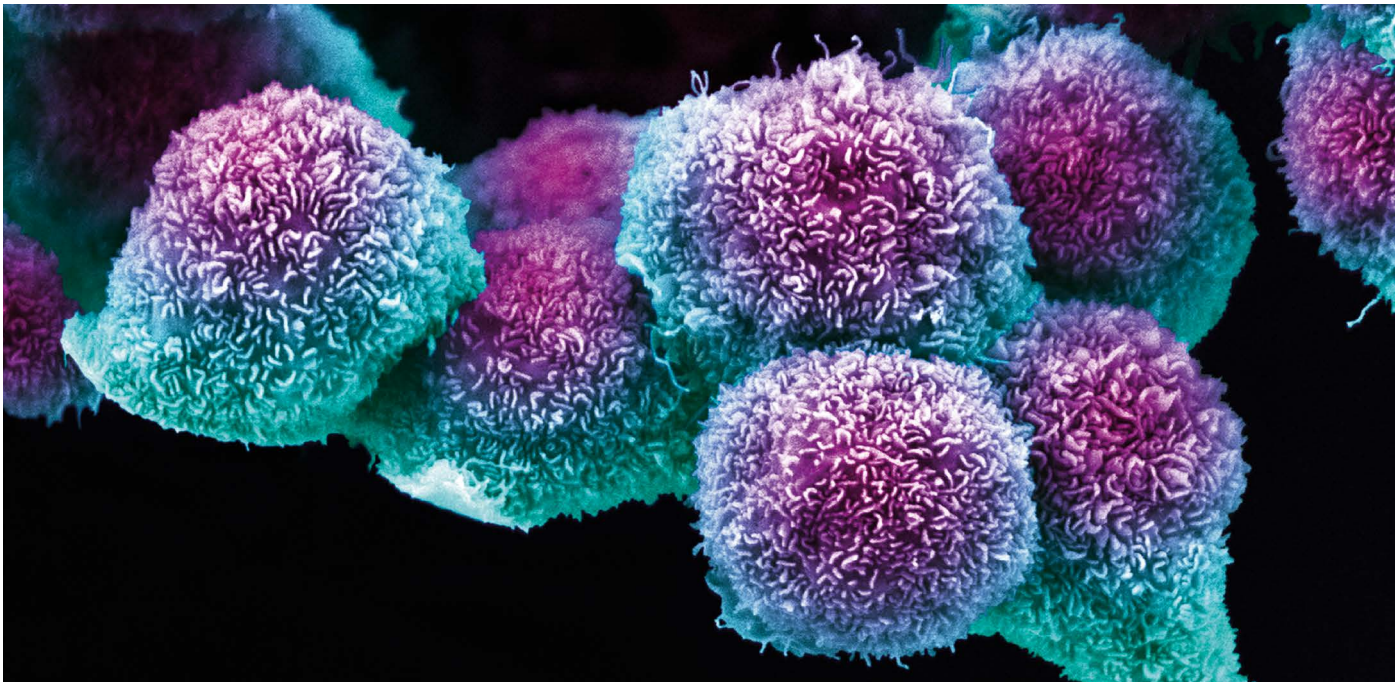
The pancreas problem

Most people with pancreatic cancer die in months, largely because it is rarely caught early. Scientists are taking aim at this diagnostic challenge. **By Eric Bender**



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Pancreatic cancer cells are difficult to detect, making early diagnosis the exception.

Pancreatic cancer is not one of medicine's greatest success stories. For most people, diagnosis is a death sentence; in the United States, only 10% of people survive five years. The only treatment for long-term survival is removal of the tumour before it starts to spread, says Jeffrey Drebin, a surgeon specializing in pancreatic cancer at Memorial Sloan Kettering Cancer Center in New York. But the disease is typically detected months after people begin to experience hard-to-assess symptoms such as abdominal pain and fatigue, at which point only about 15–20% are still eligible for this surgery.

Pancreatic cancer is rare — it is the 14th most common cancer worldwide. But it's one of the most lethal, killing more than 430,000 people globally each year. By 2030, the disease is expected to be the second biggest cause of cancer deaths in the United States. As populations age and levels of obesity rise, it's only expected to become more common and claim more lives. In the European Union, mortality from the disease is predicted to increase by almost 50% by 2025, compared with 2010 levels.

