Decoding cancer patients' genomes is powerful diagnostic tool

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Timothy Ley, M.D., left, and Richard Wilson, Ph.D., and their Washington University colleagues have shown the power of sequencing cancer patients' genomes as a diagnostic tool. Credit: Washington University

Two new studies highlight the power of sequencing cancer patients' genomes as a diagnostic tool, helping doctors decide the best course of treatment and researchers identify new cancer susceptibility mutations that can be passed from parent to child.

Both studies, by researchers at Washington University School of Medicine in St. Louis, are reported April 20 in the Journal of the American Medical Association.

In one case, sequencing the genome of a 39-year-old woman with acute myeloid leukemia (AML) uncovered a novel genetic mistake, leading

doctors to change the course of her treatment. Instead of a stem cell transplant, which had been recommended because standard testing indicated poor survival odds, she was treated with a targeted chemotherapy regimen and is now in remission.

In another, sequencing the genome of a woman who died at age 42 after developing breast and ovarian cancer and then leukemia allowed researchers to identify a new mutation in a gene known to dramatically increase cancer risk. The patient's family members were informed of the finding, and genetic counseling and testing were recommended for the woman's three children, who have a very high risk of developing cancer at a young age if they inherited the mutation.

"These cases of personalized genomic medicine are just some of the first examples of what will likely be commonplace in the near future," write Boris Pasche, MD, PhD, of the University of Alabama in Birmingham, and Devin Absher, PhD, of the HudsonAlpha Institute for Biotechnology in Alabama, in an editorial that accompanies the papers.

"We are beginning to see how genome sequencing can make a real difference in the lives of cancer patients and their families," says senior author Richard K. Wilson, PhD, director of Washington University's Genome Institute and a leader in the field of cancer genome sequencing. "Both studies underscore the value of whole-genome sequencing as a diagnostic tool. We could not have identified these mutations using conventional tests or targeted sequencing approaches because they involved unexpected structural changes to the DNA, which can only be found by looking across the entire genome."

Advances in technology have enabled scientists to sequence the genomes of cancer patients at a cost and speed that was unimaginable even a few years ago.

But Wilson cautions that it's not yet practical to routinely sequence cancer patients' genomes because the cost is still relatively high, and scientists don't yet fully understand the breadth of genetic changes that drive cancer development. Select cases like these, however, offer a glimpse of the way personalized genome sequencing can transform the way doctors diagnose and treat cancer patients and their families.

In the first study, the patient was referred to the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine for a stem cell transplant. But doctors quickly realized her case was a diagnostic conundrum. On the one hand, many features of her leukemia cells indicated a classic case of acute promyelocytic leukemia (APL), a subtype of AML.

But the patient did not have a common genetic alteration associated with APL: a piece of chromosome 15 that is swapped with a piece of chromosome 17, which would have provided a definitive diagnosis. This defect creates a fusion of two genes that prevents white blood cells from maturing, and it is known to initiate APL.

Patients who have the 15;17 chromosome swap don't need a stem cell transplant because they can be effectively treated with a chemotherapy regimen that includes all-trans retinoic acid, or ATRA, which targets the genetic error.

The stem cell transplant had been recommended for this patient because a standard diagnostic test indicated her odds of long-term survival were less than 15 percent. The test showed that a number of chromosomes in her leukemia cells were missing, broken or rearranged, which is associated with a very poor prognosis.

The patient's oncologist, Peter Westervelt, MD, PhD, director of the Bone Marrow Transplant/Leukemia Section in the Division of Oncology

at Washington University, suggested that sequencing her genome could resolve the diagnostic dilemma.

"We didn't want to go through with a stem cell transplant unless we were absolutely certain she needed it," he says. "It's a very rigorous therapy, with a significant risk of mortality and long-term complications. Sequencing the genome of the patient's leukemia cells offered the opportunity to resolve this dilemma in 'real time' and allowed us to make the correct call in recommending further therapy."

The researchers sequenced both the genome of the patient's cancer cells and the genome of her normal, healthy cells, taken from a skin sample. By comparing the DNA sequences side by side, they could identify changes in the leukemia cells that contributed to her cancer.

Notably, they discovered a novel genetic rearrangement: a small piece of chromosome 15 was inserted into chromosome 17, creating the same genetic defect that results from swapping pieces of the two chromosomes.

"This tiny insertion trumps everything else we see in the patient's cancer cells and told us that chemotherapy with ATRA — not a stem cell transplant — was the best treatment option for her," explains lead author John Welch, MD, PhD. "Conventional testing could not detect the insertion because it is so small, but with whole-genome sequencing we can find all the mutations that underlie a patient's cancer, even those that are unexpected and rare, like this one."

