A simple blood test is used to measure prostate-specific antigen, or PSA, but researchers continue to debate how best to use the test to save lives.

SCREENING

Diagnostic dilemma

The standard blood test for prostate cancer led to a spike in diagnoses of the disease. But the technique's results are often misleading — and conflicting studies have not helped to forge a consensus.

BY EMILY SOHN

It was an appealing idea: a simple blood test that could detect prostate cancer early, before it could become life threatening. So appealing, in fact, that enthusiasm for the prostate-specific antigen (PSA) test caught on long before there was strong evidence to support it.

PSA is a protein that is produced by the prostate gland and is usually found in the blood at higher levels when a prostate tumour is present. The US Food and Drug Administration initially approved the PSA test for cancer monitoring in 1986, and by 1992 the US incidence rate for prostate cancer had more than doubled from 119 to 237 cases per 100,000 people. From 1992 to 2012, deaths from prostate cancer halved, from about 39 cases per 100,000 people to 20. "When you look at the curves, there's nothing else like it with other cancers," says Laurence Klotz, a urologic oncologist at the Sunnybrook Research Institute at the University of Toronto in Canada.

But scepticism also emerged early and deepened over time, especially as two closely watched trials produced drastically different results — one showing a substantial benefit of screening and the other showing no benefit at all. In the meantime, studies have shown that whereas many men have had their lives saved by early detection with the test, many others have been diagnosed and treated for cancers that in all likelihood would never have caused them harm.

"The PSA was a genie that got out of the bottle well before randomized trials were initiated," says Michael Barry, a primary care doctor at Massachusetts General Hospital in Boston and president of the Informed Medical Decisions Foundation, a Boston-based organization that advocates for evidence-based shared decision-making between doctors and patients. Even when trial results became available, he adds, they failed to resolve the question of whether the test was worthwhile.

Hundreds of studies have now analysed the consequences of screening. The results have led to important developments in testing protocols, treatment decisions and public trust in the PSA test. And taken together, these findings are starting to reveal how best to use the test to help more people and harm fewer of them. Still, researchers and clinicians continue to debate everything from what level of PSA should be considered alarming to which men should have the test in the first place. Some 30 years after the PSA test was introduced, the question it raised still lacks a definitive answer — what is the best way to protect men from prostate cancer without treating those who are better off left alone?

"You can support any argument you want depending on which data you quote," says Klotz. "We are not nearing consensus."

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THE GOOD, THE BAD AND THE OPINIONS

PSA emerges from the prostate and circulates through the blood at levels that become increased for various reasons. By the mid-1980s, it was clear that prostate cancer was one of those reasons, and doctors began using the test to track progression of the disease. One of the first studies to suggest that the PSA test might also revolutionize the ability to screen for cancer emerged in 1991 (ref. 1), when researchers found that the test detected many more cancers than did rectal examination, which at the time was the best screening method available.

The study included more than 1,600 men who received the PSA test, which was

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followed up with rectal exams and ultrasound scans if PSA levels were deemed high, as well as 300 men who underwent biopsies after being flagged during the course of clinical care. Of the 37 men in the study group who were diagnosed with prostate cancer, 12 of them would have been missed if they had received only rectal exams.

At the time, nearly 20% of men diagnosed with the disease had an advanced form that had already spread outside the prostate, so doctors were eager for a way to pinpoint the disease at an earlier, more treatable stage. The new findings offered hope that the PSA test might be the answer. When the study came out, media coverage was enthusiastic, and lead author William Catalona appeared on the television talk show *Good Morning America*. "I think that kind of kicked off the PSA era," says Catalona, who is director of the clinical prostate-cancer programme at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

Fritz Schröder, a professor of urology at Erasmus University Medical Center in Rotterdam, the Netherlands, remembers hearing of the study's results with excitement and meeting with a colleague in Belgium to discuss them. Recognizing a clear need for a randomized trial to assess the PSA test's ability to save lives, they put together the European Randomized Study of Screening for Prostate Cancer (ERSPC). This trial eventually grew to include 240,000 men from eight countries, who were randomly assigned into control and test groups, with the latter receiving PSA tests every one to four years. The first results from the ERSPC, which were published in 2009 and included nine years of follow-up data, reported a 20% drop in deaths from prostate cancer as a result of early detection with the PSA test[2]. In 2014, that figure grew to 27% after analyses were adjusted to include only men who had actually complied with the screening regimen to which they were assigned[3].

