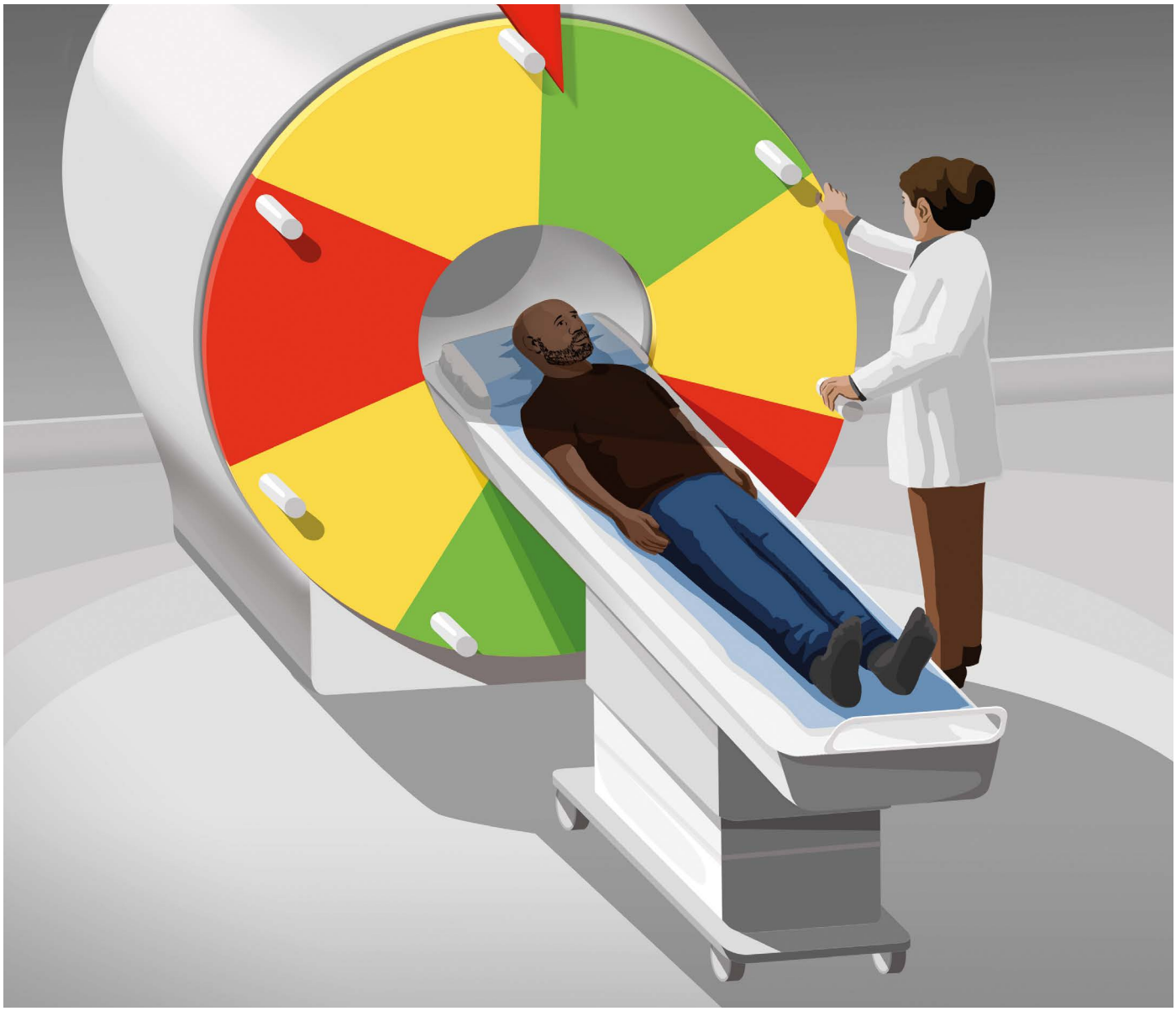


ILLUSTRATION BY SAM FALCONER

An uncertain diagnosis

Increasingly sensitive tests have raised the risk of overdiagnosis. Understanding a person's chance of disease could reduce the harms of screening. **By Natasha Gilbert**

Impotence and incontinence are common side effects of treatment for prostate cancer. For men with aggressive forms of the disease, these treatment consequences will outweigh the alternative — prostate cancer is one of the biggest cancer killers in men. But a large proportion of people diagnosed with prostate cancer are treated for slow-growing tumours that would have been unlikely to cause harm if left alone — the potential side effects of treatment overshadow the gains.

