



Looking for a Target On Every Tumor

Lethal threat. Even some advanced lung tumors have been slowed by focused drugs.

Major cancer centers say they're getting ready to genotype every patient's tumor, hoping to match them with drugs specifically tailored to halt tumor growth

IN AUGUST 2007, KEVIN BRUMETT, AN athletic 29-year-old Massachusetts man, was stunned to find out why he was having severe back and stomach pain: He had advanced lung cancer. Brumett was young and had never smoked. Doctors at Beth Israel Deaconess Medical Center in Boston gave him standard chemotherapy, but the drugs became toxic over time, so they tried something new. They tested biopsies from his lung tumor for several mutations known to drive cell growth. "There was a small hope that if we found [the right sequence], there would be an approved drug or a clinical trial he would qualify for," says Daniel Costa, his oncologist at Beth Israel.

Brumett was lucky. His tumor cells had a fusion of two genes, *EML4* and *ALK*, recently found in a small fraction of patients with his type of cancer, non-small cell lung cancer, the most common form. A trial to test a drug targeted at *EML4-ALK* was just beginning at Beth Israel. A week after taking two pills daily to block the fusion gene's protein product, Brumett felt better. His nausea and fatigue were minimal, and the knifelike pain in his chest stopped.

Last summer on a patient message board,

Brumett shared the good news that his tumor was shrinking. His advice: "I want every single patient who has been diagnosed with non-small cell lung cancer to tell your doctor that you want to have your tumors biopsied and tested for every type of genetic mutation they know of." That fall, Brumett told his story on local television and at events held by patient advocates.

Tumor genotyping is not part of standard treatment. But that is changing. A handful of major U.S. cancer centers are laying plans to analyze the tumors of every lung cancer patient who comes in the door and check for an array of mutations. The aim is to match patients with a drug that goes after the tumor's genetic weak spot. Two centers, Harvard's Massachusetts General Hospital (MGH) in Boston and Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, have already begun; they will add several other cancer types in the coming months. Proponents hope that comprehensive tumor genetic testing—aided

by a major U.S. research effort to catalog mutations in tumors, called The Cancer Genome Atlas—will soon become a standard part of a patient's medical record. "The data are most useful if they're not squirreled away in a research lab," says medical oncologist Leif Ellisen of MGH.

But there are challenges. Even big cancer centers are still building the infrastructure needed to comprehensively genotype tumors. And testing is likely to help only a small fraction of cancer patients. Many tumors don't have any of the well-studied mutations. Only about 15% to 20% of all lung cancer patients have mutations that can be matched to targeted anticancer drugs, for example.

The grimmest reality, however, is that even when a match is found, the new targeted drugs have mainly slowed tumors, not stopped them in advanced lung cancer. After Brumett spent 8 months on the experimental drug, during which time he felt almost normal, his cancer developed resistance and began to spread. He died last May, 4 days after his wedding.

It's still early days for this technology, says Bert Vogelstein, a cancer biologist at Johns Hopkins University in Baltimore, Maryland. "I don't think there's any argument that, from a research perspective, these kinds of initiatives are great." But, he asks: "Is this something that's going to reduce suffering and death and prolong lives? I think it will, but it's still new."

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Jocelyn Kaiser.

Sharpshooters

Many agree with Vogelstein that tumor genotyping makes perfect sense as a tool for research. It's creating biobanks that make it easier to identify cancers that might be vulnerable to a new drug and will help attract companies to pay for trials aimed at the subset of patients most likely to benefit. That should speed treatments to the clinic, proponents say. "We simply cannot do another [large clinical] trial without having this kind of information," says John Niederhuber, director of the National Cancer Institute (NCI) in Bethesda, Maryland, a booster of the approach. Personalized treatment is exactly what NCI hopes will come out of The Cancer Genome Atlas, a huge sequencing initiative to find mutations in tumors. It is ramping up from a pilot phase and expects to tackle more than 20 cancer types in the next 5 years at a cost of \$275 million the first 2 years.

