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Big data promise exponential change

Information explosion excites both experts and worries about privacy, reports *Gonzalo Viña*

When a top Formula One team is using pit stop data-gathering technology to help a drugmaker improve the way it makes ventilators for asthma sufferers, there can be few doubts that big data are transforming pharmaceutical and healthcare systems.

GlaxoSmithKline employs online technology and a data algorithm developed by F1's elite McLaren Applied Technologies team to minimise the risk of leakage from its best-selling Ventolin (salbutamol) bronchodilator drug.

Using multiple sensors and hundreds of thousands of readings, the potential for leakage is coming down to "close to zero", says Brian Neill, diagnostics director in GSK's programme and risk management division.

This apparently unlikely venture for McLaren, known more as the team of such star drivers as Fernando Alonso and Jenson Button, extends beyond the work it does with GSK. It has partnered with Birmingham Children's hospital in a £1.8m project utilising McLaren's expertise in analysing data during a motor race to collect such information from patients as their heart and breathing rates and oxygen levels. Imperial College London, meanwhile, is making use of F1 sensor technology to detect neurological dysfunction.

Elite engineering: data technology from Formula One's McLaren team is being used by GSK on an asthma project — Steven Tee

Few people would contest that big data are going through a period of explosive growth, yet it is anyone's guess what that will amount to. In healthcare, one measure, by the McKinsey Global Institute in 2013, estimated that making greater use of big data could soon be worth some $100bn annually across the US healthcare system. Another, in PLOS Biology, the US Public Library of Science journal, forecast that data generated by genomics alone will be on a par with that generated by astronomical science, YouTube and Twitter by 2025.

Big data analysis is already helping to reshape sales and marketing within the pharmaceuticals business. Great potential, however, lies in its ability to fine tune research and clinical trials, as well as providing new measurement capabilities for doctors, insurers and regulators and even patients themselves. Its applications seem infinite.

BC Platforms, a Swiss-Finnish company that manages clinical and genomic data with its own analytics platforms for academics, healthcare providers and life science companies, recently signed an agreement with Microsoft Azure and Codigo46 of Mexico to create the largest biobank in Latin America. It aims to take genomic data from 1m people over the next three years.

Tero Silvola, BC's chief executive, says the problem is in "making sense" of the future biobank's 100m data points, as well as those of the other 19 biobanks around the world, if data are to support drug companies in their quest for ever more personalised medicine.

Stephen Cleaver, head of informatics systems at Novartis Institutes for Biomedical Research in Cambridge, Massachusetts, says he sees "almost exponential growth" in gene sequencing in the years ahead. This will be helped in no small measure, he adds, by continued falls in data storage costs and improving computing power.

"We are doing stuff today we couldn't even dream of five years ago," he adds. "Our work is becoming increasingly data driven. We are now taking a direction towards deep learning, which is a subfield of artificial intelligence, in which we will be able to detect and understand hidden patterns in these huge data sets."

Given such possibilities, the Boston-based biotech company PureTech says its adaptive computer game, Akili, provides "statistically significant improvement" in trials with children suffering attention deficit disorder. Meanwhile,

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Inside

R&D The era of isolation has given way to a desire for greater collaboration, writes *David Crow*

Drugmakers step out from behind their high walls

On Chicago's outskirts sits a sprawling corporate campus set on more than 450 acres. It is home to Abbott Laboratories, the healthcare group, and AbbVie, the drugmaker it spun out in 2013. A grid of roads connects rows and rows of laboratories and offices surrounded by car parks the size of football stadiums. Abbott Park feels like a small town in itself.

For decades, this is how large pharmaceutical companies have organised themselves. Each day, armies of white-coated scientists have made the drive from their suburban homes to work.

Eli Lilly has a similar set-up in Indianapolis. Johnson & Johnson, the world's largest healthcare group, is a leading feature of life in New Brunswick, New Jersey. But over the last ten years, big pharma has had a radical rethink over where to base its scientists. Increasingly, it is opening satellite offices and labs in areas that have become magnets for newer biotech companies.

One of the first to make the move was Swiss group Novartis. In 2002, it moved its worldwide research base from Basel to Cambridge, near Boston. Now almost all the large drugmakers have facilities in the two top biotech clusters — the one around Boston and one in parts of California. "The key thing they are looking for is adjacency to innovative, collaborative biotech companies and academic institutions that are world-class," says Joel Marcus of investment trust Alexandria Real Estate Equities.

Many of these innovative biotech companies are created as vehicles to commercialise scientific discoveries made by academics, and large drugmakers want to be close to the action. This reflects a broader trend: big pharmaceutical groups are looking for new drugs outside their own walls and bringing them in-house through licensing deals and acquisitions.

