PROTEOMICS

Lifting the Screen

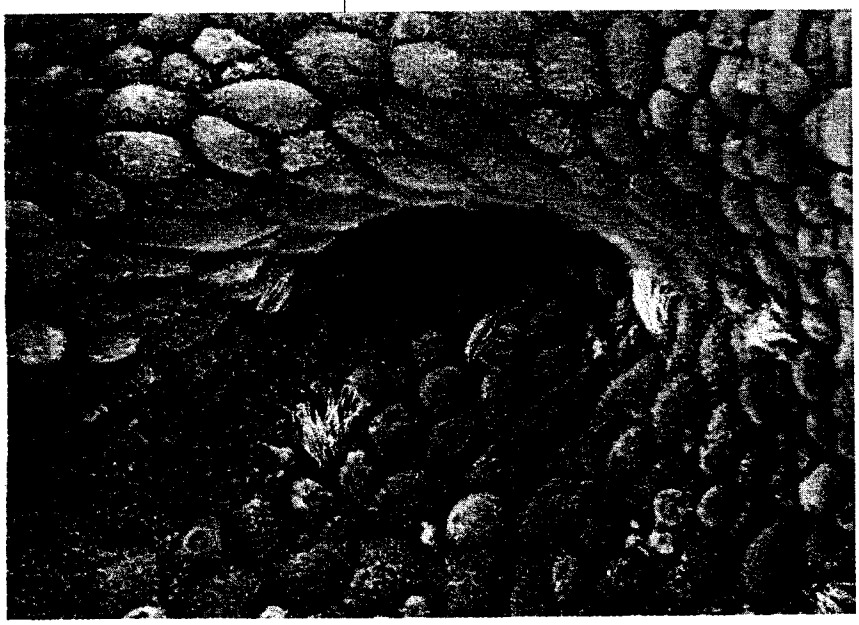
AN ACCURATE TEST IS NOT ALWAYS THE BEST WAY TO FIND CANCER **BY ALISON McCOOK**

Cancer screening is notoriously unreliable: a positive test often does not indicate disease, and a negative result does not always mean the patient can walk away with a handshake and a smile. In February many physicians and patients were encouraged by the results of a new test for ovarian cancer, hoping that it would be a noninvasive, cost-effective way to save thousands of lives. The findings offered proof of the enticing idea that within the thousands of proteins swimming in the blood lies a simple code that, if broken, will reveal whether cancer lurks in the body. But although the concept is promising, this technique is a long way from being useful within the general population.

News of this latest approach sparked widespread interest because none of today's diagnostic tests for ovarian cancer—including ultrasonography, pelvic exams and blood tests to detect levels of a protein called CA 125—can consistently detect the disease early, when the cure rate is around 90 percent. Instead most women are diagnosed once their cancer has progressed, when the chances of surviving five years drop to 35 percent.

In the recent paper, scientists led by Lance A. Liotta of the National Cancer Institute and Emanuel F. Petricoin of the U.S. Food and Drug Administration mapped, with the help of an artificial-intelligence algorithm, the particular blood proteins or protein fragments that differ in samples from women with ovarian cancer. Other researchers have published reports using proteomics to diagnose disease, but because Liotta and Petricoin's results appeared in a prestigious publication, the *Lancet,* they received additional attention. Indeed, they sound impressive: in 116 samples, that protein "fingerprint" picked out every woman with ovarian cancer, including 18 early cases, and designated 63 out of 66 healthy women as disease-free.

Within 48 hours of the study's publica-



TOO OFTEN, TOO LATE: Ovarian cancer cells, as seen by a scanning electron microscope. The image shows secretory cells with hairlike protrusions called microvilli (*pink*) as well as cilia (*green*) and mucus (*yellow*).

P. MOTTA AND S. MAKABE *Photo Researchers, Inc.*

tion, Carol L. Brown of Memorial Sloan-Kettering Cancer Center in New York City received calls from an estimated 75 percent of her patients who were in remission for ovarian cancer, asking about the test. But, as Brown told them, it is "not something that's going to be a commercially available test for, I think, many, many years—if at all," she says.

That's because, surprisingly, the ability to find all cases of cancer is not the best way to judge the value of a screening test. To calculate the likelihood that a positive test indicates cancer, epidemiologists use an equation that includes the test's sensitivity (how well it finds cancer when it is there), its specificity (its ability to diagnose healthy patients accurately) and the disease prevalence. The sensitivity of the new test is 100 percent, the specificity is around 95 percent (63 of 66 healthy patients found), and ovarian cancer occurs in only one in 2,500 women who are older than 35 years in the U.S. each year. Plugging those numbers into the equation shows that for every woman who gets a positive proteomics test result, there is a less than 1 percent chance she has the disease.

If a screened woman gets a positive result, her doctor conducts further analyses, such as a laparotomy, a surgery that opens the abdomen to explore for disease. In public health terms, subjecting 100 women to the anxiety, expense and risks of surgery to find cancer in just one patient is unacceptable. But the only value in the equation that can be improved is the specificity, which is already quite high. Ironically, increasing the test's specificity may mean lowering its overall accuracy, explains Sudhir Srivastava of the National Cancer Institute; in other words, the test would be capable of "finding" cancer in healthy people. But even if little tweaking of the numbers is possible, researchers may be able to give the test to women who are more likely to develop ovarian cancer, such as those with a family history of the disease. "It may be that in the high-risk population, these numbers are approaching acceptability," says Martee L. Hensley of Sloan-Kettering.

There is additional concern that other institutions may not be able to repeat the procedure using their own equipment and software. The unidentified proteins and protein fragments that make up the *Lancet* fingerprint are so small that any slight variations between machines, algorithms or the solutions used to prepare blood samples may skew the results. "So if you ran samples three months ago and got beautiful results, can you repeat that three months later, and can you repeat it on different instruments?" asks George L. Wright of Eastern Virginia Medical School.

Despite the reservations, these results may herald a future in which tests use multiple, not single, biomarkers to spot disease. Researchers are looking at patterns that may identify prostate and breast cancer, among others. Given the heterogeneity of cancer, this approach makes intuitive sense. Declares Wright: "One marker will not be found to improve the early detection, diagnosis, prognosis of any cancer or disease."

Alison McCook is a science writer based in New York City.

TO SCREEN OR NOT TO SCREEN?

Some screening techniques are facing increasing controversy. Experts debate whether mammography and PSA testing hurt more people than they help by detecting cancers at too early a stage, when it is unclear if the disease is benign or requires treatment. A study in the April 4 *New England Journal of Medicine* found that about two thirds of one-year-olds whose urine tests came back positive for neuroblastoma actually had completely harmless tumors.

But testing rates for most cancers remain high, says William C. Black of Dartmouth-Hitchcock Medical Center, because managed care physicians do not have the time to explain the nuances of screening and all are afraid of being sued by cancer patients who did not receive the test. And in the end, doctors can never be sure which patients treated for the disease could have postponed or even avoided the medical intervention. "Ironically, the people who are harmed by the overdiagnosis become the most vocal advocates for screening," Black remarks, "because they think, of course, they've been saved."

ML Exercise 2:

The "equation" here is Bayes' Rule. Use it to compute a more precise answer than "less than 1 percent."

Due: November 4.