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Portrayal of Biomarkers in Clinical Diagnosis of Diseases

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ABSTRACT

Clinical laboratory reports form the scientific basis upon which medical diagnosis management of patients and hence well equipped standard laboratory will not only continue to have demand for newer diagnostic tests but also will make a benchmark in near future. In this era, laboratory plays a central role in health care and 70% of all medical decisions are based on laboratory results. To understand and interpret cancer markers is mind -Boggling. It is the dawn of immunotherapy brings a new beginning. The study gives an idea of how far we have come and where we need to go. Biochemistry, Microbiology, and Pathology are the evidence-based medicine subjects. cancer biomarker refers to a substance or process that is indicative of the presence of cancer in the body. It may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. Cancer remains the second leading cause of death in US, behind heart disease. Cancer markers are substances found in the blood, urine or other body fluids, and their levels indicate the presence of certain types of cancer, according to the National Cancer Institute. However, there are also non-cancerous conditions that can affect these markers; therefore, the laboratory personnel performs additional testing, such as biopsies, prior to making a diagnosis Tumor markers are different from substances produced by normal cells, in quality and quantity. Tumor markers may be used to help diagnose cancer, predict and monitor response to treatment and determine whether cancer has recurred after treatment.

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INTRODUCTION

The use of "biomarkers" has become a rapidly expanding field playing a central role not only in the diagnosis of neoplasia but also in the selection of "tailored" anti-cancer therapies. (1)

Worldwide, more than 90% of esophageal cancers are squamous cell carcinoma; however, in the US there has been a decline in the incidence of squamous cell carcinoma paralleled by a dramatic rise in the incidence of adenocarcinoma. (2)

Biomarkers and emerging molecular detection tools hold enormous potential for improving ED-based diagnosis, treatment, and disposition of septic patients.

Research and development in this arena, from academic medical centers, government, and industry, has been dramatic over the past decade. (3)

Biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones.

Although the term biomarker is relatively new, biomarkers have been used in pre-clinical research and clinical diagnosis for a considerable time. (4)

Biomarkers are useful in a number of ways, including measuring the progress of disease, evaluating the most effective therapeutic regimes for a particular cancer type, and establishing long-term susceptibility to cancer or its recurrence. (5)

The use of biomarkers in cancer medicine is for disease prognosis, which take place after an individual has been diagnosed with cancer. Examples of such prognostic biomarkers include elevated levels of metallopeptidase inhibitor 1 (TIMP1), a marker associated with more aggressive forms of multiple myeloma. (6)

Much research is going into this area, since successful biomarkers have the potential of providing significant cost reduction inpatient care, as the current image-based tests such as CT and MRI for monitoring tumor status are highly costly. (7)

Biomarkers are also useful for diagnosis, monitoring disease progression, predicting disease recurrence and therapeutic treatment efficacy. In years to come, a serum or urine test for every phase of cancer may drive clinical decision making, supplementing or replacing currently existing invasive techniques. (8)

With the emergence of genomic profiling technologies and selective molecular targeted therapies, biomarkers play an increasingly important role in the clinical management of

cancer patients. (9)

Cardiac marker can be useful in the early prediction or diagnosis of disease. Although they are often discussed in the context of myocardial infarction, other conditions can lead to an elevation in cardiac marker level. (10)

Measuring cardiac biomarkers can be a step toward making a diagnosis for a condition.

In many cases, medical societies advise doctors to make biomarker measurements an initial testing strategy, especially for patients at low risk of cardiac death.(11,12)

Multiple sclerosis (MS) is a progressive autoimmune disorder that affects the central nervous system (CNS). Pathologically, it is characterized by demyelination in the spinal cord and brain as well as the presence of inflammatory lesions. (13)

The prevalence of an ideal biomarker should be low in precancerous lesions and should go up in early cancer stages like dysplasia. The discovery and validation of biomarkers prior to clinical use is not an easy task. The National Cancer Institute recommends five phases to facilitate this process. (14)

