

# Biomarkers: The Indispensable Healthcare Tools

Dr. Gauri Awasthi<sup>1</sup>

## Abstract

Biomarkers have reformed the game of diagnosis and prognosis of diseased conditions over the last 50 years. They have become powerful tools to classify patients according to their risk of disease progression, severity of the disease and guide drug therapy. The Food and Drug Administration (FDA) currently listed over 39 biomarkers that may be used as outcomes for FDA-approved therapeutics. Moreover, in association with NIH, FDA has published the B.E.S.T. resource to establish uniformity and harmonization categorically for the discussion of biomarkers. This article briefly touches upon this harmonization and uniformity brought in by FDA and NIH in terms of discussions related to biomarkers for the ease of everyone's understanding and information, its Biomarker Qualifying Programme, what are the Top 10 diseases causing deaths worldwide according to WHO and which biomarkers are used for their diagnosis and prognosis. Briefly, this article captures how far we have progressed in these 50 years and how elusive and distant the dream of gold standard biomarkers still is.

**Keywords:** Biomarkers, FDA, NIH, FDA-NIH Biomarker Working Group, B.E.S.T resource, WHO

**Conflict of Interest:** None declared

**Sources of Support:** None declared

## What is a Biomarker?

According to FDA-NIH Biomarker Working Group (FNBWG), a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions is the standard definition of a 'Biomarker'.

<sup>[1]</sup> The FNBWG laid this definition with the intention that consistent and mutually understood terminology will help accelerate development, validation and qualification of medical product development tools. Furthermore, the FNBWG established the B.E.S.T. (Biomarkers, Endpoints & other Tools) resource to elucidate the -information on Biomarkers efficiently.

<sup>[2]</sup> Interestingly, the B.E.S.T. glossary aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical

research, clinical practice, medical product development, and in the regulation of products by FDA. The rationale and intent to use the definitions included in the glossary when communicating on topics related to biomarkers is to ensure a consistent use of the terms and therefore, a common understanding of the issues, as per FDA.<sup>[2]</sup> To understand biomarkers, it is important to understand their categorization, their journey from being a novel putative hypothetic marker to making it to the clinical setup, a feat rarely achieved by many.<sup>[3,4]</sup>

## Biomarker Categorization

### 1. Clinical Biomarkers:

According to FNBWG, following are the seven categories of biomarkers based on their main clinical applications or diseased states (Figure 1).<sup>[3]</sup>

<sup>1</sup> Project & Portfolio Manager, Yashraj Biotechnology Limited, Mumbai-400705, India.

Email:gauri@yashrajbio.com

- **Diagnostic Biomarkers:** Confirm the presence or absence of a disease, thus, facilitating the diagnosis.
- **Monitoring Biomarkers:** Assess the presence, status or extent of a disease.
- **Response Biomarkers:** Implicate responses from the early phases of the discovery research to clinical trials and clinical practice.
- **Predictive Biomarkers:** Inform about the positive or negative effect after exposure to a medical product or environment agent.
- **Prognostic Biomarkers:** Indicate disease recurrence or progression in patients diagnosed with a disease.
- **Safety Biomarkers:** Help in the prediction of toxicity induced by drugs medical interventions or environmental agents' exposure
- **Susceptibility/Risk biomarkers:** Indicate the potential for developing a disease or medical condition in an individual not currently presenting clinical or medical conditions.

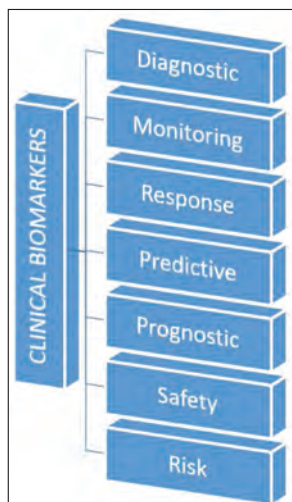


Figure 1: Seven categories of Biomarkers as per Clinical application or diseased state

## 2. Omics Biomarkers:

Based on the biomolecules, the biomarkers are grouped into the following six categories (Figure 2).<sup>[3]</sup>

