

# TESTING TREATMENTS

## Chapter 4, 4.2 EARLIER IS NOT NECESSARILY BETTER

### DON'T ASSUME EARLY DETECTION IS WORTHWHILE

'Screening for neuroblastoma illustrates how easily one can fall into the trap of assuming that because a disease can be detected early, screening must be worthwhile . . . The two studies demonstrate how neuroblastoma screening was not only worthless, but led to "over-diagnosis" and must have identified tumours that would have spontaneously regressed. Both studies mentioned children in the screened group suffering severe complications due to the treatment . . . Hopefully these lessons will be learned when considering the implementation of other screening programmes - for example screening for prostate cancer.'

Morris JK. Screening for neuroblastoma in children.  
*Journal of Medical Screening* 2002;9:56.

But the Japanese results, as mentioned above, showed longer survival from date of diagnosis for the screened infants; survival from date of birth had not been analyzed. So, an Australian specialist stepped in and re-analyzed the Japanese results from dates of birth of the infants rather than from dates of diagnosis - this analysis did not show any difference in the survival rates of the screened and unscreened infants. This convinced the New South Wales authorities to abandon their screening programme, thereby saving the infants from unnecessary harms and the health service from unnecessary expense.

### WEIGHING BENEFITS AND HARMS

There are many examples of beneficial screening. Perhaps the most widely used in adults is the checking of risk factors for heart disease and stroke that is routinely done in primary care. There is good evidence that high blood pressure, high blood cholesterol levels, and tobacco smoking increase the risk of these diseases, and that identifying, advising, and treating people with such risk factors can prevent heart attacks and strokes.

**Phenylketonuria screening: clearly beneficial**

Newborn babies are routinely screened for an inherited disease called phenylketonuria (PKU). Babies with PKU are unable to process phenylalanine, a substance which is present in everyday foods such as milk, meat, fish, and eggs. If the condition is left untreated, phenylalanine accumulates in the blood and leads to serious, irreversible, brain damage. PKU testing involves taking a few drops of blood from the baby's heel, which are analyzed in a laboratory. If this 'heel prick test' is positive, and the diagnosis is confirmed by further tests, babies are treated with a special diet to help them develop normally.

**Abdominal aortic aneurysm screening: proceed with care**

At the other end of the age spectrum, abdominal aortic aneurysm screening can also be beneficial. The aorta is the main blood vessel in the body, running from the heart through the chest and abdomen. In some people the wall of the aorta in the abdomen weakens as they become older and the vessel starts to expand – this is an aneurysm, a condition that seldom gives rise to symptoms and is most common in men aged 65 and over. Large aneurysms can eventually rupture and leak without warning, often causing death.<sup>8</sup>

This evidence concerning the frequency of aneurysms in older men can be used as the basis for introducing a screening programme. In the UK, for example, men (but not women) as they turn 65 are being offered a screening ultrasound scan. The scans can show the large aneurysms so that these men can receive specialist advice and treatment, usually surgery. Men with smaller aneurysms are monitored by further scans, and those whose aorta is not enlarged need not be screened again. The quality of the screening and the surgery is crucially important. Aneurysm surgery is a major procedure and if complication rates are high then more men would be harmed than helped.

**Breast cancer screening:  
well established but remains contentious**

Since routine breast screening with mammography is well established in many countries one could well assume that

mammographic screening must be based on sound evidence of benefits outweighing harms. As one US public health expert remarked in 2010: 'No screening test has ever been more carefully studied. In the past 50 years, more than 600,000 women have participated in 10 randomized trials, each involving approximately 10 years of follow-up'. But he went on to say 'Given this extraordinary research effort, it is ironic that screening mammography continues to be one of the most contentious issues within the medical community'.<sup>9</sup>

Why is mammographic screening so contentious? A fundamental reason is that it has been 'sold' to women as a sensible thing to do by those providing screening and by patient groups. The information provided to women who are invited for breast screening emphasizes the benefits while glossing over the harms, limitations, and consequences.<sup>10</sup> Yet mammography not only leads to early diagnosis but also, much as with prostate cancer (see below), to diagnosis of cancers that would never have become apparent in a patient's lifetime. And inevitably there will be false-positive results too.