A decade ago, one-third of approved drugs sold by big pharma companies were sourced from outside their organisations. The number today is 51 per cent, according to Mr Marcus. With experimental drugs in the pipeline included, that jumps to 75 per cent.

The drugmaking industry used to suffer from "not invented here syndrome" — an aversion to science that comes from outside — but now is among the most collaborative. Big pharma companies want partnerships with smaller biotech groups at a much earlier stage.

Companies have their own labs and offices in the clusters but share dining areas and communal spaces, where scientists from different companies can meet to discuss their work. "This is an ecosystem that's different, which requires physical proximity because of laboratory work and the complicated nature of scientific research," adds Mr Marcus. "It's pretty stunning how much people interact."

Lab intensive: big pharma wants to share the action generated by biotech start-ups
Scott Eisen/Bloomberg

For companies that might have struggled to attract scientists to live in humdrum suburbs, the shift represents a chance to hire talent. Dave Ricks, due to be Eli Lilly chief executive from January, says it has not been "easy to get people to Indianapolis". The company has been "swimming upstream" when trying to convince people to relocate.

"To compensate for that [we have] this more distributed research model," says Mr Ricks. "We've set up satellite research hubs in many other locations," he says, citing Eli Lilly 's facility in New York and a new building in San Diego, California.

Merck has been looking at 300,000 sq ft of space in San Francisco, while Bristol-Myers Squibb is expanding its campus in nearby Redwood City. Genentech, a division of Roche, has decided to buy four buildings in San Francisco.

'Drug groups used to suffer "not invented here" syndrome'

The rush for premises in the biotech clusters is not without problems, soaring rents among them. "All of a sudden now, you can barely get space — all the big pharmas have come in and taken huge space," says Nick Leschly, chief executive of Bluebird Bio, a biotech group based in Cambridge.

Some of the facilities being developed by the largest drugmakers are almost "quasi campuses" themselves, Mr Leschly adds. Yet he feels that the benefits outweigh the negatives.

"There's a fluidity among a lot of the great scientists and developers, so if you just want to meet them for lunch, then it's easy."

Furthermore, "it's created this hugely vibrant ecosystem which is great for recruiting talent."

Big data promise exponential change

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Isabel Torres, the Japanese pharmaceutical company Takeda's head of access to medicines, says it uses data readings from mobile phones to deploy mobile health clinics in some of the poorest parts of Kenya.

All such excitements aside, handling the personal details of millions of people creates huge data quality, privacy and security problems. Doug Given, director of Health2047, a San Francisco-based health systems consultancy, says much of the data gathered to date will be of limited use for healthcare providers.

"The risk is in big bad data," he says. "Take BMI [body mass index] data. We don't know how it was measured. Did people have their clothes on?"

Mr Given adds: "Also, data gathered 10 years ago by a brain scan is infinitely less detailed than what you would get today. There is a real issue around quality."

'The risk is in big bad data. There is a real issue around quality'

The OECD last year said governments needed better data governance rules given the "high variability" among OECD countries about protecting patient privacy. Recently, DeepMind, the artificial intelligence company owned by Google, signed a deal with a UK NHS trust to process, via a mobile app, medical data relating to 1.6m patients. Privacy advocates say this as "worrying". Julia Powles, a University of Cambridge technology law expert, asks if the company is being given "a free pass" on the back of "unproven promises of efficiency and innovation".

Brian Hengesbaugh, partner at law firm Baker & McKenzie in Chicago, says the process of solving such problems remains "under-developed".

Pharma giants contemplate a future of lower profits

Pricing

Political attacks have raised the pressure on drugmakers, reports *Gonzalo Viña*

For the hundreds of executives gathered in London recently for the FT's annual pharmaceutical conference, the words of GlaxoSmithKline chief Sir Andrew Witty highlighted the problems facing the industry in the decades ahead.

Despite pouring many billions of dollars into new treatments and extending lives in ways that were merely a dream a few years ago, drugmakers may have to get used to making less money. The world's big markets "will still pay for innovation", Sir Andrew told delegates. "But it is not going to pay blindly for innovation."

He was speaking days after the electoral victory of Donald Trump in the US following a campaign marked by attacks on the industry by Mr Trump and, more vociferously, by Hillary Clinton.

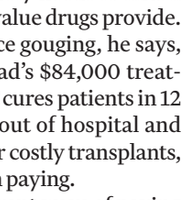
Politicians took aim at the industry late last year after Martin Shkreli, the "bad boy" of pharma, generated a public backlash by raising the price of a life-saving cancer and Aids drug from $13.50 a pill to $750. Mrs Clinton spent much of her campaign tapping into public anger at the soaring price of medicines. Her pledge in September last year to end "outrageous price gouging" wiped $38bn off drugmakers' shares.

All this is despite drugs accounting for about half of the 30-year rise in life expectancy worldwide over the last century, says David Taylor from University College London's school of pharmacy. Prof Taylor adds that continuing advances at the present rate imply that "virtually everyone will in the second half of this century be able to live in good health into their 80s."

