**Biomarkers**

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**Abstract**

A biomarker is a biological finding that, in theory, predicts and serves as a stand-in for a clinically significant endpoint or intermediate outcome that is more challenging to observe. Because biomarkers are used so often in scientific and clinical research, as well as in clinical practise, it is now nearly universally acknowledged that they should be used as primary endpoints in clinical studies. This use is totally legitimate and suitable in the case of certain biomarkers that have been thoroughly defined and consistently demonstrated to accurately predict pertinent clinical outcomes across a range of treatments and demographics.

The "validity" of biomarkers is commonly assumed, despite the fact that it should be tested and then tested again. This article will analyse the present conceptual position of biomarkers as clinical and diagnostic tools and as surrogate endpoints in clinical research to give context for evaluating studies that heavily depend on such biological measurements.

Clinical biomarkers are typically assessed over a shorter time than the final clinical objective, making their application simpler and less expensive. They can be utilised for pharmacodynamic and dose-response investigations as well as for illness screening, diagnosis, characterisation, and monitoring as prognostic markers for developing tailored therapeutic interventions for predicting and treating adverse drug responses. Good biomarkers should have a large signal-to-noise ratio, be quantifiable with little to no fluctuation, and change quickly and consistently in response to changes in the condition or its treatment.

The creation of novel therapies for patients with a range of conditions, such as tumours, cardiac issues, etc., has the potential to be significantly improved and sped up thanks to biomarkers, which are the foundation of a precision approach to clinical medicine.

**Introduction**

Although the term "biomarker" has gained popularity since the 1980s, biological markers were important long before laboratories were able to routinely measure them. In fact, clinical treatment has been centred on evaluating clinical symptoms since the development of medicine.

"A trait that is objectively measured and assessed as an indication of normal biological processes, pathogenic processes, or pharmacological reactions to a therapeutic intervention," was how the term "biomarker" was defined by a working committee of the National Institutes of Health in 2001.

All elements of the body, including body fluids and tissues, contain biomarkers. Most clinical laboratory tests are performed on bodily fluids like blood and urine. Imaging scans or examinations of body tissues can find biomarkers. Biomarkers can be found in even exhaled breath. **[1]**

A biomarker is "a specific feature that is judged as a sign of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic treatments," according to the FDA/NIH Biomarker Working Group. A biomarker may be molecular, histologic, radiographic, or physiological in nature; nevertheless, it does not evaluate a person's thoughts, actions, or general well-being.

The International Programme on Chemical Safety, which was created by the World Health Organization (WHO) in cooperation with the United Nations and the International Labor Organization, defines a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease." A definition that goes even farther takes into account not just the onset and progression of disease but also the outcomes of treatments, therapies, and even unintentional exposure to nutrients or poisons from the environment. **[2]**

For instance, it is said that the ancient Hindus identified "honey urine" as an indication of diabetes after seeing how it attracted flies. [3]

Genes, proteins, genetic variants, and differences in metabolic expression from various sources, such as bodily fluids or tissues, are examples of biomarkers.

In order to assess organ function or other elements of health, a chemical known as a biomarker is injected into an organism. It may be a molecule that, when found, indicates the existence of a certain disease state, much like the presence of an antibody might indicate an infection.

A biomarker is often a quantifiable characteristic that, in medicine, may be used to determine the existence or severity of a medical condition. A biomarker is, broadly speaking, anything that may be used to identify a certain illness condition or another physiological state of an organism. [4]

Before being made available in the clinic, biomarker tests that are used to treat patients would in an ideal world undergo a careful assessment. [5]

A biomarker is a biological discovery that, in principle, predicts and serves as a stand-in for a clinically significant intermediate endpoint that is more challenging to see.

Therapeutic biomarkers are usually studied for a shorter amount of time than the final therapeutic aim, which makes their use simpler and less expensive. They may be used for prognostic indicators, identifying cell types, pharmacodynamic and dose-response studies, predicting and treating adverse drug responses, developing individualised therapeutic interventions, and screening, diagnosing, characterising, and monitoring illnesses. [6]

Cells, chemicals, genes, gene products, enzymes, and hormones could be related to one another. helps in early diagnosis, pharmaceutical target identification, therapeutic response, and illness prevention, among other things. **[7]**

In the age of molecular biology, molecules are referred to as "biomarkers," and they fall into three broad categories:

1. For the illness to worsen over time and follow established clinical parameters

2. People who are aware of a drug's effects

3. those that act as substitute goals in clinical trials

A lab test might be a biomarker, or it could be something more complicated like the pattern of gene or protein expression. The biomarker might be utilised for diagnosis as well as disease monitoring during and after therapy since it would accurately and uniquely represent a disease state. A marker that is inadequate or absent in a disease is referred to as a "negative biomarker."**[1]**

The majority of the fields in applied medicine and biomedical research are focused on the search for biomarkers. Generally speaking, biomarkers are clinical symptoms that may be quantified quantitatively as indicators of health and sickness and are objectively observable. [3]

Therefore, compatibility with readily available sample types, precision and accuracy, acceptable analytical sensitivity, analytical specificity/selectivity, robustness, and throughput are among the technical attributes of a biomarker test that are frequently thought to contribute to therapeutic efficacy. **[3]**

**Clinical outcome measurements, biomarkers, and endpoints**

A biomarker is a trait that has been identified and is used to quantify the occurrence of common biological processes, pathogenic processes, or responses to exposure or intervention. This broad definition encompasses therapeutic approaches and can be inferred from molecular, histologic, radiographic, or physiological traits. Biomarkers should be separated from clinical outcome evaluations, a type of measurement that directly evaluates how a person feels, performs, or survives, for the purpose of clarity (COA). This distinction between COAs and biomarkers is crucial because COAs assess patient-relevant outcomes and may be used to satisfy regulatory requirements for therapeutic product approval, whereas biomarkers have a number of purposes, one of which is to link a measurement to a prediction of COAs. Except in situations when no effective medicine is available, a biomarker can only be used as the main justification for regulatory permission for marketing once it has been validated.