These people are treated because their cancers are flagged by screening programmes. Overdiagnosis and overtreatment are also common outcomes of breast-cancer screening, leading researchers to question whether screening for these cancers is doing more harm than good.

"Used wisely, screening for breast and prostate cancer can significantly reduce an individual's risk of dying from those cancers. However, the potential benefits may not necessarily outweigh the expected harms and costs of screening on a population level," says Sigrid Carlsson, an epidemiologist at the Memorial Sloan Kettering Cancer Center in New York.

Screening for cancer is designed to catch disease early, when physicians have the best chance of treating it. But differences in opinion over the benefits of breast- and prostate-cancer screening have led to confusing and contradictory recommendations about which people to screen, when and how often. Screening for other types of cancer such as colorectal and cervical cancer is less controversial because they tend to be slower growing, more homogeneous and more readily detected and removed with fewer serious side effects, say researchers.

Scientists are trying to resolve the issues over breast- and prostate-cancer screening by developing more-accurate screening tools. One persistent theme is the push for an individualized approach — each person's risk is assessed in a way that allows them to make an informed decision.

Harmful effects

Prostate and breast cancer account for around one-quarter of all new cancer diagnoses in the United States, according to data from the American Cancer Society. The common occurrence of these cancers is partly due to widespread screening practices that began in the 1980s and 1990s. Breast-cancer screening typically uses a mammogram — a low-energy X-ray of the breast to look for masses that can't be seen or felt through physical examination. Prostate-cancer screening involves testing the blood for elevated levels of prostate-specific antigen (PSA), a protein produced by the prostate gland.

Early screening studies showed benefits. For example, the first US trial of annual breast-cancer screening, launched in 1963, reduced mortality by 25% in its first 18 years[1]. But over the following three decades, scientists became concerned when they saw the rate of cancer incidence rise. In 2000, a comparison of prostate-cancer incidence and mortality in the United States, where screening is common, and United Kingdom, where it is not, found that PSA screening in the United States dramatically increased the number of people diagnosed with the cancer, but did not result in lower mortality than in the United Kingdom[2].

Researchers began to realize that screening resulted in the frequent diagnosis and treatment of slow-growing cancers that were unlikely to cause harm, as well as false-positive results — when a person is told that they might have cancer when they do not. One study reported that up to 75% of positive PSA tests are a false-positive result[3]. These results, and the unnecessary diagnostic biopsies and treatment that can follow, can have harmful consequences for people, including psychological distress, incontinence and erectile dysfunction.

Other results showed that 97% of men whose prostate cancer was monitored for growth rather than treated were still alive 10 years after diagnosis. But more than 90% of tumours are treated with radiation or surgery, and up to one-fifth of people have sexual, urinary or gastrointestinal side effects[4]. "It turns out that whenever you screen you are necessarily going to surface indolent disease that might never come to your attention," says Laura Esserman, a surgeon and breast-cancer oncologist at the University of California, San Francisco. She and other researchers are pushing for reforms to improve accuracy, maximize benefits and reduce the adverse effects of screening. "Overdiagnosis and overtreatment causes harm," says Esserman. "We need to do better."

Widespread disagreement

Part of that approach is to better understand each person's risk of cancer, using a suite of tests including genetic profiles, and to tailor tests and screening accordingly. Olena Mandrik, who studies the detection and prevention of cancer at the University of Sheffield, UK, hopes that focusing assessments on a person's risk of breast cancer will help to move the field beyond disputes over screening programmes. A proliferation of reviews and meta-analyses of breast-cancer-screening trials over the past 25 years has attempted to clarify results — but the outcome has been the opposite.

"Most reviews completely disagree regarding their recommendations for mammography," Mandrik says. Last year, she reported the results of a systematic review of the existing reviews and meta-analyses, in which she attempted to determine where they agree on the risks and benefits of breast-cancer screening[5]. Mandrik found evidence that, compared with not testing, screening reduced the risk of late-stage cancers in women aged 50–69, and cut mortality by 15–25% across all ages in randomized controlled trials. But she found no consistency in the results regarding mortality reduction for women younger than 50 or older than 69.

