BIOMARKERS

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.

However, the "validity" of biomarkers is frequently presumed when it should be tested and retested. To provide context for interpreting studies that extensively rely on such biological measures, this article will examine the current conceptual position of biomarkers as clinical and diagnostic tools and as surrogate endpoints in clinical research. [1]

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.

Biomarkers are the cornerstone of a precision approach to clinical medicine and have the potential to dramatically improve and speed up the development of new therapeutics for patients with a variety of diseases such as tumours, heart problems, etc.

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I. 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. **[2]**

According to the FDA/NIH Biomarker Working Group, a biomarker is "a particular attribute that is appraised as an indication of normal biological processes, pathogenic processes, or reactions to an exposure or intervention, including therapeutic therapies." A biomarker can be a molecular, histologic, radiographic, or physiological feature, but it is not an assessment of a person's feelings, behaviours, or quality of life.

The World Health Organization (WHO), in collaboration with the United Nations and the International Labour Organization, established the International Programme on Chemical Safety, which 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 considers not only the occurrence and course of disease, but also the results of interventions, therapies, and even inadvertent environmental exposure to substances like toxins or nutrients. **[1]**

For instance, the ancient Hindus are credited with discovering "honey urine" as a sign of diabetes after seeing its propensity to attract flies. **[3]**

Biomarkers include things like genes, proteins, genetic variations, and variations in metabolic expression from different sources like body fluids or tissues.

A biomarker is a substance that is injected into an organism to evaluate organ function or other aspects of health. It might be a chemical that, when discovered, denotes the presence of a specific illness condition, such as an infection might be deduced from the presence of an antibody.

In general, a biomarker is a measurable property that in medicine identifies the presence or severity of a disease condition. In a broader sense, anything that can be used as a marker for a certain disease condition, or another physiological state of an organism is referred to as a biomarker. **[4]**

In a perfect world, biomarker tests that are used in patient treatment would go through a thorough review before being made available in the clinic. **[5]**

A biomarker is a biological finding that, in theory, foretells and acts as a proxy for an intermediate or clinically relevant endpoint that is more difficult to observe.

Therapeutic biomarkers are frequently evaluated over a shorter time period than the ultimate clinical goal, simplifying and lowering the cost of their implementation. They can be utilised for pharmacodynamic and dose-response research, for anticipating and treating adverse drug reactions, for identifying cell types, for prognostic indicators, for generating individualised therapeutic interventions, and for screening, diagnosing, describing, and monitoring diseases. **[6]**

There could be a connection between certain cells, substances, genes, gene products, enzymes, or hormones. assists, among other things, in early diagnosis, medication target identification, therapeutic response, and sickness prevention. **[7]**

"Biomarkers" refers to molecules in the era of molecular biology and can be divided into three basic categories:

1. For the disease to progress through time and align with recognised clinical metrics
2. Those who can recognise a drug's effects
3. those that serve as replacement objectives in clinical trials

A biomarker could be as simple as a lab test or as complex as the pattern of gene or protein expression. Since the biomarker would sensitively and specifically represent a disease state, it might be used for diagnosis as well as disease monitoring during and after therapy. A "negative biomarker" is a marker that is insufficient or absent in a condition.**[2]**

Most of the applied medicine and biomedical discovery domains centre on the pursuit of biomarkers. Biomarkers are generally understood to be objectively observable clinical symptoms that may be precisely and consistently measured as quantitative indications of health and illness. **[3]**

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

II. CLINICAL OUTCOME MEASUREMENTS, BIOMARKERS, AND ENDPOINTS

A biomarker is a defined characteristic that is measured as an indicator of typical biological processes, pathogenic processes, or reactions to an exposure or intervention3. This expansive definition covers therapeutic interventions and can be derived from molecular, histologic, radiographic, or physiologic characteristics. For the sake of clarity, biomarkers should be distinguished from clinical outcome assessments, a kind of measure that directly assesses how a person feels, performs, or survives (COA). This distinction between COAs and biomarkers is significant because COAs measure outcomes that are directly relevant to patients and can be used to meet regulatory requirements for therapeutic product approval, whereas

biomarkers have a variety of uses, one of which is to connect 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]**

III. 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.

However, other well-defined, unambiguous clinical variables, such as stroke, myocardial infarction, and occurrence of predefined opportunistic infections, have also been used as endpoints in appropriate circumstances. These clinical variables offer clear, unambiguous data with the potential to show definitively whether interventions are effective or ineffective, as well as safe or unsafe. Survival is often regarded as the gold-standard clinical endpoint for most HIV trials. But not all clinical endpoints are the same. Breath sounds, pain, and the alleviation of "symptoms" in situations where symptoms are not predefined are examples of clinical data items that convey less accurate, less quantitative information.