Biomarkers are used to distinct a pathological condition from a physiological state and also monitoring treatment and disease progression. There is a general inclination of clinicians as well as pathologists' to consider fecal biomarkers due to its non-invasive nature with likely acceptability to the patient. (15)

Urinary biomarkers that might reflect local immunological responses by the bladder epithelium include nerve growth factor (NGF), chemokines including IL-8/CXCL8. (16)

Antimicrobial peptides (AMPs), human a-defensin 5 (HD5) and neutrophil gelatinase-associated lipocalin (NGAL). (17)

Several promising serum and urine biomarkers of UTI such as leukocyte esterase, C-reactive protein, procalcitonin, interleukins, elastase alpha (1)-proteinase inhibitor, lactofferin, secretory immunoglobulin A, heparin-binding protein, xanthine oxidase, myeloperoxidase, soluble triggering receptor expressed on myeloid cells-1, a-1 microglobulin (a1Mg) and tetrazolium nitroblue test (TNB). (18)

Biomarkers are a critical component of the drug development and approval process.

For chronic obstructive pulmonary disease (COPD) the only biomarker currently widely used

in drug trials is lung function testing, typically forced expiratory volume in 1 (FEV1). (19)

Many inflammatory cells, mediators, and enzymes are involved in the complex pathophysiology of COPD so that there are many possible biomarkers to study and there is a high degree of redundancy (20)

Chronological record of significant events

First biomarker used in the diagnosis of cancers being the Bence-Jones protein in the year 1848. Early in 20 th century the discovery of the other tumor biomarker such as human chorionic gonadotropin (hCG) In 1928, prostatic acid phosphatase (PAP). In 1936,Tissue peptide antigen (TPA).In 1957, alfa-fetoprotein(AFP)CEA was first identified. In 1963, carcinoembryonic antigen (CEA)in 1965 by Phil Gold and Samuel O. Freedman in human colon cancer tissue extracts.

The first recognized test for a type of common cancer was reported by Dr. Joseph Gold (21) He found a substance in the blood of patients with colon cancer that was normally found in fetal tissues and named it carcinoembryonic antigen (CEA). By the end of the 1970s, potential serum tests had been developed for a variety of cancers (22). In Carbohydrate antigen (CA19-9).Their clinical utility has led to their use today as an efficient tool in the diagnosis or the evaluation of response to therapy in the case of various forms of cancer.

Additional biomarkers developed in the 1980s were CA 19-9 for colorectal and pancreatic cancer, CA 15-3 for breast cancer and CA-125 for ovarian cancer. However, these early markers have proven to be reliable indicators of early disease as they are present in basal levels in normal individuals and are substantially higher only when there is a considerable amount of cancer present. Furthermore, these markers are for the most part not specific for a single cancer. (23)

The best-known cancer biomarker that has been used by physicians to detect early disease is the prostate-specific antigen (PSA). The serum PSA test has been widely used in screening for prostate cancer in the last decade and has brought about a dramatic change increase in early detection of the disease. (24)

The upper limit of normal PSA level was considered to be 4 ng/ml.

Nevertheless, 33% of tumors spread beyond the prostate in men, with PSA values between 4 and 10 ng/ml, rendering many of these tumors refractory to treatment. Between 1989 and 1996 prostate cancer incidence rates increased steadily with a parallel decrease (2.5% per

year) in mortality rate. The above observations have been attributed to the dramatic increase in the use of serum PSA which allowed earlier diagnosis of asymptomatic prostate cancer. (25, 26)

Although PSA screening may provide a suspicion of prostate cancer, a clinical diagnosis still relies on a pathological tissue examination.