- **Genomic Biomarkers:** A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.
- **Epigenomic Biomarkers:** Any epigenetic mark or altered epigenetic mechanism measured in the body fluids or tissues.
- **Pharmacogenomic Biomarkers:** Used to measure the response to the intake of drugs, metabolism of the drugs, the target and the pathophysiological characteristics of the patient etc.
- **Transcriptomic Biomarkers:** Measure the expression of the genes in an organism as a snapshot in different cells, tissues, organs and even in a whole body under different conditions or time points to understand gene regulation.
- **Proteomic Biomarkers:** Using advanced technologies such biomarkers analyse several proteins si-

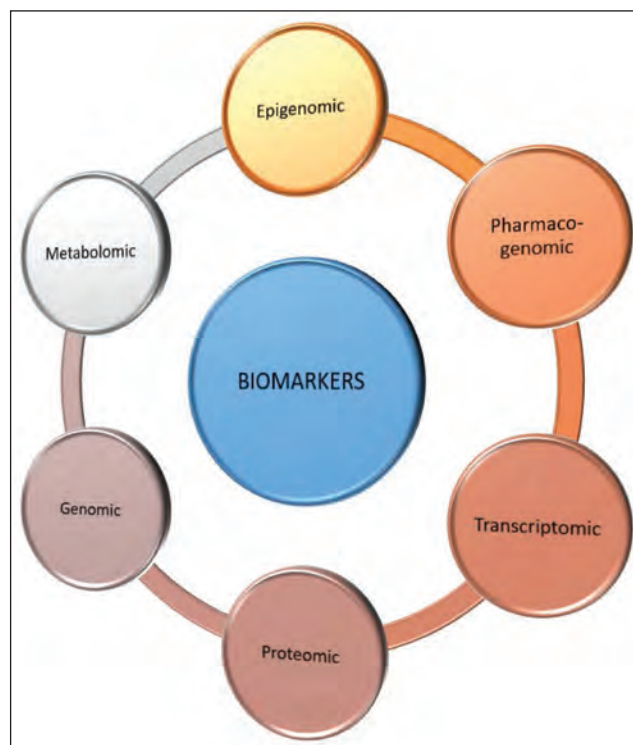


Figure 2: Six categories of Biomarkers as per biomolecules

multaneously in normal and diseased scenarios.

- **Metabolomic Biomarkers:** Presence of metabolites, the small molecule substrates, intermediates and products of metabolism in various complex matrices like cerebrospinal fluid (CSF), blood, urine, saliva, and other human fluids.

## FDA qualified Biomarkers

The FDA division, Centre for Drug Evaluation & Research (CDER) has initiated a Biomarker Qualification Program (BQP) to work with external stakeholders to develop biomarkers as drug development tools to advance public health by encouraging efficiencies and innovation in drug development.<sup>[5]</sup> In this regard, FDA has published a list of 39 qualified biomarkers (23 protein tumor markers and 16 clinical biomarkers) as per the FDA data published in July, 2021. Table 1a lists all the FDA qualified biomarkers as per FDA. Table 1b lists all the protein tumor markers currently used in clinical practice and approved by FDA.<sup>[6]</sup>

## Top 10 Diseases Causing the Most Deaths Worldwide with Prospective Biomarkers

According to a report published by WHO, following are the Top 10 diseases causing the most deaths worldwide (Figure 3).<sup>[7]</sup> The author has tried to map



Table 1: List of FDA qualified biomarkers

S.no	LIST OF FDA QUALIFIED BIOMARKERS	TYPES
<b>1</b>	<b>Urinary nephrotoxicity biomarkers</b>	
1.1	Albumin	Safety Biomarker
1.2	β2- Microglobulin	Safety Biomarker
1.3	Clusterin (CLU)	Safety Biomarker
1.4	Cystatin C (CysC)	Safety Biomarker
1.5	Kidney Injury Molecule-1 (KIM-1)	Safety Biomarker
1.6	Total Protein	Safety Biomarker
1.7	Trefoil factor-3	Safety Biomarker
1.8	Renal Papillary Antigen (RPA-1)	Safety Biomarker
1.9	N-acetyl-beta-D-glucosaminidase (NAG)	Safety Biomarker
1.10	Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Safety Biomarker
1.11	Osteopontin (OPN)	Safety Biomarker
<b>2</b>	<b>Serum/plasma cardiotoxicity biomarkers</b>	
2.1	Cardiac troponins T (cTnT) and I (cTnI)	Safety Biomarker
<b>3</b>	<b>Serum/broncho-alveolar lavage fluid biomarker</b>	
3.1	Galactomannan	Diagnostic biomarker
<b>4</b>	<b>Plasma biomarker</b>	
4.1	Fibrinogen	Prognostic biomarker
<b>5</b>	<b>Polycystic Kidney Disease biomarker</b>	
5.1	Total Kidney Volume (TKV)	Prognostic biomarker
<b>6</b>	<b>Malaria vaccine/Drug development</b>	
6.1	Plasmodium 18S rRNA/rDNA	Monitoring biomarker

the potential and proposed biomarkers used for the diagnosis and prognosis of these diseases based on the published literature.

