SIEMENS HEALTHCARE

Computed tomography can detect tumours early, but is not yet widely used for lung-cancer screening.

DIAGNOSIS

Early warning system

The costs of lung-cancer screening overshadow the benefits of swift diagnosis — but ingenious technologies could help.

BY KATHERINE BOURZAC

At the age of 56, Gordon Green, a former smoker with two young children, was referred to a lung-cancer screening programme by his primary-care doctor, even though at the time he reported no health problems. A low-dose computed tomography (CT) scan that took less than a minute revealed a nodule in his lung that turned out to be a small, early-stage tumour. Doctors removed the growth and, two years later, Gordon is cancer free.

In patients such as Gordon, whose tumours are detected early, doctors see the potential that screening has to transform lung cancer from essentially a death sentence into a treatable disease. One of the reasons why lung cancer is so lethal is that diagnoses tend to be made after the cancer has advanced to late stages. Data collected by the US National Cancer Institute from 2004 to 2010 indicate that just 17% of people diagnosed with lung cancer are alive five years later. But it is not all bad news — some people who show no symptoms but whose cancer is detected in time have an 88% chance[1] of living another full decade, says radiation oncologist Andrea McKee, who runs the screening programme that detected Gordon's cancer at the Lahey Hospital and Medical Center in Burlington, Massachusetts.

Lung-cancer screening is not widely available anywhere in the world outside clinical trials and pilot programmes such as Lahey's, but that may be about to change. In a 2011 clinical trial in the United States[2], screening by low-dose CT reduced deaths from lung cancer by 20%. Based on these results, and on a recommendation by the US Preventive Services Task Force (an independent scientific body that advises the government), private insurers in the United States will have to start covering the costs of screening in January 2015 for current and former smokers aged 55–80 who are classed as high-risk: people with a history of smoking the equivalent of at least one pack of cigarettes a day for 30 years and, if former smokers, have quit smoking less than 15 years ago.

Yet there is uncertainty about who would foot the bill: Medicare, the national insurer for Americans aged 65 and older, is evaluating whether to pay for lung-cancer screening given the uncertainty about the procedure's cost-effectiveness. And CT screening comes with a high rate of false positives: Green had cancer, but 19 of 20 people in the same risk group — current and former smokers aged 55–74 — who were referred for further screening or biopsies did not test positive for cancer, and therefore underwent unnecessary and potentially risky surgical interventions.

Against this background, scientists and engineers are working on technologies to supplement, and perhaps eventually replace, CT scans. Too often, what seems to be a tumour is a harmless spot, so researchers are developing software to help to extract more accurate data from the images. Other research teams are evaluating biomarkers — biochemical or genetic indicators such as anti-cancer antibodies — in blood, sputum and even breath to ensure that healthy people are not sent for unnecessary biopsies.

After decades of poor outlooks for patients, the imminent availability of screening will change what it means to have lung cancer, says McKee. So far it's available only under the aegis of academic early adopters, but where it is in place, "I see a shift happening", she says.

SCREEN TEST

The research indicating that low-dose CT screening can lead to a 20% reduction in lung-cancer mortality in the United States was the outcome of a study[2] by the National Lung Screening Trial (NLST). The team compared screening (chest X-ray and low-dose CT) with non-screening in a nine-year, 53,000-patient randomized study that was completed in 2011. The trial administered three annual screening scans to half the participants, who were aged 55–74 when the trial started and were randomly selected to receive CT scans or X-rays. Participants were all classified as high risk.

Some scientists crave definitive information about lung-cancer screening. For example, Pierre Massion, a pulmonologist who runs the Nashville Lung Cancer Screening Trial at the Vanderbilt-Ingram Cancer Center in Tennessee, would like to know the effect of changing the screening interval from one to two years. But answers will have to wait: at a cost of about US$250 million, the large, complex trial needed to assess this is not likely to be done in the United States or anywhere else in the near future.

