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Biomarkers In Disease Diagnosis

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ABSTRACT

Biomarkers provide a dynamic and powerful approach to understanding the spectrum of disease with applications in observational and analytic epidemiology, randomized clinical trials, screening, diagnosis and prognosis. Biomarker is defined as alteration in the constituents of tissues or body fluids, these markers offer the means for homogeneous classification of a disease and risk factors, and then can extend our base information about the underlying pathogenesis of disease. A prerequisite for the clinical use of biomarker is elucidation of the specific indication, standardization of analytical methods, characterization of analytical features, incremental yield of different markers for given clinical indications. Biomarkers can also reflect the entire spectrum of disease from the earliest manifestations to the terminal stages. The major use of biomarkers has been employed in clinical investigation. The article features biomarkers in drug development and in disease diagnosis.

Keywords: Disease diagnosis, Biomarker, Drug development, Clinical investigation.

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INTRODUCTION

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]. Biomarker is a term often used to refer to a protein measured in blood whose concentration reflects the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other biological state of an organism. Biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers.

- Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human Disease [2]
- Although the term 'biomarker' is relatively new, biomarkers have been used in preclinical research and clinical diagnosis for some considerable time for e g, body temperature is a well-known biomarker for fever. Blood pressure is used to determine the risk of stroke.
- It is also widely known that cholesterol values are a biomarker and risk indicator for coronary and vascular disease ,and that C-reactive protein (CRP) is a marker for inflammation.
- In practice, biomarkers include tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression, or outcome of treatment of diseases.
- A biomarker is a parameter that can be used to measure the progress of disease or the effects of treatment.
- The parameter can be chemical, physical or biological. In molecular terms biomarker is the subset of markers that might be discovered using genomics proteomics technologies or imaging technologies.
- Biomarker brings the future things in our hand by helping in early diagnosis, disease prevention, drug target identification, drug response etc.
- Several diseased based biomarkers had been identified for many diseases such as serum LDL for cholesterol, blood pressure, P53 gene and MMPs for cancer etc[3].
- Gene based biomarker is found to be an effective and acceptable marker in the present scientific world.
- Biomarkers can also reflect the entire spectrum of disease from the earliest manifestations to the terminal stages. The major use of biomarkers in clinical investigation.

HISTORY OF BIOMARKERS

The idea of using biomarkers to detect disease and improve treatment goes back to the very beginnings of medical treatment. The practice of uroscopy — examining a patient's urine for signs of disease — dates back to the 14th century or earlier, when practitioners would regularly inspect the colour and sediment of their patient's urine.

Philadelphia Chromosome:

In 1960, researchers discovered that some patients with chronic myelogenous leukaemia (CML), a form of adult leukaemia in which there is a proliferation of myeloid cells in the bone marrow, have a specific genetic change associated with their cancer, a shortened version of chromosome 22. This abnormality, known as the Philadelphia chromosome, is caused by a translocation between chromosomes 9 and 22. Researchers were able to use the Philadelphia chromosome as a biomarker to indicate which patients would benefit from drug candidates (tyrosine kinase inhibitors) specifically targeting the rogue protein[4].

HIV viral load:

In the late 1980's, scientists discovered that HIV viral load could be used as a marker of disease progression, and subsequently, as a measure of antiretroviral treatment efficacy. Viral load was used to show that patients receiving combination therapy had a higher reduction in viral load than those on immunotherapy and was therefore more effective in slowing the progression of the disease. Eventually, the viral load biomarker was used in the development and assessment of Highly Active Antiretroviral Therapy (HAART) treatment regimens involving a combination of several drugs used by many people living with HIV today.

