

FEATURE STORY

# Bittersweet Gene

BY HEATHER L. VAN EPPS, PHD

*A gene called KRAS can predict which colorectal cancers will respond to a certain type of treatment—and which will not.*

On Easter Sunday in 2007, Doris Banks awoke from a nap with excruciating abdominal pain. Suspecting a burst appendix, she and her husband rushed to the emergency room. Her suspicion was confirmed, and Banks had an emergency appendectomy. But her surgery revealed something far more sinister than a ruptured appendix—Banks had colorectal cancer that had spread to her abdomen. The surgeon removed a large section of her colon and several lymph nodes along with her appendix.

Banks' initial reaction was shock. "I had probably only missed five or six working days in my life," she says. "I was just one of the healthiest people you would ever meet."

Banks, a 53-year-old salon owner from North Carolina, was diagnosed with metastatic colon cancer; tests showed the cancer had spread to her liver. Over the next year, Banks received multiple rounds of chemotherapy and had a large portion of her liver removed.

After recovering from liver surgery, Banks faced more bad news. A CT scan in early 2008 revealed the cancer had continued to spread. "At that point, I was extremely discouraged," recalls Banks, who had hoped the liver resection would remove the last of the cancer. "In your mind you think, 'OK, this is going to get it, and then I'll be on my way.' "

---



Doris Banks' cancer tested positive for mutated KRAS. Photo by Dylan Ray

With standard treatment failing, Banks' oncologist, Richard Goldberg, MD, director of oncology at the Lineberger Comprehensive Cancer Center at the University of North Carolina, considered putting Banks on a new cancer-fighting drug. But first he wanted to test her tumor for mutations in a gene known as KRAS, which, if positive, could mean she would have little chance of benefiting from the drug.

The drug Goldberg had in mind was Erbitux (cetuximab), which belongs to a growing family of targeted therapies that are changing the way doctors approach cancer treatment. By studying each patient's tumor to determine which biological pathways have gone awry, oncologists can use targeted drugs to hone in on precisely those pathways. This tumor characterization strategy will also help doctors to pinpoint which patients are most likely—or least likely—to benefit from a given drug.

### Predicting Response

Erbitux and a related drug called Vectibix (panitumumab) both block a protein called EGFR (epidermal growth factor receptor), which promotes the growth and survival of tumor cells and is often expressed at high levels on colorectal tumors.

In patients such as Banks who have advanced disease and do not respond to standard chemotherapy, Vectibix and Erbitux can be beneficial. Recent studies have shown that both drugs, given alone or in combination with standard chemotherapy, can improve response rates and progression-free survival in these patients. Despite the benefit of these drugs, however, the five-year survival rate for patients with stage 4 disease still hovers at a discouraging 5 to 10 percent.

The likelihood of benefiting from EGFR inhibitors is not equal among all patients. Erbitux and Vectibix were initially approved in 2004 and 2006, respectively, for the roughly 75 percent of colorectal cancer patients whose tumors express EGFR. And, in some studies, higher than normal expression of the receptor was linked to an even better response.

Although it made sense at the time to assume that only EGFR-expressing cancers

would respond to EGFR inhibitors, this logic hasn't held up, says Wells Messersmith, MD, director of the Gastrointestinal Medical Oncology Program at the University of Colorado in Denver. More recent studies show that the detection of EGFR has no impact on whether a patient will respond to these drugs.

So far, the most reliable way to predict whether a patient will respond to EGFR inhibitors is to test for certain "activating" mutations in the gene that encodes KRAS—a protein that transmits growth signals from EGFR—which occur in 30 to 50 percent of colorectal cancers. New studies show that patients whose tumors express a mutated version of KRAS will not respond to Erbitux or Vectibix.

"The trouble with the KRAS mutation is that it's downstream of EGFR," explains Goldberg, "It doesn't matter if you plug the socket if there's a short downstream of the plug. The mutation turns [EGFR] into a switch that's always on." But this doesn't mean that having normal, or wild-type, KRAS is a fail-safe.

### View Illustration: Following A New Path

"It isn't foolproof," cautions Goldberg. "If you have wild-type KRAS, you're more likely to respond, but it's not a guarantee." Tumors shrink in response to these drugs in up to 40 percent of patients with wild-type KRAS, and progression-free and overall survival is increased.

While it has been proven that KRAS status can predict whether a patient will respond to an EGFR inhibitor, it is not clear whether it affects overall prognosis—in other words, the overall survival of a patient regardless of treatment strategy. Some prospective studies have suggested that mutated KRAS is associated with shorter overall survival but others revealed no difference. And KRAS status did not influence overall survival in patients who received supportive care alone.

KRAS is also relevant for some patients with lung cancer. Although studies in lung cancer are less clear, they suggest patients with mutated KRAS are less likely to respond to the small-molecule EGFR inhibitors Iressa (gefitinib) and Tarceva (erlotinib). In these patients, however, EGFR overexpression or certain mutations in the receptor have been linked to better drug responses and longer life. Lung tumors with EGFR mutations are addicted to this pathway for their growth and survival, explains Phil Bonomi, MD, a lung cancer specialist at Rush University Medical Center in Chicago, so blocking this pathway cripples the cancer.

### Who Gets Treated?

Testing KRAS status in patients who qualify for EGFR inhibitors is not yet routine. (EGFR inhibitors are generally given to patients with advanced disease, although new data demonstrate Erbitux's efficacy as first-line treatment in combination with chemotherapy.)