The most reliable evidence comes from reviewing, systematically, the results of clinical trials in which women have been randomly allocated to screening or no screening. And the results make for interesting reading. They show that if 2,000 women are screened regularly for ten years, one will benefit from screening, as she will avoid dying from breast cancer. But at the same time, ten healthy women will, as a consequence of screening, become 'cancer patients' and will be treated unnecessarily. Mammography in these women has in fact detected lesions that are so slow-growing (or even not growing at all) that they would never have developed into a real cancer. These healthy women will go on to have either part of their breast removed, or even the whole breast, and will often receive radiotherapy and sometimes chemotherapy.<sup>11</sup>

Furthermore, 200 screened women out of 2,000 will experience a false alarm, and the psychological strain until the woman knows whether it was cancer, and even afterwards, can be severe. And mammography is often promoted to women alongside advice on breast self-examination or breast awareness,

when both these methods have also been shown to result in more harm than benefit.<sup>12</sup>

A British public health expert noted that the potential for individual benefit from mammography is very small. He remarked: ‘this is not widely understood. In part this is due to obfuscation from organisers of mammography services assuming that a positive emphasis is needed to ensure reasonable compliance [with screening]’. Assessing the available evidence in 2010, he commented: ‘Mammography does save lives, more effectively among older women, but does cause some harm.’ The harms he is referring to are overdiagnosis and false positives. Critically, he observed that full examination of all the individual results from recent screening studies had yet to be examined dispassionately.<sup>13</sup> While such an impartial evaluation is awaited, women continue to be invited for mammographic screening. At the very least, they need to be given sufficiently balanced information to enable them to decide (together with their family and their doctor if they wish), whether to attend for screening – or not.

### **Prostate cancer screening: clear harms with uncertain benefits**

Prostate cancer is the second most common cancer in men worldwide,<sup>14</sup> and broadly falls into two types. Some men have an aggressive form of the disease; these dangerous cancers spread rapidly and the death rate is high. But many men have slow-growing cancers that would never progress to cause a danger to health during a man’s lifetime. Ideally, a screening test would detect the dangerous cancers – with the hope that they could be treated – but not the slow-growing ones. The reason is that treatment of any sort of prostate cancer risks distressing side-effects such as incontinence and impotence – a heavy price to pay if the cancer would not have caused problems in the first place.<sup>15</sup>

Blood levels of a substance called prostate-specific antigen (PSA) are raised in most men with prostate cancer. However, there is no clear cut-off level that will distinguish between men who have cancer and those who do not,<sup>16</sup> and as many as one in five men with clinically significant cancers will have normal PSA levels. Moreover, despite its name, PSA is anything but ‘specific’

### OVERDIAGNOSING PROSTATE CANCER

'Prostate cancer has been described as the *par excellence* example of overdiagnosis. This does *not* mean that there are not men whose lives are saved from early death from prostate cancer by early diagnosis. But . . . we have little way of knowing in advance *which* men will benefit from screening and which will be unnecessarily treated, often with serious adverse consequences to their life. The fundamental problem is that by screening and testing for prostate cancer we are finding many more prostate cancers than we ever did before, and strange as it may seem, many of these cancers would never become life threatening. In the past these men would never have known they had prostate cancer, they would go on to die of something else, dying *with* their prostate cancer, rather than *because of* it. By finding all these prostate cancers that are indolent we are giving many more men a prostate cancer diagnosis than ever before. Hence the term "overdiagnosis". This is the core dilemma that each man contemplating being tested faces.'

Chapman S, Barratt A, Stockler M. Let sleeping dogs lie? *What men should know before getting tested for prostate cancer*. Sydney: Sydney University Press, 2010: p25

– for example, non-cancerous prostate tumours, infections, and even some over-the-counter pain-killers can cause raised PSA levels. On these grounds alone, PSA clearly has serious limitations as a screening test.

Yet routine PSA testing of healthy men has been enthusiastically promoted for prostate cancer screening by professional and patient groups and by companies selling the tests, and has been widely adopted in many countries. The pro-PSA-screening lobby has been especially vocal in the USA, where it is estimated that, each year, 30 million men are tested, believing that this is the sensible thing to do. So what is the evidence that earlier detection of prostate cancer with PSA screening improves a man's outcome;

## DISCOVERER OF PSA SPEAKS OUT

'The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with - I discovered PSA in 1970. . . .

Americans spend an enormous amount testing for prostate cancer. The annual bill for PSA screening is at least \$3 billion, with much of it paid for by Medicare and the Veterans Administration.