HER-2 gene and receptor:

Probably the most famous biomarker in recent drug development history is the HER-2gene and receptor, discovered in the mid 1980's. Between 20–30% of breast cancer patients show an over-expression of the HER-2 receptor on their cancer cells. Although this biomarker indicates a higher risk of adverse outcomes, it also gave clinicians a new target for novel therapies. The antibody trastuzumab (Heretic) was developed to target HER-2 receptors in these over expressing patients, and successfully reduces the proliferation of cancer cells in many of these women[5]. Diabetic patients can test their glucose levels using one test – haemoglobin A1C (HbA1c) – that provides glucose levels from the most recent two weeks [6]. Liver function tests (LFT) assess liver toxicity and prostate-specific antigen (PSA) assesses prostate cancer risk and disease state. These common biomarkers have historically taken decades to become part of medical practice[7].

CHARACTERISTICS OF BIOMARKERS

An ideal biomarker should be safe and easy to measure the cost of follow-up tests should be relatively low, there should be proven treatment to modify the biomarker. It should be consistent across genders and ethnic groups. If the biomarker is to be used as a diagnostic test, it should be sensitive and specific and have a high predictive value[5]. A highly sensitive test will be positive in nearly all patients with the disease, but it may also be positive in many patients without the disease. To be of clinical value, a test with high sensitivity should also have high specificity, in other words, most patients without the disease should have negative test results. For predicting the likelihood of disease based on the test result, rather than the converse, the appropriate measures are positive and negative predictive values. Unfortunately, the positive predictive value falls as the prevalence of the disease falls, so tests for rare conditions will have many more false positive results than true positive result.

Figure 1: Collected Samples of Biomarkers

(https://encrypted-tbn2.gstatic.com/images)

BIOMARKERS REQUIREMENT

For chronic diseases, whose treatment may require patients to take medications for years, accurate diagnosis is particularly important, especially when strong side effects are expected from the treatment. In these cases, biomarkers are becoming more and more important, because they can confirm a difficult diagnosis or even make it possible in the first place[8]. A number of diseases, such as Alzheimer's disease or rheumatoid arthritis, often begins with an early, symptom-free phase. In such symptom-free patients there may be more or less probability of actually developing symptoms. In these cases, biomarkers help to identify high-risk individuals reliably and in a timely manner so that they can either be treated before onset of the disease or as soon as possible thereafter. In order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible[9]. This may be a blood sample taken by a doctor, a urine or saliva sample, or a drop of blood like those diabetes patients extract from their own fingertips for regular blood-sugar monitoring.

Figure 2: Blood and Urine Sample

(https://encrypted-tbn1.gstatic.com/images)

For rapid initiation of treatment, the speed with which a result is obtained from the biomarker test is critical. A rapid test, which delivers a result after only a few minutes, is optimal. This makes it possible for the physician to discuss with the patient how to proceed and if necessary to start treatment immediately after the test. Naturally, the detection method for a biomarker must be accurate and as easy to carry out as possible. The results from different laboratories may not differ significantly from each other, and the biomarker must naturally have proven its effectiveness for the diagnosis, prognosis, and risk assessment of the affected diseases in independent studies [10].

BIOMARKER AS AN EMERGING TOOL:

Biomarker in Drug Development:

Biomarkers are useful throughout the drug discovery and development process. In the past, biomarkers have tended to appear in drug development programmes as opportunists – taking advantage of spare samples and leftover money in the budget – often resulting in incomplete or inadequate data.

Figure 3: Biomarkers in Drug Research

(https://encrypted-tbn0.gstatic.com/images)

However, they are now becoming more and more integrated into all stages of the development process, ranging from:

- ✓ Target discovery
- ✓ Evaluation of drug activity
- ✓ Understanding mechanisms of action
- ✓ Toxicity and safety evaluation
- ✓ Internal decision making
- ✓ Clinical study design
- ✓ Diagnostic tools
- ✓ Understanding disease processes

Biomarker studies will eventually become an integral part of the drug development process. The ultimate aim is the development of more effective drugs at a lower cost. Although still at early stages and with many issues to be resolved, the outlook for biomarkers is promising. The clinical development of gefitinib, an orally available epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is a more complex example of biomarker development [11]. Evolution of biomarkers during the conduct of large randomized trials might become the rule rather than the exception. Although initial candidate biomarkers are evaluated early in development, knowledge increases exponentially as research and clinical experience become more widespread and increased clinical data with which to correlate the translational work become available[12].

