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Conquering cancer

How faster diagnosis will pay dividends

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Diagnosing cancer more deftly will pay dividends

Given that 50% of Britons will develop the disease during their lifetimes, we need to get better at detecting it, says Matthew Partridge. These firms are leading the technological charge

Earlier this year, I found myself in hospital undergoing various scans and tests. While I thankfully got the all-clear, others aren't so lucky. There were 391,000 cancer diagnoses in the UK alone in 2019, according to Macmillan Cancer Support. There is therefore huge demand for better ways to diagnose cancer as fast as possible. The cancer diagnosis market is already worth an estimated $135bn, and is expected "to exceed $250bn by 2030", says Maximilian Martin, global head of philanthropy at Lombard Odier. Ageing populations in developed countries and greater access to treatment in emerging markets are driving demand. On the supply side, recent progress has "opened up vast possibilities".

From sick care to healthcare

Better diagnosis is a key part of responding to the challenge posed by ageing populations. Creaking healthcare systems around the world are realising that they will need to take a big step away from "reactive treatment toward targeted, preventative medicine", says Luke Barrs, global head of fundamental equity client portfolio management at Goldman Sachs' Asset Management. Elena Viboch, partner at venture capital firm General Catalyst, agrees that there needs to "be a move from sick care to health care".

This type of pre-emptive approach is especially useful when it comes to cancer, since catching the disease at an earlier stage enables "higher survival rates, less costly treatments, and a situation where people's quality of life can be maintained for longer", says Viboch. Earlier interventions can also help even out "very unequal", cancer outcomes, with minorities and people living in rural areas "doing particularly badly" in the US.

These long-term problems have been greatly exacerbated by the pandemic, which delayed non-urgent treatment, creating an "extensive care backlog", says Owain Rhys Hughes, an NHS surgeon and founder of healthtech start-up Cinapsis. While the resulting delays and waiting lists in the UK affect everyone, they are "particularly critical for cancer patients, who are receiving diagnoses far later and struggling to access treatment before their condition worsens as a result". We "desperately" require solutions to shorten the time it takes to detect cancer.

Better diagnosis won't only help catch cancer, says Ovid Amadi, senior analyst at RTW Investments. It can also help doctors gauge which stage the cancer has reached (there are four stages, with stage one being the mildest) and find any particular mutations, which can in turn help "match the right treatment to the right patient". Diagnostic technology can also assess whether the cancer has recurred in those who have already received treatment. The best technology can now detect the return of malignancy between ten and 12 months sooner than previously, notes Amadi.

"New technology can detect the return of a cancer a year sooner than previously"

Today's methods are unreliable

Current diagnostic methods have many drawbacks. Simply relying on symptoms can be extremely inaccurate, as many cancers develop without symptoms, or share symptoms with other, less serious, conditions. For instance, ovarian cancer tends not to be diagnosed until it has reached a late stage, as its main symptoms, stomach pain, feeling full and needing to urinate, can easily be ignored, says Gareth Powell, head of healthcare at fund managers Polar Capital. Similarly, in the case of oesophageal cancer, many people will try and use over-the-counter medicine to deal with the heartburn that can be the main warning sign, says Fiona Labrooy of Heartburn Cancer UK.

However, even when screening tests exist, they "tend not to be very accurate", says Powell. The classic example is the PSA test, which measures levels of antigens associated with prostate cancer in the blood. While its high sensitivity for symptomatic patients means it can detect most prostate cancers, it has a low specificity, which means that it also produces a lot of false positives. It also works less well in picking up cases in men without symptoms. Mammograms (breast x-rays), while similarly saving lives, struggle to detect cancer in women with dense breast tissue.

Most suspected cancers still have to be confirmed through "invasive and expensive" tests, says Powell. In some cases, this involves taking a biopsy, a tissue sample from the suspected organ. Another method is to put a miniature camera into the body, as happens in a colonoscopy (bowel and intestines) or OGD (an endoscopy, with a camera in the oesophagus and stomach). Both require arduous preparation the day beforehand, and so sadly many patients choose not to do them, even when they have been advised to.

