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IU, Paradigm team up to test genomic sequencing for women with aggressive breast cancer

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Indiana University cancer researchers are testing whether therapy incorporating advanced genomic technology will provide better outcomes than current treatments for those with an aggressive form of breast cancer.

Researchers at the Indiana University Melvin and Bren Simon Cancer Center, led by Bryan Schneider, M.D., associate professor of medicine, and Milan Radovich, Ph.D., assistant professor of surgery and of medical and molecular genetics, are using targeted DNA sequencing in a new clinical trial for women with triple negative breast cancer, to test whether certain treatment choices improve survival rates.

"This trial takes a group of patients who have received standard chemotherapy but haven't had the response one would hope," said Dr. Schneider, who is also the Vera Bradley Investigator in Oncology, associate professor of medical and molecular genetics, and associate director of the Indiana Institute for Personalized Medicine.

Following chemotherapy and surgery, patients who are at high risk for relapse will be eligible to participate in the trial.

"In this group, we will use our understanding of genomics to identify the gas pedal for each woman's specific cancer and see if we can find a drug that will block the gas pedal in a way that is better than non-specific

chemotherapies," Dr. Radovich said.

The researchers' goal for using a genomic approach is to improve survival in this group of patients.

The trial will enroll 130 women. Half will receive the standard of care, while genomic sequencing will direct therapy for the other half. Sequencing is used to find mutations (changes in the blueprint of the tumor) or changes in expression (over- or under-excitement of specific genes) that may drive the cancer.

In partnership with Paradigm, a nonprofit genomic sequencing and molecular information company based in Ann Arbor, Mich., and Phoenix, the researchers will analyze the DNA and RNA (the cancer cell's blueprint genomic landscape) from the tumors that remain after standard chemotherapy. They will then search for any known therapies that might help eliminate the cancer.

After the sequencing is completed, the IU Simon Cancer Center researchers will evaluate and discuss each patient's results. Each woman in the sequencing group will then be assigned a drug that has been selected to best treat her particular form of triple negative breast cancer based on her individual results. This form of therapeutic individualization that uses the unique genetic blueprint of each tumor to guide therapy is a departure from the "one-size-fits-all" approach that has been commonly used in cancer care.

"This trial is one of only a handful in the world that tests, through a controlled scientific study, whether the use of next-generation sequencing (NGS) to identify specific disease drivers—and the selection of treatments for women based on those genetic markers—actually improves survival rates for women," said Paradigm CEO Robert Penny, M.D., Ph.D. "Our ability to interrogate the patient's tumor for DNA

mutations, DNA copy number variations, chromosomal changes and mRNA gene expression with next-generation sequencing with clinical quality results is a real differentiator in helping to improve patient care."

Dr. Schneider likened tumor mutations to typos. A minor typo in a sentence doesn't usually prevent a reader from being able to read the sentence. But add a lot of typos or a typo in the wrong place, and the sentence becomes unreadable. Thus, mutations can make a normal, well-behaved cell turn into a problematic cancer cell with a new set of instructions. Dr. Schneider and colleagues will be looking at a set number of targets in which they know the mutations can signal cells to become cancerous.

"If the mutation is taking place in a certain gene or protein that controls a certain function, and if the mutation has caused damage in that pathway, one can intuitively pick a drug that may also be interacting in that very same pathway to either try to stop or shut down an overly activated pathway," Dr. Schneider said.

Work from this innovative trial may eventually lend itself to other cancers.

"We envision a day when we can predict a handful of drugs that will best treat the tumor, derived from the tumor's unique acquired genetic variability, and then further counsel the patient on which of these might be least toxic based on a person's unique inherited genetic variability," Dr. Schneider said.

More information: The trial, managed by the Hoosier Cancer Research Network, is open to women with triple negative invasive breast cancer (stage I-III), who have completed preoperative chemotherapy and have completed surgery of their primary tumor with significant residual disease at time of surgery.

Provided by Indiana University