Biomarker in Diseases:

Biomarkers depicting prodromal signs enable earlier diagnosis or allow for the outcome of interest to be determined at a more primitive stage of disease. Biomarkers are used as an indicator of a biological factor that represents either a subclinical manifestation, stage of the disorder, or a surrogate manifestation of the disease. Biomarkers used for screening or diagnosis also often represent surrogate manifestations of the disease. The potential uses of this class of biomarkers includes Identification of individuals destined to become affected or who are in the "preclinical" stages of the illness, reduction in disease heterogeneity in clinical trials or epidemiologic studies, reflection of the natural history of disease encompassing the phases of induction, latency and detection, target for a clinical trial. The improvement in validity and precision far outweigh the difficulty in obtaining such tissues from patients. Diagnostic tests for diseases are used with increased frequency in clinical research and practice. In the diagnostic effort, collection of information from various sources, some of which includes results from diagnostic tests, helps to achieve the ultimate goal of increasing the probability of a given diagnosis.

Clinical tests are also performed, though probably less often, for other reasons such as the following**:** To measure disease severity, to predict disease occurrence, or to monitor the response

to a particular treatment. Another advantage of this type of diagnostic test is the reduction in disease heterogeneity in clinical trials or observational epidemiologic studies, leading to better understanding of natural history of disease encompassing the phases of induction, latency and detection[13].

The use of biomarkers is growing, with a steady stream of new products being brought out by the diagnostics industry. Some of these assist in diagnosis, while others provide a means of monitoring the state of progression of disease and the effectiveness of therapeutic options. However, in many cases, the evidence which supports the use of these new methods as opposed to traditional biochemical tests has not yet been demonstrated, and it is intended that this volume will help clarify the strengths and weaknesses of using these biomarkers across a wide range of applications and in the various organs of the body. This approach will provide clinicians, pathologists, clinical biochemists and medical laboratory scientists with an invaluable overview of the diverse applications of biomarker in medicines[12]. The application of biomarkers in the diagnosis and management of cardiovascular disease, infections, immunological and genetic disorders, and cancer are well known. Their use in research has grown out of the need to have a more direct measurement of exposures in the causal pathway of disease that is free from recall bias, and that can also have the potential of providing information on the absorption and metabolism of the exposures[14]. Neuroscientists have also relied on biomarkers to assist in the diagnosis and treatment of nervous system disorders and to investigate their cause.

CLASSIFICATION BIOMARKERS:

Biomarkers can be classified based on two different parameters:

1 Based on their characteristics: *Imaging, Non-Imaging*

2 Based on genetic and molecular biology method: Type 0 - *Natural history markers***,** Type 1 - *Drug activity markers***,** Type 2 - *Surrogate markers.*

3 Based on disease related: Predictive biomarker, Diagnostic biomarker, Prognostic biomarker

4 Based on drug related.

1.1 Imaging Biomarkers:

Biomarkers are measures of a normal biological process in the body, a pathological process, or the response of the body to a therapy. Imaging-based biomarkers employ a variety of technologies to capture images of anatomical and physiological changes in the body. They are usually noninvasive, and they produce intuitive, multidimensional results. Yielding both qualitative and quantitative data, they are usually relatively comfortable for patients.

a X-Ray:

X -ray technology has been in use for over 100 years and has served to identify structural markers in biomedicine for almost as long.

Figure. 4: X-image

(https://encrypted-tbn0.gstatic.com/images)

b Computed Tomography (CT):

Sometimes also called computed axial tomography. In this 2-dimensional images which are then digitally converted to a 3-dimensional image. CT was introduced during the 1970s and its use has expanded widely.

