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BIOMARKERS: AN INDICATOR IN BIOLOGICAL SYSTEM

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Abstract: In last decade the use of biomarker is increased as early warning system in the evaluation of disease risk. In recent years, biomarkers plays an important role in the identifying the drug's mechanism of action, investigation of toxicity and patients response. Biomarkers used in clinical practice to personalize medication or healthcare. They are created by organs suffers with disease or body in response to various disease. The biomarkers are targeted to improve the diagnosis, prognosis, and therapeutics. The identification of ideal biomarkers holds the keep potential for personalized medicine and clinical outcomes. Clinical trials are essential for the improvement of healthcare and advancement of Medical Sciences. In this review, we discuss the history, various definitions, classifications, characteristics and discovery of biomarkers. The use of biomarkers for clinical applications depends on their efficacy in terms of disease diagnosis, disease staging, and treatment selection. The aim of the present review to inspire the reader to investigate the new approaches in biomarker research and development.

Keywords: Biomarker, Diagnosis, Heart Failure, Cancer, Imaging, Treatment.

I. INTRODUCTION:

In recent years, biomarkers have an important role in the Pharmaceutical discovery, which identifies the mechanism of action of drugs, investigate the toxicity of the drugs and identify the patients who gives better response to the therapy. Biomarkers are used to personalize medication or healthcare as well as analyze the safety of pharmaceuticals in clinical practice. Biomarkers are invented by body in response to various disease or by organs that suffers with the disease. Biomarkers can deliver as advance altering systems for our health. For example high level of cholesterol in our blood stream is common biomarker for heart disease. High level of lead in our blood which indicates the need of test for cognitive disorders and nervous system. The role of biomarkers have been aggressively increasing in guiding decision of every phase of drug development, from drug discovery and preclinical evaluation through each phase of clinical trials and into post marketing studies. Clinical trials are needed for the development of medical science and healthcare sector. For the clinical application biomarkers to be influenced on their efficacy in terms of disease diagnosis, disease staging and treatment selection. For many disease clinical endpoint such as mortality or disease recurrence may take a long time for efficient studies. For demonstration of biomarkers in biomedical research, the present review

highlights the history, classification, characteristics, and discovery of biomarkers. The approaches serve as adviser for biomarker researchers in pharmaceutical industry.

II. HISTORY & DEFINITION OF BIOMARKERS:

The term "Biological Marker" was introduced in 1950s. From last five decades, the various definitions of biomarkers modified according to scientific research and clinical progress. In 1973, the Biomarker term used first time by Rho et al. to the absence or presence of biological material. In 1987, Biomarker (biological marker) was defined as the indicator, which signaled the events in biological systems or sample that could be classified into the three classes: exposure, effect, and susceptibility markers.

In 2000, The National Institutes of Health Biomarkers Definitions Working Group defined the biomarker as the indicator of normal biologic & pathogenic processes or pharmacologic responses to a therapeutic intervention that are objectively measured and evaluated. This definition mainly accepted by the international definition of the biomarker in clinical pharmacology. Biomarkers are the characteristics that are mainly measured and evaluated as sign of normal biological, pathogenic processes or pharmacologic responses to a therapeutic intervention. Biomarker play an important role in the healthcare including detection of disease and its prevention and disease monitoring. They help to measure safety or toxicity of drug in our body.

III. CLASSIFICATION OF BIOMARKERS:

Biomarkers are classified on the basis of different parameters, including their genetic and molecular biology methods, characteristics, types of Biomarkers on the basis of clinical trials.

A). Genetic and molecular biology methods:

As per the genetic and molecular biology methods, Biomarkers are classified into three types: Type 0, 1, and 2. Type 0 biomarkers are measure of the natural history of disease and correlated with clinical outcomes. Type 1 biomarkers usually determine the biological effect of a therapeutic intervention. And Type 2 biomarkers are the equivalent of "surrogacy" markers.