Drugmakers argue that they are unfairly treated and that politicians and the public need to consider that drugs make up only a small part of total health spending. About three quarters of it in the US is to treat chronic diseases, with drugs comprising 14 per cent of overall health expenditure.

Jim Greenwood, chief executive of trade body BIO, which represents some 1,200 biotech companies in the US, lays part of the blame for the controversy over pricing on insurers, who have "low-balled their premiums" to gain market share after the introduction of the Affordable Care Act, also known as Obamacare.

Mr Greenwood says the insurance industry has sought to "vilify" drugmakers for the subsequent rise in costs, when hospital charges are the chief reason for increased premiums. For Mr Greenwood, a former Republican member of Congress, society needs to take a broader look at the value drugs provide. While critical of price gouging, he says, for example, if Gilead's $84,000 treatment for Hepatitis C cures patients in 12 weeks, keeps them out of hospital and removes the need for costly transplants, then it is a cost worth paying.



The world is no longer 'going to pay blindly for innovation', says GSK chief Sir Andrew Witty

Despite very different ways of paying for drugs in the UK's publicly funded National Health Service, it is not a point lost on Prof Taylor at UCL. He says cost effectiveness analyses need to take into account the savings drug treatments bring if they replace more expensive forms of healthcare, for instance lengthy stays in hospital. Prof Taylor argues that a broader gauge of the benefits of drugs — including the hope they may give to people with incurable diseases — needs to developed.

Experts say the industry is full of examples where innovation can help lower the costs of previously more expensive treatments. Disruptive drugs such as SciFluor's eye drops to treat retinal disease could replace expensive injections administered by clinicians. PureTech's Gelesis 100, a capsule that produces a viscose-like substance to fill the stomach, could help reduce the need for operations to tackle obesity.

Mr Greenwood sees few alternatives to the high-stakes venture capital model of financing drug development, a system which he says would have produced 117 fewer drugs had it been supported by the sort of state-funded healthcare systems seen in Europe.

"Our pact is, we take the risk, we put all this money in, we fail and we fail and we try and we try again," he says. "This is the system that drives innovation."

Against today's social and political currents, the pharmaceutical industry is having to navigate a narrow course, providing breakthrough advances, making a profit and keeping the goodwill of their customers. Getting the price right to satisfy all three objectives will be the difference between success and failure, industry veterans say.

GSK's Sir Andrew says drug companies need to look more at selling beyond the rich markets of the US, Europe and Japan and make a virtue of the higher volume — even at a lower price — which the world's other 6bn people will need.

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Need for speed impels diagnostic advances

Disease analysis
Simpler test procedures, increased accuracy and faster delivery of results are crucial, reports *Sarah Murray*

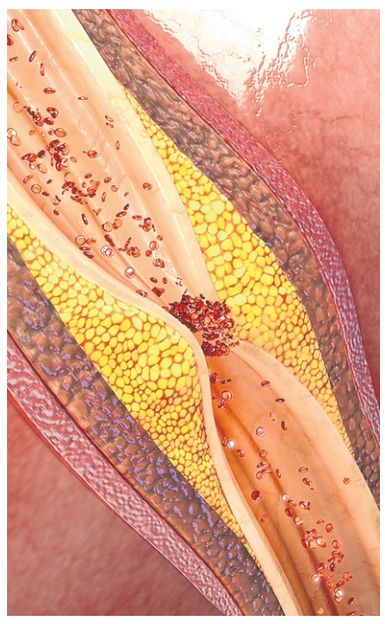
Scientists at the Cleveland Clinic in the US have found how to explain why, of two people on the same diet, only one might develop heart disease. Genetics plays a role but it turns out that intestinal bacteria — microorganisms in the digestive system — are a strong indicator of risk of heart attack and stroke.

Considerations of speed, costs and more personalised treatments are key factors behind today's greater focus on improving diagnostic technology. Many recent advances have focused on improving the accuracy of results.

An example of this is the blood test used by the Cleveland Clinic, which measures levels of trimethylamine-N-oxide (TMAO), a metabolite derived from gut bacteria. In research published in the Journal of the American Heart Association, Stanley Hazen, the clinic's head of preventive cardiovascular medicine, and a team tracked the build up of plaque in the arteries of 1,000 patients and looked for risk predictors. "TMAO beat everything, even after adjusting for all the risk factors," he says.

As well as accuracy, speedy delivery of results is important too, not least in the case of such infections as sepsis, when even short treatment delays can be life threatening. UK-based DNA Electronics is developing a diagnostic for bloodstream infections that will yield results in two to three hours, compared with two to three days using present blood culture-based diagnostics.

