REVIEW ARTICLE

THE EMERGING FIELD OF BIOMARKERS

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ABSTRACT

Biomarkers or biological markers as the name suggests are by definition objective, quantifiable characteristics of biological processes. Before a biological marker is used in human health studies, its validation is fundamental; therefore, the selection and approval process requires careful consideration of specificity and sensitivity, and accuracy. This article would highlight about the various definitions, and a conceptual framework to understand the roles of biomarkers in clinical research.

KEY WORDS

Biomarkers, biologic process, clinical research

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INTRODUCTION

The term "biomarker", a portmanteau of "biological marker", refers to a broad subcategory of medical signs - that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly.[1-3] The term biomarker (biological marker) was introduced in 1989 as a Medical Subject Heading (MeSH) term: "measurable and quantifiable biological parameters (e.g. specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health - and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, epidemiologic studies, etc".[1,2] The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence as primary endpoints in clinical trials is now accepted almost without question. The National Institute of Health (NIH) working group standardized the definition as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[2-4] A joint venture on chemical safety, the International Programme on Chemical Safety, led by the World Health Organization (WHO) and in coordination with the United Nations and the International Labor Organization, has defined 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".[5] Thus, a simplistic way to think of biomarkers is as indicators of disease trait (risk factor or risk marker), disease state (preclinical or clinical), or disease rate (progression). Before diagnosis, markers could be used for screening and risk assessment. During diagnosis, markers can determine staging, grading, and selection of initial therapy. Later, they can be used to monitor therapy, select additional therapy, or monitor recurrent diseases. Thus identifying biomarkers include all diagnostic tests, imaging technologies, and any other objective measures of a person's health status.

Biomarkers characterization & their uses:

An ideal biomarker should be safe and easy to measure. There are different types of biomarkers; the ideal biomarker must be specific, sensitive, predictive, rapid, economical, non-invasive, and stable in vivo and in vitro. Additionally, it must have enough preclinical and clinical relevance to modify decisions regarding the pathological process in which applies. To identify biomarkers as surrogate endpoints requires the determination of relevance and validity. Relevance refers to a biomarker's ability to appropriately provide clinically relevant information on questions of interest to the public, healthcare providers, or health policy officials. Validity refers to the need to characterize a biomarker's effectiveness or utility as a surrogate endpoint.[1] Unfortunately, validity is not typically black or white, but instead a spectrum. The cost of follow-up tests should be relatively low, there should be proven treatment to modify the biomarker. It should be consistent across genders and ethnic groups. Before biomarkers can be used for personalized medicine, they must be sorted and assigned defined roles. Some researchers have in fact rejected the term validation as "unsuitable" to the study of biomarkers since it suggests that there can be a complete biological understanding of the relationship between a given biomarker and a clinical endpoint, an assumption they reject.[1-5] Instead, an alternate term that has been offered is "evaluation" to refer to the ongoing process of studying biomarker's success at acting as surrogates for individual clinical endpoints.[2] Biomarkers can be categorized into four different categories[3-6] each with a unique diagnostic application which are as follows:

a. Screening biomarkers : These markers are used to differentiate a diseased physiological state (preferably in an early state) from a normal state. Ideally, patients would be tested routinely for these screening markers, giving them early detection. An example of screening markers is prostate-specific antigen, the current standard of prostate cancer screening.

b. Prognostic biomarkers: These markers used to predict the natural outcome of a confirmed disease. For example, these markers could be used to discriminate an aggressive cancer likely to recur from one which is less likely to recur.

c. Predictive biomarkers: These would be used to predict a patient's potential benefit from a drug. These predictive markers are the main guide in pairing a patient with the optimal drug. For example, breast cancer patients are screened for extra copies of the ERBB2gene.

d. Pharmacodynamic biomarkers: They can be observed to determine the effectiveness of the drug and decide drug dosage during treatment.

These four types of biomarkers allow for better disease detection, treatment selection, and recovery monitoring. Used in parallel to traditional doctor assessments, biomarkers will establish an accurate and robust decision tree to tailor treatments for patients.[5,6]

Biomarkers are much better predicators of disease (illness)and death than self-reported health status.[6-8] Even when individuals have already provided information on their physical, mental, and cognitive health, biomarkers provide additional information that improves our ability to predict whether an individual is likely to live or die. Biomarkers collected in physical exams, such as markers of cardiovascular disease and diabetes, and those not usually part of routine physicals, such as immune markers, are useful predictors of health.

