Photo provided

Beating the Silent KILLER

Once considered a terminal diagnosis, ovarian cancer is responding to new methods of prevention and treatment in a collaborative effort between doctors and patients at OUHSC.

By April Wilkerson

For its ability to grow unnoticed and ultimately recur, ovarian cancer is called the "silent killer."

Unlike breast or colon cancer, there are no good screening tests for ovarian cancer. Most diagnoses are made at stage three or four, making treatment more challenging. Women may respond favorably to an initial round of surgery and chemotherapy, but ovarian cancer almost always returns and often becomes resistant to the next round of treatments.

But the outlook is far from grim. Physicians and researchers at the Peggy and Charles Stephenson Cancer Center and the OU Health Sciences Center offer numerous clinical trials for ovarian cancer drugs, and researchers are dedicated to discovering new ways of preventing, screening and treating the disease.

"We are arriving at a point where novel therapies and targeted therapies are being developed that offer a chance at prolongation of life for people with ovarian cancer, and those clinical trials are being designed and opened very quickly. There's a sense of urgency to answering questions now for people with gynecologic malignancies that hasn't existed before," says Kathleen Moore, M.D., associate director for clinical research at the Stephenson Cancer Center, medical director for the clinical trials program and director of the Oklahoma TSET Phase I Clinical Trials Program.

Hearing the News

At first, Cathy Keller didn't think much about the knot she discovered at the bottom of her rib cage, nor did a visit to her primary care physician elevate her concern. But the discomfort persisted and the lump felt bigger, so she made an appointment with her gastroenterologist. A scan was performed, and her doctor called the next day with a recommendation: that Keller should see Joan Walker, M.D., at the Stephenson Cancer Center.

In April 2016, Walker confirmed the bad news – that Keller had advanced ovarian cancer. Surgery and several rounds of chemotherapy were successful, but about six months later, Keller resumed treatment because a tumor marker associated with ovarian cancer was rising again. She is taking a slightly different chemotherapy regimen this time in the hopes it will push back the cancer's advance. Keller knows the outcome of her journey with ovarian cancer is uncertain, but she is glad to have made her way to the Stephenson Cancer Center.

"Dr. Walker was very straightforward about my diagnosis, but she has also been very empathetic and comforting," Keller says. "I have had tons of support from my family and friends and from people I don't even know. My faith keeps me going. I believe your attitude makes a huge difference in the way that you heal."

Keller's arrival at Stephenson Cancer Center was similar to the paths others have taken. By the time they arrive, most women have had symptoms for about three months, but the signs are easy to dismiss: indigestion, feeling full earlier than usual,

Opposite page - Dr. Joan Walker has been by patient Cathy Keller's side since she first received a diagnosis of advanced ovarian cancer more than a year ago. Like Keller, most women have symptoms of ovarian cancer for several months before realizing that they are ill.

Hugh Scott

Dr. Katherine Moxley is the "clinical crazy glue" who helps bring gynecologic oncology discoveries made by researchers at the Stephenson Cancer Center to the bedside of patients, particularly in the area of drug resistance.

abdominal cramping and constipation. The median age of diagnosis is 65, although it is 10 years younger for women with the BRCA1 and 2 mutations, which greatly increase the risk.

The seven-member team of gynecologic oncologists at OU are driven to provide the best possible treatment today while also conducting research that may lead to better treatment tomorrow.

Treatment and Trials

Every woman diagnosed with ovarian cancer at the Cancer Center receives a combination of surgery and chemotherapy, individualized according to how sick she is, the distribution of her cancer and whether she has a BRCA mutation. But the best care for patients is on a clinical trial, and numerous Phase I, II and III clinical trials are available for those who want to participate and qualify to do so. The Cancer Center leads the nation in enrolling patients with gynecologic malignancies to clinical trials.

"We have a large clinical trial palette," Moore says. "Our trials cross the gamut of the ways we are trying to individualize therapies for patients based on their molecular profile. We try to have a trial for any patient who is interested in participating."

In Phase I clinical trials, a small number of patients receive drugs for the first time in humans, and physicians gather information on the drug's safety and dosage. Phase 2 and 3 trials increase in the number of participants and last longer while physicians monitor a drug's efficacy, side effects and adverse reactions.

Because the majority of ovarian cancers will recur, there is significant interest in developing strategies to prevent or delay their reappearance for a longer period of time, Moore says. Several clinical trials focus on adding PARP inhibitors to a chemotherapy regimen and continuing them after chemotherapy. PARP inhibitors are proteins thought to aid in cell repair, especially for patients with BRCA gene

Hugh Scott

Dr. Aleia Crim (right) and Dr. Laura Holman visit with a patient. Holman is working on a study that may someday predict a patient's risk level for ovarian cancer. The lack of such screening exacts a devastating toll in human lives.

mutations. Other trials use new immunotherapy agents in the same way, with the aim of prompting a person's immune system to delay the cancer's return. Yet another clinical trial involves screening a patient's tissue for certain receptors that can be targeted with chemotherapy and antibody drug conjugates, in the hopes of killing more of the cancer cells than surrounding healthy cells.