IV. SURROGATE ENDPOINT

1. This type of biomarker is unique. It serves as a stand-in for a clinical endpoint.
2. Based on epidemiological, pathophysiological, pharmacological, or other evidence, it is supposed to forecast clinical gain and damage.
3. There must be strong scientific evidence for a surrogate endpoint.

4. In this respect, a surrogate endpoint is a biomarker that may be relied upon to act as a substitute for a clinical endpoint, but not as a substitute for it. **[9]**

5. For instance, blood pressure in preventing strokes, the Q-T interval in determining the safety of drugs, the time until cancer progresses, and plasma glucose in determining diabetes.
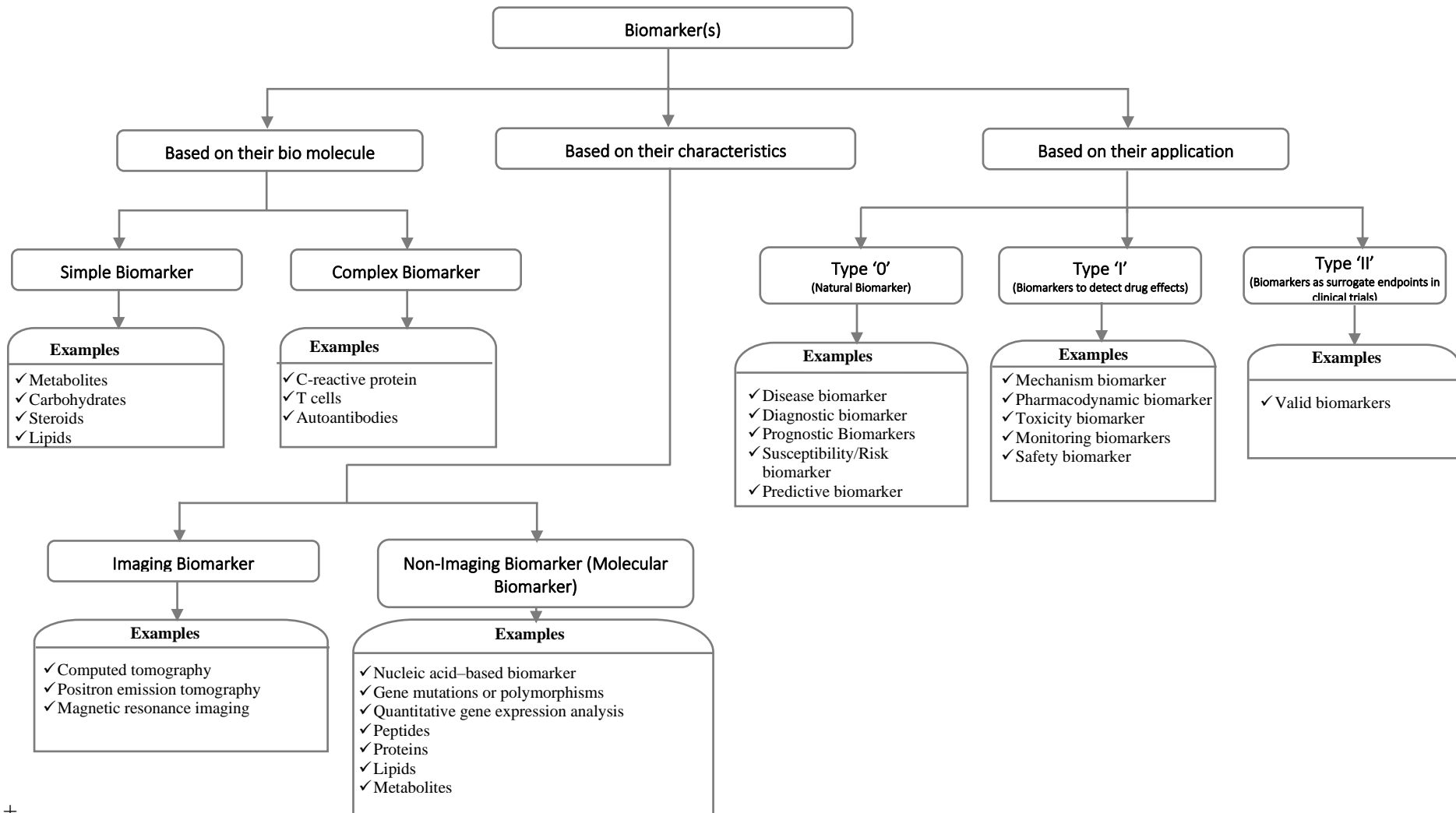
V. DIFFERENTIATING BIOMARKERS