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Other lines of evidence have emerged to support screening. Since the beginning of widespread PSA testing, Catalona says, there has been an 80% drop in the percentage of patients in the United States whose cancers are metastatic at the time of diagnosis — a major factor in the declining US death rate from the disease. Trends are similar in other countries that have adopted screening, Catalona adds, with a link between when screening started and when death rates began to drop. Denmark, for example, started encouraging screening later than did other Nordic countries, and Danish prostate-cancer mortality levelled off later than in those neighbouring countries. Other researchers disagree about how many of those lives were saved as a result of the PSA test because treatment has also improved during the same period.

Still, PSA-test advocates also point to an intangible benefit: peace of mind for men whose result indicates a low risk of prostate cancer. In two studies — one of men in their 40s and the other of men aged 60 — a PSA value of below 1 has been linked to a very low likelihood of developing aggressive cancer for many years afterwards. "There is no other biomarker," Klotz says, "that gives you a 20-year predictive value of getting a common cancer."

As encouraging as these findings may sound, consensus on them has been maddeningly elusive. When the ERSPC published its first results, the same journal issue published conflicting findings from another large trial, which included more than 76,000 US men who were randomly assigned to two groups: one that received a PSA test and rectal exam, and one that did not. This study, the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, showed no reduction in deaths from PSA testing after 11 years of follow-up[4].

The two contradictory trials remain at the centre of debates about the benefits of PSA screening. The PLCO trial in particular has been criticized for widespread failure of subjects to comply with experimental conditions. Many men in the control group had a PSA test, whereas many assigned to the screening group went unscreened. Without adjustments to account for compliance rates, critics argue that the two groups were essentially the same. Still, the results continue to be included in major reviews, including the most recent analysis by the US Preventive Services Task Force (USPSTF), an independent panel of experts based in Rockville, Maryland, that makes evidence-based recommendations about preventive services.

The European trial has not escaped criticism, however. Even a 20% reduction in risk of death would add up to just one fewer case of metastatic prostate cancer per 1,000 men screened over 13 years. That short time horizon is problematic, says Barry, who argues that 13 years is not sufficient to assess the long-term effects of a test on a disease that often occurs later in life. Moreover, during the same time period that the PSA tests were being introduced, drastically improved treatments were entering the clinic — a development that may well account for better outcomes. "People accept that there is some benefit due to screening," Barry says, "but how much is a subject of debate."

TO SCREEN OR NOT TO SCREEN

Screening for prostate cancer with the prostate-specific antigen test produces an array of outcomes. If 1,000 men between the ages of 55 and 69 are screened every 1 to 4 years for a decade then …

BETTER NOT TO KNOW?

Whatever their magnitude, the benefits of PSA screening come with some serious downsides. One complicating factor is that PSA levels can be increased for reasons that have nothing to do with cancer, including urinary-tract infections, inflammation and enlargement of the prostate, a benign

condition that becomes increasingly common as men age. As a result, many men who are flagged for follow-up by their high PSA levels do not have cancer at all. It is also common for men to harbour non-aggressive, slow-growing tumours for many years, and to eventually die from some other cause — which means that even men who do have cancer often do not need to know about it. The authors of one autopsy study found prostate cancers in 64% of men in their 60s who had died of something other than prostate cancer[5]. In the United States, a man has about a 14% risk of developing prostate cancer in his lifetime, but less than a 3% risk of dying from it. As a result, attempts to catch aggressive prostate cancers early have ensnared many men who never should have become cancer patients in the first place.

The discovery of an increased PSA level presents an array of potential risks. Biopsies can cause pain, fever, blood in the urine and infections, which are increasingly resistant to antibiotics. And because biopsies sample only a fraction of the prostrate, they are not regarded as conclusive — uncertainty that often means further tests and biopsies even after a negative result. "Patients are happy to get a blood test," says Peter Albertsen, a urologist at the University of Connecticut Health Center in Farmington, "but that starts the ball rolling downhill, and it can lead to all sorts of consequences."

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Wherever screening is widespread — including the United States, Australia and parts of Europe — unnecessary treatments are rampant, says Barry. The US National Cancer Institute estimates that for every 1,000 men screened regularly with the PSA test over the course of a decade, as many as 120 will get a false-positive result that may lead to a biopsy. Another 110 will get a cancer diagnosis (see 'To screen or not to screen'). And nearly half of those 110 will have complications from treatment, including incontinence and sexual dysfunction. "Overdiagnosis," Schröder says, "occurs at a rate that we find very disturbing."

