Detecting the Future:
A Perspective on the Rising Value of Diagnostics in Oncology Therapeutics

Introduction

"Biomarker" is the new buzzword in oncology diagnostics and it holds promise to steer the industry toward a new frontier. Traditionally, diagnostics such as CTs, MRIs, and PET scans among others were tools used to help complement a list of symptoms to assist in identifying a cancer diagnosis. However, progress in research has broadened the use of diagnostics to include identifying specific patients who should be recommended to a particular therapy, or even who would be susceptible to a particular type of cancer. This evolving discovery is leading the oncology industry toward the promise of personalized medicine and has significant ramifications for both the development and commercialization of cancer therapeutics. Subsequently, pharmaceutical and biotechnology companies have to prepare for the increasing use of biomarkers and define a strategy to incorporate diagnostics into the successful development and launch of future cancer therapeutics.

Uses of Molecular Diagnostics in the Pharmaceutical Industry

Biomarkers, in the broadest sense, are measurable biological characteristics that can be associated with normal processes, a disease state, or a pharmacologic response. For example, the identification of the prostate-specific antigen (PSA) has led to the introduction of routine diagnostic testing in men in an age group that is susceptible to this type of cancer. Since then, the scientific discovery of cancer molecular markers has blossomed with advancements from genomics, proteomics, transcriptomics, metabolomics, glycomics, and epigenomics. These discoveries have paved the way for the development of new molecular diagnostics that use biomarkers to assist in cancer identification and treatment.

Since the successful launch of Herceptin [trastuzumab; Genentech], the definition and utility of an oncology diagnostic has continued to expand. Hence, molecular diagnostics are focused on three broad categories of biomarkers: those that identify disease and prognosis, those that assess susceptibility to a disease, and those that predict patient response to therapies by forecasting efficacy or toxicity of a targeted therapy.

Biomarkers of Disease and Prognosis

Diagnostic companies are using biomarkers to help determine the presence of cancer and to better define patient prognosis. Two companies, Genomic Health and Agendia, have developed tests that survey gene expression on cancerous tissue that help establish the prognosis of breast cancer patients. The Genomic Health Oncotype DX® system examines expression of 21 genes (5 of which are reference genes) on cancer cells to predict the benefit of chemotherapy and likelihood of disease recurrence. Agendia's MammaPrint™ analyzes 70 genes on the tumor cells to divide patients into low- and high-risk populations and estimates metastasis-free survival in breast cancer patients. (See related article: OBR. 2008;May:14-20). These tests offer the potential for some patients to avoid the side effects associated with adjuvant therapy.

Biomarkers of Susceptibility

Genetic biomarkers that have the ability to predict susceptibility to cancer have also been discovered. Women with a family history of breast or ovarian cancers can obtain screening for mutations of the BRCA1/BRCA2 genes that correlate with increased risk to aggressive tumors. Patients who test positively for susceptibility can pursue prophylactic treatment options or undergo frequent cancer screenings. In addition, the linkage of certain strains of the human papillomavirus (HPV) to cervical cancers has also led to the ability to test for

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disease susceptibility by screening for specific strains.

Biomarkers of Response: Efficacy and Toxicity

In addition to Herceptin, other targeted cancer therapeutics that have also found uses for predictive biomarkers include, Tarceva [erlotinib; OSI Pharmaceuticals/Genentech] and Iressa [gefitinib; AstraZeneca] for mutated epidermal growth factor receptor (EGFR) in lung cancer treatment, and Erbitux [cetuximab; ImClone/Bristol-Myers Squibb] for colon cancer. Recently, a role has been identified for the wild type K-ras gene in the ability to predict treatment response to Erbitux and Vectibix [panitumumab; Amgen] in colorectal cancer. As a result, several laboratories have developed diagnostics and have proceeded with testing for K-ras mutations.