Computed tomography, positron emission tomography, and magnetic resonance imaging are examples of imaging biomarkers. Non-imaging biomarkers, also known as molecular biomarkers, are those with biophysical properties that enable them to be measured in biological samples. These include nucleic acid-based biomarkers like gene mutations or polymorphisms and quantitative gene expression.

Additionally, biomarkers can be categorised according to how they are used, such as diagnostic biomarkers, disease staging biomarkers, disease prognosis biomarkers, and biomarkers for tracking the clinical outcome of an intervention.

The biomarkers utilised in early drug development decision-making are a different category of biomarkers. For instance, pharmacodynamic biomarkers, which serve as indicators of a specific pharmacological response, are particularly relevant to studies on dose optimization. **[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.

Biomarker(s)

Based on their bio molecule

Based on their characteristics

Based on their application

Simple Biomarker

Complex Biomarker

Examples

✓ Metabolites
✓ Carbohydrates
✓ Steroids
✓ Lipids

Examples

✓ C-reactive protein
✓ T cells
✓ Autoantibodies

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

Imaging Biomarker

Non-Imaging Biomarker (Molecular Biomarker)

Examples

✓ Computed tomography
✓ Positron emission tomography
✓ Magnetic resonance imaging

Examples

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

+

Biomarker classification

1. **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]**

2. **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.

3. **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.

4. **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.

5. **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 proteoge-nomics, or the simultaneous investigation of the genome and proteome, makes it easier to find post-translational modifications and proteolytic processes.

6. **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.

7. **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]**

8. **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]**

9. **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]**

10. **Prognostic biomarkers:** When a patient has a disease or condition of interest, a prognostic biomarker is used to predict the risk of a clinical event, disease recurrence, or disease progression. handle any connections to the change from a healthy to a diseased state.

Prognostic biomarkers are assessed at a predetermined baseline, which may include background therapy. Besides their ability to predict outcomes, prognostic biomarkers may also enhance clinical trials by identifying participants who are more likely to respond to treatment.

Prognostic biomarkers are frequently utilised in clinical trials to establish trial admission and exclusion criteria to identify higher-risk individuals. The main problem is that, rather than the sample size, the number of occurrences in a trial determines its statistical power. 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]

11. **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].

12. **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. A major growth area in predictive biomarkers is 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. Other examples include biomarkers that differentially select patients likely to respond to therapy [22, 23, 24,25] [26,27]

13. **Mechanistic/Target biomarker:** Mechanistic/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.

Discover whether the medication interacts with its receptor (protein, enzyme), its distribution at the site of action, and whether there is any downstream pharmacology, or the dose ranges in which the drug is pharmacologically active, in these biomarkers.

The 5-HT4 receptor agonists drugs such as cisapride, mosapride, and aldosterone biomarker can assess whether novel 5-HT4 agonists in development have a pharmacological effect. Aldosterone can also be used to assess at what doses the 5-HT4 agonists have an effect. Aldosterone is an example of a mechanistic biomarker because it retains sodium and water. Imaging methods can be used to assess receptor occupancy or drug distribution. **[28,29]**

14. **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]**

15. **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]**

16. **Monitoring biomarkers:** A biomarker is a monitoring biomarker when it may be evaluated repeatedly to assess the state of a disease or medical condition, look for signs of exposure to a medical product or environmental agent, or look for signs of a medical product's or biological agent's effects. Monitoring biomarkers is beneficial for assessing pharmacodynamic effects, spotting early indications of a therapeutic response, and spotting side effects of a disease or treatment. Clinical care utilises monitoring biomarkers in significant ways. The virtually unwavering conviction of many academics and doctors that changes in biomarker readings are the best indicator of the likely course of events for a patient or community is one of the more intriguing elements of monitoring biomarkers. 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]

