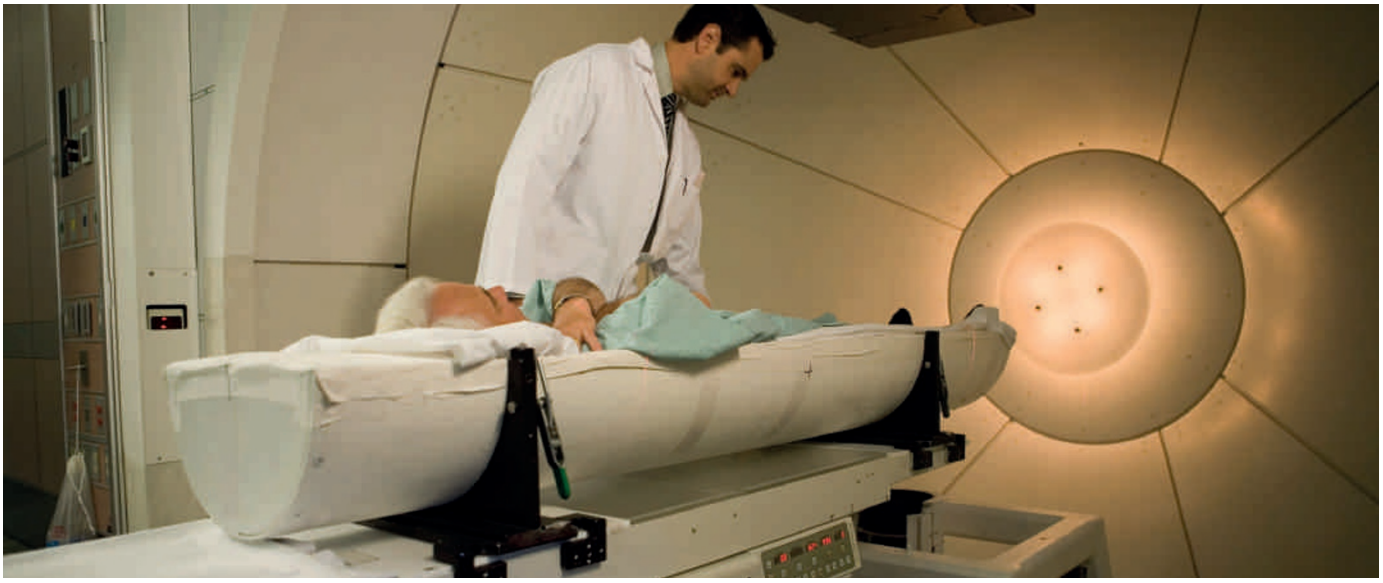


Proton computed tomography records the position, direction and energy loss from a proton beam as it traverses a patient's body.

NEXT-GENERATION SCANS

Seeing into the future

From magnetically tagged sugar to smoke-sensing surgical knives and beams of high-energy protons, the next wave of imaging technologies will provide a clearer view of the body.

BY PETER GWYNNE

Medical imaging has advanced rapidly in the early years of the twenty-first century. Doctors can now observe events at the molecular level, examine the characteristics of individual heartbeats, and study processes in the brain in minute detail — tasks all but impossible a decade ago. "We are entering the age of precision medicine," says Roderic Pettigrew, director of the US National Institute of Biomedical Imaging and Bioengineering in Bethesda, Maryland. "We try to be precise in diagnosing, fashioning treatments, targeting treatments, delivering treatments, and monitoring the effects of treatments."

Much of the progress has stemmed from improvements in existing technologies, such as computed tomography (CT), ultrasound and magnetic resonance imaging (MRI). "MRI now allows you to track the diffusion of water molecules in the brain with such precision that you can compute their trajectories along fibre pathways," Pettigrew says.

The latest imaging methods emerging from the laboratory promise to complement these advances. They can detect and monitor cancers, for example, locate individual cells for the delivery of drugs, and provide unprecedented accuracy for surgically treating heart disease and other conditions. Several technologies have yet to reach the preclinical stage, but others have begun the journey to clinical trials. In most cases, they perform tasks currently carried out by conventional systems, but do so faster, more precisely and more safely.