When utilised as endpoints in clinical investigations, biomarkers and COAs acquire added complexity and a commensurate demand for scientific rigour. A biomarker or COA may be discussed in a more general sense, but when either is used as an endpoint, a level of rigour that includes multiple dimensions is required. An endpoint is a precisely defined variable intended to reflect an outcome of interest that is analysed using statistics to answer a specific research question. **[8]**

**Clinical endpoint**

It depicts how a patient feels, behaves, and endures. E.g., Survival and patient-reported outcomes, such as pain or functional ability, are important.

For instance, the exacerbation rate is an example of an intermediate endpoint. Clinical endpoints that reflect the build-up of irreversible morbidity and survival but are not the conclusion are referred to as ultimate clinical outcomes. In a similar vein, individuals seek care for their ailments rather than the numerical measurements that commonly but not always correlate with them.

In other words, they are factors that, from the patient's perspective, describe the health and wellbeing of a research participant. There has long been widespread agreement that the main,

and in some cases, the only significant, outcomes of all clinical research—and eventually of all biomedical research—are clinical endpoints. Clinical practise should focus on reducing morbidity and death rather than altering individuals' intrinsic biochemistry, for example, which would have no discernible clinical impact. In a similar vein, individuals seek care for their ailments rather than the numerical measurements that commonly but not always correlate with them.

In the right situations, additional clear-cut, unambiguous clinical indicators, such stroke, myocardial infarction, and the development of predetermined opportunistic infections, have also been utilised as endpoints. These clinical factors provide precise, unmistakable information that has the capacity to demonstrate conclusively whether therapies are successful or unsuccessful, safe or harmful. For the majority of HIV studies, survival is frequently recognised as the gold standard clinical outcome. Nevertheless, not every clinical outcome is the same. Clinical data elements including breath sounds, discomfort, and the disappearance of "symptoms" under circumstances where symptoms are not established, for instance, transmit less precise, less quantifiable information.

**Surrogate endpoint**

It's rare to find this kind of biomarker. It acts in place of a clinical objective.

It is meant to predict clinical benefit and harm based on epidemiological, pathophysiological, pharmacological, or other information.

A surrogate endpoint requires solid scientific support.

A biomarker that may be used to replace a clinical endpoint but not the endpoint itself is referred to as a surrogate endpoint in this context. [9]

For instance, blood pressure may be used to avoid strokes, the Q-T interval to assess the safety of medications, the progression of cancer can be predicted, and plasma glucose can be used to identify diabetes.

**Differentiating biomarkers**

Imaging biomarkers include things like magnetic resonance imaging, computed tomography, and positron emission tomography. Non-imaging biomarkers, usually referred to as molecular biomarkers, are substances that may be evaluated in biological samples due to their biophysical characteristics. Quantitative gene expression and nucleic acid-based biomarkers like gene polymorphisms or mutations are examples of this.

The usage of biomarkers may also be classified, with categories including diagnostic, illness staging, disease prognosis, and biomarkers for monitoring the clinical outcome of an intervention.

A different class of biomarkers are those used in early drug development decision-making. For instance, investigations on dosage optimization are particularly important to pharmacodynamic biomarkers, which act as markers of a particular pharmacological response. **[4]**.

The rest of this study illustrates the various classification schemes used for biomarkers. The biomarkers could include straightforward substances like metabolites, sugars (like glucose), hormones, and lipids. Peptides and proteins like insulin, haemoglobin A and C, prostate specific antigen, and C-reactive protein are less straightforward. Autoantibodies and cells like platelets or T cells are examples of more complicated biomarkers. The most complex clinical phenotypes are patients; however, this subject will not be covered in this study.

**Based on their characteristics**

**Type ‘0’**

**(Natural Biomarker)**

**Type ‘I’**

**(Biomarkers to detect drug effects)**

**Type ‘II’**

**(Biomarkers as surrogate endpoints in clinical trials)**

**Examples**

* Disease biomarker
* Diagnostic biomarker
* Prognostic Biomarkers
* Susceptibility/Risk biomarker
* Predictive biomarker

**Examples**

* Mechanism biomarker
* Pharmacodynamic biomarker
* Toxicity biomarker
* Monitoring biomarkers
* Safety biomarker

**Examples**

* Valid biomarkers

**Biomarker(s)**

**Based on their application**

**Based on their bio molecule**

* Metabolites
* Carbohydrates
* Steroids
* Lipids

**Examples**

**Simple Biomarker**

* C-reactive protein
* T cells
* Autoantibodies

**Examples**

**Complex Biomarker**

**Imaging Biomarker**

**Examples**

* Computed tomography
* Positron emission tomography
* Magnetic resonance imaging

**Non-Imaging Biomarker (Molecular Biomarker)**

**Examples**

* Nucleic acid–based biomarker
* Gene mutations or polymorphisms
* Quantitative gene expression analysis
* Peptides
* Proteins
* Lipids
* Metabolites

+

**Biomarker classification**

**Complex biomarkers**

The foundation of the area of biomarkers is a set of crucial measurements that have strong correlations with disease and are explicable by a simple paradigm. For instance, higher systolic blood pressure is linked to stroke risk, while lower systolic blood pressure is preferable. Similarly, LDL cholesterol is linked to the risk of cardiovascular disease, and lower LDL cholesterol is better. Biological systems, however, are intricate and multifaceted. Evaluation of one biomarker without knowledge of others can result in incorrect findings as more complex biological models are constructed. Furthermore, because several biomarkers each have a minor impact on the important summative outcome, measuring complex, composite biomarkers may help predict outcomes more accurately. **[10,11]**

**Biomarkers for imaging**

Imaging biomarkers are non-invasive, produce quantitative and qualitative data that aid in illness research, and are generally painless for patients. Pharmacokinetic analysis is aided by these biomarkers, which are also used to identify or track minute amounts of metabolites in animals. These biomarkers identify the metabolite in vivo and generate results that are logical and multidimensional.