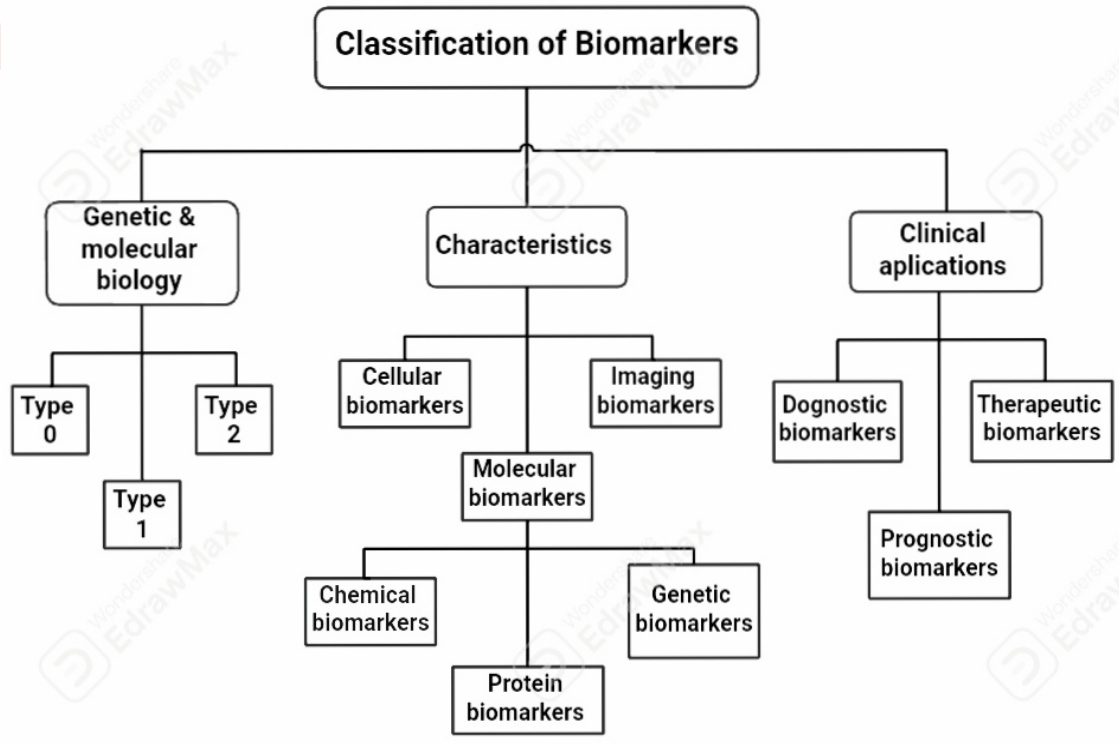

Fig.1. schematic presentation of classification of biomarkers.

B). Characteristics:

According to characteristics, Biomarkers can be classified into three types: molecular, cellular, and imaging biomarkers.

a). *Cellular Biomarkers*:

Cellular biomarkers are used in the both clinical laboratory test and act as biological and measurable indicators. These biomarkers are frequently measured and evaluated in body fluid, blood or soft tissue for prognosis or possible to reply to specific treatment. Cellular biomarkers allows cells to be isolated, sorted, quantified, and characterized by their morphology and physiology properties.

b). *Molecular Biomarkers:*

Molecular biomarkers are markers that are based on genomic and proteomic technique. Biomarkers plays an important role in diagnosis, prognosis, prediction, and therapeutic treatment of disease. They belong to non-imaging biomarkers that have biophysical properties, which allows their measurements in biological samples such as serum, plasma, cerebrospinal fluid and biopsies. They are classified into three subtypes: chemicals, protein, and genetic biomarkers.

i). Chemical biomarkers:

The chemical biomarkers contains the data of inborn errors, which are produced from metabolism or genetic conditions of cancer, disabilities and metabolism disorders, infectious types of disease, pollution exposure, dietary intake. These biomarkers are regulated by quantitatively and accurately with high precision and reliability.

ii). Protein biomarkers:

The protein biomarkers may be a single protein or panel of multiple proteins that help to diagnose illness, inform prognosis and monitor patient's biological response to the treatment. They are used as valuable indicator for the evaluation of information, immunity, and stress or related diseases, such as diabetes, neurological disorders, cancer and other syndromes, because protein is easier to measure than the complex biological events.

