GARY NEILL

PROGNOSIS

Proportionate response

Work to determine which prostate cancers are truly dangerous may finally be coming to fruition.

BY SARAH DEWEERDT

A little knowledge can be both a blessing and a curse. Ever since the prostate-specific antigen (PSA) test was introduced in the United States as a method of screening for prostate cancer in the mid-1990s, physicians, scientists and public health officials have been wrestling with the problem of how to use it.

The blood test looks for high levels of PSA — an enzyme that thins the semen to allow sperm to swim freely — and enables early detection of one of the most common forms of cancer. But it is far from infallible. A higher than average PSA reading is not necessarily the work of a malignant tumour, so the test flags many men who do not have cancer. And because prostate cancer is often indolent, meaning it is slow-growing and unlikely to spread, many of the cancers that are detected would never have threatened a man's health if left untreated. "The issue with prostate cancer is not necessarily detecting it early enough, but predicting which cancers are aggressive and which are indolent," says Vadim Backman, a biomedical engineer at Northwestern University in Evanston, Illinois.

This conundrum has led to a difference of opinion about how widely to use the PSA test, and what action to take if cancer is detected (see page S120). PSA screening had quickly become widespread in the United States, but in 2012 the US Preventive Services Task Force recommended against routine screening.

The controversy has, however, also stimulated scientific creativity. Researchers are improving the way in which men who are likely to have aggressive forms of prostate cancer are identified to reduce unnecessary biopsies. And to cut down on needless treatment, they are developing better ways to evaluate biopsy tissue and determine which tumours truly pose a threat. Because prostate cancer has a long natural history, definitive studies to address these issues take a long time to complete. But a flurry of publications over the past few years, as well as the commercial introduction of several tests, suggest that scientific patience is paying off.

BEYOND PSA

To do a better job of deciding which men should have prostate biopsies, physicians need non-invasive tests, either to supplement PSA screening or to replace it entirely. "The most pressing need is to identify biomarkers that are specific for high-grade cancer," says urologist Scott Tomlins at the University of Michigan in Ann Arbor. An ideal biomarker would only be expressed in prostate tissue, not elsewhere in the body, and only be found in aggressive cancer, not low-grade disease. To be useful as a screening test, the biomarker would also need to show these patterns in blood or urine, not just intact tissues[1].

One approach is to improve on the concept of the PSA test with tests that can be used to spot patterns in particular forms of PSA or suites of other, related molecules in the blood that are more specifically linked to aggressive prostate cancer. One version of this approach, the prostate health index, integrates three forms of PSA into a single score, which is then used to determine the risk of an aggressive tumour. Whereas another, the 4Kscore test, measures a panel of four molecules, including two forms of PSA that, like PSA measured in the established test, belong to a group of enzymes called kallikreins.

A study of biopsy tissue from more than 6,000 men found that screening using the four-kallikrein panel could reduce the number of unnecessary biopsies — 43% fewer biopsies compared with the standard PSA test and a delay in the diagnosis of only a handful of aggressive cancers[2]. Another study bolsters these results. Researchers followed a cohort of men for more than 15 years, and found that the blood test predicts which men are more likely to develop metastatic prostate cancer in the long

term[3]. "I think that sends a very strong message that the way we measure this actually predicts something biological and disease-relevant," says Hans Lilja, a clinical chemist at Memorial Sloan Kettering Cancer Center in New York and a leader of both studies.

Scientists are also developing urine-based screening tests. One of these tests measures levels of the biomarkers TMPRSS2-ERG and PCA3. About 80% of men with prostate cancer have at least one tumour that produces TMPRSS2-ERG — the result of a genetic scrambling that occurs very early in the development of many prostate cancers, leading to the fusion of two genes. PCA3, a molecule normally produced by prostate tissue, occurs at abnormally high levels in at least 90% of prostate cancers — but, unlike PSA, it is almost never elevated in benign conditions. "The unique thing about those is they're very prostate-cancer specific," says Tomlins.

Individuals with high levels of these two biomarkers in their urine tend to have a large amount of tumour in their prostate, Tomlins says. This itself is a good indicator that an aggressive cancer is at work. In May, his team reported that the two markers do a better job of zeroing in on aggressive cancers than the standard PSA blood test[4]. Next, they plan to test whether adding an assay for another molecule associated with aggressive cancer, SchLAP1, will further improve the test.

MAKING SENSE OF SCREENING

More informative screening methods are good as far as they go, but researchers are also searching for another piece of the puzzle: how to improve the analysis of tissue taken in biopsies after a positive screening test. These advances would allow physicians to better distinguish which cancers require immediate treatment, and which can be monitored — an approach known as active surveillance (see page S126).

Oncologists currently evaluate prostate biopsies by Gleason grading, a method of scoring prostate tissue on a scale of 1 to 10 by how abnormal its cells appear (see 'Scoring cancer'). Prostate tissue with a Gleason score of 5 or below is generally quiescent; tissue with a score of 8 or above requires immediate treatment.