CT images are made by combining multiple X-ray images taken from different angles. Low-dose CT involves taking fewer images. The combined result is coarser than the images that are needed to diagnose blood clots, for example, but they are good enough to reveal lung nodules that warrant further investigation. Low-dose CT exposes patients to 1.5 millisieverts of radiation, which is about half the average person's annual radiation exposure. An annual low-dose CT scan is considered safe by the American College of Radiology, the organization that accredits radiology centres.

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The NLST results led the US Preventive Services Task Force to recommend low-dose CT screening for adults with a history of smoking. Medicare does not have to follow the recommendations made by the task force, but under the Affordable Care Act, private insurers do. The American Medical Association, the American College of Radiology and the American Lung Association all support screening using low-dose CT. But Medicare is still undecided: in April 2014, the Medicare Evidence Development and Coverage Advisory Committee — a panel of doctors and other medical professionals — made a non-binding recommendation against screening after a series of short presentations by pulmonologists. Their individual reasons varied but many were concerned about the risks of false positives.

Some doctors think of Medicare coverage for lung-cancer screening as a matter of social equality. They note that most Americans in the age group in which lung cancer is most prevalent are on Medicare (according to the National Cancer Institute, the median age at diagnosis is 70). If screening is restricted to those who can pay out of pocket, it is not equitable, says Peter Bach, a lung-cancer risk specialist at the Memorial Sloan Kettering Cancer Center in New York City, who is a strong advocate for screening.

There is a lot of money at stake. Screening can detect cancer at a much earlier stage, when treatment is less expensive and more likely to save the patient's life. But early diagnosis is not always enough to offset the costs of imaging and diagnostics. "Screening is not going to save us money," says James Mulshine, a specialist in translational medicine at Rush Medical College in Chicago, Illinois, who served on the International Association for the Study of Lung Cancer's screening advisory committee.

The NLST has not yet published the results of its cost analyses, but other researchers have been trying to fill in the billion-dollar blanks. At the annual meeting of the American Society for Clinical Oncology in May 2014, researchers at the Fred Hutchinson Cancer Research Center in Seattle, Washington, presented preliminary estimates. Joshua Roth, a health economics and epidemiology researcher who led the study, cautions that their analysis considers only the price of the screening and not the gain to society of a person living a longer, more healthy life. Assuming that the incidence of lung cancer in the Medicare population is about the same as it was in the NLST group, the first five years of lung-cancer screening would cost the government an estimated $9.3 billion, or about $1.9 billion per year. (Mammograms cost Medicare an annual $1.1 billion and prostate-cancer tests cost $500 million.) Roth says that lung-cancer screening costs are likely to fall when more test centres open and screening becomes routine, as they did with mammograms.

STRINGENT THRESHOLD

One of the benefits of low-dose CT is that it is very sensitive — a distinct advantage when doctors are looking to detect tumours early on. However, the test also detects harmless nodules, inflammation, scars from past infections and other lesions that turn out to not be cancer. Of 100 nodules flagged for additional screening in the NLST, only 4 turned out to be tumours.

False positives place a tremendous psychological burden on a patient and put healthy people at risk of complications — and even death — following unnecessary biopsies, says preventive medicine specialist Jonathan Samet at the University of Southern California's Keck School of Medicine in Los Angeles. Older people, who tend to have more underlying health problems such as heart disease, are the most vulnerable. Nonetheless, he notes, an American Lung Association committee that he chaired published a report in April 2012 recommending Medicare screening even after factoring in these concerns.

One way to reduce the number of false positives is to make the standards for detecting a positive nodule more stringent. In the NLST, nodules with a diameter of 4 millimetres or larger were considered positive; all patients scoring positive were sent on for further diagnostic tests. Increasing the size threshold should help to reduce false positives without causing a dangerous delay in the detection of true cancers, according to a study published in 2013 by a multi-institutional research effort, the International Early Lung Cancer Action Program[3]. Its finding suggests that the threshold could be raised to 7 or 8 millimetres. Roth says that his group is using the NLST data to predict the lives saved and costs lowered if Medicare were to recommend a similar cut-off.

