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Progress from unraveling proteins

By studying the complex structures, researchers may be able to detect and treat such insidious killers as ovarian cancer.

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Less than a decade ago, the study of proteins and their roles in the body was such an ill-defined field that it had no name.

Now, "proteomics" is fueling a biotechnology boom and promising a revolution in the diagnosis and treatment of disease.

It is already providing new avenues for detecting and monitoring prostate, breast, lung and ovarian cancers.

Correlogic Systems of Bethesda, Md., for example, has developed an ovarian cancer detection blood test that it plans to market. In initial studies, OvaCheck was shown to be highly accurate - even in the early, symptomless stages of the disease. Although the test still faces regulatory and other hurdles, it could be a life-saver for women at high risk of the dreaded cancer and may even become a routine population screening tool.

"The Ovarian Cancer National Alliance... and women everywhere have long awaited the development of a simple and reliable screening test," the Washington-based alliance said in a recent release. "If this screening process lives up to expectations, it has the potential to save tens of thousands of women's lives."

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Genes and proteins are complementary, like roads and vehicles. Within each cell, genes dictate the production and actions of proteins, which do many things such as digesting food, fighting germs, and carrying oxygen in the blood.

About 25 years ago, when DNA sequencing techniques were being pioneered, scientists dreamed of fingerprinting proteins in the same way. Proteins are one step closer to biological functions, so decoding them would offer better opportunities for medical intervention, at least in theory.

But until recently, that dream was beyond reach because proteins are so complex.

While the human genome contains about 40,000 genes, each made of only four molecular building blocks linked in a double-helix shape, the human "proteome" contains an estimated one million proteins, each made up of many amino acids. These acids are linked in tremendously varied shapes and sizes and are constantly morphing and interacting in response to the orders they receive.

Proteins are so hard to isolate - never mind sequence - that only several thousand have been identified. One well-known protein, the prostate-specific antigen, is shed by the prostate gland and is the basis for the PSA blood-screening test for prostate cancer.

Around 1995 - the year Australian researcher Marc R. Wilkins coined the term proteomics - technological advances began overcoming the obstacles to deciphering proteins.

Since then, there has been an international explosion in tools for protein separation, identification and analysis - and in proteomics companies, studies and government-funded initiatives. Numerous journals and a weekly newsletter have sprung up to track the booming field.

University of Pennsylvania pathologist Peter F. Davies, a heart-disease researcher who has studied how an antioxidant protein helps prevent clogging of the arteries, said: "I don't think we'll see a revolution overnight, but proteomics promises to be valuable to the frontline clinician."

In cancer research, clinical applications of proteomics are rapidly emerging. Consider these reports from the National Cancer Institute over the past year:

Researchers are homing in on an as-yet-unnamed protein that seems to promote lung-cancer cell growth.

The arthritis drug Celebrex has been shown to reduce colon cancer risk in some patients with an inherited gene mutation that makes them ultra-susceptible to the disease. Researchers are using proteomics to figure out which patients will respond to Celebrex.

Researchers are using proteomics to monitor ovarian cancer tumor growth before, during and after patients with a recurrence of the disease are treated with Gleevec, a new anticancer drug targeted at specific protein pathways.

In an initial study, a new proteomics prostate detection test correctly identified 97 percent of men with noncancerous lesions - although it missed almost half of those who actually had prostate cancer.

This new test is based on a novel approach: It looks for a pattern of proteins that change as a tumor grows, instead of focusing on a single protein "tumor marker" such as the prostate-specific antigen.

This method was pioneered with OvaCheck and required the development of supercomputing software capable of recognizing protein patterns hidden in vast amounts of data - billions of possible combinations.

The coinventor of the "hidden-pattern" technology is Peter Levine, now president and chief executive officer of Correlogic Systems, which holds the patent on the software.

Levine, a lawyer who had worked with such software to analyze legal data, was at a social gathering in 1999 with Emanuel F. Petricoin, a cancer proteomics researcher at the Food and Drug Administration, when they began talking about proteomics. "I literally sketched on a napkin the prospect of using powerful [computer] algorithms to search... for patterns of proteins in the blood," Levine recalls.

By February 2002, a team made up of Petricoin, Levine and nine others had published their stunning success in the journal Lancet.

With "a test that can be completed in 30 minutes using blood that can be taken from a finger stick, researchers were able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected" women, an FDA announcement said.

The test correctly identified 50 out of 50 cancers and 63 of 66 noncancers - exceptionally good results for any cancer detection exam.

In contrast, the only approved test for ovarian cancer measures a single protein, CA125, that can be elevated not only in women with cancer, but also in those with benign conditions such as fibroids or cysts.

CA125 is so notoriously inaccurate that it is approved only to monitor ovarian cancer patients for relapse after initial treatment, although experts also recommend the test for healthy women with genetic risk factors.

Because ovarian cancer has no definitive early-warning symptoms, 70 percent of the more than 20,000 women diagnosed each year are in late stages of the disease. At that point, the chance of long-term survival is slim.

In the two years since the Lancet paper, the lead authors have since achieved 100 percent accuracy with a larger number of cancerous and noncancerous blood samples, using a more powerful protein sequencing tool and different protein patterns, according to the National Cancer Institute.

Now, the researchers are taking different routes to make an ovarian cancer test publicly available.

Government researchers are conducting clinical trials of a proteomics test that, like CA125, would be FDA-approved for monitoring ovarian cancer patients for relapse - although, also like CA125, it could be used at a physician's discretion for screening of other women. The approval process could take two to three years, Petricoin said.

Meanwhile, Correlogic hopes to market OvaCheck under the law governing clinical laboratories. OvaCheck has been licensed to two laboratory chains - Quest Diagnostics and Laboratory Corporation of America - that are helping to validate the test before offering it for about $100 to $200, initially just to high-risk women.

Contrary to news reports that the test would be available this spring, Levine said the time frame is "driven by the science, not the calendar."

"We're working our butts off to get this out," he added. "We're very much aware of how important it could be to high-risk women."

Wendy Heacock, 54, of Kutztown, Pa., is among those women.

Ovarian and breast cancer run like a blight through her family tree, yet her gynecologist advised her not to undergo genetic testing. After she was diagnosed four years ago with late-stage ovarian cancer, genetic tests revealed that she inherited BRCA2, a mutation that predisposes her to both kinds of cancer.

"It's about time that they found a way to detect ovarian cancer early," Heacock said. "I get scared every time I go for a checkup."

If OvaCheck pans out, she said, "it would be great for me. And the same for my two daughters."

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For more information about the National Cancer Institute's clinical trials, call 1-800-422-6237,or see www.cancer.gov/clinicaltrials/. The trial of a diagnostic proteomics test for ovarian cancer relapse is protocol ID number NCI-00-C-0018.