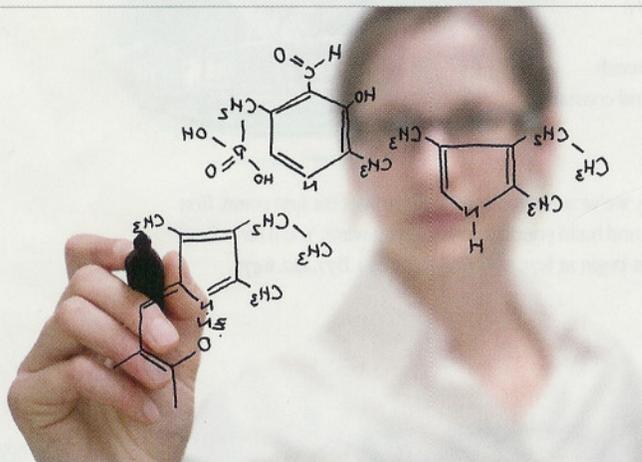# Breaking Through the Silence

Local Scientists Are Piecing Together Molecular Clues That May Lead to a Breakthrough in Ovarian Cancer Research

[WRITTEN BY HILDA J. BRUCKER]

On a February morning several years ago, 40-year-old Stephanie Armistead of Atlanta was lying in bed contemplating the day ahead of her, when her cat jumped up and landed on her abdomen. "I doubled up in pain," she remembered. "I literally crawled on my hands and knees into the bathroom, thinking 'what do I have for pain and how strong is it?' " Within days she underwent a biopsy and was diagnosed with stage one ovarian cancer, which has since been treated successfully, leaving her cancer-free. Today she acknowledges that her cat saved her life. "Every day I wake up feeling grateful to be here," she said, knowing that she is among the fortunate few to receive a lifesaving, early diagnosis.

When detected in an early stage, ovarian cancer can be cured more than 90 percent of the time, simply by removing the afflicted ovary. Unfortunately, the majority of women with the disease — more than 70 percent — aren't diagnosed until stage three or four, after the cancer has spread. Most often, the reason for the delayed diagnosis is the absence or ambiguity of early symptoms.

Stalking an Elusive Disease

Ovarian cancer received the nickname "the silent killer" because doctors believed it spread stealthily, with no early warning signs. While it's true that some women experience no symptoms at all in early stage cancers, it's

Dr. DeEtte Walker of Atlanta-based Ovarian Cancer Institue removes DNA samples from deep freeze.
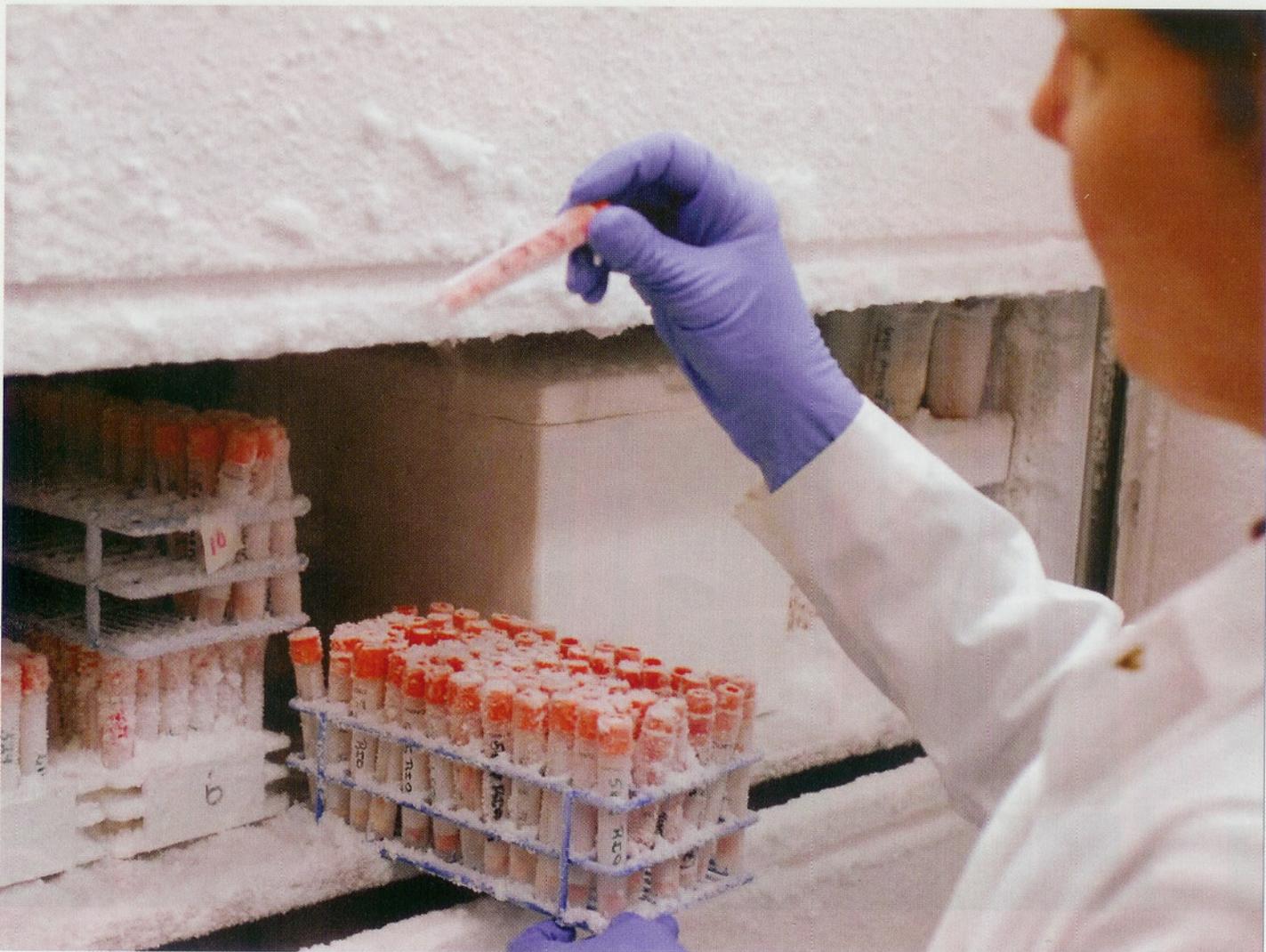
recently been recognized that symptoms sometimes are present, but are so ambiguous that they're easily dismissed or ignored. According to the Atlanta-based Ovarian Cancer Institute (OCI), it's not uncommon for women with vague but persistent symptoms to self-treat or pursue medical care for up to one year before receiving a cancer diagnosis from a specialist. Too often, the medical professional they turn to first is a family doctor who is simply not trained to think of ovarian cancer when presented with symptoms that don't seem gynecological, but rather gastric in nature (like nausea or indigestion) or typical of middle age (like weight gain or bloating).

