BIOMARKER TOOLKIT: Biomarker Backgrounder

Key Terms: Pharmacogenomics, prognostic biomarker, predictive biomarker, negative predictive biomarker, pharmacodynamic and biological heterogeneity

Personalized Medicine

In clinical practice, personalized medicine refers to the use of new methods of molecular analysis to better manage a patient's disease or predisposition towards a disease. It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best in the context of a patient's genetic and environmental profile.[i] The promise of personalized medicine is to improve the safety and effectiveness of drug therapy in an individual patient, particularly in deadly diseases like cancer.

There are several key areas where personalized medicine may have a tremendous impact on the future of healthcare:

- **Drug development:** Combining information about genetics and a drug's biologic relevance may allow companies to make earlier and better informed decisions during the drug development process, potentially saving time and money.
- **Diagnosis**: Genetic information may help to more precisely identify the specific variant of a patient's disease, or their predisposition to certain diseases.
- **Patient selection**: Biomarkers can help guide physicians in making treatment decisions for their patients by providing information on what patients may be most likely to respond to a particular treatment.

Pharmacogenomics and Biomarkers

Scientifically, personalized medicine is known as **pharmacogenomics** (drugs combined with genes), or how genetic differences in individuals affect the way people respond to drugs.[ii] Biomarkers are biological molecules found in blood, body fluids or tissues. Biomarkers can be a sign of a normal/abnormal process, or of a condition or disease.[iii] For example, blood pressure is widely accepted as a biomarker because large epidemiologic databases exist demonstrating a correlation between elevated blood pressures and adverse cardiovascular outcomes. Further, that has been supported by the numerous placebo-controlled studies showing an effect on stroke and coronary heart disease outcomes from lowering blood pressure.

U.S. Food and Drug Administration (FDA) Pharmacogenomics Guidance further defines three categories of biomarkers: exploratory, probable and known valid. Markers are included in these categories based upon available scientific information.

Biomarkers can be further divided into the categories of predictive or prognostic. A **prognostic biomarker** is associated with the likelihood of an outcome (e.g. survival, response, recurrence) in a population that is untreated or on "standard" (non-targeted) treatment.

A **predictive biomarker** can predict differential effect of treatment on outcome**.** A predictive biomarker is a biomarker that is present prior to an event occurring and which predicts that outcome. For example, the *KRAS* oncogene can be considered a **negative predictive biomarker** for response to treatment with the EGFr (epidermal growth factor receptor) class of drugs since it can identify which patients are *unlikely* to respond to treatment with an EGFr inhibitor.

Using Biomarkers

In recent years, significant advances in our understanding of human biology have yielded novel drug targets that may impact disease. Typically, early clinical trials test a drug targets safety and tolerability, while questions regarding efficacy remain unanswered until later stages in development.[iv]

Researchers may now be able to use pharmacogenomics to improve the efficiency of drug development. Using biomarkers, researchers can explore the **pharmacodynamic** effects, or how a drug works in the body, allowing earlier go/no-go decisions on whether to advance molecules in clinical trial, accurate dosing, increased biological knowledge and the selection of the patient population most likely to respond to a treatment.[v]

Biomarkers may also be used to diagnose disease and for patient selection. As research continues, our understanding of the role biomarkers can play in the management of disease areas such as cancer, cardiology, neurology, metabolic, autoimmune and inflammatory diseases has evolved. [vi]

Biomarkers in Oncology

Data shows that anti-cancer treatments may only benefit a small portion of patients. Integrating biomarkers into routine clinical practice will help physicians select the right treatment, for the right patient. Doing this could have many positive outcomes including sparing patients unnecessary toxicity from an ineffective treatment or being able to select a treatment that may be more effective in battling their disease.

