wu, S., & Chen, Z. (2011). Identification of serum biomarkers of hepatocarcinoma through liquid chromatography/mass spectrometry-based metabonomic method. Analytical and bioanalytical chemistry, 401, 1899-1904.
110. Woo, H. M., Kim, K. M., Choi, M. H., Jung, B. H., Lee, J., Kong, G., & Chung, B. C. (2009). Mass spectrometry based metabolomic approaches in urinary biomarker study of women's cancers. Clinica chimica acta, 400(1-2), 63-69.
111. Patterson, A. D., Maurhofer, O., Beyoğlu, D., Lanz, C., Krausz, K. W., Pabst, T., & Idle, J. R. (2011). Aberrant lipid metabolism in hepatocellular carcinoma revealed by plasma metabolomics and lipid profiling. Cancer research, 71(21), 6590-6600.
112. Holmes, E., Loo, R. L., Stamler, J., Bictash, M., Yap, I. K., Chan, Q., & Elliott, P. (2008). Human metabolic phenotype diversity and its association with diet and blood pressure. Nature, 453(7193), 396-400.
113. Wang, T. J., Larson, M. G., Vasan, R. S., Cheng, S., Rhee, E. P., McCabe, E., & Gerszten, R. E. (2011). Metabolite profiles and the risk of developing diabetes. Nature medicine, 17(4), 448-453.
114. Sugunendran, H., Birley, H. D. L., Mallinson, H., Abbott, M., & Tong, C. Y. W. (2001). Comparison of urine, first and second endourethral swabs for PCR based detection of genital *Chlamydia trachomatis* infection in male patients. Sexually transmitted infections, 77(6), 423-426.
115. Cook, R. L., Hutchison, S. L., Østergaard, L., Braithwaite, R. S., & Ness, R. B. (2005). Systematic review: non-invasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Annals of internal medicine, 142(11), 914-925.
116. Chernesky, M., Jang, D., Chong, S., Sellors, J., & Mahony, J. (2003). Impact of urine collection order on the ability of assays to identify *Chlamydia trachomatis* infections in men. Sexually transmitted diseases, 345-347.
117. Michel, C. E. C., Sonnex, C., Carne, C. A., White, J. A., Magbanua, J. P. V., Nadala Jr, E. C. B., & Lee, H. H. (2007). *Chlamydia trachomatis* load at matched anatomic sites: implications for screening strategies. Journal of clinical microbiology, 45(5), 1395-1402.