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Editorial

Biomarkers: The Past, Present and The Future

Biomarkers (Biological Markers) in simple words are 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. In the past biomarkers included study of pulse, blood pressure, basic chemistries, basic laboratory investigations of blood and tissues. Recently National Institute of Health and Food and Drug administration biomarker Working Group (2015) defined biomarker as "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".

Biomarkers define effects of treatments, interventions, and even unintended environmental exposure.They can be categorized into diagnostic, Susceptibility/Risk, Prognostic, Predictive, Pharmacodynamics/ Response Monitoring and Safety markers. They can be used alone or in combination to assess health or disease state of an individual.Every biological system, example cardiovascular system, metabolic system or immune systems have specific biomarkers.

Classification is based on

1. Characteristics. Imaging biomarkers (CT, PET, and MRI). Molecular biomarkers (non-imaging biomarkers-measurements in biological samples example, plasma, serum, cerebrospinal fluid, Bronchoalveolar cleavage, and biopsy) nucleic acids based biomarkers gene mutations or polymorphisms quantitative gene expression molecules.

2. Decision making in early drug development.

3. Genetic and molecular biology methods.

- Type 0: Natural history markers - natural history of a disease and correlates longitudinally with known clinical indices.
- Type 1: Drug activity markers - captures the effect of a therapeutic intervention in accordance with its mechanism of action.
- Type 2: Surrogate markers - intended to substitute for a clinical end point A surrogate end point is expected to predict clinical benefit or lack of benefit on the basis of epidemiology, therapeutic, Pathophysiological or other scientific evidence.

4. Diagnostic biomarkers to define a popula tion with a specific disease. Example; cardiac troponin for the diagnosis of myocardial infarction.

5. Prognostic biomarkers-cancer biomarkers, and biomarkers for monitoring the clinical response to an intervention - Her-2/ neu in breast cancer, EGFR expression in colorectal cancer, HbA1c in anti-diabetic treatment.

6. Predictive biomarkers define population that might respond more favourably to a particular intervention from an efficacy or safety perspective. NGAL in diabetic nephropathy.

Steps to be followed for a biomarker if to be accepted for use Discovery/Identification → confirmation → validation and refinement/ established relevance to population → Adoption/ Identify clinical utility.

An ideal marker for its acceptability needs to have certain characteristics that make it appropriate for checking a particular disease condition. It should be safe and easy to measure, cost efficient to follow up, modifiable with treatment, consistent across gender and ethnic groups and easily incorporated as a part of

routine medical examination. Uses of laboratory measured biomarkers in clinical research are not new. Key issue with biomarkers is determination of relationship between any measurable biomarker and relevant clinical endpoint. Surrogate endpoint versus clinical endpoint. Surrogate endpoint is a biomarker intended to substitute for a clinical endpoint. Clinical end points characterize how a subject in a study or clinical trial feels, functions, or survive. Surrogate endpoints can be substituted for clinically meaningful endpoints only when there are solid scientific evidences such as epidemiological, therapeutic, and/or pathophysiological factors that consistently and accurately predicts a clinical outcome either a benefit or harm. Surrogate endpoint biomarker can serve as a stand-in, but not a replacement of a clinical endpoint.

A biomarker proposed as a surrogate endpoint should be capable of being measured objectively and reproducibly. The internal validation of surrogate endpoint must be precise, reproducible and accurate within the study group and disease condition and must correlate with clinical endpoint. The external validation should look into the predictive power of the surrogate endpoint in other populations or in other related treatment studies.

Limitations of surrogate biomarkers

- Present substantial risks when trial designers confuse them with clinical endpoints and serve as true replacements for clinical relevant endpoints.
- Should always have as ultimate measures, clinical outcomes, particularly for retrospective analysis of biomarker correlation success.
- Require continual re-evaluation of the relationship between surrogate endpoints and true clinical endpoints or else a treating physician or a researcher may risk approving whole classes of drugs and diagnostics that either have no additional benefit or, worse that harm patients.
- Needs constant validation.

Conclusion

Biomarkers are of great use as diagnostic, predictive, prognostic and therapeutic (drug development) markers. New biomarkers must be a representative of clinical endpoints which has to be validated and re-evaluated constantly for its use in clinical practice.

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