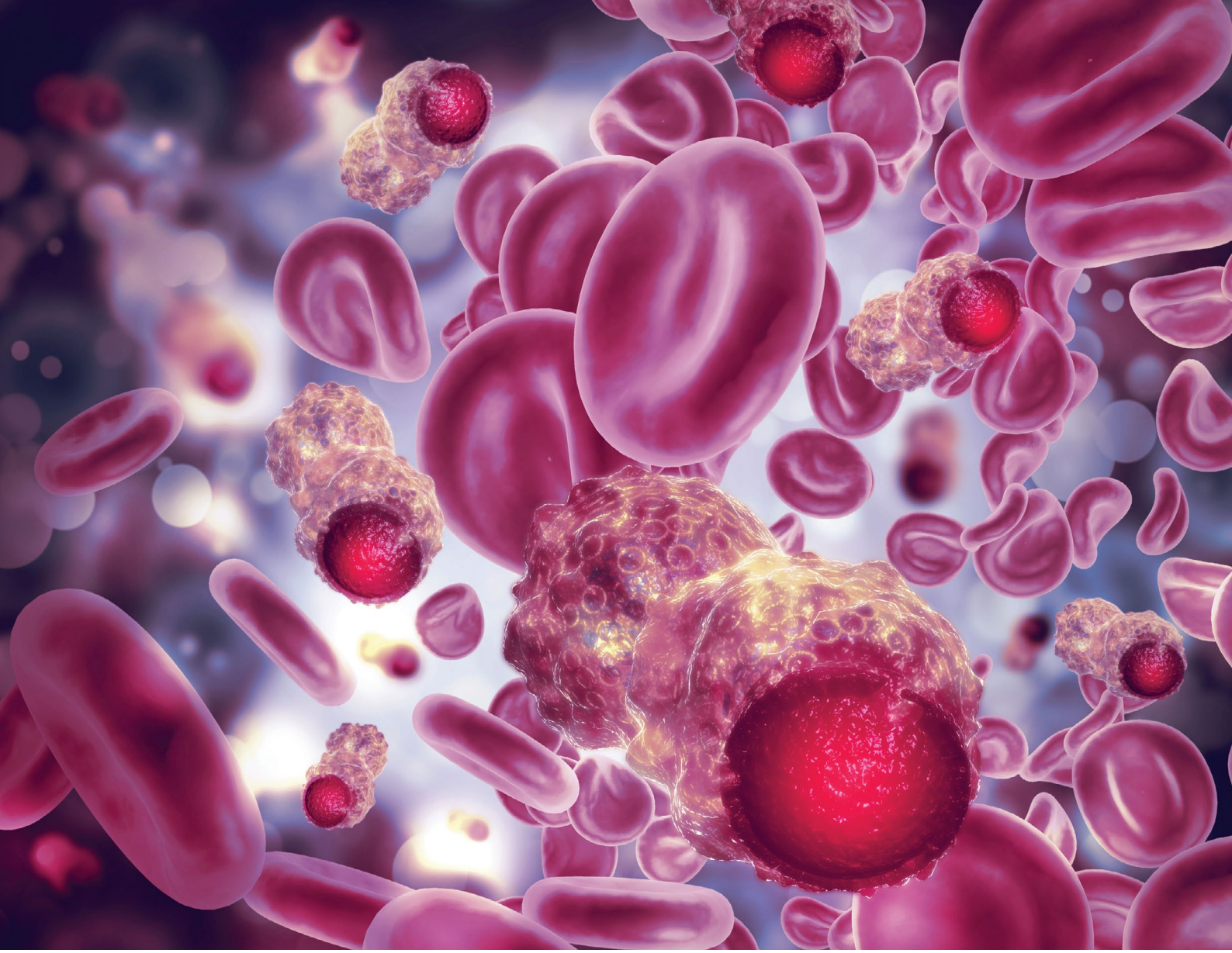
The potential in blood tests

These problems mean there has been considerable interest in cheap, reliable screening tests that can flag up cancer while minimising false positives. Perhaps the most promising research involves cancer-detecting blood tests. These "liquid biopsies" typically focus on cell-free circulating tumour DNA (ctDNA), fragments of DNA that are shed by tumour cells as they die, says Robert Sackin of patent attorneys Reddie & Grose.

The idea is that the "higher the volume of ctDNA in the blood, the more likely that someone has a malignant cancer, or in cases where cancer has already been diagnosed, changes in volume can show how fast it is progressing".