Speedy diagnosis helps prevent the spread of such a highly contagious disease as tuberculosis. For this, the World Health Organisation is promoting the molecular based GeneXpert test, which can provide results in hours rather than the months it takes when using traditional sputum smear microscopy tests.


Risk: plaque in the coronary arteries

In developing countries with poor infrastructure and insufficient numbers of skilled workers, tests need to be easy to use. Rapid diagnostic tests (RDTs) have helped to combat malaria, not only because these tests are more accurate but also because they are conducted with a simple dipstick and a drop of blood. Since they do not require sophisticated clinics and equipment, RDT's can be used in remote rural areas.

As science and medicine meet electronics, tests are being developed that need little expertise. Before DNA-based electrical circuits, genetic testing required experience of pipetting, contamination prevention and how to maintain sample temperatures.

"With chip-based systems, you don't need someone with that innate knowledge," says Amit Agarwal, a principal in Deloitte Consulting's life sciences practice. "If you can do the sample prep in a miniaturised way with a drop of blood or biological fluid, it suddenly becomes a lot easier to use but also it can go outside a laboratory."

More such simplicity is needed, argues Timothy Jinks, senior business analyst at the Wellcome Trust. He sees a gap between the development of diagnostic technologies and the availability of tools that can be used everywhere, from a general practitioner's office to an emergency room or a pharmacy.

"A lot of the wonderful ideas are things that can't be put into place given the way health systems are constructed," he says. One obstacle is that healthcare providers using different IT platforms may be unable to share data.

"One of the big barriers is getting information back and forth between systems," notes Mr Agarwal.

Digital technologies play a growing part in diagnostics. Partly, this is due to tremendous increases in computing power, which allow millions of medical records to be analysed and compared.

Advances in image processing have brought new accuracy, says Bhoopathi Rapolu, head of analytics for Europe and the Middle East at Cyient, an India-based engineering design and data management company.

He cites the work of scientists at the California NanoSystems Institute at UCLA, who have developed a device that analyses millions of images per second in search of cancer cells. "The algorithm can analyse 36m images per second and identify cancer with 95 per cent accuracy," Mr Rapolu points out.

As an increasingly wide range of experts — from medical device manufacturers to coders — contribute to diagnostic developments, different organisations will have to start co-operating.

"Technology, science and medicine are all having to evolve at the same pace and work together in a multidisciplinary way," says Steve Arlington, president of the Pistoia Alliance, which promotes research and development among life sciences companies. "We're just starting out on that journey."

Feel-good fundraising sets sights on malaria

Financing

Joining the battle against disease in Nigeria may net returns, writes *Andrew Jack*


Social impact: a health official tests for malaria in Lagos, Nigeria — Pius Utomi Ekpei/AFP

Malaria may not seem an obvious focus for financial markets but Nigeria plans an ambitious new instrument to tackle the heavy burden of the disease.

If it goes ahead, the Innovative Financing for Malaria Prevention and Treatment/Control Project (Impact) will seek up to $300m from investors to fund distribution of bed nets impregnated with insecticide for the country's malaria control programme.

Investors with a conscience would have the option of a bond, either issued or underwritten by the World Bank, delivering a 3 per cent yield and the satisfaction of seeing their money tackle an important problem — with disbursement of the funds based on performance.

Ray Chambers, a financier who is the UN Secretary-General's special envoy for health and malaria and has helped oversee discussions relating to the bond, sees considerable potential. "We are starting to see private equity groups raise significant funding for equity in social impact," he says. "There appears to be a lot of interest."

The Nigeria malaria bond is one of a number of initiatives in the field of healthcare funding, at a time when a global economic slowdown is prompting fresh debate about how to make limited resources go further and tap alternative sources of finance.

In Cameroon, the government is working with the World Bank's Global Financing Facility alongside advisory and backers Grand Challenges Canada, Toronto-based Mars Centre for Impact Investing and UK's Social Finance, on a more modest $4.5m-$6m "social impact bond". The aim is to fund the expansion of "Kangaroo care", a low-cost way to care for premature babies.

Devised in the 1970s as a simple alternative to incubators by maintaining constant skin-to-skin contact between newborns and their mothers, the approach has proved effective but is still not widely applied. Colombia's Kangaroo Foundation and other partners would develop training programmes to expand the programme across several regions, with incentive payments based on meeting agreed targets.

"We have huge, competing priorities for maternal and newborn child health programmes," says Dr Martina Lukong Baye, the co-ordinator at Cameroon's ministry of public health and a strong advocate for the bond.

There is no doubt about the desire for such instruments from health organisations and governments and the idea of paying for performance appeals to many donors and philanthropists. Ventures such as the Global Fund to Fight HIV, TB and Malaria, along with Unitaid — an airline levy system focused on tackling the same diseases — have generated significant income based on this model. But for the past few years, there have been far more reports and meetings than money generated by additional finance mechanisms.