An individual biomarker, once it exceeds a certain threshold, is an indicator of risk for future illness due to problems in a particular biological system. Disease conditions are most often signified by dysregulation of complex biological pathways involving multiple interacting gene products.[8,9] However, such indices do not tell us about specific multiple paths that may produce high risk of adverse health outcomes. One study found that older males were more frequently at high risk for adverse health outcomes due to a combination of impairments in the functioning of the immune system and the neuro-endocrine system—the interaction of the nervous system and the endocrine system.[8-10]

Discovery & life of biomarker:

We are constantly using different biomarkers in day to day clinical practice. For example, biomarkers can be anatomical or signal other changes that can be viewed with different imaging techniques.[11,12] Biomarkers have been approved by the U.S Food and Drug Administration (FDA) regulation for use as surrogate endpoints in the treatment development process.[1,10,12] The FDA allows provisional intervention approval with surrogate marker-defined efficacy but further requires phase IV follow-up studies that prove relevant clinical endpoint correlation exists.[1-5,8] Some cautious researchers and commentators have suggested that biomarkers are most effective in and best left for use as endpoints in phase I and phase II trials. Their use can help determine what potential treatments are worth the effort and resources of a large, well-powered phase III trial.[1,11-13] The biological process that led to improved clinical outcomes, in other words, was not captured by the biological mechanism proposed and predicted by the researchers.

Identification of widening periodontal ligament spaces, inter-proximal radiolucent areas in the

dentition are all biomarkers we use to elucidate pathological processes and make diagnosis. Applying clinical measures to calculate clinical attachment loss and periodontal disease progression is another use of biomarkers. However, a biomarker often is a surrogate measure of an actual disease process-clinical attachment loss to assess an inflammatory response, and therefore the interpretation and use of biomarkers must be changed and adjusted continuously in accordance with improved device and technology.

In a study, the prevalence of periodontitis in dentate adults 30 years and older in the United States was estimated to be more than 47 percent.[13] This new assessment is 1.7 to 2.4 times higher than previous estimates of periodontitis. Among other things, it highlights the drawbacks of relying on epidemiologic studies that extrapolate findings from limited clinical measures. It also underscores the need for a globally agreed-on definition of a specific disease that should be based on the same calculations and combinations of biomarkers, such as the level of clinical attachment loss, bleeding on probing or the number of sites to be measured around a tooth.

This challenge of finding better and more accurate biomarkers to understand the disease spectrum as they relate to risk stratification, diagnosis, prognosis and overall pathology is not only unique to dentistry, but in recognition of the need to develop more precise and better customized individualized medical care. Therefore, an entire discipline for studying biomarkers is emerging. Another example of how to improve disease management is the use of biomarkers to predict or detect the progression risk for oral premalignant lesions. Studying a specific group of molecular markers obtained from a large prospective group of patients at different stages of oral dysplasia, researchers were able to develop a model for predicting progression to cancer.[13-15] This line of research, using biomarkers, may improve strategies for screening, preventing and treating the oral cancer.

The biomarker can be defined as an objectively measured biological characteristic that reflects normal biological processes, pathogenic processes or even pharmacologic responses to therapeutic interventions.[16] Broadly, it can be described as cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids.[17,18]

CONCLUSION

Biomarkers play a critical role in improving the drug development process as well as in the larger biomedical research enterprise. Biomarkers could only serve as true replacements for clinical relevant endpoints if we completely understood the normal physiology of a biological process, the pathophysiology of that process in the disease state, and effects of an intervention - pharmacological, device, or otherwise - on these processes. Refinement of existing biomarkers to estimate the risk of developing disease, to establish a state of health or illness, to define prognostic criteria, and to guide and evaluate treatment strategies, provides a foundation for improving patient care. Proper understanding of the use biomarkers to determine treatment decisions gives us a rigid framework to guide individualized patient care and research. The choice of a biomarker often is based on its bioavailability, sensitivity and cost, all these factors that contribute to its likelihood of being misused and misinterpreted, or of instilling a false sense of reassurance that results in diminished enthusiasm for searching newer and better options. Biomarkersare ubiquitous throughout all disciplines of medical sciences, including the field of dentistry. They provide a dynamic and powerful approach to understanding the disease process. The emerging and overgrowing field of dentistry is at bidirectional way in which we can either continue to use our traditional tools and biomarkers to define oral disease or welcome what is emerging new as a precision tool.

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