The idea of giving a patient a drug tailored to the genetic makeup of his or her tumor goes back at least a decade. The most famous example is the leukemia drug Gleevec, which targets a genetic mistake, known as the Philadelphia chromosome, that leads to uncontrolled cell growth. Over 95% of chronic myeloid leukemia patients carry this glitch and most early-stage patients respond to the drug. Another example is the breast cancer drug Herceptin, a monoclonal antibody that blocks HER2, a protein on a cancer cell's surface that receives growth signals that trigger the cell to grow. The drug is given only to the 25% of breast cancer patients whose tumors have a mutation that overexpresses *HER2*. Its presence is determined by counting copies of the *HER2* gene or detecting protein levels.

The developers of Herceptin suspected from the start that only certain patients would benefit. But this became clear for other targeted drugs only after the drug was tested in a general population. Take Erbitux, a drug used since 2004 to treat colorectal cancer. It homes in on EGFR, a cell receptor in the same family as HER2. Retrospective studies showed that the tumor cells of patients with a mutated oncogene called *KRAS* can thwart EGFR-targeted drugs. Now the drug has been recommended only for the 60% of patients with tumors that have a normal version of the *KRAS* oncogene.

For lung cancer, a turning point came in 2004. Researchers at Harvard's Dana-Farber Cancer Institute and MGH, and at MSKCC, were exploring why Iressa, another drug that targets EGFR, didn't seem to help most patients but dramatically shrank lung tumors in about 10% of patients. They realized that these "responders," more often Asian

and nonsmokers, had certain mutations in *EGFR* that made the tumors more vulnerable (*Science*, 30 April 2004, p. 658).

The initial poor showing led the U.S. Food and Drug Administration to sideline Iressa in the United States. But a new trial in Asia published this year clearly showed that for patients with the EGFR mutations, the rate of disease progression was slower in those who were on Iressa than it was in those on chemotherapy. The drug has now been approved in Europe for targeted use in patients with the *EGFR* mutations that make the cells vulnerable, and the manufacturer,

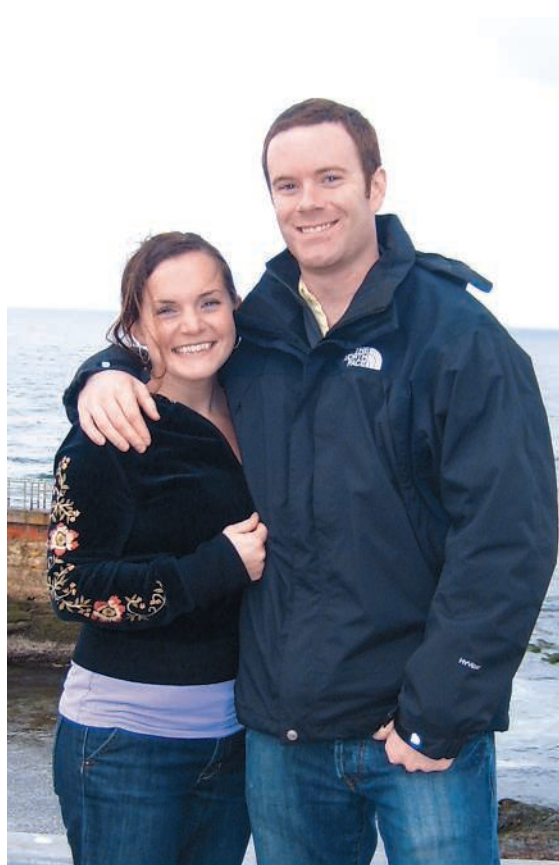
don't respond, the same pattern seen in colon cancer. In addition, *ALK-*EML4** and rarer mutations in genes such as *BRAF*, *MEK-1*, and *ERBB2*, make some patients' tumors susceptible to other kinds of targeted drugs (see graph, p. 220).

More targets

As the picture of gene-drug interactions fills in, researchers at some cancer centers have decided to make genetic profiling of lung tumors part of routine care. In January, MSKCC began to test all patients with lung adenocarcinomas, the main type of non-small cell lung cancer, for the *EML4-ALK* fusion gene and for 40 mutations in seven other genes. MSKCC is also testing colorectal cancers and will add melanoma and thyroid cancers next year. The data will go into a research database so that even if no drug is available for that patient now, oncologists can find patients with specific mutations for clinical trials months from now. This is the only way to find enough patients to test drugs targeting rare mutations, says molecular pathologist Marc Ladanyi of MSKCC. "Otherwise, it would take years," he says.