17. **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, prolongation of the QT interval on the electrocardiogram, which predicts the risk of developing the lethal arrhythmia torsades de pointes and can be used to identify patients in need of countermeasures for effective therapy. [13,30,35]

18. **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 genotype phenotype relationships). Considering the following factors can help with biomarker validation:

- Consistency between the biomarker and the process's known or anticipated physiologic or pathophysiologic consequences
- Acceptance and adoption by subject-matter specialists
- pharmaceutical firms use when deciding whether to advance certain medications into further research.[2]

19. **Ideal qualities for biomarkers**

- 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.
- It would be ideal if biomarkers could be identified using common biological sources like serum and urine.
- 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.
- Expression is noticeably increased, especially when there is an illness present.
- Simple to measure in clinical samples or widely available biological fluids
- Shown to be consistent with a fascinating result trend.
- Quick turnaround times, uniformity, and cost-effectiveness.

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

20. Biomarker validation

- 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.
- Precision (repeatability, reproducibility)
- 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.
- 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.
- Sample setup and environmental factors
- Around the cutoff, performance
- Possibility of cross-hybridization and carryover. **[8]**

VI.   BIOMARKER'S FUNCTION

1.   Biomarkers' function in translational medicine
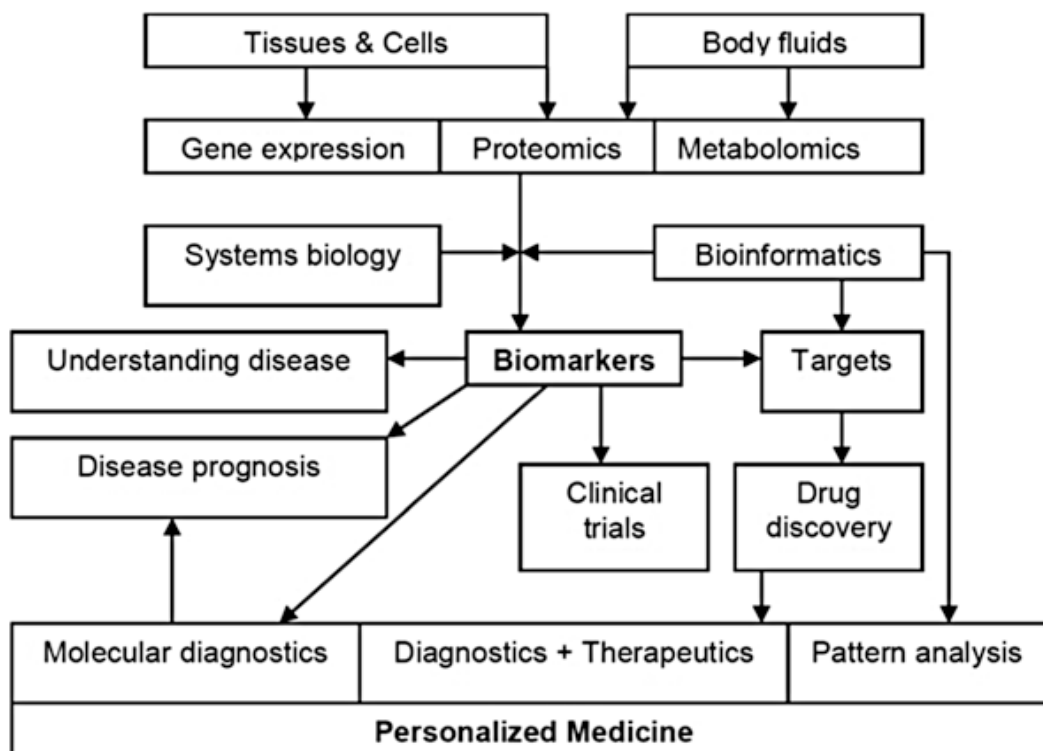
2. **Biomarkers' relationship to other technologies and healthcare:** On a variety of diagnostic biomarkers, drug research and discovery are based. They aid in anticipating the therapeutic medicine's potency and the negative effects of the medications. Study the pathomechanics and toxicity of illnesses 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. **[2]**

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

   - 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.
   - 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.
   - Different metabolism biomarkers and other biomarkers are used in clinical development to identify and categorise individuals, for example. CCR5 molecule.
   - 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.
   - 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.
   - When examining the connection between a drug's dosage or concentration and its results
   - To assess effectiveness in clinical trials
   - To further clarify the potential side effects of medication candidates.**[6]**
   - 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.
   - 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.