Of 15 million men screened in 1998 with the PSA test, 15% or approximately 2.25 million had PSA levels higher than normal and thus faced the prospect of biopsy. (27)

Any healthy individual with a PSA between 4.0 ng/ml and 10.0 ng /ml is recommended for biopsy although the lower limit for suspicion of prostate cancer has been dropped recently. Since PSA elevation is also associated with benign prostatic hyperplasia (BPH), elevated PSA levels do not always indicate the presence of cancer. The resultant specificity of PSA less than 4.0 ng/ml in detecting early disease is just 25%. Consequently, many individuals undergo an unnecessary biopsy. (28)

Despite the advances made in serum PSA screening, it is still difficult to reliably detect the early stages of prostate cancer without histological examination. (29)

Serum PSA is, perhaps, more reliable as a marker of prostate cancer recurrence or as an indicator of treatment efficacy. (30,31)

This reduction of PSA blood levels can be monitored over time, and the finding of a later increase in the level of serum PSA is considered evidence of a clinical recurrence of prostate cancer (PSA recurrence), thus triggering additional treatment. (32)

The widespread use of the term "biomarker" dates back to as early as 1980. (33)

The term "biological marker" was introduced in 1950s. (34,35)

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". (36,37)

Discovery of Biomarkers

Biomarker discovery is a medical term describing the process by which biomarkers are discovered. Many commonly used blood tests in medicine are biomarkers. There is interest in

Biomarker discovery on the part of the pharmaceutical industry; blood-test or other biomarkers could serve as intermediate markers of disease in clinical trials, and as possible drug targets.

Imaging biomarkers

Many new biomarkers are being developed that involve imaging technology.

Many believe that cardiac computed tomography (CT) has great potential in this area, but researchers are still attempting to overcome problems related to "calcium blooming," a phenomenon in which calcium deposits interfere with image resolution. Other intravascular imaging techniques involving magnetic resonance imaging (MRI), optical coherence tomography (OCT), and near infrared spectroscopy are also being investigated. Timeline of scientific discoveries. The implementation of advanced molecular diagnostics tools for discovery, quantification and validation of molecular biomarkers will be presented. This history is nicely summarized by the BDQ editors in one of the previous editorials 'qPCR, dPCR, NGS – A journey'. (38)

Today, biomarkers have immense scientific and potential clinical value in the diagnostic testing pipeline. They span the broad diagnostic sector from the genome to the phenome over various '-ome' levels and have been used since the earliest days of the application of molecular biology. (39)

There are numerous promising singular biomarkers or more complex multiple biomarker signatures available, the most important of which are currently used for assessing drug development, patient stratification or measuring the efficacy of treatment in therapeutic medicine. Clearly, there is a translation problem to transfer the results from molecular diagnostics research to drug development and finally clinical practice. (40)

The first goal in the biomarker development pipeline is the generation of reliable biological data from applied diagnostic techniques and applications. (41)

Literature Gap and Future Research

Few biomarkers progress from discovery to become validated tools or diagnostics. To bridge this gap, three European biomedical research infrastructures — EATRIS-ERIC (focused on translational medicine), BBMRI-ERIC (focused on biobanking) and ELIXIR (focused on data sharing) — are paving the way to developing and sharing best practices for Biomarker validation. (42)

Biomarker discovery and validation relies heavily on reproducible and robust analytical methodology. Many new biomarker candidates are proposed for various diseases every week – but often from small-scale studies lacking statistical power. (43)

Recent advances in diagnostic technology

New technologies are now available that simultaneously identify a wide spectrum of biomarkers and save time and costs. However, there is an urgent need for validation/standardization of the new assays before they are adopted into clinical diagnostics. It is worthy to note a new assay, T cell interferon gamma release (TIGRAs), which has recently been introduced in the diagnosis of latent tuberculosis infection. (44)

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There is interest in Biomarker discovery on the part of the pharmaceutical industry; blood-test or other biomarkers could serve as intermediate markers of disease in clinical trials, and as possible drug targets.

Research program for the next generation world

Defined as alterations in the constituents of tissues or body fluids, these markers offer the means for homogeneous classification of a disease and risk factors and can extend our base information about the underlying pathogenesis of disease. Biomarkers can also reflect the entire spectrum of disease from the earliest manifestations to the terminal stages. (45)

Furthermore, the implementation of these advanced molecular diagnostics tools for discovery, quantification and validation of molecular biomarkers will be presented.