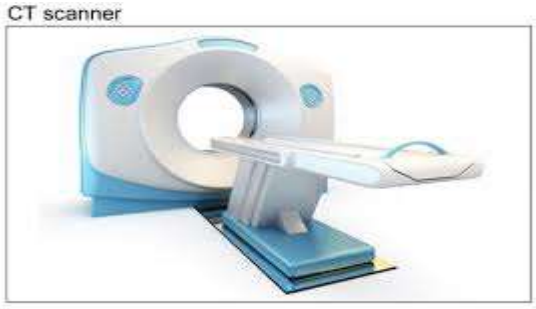

Figure 5: CT Scanner

(https://encrypted-tbn2.gstatic.com/images)

c Magnetic Resonance Imaging (MRI):

MRI is better at distinguishing soft tissues than tomography. The first MR image was published in 1973. In addition, optical imaging is frequently used in drug discovery and pre-clinical animal research, and is increasingly used in the clinic for humans, for example with optical CT scanning.

Figure 6: MRI Scanner

(http://www.popsci.com/sites/popsci.com)

d Positron Emission Tomography (PET):

Computerized tomography assembles a 3- dimensional image of the area of interest. The first PET machines for use in humans were introduced in early 1970 [15].

Figure 7: PET Scanner

(https://encrypted-tbn0.gstatic.com/images)

2 Non-Imaging Biomarkers:

Molecular biomarkers can be used to refer to non-imaging biomarkers that have biophysical properties, which allow their measurements in biological samples (example, plasma, serum, cerebrospinal fluid, bronchoalveolar cleavage, and biopsy) include nucleic acids-based biomarkers such as gene mutations or polymorphisms and quantitative gene expression molecules[16]. Another category of biomarkers includes those used in decision making in early drug development. For instance, pharmacodynamic (PD) biomarkers are markers of a certain pharmacological response, which are of special interest in dose optimization studies [17].

(Type 0) - Natural history markers*:*

A marker of natural history of a disease and correlates longitudinally with known clinical indices.

(Type 1) - Drug activity markers*:*

A marker that captures the effect of a therapeutic intervention in accordance with its mechanism of action.

Type 2) - Surrogate markers*:*

A marker intended to substitute for a clinical end point; a surrogate end point is expected to predict clinical benefit or lack of benefit on the basis of epidemiology, therapeutic, Patho physiological or other scientific evidence[18].

3 Based on Disease related:

Disease-related biomarkers give an indication of whether there is a threat of disease if a disease already exists or how such a disease may develop in an individual case[19].

Predictive biomarker:

Predictive biomarkers define populations that might respond more favourably to a particular intervention from an efficacy or safety perspective. They can be used to stratify patients for subgroup analyses.

Diagnostic biomarker:

Diagnostic biomarkers provide the means to define a population with a specific disease. (i.e., cardiac troponin for the diagnosis of myocardial infarction).

Prognostic biomarker:

Prognostic biomarkers correlate with outcomes. For example, over expression of Her-2/neu in breast cancer or EGFR expression in colorectal cancer indicates poor prognoses. Such prognostic markers are frequently the basis for establishing inclusion criteria for a clinical trial or for defining a patient population [20].

Based on Drug related biomarker:

Drug-related biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it. In addition to long-known parameters, such as those included and objectively measured in a blood count, there are numerous novel biomarkers used in the various medical specialties.

TYPES OF BIOMARKERS:

Biomarkers can be of varying types, such as physiological, physical, anatomical and histological (tissue biopsy specimens). Perhaps the most relevant type for early phase clinical research is biochemical biomarkers, derived from bodily fluids that are easily available to the early phase researchers. Once a proposed biomarker has been validated, it can be used to diagnose disease risk, presence of disease in an individual, or to tailor treatments for the disease in an individual (choices of drug treatment or administration regimes). Safety molecular biomarkers have been used for decades both in preclinical and clinical research. The blood of HIV patients can be tested for its viral load to assess the course of their disease, as well as providing a surrogate endpoint for trials of anti-HIV drugs[21].

