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Biomarkers: Its Novel Application

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Advances in biotechnology and improved understanding of cancer and disease biology have shifted the treatment paradigm to targeted therapy. We have enhanced our ability to guide application of new and existing treatments with development, assay verification, biological validation and application of biomarkers. However, to be successful, we need a thorough understanding of the relationship between putative biomarkers and treatment effects. We must consider new clinical trial designs that may consist of randomized cohorts, prospectively planned endpoints, and/or post-hoc analyses. These strategies will succeed if reliable, adequately powered, biologically validated biomarkers are identified and appropriately applied for prospective patient selection via clinical trials. Continued inclusion of preplanned biological correlates will allow ongoing optimization of targeted therapy. These events will guide future directions of proteomics, affecting how we integrate proteomic information into the selection of therapy for advanced and recurrent cancers, and other diseases.

Keyword: Diagnosis, Biomarker, Drug developments, Disease, Clinical Investigation

INTRODUCTION:

The idea of using biomarkers to detect disease and improve treatment goes back to the very beginnings of medical treatment. The practice of uroscopy — examining a patient's urine for signs of disease — dates back to the 14th century or earlier, when practitioners would regularly inspect the color and sediment of their patient's urine. Philadelphia chromosome: In 1960, researchers discovered that some patients with chronic myelogenous leukemia (CML), a form of adult leukemia in which there is a proliferation of myeloid cells in the bone marrow, have a specific genetic change associated with their cancer, a shortened version of chromosome 22. This abnormality, known as the Philadelphia chromosome, is caused by a translocation between chromosomes 9 and 22. The consequence of this genetic swap is the creation of the BCR-ABL 'oncogene'; this cancer-causing gene produces a protein with elevated tyrosine kinase activity that induces the onset of leukemia. Researchers were able to use the Philadelphia chromosome as a biomarker to indicate which patients would benefit from drug candidates (tyrosine kinase inhibitors) specifically targeting the rogue protein. The end product was the drug imatinib (Gleevec), which decreases the proliferation of Philadelphia chromosome cells and slows the progression of the disease.

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As a postscript to this story, researchers further found that specific mutations in the BCR– ABL gene were biomarkers that predicted resistance to imatinib, leading to the development of newer tyrosine-kinase inhibitors dasatinib and nilotinib.

HIV viral load: In the late 1980's, scientists discovered that HIV viral load could be used as a marker of disease progression, and subsequently, as a measure of antiretroviral treatment efficacy. Viral load was used to show that patients receiving combination therapy had a higher reduction in viral load than those on immunotherapy, and was therefore more effective in slowing the progression of the disease. Eventually, the viral load biomarker was used in the development and assessment of Highly Active Antiretroviral Therapy (HAART) treatment regimens involving a combination of several drugs used by many people living with HIV today. HER-2 gene and receptor: Probably the most famous biomarker in recent drug development history is the HER-2 gene and receptor, discovered in the mid 1980's. Between 20–30% of breast cancer patients show an over-expression of the HER-2 receptor on their cancer cells. Although this biomarker indicates a higher risk of adverse outcomes, it also gave clinicians a new target for novel therapies. The antibody trastuzumab (Heretic) was developed to target HER-2 receptors in these overexpressing patients, and successfully reduces the proliferation of cancer cells in many of these women [1, 2].

Biomarkers are already embedded into our language and medical care today. Cardiovascular risk can be assessed through blood pressure and cholesterol checks. Diabetic patients can test their glucose levels using one test – haemoglobin A1C (HbA1c) – that provides glucose levels from the most recent two weeks. Liver function tests (LFT) assess liver toxicity and prostate-specific antigen (PSA) assesses prostate cancer risk and disease state. These common biomarkers have historically taken decades to become part of medical practice. For example, PSA is a biomarker for diagnosing and monitoring prostate disease, the most prevalent cancer in men. The 30-year evolution of PSA, illustrating how it took decades for PSA to evolve into an accepted biomarker and finally be used to help develop new therapies. PSA evolution and use reveals some common themes in biomarker lifestyle. This progress came from 30 years of one biomarker's evolution. Biomarker development should follow different pathways depending on the stage of drug development. For early stages of clinical development, biomarkers can identify or confirm molecular targets, help to optimize dose schedules for the anticancer agent and might correlate with clinical benefit. Identifying clinically relevant targets is challenging; in numerous examples, the intended target was found to be irrelevant. As not all molecular targets are legitimate therapeutic targets, however, biomarkers can provide a means of determining which target(s), when inhibited, correlate with tumor control. In the case of some anticancer agents [e.g. cetuximab, gefitinib, erlotinib and inhibitors of vascular endothelial growth factor (VEGF)]; it appears that the molecular target is the therapeutic target. In the later stages of clinical development, identified markers could be used to select the patients most likely to respond to the targeted agent. Any biomarker used as a basis for patient otherwise, the risk of not treating patients who might benefit would be unacceptably high. Proper patient selection enables efficient clinical trial design for targeted therapies and ensures that the number of individuals exposed to the risks of anticancer therapy is minimized [3, 4].

