

Biomarkers: A Comprehensive Review

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Abstract: Biomarkers are very important and can provide crucial information on the rapid events and molecular mechanisms in pathophysiology. Obtaining a profile of distinct classes of biomarkers reflecting core pathologic mechanisms could enable us to identify and characterize the initial injury and the secondary pathologic cascades. Accordingly, great effort has been put into the identification of novel biomarkers in the past 25 years. However, the role of various organs injury markers in clinical practice has been long debated, due to inconsistent regulatory standards and lack of reliable evidence of analytical validity and clinical utility. We present a comprehensive overview of the markers currently available while characterizing their potential role and applications in diagnosis, monitoring, drug discovery, and clinical trials.

Keywords: Biomarkers, Classification, Application, Skin & lungs cancer.

Introduction:

Biomarkers can be used as a diagnostic tool for the identification of patients with an abnormal condition or as a tool for staging the extent of disease, as an indicator of disease prognosis, or for the prediction and monitoring of response to an intervention. Biomarker is short for biological marker, and is used as an indication that a biological process in the body has happened or is ongoing. While some biomarkers are used to show that the body has been exposed to a chemical, toxin or other environmental impact — most associate biomarkers with medicine. Biomarkers are measurable and do not define how a person feels or functions. **Biomarkers** are objective medical signs (as opposed to symptoms reported by the patient) **used to** measure the presence or progress of disease, or the effects of treatment.

Definition of Biomarker

The word 'biomarker,' has more than one definitions.

The classic definition, as given by S. Naylor (2003), is that, "A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a physiological as well as a pathological process or pharmacological response to a therapeutic intervention."¹

Biomarkers help not only in disease diagnosis but also in tracking progression, regression and outcome after intervention.

Biomarkers range from biomolecules like carbohydrates, proteins, lipids to genes, DNA, RNA, platelets, enzymes, hormones etc. Anything that helps in the identification of a disease can serve as a biomarker be it a metabolite, a change in biological structure or a characteristic feature.

CLASSIFICATION OF BIOMARKERS

1. According to Genetics and Molecular Biology methods, biomarkers can be classified as follows:

i) Type 0 biomarkers

(natural history biomarkers): They help measure the natural history of a disease and correlate over time with known clinical indicators.

ii) Type 1 biomarkers

(drug activity biomarkers): These indicate the effect of drug intervention. They may be further divided into:-

a) *Efficacy biomarkers* – indicating the therapeutic effects of a drug

b) *Mechanism biomarkers* – giving information about the mechanism of action of a drug

c) *Toxicity biomarkers* – indicating the toxicological effects of a drug

iii) Type 2 biomarkers

(surrogate markers): They serve as a substitute for a clinical outcome of a disease and also help predict the effect of a therapeutic intervention in accordance with mechanism of action.

2. Another classification of biomarkers can be as follows:

i) Prognostic biomarkers:

Prognostic (Greek) means "fore-knowing or foreseeing." Prognostic biomarkers are the ones that suggest the likely outcome of a disease in an untreated individual.

ii) Predictive biomarkers:

Used to identify those patients who are likely to respond positively to a given treatment. Thus, with the help of predictive biomarkers it is possible to give a particular therapy to the patients for which it is most likely to be effective.

iii) Pharmacodynamic biomarkers:

These help in determining the pharmacological effects of a drug.

iv) Recovery biomarkers :

They are based on the concept of the metabolic balance between intake and excretion over a fixed period of time and then provide an estimate of absolute intake levels.

Recovery biomarkers are specific biologic products that are directly related to intake and not subject to homeostasis or substantial inter-individual differences in metabolism.

v) Concentration biomarkers :

They are biomarkers that have a correlation with intake, but because they are affected by metabolism or personal characteristics (sex, age, smoking, obesity, etc), they cannot be used as measures of absolute intake or for assessing error of self-reported intakes in validation studies.

Examples of concentration biomarkers are as follows: Serum carotenoids, lipids, vitamins, etc.

vi) Replacement biomarkers

They are closely related to concentration biomarkers and often the distinction between them is difficult to make.

Their differentiating characteristic is that they refer specifically to compounds for which information in food composition databases is unsatisfactory or unavailable. Examples of these replacement biomarkers are some aflatoxins, some phytoestrogens.

