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DNA sequencing lays foundation for personalized cancer treatment

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Scientists at Washington University School of Medicine in St. Louis are using powerful DNA sequencing technology not only to identify mutations at the root of a patient's tumor – considered key to personalizing cancer treatment – but to map the genetic evolution of disease and monitor response to treatment.

"We're finding clinically relevant information in the tumor samples we're sequencing for discovery-oriented research studies," says Elaine Mardis, PhD, co-director of The Genome Institute at the School of Medicine. "Genome analysis can play a role at multiple time points during a patient's treatment, to identify 'driver' mutations in the tumor genome and to determine whether cells carrying those mutations have been eliminated by treatment."

This work is helping to guide the design of future cancer clinical trials in which treatment decisions are based on results of sequencing, says Mardis, who is speaking April 1 at the opening plenary session of the American Association for Cancer Research annual meeting in Chicago. She also is affiliated with the Siteman Cancer Center at the School of Medicine and Barnes-Jewish Hospital.

To date, Mardis and her colleagues have sequenced all the DNA – the genome – of tumor cells from more than 700 cancer patients. By comparing the genetic sequences in the tumor cells to healthy cells from the same patient, they can identify mutations underlying each patient's cancer.

Already, information gleaned through whole-genome sequencing is pushing researchers to reclassify tumors based on their genetic makeup rather than their location in the body. In patients with breast cancer, for example, Mardis and her colleagues have found numerous driver mutations in genes that have not previously been associated with breast tumors.

A number of these genes have been identified in prostate, colorectal, lung or skin cancer, as well as leukemia and other cancers. Drugs that target mutations in these genes, including imatinib, ruxolitinib and sunitinib, while not approved for breast cancer, are already on the market for other cancers.

"We are finding genetic mutations in multiple tumor types that could potentially be targeted with drugs that are already available," Mardis says.

She predicts, however, that it may require a paradigm change for oncologists to evaluate the potential benefits of individualized cancer therapy. While clinical trials typically involve randomly assigning patients to a particular treatment regimen, a personalized medicine approach calls for choosing drugs based on the underlying mutations in each patient's tumor.

"Having all treatment options available for every patient doesn't fit neatly into the confines of a carefully designed clinical trial," Mardis acknowledges. "We're going to need more flexibility."

When during the course of cancer mutations develop also is likely to be important in decisions about treatment. In a recent study, Mardis and her team mapped the genetic evolution of leukemia and found clues to suggest that targeted cancer drugs should be aimed at mutations that develop early in the course of the disease.

Using "deep digital sequencing," a technique developed at The Genome Institute, they sequenced individual mutations in patients' tumor samples more than 1,000 times each. This provides a read-out of the frequency of each mutation in a patient's tumor genome and allowed the researchers to map the genetic evolution of cancer cells as the disease progressed.

They found that as cancer evolves, tumors acquire new mutations but always retain the original cluster of mutations that made the cells cancerous in the first place. Their discovery suggests that drugs targeted to cancer may be more effective if they are directed toward genetic changes that occur early in the course of cancer. Drugs that target mutations found exclusively in later-evolving cancer cells likely may not have much effect on the disease because they would not kill all the tumor cells.

Mardis says that sequencing the entire genome of cancer cells is essential to piecing together an accurate picture of the way cancer cells evolve. If the researchers had sequenced only the small portion of the genome that involves genes, they would not have had the statistical power to track the frequency of mutations over time. (Only 1 to 2 percent of the genome consists of genes.)

In another study, a phase III clinical trial of post-menopausal women with estrogen-receptor positive breast cancer, the Washington University researchers have shown that sequencing can help to predict which women will respond to treatment with aromatase inhibitors. These estrogen-lowering drugs are often prescribed to shrink breast tumors before surgery. But only about half of women with estrogen-receptor positive breast cancer respond to these drugs, and doctors have not been able to predict which patients will benefit.

Interestingly, by sequencing patients' breast tumors before and after

aromatase inhibitor therapy, the researchers identified substantive genomic changes that had occurred in responsive patients, whereas the genomes of unresponsive patients remained largely unchanged by the therapy.

"No one has ever looked at treatment response at this level of resolution," Mardis says. "It's so obvious who is responding."

In addition, the researchers have identified a series of mutations in the breast tumors that have corresponding small-molecule inhibitor drugs that target defective proteins. This finding indicates that for women who are not responding to aromatase inhibitors, treatment options may include combining conventional chemotherapy with the indicated small-molecule inhibitor.

"We felt it was important to show there could be therapeutic options available to patients who are resistant to aromatase inhibitors," Mardis says. "As we move forward, we think sequencing will contribute crucial information to determining the best treatment options for patients."

Provided by Washington University School of Medicine

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