Treating Cancer Based on Its Genome
A "watershed" in sequencing technology helps physicians choose drugs for cancer patients.
By Emily Singer

1. Just two years ago, scientists published the sequence of the first cancer genome, detailing the constellation of genetic mutations that likely enabled tumor cells to grow out of control. Now a handful of scientists and physicians are starting to use data from this "whole genome analysis" to help them choose the best drugs for their patients. Over the weekend at the Personal Genomes conference in Cold Spring Harbor, New York, three researchers presented cases highlighting how the approach can work on rare tumors and other unusual cases. "It's time to use whole genome sequencing as a diagnostic tool to understand atypical cancer cases," said Richard Wilson, a geneticist at Washington University School of Medicine who led one of the studies.

2. Scientists have long known that cancer results when healthy cells acquire a combination of genetic mutations that let them grow out of control. Previous research has identified genetic variations that increase the risk that an individual will develop certain kinds of cancer, as well as specific mutations within the cancer cells themselves that render them sensitive to certain drugs.

3. With the advent of cheap sequencing, researchers can now scour tumors with unprecedented depth. They can compare almost all of the three billion letters of DNA in a patient's healthy cells and cancer cells and look for differences. Using this approach, researchers have sequenced hundreds of cancer genomes in the last year.

4. In one of the first cases to apply the technology to clinical practice, scientists from the BC Cancer Center in Vancouver twice sequenced the genome of cancer cells in a patient with a very rare type of tumor--an adenocarcinoma (en français = adénocarcinome) of the tongue. They sequenced the DNA after the cancer had spread, and then again after it developed resistance to a drug.

5. Because the cancer is so rare, there were no standard courses of treatment for oncologists to choose from. So Steven Jones and collaborators used the genetic variations that they had identified, along with their knowledge of the molecular pathways that have been implicated in cancer, to create a model for what might be driving cancer in that patient. They narrowed in on a defect in a specific molecular pathway linked to cancer cell growth. The patient's physician then chose to treat him with a drug that inhibits that pathway, and the patient's tumor stopped growing for eight months. "A rare tumor is never going to have clinical trials," says Jones. "With diseases with no options, any level of information is appreciated."

6. Unfortunately, as often happens with molecularly targeted drugs, the cancer eventually grew resistant to the treatment and started growing again. So researchers sequenced the new tumor tissue to determine what kind of genetic changes gave the cancer its new power. They found that the pathway implicated in the previous analysis had become even more active, and that a second pathway, also linked to cancer, had been altered as well. The research was published last month in *Genome Biology*.

7. The second set of findings came too late to help the patient. But Jones envisions how to move forward should a similar case come along. In a technique that is gaining traction in clinical cancer research, scientists implant tumor cells biopsied from a patient into a mouse, which then grows a tumor similar to the patient's. Jones's team could then hypothesize which drugs would work best using the model created from the genome analysis, and test those drugs on the mouse before trying them in the patient.

8. In a second case, Wilson and collaborators at Washington University sequenced the cancer genome of a 39-year-old woman with an unusual case of acute myeloid leukemia (AML), a disease that originates in bone marrow and grows from blood-forming stem cells. Wilson's team has sequenced

about 50 AML cancers, most purely for research; this was the first instance of trying to use the findings to aid a patient.

9. Physicians currently try to predict the prognosis for patients with different subtypes of AML by looking for certain abnormalities in their chromosomes. One common abnormality--a fusion of two different proteins--means that the patient is likely to respond to a drug called all-trans-retinoic acid (*ATRA*), which replaces the role of one of the proteins mutated in the fusion. "ATRA is basically a cure for people with this fusion," says Elaine Mardis, another senior scientist on the study.

10. Standard testing showed the patient did not have the typical fusion, but genome analysis revealed that she had a never-before-seen version of it not detectable with the other test. She was given the drug and has been in remission for several months. "I'm not trying to hype it at all, but the treatment saved the patient's life," says Wilson. Adds Mardis, "This might be the watershed event that makes cancer patients begin to ask for this."

11. The researchers are now looking at other patients with unusual cases of leukemia and are working on a simple test to detect this more unusual form of the fusion, without whole genome sequencing. "If they have truly found a new marker, that is something that could be tested in the clinic immediately," says Jones. "This is an example of an incredible stride forward for the field."

12. The opportunity to use whole genome sequencing to help cancer patients is still extremely rare. It's limited to medical centers with large sequencing facilities, the funding to undertake such a project, and ethical review procedures in place to assess and approve this type of experimental approach. But the cost of sequencing itself--about $10,000 to $20,000 for a human genome--is quickly becoming less of a roadblock. It's now on par with other medical tests and treatments for cancer; an MRI scan costs about $6,000, and cancer patients typically have several. But both Jones and Wilson point out that the process of interpreting the genome and using it to make decisions is still very labor-intensive, requiring a large team with diverse expertise in medicine, oncology, genomics, and information technology.

13. Some scientists are concerned that the research is too preliminary to be applied to patients, and that its success will be difficult to evaluate. Commenting broadly on the concept of using whole genome data to guide treatment decisions, David Altshuler, a geneticist at the Broad Institute, in Cambridge, Massachusetts, points out that it's impossible to conclude from individual cases whether a particular treatment worked because of a mutation identified in the genetic analysis. It might have worked for some other reason. The scientists carrying out the research say that these patients have no other options, and that the genetic information is just one piece of data that might help doctors chart the best course.

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