Characteristics of Biomarkers:

An ideal biomarker should be safe and easy to measure. 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. If the biomarker is to be used as a diagnostic test, it should be sensitive and specific and have a high predictive value. A highly sensitive test will be positive in nearly all patients with the disease, but it may also be positive in many patients without the disease. To be of clinical value, a test with high sensitivity should also have high specificity, in other words, most patients without the disease should have negative test results. For predicting the likelihood of disease based on the test result, rather than the converse, the appropriate measures are positive and negative predictive values. Unfortunately, the positive predictive value falls as the prevalence of the disease falls, so tests for rare conditions will have many more false positive results than true positive result.

Biomarker in Drug Development:

Biomarkers are useful throughout the drug discovery and development process. In the past, biomarkers have tended to appear in drug development programmes as opportunists – taking advantage of spare samples and leftover money in the budget – often resulting in incomplete or inadequate data. However, they are now becoming more and more integrated into all stages of the development process, ranging from:

- Target discovery
- Evaluation of drug activity
- Understanding mechanisms of action
- Toxicity and safety evaluation
- Internal decision making
- Clinical study design
- Diagnostic tools
- Understanding disease processes Biomarkers can be of varying types, such as physiological, physical, anatomical and histological (tissue biopsy specimens). Perhaps the most relevant type for early phase clinical research is biochemical biomarkers, derived from bodily fluids that are easily available to the early phase researchers. The use of pharmacodynamic markers in drug development, typically blood based biomarkers that are influenced by drugs, is a fresh approach [5].
- Once a proposed biomarker has been validated, it can be used to diagnose disease risk, presence of disease in an individual, or to tailor treatments for the disease in an individual (choices of drug treatment or administration regimes).
- In evaluating potential drug therapies, a biomarker may be used as a surrogate for a natural endpoint such as survival or irreversible morbidity. If a treatment alters the biomarker, which has a direct connection to improved health, the biomarker serves as a surrogate endpoint for evaluating clinical benefit.
- Some of the main areas in which molecular biomarkers are used in the drug development process are, early drug development studies, safety studies, proof of concept studies, molecular profiling.
- Molecular biomarkers are often used in early drug development studies. For instance, they are used in phase-I study for establishing doses and dosing regimen

for future phase II studies. PD biomarkers are commonly observed to respond (either decrease or increase) proportionally with dose. This data, in conjunction with safety data, help determine doses for phase II studies.

- In addition, Safety molecular biomarkers have been used for decades both in preclinical and clinical research. Since these tests have become mainstream tests, they have been fully automated for both animal and human testing.[4] Among the most common safety tests are those of liver function(e.g., transaminases, bilirubin, alkaline phosphates) and kidney function(e.g., serumcreatinine, creatinine clearance, cystatin C). Others include markers of skeletal muscle (e.g., myoglobin) or cardiac muscle injury (e.g., CK-MB, troponin I or T), as well as bone biomarkers (e.g., bone-specific alkaline phosphates).

- Biochemical and molecular markers have revolutionized medicine and drug development in recent decades, giving clinicians and researchers the opportunity to infer biological states in patients and in response to drug interventions. For example, the blood of HIV patients can be tested for its viral load to assess the course of their disease, as well as providing a surrogate endpoint for trials of anti-HIV drugs.

- Biomarker studies will eventually become an integral part of the drug development process. The ultimate aim is the development of more effective drugs at a lower cost. Although still at early stages and with many issues to be resolved, the outlook for biomarkers is promising.

- The clinical development of gefitinib, an orally available epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is a more complex example of biomarker development.

- Evolution of biomarkers during the conduct of large randomized trials might become the rule rather than the exception. Although initial candidate biomarkers are evaluated early in development, knowledge increases exponentially as research and clinical experience become more widespread and increased clinical data with which to correlate the translational work become available [6, 7, 8, 9].

Biomarker in Diseases:

Biomarkers depicting prodromal signs enable earlier diagnosis or allow for the outcome of interest to be determined at a more primitive stage of disease. Blood, urine, and cerebrospinal fluid provide the necessary biological information for the diagnosis. In these conditions, biomarkers are used as an indicator of a biological factor that represents either a subclinical manifestation, stage of the disorder, or a surrogate manifestation of the disease.

- Biomarkers used for screening or diagnosis also often represent surrogate manifestations of the disease.