Mandrik was also unable to draw conclusions regarding how often screenings should take place, or how often overdiagnosis occurs. She attributes some of the variation in the reviews' conclusions to differences in how the studies were designed and implemented. Reviews also reach different conclusions using the same data because authors interpret the studies differently — those who are generally supportive of screening might see results more favourably, Mandrik suggests. Moreover, she says, the original radiologist's level of experience in carrying out and analysing mammograms can affect results; more seasoned practitioners are likely to have fewer false-positive results.

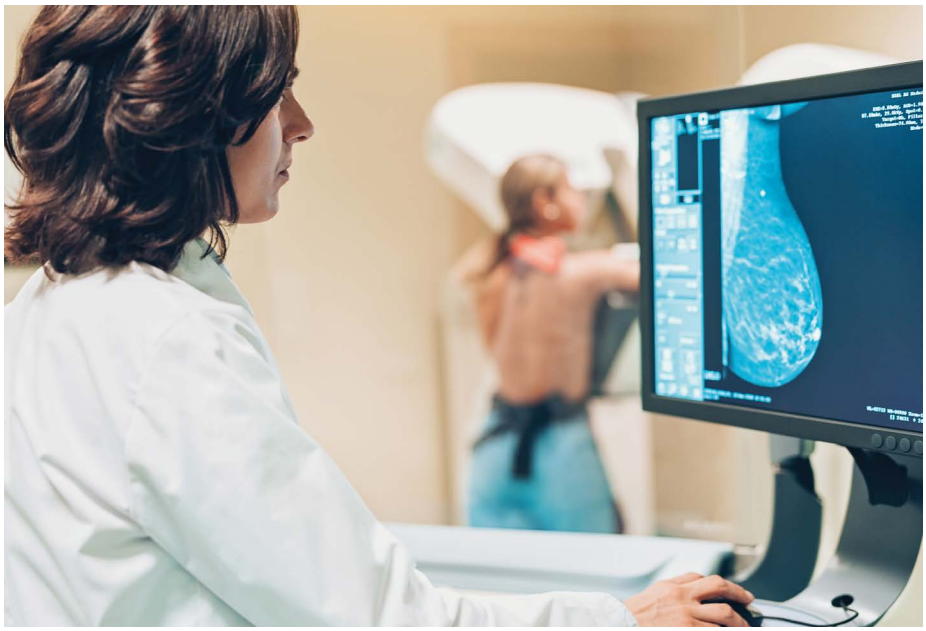
Differences in the reviews' conclusions are reflected in discrepancies in recommendations for breast-cancer screening. For example, the US Preventive Services Task Force, an independent panel of health-care specialists, concluded in 2009 and 2016 that those aged 50–74 years should be screened every 2 years. However, the American College of Radiology recommends annual mammography screening from the age of 40 for those with average risk. In the United Kingdom, women aged 50–70 are offered mammograms every 3 years.

Esserman says that the differences in opinion indicate the need for a "course correction" in the way researchers and physicians approach breast-cancer screening. In particular, she says, screening programmes need to better reflect the fact that breast cancers differ considerably from person to person on metrics such as the degree of invasiveness. "There's lots of different types of breast cancer, so it doesn't make sense to be approaching screening as one size fits all," she says.

"We're trying to figure if there are better ways to screen people who have the highest risk."

Esserman is trying to better understand who is at risk of developing breast cancer. She hopes that this will reduce diagnoses of cancers that are unlikely to be harmful and unnecessary treatment. She also wants physicians to make better and earlier use of preventive measures for women at higher risk of breast cancer, such as avoiding hormone replacement therapy — known to increase the risk of the disease. Since 2016, she has been conducting a trial to test how screening strategies based on an individual's risk compare with conventional annual mammography. The trial — called WISDOM (Women Informed to Screen Depending on Measures of risk) — models risk using a range of measures, including blood tests that look for markers of genetic predisposition, breast density and family history. "We're not throwing away screening," Esserman says. "We're trying to figure if there are better ways to screen people who have the highest risk" (see page S5).