Data from the latest KRAS studies are brand new, says Goldberg. "There are a lot of physicians who may not be aware of it yet."

For Goldberg and Messersmith, KRAS testing is becoming more important for any patient eligible for treatment with EGFR inhibitors. If testing becomes routine, says Messersmith, insurance companies may refuse to cover the cost of these pricey drugs for patients with mutated KRAS. The Food and Drug Administration may also change the labels on Erbitux and Vectibix to reflect the emerging KRAS data, although representatives from the FDA declined to comment at this time.

Mary Lou Kinder, a retired teacher from Arkansas, was diagnosed with stage 2 colon cancer in 2003. Chemotherapy with 5-FU put her cancer into remission for two years, but it returned in 2005, showing up in her lungs, liver, and uterus. She was put on a chemotherapy regimen known as FOLFOX (5-FU, leucovorin, and Eloxatin [oxaliplatin]) along with Erbitux. The chemotherapy caused severe neuropathy, making her painfully sensitive to extremes in temperature, and Erbitux had no effect on the cancer.

Kinder was spared the most frequent side effect of EGFR inhibitors—severe rash, which occurs in roughly two-thirds of patients. Developing a rash isn't necessarily bad, as it tends to crop up when the drug is working and has even been linked to increased survival. Kinder, who moved to Colorado this year, recently found out why she didn't respond to Erbitux and perhaps why she didn't develop a rash—her tumor expresses mutated KRAS. She was tested for KRAS status to determine whether she was eligible for a clinical trial that included Erbitux.

Another important reason to identify patients who are unlikely to benefit from EGFR inhibitors is to avoid unnecessary side effects. “What we shouldn't do is give a patient a drug with side effects that doesn't work. That's a no-brainer,” says Messersmith, who is now Kinder's oncologist.

In the worst-case scenario, the drugs can do more harm than good. Indeed, in two small studies of lung cancer patients (approximately 200 patients per study), patients whose tumors expressed mutated KRAS had an increased risk of death when treated with Tarceva compared with those treated with chemotherapy alone.

Whether patients currently on an EGFR inhibitor should be tested for KRAS status is less clear. Goldberg says he would consider ordering the test, particularly if the patient was suffering from side effects. But if the patient was tolerating the drug well, it may be difficult to justify stopping treatment.

“If a patient found out they had [a KRAS mutation] but was doing OK and had stable disease, I probably wouldn't take them off the drug,” says Bonomi. “You don't change a winner.”

## Other Options

Finding out that you're not eligible for the latest drugs can be hard on a patient. “We're taking away a therapeutic option for patients, which is very upsetting,” says Al Benson, MD, professor and associate director for clinical investigations at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago.

Patients may also wonder about the reliability of KRAS testing and the possibility that their test result might be wrong. But this possibility is slim, says Messersmith, because of the nature of the test. “Because [the test detects] a genetic mutation, there is no subjectivity; it’s either mutated or not.” And because the mutation can be detected in a tiny amount of DNA, the quality and purity of the sample is not critical. It also appears that KRAS mutation is an early event, so testing either the primary or metastatic tumor tissue should yield the same result.

The FDA-approved DakoCytomation EGFR pharmDx test, which detects EGFR on the surface of tumor cells, does not share the virtues of the KRAS test, and this may explain why detection of EGFR may not predict response to EGFR inhibitors. Not only is the EGFR pharmDx assay sensitive to the quality of the tumor sample, the results are subjective. Most tumors are a mixed bag, with only some cells expressing EGFR; if the cells that do not express EGFR significantly outnumber those that do, the test could come out negative. Poor quality tumor samples can also lead to false-negative results, and the expression of EGFR is not always the same at different tumor sites.

Banks, who tested positive for mutated KRAS, took the information in stride. Knowing she would probably not respond to EGFR inhibitors, her first question was, “OK, so what’s our next treatment?”

Often, the answer is Avastin (bevacizumab), which blocks the growth of blood vessels that feed the tumor. Plus, the effectiveness of Avastin does not seem to be influenced by KRAS status. Avastin was the next step for Kinder, who took the drug for six months before developing potentially dangerous blood clots, a side effect of the targeted agent.

But for patients such as Banks, who had already tried Avastin without success, the options are limited to experimental treatments in clinical trials.

“There really is no other standard approach for these individuals,” says Benson, who emphasizes the importance of continued research and innovation to identify potential new targets for drug development. “We need to understand tumor biology to get us closer to developing treatment strategies for those with mutated KRAS and those with wild-type KRAS who don’t appear to benefit from the anti-EGFR therapies.”

Researchers have tried to block KRAS itself, so far without much success. “But there are hundreds of other targets researchers are looking at,” says Messersmith, all of which are involved in tumor growth and survival.

Having exhausted other options, both Banks and Kinder opted for clinical trials. Banks recently enrolled in a phase II trial to test the efficacy of everolimus, a new drug that blocks a key protein called mTOR that is even further downstream from KRAS. Kinder is approaching her first evaluation in a phase I trial of an agent called GDC-0152, which blocks a protein that keeps tumor cells alive.

Banks is relying on her family and her strong faith as she begins the next phase of her treatment. Kinder, who also stresses the importance of a strong support system, has had three treatments and is feeling better than she has in the past year. “The only side effect I seem to be having is that I’m extremely tired,” Kinder says, “But I think that’s part of being a cancer patient—you’re not going to be jumping up and down and turning handsprings.”

*Editor's note: Doris Banks passed away at her home in Carteret County, North Carolina on April 11, 2009. CURE is proud to honor her memory.*