Some companies are also using biomarkers to predict the toxicology of a targeted therapeutic and optimize drug dosage. Camptosar [irinotecan; Pfizer], indicated for colorectal cancer, was found to cause severe diarrhea and neutropenia in a subset of patients who were homozygous for a specific allele of the UDP-glucuronosyltransferase

Table 1. Examples of Companion Diagnostics for Cancer Therapeutics

Diagnostic Function	Therapeutic	Cancer Type	Diagnostic Target
Efficacy	Herceptin, Tykerb	Breast Cancer (BrC)	Her2/neu
	Tamoxifen, Arimidex, Aromasin, Femara	BrC	Estrogen receptor / Progesterone receptor
	Tarceva, Iressa	Non-Small Cell Lung Cancer (NSCLC)	EGFR
	Erbitux	Colorectal Cancer (CRC)	EGFR
	Erbitux, Vectibix	CRC	K-ras
	Gleevec	Chronic Myelogenous Leukemia (CML)	Brc-Abl mutations
	Gleevec	Gastrointestinal Stromal Tumor (GIST)	c-Kit
	Rituxan	Non-Hodgkin Lymphoma (NHL)	CD20
	Tamoxifen	BrC	Cytochrome P450 (CYP450)
	Gemzar	NSCLC, BrC, Ovarian Cancer (OC), Pancreatic Cancer	Ribonucleotide reductase subunit 1 (RRM1)
	Cisplatin	NSCLC, CRC	Excision repair cross-complementation group 1 (ERCC1)
	Cisplatin	NSCLC, CRC	Thymidylate synthase (TS)
Toxicity	Camptosar	CRC	UGT1A1
	Purinethol	Leukemia	Thiopurine methyltransferase (TMPT)
	5-Fluorouracil, Xeloda	CRC	Dihydropyrimidine dehydrogenase (DHD)
	Elitek	Supportive care: Leukemia, Lymphoma	Glucose-6-phosphate dehydrogenase (G6PD)

Source: Campbell Alliance

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UGT1A1 gene. Third Wave Technologies (now Hologic) created a genetic test for this allele for patients starting treatment. The outcome of the test affects dosing, as those with the variant would require lower starting doses. (Table 1 contains further examples of cancer therapeutics with companion diagnostics for both efficacy and toxicity.)

Growing Commercialization of Molecular Diagnostics

With the many different causative factors and tissue origins associated with aberrant cell growth, there is obviously no panacea for cancer. Systemic chemotherapeutic agents can target the rapidly dividing cancer cells, but they remain toxic to normal cells and the patient. Targeted therapies hold the potential for better disease outcomes and reductions in harmful side effects. However, these drugs are very expensive and can cause severe adverse effects in select patient populations.

In addition, the very nature of these therapies requires that the proper target be present, and some of these drugs will only be effective on subpopulations of cancer patients. With increased potential for diagnostics in the pharmaceutical industry, several diagnostics companies have begun marketing products for the most prevalent cancer types. Since biomarkers can determine the patient populations most likely to respond to therapy and resist toxicity, there lies the potential to enhance probability of regulatory approval. As a result, more pharmaceutical companies have recently partnered or acquired diagnostic companies to assist with the development of cancer therapies.

Current Diagnostics in Prevalent Cancers

As demand for molecular diagnostics continues to grow in cancer therapy, an increase in emerging products entering the field would be expected. Original thinking was that the supply of available diagnostics was not yet keeping up with demand. Contrary to this hypothesis, a review of the current molecular diagnostic landscape for the four most prevalent cancer types found commercially-available tests offered through several companies (Table 2).

The diagnostics span a majority of the three primary uses for biomarkers: detection/prognosis, prediction of therapeutic response, and detection of susceptibility. However, as diagnostics can be approved by more than one regulatory pathway and are not required to be FDA approved to be reimbursable by payers, some of these are confined to testing through CLIA-approved laboratories. Several more diagnostics for these diseases are also in the development pipeline and will likely be launched in the near future.

Biomarkers for Clinical Development

Biomarkers are now being used during the clinical development process to increase chances of hitting critical endpoints. New therapies need to demonstrate a significant improvement over current standards of care to gain acceptance, and selectively targeting the responsive patient population to enhance efficacy and lower toxicity can help clear these hurdles.