**Biomarkers for non-imaging**

The term "molecular biomarkers" refers to biomarkers that can be found utilising common and acceptable platforms like proteomics and genomics. There are numerous genomes and proteomics methods available for the finding of biomarkers; a few recently applied methods are listed below. The most widely used methods for identifying biomarkers include metabolomics, lipidomics, glycomics, and secretomics in addition to biomarker assay approaches using genomes and proteomics platforms.

**Genomics strategy**

The discovery and identification of biomarkers has made substantial use of genomics. With over 30,000 genes in the human genome, new ways for viewing, evaluating, and exploiting the complicated, large-scale biomarker data are necessary to fully utilise the clinical potential of genome-scale information. With the help of genomics, disease-related genes, abnormal cellular signalling pathways, and expression signatures can all be found. Numerous methods, including Positional cloning, microsatellites, and single nucleotide polymorphism (SNP) genotyping, are used to cut into nucleated cells to map disease loci and identify the disease gene. Other methods, including expression arrays, comparative genomic hybridization arrays, and gene amplification and loss of heterozygosity detection, made use of pathologically compromised cells to identify dysregulated genes and find evidence of gene amplification.

**Proteomics strategy**

Proteomics can be a useful technique for comprehending the intricacies of human physiology and the state of disease, perhaps even more so than gene expression studies. The discovery of new diagnostic and prognostic biomarkers has a lot of potential thanks to proteomics. Western blotting, immunohistochemical staining, enzyme-linked immunosorbent assays, and mass spectrometry are examples of methods. Secretomics, a branch of proteomics that uses proteome methods to study secreted proteins and secretion pathways, has lately gained prominence as a key resource for the identification of biomarkers. Proteomic methods are also applied to enhance gene annotations in what is now known as proteogenomics. Comparative proteoge­nomics, or the simultaneous investigation of the genome and proteome, makes it easier to find post-translational modifications and proteolytic processes.

**Metabonomics strategy**

The comprehensive examination of all metabolites in a biological sample is referred to as metabolomics in modern times. The investigation of metabolic responses to medications or illnesses has been given its own word, metabonomics. To find biomarkers for diverse diseases, complex biological systems are studied in metabonomics, a rapidly growing field of study. It is unclear if this specialisation will also succeed in finding biomarkers for regenerative medicine.

**Lipidomics strategy**

The term "lipidomics" describes the study of lipids. Lipids have historically been challenging to research because they have distinct physical features that are specific to cells and cell-based products. Although it is now possible to identify and quantify most lipid metabolites from a single sample thanks to advancements in modern analytical platforms. Nuclear magnetic resonance, chromatography, and mass spectrometry are the three main platforms for lipid profiling. **[12]**

**Disease biomarker**

Condition biomarkers are biomarkers that statistically correlate with the phenotype (syndrome) of the disease for which a treatment is being developed. The onset, progression, regression, remission, or recurrence of a disease should be indicated by a correlation of levels (in the bloodstream, other bodily fluids, or tissue) or patterns of expression (gene, protein) in peripheral blood cells or tissues. It becomes clear that our existing methods for clinical testing are ineffective when we apply these criteria to our empirical approach to current attempts to create medications for specific ailments. The way the industry has approached the creation of therapies for schizophrenia is one significant example. **[13]**

These biomarkers can serve as functional biomarkers for blood flow, platelet aggregation, or cognitive function, which can be used to track the development of diseases. It can offer endpoints relevant to a particular condition. As quantifiable markers of protein/amino acid damage, oxidised lipids, and oxidised DNA bases (e.g. lens opacity). **[14]**

**Diagnostic biomarkers**

A diagnostic biomarker identifies a person who has a certain subtype of the disease or detects or verifies the presence of a disease or condition of interest3. These biomarkers may be used to reclassify the disease in addition to identifying those who have it. These biomarkers' major objective is to measure the disease affordably, accurately, and repeatedly. These biomarkers establish the connection between diagnostics and treatment.

For instance, the molecular diagnostic biomarker CA-125 is used to diagnose ovarian cancer. In situ hybridization (ISH), microarrays, PCR, and LNA are examples of molecular diagnostic methods. have been used to identify many biomolecules, including miRNA. These miRNAs serve as biomarkers, and miRNA measurement can be used to diagnose disorders, including cancer. Use of diagnostic biomarkers as a foundation for drug development, including translational toxicology, the research of illness pathomechanism, and the provision of scoring systems to assess such drugs' predictive potency. **[15,16,17,18]**

**Prognostic biomarkers**

A prognostic biomarker is used to determine the likelihood of a clinical event, a return of the illness, or the course of the disease in a patient with a disease or condition of interest. Take care of any ties to the transition from a healthy to a sick state. At a set baseline, which can include background treatment, prognostic biomarkers are evaluated. Prognostic biomarkers may improve clinical trials by identifying individuals who are more likely to respond to therapy in addition to their capacity to predict outcomes.

Clinical trials routinely use prognostic biomarkers to define trial entrance and exclusion criteria and to identify higher-risk participants. The major issue is that the number of events in a trial dictates its statistical power rather than the sample size. The event rates rise when trials are enhanced in this way.