> 'If we get a couple of big bonds out there . . . that will really open the doors'

"I count seven social impact bonds for health that have been discussed but none of them has happened," says Amanda Glassman, director of global health policy at the Center for Global Development, a US think-tank. "There is so much uncertainty over whether they can do the job that no one wants to put the money in."

One issue is complexity — most are not really traditional bonds. A study by Social Finance identified 60, mainly in high-income countries in the fields of education, housing and criminal justice. Most were very small and just four have so far paid out bonuses based on strong performance.

There can be high costs and complexities in structuring them and uncertainties and heavy administrative burdens in measuring performance. Some also caution that they may distort countries' own priorities.

Mr Chambers says social impact bonds up till now have been too small to appeal to large investment funds.

He even suggests that calls by US president-elect Donald Trump for the repatriation of profits held abroad by some US companies could offer fresh finance for such social purposes. "I think if we get a couple of big bonds out there and some of the large institutions to invest, that will really open the doors."

Meanwhile, other sources of experimental funding for healthcare are being launched: from debt buy-downs by donors to "sin taxes" such as the levies on sugary drinks, which are channelled to public health programmes.

Ms Glassman says there also needs to be greater emphasis on government purchasing, with a focus on value. "We should work for more money and focus on what is best to provide."

Sequencing makes its way out of the lab into clinical practice

Genomics

Some two decades on, the discipline comes of age, reports *Clive Cookson*

Twenty years after scientists started to read the DNA of bacteria — and 15 years after the completion of the first draft of the human genome, the greatest achievement of modern biology — the field of genomics is beginning to deliver on its vast medical promise.

Applications of genomics — reading and analysing the DNA that stores genetic information in all living cells — are moving from lab research into clinical practice for diagnosis and therapy, as a range of "next generation sequencing" technologies help cut costs and improve performance. "Genome sequencing is already changing the face of medicine, making possible more accurate and personalised treatments," said Jeremy Farrar, director of the Wellcome Trust, the largest UK bioscience charity.

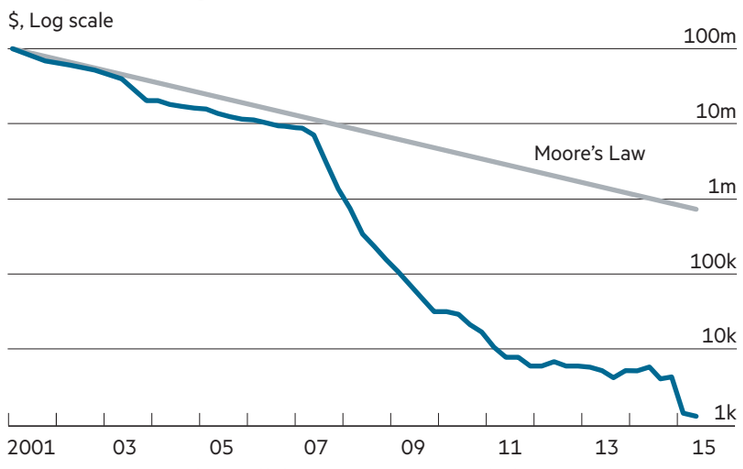
While the electronics industry as a whole has followed Moore's Law — originally formulated by Intel founder Gordon Moore in 1965 — which holds that performance per dollar spent doubles every two years, DNA sequencing has done far better (see chart). The human genome naturally receives most attention, as the cost of sequencing accurately all 3bn biochemical "letters" of an individual's DNA falls below the $1,000 barrier. But diagnostic applications are also focusing on microbial and viral genomes, which can be read for as little as tens of dollars each.

The DNA sequencing industry, led by Illumina of the US, is still rooted in its origins providing large and expensive instruments to research labs. Some newer companies, however, are developing smaller and more portable kit aimed at the diagnostic applications.

One is London-based DNA Electronics (DNAe). "I have always wanted to apply sequencing in a domain where rapid results and ease of use are important," says Imperial College London's Chris Toumazou, founder and executive chairman of DNAe. "And in the medical sector, diagnosis of infectious diseases is a perfect application for our semiconductor-based technology."

DNAe's prospects were boosted in September, when it won a $51.9m contract from the US government's Biomedical Advanced Research and Development Authority (Barda) to develop a DNA sequencing system for rapid diagnosis of two types of infection from patients' blood samples: influenza and antimicrobial resistant bacteria.

Cost per human genome



Sources: genome.gov/sequencingcosts; National human genome research institute

DNAe aims to provide conclusive identification of the disease agent within a few hours directly from clinical samples. Its first product, for commercial launch in 2018, will be a system to diagnose serious bloodstream infections leading to sepsis, the cause of more than 200,000 deaths a year in the US.