iii). Genetic biomarkers:

The genetic biomarker is a DNA sequence that causes disease or is associated with susceptibility to disease. They can be used to create genetic maps of whatever organism is being studied. DNA biomarkers linked with above 319 diseases or conditions. Genetic biomarkers are regulated in the DNA of nucleated cells.

c). Imaging Biomarkers:

Imaging biomarkers are one of the most commonly used path in clinical settings due to their availability, cost-effectiveness, and noninvasiveness. As compared to molecular biomarkers, early disease detection is a clinical advantage of imaging biomarkers. An imaging biomarker is characteristic that is frequently evaluated and measured as indicator for pathogenic and biological processes, or pharmacologic responses to a therapeutic intervention. These biomarkers are classified into three subtypes: positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI). PET tracks and measures the glucose uptake in the body cells, and used to assess the efficacy of oncologic treatments. CT is diagnostic modality which uses ionizing radiation for monitor the tumor status and obtaining three-dimensional images (3D) from the human body. MRI is most widely used to understand neurodegenerative and cancer disease. It has many benefits such as its high spatial resolution, superior soft-tissue contrast and ability to assess physiology. Ex. Oxygenation, Diffusion and Vascularization. They are necessary to mention that other methods, such as X-ray, endoscopic, mammography, optical coherence tomography, ultrasonography, and near-infrared

spectroscopy. They are applied as imaging biomarkers to get information for the diagnostics of various diseases. Example of imaging biomarkers are X-ray, CT or MRI.

C). Types of Biomarkers on the basis of Clinical applications:

According to their classification in different stages of diseases, biomarkers can be classified into different types such as Diagnostic, Prognostic, Therapeutic, Pharmacodynamics/Response, Predictive, Susceptibility/Risk and Safety biomarkers as shown in the fig. 2. The important use of biomarkers in clinical medicine is the detection and diagnosis of chromosome and single-gene disorders. Cellular biomarkers are biological and measurable indicators that can be used in clinical and laboratory tests.

a). Diagnostic biomarkers:

A diagnostic biomarkers detects or conforms the presence of disease or identifies an individual with types of disease. This biomarkers used to identify people with disease and redefine the classification of disease. These are biological parameters that are used to diagnosis of diseases. The examples of diagnostic biomarkers are blood pressure, body temperature, and body mass index. Chest X-ray one of the most commonly performed diagnostic medical tests.

b). Prognostic biomarkers:

Prognostic biomarkers provides information about the status of disease by screening and monitoring of disease. For example, blood pressure and cholesterol for cardiovascular diseases, N-acetyl-beta-D-glucosaminidase for heart failure and renal impairment, D-serine for antidepressant response to ketamine and osteocalcin for bone and skeleton metastasis as the prognostic biomarkers they are used. Prostate-specific antigen (PSA) is used as the prognostic biomarker for assessing the disease progression in prostate cancer patients. Plasma fibrinogen can be used as prognostic biomarker for patients with chronic obstructive pulmonary disorder (COPD) to determine risk.

c). Therapeutic biomarkers:

Therapeutic biomarkers plays an important role in monitoring the clinical response and the effect of therapy on stress or disease. And they are effective in the treatment of disease. These biomarkers are mainly proteins such as m-RNAs and exosomes. These are mainly used for targeted therapies. CA15-3 biomarker use to monitor the therapy for breast cancer treatment. HbA1c biomarker used to monitor the progress of anti-diabetic therapy. The serum tumor biomarker used to monitor the therapy for breast cancer treatment.

d). Pharmacodynamics/Response biomarkers:

Pharmacodynamics biomarkers are indicators of drug's pharmacological action on its target or targets. For example, the target might be a receptor molecule that initiates a complex signaling cascade. Changes in the level of protein along the signaling cascade or modifications to them could be considered pharmacodynamics responses. These biomarkers used to examine the link between drug regimen, target effect and biological tumor response.