Prognostic biomarkers are furthermore crucial for estimating an individual's risk of an event or a poor result. The choice of how long to stay in the hospital or in intensive care units depends on this information. Another significant application of prognostic biomarkers is in population health resource allocation. By categorising the risk of unfavourable clinical and financial outcomes, a healthcare organisation can determine which patients would benefit from more thorough evaluation while allowing others to forego needless additional diagnostic procedures or medical interventions. Additionally, they differ from predictive biomarkers, which pinpoint variables linked to the likelihood of a specific outcome. Prostatic specific antigen, for instance, is used to forecast survival in patients with prostatic cancer. **[19,20]**

**Susceptibility/Risk biomarker**

A susceptibility/risk biomarker is one that predicts the likelihood of acquiring a disease or medical condition in a person who does not already have the disease or condition in a clinically apparent form.

Although the major concern is the relationship with the onset of a disease rather than the prognosis after a diagnosis, the approach is like prognostic biomarkers. These kinds of biomarkers are essential for carrying out epidemiological investigations on illness risk… **[21]**.

**Predictive** **biomarkers**

to identify those who are more likely to have positive or negative effects from being exposed to a medicinal product or an environmental contaminant. These biomarkers are necessary for the design and execution of clinical studies to decrease the sample size and assess the increased efficacy of therapeutic drugs. Examples include giving patients with high blood pressure antihypertensive drugs; giving blood transfusions to persons whose anaemia is indicated by low haemoglobin levels; and telling patients whose electrocardiograms show ST-segment elevation that they need immediate reperfusion **[22,23,24,25].** The development of genetic and genomic markers for precision medicine, as in the case of cancer patients with HER2 receptor positive assays who are more likely to respond to treatment with herceptin, is a major growth area in predictive biomarkers. Biomarkers that distinguish between patients who are likely to react to medication are another example. **[26,27].**

**Mechanism /Target biomarker**

Mechanism/Target biomarkers can be utilised to inform crucial "go/no go" decisions during the drug development process to assess the pharmacological impact of a given substance.

Learn about the drug's distribution at the site of action, if there is any downstream pharmacology—that is, the dosage ranges at which the drug is pharmacologically active—in these biomarkers, as well as whether it interacts with the receptor (a protein or an enzyme).

Drugs that bind to the 5-HT4 receptor, such as cisapride, mosapride, and aldosterone biomarkers, can be used to determine if newly developed 5-HT4 agonists have any pharmacological effects. Aldosterone can be utilised to determine the dosages at which 5-HT4 agonists are effective. Since it holds onto salt and water, aldosterone is an illustration of a mechanistic biomarker. To determine receptor occupancy or medication distribution, imaging techniques can be utilised. **[28,29]**

**Pharmacodynamic/response biomarkers**

To demonstrate that a person who has been exposed to a medication or environmental contaminant has experienced a biological reaction. These biomarkers support medication target identification and dose determination. These biomarkers were employed in phase I trials on healthy volunteers and in clinical practise in both the early stages of therapeutic medicine development. These biomarkers offer the initial information that shows proof that the drug will be safe to use in healthy human bodies with the targeted condition. Since they give a reliable indication for the anticipated therapeutic response, these biomarkers are essentially utilised to validate the measured change in response. Examples are the FEV1 or 6-minute walk test, LDL-C, and blood pressure in hypertension. **[13,30]**

**Toxicity biomarkers**

These reports discuss a drug's toxicological impact in in vivo or in vitro systems. The toxicity biomarkers aid in predicting safety margins and helping to determine the best dose. However, clinical research and patient care represent the scope of biomarker analysis. To determine patient response and create efficient and secure dose regimens, biomarkers may be used. During medication therapy, biomarkers may potentially show on-target versus off-target responses and toxicological effects. The liver, kidneys, brain, and heart are the main organs impacted by drug toxicity. Toxicology biomarkers are used to identify presymptomatic toxicity. The toxicity biomarkers aid in predicting safety margins and helping to determine the best dose. However, clinical research and patient care represent the scope of biomarker analysis. To determine patient response and create efficient and secure dose regimens, biomarkers may be used. **[31]**

**Monitoring biomarkers**

When a biomarker is evaluated repeatedly to determine the severity of a disease or medical condition, look for indications of exposure to a medical product or environmental agent, or look for indications of a medical product's or biological agent's effects, the biomarker is considered a monitoring biomarker. Assessing pharmacodynamic effects, identifying early signs of a therapeutic response, and identifying adverse effects of a condition or therapy are all aided by monitoring biomarkers. Monitoring biomarkers is heavily used in clinical treatment. One of the more fascinating aspects of monitoring biomarkers is the unwavering belief of many academics and medical professionals that changes in biomarker readings are the greatest predictor of the expected course of events for a patient or community. Even though the change is the strongest indicator of whether the therapy is working, in many cases the actual measure rather than the change is the best predictor of result.

Examples include monitoring blood pressure or LDL cholesterol levels when low-density lipoprotein (LDL) cholesterol-lowering medications are used. Like this, CD4 counts are tracked during HIV treatment. Another illustration is how angiotensin-converting enzyme (ACE) inhibitors may increase serum creatinine and/or potassium levels, which serves as a pharmacological impact indicator. **[32,33,34]**

**Safety biomarkers**

to gauge the possibility, existence, or severity of toxicity as a negative outcome before or after exposure to a medical product or environmental contaminant. These biomarkers' evolving balance between safety and the possible therapeutic benefit is an intriguing reality. For effective medication, these biomarkers are utilised to determine the degree of toxicity as an adverse event in several organs, such as the hepatic, renal, and cardiovascular. The Cardiac Safety Research Consortium, which consists of representatives from the FDA, industry, and academia, is working on strategies for establishing an ideal balance between the ability to measure risk through early biomarker detection with the potential for benefit. In short, it provides assurance that a given therapy can be sustained safely. Examples include the use of safety biomarkers such as ALT, eGFR, troponin, creatinine, urinary kidney injury biomarkers, etc. when prescribing antiarrhythmic medications, and prolongation of the QT interval on the electrocardiogram, which predicts the risk of developing the lethal arrhythmia and can be used to identify patients in need of countermeasures for effective therapy.