- The potential uses of this class of biomarkers includes, Identification of individuals destined to become affected or who are in the “preclinical” stages of the illness, reduction in disease heterogeneity in clinical trials or epidemiologic studies, reflection of the natural history of disease encompassing the phases of induction, latency and detection, target for a clinical

trial. The improvement in validity and precision far outweigh the difficulty in obtaining such tissues from patients.

- Diagnostic tests for diseases are used with increased frequency in clinical research and practice. In the diagnostic effort, collection of information from various sources, some of which includes results from diagnostic tests, helps to achieve the ultimate goal of increasing the probability of a given diagnosis. Clinical tests are also performed, though probably less often, for other reasons such as to measure disease severity, to predict disease occurrence, or to monitor the response to a particular treatment [10].

- More importantly, biomarkers for disease easily lend themselves to clinical trials. Another advantage of this type of diagnostic test is the reduction in disease heterogeneity in clinical trials or observational epidemiologic studies, leading to better understanding of natural history of disease encompassing the phases of induction, latency and detection [11].

- The use of biomarkers is growing, with a steady stream of new products being brought out by the diagnostics industry. Some of these assist in diagnosis, while others provide a means of monitoring the state of progression of disease and the effectiveness of therapeutic options. However, in many cases, the evidence which supports the use of these new methods as opposed to traditional biochemical tests has not yet been demonstrated, and it is intended that this volume will help clarify the strengths and weaknesses of using these biomarkers across a wide range of applications and in the various organs of the body. This approach will provide clinicians, pathologists, clinical biochemists and medical laboratory scientists with an invaluable overview of the diverse applications of biomarker in medicines.

- Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human disease. The application of biomarkers in the diagnosis and management of cardiovascular disease, infections, immunological and genetic disorders, and cancer are well known. Their use in research has grown out of the need to have a more direct measurement of exposures in the causal pathway of disease that is free from recall bias, and that can also have the potential of providing information on the absorption and metabolism of the exposures [12]. Neuroscientists have also relied on biomarkers to assist in the diagnosis and treatment of nervous system disorders and to investigate their cause. Blood, brain, cerebrospinal fluid, muscle, nerve, skin, and urine have been employed to gain information about the nervous system in both the healthy and diseased state. This paper focuses on biomarkers as defined by Houlka i.e., direct measures of biological media, and other papers in this issue will address brain imaging and other markers. The rapid growth of molecular biology and laboratory technology has expanded to the point at which the application of technically advanced biomarkers will soon become even more feasible [13, 14, 15]. Molecular biomarkers will, in the hands of clinical investigators, provide a

dynamic and powerful approach to understanding the spectrum of neurological disease with obvious applications in analytic epidemiology, clinical trials and disease prevention, diagnosis, and disease management.

Markers of Disease in Prostate Cancer:

There are no reliable biomarkers for disease progression in aggressive prostate cancer that has demonstrated utility in product development. Although prostate specific antigen (PSA) is used for a variety of purposes (e.g., determining when further diagnostic testing is indicated, assessing response to therapy), there is no consensus on how best to use PSA in cancer therapeutic trials. Uses of PSA that should be further investigated including identifying high risk populations, providing an early marker of drug activity and dose range, and use of PSA as a marker of disease progression. Other markers may also prove more predictive of clinical outcomes in some patients (e.g., alpha methyl aryl CoA racemes expression as a predictor of disease progression in local disease). A gap analysis to rigorously identifying what is proven and unproven about PSA and other potential indicators would be an important first step to improving prostate cancer biomarkers.

Markers of Disease Activity in Systemic Lupus:

Erythematosus, Inflammatory Bowel Disease, and Related Diseases: Development of new therapies for these diseases has been hampered in recent years by a lack of reliable markers of disease activity that can be used to predict clinical benefit. Development of predictive biomarkers and accepted clinical outcome measures would help in the evaluation of needed new therapies for these diseases.

Biomarkers in Arthritis:

Targeted research could identify how to apply MRI technologies to measure the effects of potential therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis. In this regard, MRI has demonstrated promise for detecting soft tissue inflammation and cartilage erosion in rheumatoid arthritis. If established as a reproducible biomarker, use of MRI could help determine the potential of a new therapeutic product, identify dose ranges, and stratify patients by risk while serving as an early response measure.

Biomarkers in Cardiovascular Diseases:

To advance efficient development of new therapies, new imaging techniques are needed to measure progression and treatment of cardiovascular disease. Examples include the potential use of intravascular ultrasound (IVUS), MRI, or multi-slice CT in the assessment of atherosclerosis progression and volumetric measures of cardiac function in trials of congestive heart failure. Development of these techniques for measuring progression will require a complete analysis of the current state of knowledge of the imaging modality, standardization of the technical aspects of the measurement, and performing the trials necessary to evaluate the degree of correlation with clinical responses.

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