

Looking at Big-Picture DNA and Protein Changes in Ovarian Cancer Patients

Team uses large-scale proteogenomic changes to identify which ovarian cancer patients should look beyond standard treatment options.

August 28, 2023 By Fred Hutch News Service and Sabrina Richards

Precision oncology research is typically about finding ways to match patients with a treatment tailored to their tumors. But in [new work published this month in Cell](#), a research team instead developed a potential diagnostic that can identify patients with high-grade serous ovarian cancer who won't benefit from standard treatment.

The collaborators, including investigators from Fred Hutchinson Cancer Center, the University of Arkansas for Medical Sciences and Icahn Mount Sinai, hope that the results could someday be used to help these patients access alternative treatments.

The promising new results come from a different experimental approach: rather than looking gene by gene, or protein by protein, the team took a big-picture computational approach. They used machine learning to look at large-scale protein and DNA changes to discern patterns that could distinguish patient tumors.

"To fully realize precision oncology, we need to get beyond single protein and single gene biomarkers in diagnostics," said Fred Hutch oncologist, proteomics expert and Aven Foundation Endowed Chair holder [Amanda Paulovich, MD, PhD](#). "The next generation of diagnostics are going to be multi-analyte panels coupled with clinical data and algorithm-driven patient care. We're trying to move in that direction with this project."

The [large, multi-institutional collaborative team](#) was part of the National Cancer Institute's [Clinical Proteomic Tumor Analysis Consortium](#), or CPTAC. Computational biologist and co-senior author [Pei Wang, PhD](#), at Icahn School of Medicine at Mount Sinai, helped the team develop an approach that integrates information about large-scale protein and DNA changes to reveal alterations in biological processes that could play a role in ovarian cancer development, progression and response to treatment.

"Right now, we can't identify chemo-refractory ovarian cancer patients up front," said co-senior author [Michael Birrer, MD, PhD](#), who directs UAMS' Winthrop J. Rockefeller Cancer Institute. "We find them by default: They get sick and pass away so quickly that they can't even be put on new

clinical trials.”

The team’s new predictive algorithm could change that.

“We now have a 64-protein predictor that identifies up front — before they get treatment — about 35% of patients with refractory disease, at a very high specificity,” Paulovich said.

In addition to honing the 64 proteins that best signified potential drug resistance, the researchers identified five different types of [high-grade serous ovarian tumors](#) that seem to be driven by different biological mechanisms.

In the long term, the scientists hope that the tumor subtypes they identified can aid in the discovery of new treatment targets and form the basis of diagnostic tests that will help ovarian cancer patients get matched to the best, most tailored treatment for them.

Diagnostic Gaps Need Filling

Paulovich’s drive to develop better cancer diagnostics was inspired by her experience treating cancer patients — seeing some patients with tumors that responded well, while others had tumors that recurred, developed treatment resistance or never responded to begin with.

“And we had really no way of predicting that and we still oftentimes struggle with adequate diagnostics to personalize treatment based on a person’s tumor characteristics,” Paulovich said.

At the time, precision oncology efforts aimed at finding drug targets and predict treatment responses only focused on changes in DNA.

“It was clear that [DNA] was going get us part way there — which it has — but it wasn’t going to be the complete solution to the problem, and that one missing piece was the proteome,” she said.

The [proteome is the collection of all the proteins](#) in a cell or tumor. Proteins are the molecules that our genes encode, and they run all the biological processes that allow our cells to function properly. When gene mutations promote cancer or influence its response to treatment, they do so by changing how proteins function. In fact, most therapies target proteins, not genes. Because cancer-driving protein changes are not always reflected in tumor DNA, making insights into the proteome is a critical piece of biomarker discovery.

Two decades ago, Paulovich dedicated herself to [proteomics precision oncology research](#), seeking to find the proteins that could be used as treatment matchmakers or treatment targets.

Ovarian Cancer Treatments: In Need of a Shake-Up

People diagnosed with ovarian cancer need better treatment options and improved ways to tailor their treatments. The standard of care is chemotherapy, a combination of paclitaxel and platinum-

based drugs, that causes most patients' tumors to shrink — but not every tumor responds.

"The common theme for almost 40 years is that 10-15% of patients [with high-grade serous ovarian tumors] are refractory, meaning they do not respond to initial therapy," Birrer said.

Roughly [19,700 U.S. women are diagnosed with ovarian cancer each year](#), and 75% of them have serous ovarian cancer. Three-quarters of those patients are diagnosed with advanced disease, which means that anywhere from about 1,000 to 1,600 people with ovarian cancer may have tumors that will resist standard treatments from the beginning. Only half of patients whose tumors don't respond to initial treatment will survive past 12 months. While the 11th most common cancer among women, ovarian cancer is the fifth leading cause of cancer-related death among women, according to the Surveillance, Epidemiology and End Results ([SEER](#)) statistics.

Unfortunately, prior to treatment, there's no way to know whose tumor will fall into that refractory 10-15%. As a result, all ovarian cancer patients receive paclitaxel and a platinum drug, and all ovarian cancer patients run the risk of side effects — whether the therapy treats their tumor or not.

"We need to be able to determine whose tumor will respond to platinum-based therapies or not, so we can spare patients with chemo-refractory tumors the toxicity of ineffective therapy, and quickly refer them to clinical trials to help identify an effective treatment," Paulovich said.