One reason that the cancer is so deadly is that it's very difficult to live without your pancreas. Tucked away behind the stomach, the organ is also trickier to scan for tumours than most other body parts. And pancreatic cancer is an unusual form, in which "the cells that surround the cancer cells are equally as important, if not more important, in the cancer formation", says Teri Brentnall, a gastroenterologist at the University of Washington in Seattle.

Given these difficulties, pancreatic cancer is the toughest major cancer to detect early (see 'Caught too late'). Thousands of papers detail attempts to develop diagnostics, but so far none has been clinically proved to aid existing imaging techniques.

Imaging often misses early tumours, and it is too expensive and cumbersome to offer to people who show no symptoms — about 90% of those with the cancer. Liquid biopsies (tests for disease markers in fluids such as blood) might eventually make it to the clinic, but they are still struggling to prove their worth.

Improving early detection of pancreatic cancer requires advances on two fronts. "One is the technology for screening, and the other is applying that technology to the right population," says Alison Klein, a population scientist at Johns Hopkins University in Baltimore, Maryland. "You need both of those and you need to develop them jointly."

Improving imaging

Both lines of research begin with people who either have the condition already or have a high risk of developing it. Anirban Maitra, a pathologist at the University of Texas MD Anderson Cancer Center in Houston, thinks of early detection as a series of sieves that filters out the people at greatest risk. The sieves can incorporate not only known risk factors such as family history and genetics, but also electronic medical records gathered over a person's lifetime. "These cancers don't arise overnight," Maitra says. "This process takes a long time and goes through a significant number of steps before it becomes metastatic disease." Powerful computer analytics

that combine electronic-medical-records data with family history, genetics, smoking history, weight trends and other factors can generate much more powerful risk scores than any other factor alone, he says.

Related efforts are building large cohorts of people either with pancreatic cancer or at high risk of developing the disease. The Precision Promise programme, launched in 2016 by the charity Pancreatic Cancer Action Network in Manhattan Beach, California, includes 35 research centres around the world that are tracking more than 3,000 people with a high risk of inherited pancreatic cancer. "We've been lacking a higher-level organizational structure to rigorously vet work, and I think that's where the field is moving now," says Diane Simeone, a surgical oncologist at New York University Langone Health.

The leading candidates to develop the disease are those with a family history or with genetic mutations that predispose them to the cancer. Previous genetic analyses have revealed risks associated with mutations in potential cancer-causing genes such as *KRAS* and tumour-suppressor genes such as *BRCA2*. People with type 2 diabetes, pancreatic cysts or chronic pancreatitis, are also at greater risk of developing cancer than the general population. People at high risk can be regularly screened for signs of cancer – and such surveillance programmes have been shown to pay off (M. I. Canto *et al. Gastroenterol.* **155**, 740–751; 2018). If a tumour is found in this way, the chance of removing it surgically climbs from around 15% to 85% or more, says Simeone.

None of the three main imaging technologies for spotting pancreatic cancer is inexpensive or simple enough for more widespread screening, however. Endoscopic ultrasound, in which a flexible ultrasound probe is inserted through the mouth, is probably the most sensitive to early signs of cancer, Klein says. But people must be sedated and examined by a highly skilled endoscopist. Magnetic resonance imaging (MRI) is less invasive, and thought to be slightly more sensitive than computed tomography (CT), which also carries risks associated with radiation exposure. But MRI scanning is expensive, and requires an experienced radiographer to interpret the images.

Researchers are developing algorithms that can identify subtle changes in images that indicate early tumours – or even changes that precede pancreatic tumours, says Maitra. MD Anderson Cancer Center is one of a group of hospitals sharing scans of patients taken for other conditions, before they were diagnosed with pancreatic cancer. "Each of us has our own algorithms and we are playing in the sandbox to see what works best," Maitra says.

Other signals that MRI might detect in the pancreas, such as high fat content, could be risk factors for cancer, says Michael Goggins, a gastroenterologist at Johns Hopkins. Some researchers are also creating molecular probes for advanced CT or MRI imaging that can target proteins such as plectin, which is expressed in pancreatic tumours.

