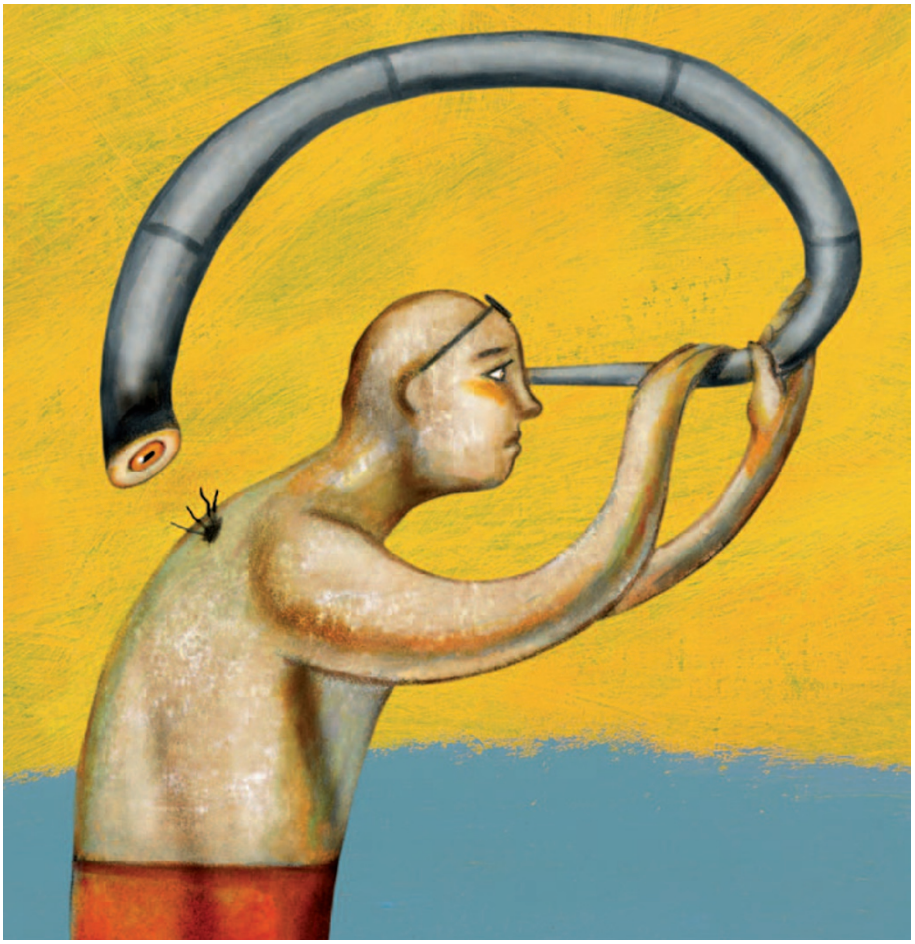

ILLUSTRATION BY ALBERTO RUGGIERI

EARLY DETECTION

Spotting the first signs

The sooner a cancer is found, the better. New technologies are pushing the limits of detection — towards the frontier of prevention.

BY NEIL SAVAGE

One day, a few years hence, a patient having a routine check-up might do little more than blow into a small machine at the doctor's office and, within a couple of minutes, be told whether there are any early signs of cancer. For another patient, a routine blood test to monitor cholesterol might present an opportunity to check for stray cells from tumours too small to spot. A dermatologist, instead of eying a mole and perhaps slicing it off to biopsy, could instead peer at it through a machine to instantly tell whether it is malignant or benign.

These, at least, are the visions of researchers developing technologies to detect the early signs of cancer. Better screening — looking for signs of cancer in people with no symptoms, as opposed to diagnosing suspected cancer — increases the odds that doctors will find cancer at its earliest stages when chances of a cure are higher. Screening has already reduced cancer deaths: the US National Cancer Institute (NCI) estimates that colonoscopies can lower mortality from colorectal cancer by at least 60%, and the National Lung Screening Trial recently found that computed tomography scans of heavy smokers could cut lung cancer deaths by as much as 20%. Researchers are exploring a new suite of potential screening methods that could one day join or even supplant today's colonoscopies, mammograms and pap smears. If some of these approaches can be shown to prevent cancer deaths and cut costs, they stand a good chance of becoming part of regular patient care.

LIGHT PROBES

Many researchers are trying to improve on existing techniques such as endoscopy, delivering images from inside the body through fiber optics. Engineers at Duke University, North Carolina, for instance, have designed an optical system to search for premalignant changes in patients with Barrett's esophagus, in which stomach acid alters the cells lining the esophagus. The condition more than doubles the risk of esophageal cancer. Unlike conventional endoscopy, the Duke technique, called angle-resolved low-coherence interferometry, images structures beneath the surface of a cell for a sort of optical biopsy. Adam Wax, one of the Duke engineers, says looking at the basal layer of the epithelium, about 300 micrometers beneath the surface, seems most diagnostically useful. The system splits infrared light into two beams, and compares how far each travels to determine how deep it penetrates into the cell. Measuring the angle at which light bounces off cellular structures reveals the size of structures at increasing depth. The resolution is high enough to distinguish a normal-sized nucleus, about 10 micrometers in diameter, and a larger, precancerous one at least 13 micrometers.

Wax says his enhanced endoscopy could provide better targets for biopsies — and, eventually replace biopsies altogether. According to the NCI, esophageal cancer causes nearly 15,000 deaths in the United States each year. "We hope that by contributing this tool we'll be able to shift that number downwards — the way it's gone with colonoscopy," says Wax, who has launched a company, Oncoscope, to raise funds for clinical trials.