Cancer diagnosis by liquid biopsy — sequencing DNA shed by growing tumours into the bloodstream — is another application drawing academic and commercial interest. "Within the next three to five years we should be there with liquid biopsy to detect cancer metastases," says Prof Toumazou.

Oxford Nanopore is another UK company developing small portable DNA sequencing machines. It uses a technology based on nanopores, microscopic holes within protein molecules. As a strand of DNA passes through an electrically changed nanopore, each of the four biochemical "letters" of DNA (G, A, T and C) produces a distinct change in current, which makes it possible to deduce the genetic sequence.

Oxford Nanopore's MinIon sequencer has won academic fans, who are using it for identifying pathogens. It was used in sequencing strains of Ebola virus in the recent African epidemics. Two US rivals' complaints of patent infringement have hit the company in 2016, signs of how increasingly competitive the DNA analysis business is.

The first claim, by Illumina, was settled out of court in August. The second, by Pacific Biosciences this month, is "without merit", says Oxford Nanopore chief Gordon Sanghera: "We do not anticipate any disruption to our ongoing commercial progress as a result."

Of course, genomics extends beyond DNA sequencing equipment into companies building huge databases linking genes to health and disease. This is a far more complex undertaking than scientists suspected when the first draft of the human genome was completed.

For a start, less than 3 per cent of the genome represents genes in the traditional sense — coding for proteins that have specified biochemical roles in the body. Some of the remaining DNA performs known regulatory functions but much is a mystery. Even the 20,000 genes are far from well understood.

The most ambitious corporate attempt to make sense of the genome may come from Human Longevity, the US company set up in 2014 by Craig Venter, who had led the private sector challenge to the public Human Genome Project in the 1990s. Human Longevity has raised more than $300m from investors and in April reached a far-reaching genomics deal with UK-based pharmaceutical group AstraZeneca.

Some 500,000 human genomes will be analysed from DNA samples taken during AstraZeneca's clinical trials with the informed consent of participants.

"This 10-year deal is the largest ever in genomics," says Dr Venter. "It shows that AstraZeneca is incorporating genomics at every level of the organisation."

Robots gown up for the operating theatre

Automation Next wave of surgical 'slaves' will do more and be cheaper, reports *Madhumita Murgia*

The surgeon operating on 42-year-old Siobhan Morris at London's Guy's Hospital in September had four arms, 3D vision and not a suggestion of a wrist tremor. Ms Morris' kidney transplant was carried out with superhuman precision, not least because it was not a human that performed it but a robot known as da Vinci.

Da Vinci machines have operated on more than 3m patients worldwide. They are controlled by a human surgeon, their accuracy helping to reduce bleeding and unexpected surgical tremors.

"The robot kidney transplant was the first in the UK," says Professor Prokar Dasgupta of Guy's Hospital. "My main work is prostate, bladder and kidney illnesses but we've used it on lungs, gynaecological and paediatric surgery."

Robot surgery has become widespread around the world. Intuitive Surgical, the US company that created the da Vinci, says it has 3,600 machines operating globally and that the number of procedures conducted rose 16 per cent in the second quarter of 2016, compared with the same period last year.

In the UK, some 60 robots are at work performing surgery. Guy's owns two, each of which cost £1.8m, a price met by grants and donations. "There is less blood loss, quicker recovery, less pain, no question but cost is a major issue," Prof Dasgupta says.

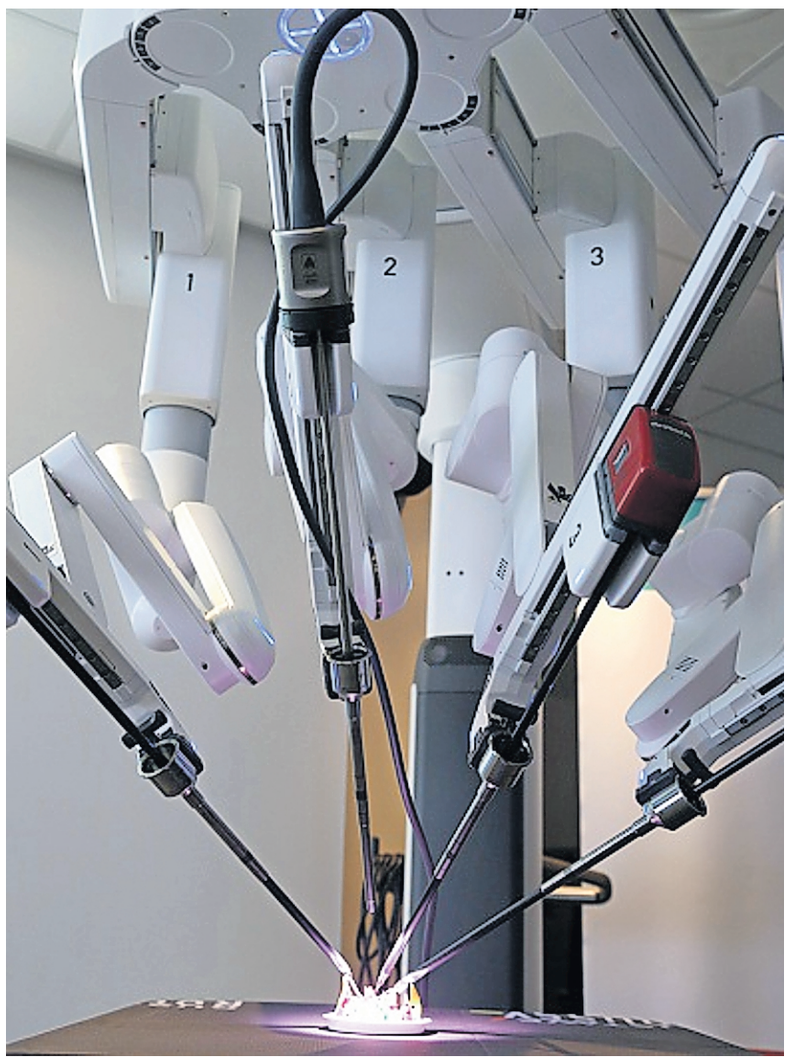
"All this is going to change in the next few years," he adds. Several companies are working on rivals to the da Vinci, which enjoys a monopoly on the surgical market but other robots coming into play and "that will drive the cost down, just [as] happened with mobile phones."

