



BIOMARKER TOOLKIT: Case Studies

Key Terms: Surrogate endpoint

Evolution of Biomarkers in Personalized Medicine

While scientific advances have increased interest in new safety and efficacy biomarkers, their application in practice has been slowed by a number of challenges inherent in the development process. For example, many biomarkers are developed for use in the early detection of disease or as surrogate endpoints for evaluating treatment or response. **Surrogate endpoints** are markers that can be used to substitute for a clinical endpoint that may be more difficult to measure (e.g. cholesterol for heart disease). However, it has proven difficult to achieve validation of a biomarker as a surrogate endpoint since the standard of evidence for such a biomarker is extremely high.^{i,ii,iii}

The overemphasis on “surrogacy” as an objective of biomarker development, coupled with unclear standards of evidence and an undefined regulatory path, have made the qualification and validation of biomarkers a difficult process.^{iv}

Biomarker Classes

FDA Pharmacogenomics Guidance defines three classes of biomarkers:

- **Exploratory:** Less well-developed tests (or biomarkers) that alone are insufficient for making regulatory decisions.
- **Probable Valid:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results.
- **Known Valid:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.^v

The validity of a biomarker is closely linked to its intended use. This drives how the biomarker will be defined and qualified. A biomarker can only move from the probable to the known valid class with broad consensus from the medical and scientific community, a time consuming process. A closer alignment of the development and regulatory process is needed to help accelerate the application of biomarkers in clinical practice.ⁱ

Select Validated Biomarkers

The inclusion of biomarker information in a drug label is one example of biomarker validity. Over the past ten years, there has been a significant increase in the number of labels containing such information. In oncology, some validated clinical biomarkers have already helped to change clinical practice in a variety of tumor types.

- **HER2 Protein:** Herceptin[®] (trastuzumab) specifically inhibits the HER2 receptor and was developed by researchers to provide patients with HER2 positive breast cancer a treatment option. Ten years ago, Herceptin received FDA approval for use in women with metastatic breast cancer who have tumors that overexpress the HER2 protein. It was indicated for treatment of patients both as first-line therapy in combination with paclitaxel chemotherapy and as a single agent for those who have received one or more chemotherapy regimens. In 2006, the FDA approved Herceptin for the adjuvant treatment of patients with early-stage HER2-positive, node-positive breast cancer.

As part of FDA label, the overexpression of HER2 is necessary for the selection of patients appropriate for drug therapy.

The approval of Herceptin ushered in a new era of cancer treatment and was the first clinically adopted step towards personalized medicine in oncology. In order to determine what patients will benefit from Herceptin, diagnostic tests that measure either HER2 protein levels or gene copy numbers have been developed and are used by physicians to guide treatment decisions.^{vi,vii,viii}

- **Philadelphia chromosome:** Philadelphia chromosome is a genetic abnormality that is found in blood cancers chronic myeloid leukemia (CML), and acute lymphoblastic leukemia (ALL). The discovery of the chromosome led to research that identified the BCR-ABL fusion gene in CML cancer cells. As a result, researchers began development of the drug Gleevec[®] (imatinib mesylate), a tyrosine kinase inhibitor that specifically inhibits BCR-ABL. Its efficacy in CML proved that the BCR-ABL oncoprotein causes CML. Gleevec was first approved in May 2001 by the FDA as a treatment for patients with advanced stage Philadelphia chromosome-positive (Ph+) CML, and has subsequently received approval for the treatment of all forms of the disease.^{ix}

In ALL, the Philadelphia chromosome is present in one quarter of the cases diagnosed each year. Most forms of chemotherapy were ineffective against this form of the disease. As a result of the success of Gleevec against CML, researchers created next generation tyrosine kinase inhibitors like Sprycel[®] (dasatinib). The FDA approved Sprycel for treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

A test for the Philadelphia chromosome is required as a marker for the drug's potential effectiveness.^{vii,x}

- **CYP2C9 and VKORC1 Genes:** Outside of oncology, the FDA made news in 2007 with the approval of an updated label for the widely prescribed blood thinner Coumadin[®] (warfarin), a drug used to prevent blood clots, heart attacks and stroke. Studies show that about a third of patients who receive warfarin metabolize the drug much differently than expected. Further research found that variations of two genes, CYP2C9 and VKORC1 were common characteristics among the patients who metabolized the drug differently. The FDA concluded that people with these variations may need lower warfarin doses than individuals without the gene variation.

In August of 2007, the FDA approved updated labeling for warfarin that incorporated this genetic information. At this time, the FDA does not require physicians to conduct genetic testing before initiating therapy; however they are encouraged to use laboratory developed tests to determine if a patient has certain CYP2C9 and/or VKORC1 gene variants that may influence their response to the drug. This label update was cited as a major advance resulting from progress associated with the Critical Path Institute and the FDA's commitment to personalized medicine.^{xi,xii}

Select Emerging Biomarkers

In oncology, data was released for a number of potential clinical biomarkers discovered over the past few years, including:

- **KRAS status:** The *KRAS* (Kirsten rat sarcoma 2 viral oncogene homolog) gene is a member of a family of genes called RAS proto-oncogenes. *KRAS* plays an important role in the EGFR signaling cascade, which may lead to cancer spread and growth. *KRAS* mutations have been detected in a range of tumor types including lung, colorectal and pancreatic cancers. The data show cancer patients with wild-type *KRAS* have a better response and longer progression-free survival (PFS) to anti-EGFR therapy.
- **EGFR mutations:** Somatic mutations in the epidermal growth factor receptor (EGFR) correlate with increased response in patients with non-small-cell lung cancer (NSCLC) treated with EGFR tyrosine kinase inhibitors like Iressa[®] (gefitinib). New research suggests that genetic screening of these NSCLC for EGFR mutations may allow physicians to identify the patients who will derive the greatest benefit from first-line treatment with Iressa.^{xiii}

ⁱ Goodsaid F, Frueh F. Biomarker Qualification Pilot Process at the US Food and Drug Administration. *AAPS Journal* (2007) 9(1):E105-E108.

ⁱⁱ Simon R. Validation of pharmacogenomic biomarker classifiers for treatment selection. *Disease Markers* (2005) 21:1-8

ⁱⁱⁱ Woodcock J. The Role of Biotechnology and Bioinformatics in FDA's Critical Path Initiative. September 25, 2007.

^{iv} *Ibid*

^v US Food and Drug Administration. Guidance for industry—pharmacogenomic data submissions. Accessed October 22, 2008.

<http://www.fda.gov/cder/guidance/6400fnl.pdf>.

^{vi} Piccart-Gebhart et al. (2005)

^{vii} Romond et al. (2005)

^{viii} US Food and Drug Administration. Table of valid genomic biomarkers in the context of approved drug labels. Available at:

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm. Accessed October 21, 2008.

^{ix} Kurzrock R, Kantarjian HM, Druker BJ, Talpaz M. Philadelphia chromosome-positive leukemias: from basic mechanisms to molecular therapeutics. *Ann. Intern. Med.* (2003) 138 (10):819–30.

^x Ottmann OG, Wassmann B. Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. *Hematology*. (2005)

^{xi} Food and Drug Administration. Questions and Answers on New Labeling for Warfarin (marketed as Coumadin). Accessed October 21, 2008.

<http://www.fda.gov/cder/drug/infopage/warfarin/qa.htm>

^{xii} Food and Drug Administration. Press Release: FDA Approves Updated Warfarin (Coumadin) Prescribing Information. Accessed October 21, 2008. <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html>

^{xiii} Sequist LV, Martins RG, Spigel D, et al: First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol* (2008) 26:2442-2449