At present, a few specific conditions, such as colon cancer, have tended to secure most of the investment from companies, says Viboch. This is because "there is already a gold standard test in the form of a colonoscopy, which you can benchmark any test against". However, once the tests are shown to work for a few specific conditions, she is confident that companies will start to adapt them for other types of cancers, "including those that aren't currently diagnosed until it is too late".

Detecting one type of cancer through drawing blood is impressive enough, but the ultimate goal is a test that can detect multiple types of cancer (known as a MCED) "so that you can go to the doctor each year for a simple blood test that will tell you if you have cancer or not",



Illumina has developed a blood test that detects multiple types of cancer

says Amadi. The problem is that accurately detecting multiple cancers and distinguishing between them, "so the doctors know which part of the body to search... to carry out follow-up tests", is "exponentially more difficult than just detecting just one".

Still, that hasn't stopped Illumina from developing Galleri, the first commercially available MCED. Galleri's relatively modest sensitivity means that a significant number of people with cancer will get a false negative result, and it is also extremely expensive. But Amadi notes that "there are many people who are currently willing to pay the $1,000 cost out of their own pocket". A reliable, cheap MCED could be here in ten years' time, especially if health systems and insurance companies around the world agree to cover their costs.

The NHS (among others) has been running a large-scale evaluation of the Galleri test with 140,000 patients to see if it could be useful for various high-risk groups. This trial will report later this year, with preliminary results last week suggesting that it can detect two-thirds of cancer in symptomatic patients.

Meanwhile, the Imperial College NHS Trust has confirmed that it is in talks to run clinical trials of HrC, a second generation MCED developed by Epigeneres Biotech and Tzar Labs. This test is based around monitoring changes in VSELs, a type of rare adult stem cells.

Looking beyond blood tests

Blood tests aren't the only way to catch cancer early. German biotechnology firm Mainz BioMed has developed a stool-based screening test (ColoAlert) for colorectal cancer. In contrast to the standard faecal immunochemical test (FIT), which just seeks human blood in the stool, ColoAlert looks "for specific DNA markers associated with tumours", says Guido Baechler, CEO and director at Mainz BioMed. So it is better at detecting potential cancer, "especially when the tumour is at an early stage and is not yet bleeding".

Baechler points to a female patient who wasn't gaining as much weight as she expected, "but was told by her doctors not to worry". She insisted on doing a test with ColoAlert, which came up positive, finally leading them to do a colonoscopy. This revealed that she did indeed have cancer, although the fact that it was eventually caught and treated before it spread to other organs means that she may now survive.

Although blood and stool tests have a higher uptake than colonoscopies, some people still find even these methods uncomfortable. This bodes well for urine-based tests. Urine is an "easy, effective and non-invasive method for diagnosis".

There is also strong evidence that it contains "extracellular vesicles (EVs) that carry biomarkers from parent cells and are believed to be involved in cell-to-cell communication, metastasis and proliferation of cancers", says Kunanon Chattrairat of the department of biomolecular engineering at Nagoya University in Japan. His team has developed a system to capture EVs from urine samples, which he hopes could be rolled out soon.

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"A cheap test able to detect multiple types of cancer could be ready in ten years' time"

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In addition to better non-invasive screening tests, there are also some interesting minimally invasive methods in the pipeline. The British biotechnology firm Cyted has developed the Cytosponge, which helps diagnose both oesophageal cancer and the pre-cancerous Barrett's oesophagus. Instead of having an OGD, patients swallow a pill on a string containing a sponge that expands before being withdrawn, collecting a sample of cells. This needs minimal preparation and can be done by a nurse instead of a surgeon, says Labrooy.

This test's convenience and high sensitivity means that it could help save healthcare systems money by reducing the need for OGDs. Indeed, during the pandemic, with social distancing making gastroscopies difficult to perform, the test briefly replaced OGDs as the main diagnostic method. However, Marcel Gehrung, Cyted's co-founder and CEO, believes that in the longer run it could be used to expand the number of people screened to include those who are at risk but would not normally qualify for an OGD, thus finding and preventing cancer in the early stages.

Imaging and artificial intelligence

Advanced imaging systems, such as CT, MRI and ultrasound scans, are also frequently used to help diagnose cancer. However, while non-invasive, they have drawbacks. For instance, CT scanners produce ionising radiation, which slightly increases the lifetime risk of catching cancer. All three systems are extremely expensive, with most MRI machines "so large that up until now they have had to be located in hospital basements", says Sackin. MRIs are also "slow and noisy, with many patients finding them claustrophobic".