Anticipated newcomers include surgical robots being developed by Verb Surgical — a start-up spun out of Google with Johnson & Johnson — and by Dublin-based Medtronic, which has worked with the German aerospace centre, DLR. Miniaturised surgical robots are being tested in labs in Italy, Germany, Korea and Japan.

The products of this new wave of surgical "slaves", as surgeons call them, are expected to be cheaper and add capabilities such as ultrasound. "I hear the Google robot is going to integrate image guidance like MRI and CT scans during surgery, which would be of great benefit," Prof Dasgupta adds.

In Bristol university's robotics laboratory, the largest in the UK, roboticist Professor Sanja Dogramadzi aims to invent an entire family of surgical robots that can have a human surgeon's biggest advantage: a sense of touch, or "haptic feedback" as it is known.

> 'Choose your surgeon cleverly. It is not just about the technology but the years of experience'



Robotic art: da Vinci machines will soon face market rivals — Francois Guillot/AFP/Getty Images

"In [human] surgery, the benefits are you have good visibility, you have direct touch so can feel the tissue and are performing with the dexterity of your own hands," she says. Current systems have solved the visibility question: stereoscopic and 3D cameras give surgeons an even better view than their own eyes. Touch remains the biggest problem. Most surgeons crave the physical feedback they have honed with years of prodding living human tissue.

"We want to create it so you can feel the force — is it soft or hard?" says Prof Dogramadzi. "It's the same feelings a surgeon would want to feel — is there something hard inside, a hard lump? How hard? How big is it?"

Prof Dasgupta's lab at Guy's is developing an octopus-inspired robot called the Stiff Flop. "It will provide haptic feedback to the surgeon. So far it has only been tested in cadavers so we are still at the research phase."

Changes soon could cause something of a shift in power around the operating table. Surgical robots may cease to be dumb, programmable machines and transform into smart assistants.

"The Stiff Flop is a smart robot which can learn from surgeon's movements and steer clear of crucial structures like blood vessels," Prof Dasgupta says. "There will be some parts that robots can learn from surgeons and perform in an automated fashion, perhaps using image guidance."

A study this year by the Children's National Medical Center in Washington DC had a Smart Tissue Autonomous Robot stitch together, mostly on its own, a pig's bowels in open surgery.

Could this mean that robots will one day do away with human surgeons? "Clinical trials have shown us one thing only," Prof Dasgupta notes. "Choose your surgeon cleverly. Ultimately, it is not just about the technology but about years of experience.

"A fool with a tool is still a fool."

Clean up of city air means tackling pollution at source

Environment

Apps telling you it is safe to breathe are all very well but what is needed is widescale action, writes *Pilita Clark*

Go to any number of capital cities today and chances are you will be able to do something that was impossible 10 or even five years ago: check how safe it is to breathe the air there.

From London to Los Angeles to Beijing, information about air pollution levels is available at the tap of a smartphone app.

Many applications use data from public air quality monitoring stations. Some companies have gone further, producing small wearable gadgets that they say can monitor pollution in real time.

"This will allow you to make lifestyle decisions such as where to find the freshest air to go for a run, where to plan a picnic, or even allow you to find the hotspots of air pollution in your neighbourhood," says California-based Tzoa, a company that develops trackers small enough to be clipped to a backpack.