- **Ischemic Heart Disease (IHD)/ Coronary Artery Disease (CAD)**

The deadliest disease in the world is coronary artery disease (CAD). Also called ischemic heart disease,

CAD occurs when the blood vessels that supply blood to the heart become narrow. Untreated CAD can lead to chest pain, heart failure, and arrhythmias.

**Biomarkers for Diagnosis and Prognosis of IHD/CAD:** hs-CRP, B-type natriuretic peptide (BNP) and NT-proB-type Natriuretic Peptide (NT-proBNP), T and I Troponins, Creatinine Kinase (CK-MB), Fatty Acid Binding Protein-Heart type (H-FABP), D-Dimer, Homodimeric Pregnancy-associated plasma protein A (PAPP-A).

- **Stroke**

A stroke occurs when an artery in the brain is blocked or leaks and this causes the oxygen-deprived brain cells to begin dying within minutes. During a stroke, one feels sudden numbness and confusion or has trouble walking and seeing.

**Biomarkers for Diagnosis and Prognosis of Stroke:** Vesicular Cell Adhesion Molecule

(V-CAM), Glial Fibrillary Acidic Protein (GFAP), Brain Derived Neurotrophic Factor (BDNF), Neuron Specific Enolase (NSE), Matrix metalloproteinase 9 (MMP-9), Tumour Necrosis Factor (TNF-α).

- **Lower Respiratory Infections (LRI)**

A lower respiratory infection is an infection in the

Table 2: List of FDA-approved protein tumor markers currently used in clinical practice

List of FDA-approved protein tumor markers currently used in clinical practice			
S.no	Biomarker	Clinical use	Cancer type
1	Pro2PSA	Discriminating cancer from benign disease	Prostate
2	ROMA (HE4+CA-125)	Prediction of malignancy	Ovarian
3	OVA1 (multiple proteins)	Prediction of malignancy	Ovarian
4	HE4	Monitoring recurrence or progression of disease	Ovarian
5	Fibrin/ fibrinogen degradation product (DR-70)	Monitoring progression of disease	Colorectal
6	AFP-L3%	Risk assessment for development of disease	Hepatocellular
7	Circulating Tumor Cells (EpCAM, CD45, cytokeratins 8, 18+, 19+)	Prediction of cancer progression and survival	Breast
8	p63 protein	Aid in differential diagnosis	Prostate
9	c-Kit	Detection of tumors, aid in selection of patients	Gastrointestinal stromal tumors
10	CA19-9	Monitoring disease status	Pancreatic
11	Estrogen receptor (ER)	Prognosis, response to therapy	Breast
12	Progesterone receptor (PR)	Prognosis, response to therapy	Breast
13	HER-2/neu	Assessment for therapy	Breast
14	CA-125	Monitoring disease progression, response to therapy	Ovarian
15	CA15-3	Monitoring disease response to therapy	Breast
16	CA27.29	Monitoring disease response to therapy	Breast
17	Free PSA	Discriminating cancer from benign disease	Prostate
18	Thyroglobulin	Aid in monitoring	Thyroid
19	Nuclear Mitotic Apparatus protein (NuMA, NMP22)	Diagnosis and monitoring of disease	Bladder
20	Alpha-fetoprotein (AFP)	Management of cancer	Testicular
21	Total PSA	Prostate cancer diagnosis and monitoring	Prostate
22	Carcino-embryonic antigen	Aid in management and prognosis	Not specified
23	Human hemoglobin (fecal occult blood)	Detection of fecal occult blood (home use)	Colorectal