4. **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. An antibody, a biological molecule made specifically to bind to a biomarker, can be added to each transistor. The biomarker's presence is shown by a modest alteration in the transistor's ability to conduct electricity when the antibody binds to it. The long-term

objective is to create a circuit like a minuscule computer chip that can identify hundreds or thousands of indicators in a single test, allowing for the early detection of tumours that would otherwise go undiagnosed. **[2]**

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 **[2]**.

5. **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.

In the end, it's likely that digital biomarkers will open completely new ways to measure already-used phenomena. For instance, it's possible that total activity throughout the day or a composite of peak activity and continuous activity would serve as a better indicator of risk or susceptibility for developing new diseases, prognosis for those who already have a disease, or response to treatment (response biomarker).

Like this, it is likely that derivative measures from a variety of blood pressures and activities will be a better indicator of response to therapy for hypertension than seated resting blood pressure measurement when very frequent blood pressure measurements are possible. **[8,37,38]**

6. **Summary of various biomarker in different diseases**

Disease	Biomarkers	Study Of Outcome
COVID-19	Lymphocytes, IL-6, D-dimer, platelet count	Compared to non-ICU patients, ICU patients had higher plasma levels of IL-6, D-dimer, and platelets. Lymphopenia was more common in ICU patients than non-ICU patients [39]
	CRP, WCC	Critically severe patients had significantly higher CRP and WCC than severe or no severe patients [40]
	LDH, NC, CRP, platelet count	LDH, NC, CRP and platelet count were higher in refractory vs general patients. Refractory patients had more cases of lung abnormalities, suggesting these biomarkers correlate with development of disease [41]
	D-dimer, Platelet count, CRP lymphocytes and LDH	Although there were evident differences in lymphocytes (lymphocytopenia), platelet count (rose) and D-dimer (rose) in patients who experienced composite endpoints (ICU admission, invasive mechanical ventilation, and death) there was no statistical analysis performed [42]
	Lymphocytes, Albumin, Neutrophils, CRP, PaO2/FiO2, platelet count, creatinine and LDH	Ct value of virus correlated strongly with CRP, albumin and LDH among others. Murray score for ARDS correlated with the same markers. [43]
Sepsis	High mobility group-box 1 protein (HMGB-1)	No difference between survivors and non-survivors at 28 days [44,45]
	IL-1β	Increased in septic compared with non-septic individuals [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	CKD patients had elevated serum and urinary tenascin and TIMP-I compared with controls [51]
	u-L-FABP	u-L-FABP was a more sensitive biomarker of CKD progression than proteinuria. u-L-FABP increased with reduced kidney function [52]
	GGT	Serum GGT predicted microalbuminuria in those with hypertension and diabetes [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 is involved in signal transduction pathway and stimulate cell proliferation. ✓ p53 is involved in DNA damage, DNA repair and cell death. ✓ Mutations in p53 lead to genomic instability and malignant progression. Mutations in APC are considered "gatekeeper" mutations which initiate the carcinogenesis process [56,57]
Kidney cancer	kallikrein 1	Kallikreins are present on the walls of blood vessels of kidney and abnormal expression of the gene results in cancer development. [58,59]
Gastric cancer	LOH and PTEN	LOH and PTEN mutations have been detected in gastric cancer [60,61,62]
Thyroid cancer	CA125	Detected in cells isolated from circulating blood can distinguish malignant from benign follicular thyroid tumours [63]

VII. 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 support research on potential new biomarkers that could be used as surrogates in upcoming trials as well as the use of biomarkers in fundamental and clinical research. It is however easier to identify useful biomarkers for diagnosing an illness, for monitoring the response to a drug, and for studying disease progression the more that is understood about the underlying abnormalities associated with the condition and the mechanism of drug action. This is because the events linking disease pathogenesis to outcome are typically complex. For basic and clinical pharmacologists as well as other people involved in the identification of biomarkers, gathering this information might be difficult. Biomarkers 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.

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