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Powers of Prediction

BY AMY K. ERICKSON

Predictive markers help oncologists match patients with the most effective treatments.

When Troy Richards was diagnosed in 1999 with a rare cancer of the adrenal glands called adrenocortical carcinoma, or ACC, his treatment options were either surgery or a drug called Lysodren (mitotane), a decades-old agent associated with severe side effects. The 44-year-old Scottsdale businessman opted for surgery, but in 2004, the cancer showed up in his left lung and then in his liver six months later.

After surgeries to remove the tumors, Richards had a molecular profile to identify any unique attributes contained within the genetic signature of his cancer. Based on the results, Richards and his oncologists were able to locate a target for attack.

“I think of a molecular profile as an educated review of the tumor’s genetics. My molecular profile identified several targets,” says Richards, who was so impressed with the promise of targeted genetic research that he initiated the ATAC Research Project (www.atacfund.org) to rapidly advance new treatments for ACC.

“We decided to go after one target in particular—an up-regulated gene that is highly expressed in multiple myeloma,” says Richards. Even though he didn’t have multiple myeloma, he received 21 treatments of the multiple myeloma drug Velcade (bortezomib). “I am now coming up on two years in remission.”

Examining a patient’s tumor for predictive markers allows oncologists to know ahead of time whether the tumor is likely to respond to the therapy being considered. Even among patients with the same type of cancer, responses can vary considerably, not only in terms of the drug’s impact on the tumor, but also in terms of the severity of side effects experienced by a patient.

The one-drug-heals-all approach is falling to the wayside as a person’s genetic information foretells which medical therapy has the greatest odds for benefit. Although they’re not yet widely available and the results aren’t foolproof, predictive markers—a class of biomarkers—can be used to match patients with therapies that are more likely to be effective with potentially fewer side effects, or rule out drugs that won’t be effective.

Finding the Target

“In cancer genetics, researchers study mutations in the tumor to figure out what caused the tumor in the first place,” says Carl Yamashiro, PhD, a senior researcher at the Biodesign Institute at Arizona State University. “In contrast, human genetics usually deals with inherited mutations that are passed down from generation to generation, or mutations that give a person an increased predisposition to developing a disease.”

New technology allowed researchers the ability to analyze multiple gene interactions and multiple gene pathways to develop cancer genetic tests. Understanding the interplay between numerous genes and their associated proteins increases the accuracy of predictive marker tests.

“The molecular profile gave me a better idea of what genetic pathways are causing my cancer to spread,” says Richards. “It gave me a little more hope that we may be able to try something that no one had ever tried on ACC.”

The challenge, says Yamashiro, is to develop drugs that kill the tumor without harming the patient. “The idea is to develop more targeted therapies to reduce toxicity to the body, while saving a patient from unnecessary side effects,” says Yamashiro.

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—Troy Richards

Translating to Therapy

The most successful predictive factors to date—the hormone receptors, estrogen receptor and progesterone receptor, and the HER2 (human epidermal growth factor receptor 2) protein—have made a significant impact on the way oncologists treat breast cancer.

Estrogen and progesterone receptors are powerful predictors for the effectiveness of hormonal therapy with tamoxifen and aromatase inhibitors. Doctors also use overexpression of HER2 as the marker for prescribing Herceptin (trastuzumab).

Beyond hormone receptor status, tamoxifen effectiveness can be predicted by CYP2D6, a gene that controls production of an enzyme needed to metabolize the drug. Natural variations in the gene can be associated with lower enzyme functioning, thus precluding any benefit from tamoxifen.

Matthew Ellis, MD, PhD, section head of medical oncology at Washington University in St. Louis, and colleagues at several institutions across the country have initiated the Breast Cancer Genome Atlas Project to further study and identify new markers in breast cancer. Although numerous biomarkers exist that indicate breast cancer risk or recurrence, “The question now is, where are the

[predictive] markers that are as useful as estrogen receptor and HER2?” asks Dr. Ellis. “We need more [predictive] markers that are strong indicators for specific targeted therapies.”

A currently available genetic test for colorectal cancer patients is the UGT1A1 molecular assay. The test detects variation in the enzyme responsible for the metabolism of the drug Camptosar (irinotecan). Patients who inherit two copies of this variation may not be able to metabolize the drug properly, which could lead to increased serious side effects. With this information, a doctor can better determine the right dosage for a specific patient to minimize harmful drug reactions.

In addition to uncovering new gene and protein markers, clinical trials are putting those discoveries to use by pairing novel predictive markers with new and existing therapies.

Studies suggest biomarkers can also vary with ethnicity. A recent study published in *Public Library of Science Medicine* found East Asians with non-small cell lung cancer respond better to chemotherapy than whites because East Asians are more likely to start with a so-called weaker form of epidermal growth factor receptor, which drives cell division. Ultimately, researchers hope studies will explain why specific drugs kill some tumors more effectively than others.

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—Matthew Ellis, MD, PhD

Treatment choices are also impacted by prognostic biomarkers. One approved and increasingly used prognostic marker test is Oncotype DX, a 21-gene test designed to predict the risk of recurrence for node-negative, estrogen receptor-positive breast cancer. By looking at specific genes that are active in breast cancer cells, a patient’s likelihood of recurrence can be estimated up to 10 years after surgery. By forecasting the degree of risk, Oncotype DX can help patients and oncologists select the most appropriate type of treatment.

A new prognostic test still under investigation is the Lung Metagene Predictor. Researchers from Duke University published a study in the *New England Journal of Medicine* in August 2006 that used a metagene model to predict which early-stage lung cancer patients need chemotherapy. The Lung Metagene Predictor test scans thousands of genes to identify patterns of gene activity in individual tumors that indicate whether a patient is likely to suffer a recurrence. Because recurrent lung tumors are typically fatal, identifying at-risk patients is critical in determining treatment.

From Genes to Proteins

Another type of genetic testing leverages breakthroughs in the field of proteomics, where investigators look at proteins, rather than genes, to help predict a patient's prognosis or response to therapy.

Emanuel Petricoin, PhD, is chief science officer for Theranostics Health, a newly formed protein biomarker company. "Our vision is to truly personalize therapy by providing key, missing information to the physician about the state of their patients' cellular circuitry, which contains the drug targets," says Petricoin, also a professor and co-director of the Center for Applied Proteomics and Molecular Medicine at George Mason University in Virginia.

Next year, Theranostics Health will use technology invented by Petricoin and his George Mason colleagues to give physicians a missing piece of information that was impossible to obtain before—a diagram of the activation of drug targets in each patient's tumor.

Gene expression and DNA analysis are unable to measure the activity of the drug targets, so this critical piece of information is lacking, says Petricoin. "While DNA is the information archive, it's the proteins that do the work of the cell—and it's the proteins that are drug targets. Physicians will be able to prescribe the best therapy, tailored to patient-specific information. Theranostics Health can do this with a proprietary protein microarray technology that enables the measurement of hundreds of drug targets directly from a tiny biopsy specimen."

As the research continues, use of predictive markers that predetermine outcomes based on a tumor's molecular makeup is quickly gaining a foothold in modern medicine. For some patients, like Troy Richards, it's already a reality.