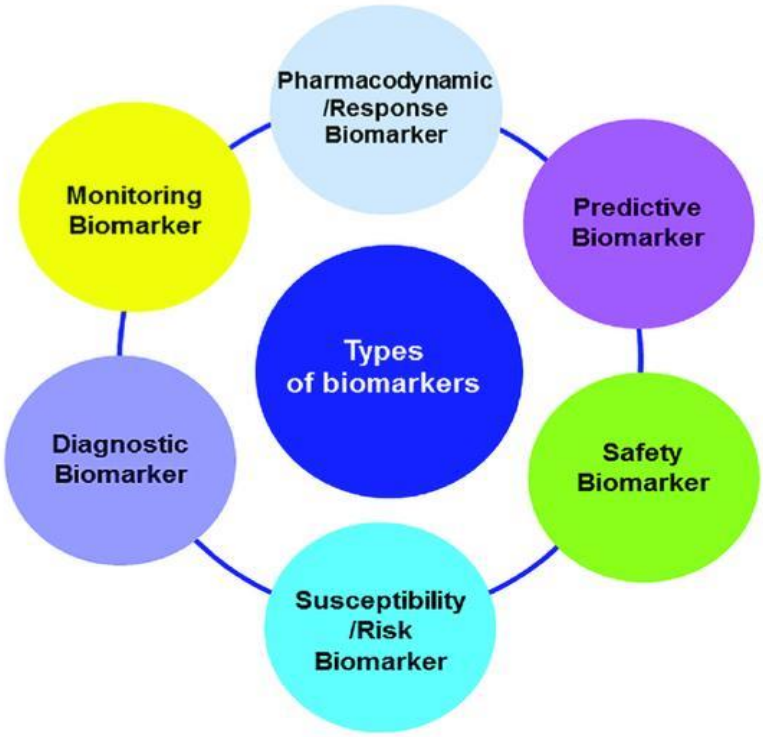

Fig.2. classification of biomarkers based on clinical applications.

c). Predictive biomarkers:

Predictive biomarkers can be calculate the possibility of response or lack of response of a particular therapy, and allows identification of patients most likely to benefit from a given treatment. The examples of the biomarkers distinguish the disease process or medical condition include Protein level in diseased tissues, mutation in tumors, or serum protein levels pregnancy. An example of predictive biomarker in breast cancer is expression of the HER2/ neu protein. Predictive biomarkers in oncology are features that indicates sensitivity or resistance to a specific type of therapy. One method to identify biomarkers is through in vitro screens, using cancer cell line panels or more recently tumor organoids.

d). Susceptibility / Risk biomarkers:

Susceptibility/Risk biomarker is a biomarker that is associated with an increased or decreased chance of a developing disease or medical condition in an individual from the clinical standpoint. These biomarkers indicates the potential for developing a disease or medical condition in an individual who does not have clinically apparent disease or the medical condition.

e). Safety biomarkers:

Safety biomarker measured before or after submission to a medical products or an environmental agent to indicate the possibility, presence or extent of toxicity as an adverse effect. For example, serum lead levels may be evaluated to detect exposure to lead or urinary cotinine levels may be evaluated to detect exposure to nicotine (i.e. cigarette smoke). The safety biomarkers can needed treatment. Ex hypokalemia with a diuretic can indicate need for potassium supplementation, and hyperkalemia with an aldosterone antagonist can indicate need for dose adjustment or increase in loop diuretics. Periodic monitoring of such biomarkers is required for many drugs to ensure that their potential toxicity is detected and managed. Ideally, a safety biomarker would signal developing toxicity.

IV. BIOMARKERS DISCOVERY:

Biomarker discovery is a medical term describing the process by which biomarkers are discovered. Most commonly use the blood tests in medicine are known biomarkers. Biomarkers discovery starts with defining a target 'normal' biological process, pathogenic process or pharmacological response that biomarker could highlight. As part of this process multiple candidates will be identified.