Prostate cancer may get a lot of press, but consider the numbers: American men have a 16 percent lifetime chance of receiving a diagnosis of prostate cancer but only a 3 percent chance of dying from it. That's because the majority of prostate cancers grow slowly. In other words, men lucky enough to reach old age are much more likely to die with prostate cancer than to die of it.

Even then the test is hardly more effective than a coin toss. As I've been trying to make clear for many years now, PSA testing can't detect prostate cancer and, more important, it can't distinguish between the two types of prostate cancer - the one that will kill you and the one that won't.'

Ablin RJ. The great prostate mistake. *New York Times*, 10 March 2010.

and what is known about harms associated with testing?

High-quality evidence about the benefits and harms of PSA screening is now becoming available. In 2010, the results from all relevant trials were systematically reviewed. This assessment showed that, although PSA screening increased the likelihood of being diagnosed with prostate cancer (as would be expected), there was no evidence of an impact on either the rate of death from the cancer or the overall death rate.<sup>17</sup>

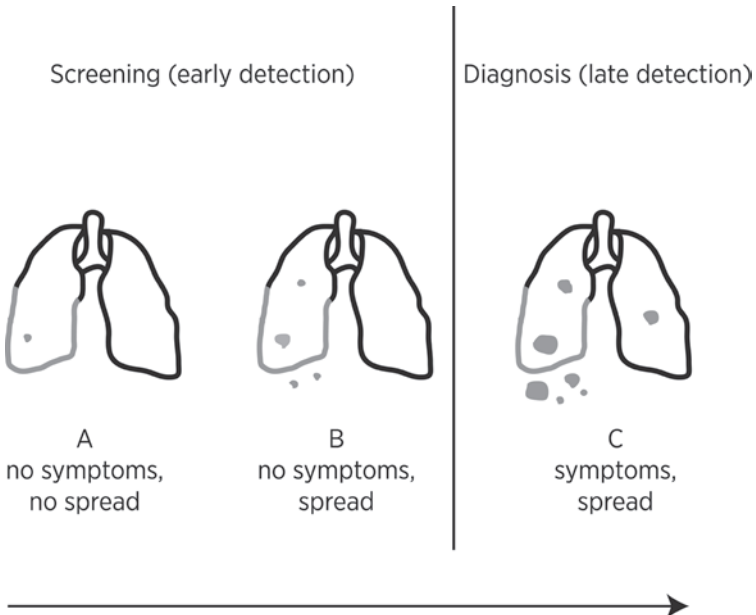
So, is the tide turning against PSA screening? Richard Ablin, the discoverer of PSA, certainly thinks it should and has been saying as much for years. Writing in 2010, he commented 'I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster. The medical community must

confront reality and stop the inappropriate use of PSA screening. Doing so would save billions of dollars and rescue millions of men from unnecessary, debilitating treatments'. At the very least, any man, before undergoing PSA testing, should be informed of the test's limitations and possible adverse consequences. As one group of experts noted: '[men] should be advised that the test cannot tell [them] whether they have a life-threatening cancer but that it could lead them through a thicket of tests and treatments that they might have better avoided'.<sup>18</sup>

**Lung cancer screening: early but not early enough?**

Screening may detect disease earlier, but not always early enough to make a difference (see Figure).

Some cancers, for example lung cancer, spread within the body before the patient has any symptoms and before any tests can detect the presence of the cancer. Attempts to detect lung cancer by the use of chest X-rays illustrate this problem (See stage B in Figure). In the 1970s, several large studies in heavy smokers



**Growth and spread of lung cancer in heavy smokers.**

## SELLING SCREENING

'Selling screening can be easy. Induce fear by exaggerating risk. Offer hope by exaggerating the benefit of screening. And don't mention harms. It is especially easy with cancer — no diagnosis is more dreaded. And we all know the mantra: early detection is the best protection. Doubt it, and someone may suggest you need your head examined.

*"If you are a woman over 35, be sure to schedule a mammogram. Unless you're still not convinced of its importance. In which case, you may need more than your breasts examined."* Old American Cancer Society Poster.

Messages selling screening are everywhere. The news regularly tells the story of celebrities asserting that their lives have been saved because of the early diagnosis of a cancer. It is very unusual to hear stories of those injured by overdiagnosis and overtreatment.