European lung-cancer specialists are also tackling the false-positive issue. Researchers running the 15,000-person lung-cancer screening trial (NELSON) based at Erasmus Medical Centre in Rotterdam, the Netherlands, factored the false-positive problem into the design of their 12-year trial[4], which is on target to wrap up late in 2015. If a person in the trial has a small lung nodule that doctors suspect is a tumour, a biopsy is not taken immediately. Instead, the patient returns for follow-up scans and a biopsy is performed only if the nodule has grown sufficiently in that time. NELSON's threshold for a positive CT is based not on the diameter of the nodule, as in the US studies, but on volume and growth rate: a biopsy is done if the nodule is larger than 500 cubic millimetres, or has doubled in volume in 400 days or less. Harry de Koning, a specialist in screening at Erasmus who runs NELSON, says that in the United States the screening recommendations are appropriate given the results of the NLST. But he contends that it would be advisable to wait to implement screening in Europe until the trial is finished, because incidence and risk differ between populations.

READING THE RESULTS

A successful screening programme relies on first-rate interpretation of results. Robert Gillies, chairman of cancer imaging at the Moffitt Cancer Center in Tampa, Florida, says that current interpretive methods, no matter how they classify the nodules, are not gleaning as much detailed information from the CT images as they could. Gillies hopes to cut CT false positives in half by using more sophisticated software. Radiologists typically factor in whether the nodule is calcified — usually a sign that it is benign — as well as its size, location and a few other features.

In an effort to improve the interpretation of the scans, Gillies has developed software called radiomics, which bases its analysis on 400 quantitative features from CT scans taken of people with lung and head-and-neck cancer. Radiomics factors in features such as shape and texture, which Gillies says may significantly improve the ability to discern whether a nodule is malignant. "Computers can pick up differences in these images that are too subtle for a human radiologist to see," Gillies says. His group has used the software to analyse existing data sets in which the outcomes are known. In retrospective studies run on the NLST database, for example, the software predicted which patients had cancer with 79% accuracy[5].

Gillies' group was awarded a $1.6-million grant this year from the state of Florida to establish infrastructure for a screening programme, which began in July, that incorporates automated image analysis. It is important to expand screening programmes to as large a population as possible, says Gillies. However,

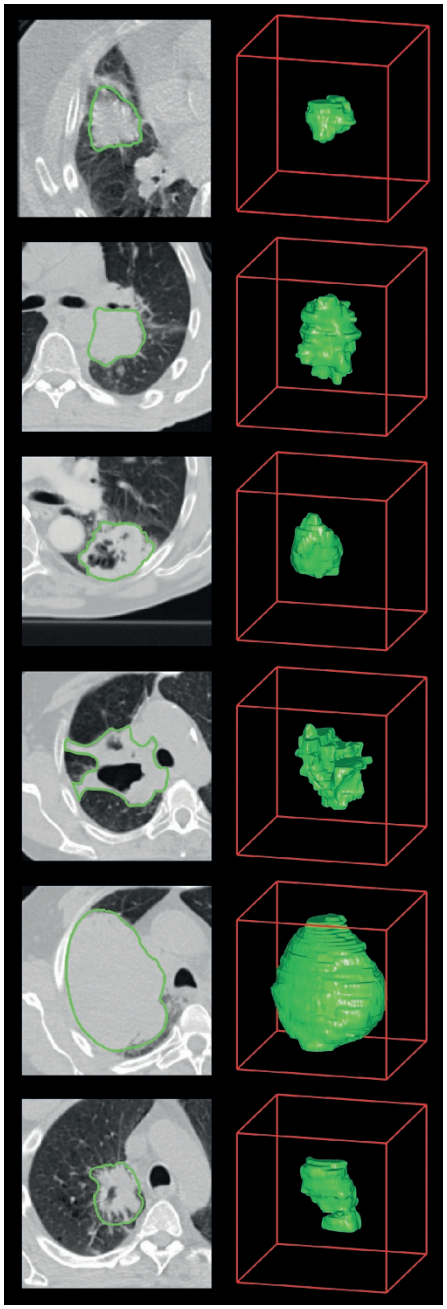
even though the tens of thousands of patients in the NLST provide his group with plenty of data to process, when it comes to making predictive models Gillies says that there is not actually a huge amount of information to work with. Because automated analyses get better only by being fed more data, Gillies wants states and countries to develop one database to share among researchers from across the globe. A good model to build on is a system run by the American College of Radiology called Lung-RADS. Although currently used as a quality assurance tool to standardize the reporting of screening results, Lung-RADS could one day integrate the sophisticated automated analyses that Gillies' group works with. Gillies is working on scaling up the Florida project as a testbed, but broader implementation of such a system will hinge on a favourable decision from Medicare.