**[13,30,35]**

**Valid biomarkers**

Physiologic, toxicologic, pharmacologic, or clinical significance of test results are clarified by an established scientific framework or body of evidence for a valid biomarker, which is a biomarker that is measured in an analytical test system with well-established performance characteristics. The criteria for validating a biomarker will change depending on how the biomarker is going to be used. Approaches that can be used to decide the essential requirements for validation include the clinical utility (e.g., forecast toxicity, effectiveness, or dose) and use of epidemiology/population data (e.g., strength of genotypephenotype relationships). Considering the following factors can help with biomarker validation:

1. Consistency between the biomarker and the process's known or anticipated physiologic or pathophysiologic consequences

2. Acceptance and adoption by subject-matter specialists

3. pharmaceutical firms use when deciding whether to advance certain medications into further research.**[1]**

**Ideal qualities for biomarkers**

1. The FDA states that the ideal biomarker should be capable of distinguishing between physiological characteristics that are like one another and specifically linked to a certain disease or disease state.

2. It would be ideal if biomarkers could be identified using common biological sources like serum and urine.

3. It should be possible to identify the necessary marker quickly, easily, accurately, and affordably, and a quantifiable baseline should be given as a point of comparison.

4. Expression is noticeably increased, especially when there is an illness present.

5. Simple to measure in clinical samples or widely available biological fluids

6. Shown to be consistent with a fascinating result trend.

7. Quick turnaround times, uniformity, and cost-effectiveness.

8. The ability to make medical decisions should be aided by knowing the measured level. **[36]**

**Biomarker Validation**

1. Accuracy (according to a reference): Analytical validation to evaluate the precision and dependability of the suggested test to quantify the potential biomarker The number of true positives and true negatives divided by the total number of assessments is how accurate a test is in a particular demographic. Accuracy is influenced by a test's sensitivity, specificity, and prevalence of the target marker in the population under study.

2. Precision (repeatability, reproducibility)

3. Limit of Detection (sensitivity): A test's sensitivity, or its inherent capacity to "detect" a true positive when one is present, is calculated by dividing the number of true positives by the sum of true positives and false negatives.

4. Specificity, also known as interference and cross-reactivity, is the ratio of true negatives to true negatives plus false positives, or the test's inherent capacity to discriminate between a true negative.

5. Sample setup and environmental factors

6. Around the cutoff, performance

7. Possibility of cross-hybridization and carryover. **[8]**

**Biomarker's Function**

**Biomarkers' function in translational medicine**



**Biomarkers' relationship to other technologies and healthcare**

On a variety of diagnostic biomarkers, drug research and discovery are based. They aid in anticipating the therapeutic medicine's potency and the negative effects of the medications. Study the pathomechanics and toxicity of illnesses using biomarkers. In the shift from preclinical to clinical trials, biomarkers are also crucial. The research of the transition from preclinical to phase III studies used a diverse consistent set of biomarkers. Using the same imaging biomarker analysis programme for both preclinical and clinical research. **[1]**

**Drug development, regulation, and clinical practise: The role of biomarkers**

1. The FDA has devised a voluntary submission method to make it easier to use these biomarkers in drug development and clinical practise. created online teaching resources and works to ensure that information about genetic/genomic biomarkers is included on drug labels.

2. The set of preclinical safety of biomarkers that will be further assessed for clinical application was identified throughout preclinical development through a lot of work.

3. Different metabolism biomarkers and other biomarkers are used in clinical development to identify and categorise individuals, for example. CCR5 molecule.

4. During the drug development process, substances can be used as targets for screening; for instance, cyclooxygenase activity can be measured to find prospective anti-inflammatory drugs.

5. As well as in pharmacokinetic/pharmacodynamic studies as endpoints, such as serum cholesterol as a marker for the activity of a medicine intended to prevent cardiovascular disease.

6. When examining the connection between a drug's dosage or concentration and its results

7. To assess effectiveness in clinical trials

8. To further clarify the potential side effects of medication candidates.**[6]**

9. The qualifying of biomarkers for use in drug research, regulation, and clinical practise will be made easier by a process that is currently being created.

10. To effectively integrate and use biomarkers in drug development, regulation, and clinical practise, it is crucial to consider key factors including resource and data sharing.

**Nanobiotechnology's Function in Biomarkers**

The development of nanobiotechnology will have an impact on the identification of biomarkers. The development of devices that can rapidly screen for illness biomarkers using nanotechnology is a potential. The instruments will be created by locating biomarkers for specific diseases, which can subsequently result in diagnostic testing. One effort in this field combines the knowledge of a group of experts from the Fred Hutchinson Cancer Research Center (Seattle, WA), the Seattle Biomedical Research Institute, and the Australian Institute for Bioengineering and Nanotechnology at The University of Queensland (UQ). The Queensland State Government has donated $2 million to this research as part of the National and International Research Alliances Program. The research will also be supported by the partnering institutes and UQ spin-off company Nanomics Biosystems Pty Ltd. in addition to financing from Alliances. Researchers at the California Institute of Technology (Pasadena, CA) are working on an early cancer detection strategy based on nanoscale transistors in extremely small circuits. Each transistor can incorporate an antibody, a biological molecule designed particularly to attach to a biomarker. When the antibody attaches to the biomarker, a slight change in the transistor's capacity to conduct electricity indicates the existence of the biomarker. The long-term goal is to develop a circuit the size of a tiny computer chip that can distinguish between hundreds or thousands of markers in a single test, enabling the early identification of cancers that would otherwise go undetected. **[1]**

When treatment is initiated relatively early on, cancer is simpler to treat and less prone to develop drug resistance. Early-stage cancer cells are less likely to have mutations that make them immune to therapy. Cancer cells may be hard to spot at first, but they leave a fingerprint in the form of a pattern of alteration in blood-circulating biomarker proteins. There could be 20–25 biomarkers, and each assessment could require as much as 500 samples of blood drawn from a pinprick. Nanoscale diagnostics will therefore be crucial to this effort **[1]**.