Popular magazines report emotionally charged but wholly unrepresentative stories about young women with breast cancer and their fears of dying and leaving their young children.

Medical centers use screening as a business strategy, offering free tests to attract patients. Public service announcements — like the American Cancer Society's slogan above — speak for themselves.'

Woloshin S, Schwartz LM. Numbers needed to decide.  
*Journal of the National Cancer Institute* 2009;101:1163-65.

showed that, although the cancers were detected earlier, there was no evidence this led to a decrease in deaths from the disease. The lung cancers detected on the X-rays had already spread beyond the lungs. So, these patients lived longer with their cancer diagnosis and were treated earlier, but there was no evidence that it made any difference to their life expectancy.

More recently, a large randomized trial involving 53,000 current and former heavy smokers compared chest X-ray



screening with screening by a special sort of computed tomography (CT) scan called a spiral CT. Both groups were assigned to three annual screening procedures. Spiral CT diagnosed lung cancers at an even earlier stage than did chest X-rays, and in a small proportion of patients this was sufficiently early (stage A in Figure) for treatment to be of benefit (346 deaths from lung cancer in the spiral CT group vs 425 in the chest X-ray group). But this beneficial outcome came at the expense of a large proportion of people wrongly labelled with lung cancer. Overall, for every 1,000 heavy smokers who had three annual X-rays or scans, over eight years of follow-up, three fewer died of lung cancer. But 13 still died of lung cancer despite earlier detection, and 233 received a false-positive result that required further investigation.<sup>19</sup>

#### **Genetic tests: sometimes useful, often dodgy**

Not so long ago ‘genetic testing’ was more or less confined to generally rare, single-gene disorders – for example, the childhood-onset muscle-wasting disease Duchenne muscular dystrophy, or Huntington’s disease, a progressive nervous system disorder that usually starts to affect people in middle age. Genetic tests are done to diagnose such conditions but can also be used to screen healthy people whose family history indicates that their chances of developing the disorder in question are above average, and to guide their family plans.

However, most diseases cannot be attributed to a single faulty gene. Usually, diseases depend on the way in which risk variants in several genes interact, and on the interaction of these genetic risk variants with environmental factors. Only when there is a ‘critical’ combination of genetic risk variants and environmental factors will a disease become apparent.<sup>1</sup>

Despite the complexity of ascribing most conditions to aberrant genes, media and promoters of direct-to-consumer genetic testing extol the supposed virtue and simplicity of genetic risk profiling. All you need to do is send off a saliva sample to a company for DNA analysis and they will take your money and send you your profile. But the information you receive is unlikely to help you – or your clinician – make any sensible predictions

## **DON'T PLAY POKER WITH YOUR GENES**

'Acting on the knowledge of a single (or even a few) gene variants is similar to betting all your money on a poker hand when you've only seen one card. You don't know what hand genetic factors has dealt you, nor what effects your environment will have, and here, instead of 5 cards, there are over 20,000 genes and many thousands of environmental factors. And the effect of one gene may be cancelled out by the effect of lifestyle, family history or by the presence of other, protective genes. Many of us carry faulty genes without them ever causing disease.'

*Sense About Science. Making sense of testing: a guide to why scans and other health tests for well people aren't always a good idea. London: Sense About Science 2008, p7. Available from [www.senseaboutscience.org](http://www.senseaboutscience.org)*

about your risk of disease, let alone what might be done about it, if anything. This 'do-it-yourself' approach clearly does not meet the criteria for a useful screening test (see below). However, the result may well make you anxious and decision-making difficult, and may have wider implications too – on members of your family, for example. As one Australian health journalist put it 'For anyone concerned about the creeping medicalisation of life, the marketplace for genetic testing is surely one of the latest frontiers, where apparently harmless technology can help mutate healthy people into fearful patients, their personhood redefined by multiple genetic predispositions for disease and early death.'<sup>20</sup>

### **What screening aims to achieve and why evidence matters**

The examples we have already given show that, before rushing headlong into widespread screening, it is worth pausing a moment to consider the key features of screening programmes and to remind ourselves what they aim to achieve. People being offered screening do not have, or have not noticed, the symptoms or signs of the condition being tested for – they have not sought medical attention for the disorder in question. The purpose of screening

individuals or populations is to reduce the risk of death or future ill health from a specific condition by offering a test intended to help identify people who could benefit from treatment.<sup>1, 21</sup> The aim of screening is not simply to diagnose disease earlier – this may not help anyone and it can even do harm.