3. There is yet another classification that divides biomarkers into two broad types:

i) Biomarkers of exposure :

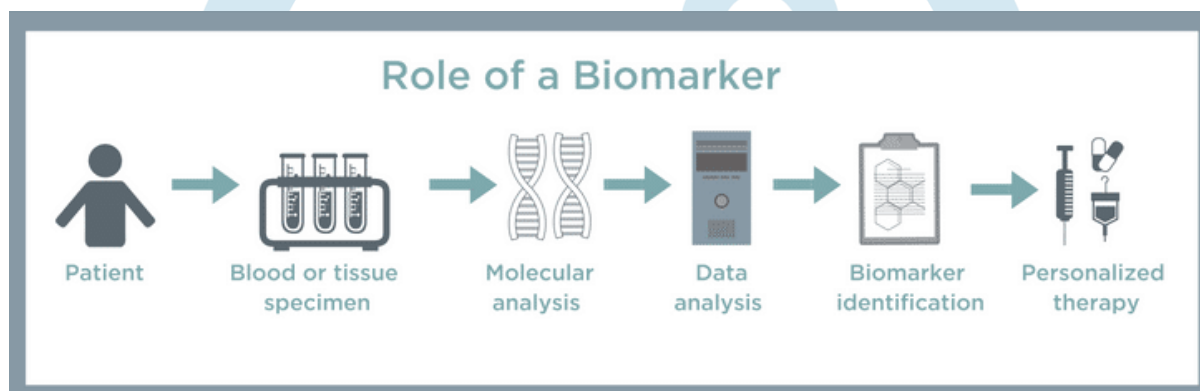
or antecedent biomarkers that are used in risk prediction.

Biomarkers of exposure are the actual chemicals, or chemical metabolites, that can be measured in the body or after excretion from the body to determine different characteristics of an organism's exposure. For example, a person or fish's blood can be tested to see the levels of lead and therefore determine the exposure.

ii) Biomarkers of disease :

That are used in diagnosis and tracking progress of a disease.

Biomarkers can also be classified as **drug-related** or **disease-related**.



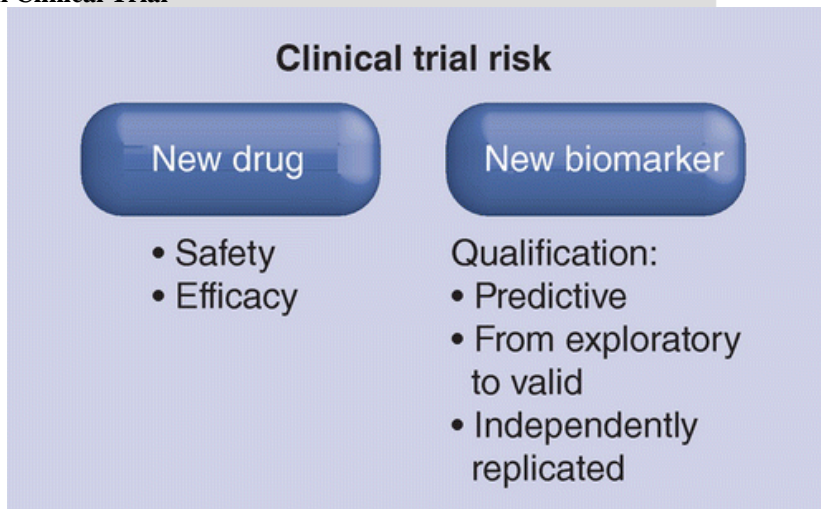
IMPACT OF BIOMARKERS

A measurable biochemical, physiologic, behavioral, or other alteration in an organism that, depending on the magnitude, can be recognized as associated with an established or possible health impairment or disease.

There is a need to understand how biomarkers are defined, how they are used in clinical trials, and most importantly how they are used in conjunction with drug treatment.

Biomarker approaches have entered into early clinical trials and are increasingly being used to develop new diagnostics that help to differentiate or stratify the likely outcomes of therapeutic intervention.

Impact of biomarkers on Clinical Trial



Biomarkers Vs Surrogate End Points

A "surrogate marker" can be defined as "

A laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”

The primary difference between a biomarker and a surrogate marker is that a biomarker is a “candidate” surrogate marker, whereas a surrogate marker is a test used, and taken, as a measure of the effects of a specific treatment.