EXPERT OPINION

The number of candidate biomarkers for the diagnosis of cervical cancer is overwhelming. However, the majority of these biomarkers are tested on histological samples only. Cytological biomarkers are needed to improve the performance of cervical cancer screening programs. The PROBE design may be used to evaluate the accuracy, but unfortunately, the majority of the candidate biomarkers do not meet these criteria. (46)

Current altercation

Tumor markers can't be construed as primary modalities for the diagnosis of cancer.

Their main utility in clinical medicine has been a laboratory test to support the diagnosis. New investigative techniques at the cellular and molecular level show great promise at different molecular level show great promise at different potentially malignant lesions but further perspective, in-depth studies are required to determine their practical usefulness. (47)

The development of personalized medicine for cancer is closely linked to biomarkers, which may serve as the basis for diagnosis, drug delivery and monitoring of diseases.

A major challenge in the development of cancer biomarkers will be the integration of proteomics with genomics and metabolomics data and their functional interpretation in conjugation with data and epidemiology.

Tumor markers are the products of malignant neoplasms that can be detected in the cells themselves or in body fluids. The ultimate tumor marker would be one that allows the unequivocal distigction between benign and malignant cells, but unfortunately, no such marker is in sight. Nevertheless, markers do exist that are often useful in identifying the cell of origin of a metastatic or poorly differentiated primary tumor.

Future directions and challenges

In 1970-80 no effective therapy. In 1990 improved surgical outcomes. In 2010, new molecular insights in to PDA (Pancreatic ductal adenocarcinoma.) Biology. Tumor markers and predictors of response to chemoradiation would be helpful to predict which tumors have higher likelyhood of responding to radiation or chemoradiation. Frequently used markers to identify tumors.

1. Cyto keratins----------Carcinomas

2. CK7----------Many adenocarcinoma

3. HMB 45----------Malignant melanoma

4. CK 20---------- Gastrointestinal carcinomas

5. Vimentin---------- Most sarcomas

6. Prostate-specific antigen------Prostate cancer

CD Markers

CD 4----------T-Cell malignancies

CD 13----------Myloid leukemia

CD 19----------B-Cell malignancies

CD 33 ---------Myeloid leukemia

CD 34---------Leukemia

An opinion arrived at through a process of reasoning

Biomarkers can be separated into three categories. Diagnostic biomarkers detect the presence of disease. They are relevant for early detection as well as to measure disease burden in response to therapy. Prognostic markers gauge disease aggressiveness or tumor biopsy and are used to forecast outcome or recurrence pattern.

Predictive markers predict treatment response and are the key ingredient to a personalized therapeutic approach. Tumor markers are the products of malignant neoplasms that can be detected in the cells themselves or in body fluids. The ultimate tumor marker would be one that allows the unequivocal distinction between benign and malignant cells, but unfortunately, no such marker is in sight.

Nevertheless, markers do exist that are often useful in identifying the cell of origin of a metastatic or poorly differentiated primary tumor.

Shortened version of a large work

Biomarkers provide a dynamic and powerful approach to understanding the spectrum of disease with applications in observational and analytic epidemiology, randomized clinical trials, screening and diagnosis and prognosis. To study the Cancer markers is mind - Boggling. It is the new dawn of immunotherapy. Biochemistry, Microbiology, and Pathology are the evidenced-based medicine subjects. cancer Biomarker refers to a substance or process that is indicative of the presence of cancer in the body. A Biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. Cancer remains the second leading cause of death in US, behind heart disease.

Cancer markers and tumor markers are the same things. These markers are substances found in the blood, urine or other body fluids, and their levels indicate the presence of certain types

of cancer, according to the National Cancer Institute.

However, there are also non-cancerous conditions that can affect these markers; therefore, the laboratory personnel performs additional testing, such as biopsies, prior to making a diagnosis. For monitoring during treatment of the patient and for easy detection of cancer Tumor markers are different from substances produced by normal cells, in quality and quantity.

Tumor markers may be used to help to diagnose cancer, predict and monitor response to treatment and determine whether cancer has recurred after treatment. (48)

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