**Digital biomarkers' function**

The subject of digital biomarkers is one that is advancing quickly. The ability to assimilate information quickly and continuously about a person that offers insight into complicated metrics including psychological state, exercise level, cognitive capacities, eating patterns, mobility, and tremor has been made possible by sensors and mobile gadgets. Standards for evaluating these biomarkers are just now emerging because this data are largely collected from new sources like cell phones and wearable electronic devices and supported by modern technologies that enable the streaming and storing of complicated data. Although the Clinical Trials Transformation Initiative has just recently released guidelines on industry-wide quality

standards, much more research is still required to establish a connection between digital phenotypes and endpoints and conventional outcome measurements. For instance, the 6-minute walk test and sitting resting systolic blood pressure are now accepted methods for evaluating exercise tolerance and blood pressure, respectively. While sensors and smartphone apps for blood pressure measurement are evolving, the relationship between the patient's activity status and measurements obtained from wearable accelerometers, such as ones embedded in wristwatches or cell phones, is still under development. Dealing with missing data, outlier values, and the reduction of enormous volumes of data into measures that can guide decisions will take a lot of work.

Digital biomarkers will probably ultimately bring us brand-new avenues for measuring phenomena that have already been studied. For example, it's feasible that total daily activity or a composite of peak daily activity and continuous daily activity might be a better indication of risk or susceptibility to acquire new diseases, prognosis for people who currently have a condition, or responsiveness to therapy (response biomarker).

In this way, when extremely frequent blood pressure measurements are feasible, derivation measures from a range of blood pressures and activities are expected to be a stronger signal of response to medication for hypertension than sitting resting blood pressure measurement. **[8,37,38]**

**Summary of various biomarker in different diseases**

|  |  |  |
| --- | --- | --- |
| **Disease** | **Biomarkers** | **Study Of Outcome** |
| COVID-19 | Lymphocytes, IL-6, D-dimer, platelet count | The plasma levels of IL-6, D-dimer, and platelets were greater in ICU patients than in non-ICU patients. ICU patients were more likely to have lymphopenia than non-ICU patients **[39].** |
| CRP, WCC | Compared to severe or no severe patients, critically ill patients exhibited noticeably higher CRP and WCC levels **[40].** |
| LDH, NC, CRP, platelet count | Refractory patients had greater levels of LDH, NC, CRP, and platelet count than general patients. Lung abnormalities were more common in refractory individuals, indicating that these indicators are related to the progression of the illness **[41].** |
| D-dimer, Platelet count, CRP lymphocytes and LDH | There was no statistical analysis carried out despite the fact that patients who had composite outcomes (ICU admission, invasive mechanical ventilation, and mortality) had clearly different lymphocytes (lymphocytopenia), platelet count, and D-dimer **[42].** |
| Lymphocytes, Albumin, Neutrophils, CRP, PaO2/FiO2, platelet count, creatinine and LDH | Among other things, the Ct value of the virus showed a high correlation with albumin, CRP, and LDH. The same indicators were associated with the Murray score for ARDS. **[43]** |
| Sepsis | High mobility group-box 1 protein (HMGB-1) | At 28 days, there is no difference between survivors and non-survivors. **[44,45]** |
| IL-1β | increased in septic people compared to non-septic people **[46,47]** |
| IL-2 | Increased in parallel with disease severity **[48]** |
| IL-6 | Distinguished between survivors and non-survivors at 28 days **[49,50]** |
| CKD | Tenascin and TIMP-I | When compared to controls, CKD patients reported higher levels of tenascin and TIMP-I in their urine and serum. **[51]** |
| u-L-FABP | Proteinuria was not as sensitive an indicator of CKD development as u-L-FABP. u-L-FABP went up as renal function dropped. **[52]** |
| GGT | Microalbuminuria was predicted by serum GGT in people with diabetes and hypertension. **[53]** |
| ADMA | ADMA levels predicted development of ESRD **[54]** |
| Brain Cancer | Short arm chromosome 1 (1p) and the long arm of chromosome 19 (19q) | Deletions of these chromosomes act as diagnostic markers. **[55]** |
| Colorectal cancer | K-ras, p53, APC | * K-ras participates in the signal transduction pathway and promotes cell growth. * p53 is involved in DNA damage, DNA repair and cell death. * p53 mutations cause genomic instability and the development of cancer. APC mutations are referred to as "gatekeeper" mutations since they start the carcinogenesis process. **[56,57]** |
| Kidney cancer | kallikrein 1 | The walls of the kidney's blood arteries contain kallikreins, and when the gene is expressed abnormally, cancer develops. **[58,59]** |
| Gastric cancer | LOH and PTEN | Mutations in LOH and PTEN have been found in gastric cancer. **[60,61,62]** |
| Thyroid cancer | CA125 | Malignant and benign follicular thyroid tumours can be distinguished by markers found in cells isolated from circulating blood. **[63]** |

