

The New York Times

February 3, 2004

New Cancer Test Stirs Hope and Concern

By ANDREW POLLACK

Jill Doimer's mother died in 2002 from ovarian cancer, detected too late to be effectively treated.

So Ms. Doimer is eagerly awaiting the introduction of a new test that holds the promise of detecting early-stage ovarian cancer far more accurately than any test available now, using only blood from a finger prick.

Not only does she plan to be tested, but an advocacy group she helped found, Ovarian Awareness of Kentucky, also intends to spread the word to women and doctors.

"If it's going to happen to me or anyone I know, I want it to be caught at an early stage," said Ms. Doimer, who lives in Louisville.

The new test, expected to be available in the next few months, could have a big effect on public health if it works as advertised. That is because when ovarian cancer is caught early, when it is treatable by surgery, more than 90 percent of women live five years or longer. But right now, about three-quarters of cases are detected after the cancer has advanced, and then only 35 percent of women survive five years.

The test is also the first to use a new technology that some believers say could revolutionize diagnostics. It looks not for a single telltale protein -- like the prostate-specific antigen, or P.S.A., used to diagnose prostate cancer -- but rather for a complex fingerprint formed by all the proteins in the blood. Similar tests are being developed for prostate, pancreatic, breast and other cancers. The technique may work for other diseases as well.

"I've been in cancer research for 40 years and I think it's the most important breakthrough in those years," said Dr. John S. Kovach, director of the Long Island Cancer Center at Stony Brook University. "I think in 10 years ladies will have blood tests instead of a mammogram for breast cancer."

Some experts, however, say that the technique, while promising, is still unproved. They say the ovarian test in particular has not been adequately validated and is being put on the market prematurely through a route that does not require approval by the Food and Drug Administration. If the test is not accurate, they say, it could result in unnecessary surgery for biopsies or ovary removal for many women.

"Certainly there's no published work that would make me tell a woman she should get this test," said Dr. Nicole Urban, head of gynecologic cancer research at the Fred Hutchinson Cancer Research Center in Seattle.

Three statisticians from the M. D. Anderson Cancer Center in Houston analyzed data put on the Internet by the test developers and say they found various inconsistencies.

"We're saying that on the basis of the data they posted, no, we don't believe this works," said one of the statisticians, Dr. Keith A. Baggerly, assistant professor in the department of biostatistics and applied mathematics.

The test, called OvaCheck, was developed by Correlogic Systems Inc., of Bethesda, Md., with scientists from the National Cancer Institute and the Food and Drug Administration.

Correlogic Systems has licensed the test to Quest Diagnostics of Teterboro, N.J., and Laboratory Corporation of America Holdings, known as LabCorp, of Burlington, N.C., the nation's two biggest clinical laboratory companies. Quest Diagnostics and LabCorp, which will compete, say they expect to begin offering the test in the next few months. The price is expected to be \$100 to \$200.

Quest Diagnostics and LabCorp will analyze blood samples sent by doctors, rather than sell test kits to doctors and hospitals. Tests performed at a central location do not require F.D.A. approval.

Diagnostic companies say such "home-brew" tests are a common way to make them available quickly and that for some tests it would not be economically practical to conduct the clinical trials needed for F.D.A. approval. At times, though, the agency has had concerns that such tests have not been adequately validated. The agency recently ordered Roche to take a complex genetic test off the market until it could be approved by the agency.

Dr. Emmanuel F. Petricoin III, an agency scientist who helped develop OvaCheck, said the criticisms of it were based "in some instances on not understanding the entirety of the science." And executives at Correlogic Systems, Quest Diagnostics and LabCorp say it is not fair to cite lack of validation because they are validating the test now.

Gary Samuels, a spokesman for Quest Diagnostics, said his company and LabCorp were each testing the same 1,000 samples to see if they got the same results, a validation process he called "lengthy and meticulous." He said Quest Diagnostics expected to decide by the end of the month whether the test was reliable enough to market.

Brad Smith, executive vice president for public affairs at LabCorp, agreed, saying, "If we're not comfortable with it, it won't launch."

Many companies and academic labs have joined the race to find so-called biomarkers, blood components like proteins or lipids that can signal disease.

"There are very few diseases, when you really go through it, that we can diagnose with a simple blood or urine test," said Dr. Gordon Ringold, chairman and chief executive of SurroMed, a Menlo Park, Calif., company looking for such markers.

Until now, said Dr. Howard Schulman, vice president of research and development at SurroMed, "biomarker discovery has relied on knowing everything possible about the disease," searching for proteins involved in the cause of the disease.

But results have been sparse. In the last decade only about 10 proteins have been the basis for diagnostic tests approved by the F.D.A. For instance, Matritech Inc., a company in Newton, Mass., sells a bladder cancer screening test that looks for a protein called NMP22.

A single biomarker may not work because a disease is heterogeneous or because more than one condition can cause a protein's level to rise, resulting in false positives. That is the case with the P.S.A. for prostate cancer.

So, now, the search for biomarkers is shifting. Instead of trying to understand disease mechanisms, some companies are using new technology called proteomics to screen cells or blood rapidly, looking for proteins present in diseased people but not in healthy ones. Similar efforts are being used for genes and metabolites, substances like fatty acids made by cells.

Moreover, in many cases, scientists are trying to find not a single marker but several that could be used together to get a more accurate reading.

OvaCheck goes a step beyond that. It analyzes patterns made by all the proteins in the blood without even knowing what the proteins are.