In the past decade, the several changes occurs in the diagnosis and investigation of disease due to appearance of advanced technologies and promotion in chemistry and physics. These evaluations leads to the discovery of new and innovative disease markers in endocrine diseases, genetic disorders, autoimmune disorders, sensory damage, intestinal disease, etc. In many cases, these evaluations leads to the discovery of biomarkers explained by traditional or conventional methods, such as histopathology, or clinical biochemistry. The basic purpose of biomarker discovery is to recognize a small group of characteristics that can be used to classify a new sample efficiently and cost-effectively, and to apply it into the clinical practice. Over the past decade, the discovery of biomarkers has significantly increased. The biological techniques and chemo metrics can be used for the development and discovery of biomarker s. In the study of biomarker discovery the study design, sample measurement, sample collection procedure, data analysis, and interpretation are clinical parameters. Basically, targeted and untargeted are two main types of approaches that have been used for biomarker discovery from bio-fluid sources such as blood, urine, milk, and cell culture media. The targeted approach allows for the discovery of new biomarkers that may be produced or released throughout the disease condition and measured by particular methods. An untargeted approach is an objective approach to biomarker discovery that depends on a range of "omics" profiling techniques used for regular screening body fluids. The molecular biomarkers discovered by using genomics, proteomics, metabolomics, lipidomics, transcriptomic, glycomics, and secretomics platforms.

V. APPLICATION OF BIOMARKERS:

The applications of biomarker in medicine for screening, prognosis, diagnosis, and therapy of diseases have much expanded. Some of the various applications of biomarkers are presented in the following section.

A). Heart Failure:

Heart failure (HF) is caused by various cardiac and extracardic mechanisms, leading to a complex clinical disease with numerous phenotypes. There are two types of heart failure, 1). Systolic failure: The left ventricle loses its ability to contract normally. The heart cannot pump with enough force to push enough blood into circulation. 2). Diastolic failure: The left ventricle loses its ability to relax normally because the muscle has become stiff. Biomarkers have multiple roles such as diagnosing, monitoring therapy, assessing prognosis, and stratifying risk in cardiovascular diseases in clinical management. Imaging Biomarkers provide important insights into the functional and structural abnormalities of the heart. Protein biomarkers are used to predict the prognosis of heart failure are release from the heart, or they are release from other cells as a systematic response to heart failure. Protein based biomarkers are the clinical gold standard for heart failure prediction because they provides many benefits such as simple handling, low cost and easy accessibility. However, protein based biomarkers are not specific for heart failure then prognostic indicates for heart failure are used. For the management of heart failure further investigation is required to determine the ideal biomarker combination.

B). Cancer:

Cancer is the disease in which abnormal cells divide uncontrollably and destroy body tissue. It is most important cause of death worldwide, and it is spatial and complex genetic disease marked by metastasis in vital organs of the body. Cancer biomarker play an important role in enhancing the knowledge of cancer process in clinical practice. Cancer biomarkers are proposed for use in assessing cancer risk, studying tumor host interactions, and reflecting tumor load and cellular activity. Cancer biomarkers are found in the circulation

(blood, plasma, serum), in secretions (urine, stools, sputum, or nipple discharge), or in other biological fluids. An ideal tumor biomarker should have the following characteristics such as a) produced by only tumor cells, b) detectable in early stages in the blood of cancer patients, c) associated with the tumor burden and provided with an adequate lead time, d) undetectable in the blood or other biological fluids of healthy people of patients, e) easy to measure even in small amounts and with little preparation, using a reliable test.

The various biomarkers are used for various cancers such as KARS mutation as prognostic biomarkers in pancreatic cancer, serum microRNA-21 as diagnostic biomarker in breast cancer, pro calcitonin as biomarker for medullary thyroid cancer, cigarette smoking as a biomarker in lungs cancer, and Carcinoembryonic antigen in colon, medullary thyroid, and stomach cancer.