Endpoints used in Clinical trial:

A clinical trial’s “endpoints” are measurements of what happens to people in the trial.

When a trial is intended to evaluate the efficacy and safety of a new medical product or a new use of an approved product, its endpoints usually measure benefit. Investigators typically use either clinical or surrogate endpoints.

Clinical Endpoint:

These are the most reliable clinical trial endpoints. They directly measure what matters most to people—whether they feel or function better, or live longer.

Therapies can be recommended with confidence when clinical trials show that benefits, as measured by clinical outcomes, outweigh the adverse effects.

Surrogate endpoints:

These are used instead of clinical outcomes in some clinical trials. Surrogate endpoints are used when the clinical outcomes might take a very long time to study, or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood.

Clinical trials are needed to show that surrogate endpoints can be relied upon to predict, or correlate with, clinical benefit.

Surrogate endpoints that have undergone this testing are called validated surrogate endpoints and these are accepted by the FDA as evidence of benefit.

Between 2010 and 2012, the FDA approved 45 percent of new drugs on the basis of a surrogate endpoint.

Surrogate endpoints important for medical product development:

When a surrogate endpoint is clearly shown to predict a beneficial effect through appropriate studies, its use generally allows clinical studies to be conducted in smaller numbers of people over shorter periods of time.

For example, a sufficient number of clinical trials have demonstrated that reducing systolic blood pressure reduced the risk of stroke. Hence, measurement of reduction in the surrogate endpoint of systolic blood pressure can stand in for the clinical outcome of stroke, and clinical trials targeting the reduction of risk of stroke can be conducted more rapidly in smaller populations using this validated surrogate endpoint.

Imaging Biomarkers:

An **imaging biomarker** is a biologic feature, or biomarkers detectable in an image.

In medicine, an imaging biomarker is a feature of an image relevant to a patient’s diagnosis.

For example, a number of biomarkers are frequently used to determine risk of lung cancer .

First, a simple lesion in the lung detected by X-ray, CT or MRI can lead to the suspicion of a neoplasm.

The lesion itself serves as a biomarker, but the minute details of the lesion serve as biomarkers as well, and can collectively be used to assess the risk of neoplasm.

Some of the imaging biomarkers used in lung nodule assessment include size, spiculation, calcification, cavitation, location within the lung, rate of growth, and rate of metabolism. Each piece of information from the image represents a probability.

Spiculation increases the probability of the lesion being cancer.

A slow rate of growth indicates benignity.

These variables can be added to the patient’s history, physical exam, laboratory tests, and pathology to reach a proposed diagnosis. Imaging biomarkers can be measured using several techniques, such as CT, electroencephalography, magnetoencephalography, and MRI.

For Example :

The use of novel imaging technique that have the ability to evaluate tumour biology and function shows a great deal of promise in providing early surrogate biomarkers of response to therapy which may allow for individualised or patient-specific regimes.

Applications of biomarkers

1. Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human disease.

- The **application of biomarkers** in the diagnosis and management of cardiovascular disease, infections, immunological and genetic disorders, and cancer are well known.
- In medicine, biological **markers** are **used** to detect a **disease**, discover drugs, and monitoring care of patients.
- Among all these types of biomarkers, **proteins can** be very sensitive to be detected in a very tiny amount of a sample to diagnose a specific type of **diseases** in its early diagnosis.
- While some **biomarkers** are used to show that the body has been exposed to a chemical, toxin or other environmental impact — most associate **biomarkers** with medicine.

Biomarkers for cancer

Breast Cancer –

Blood tumor marker tests:

Serum tumor markers or biomarkers are tumor proteins found in a person's blood.

They are made by the tumor or by the body in response to the cancer.