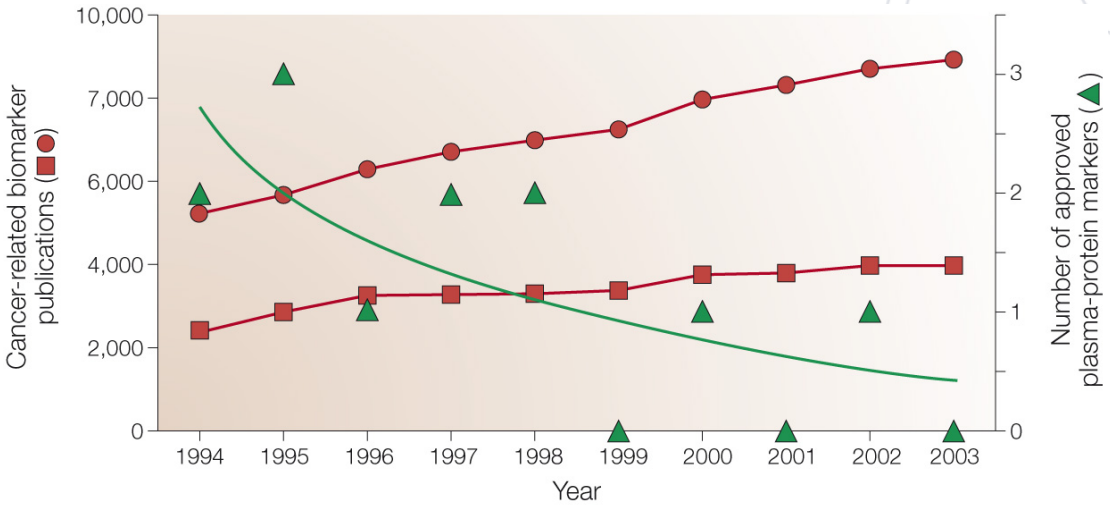
While biological and technical advances have advanced the scientific understanding of the role of biomarkers in cancer, there are a number of practical challenges that remain in the development of predictive and prognostic biomarkers. Some of these challenges include:

- **Better understanding of biological heterogeneity (the differences between cancers):** In cancer, tumor cells are known to continuously evolve and present themselves differently at various points over the course of the disease. Biologically, there also may be varied pathways to reach the same clinical endpoint. These factors may all impact the detection or utility of potential biomarkers.
- **Variation with age and disease:** Normal, reparative, aging, or other physiologic or pathologic processes may generate biomarker profiles that appear similar to those found in some cancers.
- **External factors:** Foods, drugs, and other external factors may impact the presence and manifestation of biomarkers.
- **Health system factors**: Biomarkers will not only need to be qualified in the clinical sense, but to be successfully integrated into the practice of medicine, biomarkers will need to show cost-effectiveness, cost-benefit and overall value on reducing the burden of disease to be accepted by the health system.
- **Testing:** Both analytic validation and standardization of routine testing for biomarkers will need to be addressed.[vii]
- **Regulatory qualification:** Biomarkers will only be useful if we are able to bridge the gap between what are considered exploratory and valid biomarkers. To do so, the processes through which biomarkers are introduced and accepted in drug development and regulatory review must become more closely aligned.[viii]

Biomarkers and the FDA

In 2005, the FDA announced a first-of-its-kind partnership with the Critical Path Institute (C-Path), an independent, publicly funded institute bringing together scientists from FDA, academia and industry. The Critical Path Institute was created to support the FDA in its effort to implement the Critical Path Initiative, a proposal designed to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product or medical device is transformed from a discovery or "proof of concept" into a medical product. As part of the initiative, experts are working together, sharing resources in order to help qualify biomarkers.[iv, ix]

The FDA also recently announced that it is working on a 'Fit-For-Use' document that will help clarify the type of evidence required and process that should be followed to establish the validity of a biomarker. The guidance would make the evidentiary standard for validation contingent upon the intended use of the biomarker, since the burden of evidence differs tremendously depending upon the intended use of the biomarker.[x]



Numbers of publications on biomarkers and FDA approval of biomarkers.

Personalized Medicine, Cancer and the Future

The future of cancer treatment, prevention and detection will be guided by the use of more effective cancer biomarkers. New biomarkers that help to target and monitor therapy are continuing to emerge as the path forward on the best way to integrate them into clinical practice and regulatory strategies evolves. These and future biomarkers will need to be qualified based on their intended use and the entire process will be reliant upon multi-stakeholder collaboration including government, academics and industry. Ultimately, biomarkers have the potential to spur innovation, streamline the development process and help patients by providing treatment tailored to their genetic makeup.[iv,vii]

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