Biomarker

Molecular Detectives: Personalized Medicine; the Next Generation of Diagnosis and Treatment

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Published: January 2015

Executive Summary

Personalized medicine is transforming how physicians diagnose and treat medical conditions. Rather than being limited to tools featuring the same therapies to treat patients with similar or specific disorders, therapies can now be tailored to the patient's individual characteristics and needs. This opportunity includes all stages of care – prevention, diagnosis, treatment and follow-up.[1] Ultimately, this custom approach enables physicians to diagnose and treat disorders more quickly and accurately, or even to prevent them before they occur.[2] Personalized medicine has the potential to transform the practice of medicine, enabling health care providers to shift the emphasis from response to prevention. It can predict predisposition (or susceptibility) to certain disorders, improve detection, preempt progression, customize prevention strategies, and even reduce the time, cost, and failure rate of clinical trials.[3] Central to this new medical model is the identification and detection of biomarkers, or the molecules that occur naturally in the human body. These molecules can be used to identify normal or abnormal conditions in the body, diagnose disorders or predict the likelihood of a biological disorder in the future.[4]

Biomarkers

The term "biomarkers" is generally used as a reference to measurable indicators of some biological state or condition.[5] Biomarkers can be used alone or in combination with other diagnostics to assess patient health or disease states.[6] They can also be introduced into the body as traceable substances to help evaluate organ function or other characteristics.[7] For personalized medicine, there are two types of key biomarkers.

- Genetic material within DNA sequence - This is responsible for expression of a specific trait.[8] Physicians can compare a patient's DNA sequence to either a normal sequence or a mutated sequence that results in a specific disorder. The comparison can determine patient health and their predisposition to those genetic disorders. The identification and evaluation of genetic biomarkers is largely a product of the Human Genome Project.[9] Scientists have used data from this project to develop data on human chromosomes and the genetic material within them, including many associated with genetic disorders. They have made this data available to scientists and the public alike.[10] This ready access has led to the development of clinical and consumer tests that can be used to identify genetic conditions.

  Protein receptors – Certain genetic conditions generate tell-tale proteins that may be present in the bloodstream, organs or tissues. Protein receptors bind to such proteins and can be detected to provide a diagnostic of a specific disorder.[11] The detection is commonly done through the diagnostic test ELISA (enzyme-linked immunosorbent assay).[12] ELISA typically uses molecules of antibodies that are linked to an enzyme. These antibodies are attracted to the target proteins and will bind with them when in contact. Upon binding, they undergo a color change which can be detected through colorimetry, a process used by diagnostic tools to detect a specific color. The concentration or intensity of the color correlates to the concentration of the protein in question. The detection of proteins using this method has traditionally been held back

by its detection limits. Many proteins expressed at very low levels were generally undetectable. However, recent advancements in nanoscale assay technologies now allow for the detection at very low concentrations. In some cases these technologies are capable of detecting a single protein molecule of interest.[13] This advancement in technology and resolution has opened up many previously undetectable proteins to their potential for detection, diagnosis, and therapy.[14] [15]

Regulation and Advancement

Regulatory agencies and independent industry-affiliated organizations recognize the value of biomarkers in identifying disorders and developing therapeutics. With the emerging interest in personalized medicine, there is a high level of priority to identifying biomarkers, research tools, development methods and pathways for regulatory approval. The U.S. Food and Drug Administration ("FDA") is uniquely positioned to play a role in fostering biomarker product development.[16] They have identified key areas to quickly bring biomarkers through the development stage for therapeutic use.[17] Among these are:

- Early Stage Development – This includes the development of regulatory science standards, reference libraries, research methods and tools necessary for characterizing biomarkers, steering them into development pipelines and defining clinical protocols for evaluating their efficacy.
- Regulatory Pathways and Policies – Over a decade ago, the FDA recognized the need for regulatory pathways, policies and the infrastructure necessary for supporting anticipated breakthroughs in biomarker science. They have since established guidance on a broad range of topics to provide consistency and timeliness to the biomarker regulatory and development processes.[18]
- Product Use – The FDA recognizes that biomarkers represent a unique approach to drug therapy because dosing occurs on an individual rather than general population level. Product labeling is identified as a critical control point to ensure that patients receive the correct therapy at the appropriate dose. Post-market surveillance becomes more important as well. Due to smaller population groups, relatively rare adverse events from product use are unlikely to surface. This could delay initiating corrective actions.

The FDA has established the Biomarker Qualification Program to support and cooperate with scientists and clinicians in biomarker development.[19] The program facilitates the movement of biomarkers through the regulatory, development and qualification processes.[20] Institutions, scientists and clinicians anticipate growth in the use of biomarkers for diagnostic and therapeutic use.