Cancer diagnoses carry an understudied psychological burden, Barry adds, and anxiety can linger even after reassuring biopsy results. There are hefty financial costs, too. In a 2011 analysis of data from the ERSPC that was extrapolated to the United States, researchers estimated that preventing one death from prostate cancer costs more than US$5 million in screening, biopsies and treatments[6]. "If we treat patients for cancer and they die the same day they were destined to die from a heart attack," says co-author Alex Shteynshlyuger, a urologist in private practice in New York, "what good have we achieved?"

Based on the seemingly high rate of potential harm, the USPSTF updated its recommendations in 2012 to advise against routine PSA screening for all men. The United Kingdom has also decided against a national prostate-cancer screening programme owing to a lack of convincing evidence to support the PSA test. Still, other doctors and organizations continue to recommend screening, with variations in what age it should begin, how frequently tests should occur and what PSA levels should be considered concerning. The result is confusion for men who want to make informed decisions about their health.

BLAMING THE MESSENGER

As scientists grapple with the data, there is another ongoing problem: the data keep changing because doctors are getting better at selecting the most eligible patients for screening and treatment. People are also making different choices about screening, with drops in both the number of US men having the PSA test and the number of prostate-cancer diagnoses, according to two studies published in November[7,8]. Still, disagreement persists about where the balance lies, and those arguments continue to rely on trial data that are becoming obsolete. "There are very few things we are doing today that we were doing the same way when the studies began," Shteynshlyuger says. "The tectonic plates keep moving under our feet."

Part of the shift is a result of advances in screening, which are helping doctors to zero in on aggressive cancers that need the most attention. Among the new strategies is a tool called the prostate health index (PHI), which measures three types of PSA. According to some research, the PHI is three times more specific than the standard PSA test, an improvement that reduces the number of unnecessary biopsies. Doctors around the world also now factor in a tumour's Gleason score, which assesses aggressiveness based on the way that cancer cells look under a microscope. And researchers are continually re-examining the level at which the quantity of PSA in the blood should be considered abnormal. Some evidence, for example, supports the idea that the threshold for concern should be raised from its present value of 3–4 nanograms per millilitre to 10 nanograms per millilitre. Beyond PSA, scientists are also using magnetic resonance imaging to guide biopsies making false negatives less likely, as well as genetic tissue tests to screen for biomarkers that signal a cancer's degree of aggressiveness (see page S124). These tests can be expensive, and health-insurance companies in the United States do not necessarily cover them. Many are so new, Barry adds, that there are insufficient data on outcomes. Rushing to accept newer tests before sound trial evidence arrives, in other words, might bring a repeat of the troubled PSA era all over again.

But the real crux of the screening debate is what happens when results come in — and that is where big changes are happening. Within the past decade, for example, there has been a major spike in the number of men with low-risk cancers who choose to forgo treatment, instead taking a wait-and-see approach known as active surveillance, which, depending on the situation, could mean periodic screening or careful observations of symptoms (see page S126).

In 2006, 90% of US men diagnosed with prostate cancer were treated for it, says Stacy Loeb, a urologist at New York University School of Medicine. Today, only 50–60% opt for treatment. Sweden has been particularly quick to adopt the strategy: 91% of men with very low-risk and 74% of men with low-risk prostate cancer in the country now opt for active surveillance. As fewer men are treated, one hope is that the benefits of PSA testing will begin to outweigh the harms. "There is a lot of controversy about screening because it used to be done in such a very rudimentary fashion," Loeb says. "We have come to recognize that it's not so black and white."

Given the uncertainties, many experts now recommend an approach that considers each patient's situation individually. Statistical tools are helping with the process; at the University of Texas in San Antonio, for example, researchers used data from thousands of biopsies to create an online calculator that incorporates age, race, family history, PSA score and other factors into a recommendation that doctors and patients can consider together. This kind of shared-decision-making strategy is currently recommended by organizations such as the American Urological Association.

Forthcoming data may soon make screening decisions even more informed. In January 2016, researchers are expected to release 10-year follow-up results from the Prostate Testing for Cancer and Treatment (PROTECT) trial, which includes more than 1,600 British men who were diagnosed with localized prostrate cancer using PSA tests and then randomly assigned to one of three treatment options, including active surveillance. But based on the history of PSA testing, it is hard to imagine that any fresh results will settle disagreement about screening once and for all. ■

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