A SPOONFUL OF SUGAR

One such advance in safety relates to a way of identifying tumours. Tumours are avid consumers of glucose, so patients are usually given radioactively labelled analogues of glucose, which congregate in the tumours and are detected by positron emission tomography (PET). But the danger of radioactive exposure prevents this method being used in certain individuals, such as young children and pregnant women, and limits the number of doses for other patients. A team headed by Simon Walker-Samuel at University College London has developed a method that avoids this problem by labelling glucose magnetically with bursts of radio waves instead, so it can be detected by standard MRI. This non-invasive approach is safer — patients merely need to take a sugary drink, rather than a radioactive isotope. It also enables medical teams to differentiate among various types of tumour[1], allowing them both to determine the appropriate therapy more effectively and to assess its effect.

The technique — dubbed glucoCEST, for glucose chemical exchange saturation transfer — measures the exchange of protons between the hydroxyl groups in glucose molecules and water molecules in biological tissue. The pulses of radio waves alter the magnetic character of the protons in the hydroxyl groups, masking the signal from water molecules detected by MRI. "The effect is small, but can be measured if we repeat the experiment a large number of times," says team member Xavier Golay.

The researchers applied the technique to two types of human colorectal tumour transplanted into mice. Studying MRI images taken before they injected glucose into the tumours and one hour after injection clearly revealed differences between the tumour types, as different tumours consistently take up different amounts of glucose. The researchers are now starting human studies: they are recruiting patients with tumours in their neck, and have already scanned about a dozen. For precision, the team injected the glucose into the mouse tumours, but the human patients receive it in the form of a drink. In future, the technology may not be limited to tumours. "One could imagine using it for assessing any organ with a high glucose consumption — for example, the heart or the brain," Golay says.

Other researchers are expressing cautious optimism about the technique. "We feel it is feasible but will require some more MRI development, because the human studies will have to be done at magnetic fields much lower than for the animals," says radiologist Peter van Zijl of Johns Hopkins University in Baltimore,

Maryland, whose team is performing its own human studies of glucoCEST technology.

Another technique, magnetic particle imaging, which was developed in 2001 by scientists at Philips Research in Hamburg, Germany, can potentially provide a faster, more sensitive and safer alternative to the angiography procedures used to assess heart disease, particularly during operations that require simultaneous imaging (see 'The eyes of the operation', page S88). The technique uses magnetic tracers, rather than the chemical contrast agents normally used in angiography — an important benefit because some patients, such as those with chronic kidney disease, cannot safely excrete the standard angiography tracers, iodine and gadolinium.

Magnetic particle imaging relies instead on iron oxide nanoparticles that are injected into the bloodstream. The nanoparticles are superparamagnetic, which means they have an average magnetism of zero but can be magnetized by an external magnetic field — even the weak field generated by a scanner. The process causes the particles to emit small electromagnetic signals that the scanner can detect. Changes in the concentration of the nanoparticles as they sweep through the bloodstream make it possible to monitor such critical factors as blood supply to the heart, the speed of blood flow in the heart, and other data critical to coronary surgery.

So far, researchers have built prototype scanners only suited to small animals, but Steven Conolly, who works on magnetic imaging at the University of California, Berkeley, says the technology has the potential to revolutionize biomedical imaging. Anna Samia, a nanomaterials scientist at Case Western Reserve University in Cleveland, Ohio, says the technology's contrast and sensitivity will exceed those of imaging methods such as MRI, X-rays, ultrasound, PET and CT scans. She adds that it could ultimately be used for the *in vivo* tracking of stem cells and the imaging of inflammation.

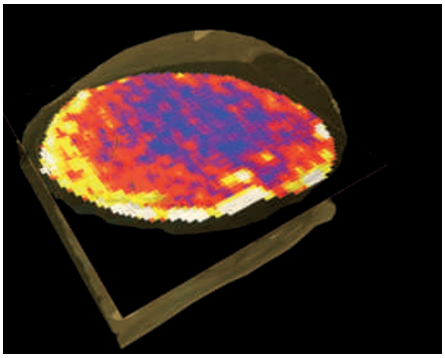
A SMOKING GUN

Working literally at the cutting edge of surgery, a UK–Hungarian collaboration has developed a device that can reveal whether surgeons are slicing through cancerous or normal tissue by sniffing and analysing the smoke it produces[2]. "Modern surgery is based on removing all the tumour," explains team member James Kinross, a surgeon at Imperial College London. "However, there is still no methodology for ensuring this during surgery." Estimates suggest that more than one in five operations intended to remove breast tumours fail to take out all malignant cells.