C). Neurological diseases:

Biomarkers plays an important role in the prevention and treatment of brain diseases, and neurological and neuropsychiatric disorders such as Parkinson, Alzheimer, Stroke and epilepsy. Plasma, urine, cerebrospinal fluid, saliva, blood, and other body fluids are used as various sources for diagnosis, and treatment of various brain disorders and diseases. 4-hydroxy-2-3-noenal, angiogenin and cystatin-c are candidate protein biomarkers for the diagnosis or Progression of motor neuron disease. The N-acetyl aspartate metabolite, myoinositol metabolite, soluble glycoprotein V and clusterin are the various types of biomarkers that are used for neurological diseases. The blood biomarkers of various brain injuries such as fibrinogen, D-dimer, and troponin treat brain injuries in COVID-19 patients. The combination of biomarker identification methods using modern genomics, proteomics, metabolomics technologies.

D). Lung diseases:

The lungs disease or respiratory disorders are clinical disorders affecting the lungs, such as asthma, chronic obstructive pulmonary disease, pneumonia, tuberculosis, pleural effusion, lung cancer and many other lung disorder. There are various biomarkers for diagnosing lung disease such as malondialdehyde, a lipids peroxidation product is reliable, cheap, and user friendly biomarker. For detecting the pleural effusion, YKL-40, a glycoprotein with three amino acids tyrosine, lysine and leucine in N-terminal are proved as biomarker. MRI and CT lung biomarkers can be used in vivo evaluation of lung biomechanics to identify lung abnormalities. Nitric oxide, acetone, hydrogen cyanide, hydrogen peroxide, carbon monoxide, acetone, isoprene, ethyl butyrate, methanol, sulfides and nitrates are exhaled volatile and nonvolatile compound which are considered as possible biomarkers for lung disease.

E). Liver diseases:

Liver is the vital organ in the human body that plays an important role in digestion of food, distribution of nutrients, and conversion of food into energy and store it, and helps to filter toxic substances and remove poison from the bloodstream. The liver is effected by various diseases such as cancer, hepatitis, fatty liver disease, Wilson's disease, chronic drug, drinking, and poison. The diagnosis of liver disease is difficult, but using the biomarkers can be diagnosed the liver diseases. The injury of liver can be determined by liver function tests, including albumin, alanine aminotransferase, and aspartate transaminase associated with alkaline phosphate. Alanine aminotransferase is a surrogate biomarker that is highly specific for liver disease and easy to detect in the blood stream. For liver disease, hyaluronic acid, bilirubin, cytokines, laminin, and fibroblast growth factors are used as potential biomarkers.

F). Kidney diseases:

The kidneys play an important role in filtration of blood, to remove toxins, and control the volume of various body fluids. N-acetyl-beta-D-glucosaminidase, fatty acids-binding proteins, and cysteine-rich proteins are used as kidney disease biomarkers. Hepcidin-25 is acts as an iron binding protein associated with acute kidney

injury and used as novel kidney biomarker in serum. The level of D-serine plasma and urine is commonly as dual biomarker for the reflection of kidney function and diseases.

H). Gastrointestinal diseases:

Gastrointestinal diseases are the diseases from the mouth to anus consisting of all the organs of the human digestive system. For the diagnosis of gastrointestinal diseases the intermediates of metabolism are used as biomarkers. Volatile organic compounds such as acetone, ethanol, indole, ammonia, carbon disulfide, and acetic acid are used as biomarkers. Calprotectin is used as biomarker for active inflammatory bowel disease (IBD) and digestive disorders. The fatty-acid binding protein evaluated as diagnostic biomarker in gastrointestinal diseases. Urinary metabolomics such as tri-carboxylic acid and amino acids are used as noninvasive biomarkers for gastrointestinal diseases.

VI. BIOMARKER DEVELOPMENT PROCESS:

Biomarker discovery and development is a lengthy process requiring hypothesis generation, sample collection, data collection, data analysis, assay development, assay validation and finally regulatory approval before it can be used clinically. The process of development of biomarker involves the several steps that begins with the discovery of the biomarker in healthy and diseased samples. The biomarker development process comprises consecutive phases: pre-analytical and analytical validation, clinical validation, regulatory approval, and demonstration of clinical utility. The pre-analytical phase regulates indicators and analyzes quality indicators like process, storage, and sample collection. A biomarker is connected to clinical and biological endpoints through qualification, a graded evidential process.