Identifying high- and low-risk tumours is also an issue in prostate cancer. Conventionally, people with elevated PSA scores or abnormalities found through physical examination are offered a biopsy in which 10–12



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Breast-cancer screening can result in overdiagnosis and overtreatment.

needles are inserted through the rectum "in the hope that you hit a cancer", says Caroline Moore, a surgeon and urologist at University College London.

It's a hit-and-miss approach that both fails to catch some clinically important prostate cancers and detects too many low-grade tumours, says Moore. Some types of prostate cancer are slow growing and unlikely to cause harm in a person's lifetime; such tumours account for anywhere between 2% and 67% of those found in screening, according to a review[6]. (This wide variation is due to differences in the populations studied and the screening methods used.) To improve accuracy and reduce unnecessary intervention, Moore has investigated using magnetic resonance imaging (MRI) before a biopsy is taken to help find tumours and gauge how dangerous they are likely to be. In an international trial of 500 men, Moore and her colleagues found that using MRI prevented unnecessary biopsies[7]. MRIs showed no evidence of cancer in 28% of the 252 men with elevated PSA scores suggestive of cancer. MRIs also helped to guide biopsies to find potentially harmful cancers – detecting them in 38% of the trial participants compared with the 26% detected using ultrasound-guided biopsy. "We found more significant cancer in the MRI group and we found less small, indolent cancers," she says.

Reducing overdiagnosis is important, given the considerable effect on quality of life after treatment for prostate cancer, and the risk of infection associated with biopsy. The results of studies such as Moore's have led several organizations to recommend the use of MRI as a pre-diagnostic tool, including Britain's National Institute for Health and Care Excellence and the European Association of Urology.

Overdiagnosis

Researchers such as Moore are also testing how well MRI performs as a screening tool compared with conventional PSA tests. Moore suggests that if MRI comes out on top it could be a "game changer" in the United Kingdom, which currently does not offer prostate-cancer screening owing to scant evidence that screening cuts death rates.

"We used to be afraid of overdiagnosis, but now we might be afraid of underdiagnosis."

Carlsson is sceptical that MRIs can be broadly applied as a screening tool because of cost and the variation in both machinery and radiologists' experience. She worries that relying solely on MRIs to determine the need for a biopsy might miss some cancers, mainly because there will be a variation in the quality of the images taken and the expertise of the people interpreting the MRIs. People who live in areas with modern, well-maintained technology, and an abundance of well-educated and experienced medical carers, are likely to get more-accurate MRI results. "We used to be afraid of overdiagnosis, but now we might be afraid of underdiagnosis instead," Carlsson says.

Carlsson says that extra biomarkers, such as the total level of PSA in the blood, which measures both PSA bound to proteins and the unbound form, can help to inform the decision of whether to take a biopsy. In addition, several tools exist for calculating a person's risk of prostate cancer. The 4Kscore, for example, uses four prostate-cancer biomarkers combined with age and medical history to give an individual risk score. Using a suite of tools including MRI can help to push the need for biopsy further down the road, says Carlsson.

Many oncologists agree that the development of increasingly sensitive imaging tests has made the overdiagnosis and overtreatment of cancers more problematic. Lessons learnt from breast- and prostate-cancer screening have made physicians more aware of these downsides when screening for other malignancies such as lung cancer, a test that can also flag a large proportion of indolent cancers.

Researchers are taking steps to resolve the dilemma, including promoting watching and waiting strategies to see if cancers develop further, rather than intervening immediately. This approach is broadly recommended for cervical and prostate cancer. Personalizing screening schedules on the basis of a person's risk of disease will also help to reduce overdiagnosis, researchers say.

But progress is hard won. Both Moore and Esserman acknowledge that caution and resistance to change in pockets of the scientific community present obstacles to the screening reforms that they are investigating. One of the biggest challenges, says Esserman, is to "shift the overinflated perception of the benefits of screening and to do a more realistic job of setting expectations of benefit and early detection". Such a change, she says, "would lessen the fear of committing malpractice by not doing enough, and help us to identify and embark on opportunities to improve".

For Mandrik, the best solution to the screening problem will come with breakthroughs in cancer treatments that could eliminate the need for screening. "If you have good treatment for all stages then you don't need to screen. Hopefully, maybe, it will be our future. But until then," she says, "screening gives us the opportunity to decrease mortality."

Natasha Gilbert is a freelance science journalist in Washington DC.

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