"Ours is a culture where we're trying to push the needle forward," Moore says. "It might be easier to use what's on the shelf and present that to patients, and it's harder to present several options. But our patients appreciate having choices. When they decide to go onto a clinical trial, they're very much our research collaborators."

Patients at the Stephenson Cancer Center tend to be altruistic when it comes to clinical trials. They are not only seeking better treatment for their own health, but want to be part of the discovery of new answers. Studies show that participation pays off: Ovarian cancer patients on OU's clinical trials live an average of six years longer; nationwide, the average survival is three years.

An Ounce of Prevention

The Cancer Center also places a priority on prevention strategies. Because gynecologic oncologists believe that ovarian cancer begins in the fallopian tubes and migrates to the ovaries, they advocate the removal of fallopian tubes and ovaries in women with a high hereditary risk of ovarian cancer, Walker says. If this is done by age 35, it reduces the risk of developing cancer by 90 percent. The prevention rate for removing fallopian tubes in the general population is 50 to 60 percent. Many women don't want their ovaries removed when they are younger because of the ensuing menopausal symptoms, so the group is conducting a prospective trial on removing the fallopian tubes as soon as childbearing is complete, then removing the ovaries later.

"We are advocating for prevention of ovarian cancer as a main strategy," Walker says. "Treatment is not pleasant, and it's uniformly unsuccessful. We cure very few people.

Prevention is a much better strategy."

Other physicians and researchers are involved in prevention efforts as well. Doris Benbrook, Ph.D., is close to launching a first-in-human clinical trial for her anti-cancer compound, OK-1, which she has already shown to prevent ovarian cancer in laboratory models – without side effects. She also plans to develop clinical trials to pair OK-1 with other drugs to treat patients once their tumors have developed. Benbrook doesn't directly treat patients, but she has kept them at the forefront of her mind during her years of developing OK-1. She also meets with women in an ovarian cancer support group and talks regularly to the gynecologic oncology team.

"I believe in focusing on prevention, but if we can also develop a drug for treatment that doesn't have side effects, then we will have made a big advance and impact on patient care and quality of life," Benbrook says. "It's important motivation to keep in touch with the needs of patients and physicians, and I try to get the people in my lab to understand more about the clinical side because that's our ultimate goal. Keeping that in mind drives our work and keeps us on track."

A New Screening Tool?

A test that could screen for and find ovarian cancer in its earliest stages would be a game-changer in the battle against this "silent killer." Research around the nation has focused on blood tests for the tumor marker CA-125. In women who already have ovarian cancer, CA-125 is monitored to follow their response to treatment and to determine if the cancer has returned. But as a screening test, CA-125 doesn't work. It can be elevated in patients who don't have cancer and normal in patients who do, depending on various factors. Researchers also have studied ultrasound as a screening tool, and ultrasound combined with a CA-125 test, neither of which works because of similar inadequacies.

Laura Holman, M.D., another member of the gynecology-oncology group, is part of a new effort to find a screening mechanism through her work with the Risk Ovarian Cancer Algorithm. The study, which OU is participating in, monitors the CA-125 level over time in women at average risk for ovarian cancer. The algorithm returns information about each person's risk and whether more testing is warranted.

"Because CA-125 can fluctuate in the same person over time, this algorithm will keep track of a person's CA-125 levels based on their blood tests each year, and we hope it will consistently tell us whether a patient is low risk, intermediate risk or high risk," Holman says.

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After that study closes, another will open that combines CA-125 with three other biomarkers known for their link to ovarian cancer: HE-4, CA 72-4 and anti-P-53 antibodies. Because ovarian tumors do not produce a significant amount of CA-125 in the early stages of disease, physicians hope all four biomarkers together will increase the sensitivity and specificity of the test. OU also will enroll patients for that study.