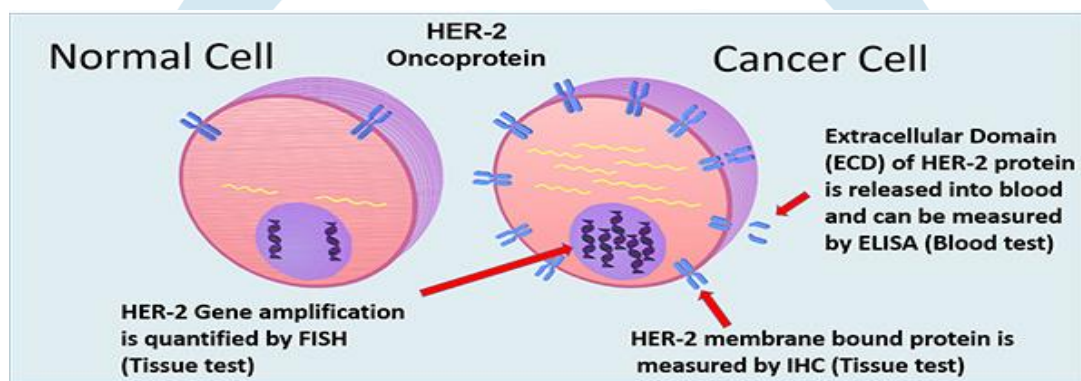
Higher levels of a serum tumor marker may be due to cancer or a noncancerous condition.

For metastatic breast cancer, testing may be done for cancer antigen 15-3 (CA 15-3), cancer antigen 27.29 (CA 27.29), and/or carcinoembryonic antigen (CEA).

These biomarkers may be found in the blood of people with breast cancer.

However, abnormal levels of these biomarkers may also be a sign of another condition that is not cancer.

Some tests may also be done for circulating DNA or circulating tumor cells.



To determine if a tumor is positive for *HER2*, a sample of tumor is tested. There are two established ways to test *HER2* status: Immunohistochemistry (IHC) measures the amount of *HER2* protein present.

Fluorescent in situ hybridization (FISH) looks at the gene level for the number of copies of the gene present; an increased number of gene copies is known as amplification.

2. Lungs Cancer

A recent study reported on a panel of serum biomarkers to aid in the diagnosis of lung cancer: CEA, RBP and alpha 1 antitrypsin. It was found that expression of these proteins had a sensitivity of 89.3% and specificity of 84.7% in correctly identifying patients with lung cancer.

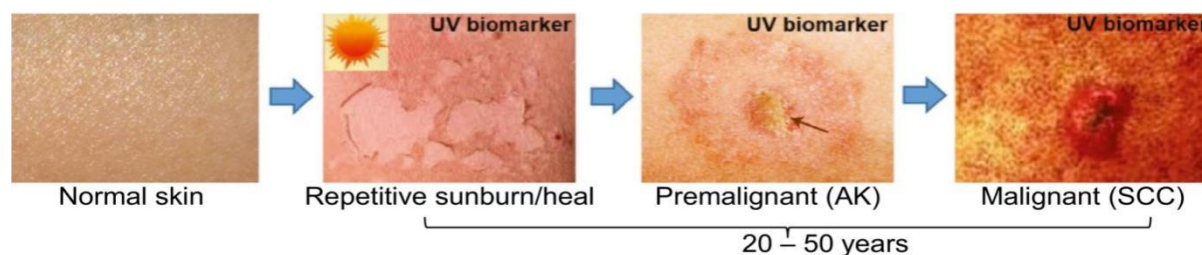
They could potentially be used to plan the management of a patient with a pulmonary lesion or as a screening tool in high-risk populations.



Skin cancer:

Epigenetic (methylation) biomarkers can be detected in tissue and in blood as circulating DNA in melanoma patients.

There is strong evidence that biomarkers in cutaneous melanoma will have an important role as companions to therapeutics and overall patient management.



Diabetes-

Diabetes is a major lifestyle disease and a leading cause of cardiovascular diseases. It is necessary to identify the potential biomarkers associated with diabetes for the early detection of the disease and its proper management.

Elevated blood pressure, low HDL cholesterol, and elevated triglycerides are some of the common biomarkers of diabetes, adiponectin, C-reactive protein (CRP), ferritin, interleukin-2 receptor A being the other counterparts.

High CRP levels have been linked to an increased risk of thrombotic events including myocardial infarction. Elevated CRP levels have also been linked to an increased risk of later development of diabetes. Furthermore, CRP levels are higher in people with diabetes compared with those without diabetes.

Conclusion:

Biomarkers are integral part of drug development; they're really critical, because we need to measure the effects of investigational drugs on people during the clinical trials. And the way we do that is to look at their effect on biomarkers. It provides a dynamic and powerful approach to understanding the complex conditions of various diseases.

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