There has also been remarkable domestic and international interest and growth in professional organizations, consortiums and conferences.[21] [22] Their goals are to further biomarker research, qualification and development. These organizations are both in the public and private sectors, and actively partner with the FDA and the Biomarker Qualification Program. By bringing together expertise and resources they hope to identify, develop and qualify potential biomarkers and influence the identification, prevention and treatment of disorders.[23]

Current and Future Uses in Medicine

The growth in biomarker research and development has resulted in their innovative use in the diagnosis and treatment of not just illnesses, but injuries as well. There are some biomarkers that can predict the likelihood of developing specific disorders even in the

absence of genetic predisposition. Some examples of biomarkers and their use in detection and diagnosis include:

- Predicting the likelihood of a woman developing breast cancer. This predisposition is associated with the presence of a mutation in the BRCA1 gene. By modifying the DNA (through a process known as DNA methylation), researchers found that the same biomarker was present in the blood of women without a BRCA1 mutation but who later developed breast cancer.[24] Such a discovery may lead to a blood-based test to identify breast cancer risk in women who don't have the BRCA1 mutation.
- Identification, early detection and potential development of treatments for Alzheimer's disease. Researchers have identified three protein-related biomarkers present in cerebrospinal fluid indicating the onset of early dementia. They continue to search further for biomarkers in both affected and healthy individuals.[25] More recent research identified a set of ten lipid metabolites (fat formed through metabolism) in blood that is linked to the eventual development of dementia. A blood test currently under development may predict if a healthy person will develop symptoms of dementia, allowing researchers to explore treatments that could be administered before its onset.[26]
- Early detection of concussions resulting from sports injuries and other causes. Researchers have identified a lipid called a tau oligomer, which is produced by the body in response to traumas, disorders, and concussions. General Electric (GE), a manufacturer of diagnostic imaging devices, partnered with the NFL to develop this biomarker to detect concussions resulting from collisions during football games. GE provides grants to organizations that could further develop the diagnostic.[27] More than four hundred organizations applied for these grants, and GE began awarding grants to those organizations whose biomarker detection technologies showed promise.[28]
- Detection of occupational and non-occupational disease and disorders. Researchers have found that the same DNA methylation process can produce a biomarker in response to exposure to polycyclic aromatic hydrocarbons (PAH). PAHs are toxic and carcinogenic byproducts of fires, a risk that firefighters often encounter. Through the use of this biomarker to detect PAH concentrations, a firefighter could be alerted to his/her susceptibility of a disease. Appropriate occupational changes and/or therapies can be administered to limit additional exposure.[29] Researchers have also discovered a biomarker that can detect manganese levels in adults and children. This is a concern since elevated levels can lead to neurological disorders.[30]

Risks

There could be a variety of risks emanating from the use of biomarkers. The level of the risk would vary on the application of the biomarkers. Examples include the following.

With human clinical trials for new drug products, there are specific classes of biomarkers that can indicate the toxicity of a drug molecule under development (therapeutic). The presence of these biomarkers can indicate how an organ such as a liver reacts to a specific drug molecule and also provide guidance on the level of toxicity to the liver. Such detection systems are used during the early stages of drug development (Phase 1) to filter out potentially toxic molecules. However, if the necessary biomarkers are undetected during this stage, higher toxicity drug molecules could go through to the next round of development. This failure could result in additional development costs to the drug manufacturer, giving rise to a potential errors and omissions claim against the manufacturer of the biomarker detection system. There could also be products liability losses if the failure resulted in property damage and/or bodily injury.

The manufacture or use of biomarkers may also present a safety exposure as it pertains to workers compensation exposures. Biomarkers are commonly identified and analyzed in laboratory and life sciences environments. Laboratories engaging in biomarker research, development and analysis should have employee safety as well as health programs and policies in place. These should be applicable to regulatory requirements and safety management best practices, including those specific to laboratories, such as the Federal OSHA Laboratory Safety Standard, section 1910.1450. These also include controls for chemical, biological, physical, general safety and any other exposures which employees might encounter in the laboratory workspace.

Conclusion

The emergence of new technologies, increasing discovery rates of novel genetic and protein-based biomarkers and new methodologies for the detection of physical biomarkers, all suggest significant clinical benefits. Advances in genomic and proteomic technologies are now allowing human diseases to be detected and diagnosed on a molecular basis, leading to customized treatment protocols. The identification and therapeutic use of biomarkers is essential to achieving a new era of predictive, preventive and targeted medicine. The ability to diagnose and treat disorders on an individual basis is limited only by researchers' ability to identify biomarkers associated with those disorders and develop a therapeutic for their treatment.

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