But most common prostate tumours score a middle-of-the-road 6 or 7, and these are more vexing to deal with. Usually, grade 6 tumours can be safely managed with active surveillance. But a few will prove to be aggressive. Grade 7 tumours are more evenly split between those that are aggressive and those that are not. "There's a lot in the kind of grey zone that we don't know," says Jack Cuzick, an epidemiologist at Queen Mary University of London.

Cuzick and his team have evaluated a biomarker known as the cell-cycle progression score, which measures the activity of genes related to cell division in biopsy tissue. The greater the rate of cell division, the more aggressive the tumour — a pattern that applies to many forms of cancer. In a study of 585 men with prostate cancer, the researchers showed that this approach provides additional information about which men with those intermediate Gleason-score biopsies are at risk of dying from prostate cancer over the course of ten years[5]. "Our feeling is that the cell-cycle progression score is a huge step forward to resolve many of the controversial cases," says Cuzick, who also consults for Myriad Genetics, the maker of one cell-cycle progression test.

The cell-cycle progression score is one of an increasing number of genomic tests for prostate cancer — others evaluate between one- and two-dozen genes associated with prostate cancer. A weakness of these tests, however, is that they work best if they are applied to biopsies taken from the most aggressive part of the cancer — and that is not always obvious.

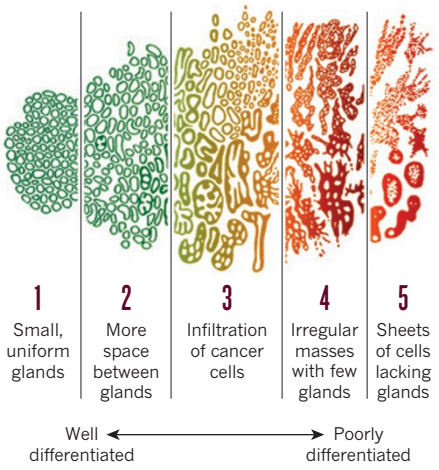
That is because many men with prostate cancer have multiple tumours of independent origin. These various tumours can differ in their aggressiveness. Studies of men who had their prostate removed have found that 15–40% of those diagnosed with low-grade cancer at biopsy actually have a more aggressive tumour elsewhere in the prostate.

Backman and his team have developed a form of microscopy that they say could overcome this difficulty by allowing pathologists to see changes inside cells that are too small to resolve with standard microscopy. The researchers, who formed NanoCytomics in Evanston, Illinois, to commercialize the technology, found that non-cancerous tissue taken from prostates that contain Gleason grade 6 tumours that turned out to be aggressive show characteristic nanoscale changes, especially in the packaging of DNA in the cell nucleus[6]. Prostates that contain non-aggressive grade 6 tumours do not show these alterations.

The advantage of this type of test is that doctors could potentially determine the aggressiveness of a tumour without having to biopsy the tumour itself. "We don't need to find the needle," Backman says. "All we have to do is sample the haystack."

SCORING CANCER

Prostate-cancer severity can be gauged by assessing how well differentiated the tissue appears under the microscope and grading it 1–5. This is done twice and the grade combined, giving a score of between 2 to 10.



SMARTER BIOPSIES

Finely locating the tumours within the prostate is still an option, though. This is the focus of a third category of efforts aimed at improving the prostate-biopsy procedure, which involves taking samples of tissue — usually 10 to 12, but sometimes as many as 50 — with a fine needle.

Prostate biopsies have generally been performed with little information about exactly where in the prostate a sample comes from. This is because it is difficult to get a clear picture of the organ using standard imaging methods. But now, an approach known as multiparametric magnetic resonance imaging (MRI) is beginning to change that[7]. The procedure combines three techniques to generate a fuller picture of prostate anatomy and function. "We can go after the area that we think is most likely to have high-grade cancer," Tomlins says.

Earlier this year, researchers found that oncologists locate more high-grade tumours when aided by multiparametric MRI than with standard biopsy procedures[8]. "It decreases the risks associated with active surveillance," says the study leader Peter Black, a urological oncologist at Vancouver General Hospital in Canada. "You're able to take these patients out of the active surveillance pool and treat them."

The technique also makes it possible to follow the development of a specific tumour and repeatedly biopsy it over time. This capability could help to address some basic questions about prostate cancer — with implications for treatment. "For example, do low-grade tumours routinely turn into higher-grade or more aggressive tumours?" Tomlins says. "It's a crucial question because it totally changes how we predict whether cancers are going to be indolent or aggressive."

The challenge now is to bring together these varied strands of research, because the new biomarkers and testing strategies have largely been developed in isolation from each other. "Very little has been done to see if these can add to each other and how much we would gain by doing that," Lilja says. So even as techniques that may yield a better understanding of a patient's prognosis begin to roll out, scientists are aiming at the next round of improvements. ■

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