Table 2. Companies with Biomarker Diagnostics Available for Prevalent Cancers

Cancer Type	Biomarker Type: Disease/Prognosis	Biomarker Type: Response to Tx	Biomarker Type: Susceptibility
Breast cancer	Dako; bioMérieux; bioTheranostics; Agendia; Genomic Health; Veridex; Power3; Abviva; DiagnoCure; Applied Genomics	Dako; Abbott; Ventana; Agendia bioTheranostics; Roche; Genomic Health; Monogram Biosciences	Myriad Genetics; deCODE
Lung cancer	Rosetta Genomics	Dako, Response Genetics, DxS Clarient; Genzyme Genetics; Caris Dx; ViennaLab/Oasis Diagnostics	
Colorectal cancer	Exiqon; DiagnoCure; bioMérieux	Dako; Response Genetics; DxS; Clarient; Caris Dx; ViennaLab/Oasis Diagnostics	Myriad Genetics; GeneNews
Prostate cancer	Aureon; bioMérieux; DiagnoCure/ Gen-Probe; OncoMethylome/ Veridex	Colorectal Cancer (CRC)	deCODE

Source: Campbell Alliance

Bristol-Myers Squibb is taking this route in attempts to gain regulatory approval for its breast cancer drug, Sprycel (dasatinib). Researchers studied a panel of biomarkers, characterized the ideal responders to the therapy, and are using these data to screen for clinical trial candidates. Other investigations include the monitoring of changes in the levels of specific biomarkers, such as serum levels in tumor antigens, as surrogate endpoints to monitor patient response to therapy, make more rapid determinations of efficacy than hard endpoints can, and allow for earlier decisions on whether to proceed with costly trials. Although there is great potential for biomarkers in clinical development, currently they are not being used consistently across all cancer trials.

Rise in Partnerships to Develop Companion Diagnostics

The increased utility of biomarkers in therapeutic development has driven further interest in the diagnostics sector from pharmaceutical and biotechnology companies. Many large pharmaceutical companies have entered into recent partnerships with diagnostic companies to identify oncology biomarkers (see Table 3 for examples). Roche's stance on the future of biomarkers was made clear when it acquired Ventana Medical Systems to increase its hold on the cancer diagnostics market. Clearly the amount of partnering activity in the last two years demonstrates that many large pharmaceutical and biotechnology companies have become cognizant of the changing landscape and emerging importance of biomarkers for the future of oncology therapeutics.

Obviously, biomarkers and molecular diagnostics appear to hold tremendous promise that is just beginning to be realized. As pharmaceutical and biotech companies move new oncology products through the development process, they are now often faced with difficult decisions about whether, how, and when to pursue biomarker strategies. Quite simply, they need to determine whether—for their specific situations—it makes sense to pair therapeutics with diagnostics. That will be the primary topic of the second article in this two-part series.

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Table 3. Recent Therapeutic-Diagnostic Company Partnerships and Acquisitions

Therapeutic Company	Diagnostic Company	Strategic Objective
Pfizer	Source MDx	Partnership to develop RNA-based pharmacodynamic and predictive biomarkers
AstraZeneca	Compendia Bioscience	Partnership to use Oncomime tools for oncology gene expression analysis
Merck	Asuragen	Collaboration to develop a biomarker test for cancer clinical trials and as a potential companion diagnostic for a cancer therapeutic
Wyeth	Singulex	Partnership to develop immuno-assays with Erenna system
GlaxoSmithKline	OncoMethylome Sciences	Partnership for development of DNA methylation biomarkers for personalized cancer treatments with pipeline therapeutics
Bristol-Myers Squibb	Dako	Partnership for development of pharmDx assays to identify likely responders to pipeline drugs
Genentech	Dako	Partnership to develop companion diagnostic for investigational cancer drug
Abbott	Celera	Collaboration to identify genetic markers to predict patient response to an investigational cancer drug
Amgen	DxS	Collaboration to establish DxS' TheraScreen K-RAS test as companion diagnostic for Vectibix
Roche	Ventana Medical Systems	Acquisition of technology to expand tissue-based cancer diagnostics

Source: Campbell Alliance