**Conclusion**

There may be advantages to using biomarkers in the greater biomedical research business, in the drug development process, in examining different aspects of disease, and in tracking the positive effects of therapeutic interventions. Expanding our toolbox of treatments for all diseases and improving our comprehension of typical, healthy physiology depend on our ability to relate quantifiable biological processes to clinical outcomes. The necessity of utilising biomarkers as surrogate outcomes in sizable trials of serious diseases, including as cancer and heart disease, has been hotly debated at least since the 1980s. The FDA continues to promote the use of biomarkers in basic and clinical research as well as research on prospective novel biomarkers that may be utilised as surrogates in forthcoming studies. However, the more that is known about the underlying abnormalities associated with the condition and the mechanism of therapeutic action, the simpler it is to discover relevant biomarkers for diagnosing an illness, for monitoring the response to a therapy, and for researching disease development. This is because the processes that relate a disease's aetiology to its outcome are frequently intricate. Collecting this data may be challenging for fundamental and clinical pharmacologists, as well as other individuals engaged in the discovery of biomarkers. These can assist medication development by helping it concentrate more on certain patient subgroups, potentially improving therapeutic efficacy and safety. Strong supporting evidence is provided by various digital biomarkers and nanobiotechnology using biological indicators, which will eventually serve as the main information in some applications. Instead, then only focusing on whether the patients are feeling better, provide an objective biological indicator. This offers a fresh perspective on treatments, diagnosis, and medication development. Possibility to promote innovation, enhance effectiveness, reduce expenses, and give research organisations a significant advantage. The internal decision-making process we use to decide whether to go to the next stage of clinical development has undoubtedly been impacted by biomarkers. The goal of a tailored healthcare future.

References

1. Jain KK. The handbook of biomarkers. The Handbook of Biomarkers. 2017. 1–760 p;14, 24, 89, 314.
2. Strimbu K, Tavel JA. What are biomarkers? Current Opinion in HIV and AIDS. 2010;5(6):463-6.
3. Sobsey CA, Ibrahim S, Richard VR, Gaspar V, Mitsa G, Lacasse V, et al. Targeted and Untargeted Proteomics Approaches in Biomarker Development. Analytical Science Journals. 2019.
4. Huss R. Biomarkers. Translational Regenerative Medicine. 2015;235-241.
5. Cagney DN, Sul J, Huang RY, Ligon KL, Wen PY, Alexander BM. The FDA NIH Biomarkers, Endpoints, and other Tools (BEST) resource in neuro-oncology. Neuro-Oncology; 2018. 20(9):1162-1172.
6. Aronson JK, Ferner RE. Biomarkers—a general review. Curr Protoc Pharmacol. 2017; 9.23.1-9.23.17.
7. Allison J, Brooks S. Biomarkers in Drug Development – A CRO Perspective,2004;15-19.
8. Califf RM. Biomarker definitions and their applications. Exp Biol Med. 2018;243(3):213–21.
9. Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Ann Intern Med. 1996;125(7):605-13.
10. Verily Life Sciences. Project baseline, www.projectbaseline.com/
11. National Institutes of Health. National Institutes of Health All of Us Research Project, https://allofus.nih.gov/.
12. Sawyers CL. The cancer biomarker problem. Nature. 2008; 452: 548-552.
13. Day M, Rutkowski JL, Feuerstein GZ. Translational Medicine-A Paradigm Shift in Modern Drug Discovery and Development: The Role of Biomarkers. Pharmaceutical Biotechnology. Adv Exp Med Biol. 2009; 655:1-12.
14. Griffiths HR, Møller L, Bartosz G, Bast A, Bertoni-Freddarie C, Collins A, et al. Biomarkers. Molecular Aspects of Medicine. 2002; 23: 101-208.
15. U.S. Food and Drug Administration. Fast track, breakthrough therapy, accelerated approval, priority review. Updated September 14, 2015, www.fda.gov/forpatients/approvals/fast/ucm20041766.htm
16. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007; 115:928-35.
17. Pencina MJ, Agostino RBD, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Statistics in Medicine. 2012; 31:101-113.
18. Coller BS, Califf RM. Traversing the valley of death: a guide to assessing prospects for translational success. Science Translational Medicine. 2009; 1:10cm9.
19. Das V, Kalita J, Pal M. Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges. Biomedicine & Pharmacotherapy. 2017; 87: 8-19.
20. Kalia M. Personalized oncology: Recent advances and future challenges. Metabolism. 2013; 62(1): S11-S14.
21. U.S. Food and Drug Administration. Susceptibility/Risk Biomarker.Updated August 27, 2020. https://www.ncbi.nlm.nih.gov/books/NBK402288/
22. FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US).2016.
23. Sager PT, Gintant G, Turner JR, Pettit S, Stockbridge N. Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J. 2014; 167(3):292–300.
24. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: are we being misled? Ann Intern Med. 1996; 125:605-13.
25. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989; 8:431–40.
26. Gerber DE, Grossman SA, Zeltzman M, Parisi MA, Kleinberg L. The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. Neuro Oncol. 2007;9(1):47–52.
27. Armstrong TS, Cao Y, Scheurer ME, Vera-Bolaños E, Manning R, Okcu MF, et al. Risk analysis of severe myelotoxicity with temozolomide: the effects of clinical and genetic factors. Neuro Oncol. 2009;11(6):825–832.
28. Bailey WJ, Ulrich R. Molecular profiling approaches for identifying novel biomarkers. Expert opinion on drug safety. 2004; 3(2): 137-151.
29. A crucial component of the toolset for drug development. The Potential of Biomarkers is being examined. Thomson Reuters, 2010
30. Mendelsohn J,Ringborg U,Schilsky RL. Personalized cancer medicine – A strategy to counteract an increasing cancer challenge. Molecular Oncology. 2012; 6(2): 109-110.
31. McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. Mol Cancer Ther. 2009; 8(1):10–6.
32. ACCORD Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358(24):2545–59.
33. The SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et. al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015; 373:2103–16.
34. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, DePalma SM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70(14): 1785–1822.
35. WHO International Programme on Chemical Safety. Biomarkers in risk assessment: validity and validation; 2001. http://www.inchem.org/documents/ehc/ehc/ehc222.htm.
36. Braunwald E. Biomarkers in Heart Failure. N Engl J Med. 2008; 358:2148-59.
37. Insel T. Digital phenotyping: technology for a new science of behavior. JAMA 2017; 318:1215-6.
38. Clinical Trials Transformation Initiative. CTTI Recommendations: developing novel endpoints generated by mobile technology for use in clinical trials.
39. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al., Clinical features of patients

infected with 2019 novel coronavirus in Wuhan, China. 2020; 497–506.