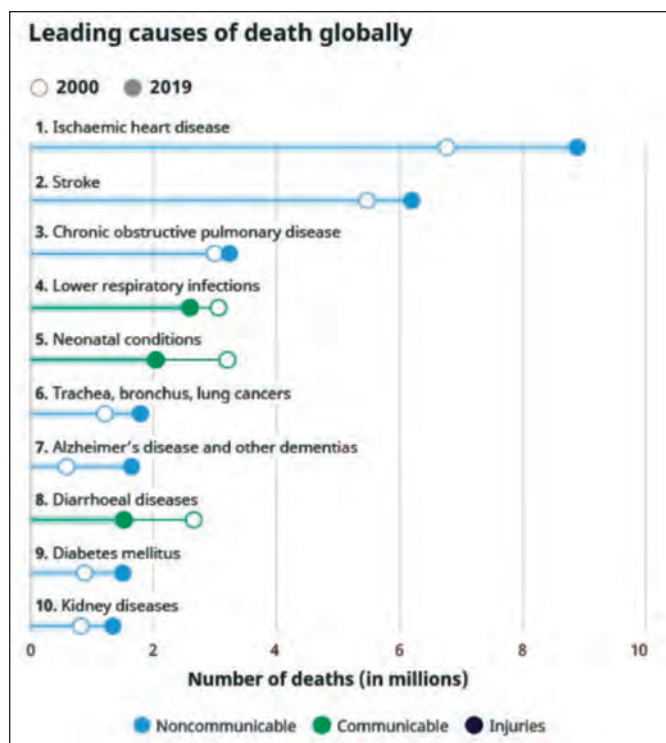


Figure 3: Top 10 diseases causing the most deaths worldwide

airways and lungs. It can occur due to influenza, flu, pneumonia, bronchitis or tuberculosis. Viruses and bacterias usually cause lower respiratory infections. Untreated lower respiratory infections can lead to breathing failure and death.

#### **Biomarkers for Diagnosis and Prognosis of LRI:**

Procalcitonin, high sensitivity-CRP, pro-atrial natriuretic peptide (MR-proANP), pro-vasopressin (CT-proAVP) and pro-adrenomedullin (pro-ADM).

#### **Chronic Obstructive Pulmonary Disease (COPD)**

Chronic obstructive pulmonary disease (COPD) is a long-term, progressive lung disease that makes breathing difficult. Chronic bronchitis and emphysema are types of COPD.

#### **Biomarkers for Diagnosis and Prognosis of COPD:**

TNF-Alpha, Interleukin-6 (IL-6), Troponin-T, Fibrinogen.

#### **Trachea, Bronchus, and Lung Cancers**

Respiratory cancers include cancers of the trachea, larynx, bronchus, and lungs. The main causes are smoking, second-hand smoke, and environmental toxins.

#### **Biomarkers for Diagnosis and Prognosis of Trachea, Bronchus, and Lung Cancers:**

Progastrin releasing peptide (Pro-GRP), Cytokeratin 19 fragment antigen (CYFRA 21-1), Epithelial Cellular

Adhesion Molecule (EpCAM), Carcinoembryonic antigen-related Cell Adhesion Molecules (CEACAM), Epidermal Growth Factor Receptor (EGFR).

#### **Diabetes Mellitus**

Diabetes is a group of diseases that affects insulin production and use. In type 1 diabetes, the pancreas can't produce insulin, while in type 2 diabetes, the pancreas doesn't produce enough insulin, or insulin can't be used effectively.

#### **Biomarkers for Diagnosis and Prognosis of Diabetes mellitus: HbA1c.**

#### **Alzheimer's Disease and Other Dementias**

Alzheimer's disease is a progressive disease that destroys memory and interrupts normal mental functions. These include thinking, reasoning, and typical behavior. The disease starts off by causing mild memory problems, difficulty recalling information, and slips in recollection. Over time, however, the disease progresses and one may not have memory of large periods of time.

#### **Biomarkers for Diagnosis and Prognosis of Alzheimer's Disease and Other Dementias: Beta-Amyloid, Tau-P.**

#### **Dehydration due to Diarrhoeal Diseases**

Diarrhoea is usually caused by an intestinal virus or bacteria transmitted through contaminated water or food. It is particularly widespread in developing nations with poor sanitary conditions. Diarrhoeal disease is the second top cause of death in children younger than 5 years. About 760,000, children die from diarrhoeal diseases each year.

#### **Biomarkers for Diagnosis and Prognosis of diarrhoeal diseases: C-Reactive protein, Calprotectin, Lactoferrin, Myeloperoxidase.**

#### **Tuberculosis**

Tuberculosis (TB) is a lung condition caused by bacteria called Mycobacterium tuberculosis. It's a treatable airborne bacterium, although some strains are resistant to conventional treatments. TB is one of the top causes of death in people who have HIV.