Table 1: Some Safety tests by biomarkers [21] .

Specific Organ	Biomarkers Tests
Liver Function	Transaminases , bilirubin, alkaline phosphates.
Kidney Function	Serumcreatinine, creatinine clearence, cystatinC.
Skeletal Muscle Marker	Myoglobin.
Cardiac Muscle Injury	CK-MB, teroponinI (or) T.
Bone markers	Bone specific alkaline phosphates.

DISEASES AND RELATED BIOMARKERS:

- Biomarkers in Prostate Cancer
- Biomarkers in SLE, IBD & related Diseases
- Biomarkers in arthritis
- Biomarkers in Cardiovascular Diseases
- Biomarkers in Chronic Obstructive Pulmonary Diseases
- Biomarkers in Neurocognitive diseases

Biomarkers in Prostate Cancer:

Prostate specific antigen (PSA) is used for a variety of purposes (e.g., determining when further diagnostic testing is indicated, assessing response to therapy), there is no consensus on how best to use PSA in cancer therapeutic trials. Uses of PSA that should be further investigated including identifying high- risk populations, providing an early marker of drug activity and dose range, and use of PSA as a marker of disease progression. Other markers may also prove more predictive of clinical outcomes in some patients (e.g., alpha methyl aryl CoA racemes expression as a predictor of disease progression in local disease) [11].

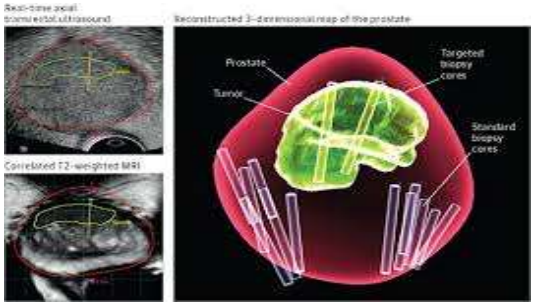

Figure 8: Prostate Cancer Image

(https://encrypted-tbn3.gstatic.com/images)

Markers of Disease Activity in Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Related Diseases:

Development of new therapies for these diseases has been hampered in recent years by a lack of reliable markers of disease activity that can be used to predict clinical benefit.

- For SLE autoantibodies such as anti double standard DNA, anti-Ro/SSA are used.
- For IBD-CRP, ESR, ASCA and fecal calprotectin are used.

Development of predictive biomarkers and accepted clinical outcome measures would help in the evaluation of needed new therapies for these diseases[12].

Figure 9: SLE Symptom

(https://encrypted-tbn2.gstatic.com/images)

Biomarkers in Arthritis:

Targeted research could identify how to apply MRI technologies to measure the effects of potential therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis.

In this regard, MRI has demonstrated promise for detecting soft tissue inflammation and cartilage erosion in rheumatoid arthritis. If established as a reproducible biomarker, use of MRI could help determine the potential of a new therapeutic product, identify dose ranges, and stratify patients by risk while serving as an early response measure[19].

Figure 10: X-ray Image of Arthritis

(https://encrypted-tbn1.gstatic.com/images)

Biomarkers in Cardiovascular Diseases:

To advance efficient development of new therapies, new imaging techniques are needed to measure progression and treatment of cardiovascular disease. Potential use of intravascular ultrasound (IVUS), MRI, or multi-slice CT in the assessment of atherosclerosis progression and volumetric measures of cardiac function in trials of congestive heart failure. Development of these techniques for measuring progression will require a complete analysis of the current state of knowledge of the imaging modality, standardization of the technical aspects of the measurement, and performing the trials necessary to evaluate the degree of correlation with clinical responses[15].