The 'intelligent knife', or iKnife, uses electrically produced heat to cut the tissue and then analyses the smoke produced using mass spectrometry. It identifies the types and concentrations of the tissue's metabolites and matches the readings to a reference library. This all takes less than 3 seconds, in contrast to the 20–30 minutes needed for histology. As well as accurate results, it also shortens the time a patient spends under anaesthetic.

A group headed by Imperial College's Zoltan Takats and Jeremy Nicholson used the system in the operating theatre to identify in real time 91 pieces of tissue removed from patients against a reference database, without informing the surgeons of the results. In each case, the iKnife's identification of the type of tumour — including tumours from the brain, lung, breast, stomach and liver — matched those determined by traditional methods.

The team is now overseeing an observational trial in three hospitals involving colonic, breast, liver, gynaecological and urological operations. "The next phase will be a randomized trial in which some surgeons will be able to make decisions based on this data and a second group will not," Kinross says. "We will then be able to determine the impact of the device on long-term oncological outcomes." This study may help to address an issue raised by biomedical engineer Nimmi Ramanujam of Duke University in Durham, North Carolina. Many surgeons, she says, would probably prefer to have an image of the tumour's margins before they cut, rather than using the iKnife to feel the edges.



A tumour viewed by glucoCEST: reds indicate higher uptake of glucose compared to blue core.

SIMON WALKER-SAMUEL, UCL CENTRE FOR ADVANCED BIOMEDICAL IMAGING.

BEAM ME UP

One of the existing imaging technologies, CT, uses X-rays, but it doesn't have to. Two approaches under development rely on more exotic forms of radiation: proton beams and synchrotron radiation.

Proton CT records the position, direction and energy loss from a proton beam as it traverses a patient's body. Appropriately treated, the data produce a three-dimensional image of the body that allows physicians to diagnose diseases such as cancer and to plan treatments. George Coutrakon of Northern Illinois University (NIU) in DeKalb explains that using protons instead of X-rays provides a more detailed image of the body's density, because protons release their energy at predictable depths in the body (whereas X-ray energy is emitted in a more continuous manner). This also allows radiologists to target their treatments more precisely, reducing the amount of healthy tissue exposed to radiation.

In 2010, a collaboration between NIU, Loma Linda University in California and the University of California, Santa Cruz, completed a prototype proton-beam imaging system. Now NIU, the Fermi National Accelerator Laboratory and the Argonne National Laboratory are working together to build a second-generation device that can produce three-dimensional images of something the size of a human head in minutes rather than hours.

While these groups are working with protons, an international collaboration is developing a CT imaging system based on synchrotron X-rays. These are produced when charged particles are accelerated around a curved path, and have much higher photon energies than conventionally generated X-rays. Researchers at Ludwig Maximilians University in Munich, Germany, and the University of California, Los Angeles, have applied a novel algorithm to images made by beams at the European Synchrotron Radiation Facility in Grenoble, France. They have produced three-dimensional CT images of the human breast with less radiation exposure than for typical two-dimensional images. Avoiding high exposure to radiation is important because the breast is highly radiosensitive. The method is still in the fairly early stages of research, but the team reports that it could "become a powerful tool for diagnosing breast cancer and allow clinicians to battle the disease more effectively."

Advances in medical imaging don't always happen on such a large scale. Pettigrew cites a recent result from an initiative on low-cost imaging that his institute started nine years ago: the Vscan, a battery-powered, hand-held ultrasound device that GE unveiled in 2009. "Leading cardiologists hold this as the stethoscope of the future," Pettigrew says. "Not only is it smaller and fully portable, it costs 20 times less than the conventional ultrasound device." Under the same initiative, Rebecca Richards-Kortum of Rice University in Houston, Texas, is working with Pentax to develop a microscope small enough to fit into a biopsy needle that can produce real-time diagnoses.

There is so much work underway to develop faster, clearer and safer imaging technologies that some of the benefits may well be coming soon to a clinic near you. "We promote scientists who develop transformative approaches to making new discoveries and acquiring knowledge about the nature of life and physiology and disease," says Pettigrew, speaking on behalf of his institute and the field of biomedical imaging generally. "And we develop new approaches to diagnosing and treating disease." ■

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1. Walker-Samuel, S. *et al. Nature Med.* **19**, 1067–1072 (2013).
2. Balog, J. *et al. Sci. Transl. Med.* **5**, 194ra93 (2013).