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Variations on a Gene, and Tools to Find Them

By ANNE EISENBERG

CANCERS were once named strictly for the tissue where they originated in the breast, prostate or other part of the body. Now, in the age of genetically informed medicine, cancers may also come with a more specific lexicon: the names of mutated genes deep within tumors that cause cells to become cancerous.

Most of these gene flaws — there are scores of them, and they have names like BRAF V600E — are relative newcomers to medical terminology, as are most of the anticancer drugs, still in early testing, that are aimed at them. Development of the new drugs has been spurred by the falling cost of decoding DNA and the prospects of premium prices for drugs that specifically attack the molecular drivers of cancer.

Even medical oncologists can be daunted by the complexity of these genes and the therapies intended to fight them, said Dr. William Pao, a physician and scientist at Vanderbilt University who studies cancer mutations in addition to seeing patients. “There are so many genes and so many mutations,” he said. “The human brain can’t memorize all those permutations.”

To guide doctors and their patients, many tools are on the market, including one created by Dr. Pao and colleagues: the Web site [My Cancer Genome](#). The site, which started two years ago, is maintained by 51 contributors from 20 institutions. It lists mutations in different types of cancer, as well as drug therapies that may or may not be of benefit. Most of the drugs are in clinical trials; a few have been approved by the Food and Drug Administration.

The typical user of this information is an oncologist, Dr. Pao said. At the Web site, the doctor can select “[melanoma](#)” and “BRAF,” for instance, or “lung cancer” and “BRAF,” and see all types of mutations in the BRAF gene that occur in those instances. The doctor can then check for national and international drug trials aimed at these alterations.

Different treatments may work in different molecular subsets of cancer, depending on the mutation. More than 700 oncology drugs are now in development, many aimed at DNA defects, Dr. Pao said, “and the number will only accelerate.”

“We are moving away from the tissue of origin to the molecular basis of the cancer, using the mutation to search for a treatment,” he said.

Users do not pay to access the Web site. “Our premise is that much of the discovery work was paid for by taxpayer dollars,” he said, “so the site is public and freely available.” The site is supported almost entirely by the university and by philanthropy.

Before doctors go to My Cancer Genome or a similar site, their patients must have a diagnostic test to find relevant mutations. At one time, such tests were limited mainly to patients at large university cancer centers, and were often hard to interpret, said [Dr. Fadi Braiteh](#), an oncologist who practices at [Comprehensive Cancer Centers of Nevada](#) in Las Vegas. Now tests for the mutations and the analyses of the results are available to neighborhood doctors.

In the last four months, Dr. Braiteh has begun using a test, called [FoundationOne](#), from [Foundation Medicine](#) in Cambridge, Mass. “In some cases, the test has allowed us to treat with a drug we hadn’t thought of,” he said. The cost is generally covered by insurance, he said; the list price is \$5,800. (Dr. Braiteh has no financial connection to Foundation Medicine.)

For the [FoundationOne](#) test, the company analyzes a bit of the tumor smaller than a garden pea, extracting the DNA and sequencing genes known to be altered in cancer, said [Dr. Michael J. Pellini](#), president and C.E.O. of Foundation Medicine. Alterations are matched with approved drugs or clinical trials. The treatment options are listed in a report that accompanies the test results. The company began offering its test last year, and it is now used by more than 1,000 doctors, he said, as well as by 15 companies developing cancer drugs.

Dr. Nicholas Koutrelakos, an oncologist who practices at [Maryland Oncology Hematology](#) in Columbia, Md., has used the [FoundationOne](#) test for the last eight months. “It wasn’t helpful for everyone,” he said, but it did help with four of 10 patients, particularly one with lung cancer who had not responded to [chemotherapy](#). “It gave me some guidance,” he said. “We were able to give a drug we’ve never used before for this mutation.” The patient began taking the drug, and it has been effective so far.

Foundation Medicine, which is privately owned, has financial backing from many sources, including Third Rock Ventures, Google Ventures, Kleiner Perkins Caufield & Byers and private investors like Bill Gates.

Many other genetic tests are coming or are already on the market. [Genomic Health](#), for example, has a test costing \$4,290 that helps determine if a woman with [breast cancer](#) should receive chemotherapy.

The [FoundationOne](#) test concerns itself with a very small subset of the three billion base pairs of DNA in a set of human chromosomes, analyzing the tumor samples for the 236 genes “known to be unambiguously involved in cancer,” a company spokeswoman said. As additional genes are identified, these will be added to the test.

Christopher Milne, [director of research](#) at the [Tufts Center for the Study of Drug Development](#) at Tufts University, said that there were still many unanswered questions in this field. “There is so much we don’t know about mutations yet,” Dr. Milne said.

[Dr. Razelle Kurzrock](#), director of the center for personalized cancer therapy at the [Moore Cancer Center](#) at the University of California, San Diego, says she thinks that comprehensive tests like FoundationOne will be invaluable in the future. “We have to know what’s inside a tumor cell that is causing it to grow,” she said, “and match that knowledge up with the specific drug that targets the abnormality.”

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