Thankfully, recent design advances are bringing down both the cost and the size of these devices, "as well as speeding them up so hospitals can scan a greater number of patients in the same amount of time", says Sackin. Developments in artificial intelligence (AI) and machine learning "also mean you can get the same image quality from a weaker signal", allowing for even smaller and cheaper MRIs.

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Artificial intelligence algorithms can help assist pathologists

These devices, then, should soon start playing an even greater role in detecting cancer.

AI has already begun to move from being "a futuristic concept to becoming a present reality", says Sara Torrecilla, senior biotechnology analyst at asset manager Candriam. For example, AI "is already powering endoscopy systems by providing an enhanced visualisation to detect polyps better and earlier when performing colonoscopies". Similarly, in the case of tissue samples, "AI algorithms can assist pathologists by analysing digitised pathology slides and aiding in the identification and classification of cancer cells". As well as speeding up the process, it "can enhance diagnostic accuracy and detect subtle features that may be overlooked by human observers".

AI could also revolutionise big-data analysis when it comes to diagnosing cancer. This means that it can use the information in large datasets to find hidden patterns, enabling people to produce screening and prevention strategies tailored to each patient. Finally, AI algorithms "can provide prognostic information to guide treatment decisions by analysing clinical data and predicting patient outcomes and survival rates".

"Advances in design and cost are lowering the cost and size of advanced imaging systems such as MRI"

What to buy now

The main multi-cancer early detection (MCED) test at present is the highly promising Galleri test developed by Grail, which was bought by Illumina (**Nasdaq: ILMN**) in 2020. While the deal may need to be unwound owing to pressure from competition regulators, "there is the possibility that Grail may be spun out directly to Illumina's shareholders, which means [they] may still be able to benefit", says Julie Utterback, senior equity analyst at Morningstar.

What's more, Illumina's legacy genomic-sequencing tools "remain a key building block of most liquid biopsy tests", ensuring that the firm will benefit when such tests take off. That justifies the 2024 price/earnings (p/e) ratio of 66.

One outfit making a splash developing liquid biopsies is **Guardant Health (Nasdaq: GH)**. This is a risky investment as the company is losing money. But Guardant recently submitted its blood test for colorectal cancer, which has an estimated patient uptake of 90% compared with 66% for colonoscopy, for approval from the US Food and Drug Administration. If it is successful, Utterback expects Medicare and Medicaid (the US insurance systems for elderly and low-income patients) to approve it as a treatment that they will pay for, which could make the blood tests extremely lucrative.

Another risky investment involved in developing liquid biopsies is **Exact Sciences (Nasdaq: EXAS)**. Its flagship product is Cologuard, an FDA-approved stool test that uses DNA markers to detect colon cancer.

It also produces Oncotype DX, a test that aims to predict recurrence by looking at how aggressive a breast cancer is, as well as OncoExTra, which provides a full genomic profile of a tumour. It is also working on tests for liver cancer, as well as its own MCED. Although it is not making any money, its sales are growing by more than 30% a year.

The leading developer of medical-imaging devices is **Siemens Healthineers (Frankfurt: SHL)**, spun out of the German engineering firm Siemens in 2016. Siemens Healthineers is the pioneer of photon counting, which the US Food and Drug Administration called "the first major new technology for CT imaging in nearly a decade". This provides "a greatly improved spatial resolution" .

The upshot is that thanks to this new technology radiologists should be able "to identify smaller anatomical structures, detect and observe tumour development and potential metastasis, and evaluate if an injected therapy drug can pass into the tumour itself", says Sara Torrecilla of Candriam. Siemens Healthineers trades at 22 times 2024 earnings.

Intuitive Surgical (Nasdaq: ISRG) is known for its robot-assisted surgery. It recently released Ion, a flexible bronchoscopy system that is aimed at improving the diagnosis of lung cancer, which is typically "diagnosed later than many other cancers", contributing to lower survival rates, says Dan Lyons, portfolio manager and research analyst at Janus Henderson Investors.

By enabling the camera to get into parts of the lungs that are hard to reach, Ion can do away with the need for a more intrusive needle biopsy. Intuitive trades on a 2024 p/e of 48 earnings, although this is justified by its 15% annual revenue growth.