Based on the sequencing, the patient received chemotherapy with ATRA and remains in remission 15 months after her diagnosis. Patients treated with this regimen have a long-term survival rate of 70 percent.

In all, it took the researchers six weeks to complete the sequencing and

validate their results, at a cost of $40,000 ($20,000 per genome). As technology improves, the time to sequence a patient's genome is expected to shorten, too.

But even a six-week time frame is reasonable for many cancers, such as breast, lung and colon, where chemotherapy often is not initiated until after the patient has recovered from surgery to remove the tumor, and for acute leukemias, where patients typically receive chemotherapy right away to induce a quick remission before doctors must decide whether additional chemotherapy or a stem cell transplant is needed to keep the leukemia at bay.

Interestingly, when the researchers examined other cases of APL, they found similar 15;17 insertions in two patients, suggesting these genetic defects are more common than they originally thought and often undiagnosed.

In the second study, researchers used whole-genome sequencing to identify a new cancer susceptibility mutation in a woman who developed breast cancer at age 37 and ovarian cancer at age 39. Despite treatment, the ovarian tumor returned at age 42 and she received additional chemotherapy. The patient died six months later, days after developing AML, a complication possibly related to the extensive chemotherapy she had received.

The patient's doctors suspected she had a genetic susceptibility that increased her risk of cancer, but her family medical history — with cancer in only one relative on her mother's side — did not suggest an inherited predisposition.

"We see cases like this all the time," says lead author and oncologist Daniel Link, MD, the Alan A. and Edith L. Wolff Professor of Medicine at Washington University. "A patient develops one or two primary

cancers at a young age, and there's no significant family history of cancer. The red light goes on; we know there has to be a reason why."

In women who develop breast or ovarian cancer at a young age, physicians typically conduct commercial testing for BRCA1 and BRAC2 mutations, which are known to increase the risk of breast cancer and ovarian cancer, but often the results are negative.

That was the case for this patient, too.

"But this patient had three children," Link says. "If we could find the mutation that increased her cancer risk, it would be important for her family to know."

When the researchers sequenced the patient's genome using a sample of skin cells and, as a comparison, the genome of her leukemia cells, the researchers uncovered a novel and unexpected mutation in TP53, a well-known tumor suppressor gene involved in DNA repair. In her case, a critical chunk of the gene had been deleted from the DNA in her skin cells, indicating she was born with the mutation, which likely increased her risk of developing cancer while young.

To determine whether the patient had inherited the genetic error from her mother, they obtained a blood sample and sequenced the gene but did not find the mutation. The patient's father had died but there was no history of cancer on his side of the family to suggest she may have inherited the mutation from him.

Rather, the researchers suspect the TP53 mutation arose spontaneously in the patient's genome and developed very early in life, likely at conception.

Finding the TP53 mutation has important implications for the patient's

three children because they have a 50 percent chance of inheriting the genetic error. Individuals who inherit TP53 mutations have a 90 percent lifetime risk of cancer and a 50 percent chance of developing cancer before age 40.

The researchers designed the study in such a way that any relevant genetic information could be relayed to the patient's family. If genetic testing indicates any of the children inherited the TP53 mutation, they would be recommended to get regular screening for early detection of cancer.

As the cost of whole-genome sequencing continues to fall, the researchers expect that it will become the standard method by which scientists search for rare, inherited cancer mutations.

Unlike sequencing techniques that focus only on genes, which make up just 1 percent of the genome, whole-genome sequencing captures the full range of genetic alterations in DNA, including both small and large insertions, deletions and other structural variations.

"Whole-genome sequencing is the most powerful diagnostic tool we've ever had to define all the mutations in the genome of a cancer patient," says co-author Timothy Ley, MD, the Lewis T. and Rosalind B. Apple Professor of Oncology at Washington University. "We no longer have to rely on techniques where we're guessing what could be wrong. Now, we can find all the genetic mutations that contributed to a patient's cancer. As we move forward, we think this will lead to more opportunities to improve the care of patients and their families."

Wilson, Ley and their colleagues at the Genome Institute have pioneered whole-genome sequencing of cancer patients' DNA to identify genetic mutations at the root of the disease. To date, they have sequenced the genomes of more 300 cancer patients and their tumors.

More information: Welch JS, Westervelt P, Mardis ER, Ley TJ, Wilson RK. Use of Whole-Genome Sequencing to Diagnose a Cryptic Fusion Oncogene. Journal of the American Medical Association, April 20, 2011.