# Biomarkers as a Diagnostic Tool in Cancer: A Boon or a Bane?

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### ABSTRACT

Cancer Screening is a hotly debated and extensively researched topic. There are several screening modalities currently in application as well as being researched with the sole aim to detect cancer early and eventually eradicate it. The development of Next Generation Sequencing in genomic analysis and identifying biomarkers has garnered an exponentially growing interest amongst cancer researchers to precisely diagnose the presence of cancer at an early stage, thereby reducing the morbidity and mortality and potentially assisting with the prognostic and predictive profiling. The diagnostic and clinical efficacy of these biomarkers is potentially instrumental in helping improve the clinical outcome of cancer and should be researched with this goal in mind.

**Keywords:** Biomarker; Diagnostic; Cancer; Precision medicine; Genetic

## INTRODUCTION

A "Biomarker" (abbreviated for Biological Marker) has been defined by the Joint Leadership Conference of United States Food and Drug Administration (FDA) and the National Institute of Health (NIH) as a defined characteristic or a biological observation, intended to predict and/ or confirm the presence of a pathogenic process, or response to a therapeutic intervention [1]. It can be a molecule present in blood, tissue, or other body fluids (cerebrospinal fluid, ascitic fluid, urine) or a symptom/ sign observed on clinical examination, radiographic imaging, or pathologic assessment, or it can be a genetic signature/ "fingerprint"/mutations indicating a pathogenic process. The same convention observed that biomarkers can be categorized as diagnostic, prognostic, predictive, safety, monitoring, pharmacodynamic response, susceptibility/ risk, and as likely and validated endpoints [1]. The biomarkers once validated can be of tremendous assistance in altering the course of a disease process by either detecting the disease at an earlier stage, thereby improving the prognosis of the treatment offered, or by quantifying the response to the offered treatment, thereby making necessary adjustments in the management of the disease/ condition in question. Regardless of the category the biomarker falls in, its utility is widespread and ultimately results in an improvement of the health care offered to the patients. This review article intends to discuss the implications and utility of the Biomarkers as a tool in diagnosing cancer.

## LITERATURE REVIEW

There are several types of biomarkers currently known and being researched for diagnosing cancer. The "conventional" tumor biomarkers currently in application are CEA, CA19-9, AFP, CA-125, CA72-4 for diagnosing Gastric Cancer [2], AFP for liver cancer, CA125 for ovarian cancer, Calcitonin for medullary thyroid cancer, CD19 and CD22 for B cell Lymphomas and leukemias, Chromogranin A for neuroendocrine tumors, Gastrin for Gastrinoma, 5-HIAA for carcinoid tumors in urine, Prostate Specific Antigen for Prostate cancer to mention a few [3].

In addition to the above, genetic biomarkers utilizing gene rearrangements, gene expression, fusion genes, genetic mutations are also being applied currently for the diagnosis of lymphomas and leukemias [3].

With the advent of precision medicine, there has been increased interest in researching further on "genetic" biomarkers utilizing Next Generation Sequencing (NGS) technology (circulating tumor DNA (ctDNA), mutations to the driver genes) [4], "transcriptomic", "epigenetic", "proteomic", and "metabolomic" biomarkers as a diagnostic tool in oncology.

The transcriptomic biomarkers make use of messenger RNA (mRNA) expression called Transcriptomics with the help of RNA sequencing technologies. These are of immense use in

prognostic application as well as currently being researched for a prospect on diagnostic capabilities to detect cancer early. An example was the upregulation of mRNA and protein expression of SEPT9 in tumor tissue in cervical cancer patients as compared to para tumor tissue suggesting its potential diagnostic utility in early detection of cervical cancer [5, 6, 7]. Micro-RNA (miRNA), on the other hand, plays a role in every aspect of cancer cell genesis, growth, invasion, and apoptosis. miRNAs are small non-coding regulatory RNA's with sizes of 17-25 nucleotides. The miRNA expression profile is being researched via several clinical trials to evaluate its diagnostic and prognostic utility in oncology [8].

The epigenetic biomarkers use DNA methylation, given hyper methylation is a common biomolecular alteration in the development of cancer. DNA from whole blood as well as cell free DNA (cfDNA) are used for assessing DNA methylation with array-based technologies (Methylation specific Polymerase Chain Reaction (PCR) and pyrosequencing). Methylated BRCA1 and RASSF1A genes were seen in Breast Cancer patients as compared to healthy females [9].