This uncertainty about the earliest warning signs is made even worse by the fact there is no simple test that can reliably detect early-stage ovarian cancer — only a biopsy can confirm a malignancy. And according to Libby King, executive director of OCI, women are often shocked to learn they are not screened for the disease at their yearly gynecological exams. "Everyone thinks a Pap smear checks for ovarian cancer and that is not the case," she stated emphatically.

Since early diagnosis is the most critical factor in surviving the disease, researchers around the world are working toward that end. The goal is to develop a simple blood test that can be performed routinely on all women during their annual exams. And with the support of the OCI, it's possible that the next big breakthrough in early detection methods will come from a lab in Georgia. Much like crime lab detectives, OCI researchers are using the latest high-tech tools to look for a molecular "fingerprint" that will identify this elusive killer.

Dedication, Innovation & Collaboration

The OCI has been described as a grassroots organization here in Atlanta, with just one administrative

PARKER H. PETIT
BIOTECHNOLOGY BUILDING

Georgia Tech's Biotechnology lab houses the Ovarian Cancer Institute.

employee and a network of local volunteers that coordinate fundraising events. The nonprofit was founded in 1999 by Dr. Benedict Benigno, a gynecological oncologist whose Atlanta practice handles more cases of ovarian cancer than any private practice in the country. In many ways it was the realization of a dream for him.

For more than two decades Benigno had watched ovarian cancer ravage his patients and their families, and he was haunted by the need for early detection and better treatments. He was also determined to find a way in which his vast clinical experience could contribute to much-needed medical research. "For about five years I played around with this in my mind, wondering 'how can we possibly do this?' My initial reaction was to build a laboratory and hire a molecular geneticist and be on our way. But in retrospect nothing could have been more foolish," he said.

Instead, Benigno contacted Dr. John McDonald, an acclaimed geneticist at the University of Georgia, to discuss the possibility of collaboration: OCI would provide financial backing and tissue samples for research, if McDonald would provide lab space and technical expertise. Intrigued by the possibilities, McDonald became OCI's chief research scientist, ultimately moving his research lab to Georgia Tech and developing a strong partnership with Benigno.

Currently, several advantages give McDonald and Benigno a good chance at the coveted breakthrough in early detection methods. Foremost is OCI's bank of nearly 800 samples of ovarian tissue. The samples are unusually pristine, having been flash-frozen in liquid nitrogen right in Benigno's operating room, before fragile genetic material like DNA and RNA could begin to degrade. The sheer size of the tissue bank gives researchers the statistical power to

identify subtle molecular patterns among ovarian cancer cells that might otherwise go undetected. Each tissue sample is also supplemented with frozen samples of the patient's blood, urine, and abdominal fluid; as well as a detailed electronic record of her diet, lifestyle, medical and family history, and other factors that may prove relevant. Both OCI's tissue bank and ovarian cancer database are believed to be the largest in the world.