1. Li H, Xiang X, Ren H, Xu L, Zhao L, Chen X, et al., SAA is a biomarker to distinguish the severity and prognosis of coronavirus disease 2019 (COVID-19), The Journal of infection. 2020.
2. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al., Clinical characteristics of

refractory COVID-19 pneumonia in Wuhan, China. Clinical Infectious Diseases. 2020; 73(11): e4208–e4213.

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 2020; 382(18):1708-1720.
2. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical

indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 2020; 63(3):364-374.

1. Karlsson S, Pettila V, Tenhunen J, Laru-Sompa R, Hynninen M, Ruokonen E. HMGB1 as a predictor of organ dysfunction and outcome in patients with severe sepsis. Intensive Care Med. 2008; 34(6):1046-1053.
2. Shao YM, Yao HG, Liang XZ, Xia YH. [Relation between level of expression of high mobility group protein B1 in hepatic tissue with the severity and prognosis of sepsis in rat]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2006; 18(11):668-672.
3. Murch O, Collin M, Sepodes B, Foster SJ, Mota-Filipe H, Thiemermann C. Lysophosphatidylcholine reduces the organ injury and dysfunction in rodent models of gram-negative and gram-positive shock. Br J Pharmacol. 2006; 148(6):769-777.
4. Kurt ANC, Aygun AD, Godekmerdan A, Kurt A, Dogan Y, Yilmaz E. Serum IL-1beta, IL-6, IL-8, and TNF-alpha levels in early diagnosis and management of neonatal sepsis. Mediators Inflamm. 2007; 31397.
5. BalcI C, Sungurtekin H, Gurses E, Sungurtekin U, Kaptanoglu B. Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. Crit Care. 2003; 7(1):85-90.
6. Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, Teoh L, Van Meter L, Daum L, Lemeshow S, Hicklin G, Doig C. Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med. 2004; 32:2173-2182.
7. Patel RT, Deen KI, Youngs D, Warwick J, Keighley MR. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Br J Surg. 1994; 81:1306-1308.
8. Horstrup JH, Gehrmann M, Schneider B, Plöger A, Froese P, Schirop T, et al. Elevation of serum and urine levels of TIMP-1 and tenascin in patients with renal disease. Nephrol Dial Transplant. 2002; 17(6): 1005-1013.
9. Kamijo A, Sugaya T, Hikawa A, Yamanouchi M, Hirata Y, Ishimitsu T, et al. Clinical evaluation of urinary excretion of liver-type fatty acid-binding protein as a marker for the monitoring of chronic kidney disease: a multicenter trial. J Lab Clin Med. 2005; 145(3):125-133.
10. Lee DH, Jacobs DR, Gross M, Steffes M. Serum gamma-glutamyltransferase was differently associated with microalbuminuria by status of hypertension or diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem. 2005; 51(7): 1185-1191.
11. Ravani P, Tripepi G, Malberti F. Testa S, Mallamaci F, Zoccali C. Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach. J Am Soc Nephrol. 2005; 16 (8): 2449-2455.
12. Hartmann C, Mueller W, Lass U, Kamel-Reid S, von Deimling A. Molecular genetic analysis of oligodendroglial tumors. J Neuropathol. Exp Neurol. 2005;64(1):4-10.
13. Wang Z, Cummins JM, Shen D, et al. Three classes of genes mutated in colorectal cancers with chromosomal instability. Cancer Res 2004; 64(9):2998–3001.
14. ArendsJ, W.Molecular interactions in theVogelstein model of colorectal carcinoma. J Pathol 2000;190(4):412–6.
15. Yousef GM, Obiezu CV, Luo LY, Magklara A, Borgoño CA, Kishi T, et al. Human tissue kallikreins: from gene structure to function and clinical applications. Adv Clin Chem. 2005; 39:11-79.
16. Obiezu CV, Diamandis EP. Human tissue kallikrein gene family: applications in cancer. Cancer Lett 2005; 224(1):1-22.
17. Li YL, Tian Z,Wu DY, Fu BY, Xin Y. Loss of heterozygosity on 10q233 and mutation of tumor suppressor gene PTEN in gastric cancer and precancerous lesions. World J Gastroenterol 2005;11(2):285–288.
18. Garza-Gonzalez E, Bosques-Padilla FJ, El-Omar E, Hold G, Tijerina-Menchaca R, Maldonado-Garza HJ, et al. Role of the polymorphic IL-1B IL-1RN and TNF-A genes in distal gastric cancer in Mexico. Int J Cancer. 2005;114(2):237-241.
19. Dai YC, Ho CL, Tsai YC, Hsu YH, Chang YC, Liu HS, et al. Allelic loss of 14q32 in the pathogenesis of gastrointestinal and ampullary malignancies: mapping of the target region to a 17 cM interval. J Cancer Res Clin Oncol. 2005; 131(2):94-100.
20. Sato T, Harao M, Nakano S, Jotsuka T, Suda N,Yamashita J. Circulating tumor cells detected by reverse transcription-polymerase chain reaction for carcinoembryonic antigen mRNA: distinguishing follicular thyroid carcinoma from adenoma. Surgery 2005; 137(5):552–558.