In the tests, proteins in the blood sample are analyzed by a mass spectrometer, a complex machine that can cost hundreds of thousands of dollars. The proteins are vaporized, given an electric charge and propelled down a tube. How fast they make the trip depends on their mass. The machine produces a squiggly graph that essentially shows the distribution of masses in the blood sample. There are thousands of data points, with spikes corresponding to particularly abundant proteins.

Correlogic Systems developed a computer program that analyzes these complex patterns and learns to distinguish between blood from patients with cancer and blood from those without.

When the technique was first tried on 116 blood samples from women whose disease status was already known, it correctly detected all cases of ovarian cancer, including 18 in the earliest stage. It classified only 5 percent of the noncancerous samples as cancerous. When the results were published in the medical journal *Lancet* in 2002, it suggested a powerful testing method was at hand.

“We think now that there is an entire ocean of biomarkers that never before was known to exist,” said Dr. Petricoin. He is co-director of the clinical proteomics program run by the F.D.A. and the National Cancer Institute with Dr. Lance A. Liotta, who helped develop the ovarian test.

Ovarian cancer, which causes about 14,000 deaths a year in the United States, is now diagnosed with a test for a single protein called Cancer Antigen 125. But CA-125 is best at detecting a recurrence of cancer or a late-stage cancer, not a disease in the early stages. Vaginal ultrasound, another often-used technique, is also not so good for early-stage disease, experts say.

But experts say OvaCheck must give virtually no false positives to make it useful for general screening. Fifteen women out of 100,000 get ovarian cancer each year, said Dr. Beth Y. Karlan, director of gynecologic oncology at Cedars-Sinai Medical Center in Los Angeles.

So if OvaCheck were used for yearly checks on the whole population, even a 1 percent rate of false positives would mean 1,000 false diagnoses for every 15 cases detected.

Peter J. Levine, president of Correlogic Systems, said for that reason, the test would be recommended only for women at high risk for ovarian cancer, a population of about 10 million in the United States. This includes women with relatives who have had ovarian cancer, women who have had breast cancer, and women with mutations in genes called BRCA1 and BRCA2 that indicate a high risk of breast and ovarian cancer. Other experts said that women who tested positive would be given the CA-125 test and vaginal ultrasound to try to confirm the diagnoses, rather than being sent for surgery immediately.

Yet another problem, some experts said, is that the samples taken to test the technique so far have come mainly from women who were scheduled for surgery, meaning their cancer had produced noticeable symptoms. Dr. Petricoin conceded that it was unclear if the test would work equally well for early-stage ovarian cancer that does not produce symptoms, as is often the case.

Some experts say they would not trust a test in which the proteins being measured and their biological relationship to cancer are unknown.

“If you don’t know what you’re measuring, it’s a dangerous black-box technology,” said Dr. Eleftherios P. Diamandis, head of clinical biochemistry at Mount Sinai Hospital in Toronto. He

said the rare proteins that might indicate cancer were likely to be drowned out by abundant proteins in the blood. “They are rushing into something and it could be a disaster,” Dr. Diamandis added.

Dr. Petricoin countered that recent studies had shown that the rare proteins adhere to more abundant blood proteins, so their concentration is increased to detectable levels. And he said the failure to develop many biomarkers so far showed how hard it was to identify specific proteins. “We don’t understand many of the basic mechanisms of cancer yet, and we think we have knowledge of what markers to use?” Dr. Petricoin said. “It’s false.”

Some critics say that for the test to be accepted, the *Lancet* data must be reproduced by others and the technique tested in larger trials.

For instance, Dr. Karlan of Cedars-Sinai said, a few years ago scientists were excited by early results of an ovarian cancer test using a marker called LPA, but results of a larger test were disappointing. LPL Technologies, a Cleveland company, is still working to validate that test.

The *Lancet* data could not be reproduced exactly even by the test developers. They found that the mass spectrometer they used, which was made for research, not high-volume work, produced different patterns even when the same samples were tested on different days. So they switched to a new machine.

William E. Rich, president and chief executive of CIPHERgen Biosystems Inc., which made the equipment used in the *Lancet* study, said that the machines were reliable and that his company had stopped working with Correlogic Systems because “we don’t have confidence in that approach.” CIPHERgen Biosystems, which is based in Fremont, Calif., hopes to introduce its own ovarian cancer test, based on three known proteins, by the end of this year, Dr. Rich said.

Developers of OvaCheck said that though different machines and sample preparation techniques resulted in different patterns, the computer could figure out how to discriminate cancer from noncancer. They retested the *Lancet* samples with different equipment and got the same good results, they said. With a larger sample, they had 100 percent accuracy, with no false positives. So as long as Quest Diagnostics and LabCorp are consistent in how they process samples, they should get good results, they said.

And others have shown the approach works. Dr. O. John Semmes, an associate professor at Eastern Virginia Medical School, is using protein patterns to develop a prostate cancer diagnostic. He said his group had found that multiple labs got the same results when they ran the same set of samples. Still, he said, more extensive validation is needed and is under way.

OvaCheck’s developers plan to conduct a clinical trial to win F.D.A. approval for diagnosing recurrences of ovarian cancer. A trial for approval as an early-stage diagnostic tool would take too long, they said.

Dr. Petricoin says that even if the test is not perfect, it is “blowing away what’s being used now,” like the CA-125 test.

“You have women right now that are getting prophylactic oophorectomies based on CA-125,” he said, referring to the surgical removal of ovaries to prevent cancer.

For that reason, some doctors think the test will be in great demand from anxious women who view ovarian cancer as a death sentence.

“Before you mass-market to the uninformed, fearful population, it should be peer-reviewed,” said Dr. Karlan of Cedars-Sinai. But when asked whether she would recommend her patients not get tested, she said: “It doesn’t matter what I recommend. They are going to do it anyway.”