Figure 11: Image of CVD

(https://encrypted-tbn0.gstatic.com/images)

Biomarkers in Chronic Obstructive Pulmonary Diseases:

High-resolution chest computed tomography might be a useful assessment of disease progression in chronic obstructive pulmonary disease where emphysema is a prominent component, especially the disease associated with alpha 1 anti-trypsin deficiency. Although data to date suggest that high resolution CT (HRCT) can offer reliable assessment of underlying lung structure in fewer patients and for shorter periods of time than would be needed to show a difference in lung function testing or in mortality, it remains unclear if changes in HRCT meaningfully predict change for the patient.

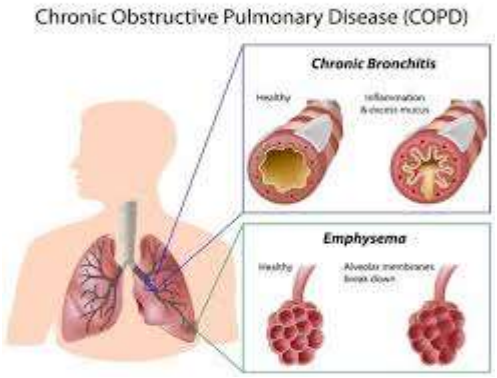

Figure 12: COPD Image

(https://encrypted-tbn2.gstatic.com/images)

Imaging Biomarkers in Neurocognitive Diseases:

Currently, therapeutic trials in chronic neurological disorders, such as Parkinson's disease and Alzheimer's disease, rely on symptomatic endpoints that may require observation over many years to evaluate progression. Functional imaging, such as FDG-PET as a measure of glucose metabolism, may provide a biomarker to assess earlier, more subtle, changes in the progression of these diseases. Focused efforts to apply new imaging techniques as diagnostic and response measures in neurocognitive disorders and depression could also produce new ways to monitor

treatment of these conditions. For example, quantitative MRI measurements as well as amyloidal content assessments by PET scan may be useful imaging techniques to demonstrate the effect of potential Alzheimer's therapies [22]. Imaging markers that provide information on early disease states could make prevention trials more feasible [17].

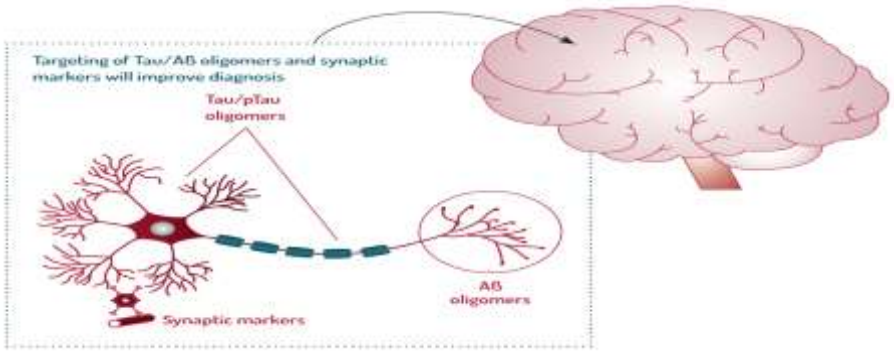

Figure 13: Alzhemer's Biomarker

(http://www.adxneurosciences.com)

CONCLUSION

Biomarker is an alteration in the constituents of tissues or body fluids provide a powerful approach to understanding the spectrum of chronic disease with application in at least 5 areas like screening, diagnosis, prognostication, prediction of disease recurrence and therapeutic monitoring. Biomarkers depicting prodromal signs enable earlier diagnosis or allow for the outcome of interest to be determined at a more primitive stage of disease. Biomarkers are used as an indicator of a biological factor that represents either a subclinical manifestation, stage of the disorder, or a surrogate manifestation of the disease. A biomarker may be specific for only one type of drug or disease, so the development costs will have to be carefully considered.

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