While proteomic biomarkers are effective in their prognostic ability for certain cancers, metabolomics or biomarkers assessing the altered metabolism can be of immense utility in early detection and hence improved survival of cancers, given that altered metabolism is signature characteristic of a cancer cell. Another review vouched for the "Multiomics" approach combining the prowess of all the above categories to deliver a comprehensive assessment of cell dynamics in cancer cells, thereby potentially leading to an earlier detection of cancer [10].

## DISCUSSION

The application of diagnostic biomarkers is far-reaching and widespread. With the advent of new technology in genomic analysis, there has been an unprecedented interest over the last decade in identifying biomarkers through "Liquid Biopsy" of all the categories mentioned above, to facilitate earlier detection of cancer, preferably before the cancer metastasizes. Liquid Biopsy entails examining body fluids for circulating tumor biomarkers, like circulating tumor DNA, mRNA, miRNA, to name a few [11,12]. Liquid biopsy is a minimally invasive procedure, quick and easy to perform, with shorter turnaround time, providing fresh sample without preservatives, often eliminating the need for a potential invasive biopsy, becoming particularly helpful in highly invasive cancers (like Non-Small Cell Lung Cancer (NSCLC), diagnosing cancer prenatally, pancreatic cancer) where a biopsy is contraindicated or if there is an inadequate sample. Biomarker like ctDNA is released from all tumor cells and is a wealth of information on the inter and intra tumor genetic heterogeneity which in turn impacts the tumor staging, metastasis, vascularization, amongst others. cfDNA, on the other hand, is fragmented DNA of the cancer cells. It can be released either passively after a pathologic process like apoptosis or cell necrosis or actively from a living cell [11]. Another category of genetic biomarker increasingly getting attention to its diagnostic capability is cell free miRNA, first discovered in cell free blood plasma and serum. It is mostly found encapsulated in Extracellular Vesicles (EV) like exosomes or micro particles [12].

Tumor-derived exosomes and circulating tumor cells can both provide supplemental information about the whole tumor as well as serve as predictive genetic fingerprints, being the source for several molecular biomarkers like DNA, RNA, miRNA, and proteins [13]. The biomarkers identifying the cancer can play a critical role when the results of the diagnostic profiling can be used as prognostic and predictive biomarkers, thereby improving the survival rates, as well as following up for minimal residual disease. This will thereby also assist in personalizing patient care by delivering targeted therapy or a likelihood of surgery being the only management needed to remove the cancer.

While the early detection of cancer is a promising prospect, utilization of these biomarkers does have its own share of challenges, including limited sensitivity (fraction of people with disease who tested positive), specificity (fraction of people without the disease who tested negative), and cellular-derived contamination leading to a falsely increased expression of the biomarker [12]. This often leads to over diagnosis, with added emotional and financial burden on the patient and the healthcare system [14]. Precision medicine looks to correct these drawbacks with a more laser sharp focus on profiling the cancer through a detailed genomic analysis. The low concentration of circulating miRNA's is countered by introducing high throughput platforms based on amplification or hybridization principles to analyze a wider spectrum of miRNAs in an assay. RNA-Seq, increasingly becoming the preferred method to analyze circulating miRNA's, is expensive, requires bioinformatics support and has a potential of introducing bias because of its multi-step library preparation process [12]. The accuracy of the biomarker test evaluating the presence of cancer, can be improved by being mindful of the demographic of the patients the test intents to diagnose and the prevalence of that cancer in that demographic. This will positively impact the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of the biomarker test in question. PPV and NPV are dependent on the prevalence of the cancer in the population being tested. The aim is to have a test with a low false positive result which leads to unnecessary intervention in the medical management as well as negative psychological and emotional impact on the patients and their families. The clinical trials designed to test and validate the new and upcoming biomarkers in question, should preferably be multi-center, prospective trials, showing a concordant result across all cohorts, involving all the clinical sites [15].

## CONCLUSION

To conclude, the novel genomic approach in precision medicine to identify biomarkers for an earlier detection of cancer is a boon in making and serves as a critical platform as a diagnostic tool; however, it comes with its very own challenges in diagnosing cancer with unknown primary source of origin. The advanced genomic analysis can be supplemented by cancer risk profiling and guided by diagnostic profile results to deliver improved performance of the test in clinical practice in early detection of cancer.

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