The basic criteria for assessing the value of screening tests were outlined in a World Health Organization report in 1968.<sup>22</sup> These criteria have been further refined to reflect the way in which healthcare is delivered today. People invited for screening need sufficient, balanced information about the test being offered – including possible harms, consequences, and limitations, as well as potential benefits – so that they can make an informed choice. Essentially, the key points can be summed up by saying don't screen unless:

- The condition being screened for is important in terms of public health – for example, it is serious and/or affects large numbers of people
- There is a recognizable early stage of the condition
- There is an effective and acceptable treatment for the condition, so screening is likely to make a difference to its outcome
- There is a valid and reliable test for the condition that is acceptable to people being offered screening
- The screening programme is of good quality and cost-effective in the setting in which it is to be offered
- The information provided to people is unbiased; based on good evidence; and clear about possible harms (eg, overdiagnosis leading to over-treatment) as well as potential benefits
- The invitation for screening is not coercive – that is, it indicates it is reasonable to decline
- The chance of physical or psychological harm to those offered screening is likely to be less than the chance of benefit
- There are adequate facilities for the diagnosis and treatment of abnormalities detected by screening

## THE SCREENING CIRCUS

In 2009, a recently retired professor of neurology with a long-standing interest in stroke prevention learnt that neighbours had received a leafleted invitation to be screened for stroke and other complications of cardiovascular disease. The leaflet, from a vascular screening company, invited them to go along to a local church (and pay £152, \$230, €170) for a series of tests. Intrigued – not least because some of the information in the leaflet was factually misleading – he decided to go along himself.

‘First up was aortic aneurysm [enlargement of the main artery carrying blood from the heart] screening with ultrasonography done by a woman who did not want to be engaged in conversation about what the implications of finding an aneurysm might be. Next it was ankle and arm blood pressure measurements “for troubles with my circulation” . . . followed by a little non-vascular bonus: osteoporosis screening of my ankle. Then there was . . . electrocardiography to detect “trouble with the two upper chambers of my heart” . . . Then, finally, carotid [artery in the neck] ultrasonography to detect “plaque build up”. When I asked them what the implications of this might be they told me that blood clots could form and cause a stroke. Pressed on the sort of treatment I might be given, they offered a vague notion of blood thinning drugs but nothing about surgery until I asked directly if that might be an option, and indeed it was. “Might that be risky?” I enquired innocently. The answer was that any risks would depend on a full work-up by my GP, with whom I should discuss abnormalities from any of the tests.

All of this was conducted without any privacy (except for the aortic aneurysm screening) . . . There seemed to be no doctor present, and the team showed no intention or will to engage in a discussion of the implications of false positive or false negative results, the prognostic implications of true abnormalities, or the risks and benefits of any treatments.

This was just screening, nothing more and nothing less, done for profit – with the results to be dumped in my lap within 21 working days and for my GP to sort out the emotional and physical consequences of any abnormality, true or false, even though she didn't request the tests. . . . Inevitably this whole screening circus is liable to whip up anxiety in vulnerable people without discussing or taking the slightest responsibility for the consequences of any abnormalities found.'

Warlow C. The new religion: screening at your parish church.  
*BMJ* 2009;338:b1940

These criteria reinforce our message at the beginning of this chapter: that any decision to introduce a screening programme should be based on good-quality evidence not only about its effectiveness but also about its potential for doing harm.

### IS ANYONE NORMAL?

#### Whole-body CT scans

Among the tests on offer at private clinics are whole-body computed tomography (CT) scans to look at head, neck, chest, abdomen, and pelvis. They are offered directly to the public, and usually done without reference to the person's general/primary care practitioner. Whole-body scans are often promoted as the way to keep one step ahead of possible illness, with the premise that a 'normal' result will be reassuring. Not only are these scans expensive, but also there is no evidence that any overall health benefit is achieved by doing these tests in people without symptoms or signs of disease.

Moreover, the radiation exposure is considerable – as much as 400 times more than a chest X-ray. So much so that in 2007 the UK's Committee on Medical Aspects of Radiation in the Environment (COMARE) strongly recommended that 'services' offering whole-body CT screening of asymptomatic individuals