However, there are some challenges in the development of biomarkers, such as:

- For some biomarkers the scientific basis is not verified always, create some difficulties in the qualification and validation of biomarkers in the future. However, it is important to avoid interpreting biomarker measurements and connecting biomarker to a disease.
- The cost of a development of biomarkers may increase due to longer clinical trials or more testing requirements.
- It takes a lot of time and resources to develop and qualify biomarkers. For qualification purpose individual drug regulatory approval, convincing evidence of a favorable benefit-risk analysis is typically needed.

VII. STATISTICAL METHODS FOR ASSESSMENT AND EVALUATION OF NEW BIOMARKERS:

After the discovery of biomarkers, the evaluation of biomarkers is necessary, especially for the diagnostic biomarkers. For the assessment and evaluation of new biomarkers analytical methods are used.

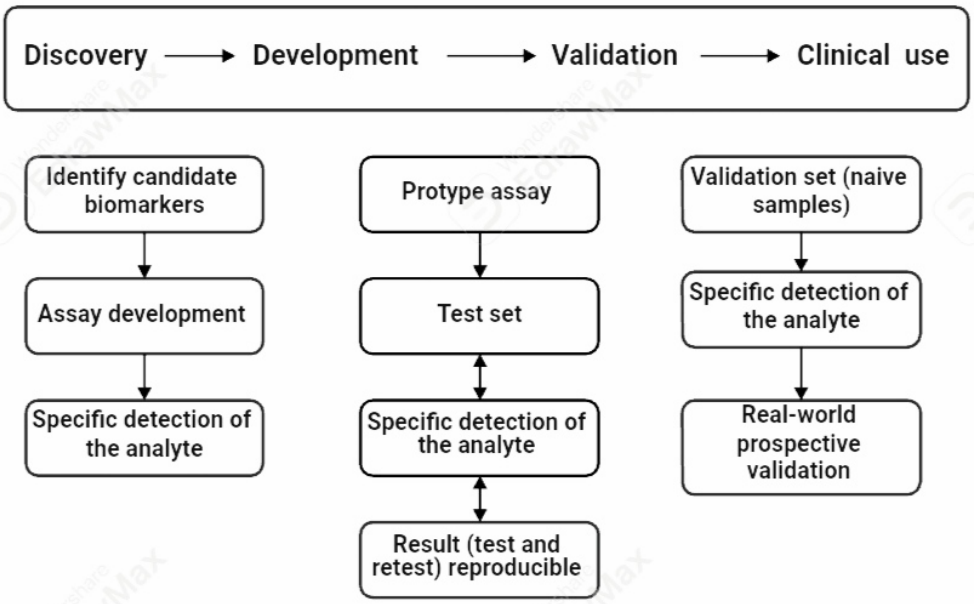

Fig.3. framework for the development of biomarkers.

Biomarkers evaluation needs proper statistical analysis for representation of valid conclusion of new biomarkers before introduced into clinical practice. The obtained datasets are analyzed by the classical statistical and multivariate methods. The classical statistical methods are used for the identification of biomarkers by monovariate statistical tests so each biomarker is considered independent of the other. The classical statistical methods are suffers from the some weaknesses, such as lack of statistical power, lack of interpretable result, and some exceptions of complex relationships between variables.

VIII. CONCLUSION:

In summary, the biomarkers are the part of novel and ideal clinical device in the diagnosis, prognosis, and treatment of various diseases. The biomarkers used for the study of various aspects of diseases, drug development, and monitoring the potential effects of therapeutic interventions. As compared to current measurements, biomarkers are likely to provide tests with specificity and sensitivity, upgrade the decision making process, and easy to development of therapies.

For the improvement of the healthcare and produce cutting-edge therapeutics, lot of efforts made to explore the biomarker borderline in search of new or better biomarkers. The effective biomarker must affect the clinical evaluation to improve patient. Clinical decisions are based on the test results that must be beneficial. Biomarkers reduce cost and negative effects and prevent the death in the risk management setting. The effectiveness of a biomarker is determined by comparing with ideal biomarker and explore its properties.

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