MGH began testing nearly all lung adenocarcinoma patients this spring for 113 mutations in 13 genes known to be involved in cancer. It aims to test most cancer types, including gastrointestinal and breast cancers, by the end of next year. Other cancer centers are jumping on board, including Dana-Farber, Duke Comprehensive, Vanderbilt-Ingram, MD Anderson, and Fox-Chase in Philadelphia. In the United Kingdom, Royal Marsden hospital has begun routinely testing some cancer patients to find subjects for early (phase I) clinical trials, says Marsden's Johann de Bono.

Genotyping is a good way to categorize tumors for clinical decisions—more robust than using tumor gene expression data to fingerprint a tumor, Vogelstein says. He and others argue that gene-expression analysis hasn't been as strongly validated. "Because DNA mutations are easy to assess and have a proven track record of response prediction, it makes good sense to start there," agrees Charles Sawyers of MSKCC, who helped develop Gleevec.



Good match. A new drug aimed at a mutation in his lung tumor made life almost normal for several months for Kevin Brumett (shown last December with fiancée Stephanie Fellingham).

AstraZeneca, is seeking approval for similar use in the United States. The Asia trial convinced even the skeptics that *EGFR* mutations should guide treatment decisions, says cancer biologist William Pao, who left MSKCC for the Vanderbilt-Ingram Cancer Center in Nashville this year.

The list of mutations that affect lung cancer patients' response to drugs, meanwhile, has continued to grow. Some *EGFR* mutations that crop up after treatment with EGFR-targeted drugs confer resistance to these agents. Patients with mutated *KRAS*

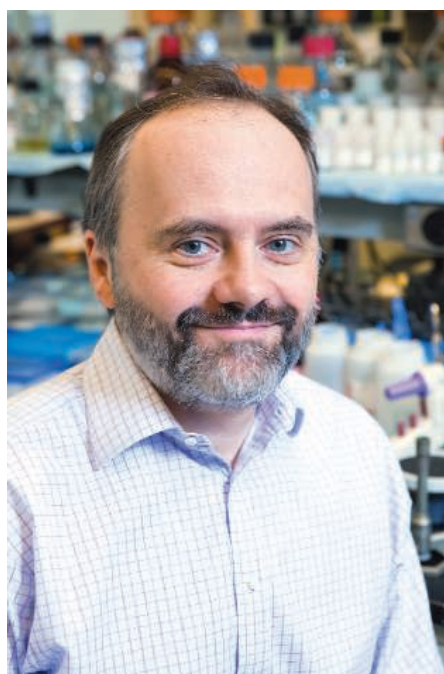
Researchers acknowledge that a broad screening effort to genotype tumors won't help most patients just yet. That's because relatively few targeted drugs have been developed, and many of the mutations isolated so far tend to rule out drugs, not rule them in. Take adenocarcinomas: A sizable portion of these tumors—at least 33%—don't have any of the known driver mutations that might be susceptible to attack, according to a literature review by Ladanyi and others. That observation is also emerging from large-scale tumor-sequencing projects such as The Cancer Genome Atlas. Still, it's worth developing new tools if they work against these tumors, Pao says. For a major threat like lung cancer, which kills 16,000 Americans a year, even if a drug helps only 1% or 2% of patients, that's a lot of people.

Gearing up

Cancer centers that hope to expand tumor genotyping still have a lot of kinks to work out. Logistics are the first challenge. "It sounds easy, but it requires top-down" organization, Pao says. Many pathology departments don't have a well-developed molecular diagnostics lab—so cancer centers are building them. Tissue banks are essential; centers that invested earlier in well-organized biobanks are at an advantage.

Because the genetic changes of interest include DNA rearrangements and deletions as well as mutations, these labs can't use just a single technology to detect them. And they must be able to produce results quickly after a sample is taken, within 2 weeks, so that oncologists can use them in time to make treatment decisions. Some cancer centers use stand-alone clinical assays to test for a few genes; others are buying genotyping systems to detect larger numbers of mutations, then adding tests to find other genetic changes. MGH's assay is "really labor intensive," says Ellisen: Technicians extract DNA from the tumor, amplify it, test for 60 loci, then perform further tests. On the plus side, once the technology is set up, it will be easy to incorporate new mutations being turned up by the cancer genome projects.

