

Biomarker Discovery: The Challenges and Rewards Ahead

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Modern scientific and medical thought believe that the root of human disease is primarily genetic in origin. Accumulated through exposure to radiation, oxidative stress, and miscoding or inherited from parents, genetic mutations encode for abnormal information carriers that disrupt normal cell function, resulting in a diseased state. The molecular indicators, primarily DNA and proteins, of the perturbed physiological state are known as biomarkers.

In the past few years, biomarkers have begun to play an increasingly important role in the pharmaceutical and clinical diagnostic industry. The continued refinement of proteomic and genomic technology has begun to uncover biomarkers sensitive and specific enough for early detection and for monitoring disease progression and treatment. The information provided by biomarkers allows doctors and researchers to understand and characterize diseases on a molecular scale, leading the way to personalized treatments for patients.

Potential of personalized medicine

Personalized medicine has the potential to revolutionize both patient treatment and entire fields of medicine. In fact, dramatic change is already underway in oncology. In the MD Anderson Cancer Center in Houston, researchers have begun to shift away from the paradigm of diagnosing cancer by location in the body.¹ Rather, they are classifying cancers through genetic biomarkers. Patients with the same defective genetic pathway are treated with the same targeted treatments. Dr. Gerald Falchook at MD Anderson states that "Traditional treatments for cancer, such as chemotherapy, are one-size-fits-all".¹ Such treatments ravage the whole body while the targeted therapies are less toxic and in cases more effective.

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Additionally, biomarkers will also bring personalization to other chronic conditions, like cardiovascular diseases. According to Dr. Robert Epstein, doctors will be able to use biomarkers to select the appropriate levels of anticoagulants and to determine the correct anti-platelet therapy.² Regardless of the disease, personalized medicine based on biomarkers is poised to deliver more precision to healthcare, enabling a doctor to make more informed medicine decisions. The personalized treatments will result in higher probabilities of favorable outcomes, lower risk of adverse effects, and significant healthcare cost savings. The use of biomarkers will provide a major advancement to early detection and disease monitoring.

Types of biomarkers and their uses

Before biomarkers can be used for personalized medicine, they must be sorted and assigned defined roles. Based on the classification by Sawyers and Zolg, biomarkers can be categorized into four different categories, each with a unique diagnostic application.^{3,4}

Screening biomarkers are markers that 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 of potential diseases. An example of screening markers is prostate-specific antigen, the current standard of prostate cancer screening.⁵

Prognostic biomarkers are 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 less likely to recur or to identify the fast progressors in rheumatoid arthritis patients.⁶ With the ability to differentiate patients based on a predicted disease course, doctors can better decide which treatments patients should receive and how aggressive it should be.

Once treatment is decided, predictive biomarkers 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. Several of these predictive biomarkers are already commonly used. For example, breast cancer patients are screened for extra copies of the *ERBB2* gene. If this biomarker is detected, then these patients will likely have a positive response to Herceptin therapy.³

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During treatment, pharmacodynamic biomarkers can be observed to determine the effectiveness of the drug and decide drug dosage. If a greater drug response is needed, the dose or treatment can be altered.

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.

Challenges in biomarker discovery and assay development

While the potential of biomarkers and their categorization are clear, the course for biomarker discovery and clinical assay development is littered with complex challenges and uncertainty. The selection and clinical validation of biomarkers is a monumental endeavor. As described by Sawyers and Zolg, introducing a biomarker into the market requires three phases: biomarker discovery, where biomarkers are identified; prototype development, where immunological assays are created; and commercialization, where assays are readied for clinical use.^{3, 4} Each of these phases holds considerable pitfalls.

Biomarker discovery

With the advances in genomic and proteomic technologies, the burden of biomarker discovery has lessened, but difficulties still remain. PCR, high-throughput gene sequencing, and microarrays are powerful techniques capable of elucidating disease-associated genetic biomarkers. However, the identification of protein biomarkers with proteomic techniques, including mass spectrometry (MS) based techniques, has proved more difficult. Current attempts at protein biomarker discovery have focused on two strategies: searching in bodily fluids (serum or urine) or searching in diseased tissue, but both approaches have serious limitations.⁷

In the serum, the largest barrier is the oversaturation of MS detection with “abundant” proteins (albumin, immunoglobulins). One technique as described by Zolg and Langen is to remove these proteins, enriching the biomarker candidates.⁴ However, other studies have found that these “abundant” proteins serve as carriers for biomarkers, hence eliminating the background proteins might also eliminate potential biomarkers.⁸

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While unique proteins are likely to be in diseased tissue, collecting the markers would require biopsies. Biomarkers only detectable through biopsies would have a greatly reduced usefulness compared to biomarkers obtained through noninvasive means.

Prototype development

Once a large array of biomarkers is discovered, a few suitable candidates are selected for prototype assay development. Because MS is impractical and too expensive for clinical applications, most biomarker assays are immunological. In prototype development, antibodies are raised against the chosen biomarkers. Once the antibodies are raised, an assay format is established and validated. Initial validation of the assay must be performed to ensure sufficient sensitivity and specificity.

Commercialization

Commercialization is an expensive and daunting task rivaling the scientific struggles. In this phase, biomarker and assay must be prepared for drug agency assessment and marketing. The commercial assay must contain monoclonal antibodies rather than the polyclonal antibodies often used in prototyping, and it must become automated. The completion of the assay must follow exacting guidelines set by regulatory agencies. After the clinical diagnostic assay is finalized, it must be validated in extensive clinical trials spanning several years.

A major obstacle in this phase is finding enough commercial incentive. According to Sawyers, one viable strategy is pairing the development of biomarker discovery and assay development with the development of a therapeutic drug.³ This model (known as the Dx/Rx model) places the incentives for biomarker identification and development with large drug companies. This model is successfully illustrated by HercepTest, an immunological assay for the ERBB2 breast cancer biomarker.³

Despite the potential of personalized medicine, the increasing investments of time and money in each phase and the uncertain medical and financial rewards dampen the enthusiasm towards biomarkers.

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Future Vision

We can envision a future where the use of biomarker diagnostic assays is integrated with traditional doctor evaluations. Patients will have their serum or urine routinely tested for screening biomarkers for early detection of chronic diseases like cancer. If a disease is detected, the patient will be further screened for prognostic and predictive biomarkers to investigate if and what personalized treatment is needed. Once treatment is decided, pharmacodynamic biomarkers will be monitored to gauge the progress of treatment and determine if additional therapy is needed.

This shift from traditional treatments with global negative effects to individualized therapies will radically alter healthcare, improving patient health and reducing costs. While significant technical and commercial challenges remain, scientists and companies need to strive boldly into biomarker discovery and implementation despite the risks. It is imperative to overcome these roadblocks due to the tremendous societal value biomarkers can bring to early detection and treatment monitoring.

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