A similar light-based technique, optical coherence tomography (OCT) — could detect non-melanoma skin cancer below the surface of the skin, where standard visual exams can't see. Where Wax aims to get a precise measurement of cell structures, OCT provides images that doctors can examine. OCT — already used by ophthalmologists to examine the inside of the eye, also uses interferometry to image intracellular structures so doctors can see if they're abnormal. A British company, Michelson Diagnostics, is developing a handheld OCT scanner to detect non-melanoma skin cancer below the surface of the skin,

"We're very good at seeing where the lesion is," says biomedical engineer Gordon McKenzie, Michelson's medical applications director. "What we're doing now is gathering the evidence of whether we're seeing a cancer or a precancer." He says the machine, VivoSight, is comparable in both appearance and cost to the ultrasound machines found in obstetricians' offices. He hopes that the device, now

in clinical trials, will reduce the number of biopsies of non-malignant lesions, and make the biopsies that are performed more accurate. Right now, he says, as many as 80% of patients who have a malignant mole removed need more tissue excised after tests find that some cancerous tissue may have been left behind. Eventually, he says, their scanner might help find new lesions in the colon and cervix as well as the skin.

NANOPARTICLES AND MOLECULES

Telling the precancerous from the cancerous is useful, but the earlier it is possible to detect aberrant cellular changes, the closer that comes to being equivalent to prevention. "Diagnosis is very nice, but screening is much more important," says Hossam Haick, a chemical engineer at Technion Israel Institute of Technology in Haifa. Haick has built an array of nanosensors that, he says, detect biomarkers of certain cancers years before they develop. He bases this assertion on histological studies showing that cells producing these molecules eventually become cancerous.

Haick's nanosensors measure volatile organic compounds released by cells into the bloodstream and then exhaled — a sort of cancer breathalyzer. The array consists of about 40 gold nanoparticles attached to molecules sensitive to various organic compounds such as alcohols, benzenes and alkenes. The patient blows into a bag, and as the breath passes through the array any volatile organic compounds bind to their complementary sensors and emits a signal. Software probes the pattern of any signals to get a signature of a type and stage of cancer (see Telltale cancer breath) . By testing patients with known cancers, Haick identified signatures for lung, breast, colorectal and prostate cancer. He is working on finding signatures for ovarian, liver and gastric cancer, and has formed a company to commercialize the technology.

One challenge in early detection is picking up a hint of cancer from tumours still too small to show up under current screening techniques. Mehmet Toner, a biomedical engineer at Harvard Medical School and Massachusetts General Hospital, is building a sensor chip that can find a single circulating tumour cell (CTC) in a billion or more blood cells. A blood sample is injected into the chip, along with antibodies that bind to proteins on the surface of the cancer cells. Also attached to the antibodies are tiny magnetic beads. Once suspect cells are tagged with those beads, they can easily be collected by other magnets for closer examination. Toner says the chip, which he is developing with Johnson and Johnson subsidiary Veridex, should prove to be far more sensitive than previous techniques.

In addition to early detection, Toner says, the blood test is attractive because it's easier — and cheaper — than something like a colonoscopy. Colonoscopy is recommended for everyone over 50 years of age, but Toner says the CTC chip could act as a screen to rule out some patients—and perhaps to rule in younger people if the chip raises any issues. The aim of the Veridex collaboration is to manufacture 10,000 to 20,000 of these magnetic-bead chips over the next two years, then use them in clinical trials to see how well they detect CTCs. Toner notes that it is still an open question whether these cells, undetectable by current methods, will ever develop into cancers that can kill. Whereas today's techniques may find cancer too late, an overly sensitive test might cause unnecessary alarm. "It could be that cancer is something we all live with, but [current] tests are such that we only look at it when it becomes a problem," he says.

SEARCH FOR RELEVANCE

In fact, such a risk of overdiagnosis is a major potential problem with early detection technologies, says Sanjiv Sam Gambhir, at the Canary Center at Stanford for Cancer Early Detection. "Our goal isn't to find all cancers early," he emphasizes. "Our goal is to find early relevant cancers — that is, cancers that will go on to kill." That will require biologists to work along with the technology developers — both to understand the significance of what the tests find and to identify new biological targets to refine the detectors. Gambhir, for instance, talks about identifying prognostic biomarkers — proteins that appear only in patients with the most aggressive tumours.

Gambhir specializes in molecular imaging, in which a molecule that binds to a specific biological target is labelled , often with a radioisotope, so that it shows up more clearly in existing imaging technologies. His group created a probe that binds to tumour cells, but instead of a radioactive label, they attached a microbubble — a tiny, gas-filled sac that reflects sound waves and shows up brightly in an ultrasound image. Another approach relies on Raman light scattering, in which a small fraction of the photons reflecting off a surface shift their wavelength in a specific way. Gambhir injects probes labelled with gold nanoparticles, then uses a colonoscope to find their Raman signal. This technique could improve the sensitivity of colonoscopy, which is good at identifying polyps but tends to miss flat precancerous lesions.

Although the ultimate goal is to develop techniques to screen the general population for early signs of malignancy, it is easier to tell if the new tests work when researchers already know a patient has cancer. Thus many techniques are first being developed for use in the easy cases — staging tumours or identifying sites for biopsy in patients with known malignancies. The technological progression, says Toner, is to go "from metastatic cancer to diagnosed but early-stage cancer to high-risk groups free of cancer to the wider population". Once researchers prove that the new technologies work in that wider population, physicians will have at their disposal a powerful set of early warning systems that can give us bad news in time for it to be not the worst news. ■

Neil Savage *is a writer based in Massachusetts.*

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TELLTALE CANCER BREATH

Everyone's breath contains certain chemicals (e.g., alcohols, benzenes and alkenes). People with early stage cancer have different concentrations of these compounds in their breath than people who are cancer free.