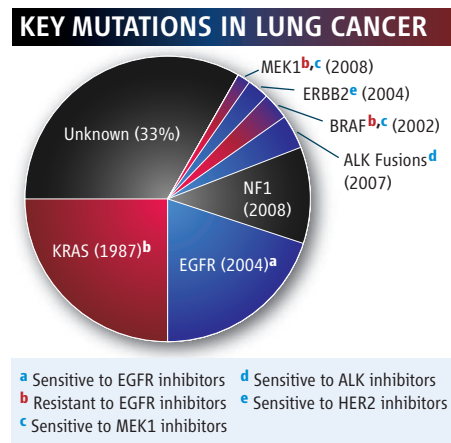
It's not yet clear how much a typical tumor test will cost or how much will be covered by insurance. Testing is often done today as part of a research project. MGH puts the actual cost of a typical tumor genetic analysis at about \$2000. (That may sound like a lot, but it's no more than a magnetic resonance imaging scan, Ellisen points out.) Ladanyi says MSKCC's assay will likely cost \$500 to \$1000. Insurers might be willing to cover that if it's done by a certified lab and costs no more



Personal touch. Memorial Sloan-Kettering's Marc Ladanyi and others want to use tumor genetic profiling to match lung cancer patients with the best drug.

than what they now pay—usually under \$1000—for standard clinical tests for *KRAS* and *EGFR*, he notes.

Looming over the field is the question of how owners of key intellectual property—such as Genzyme, Harvard, and MSKCC, which hold or have licensed patents for *EGFR* testing for lung cancer—will handle the



Points of attack. Several mutations found in lung adenocarcinomas, a common type of lung cancer, make them vulnerable to molecularly targeted drugs.

patent issues. Academic cancer centers could run into legal trouble if they test for these mutations on their own instead of using commercial labs that offer the tests. And the drugs are expensive. A year's supply of Herceptin—the standard treatment—costs about \$60,000.

Pao and others organized a "nuts and bolts" meeting of five cancer centers last

November to discuss the logistics, technologies, and data-management issues of genotyping lung tumors. One objective is to pool patients for joint trials of drugs and test them in combinations, the most promising strategy for avoiding drug resistance. Finding enough patients to get statistically significant results for a rare cancer subset "will require a type of collaboration never seen before," says Roy Herbst of MD Anderson in Houston, Texas, who heads a prototype for this kind of lung cancer trial. In a boost for such efforts, the National Institutes of Health last month awarded \$5 million in Recovery Act money to a consortium of 13 institutions that will test out tumor genotyping techniques on 1000 lung cancer patients.

Even with a system up and running smoothly, another hurdle is getting busy doctors to take an interest in the tests, says Joseph Nevins of Duke University in Durham, North Carolina, who is working on using gene-expression signatures to guide chemotherapy. They will have to go to the trouble of collecting tissue samples and getting patients' written agreement to have their genetic data used for research. "Maybe the samples will sit in somebody's freezer for 5 years and nothing will be done with them."

Indeed, one tough issue raised by tumor genotyping is how to weigh the merits of a procedure that is expensive, likely to become more complex, and rarely provides a cure—but will be intensely sought after by patients and their families. Even when the new gene-targeted drugs work, they may offer just what they gave Kevin Brumett: a few good months. In January, after a period of relatively good health—"We took vacations, we went to weddings," says his widow, Stephanie—Brumett went to the emergency room with a headache and learned that his cancer had metastasized to his brain. Although his doctors didn't seem that surprised, "for us, it came out of the blue," says Stephanie.

She expects to carry on her husband's efforts with advocacy groups to encourage patients to be tested for genetic mutations and volunteer for research. "He felt so strongly about it. It was a miracle drug, and he helped a lot of other patients get on the trial." And with more work, researchers hope to find ways to get around drug resistance. If that happens, knowing the genetic fingerprint of a patient's lung tumor will not only make life with cancer more bearable for a while but also turn this killer into a manageable disease.

—JOCELYN KAISER