More radical imaging methods have also been tested, including injecting microbubbles containing a tumour-binding protein into the pancreas before a conventional abdominal ultrasound. In experiments in mice (K. Foygel *et al. Gastroenterol.* **145**, 885–894; 2013), the proteins bind to a pancreatic tumour "and light it up like a little Christmas tree", says Brentnall.

Biopsying blood

Dozens of labs are seeking out signs of pancreatic tumours in blood and other fluids. These liquid biopsies, which are being developed for many cancers, look for biomarkers such as proteins, circulating tumour DNA and RNA, and free tumour cells, and could aid both detection and monitoring of disease (see page S6).

Hundreds of papers have been published on the use of liquid biopsies to detect pancreatic cancer. However, these tests are far from ready for clinical use. Most cannot differentiate cancer from chronic pancreatitis (permanent damage caused by inflammation), says Christian Pilarsky, a molecular biologist at Erlangen University Hospital, Germany. A panel of serum proteins developed by diagnostics company Immunovia in Lund, Sweden, might offer greater specificity. The company "put in a huge effort to identify the best antibodies for detecting pancreatic cancer", says Pilarsky, who collaborated with the company in its research. "This is really promising." Immunovia expects to begin selling its tests later this year.

If liquid biopsies are to aid the early detection of pancreatic cancer, however, they must also overcome the challenge of spotting biomarkers in vanishingly small quantities. Imaging can sometimes pick up tumours less than a centimetre in size, but "that volume of tumour may not shed enough molecules to be detected in the blood", says Goggins. Typically, the tests pick up only advanced cancers.

This is also a problem for tests that look for circulating tumour DNA, rather than proteins. DNA could offer greater diagnostic specificity, Goggins says, but changes in target genes such as *KRAS* might be hard to find when they exist in only tiny amounts. To make matters worse, some mutations can be misleading. *KRAS* mutations are found in about 90% of pancreas cancers and about 80% of pre-cancerous pancreatic cysts, but the gene is also mutated in other cancers, and most of the cysts in which it's mutated will not progress to cancer. "By itself, it's not a very sensitive marker for pancreatic cancer, and it may not even be a marker for cancer at all," Drebin says. Tests that look for both mutations in target genes as well as variations in the number of copies of certain genes might be a better alternative, Goggins says. Better yet, he suggests, would be tests that combine protein and DNA detection.

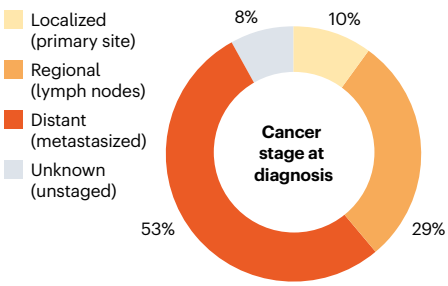
Several start-up companies are taking various forms of liquid biopsy into clinical tests for pancreatic cancer. Currently, their efforts can detect only one in five people with disease that hasn't spread. "Maybe, with the current technology, that is the ceiling," Maitra says. "But if one-fifth of individuals who would otherwise never get diagnosed until they have advanced disease now potentially have cures, that would be better than any drug that has ever been made for pancreatic cancer."

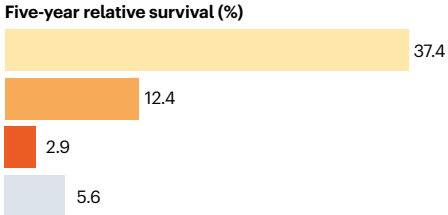
Researchers caution, however, that such tests must also deliver an extremely low rate of false positives. "As a practitioner, I cannot be calling people all the time to tell them I think they have pancreatic cancer when they don't," says Brentnall. Drebin says that a false-positive rate of below 1% should be the goal. Achieving this while also boosting the proportion of operable tumours that can be found is likely to require a combination of liquid biopsy and imaging. "As we have multimodal therapy today for pancreatic cancer, we will have multimodal detection," Pilarsky says. "There is no silver bullet for early detection."

Eric Bender is a science writer in Newton, Massachusetts.

CAUGHT TOO LATE

By the time most pancreatic cancers are diagnosed, the tumour has already spread (top). The earlier the disease is caught, the more effective treatments are at prolonging life (bottom).





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