Also distinctive to OCI is the concept of a virtual lab, which allows scientists from different disciplines to collaborate and share data electronically — these include researchers at Clark Atlanta University, Emory University, Georgia State University and the Medical College of Georgia. Along with medical researchers, experts in computer science were recruited to design databases and find new ways to analyze the molecular data gathered from tissue samples. "So this is the beauty of it — we have a number of collaborators and everybody's working on the exact same patient samples. So when the output comes from those separate analyses, it can all be brought back to a centralized database. And that allows us to look for correlations between different outputs and get better insights," McDonald said. "That's a unique feature of ours, and it's a better way to work."

Finding a Molecular Fingerprint

In the quest for a screening test for ovarian cancer, McDonald is looking for what's known as a biomarker — a specific molecule that's unique to ovarian cancer cells and can be detected in the blood even before the cancer spreads or causes symptoms. While some researchers are experimenting with proteins and metabolites to search for a biomarker, McDonald is focusing on genes. "From a geneticist's view of cancer, we would like to know what is different in the genes being expressed by cancer cells, as compared

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Above: *Dr. John McDonald and lab workers at Georgia Tech's Ovarian Cancer Institute*

to normal cells," he explained. (The term gene expression refers to the way genes are "switched on" or "switched off" in different parts of the body at different times, causing them to have very different effects. Some of these effects can be undesirable, like tumor growth.) McDonald's approach involves analyzing the genetic material known as RNA in both normal and cancer cells, then looking for telltale differences between them by comparing the gene expression profiles of each sample. The process is made possible by valuable new technologies.

At the heart of the OCI lab is a device known as the laser-capture microdissection machine. "It's the Maserati of lab machines," said research scientist Dr. DeEtte Walker, referring to both its prestige and its price tag. The machine uses a laser to isolate the actual malignant cells from a patient sample and transfer them to a test tube so researchers can, for the first time, extract RNA from a pure population of ovarian cancer cells. "The tumor contains a lot of different kinds of cells and in the old days, when you just ground up all the tissue for an experiment, you got a lot of 'noise,' " McDonald explained.

The isolated cancer cells are then analyzed by a relatively new technology called a microarray, which can screen the expression of all human genes in a single procedure. This broader view of gene activity in cancer cells saves time and gives researchers a huge advantage. "A few years ago you could look at only one gene at a time, and you had to decide, out of 25,000 human genes, what to look at. Maybe somebody else had done a study on liver cancer or something, and you could say 'let's look and see if that gene is altered in ovarian cancer.' So it was really hit and miss," McDonald said.

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With these sophisticated technologies, OCI researchers have already been able to demonstrate that malignant cells do express different genes than normal cells, and that these differences can be clearly distinguished in the lab — information that makes McDonald feel confident that this is an objective away to look for a biomarker, which in turn could be the basis of a simple blood test to screen for ovarian cancer.

A Brighter Future

In addition to earlier detection methods, genes may also provide clues to designing more effective treatments for ovarian cancer, according to McDonald. For example, by comparing the gene expression profiles of different groups of patients, he found that chemotherapy patients with a certain mutation in the gene known as p53 had a much better five-year survival rate than those without the mutation. If his research bears out, a medical treatment that disables the p53 gene in tumors might help patients survive longer.

Benigno talks optimistically about his vision for the future of cancer treatments. "It's got to be made better, it's got to be made foolproof, and it must be such

that it doesn't sap strength and dignity for the patient," he said. "I see a time where, by genetic engineering, the exact antidote to the nuclear protein in a patient's cancer will be manufactured in the lab to kill every cancer cell in her body. It'll be designer cancer therapy." **PN**

WHAT EVERY WOMAN SHOULD KNOW

Until a reliable screening test is developed, the Ovarian Cancer Institute (OCI) is dedicated to educating doctors about the easily missed, earliest warning signs of ovarian cancer. Another key message is that women should be their own advocates when talking to their doctors. "Women, unlike men, are in tune with their bodies," said Dr. Benedict Benigno, OCI founder. "And if a woman says there's something not quite right, hopefully she's armed with the right information."

Women should recognize certain symptoms, according to Benigno, without becoming unduly alarmed. He stresses that most of the time these symptoms will not turn out to be ovarian cancer — but for peace of mind, they should be investigated and the possibility of cancer ruled out, particularly when there's a family history of breast or abdominal cancers.

Symptoms include one or more of the following:
- Abdominal weight gain or bloating
- Pelvic or abdominal pain
- Difficulty eating or swallowing
- Indigestion
- Gas
- Change in bowel habits
- Frequent or urgent urination
- Unusual post-menopausal bleeding

A symptom should be investigated further if:
- It is relatively new and different from your usual state of health.
- It persists for more than two or three weeks.
- It is not relieved by over-the-counter medications. *(Note that these criteria don't apply to transient issues like premenstrual bloating or longstanding problems like a lifetime of indigestion after spicy meals.)*

When in doubt, insist that your family doctor or gynecologist listen to you. Request a pelvic exam and ask your gynecologist to schedule an ultrasound and CA-125 test. For more information, visit *www.ovariancancerinstitute.org.*