BIOMARKER BONANZA

It might yet be possible to screen for lung cancer without using CT scans. Alternative approaches that could lower screening costs and increase patient safety include analysing blood and breath biomarkers, and detecting mutations in the nasal passages of cancer patients. Several smaller screening trials are under way to help to develop such screening technologies. For example, Avrum Spira, a pulmonologist and chief of computational biomedicine at the Boston University School of Medicine in Massachusetts, is looking at patterns of gene expression in cells taken from the airways, which can be sampled with brushes, a procedure that is safer than a biopsy of the lung. There are many changes in gene expression in the upper respiratory system that are associated with lung cancer[6] but their predictive value is as yet unproven. A clinical trial will determine the value of adding these markers to image-based patient workups.

Sam Hanash, a pathologist specializing in early cancer detection at the University of Texas MD Anderson Cancer Center in Houston, wants to speed up the process of validating biomarkers and getting the results to patients. Hanash's group has reviewed the literature for promising candidates and is embarking on a large validation study that will, he says, evaluate hundreds of biomarkers to see which ones are most effective in predicting cancer. To help push the screening techniques into practical use, Hanash says that his group is going to systematically test an array of biomarkers. "We'll do a bake-off, and figure out what is the best combination," he says.

The initial study will test markers in conjunction with CT screening. But ultimately Hanash hopes that biomarkers — which include proteins, antibodies and DNA — will replace CT screening. The study at the MD Anderson Cancer Center will start in the United States, but Hanash says the plan is to extend it to other countries, including China and Brazil, and enrol at least 10,000 people — current and former smokers who will be enrolled in the CT screening programme and have blood, sputum and other samples taken periodically. People who meet NLST criteria for screening would receive CT scans on enrolment and then again after the first and second years; then they would receive follow-up appointments for two additional years. At each visit, Hanash says, blood will be drawn and biomarkers observed. The reality check — seeing which patients develop lung cancer — will make clear the biomarker panel's false-positive and false-negative rates. It will cost about $100 million and take two years to screen enough people to do the validation, says Hanash. "This is going to be a huge undertaking."



Radiomics software extracts additional data from computed tomography scans to help doctors diagnose lung tumours (2D scans from six people, above, were used to build 3D images, in green).

As CT screening is introduced in academic centres, it is "changing the way we understand lung cancer", says McKee. One assumption has been that lung cancers are highly aggressive and must be removed once detected. As innovative screening methods enable earlier discovery of tumours, however, it is becoming clear that this may not always be the case. "In our study, one-third of lung cancers are indolent," says William Rom, director of pulmonary and critical-care medicine at the New York University School of Medicine. "When we remove them after five years, they're still stage 1." That means there is probably time to monitor people's health and perform follow-up imaging studies instead of sending them for biopsies or surgery. In the future, as cancers are spotted before they become aggressive, the type of treatment used will need to change — more surgery and radiotherapy followed by long-term care and monitoring, rather than late-stage diagnoses, expensive drug treatments and patient deaths.

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US doctors such as Bach and McKee are nervous but hopeful that Medicare will approve screening. "We will have to work hard to minimize harm if screening is implemented," says Bach. Doctors and insurers will need to make sure the scans are given only to the high-risk people who benefited from them in the NLST.

Meanwhile, delaying the start of lung-cancer screening means that more people may die from the disease when they could have been treated early and lived, as Green did, says McKee. The delay in the decision about lung-cancer screening from the Medicare advisory committee, and concerns about the cost, means that it is not being implemented rapidly, but with care, she says. "We'll screen, and we'll do it well — because the bar has been set really high." And if the US model for long-term screening saves lives, other countries may find it hard to resist following suit. ■

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