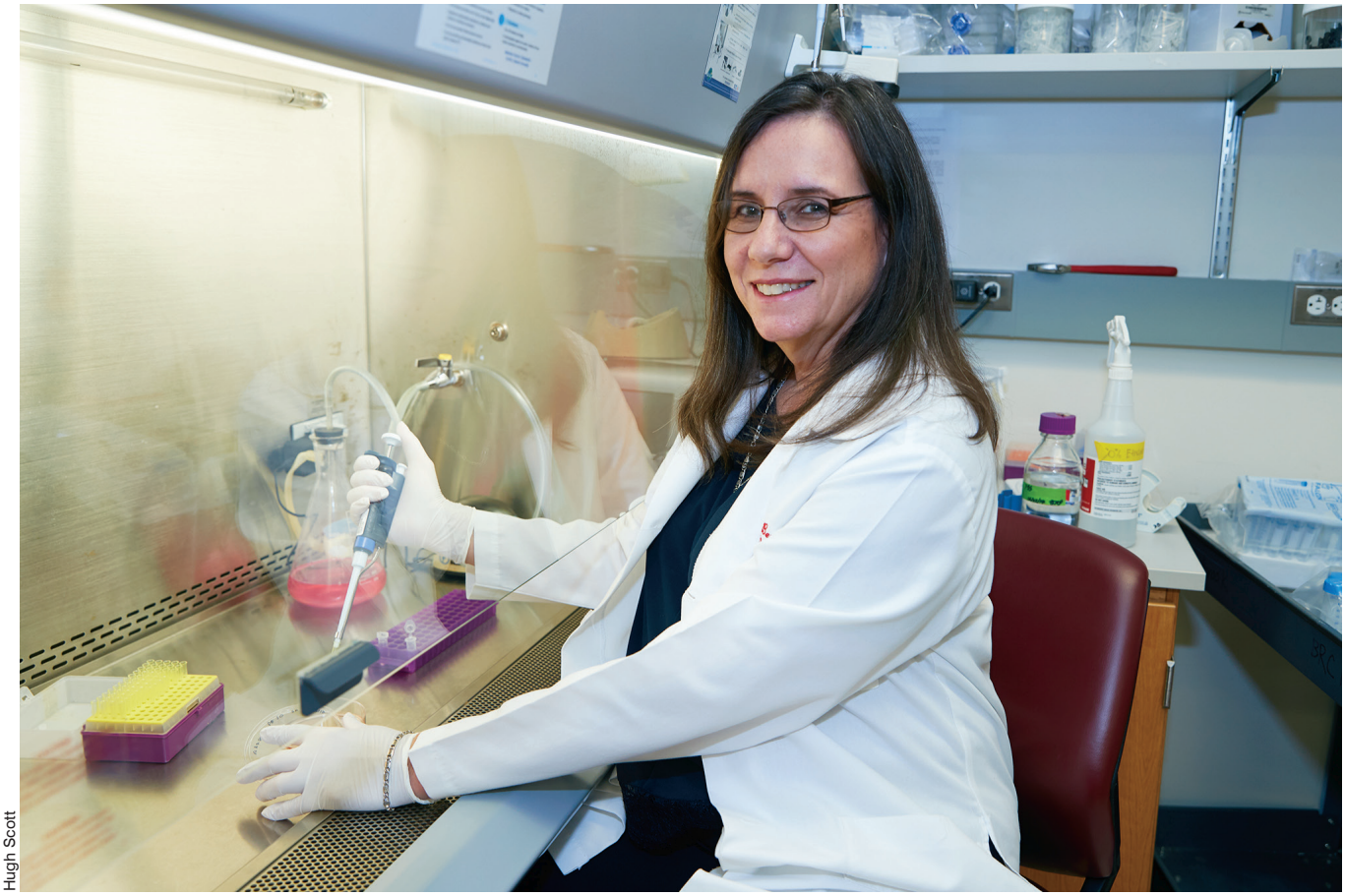
From Bench to Bedside

Like her gynecologic oncology colleagues, Katherine Moxley, M.D., treats patients, teaches the next generation of physicians and conducts research. She focuses on translational science – collaborating with basic scientists to help move their findings from the laboratory bench to the patient's bedside.

Moxley calls herself the "clinical crazy glue" who teams with scientific colleagues to find common ground in treating patients with gynecologic malignancies. Much of her work focuses on combatting drug resistance.

"Without having multiple minds thinking about the same problem in different ways, you're not going to be able to attack something as smart as cancer," Moxley says. "Cancer is a human cell that is as smart as any other cell in our bodies, and it is programmed, for whatever reason, to do nothing but grow and divide. How do you combat that if you're thinking in a vacuum? You can't. Working with groups of people to think about a clinical observation from different angles is the only way that we're going to attack a problem as big as this."

Moxley collaborates with several basic scientists, and to-



Hugh Scott

Though her work with anti-cancer compounds happens in the lab, Dr. Doris Benbrook keeps patients at the front of her mind by meeting with women in an ovarian cancer support group and collaborating with the gynecologic oncology team.

gether they have been quite successful in attracting funding for their work. She teams with Danny Dhanasekaran, Ph.D., who studies ways to mitigate the non-coding RNA that facilitates the evolution of drug resistance after exposure to platinum-based chemotherapy.

With Resham Bhattacharya, Ph.D., and Priyabrata Mukherjee, Ph.D., Moxley provides the clinical voice for studies on targets of drug resistance, including inhibition of the BMI1 protein. Moxley also collaborates with researchers at the Oklahoma Medical Research Foundation and on OU's Norman campus. One such OU partnership is with medicinal chemist Robert Cichewicz, Ph.D., who has identified several novel fungal toxins that may prove useful as chemotherapeutic agents. They are testing the fungi against ovarian cancer cell lines, trying to uncover the molecular mechanism by which they're affecting cancer cells.

As with her colleagues, Moxley wants more for her patients who bravely fight ovarian cancer. Patients like Cathy Keller, who may not know the future course of her cancer, but knows she has a team pushing for answers on her behalf.

"It's very hard with ovarian cancer because when a patient walks in the door, you know that in three to five years, about 75 to 80 percent of them are not going to be sitting across from you," Moxley says. "As a gynecologic oncologist, you take care of patients through the whole process and you get to know them and their families. It's very hard to not have anything that will cure your patients. I feel like research is a way to fight for them on a different front."

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