

# THE KRAS GENE PUT TO THE TEST

By Dan Gordon

Until recently, approximately 10,000 advanced colon cancer patients each year endured chemotherapy with certain targeted drugs that carried a host of unpleasant side effects—and that, it turns out, had no chance of producing a positive response because of the patients' genetic profiles.

Now a simple test can determine ahead of time whether patients with metastatic colon cancer can benefit from a new type of targeted cancer treatment, the so-called epidermal growth-factor receptor (EGFR) inhibitors. Armed with this knowledge, oncologists are saving precious time, money, and unnecessary pain for many of their patients, while taking a pivotal step toward a more personalized approach to treating the disease.

The test, offered at Cedars-Sinai since last year, screens metastatic colon cancer patients' tumors for a mutation in a gene called KRAS prior to initiating treatment with the EGFR inhibitors. While these drugs have been shown to extend the lives of certain patients, a large study published in the *New England Journal of Medicine* in 2008 found them to be

ineffective for the 35–40 percent of patients with a KRAS mutation.

The reason, explains Marina Vaysburd, MD, an oncologist at Cedars-Sinai's Samuel Oschin Comprehensive Cancer Treatment Institute, comes down to biology. A protein found on the surface of cells (the EGFR receptor) acts as a light switch that, when active, sends signals for cellular growth. By "turning off" that switch, EGFR-inhibiting drugs can slow cancer growth. A mutated KRAS gene, however, prevents these drugs from reaching their target. "There is, in a sense, no electrical connectivity," Dr. Vaysburd explains.

Thus, Cedars-Sinai and other major medical centers now routinely screen colon cancer patients' tissues for the KRAS mutation at the time they are diagnosed with metastatic disease. No new procedure is involved: The mutation, if present, can be detected by examining tumor tissue from the original biopsy. Patients found to have the mutation continue to be treated with standard chemotherapy and other non-EGFR inhibiting targeted agents, including those currently offered in clinical trials. "The EGFR inhibitors have side



Amin "Chris" Riley-Portuges analyses colon cancer cell samples, looking for a specific genetic mutation. If found, patients can benefit from the most effective targeted treatments.

effects that can be quite limiting," says Dr. Vaysburd. "Patients are already struggling with their treatment, so to have a tool that can protect them from unnecessary pain is extremely valuable."

Additional gene mutations are being evaluated for their potential to provide Dr. Vaysburd and her colleagues with information on which drugs are best for which patients. "Cancer treatment isn't just generalized chemotherapy anymore," Dr. Vaysburd says. "We are using our knowledge about genes and tumors to move toward targeted therapies tailored to the individual patient's biology." 