#### **Biomarkers for Diagnosis and Prognosis of Tuberculosis: Non-confirmatory markers are Interferon-gamma (IFN- $\gamma$ ), Early Secretory Antigenic Target (ESAT-6), Culture Filtrate Protein 10 (CFP10).**

#### **Cirrhosis**

Cirrhosis is the result of chronic or long-term scar-



ring and damage to the liver. The damage may be the result of a kidney disease, or it can be caused by conditions like hepatitis and chronic alcoholism.

**Biomarkers for Diagnosis and Prognosis of Cirrhosis:** Microfibril-associated glycoprotein 4 (MFAP-4), Tropomyosin.

## Conclusion

Biomarkers are indeed the indispensable tools of healthcare; however, we have only scratched the surface when it comes to our understanding of the biomarkers. More deeper and extensive search for biomarkers is the need of the hour, which will provide improved patient health care through early intervention and personalized medicine. While, we are making progress in certain disease areas (diabetes and cancer), we still have to catch up for autoimmune and CNS disorders.<sup>[3,4]</sup> Establishment of gold standard panel of biomarkers for all disease categories is the need of the hour in order to support the early interventions, precise diagnosis, prognosis and improvements in health outcomes and eventually make the world healthier and happier.

## References

1. Food and Drug Administration [Internet]. Available from: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/fda-biomarkers-working-group#:~:text=The%20mission%20of%20the%20FDA,may%20help%20address%20challenges%3B%20and>
2. Food and Drug Administration [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK326>
3. Manzanares J, Sala F, Gutiérrez MSG, Rueda FN. Biomarkers. Reference Module in Biomedical Sciences, Elsevier, 2021.
4. Aronson JK, Ferner RE. Biomarkers-A General Review. *CurrProtocPharmacol.* 2017 Mar 17;76(9.23):1-9.
5. Food and Drug Administration[Internet]. Available from: <https://www.fda.gov/drugs/biomarker-qualification-program/list-qualified-biomarkers>
6. Füzéry AK, Levin J, Chan MM, Chan DW. Translation of proteomic biomarkers into FDA approved cancer diagnostics: issues and challenges. *Clin Proteomics.* 2013 Oct 2;10(1):13.
7. World Health Organization [Internet]. The Top 10 Causes of Death. Dec 9, 2020. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>

+

## Doctors - Keep Abreast of the Latest Medical Advances & Benefit Your Practice Read & Refer The Indian Practitioner, India's foremost & oldest medical monthly now into the 75<sup>th</sup> year of publication.

Doctors would be aware that more than at any time in the past, medical technologies, advances in medicines & treatment protocols, surgical practices are moving ahead at lightning speed.

Many doctors say that they don't have time to read.

All the more reason to patronise The Indian practitioner written in brief, easy to read style, for your Quick Information Needs.

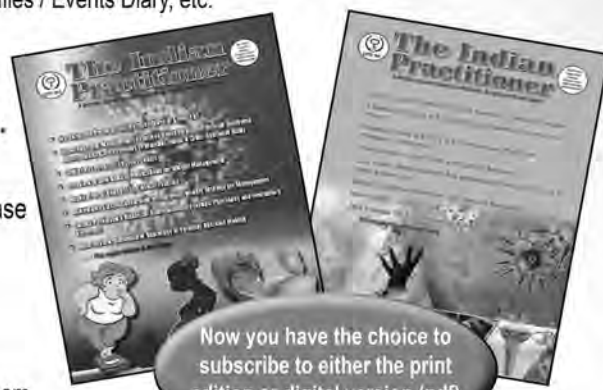
The Indian Practitioner covers Peer Reviewed Medical Articles on latest Medicines, Treatment Protocols, Surgical Practices, and from News to Important Happenings in the Medical World, Doctor / Hospital Profiles / Events Diary, etc.

**All In One – To keep You Updated.  
To Help You In Your Day-to-Day Practice.**

If your Hospital, Medical Centre, Medical College, Diagnostics Unit does not have atleast one copy, then please subscribe to **The Indian Practitioner NOW.**

**Ask for FREE sample copy.  
Digital Version also available.**

For further details contact, Email: [theindianpractitioner@gmail.com](mailto:theindianpractitioner@gmail.com)  
Mob: 9867532877/ 9821764647/ 9820210790



Now you have the choice to subscribe to either the print edition or digital version (pdf)