This is a longstanding clinical need, Birrer said.

"We've made no impact on survival for patients with chemo-refractory disease in decades, and because we can't identify these patients up front and get them into clinical trials, no one's been successful at developing regimens that would be effective for patients with chemotherapy-refractory tumors," he said.

Most research efforts have focused on individual genes and individual proteins, which are not sufficient to accurately predict chemo-refractory cancers, Paulovich said.

Ovarian cancer biomarker discovery had been hampered by technological hurdles, Paulovich said. Clinical-grade assays to detect potential biomarkers only exist for a subset of proteins, and very few can be multiplexed, where you measure several biomarkers at a time.

As a result, most studies focused on the handful of possible biomarkers for which detection assays exist, testing them one at a time. Many high-quality studies have mapped individual genes to many different cellular processes in ovarian cancer, but no biomarker test to identify chemo-refractory tumors based on a single gene or protein has made it to the clinic.

"Everyone was looking under the same lamppost," Paulovich said.

The current study aims to widen the view. It leverages decades of insights into proteins and genes that play important roles in ovarian cancer, new technologies that allow scientists to detect

multiple proteins at a time, as well as advances in data analysis and machine learning algorithms.

Wang, Paulovich's longtime collaborator, led development of a computational prediction model to assess patterns in proteomic data. It incorporates advances in computational approaches that enable researchers to look at interactions between proteins involved in pathways. This enables the algorithms to see patterns that people can't, Wang said.

"A human being can see a couple of biomarkers, and make decisions," she said. "But if there are tens of proteins, or hundreds or thousands, it's difficult for a person to see intuitively. This is how machine learning really helps."

A Complex Road to Drug Resistance

The scientists focused on high-grade serous ovarian cancer, which makes up about 75% of ovarian cancer cases and often begins in the serous membrane of cells lining the fallopian tubes. Only about 30% of patients who are diagnosed with advanced disease will survive five years.

The team drew on proteomic and genomic data drawn from 242 platinum-refractory or platinum-sensitive high-grade serous ovarian tumors. They used decades of prior research to guide the algorithms to focus on pathways strongly linked to chemoresistance in ovarian cancer.

"Importantly, instead of looking at a single gene or a single protein, we considered mechanisms at the pathway and the network level," Paulovich said.

Of over 1,000 proteins that previous studies suggested played important roles in ovarian cancer, the machine learning algorithms pulled out 64 proteins that, as a group, linked to treatment response. They also showed that loss of a specific chromosome, chromosome 17, correlated strongly with chemo-refractoriness. The team also validated the predictive model against independent sets of ovarian tumors provided by Hutch colleague Charles Drescher, MD, Scott Kaufmann, MD, PhD, at the Mayo Clinic in Minnesota, and Samuel Mok, PhD, at MD Anderson Cancer Center in Texas.

Because the model's predictive capabilities held up so well across multiple ovarian cancer datasets, "it indicates that the model effectively captures the intrinsic biology of ovarian cancer," Wang said.

While not every tumor that resisted platinum-based drugs showed the 64-protein signature, it defined nearly a third of refractory tumors. The ability to direct these patients to clinical trials testing new therapies at diagnosis would be a game-changer for these patients, Paulovich said.

"The next question is, what are the novel treatment approaches that could be tested?" she said.

To help reveal this, the team used their algorithms to sort tumors based on molecular pathways associated with response to chemotherapy. They found that treatment-refractory ovarian tumors

clustered into five biologically distinct subsets. These likely represent different biological mechanisms that help ovarian tumors resist treatment, the scientists said.

“The information may provide a nice road map for developing new drugs or more efficient treatment strategies for those patients,” Wang said.

The five different tumor and drug-resistance types also help explain why it’s been so difficult to use individual proteins to predict treatment response, Birrer said.

Working Toward the Clinic

The team’s near-term goal is to continue validating their 64-protein signature and move it to the clinic where it can help identify patients who should skip standard treatment and start on a clinical trial, Paulovich said.

“A future precision oncology approach to this is that, upon diagnosis a patient will have a prediction model applied to their tumor,” Paulovich said.

She envisions this as a two-step process: A first algorithm would help doctors determine whose tumors will respond to standard therapy and who should try an alternate therapy. A second algorithm would help match individual patients who have chemo-refractory tumors to effective therapies.

In a related paper, the team already demonstrated that the new tumor subtypes could also be reveal tumor vulnerabilities. One tumor subtype has higher-than-normal levels of fatty acid oxidation. In preclinical models of ovarian cancer, [an inhibitor of fatty acid oxidation converted the tumors from platinum-resistant to platinum-sensitive](#).

“We don’t know if it will work in humans, but we view it as a stepping stone,” Paulovich said.

Birrer is also optimistic about the clinical implications of their strategy.

The findings “are a key step for predictive biomarker,” he said. “I think this is going to lead to a lot of really interesting additional science, and I have great anticipation and hope that it will help patients with what is really a bad, bad form of ovarian cancer.”

This work was supported by the National Cancer Institute, the Department of Defense and the Aven Foundation.

[This article](#) was originally published August 3, 2023, by Fred Hutch News Service. It is republished with permission.