As the world population has ballooned, so have cars, coal power stations and other emblems of industrialisation that cloak our cities in a cloud of grime once confined to the west. Some 92 per cent of people live in places where air quality exceeds safe levels, reports the World Health Organisation, leading to an estimated 6.5m deaths each year, or 12 per cent of the global total.

That is largely because the problem is worse in lower income countries, with big populations yet to make the advances in clean energy and transport that have transformed air quality in the US and Europe. It means that air pollution is still a bigger killer than HIV-Aids, malaria or tuberculosis.

Public health experts say things are getting worse and the list of ways in which people die is long. Dirty air is linked to heart disease, strokes, lung cancer, acute respiratory infections and chronic obstructive pulmonary disease.

Does that make the growth in personal pollution monitors welcome? Not necessarily. Some air quality specialists warn that the precision of devices may be questionable in many places.

"Provision of accurate, personal air quality information to the individual is within our grasp in some major cities such as London, where there is knowledge of air pollution at a relatively fine scale," says Professor Frank Kelly of King's College London.

This is not the case in many parts of the developing world, where pollution monitoring is improving but patchy. Some 3,000 cities monitor air pollution, says the WHO, although that is up from about 1,600 two and a half years ago.

By far the best solution is tackling air pollution at its source. So what should cities and countries be doing?

They have to determine the main sources of pollution, says Carlos Dora, a public health policy expert at the WHO. Transport is a chief culprit. "You have countries which still have two-stroke engine mopeds," he says, referring to a type of small motorbike that burns petrol and diesel inefficiently and is prevalent across the developing world.

The EU still suffers high pollution from diesel vehicles that the authorities have encouraged because they produced less carbon dioxide, the main man-made greenhouse gas driving global warming. Mr Dora says this points to one of the most important policies that authorities can introduce to tackle air pollution: efficient public transport systems that reduce private vehicle use.

A prime example, he adds, is the rapid bus transit system pioneered in Curitiba, Brazil, in the 1970s by Jaime Lerner, an architect and former mayor of the city. Instead of building an expensive subway, Mr Lerner created dedicated bus lanes and bus stops with raised platforms that allowed people to board without stairs, a system so popular it was soon carrying thousands of people around the city. "He is a hero," says Mr Dora. Cities across Latin America and beyond have used the idea.

Other steps that cities can take include carving out more space for pedestrians and cyclists to reduce car use, and shutting down coal power stations anywhere near big populations.

> 'I think we're seeing the transition of India. In Africa, it will be a bit later'

Some places have different problems. In India and Africa, millions of people still burn kerosene for lighting, heating and cooking, creating health-endangering fumes.

Solar power is an increasingly cheap alternative for lighting and, in some places, cheap induction stoves are a healthy replacement. Millions still use wood, charcoal and dung for indoor fires that are especially dangerous for the health of children under five. Replacing such fuels with cleaner gas would help but progress in many countries has been slow.

Mr Dora is hopeful that global air pollution will be improved as developing countries introduce the solutions wealthier nations have turned to. China once had some of the most polluted cities in the world but its efforts to tackle the problem are bearing fruit, he says.

India, home to some of the worst examples of dirty air, shows signs of following China's example. Officials there are preparing a report following October's awful pollution when hundreds of schools had to be closed.

"I think we're seeing the transition of India," Mr Dora says. "We will see the transition in Africa and other countries a bit later."

Race is on: recent heavy pollution caused shock in India —Dominique Faget/AFP/Getty Images

'Brain training' games target dementia

Digital medicine

Flourishing industry focuses on science in attempt to shake off image of 'snake oil salesmen', writes *David Crow*

It sounds like the stuff of science fiction. What if you could delay the onset of dementia — not with a drug but by playing a video game?

Research published this summer suggests that it might not be such a fantasy after all. In a 10-year study of 2,800 patients, researchers found that those who played a specially designed video game nearly halved their risk of developing Alzheimer's disease and other forms of dementia.

The game was subsequently acquired by US company Posit Science, which sells an updated version called Double Decision as part of its BrainHQ suite.

Players are asked to identify a string of objects in the centre and periphery of their vision at an ever-increasing speed. In theory, the game encourages the brain to process information more quickly over time. "Much like with physical exercise, when you exercise your brain in specific ways, you can make it stronger," says Henry Mahncke, Posit Science chief executive.

Many people will think it sounds like junk science, and not without good reason. The research published this summer, known as the Active study, was one of the largest of its kind but most "brain training" games have not been subject to the rigorous testing that drugs and medical devices must undergo.

This year, Lumos Labs agreed to pay the US Fair Trade Commission $2m to settle false marketing allegations against its Lumosity brain-training game. The company had claimed that its games helped users to perform better at work and could even alleviate symptoms of Alzheimer's. The FTC said Lumosity "simply did not have the science to back up its ads".

Mr Mahncke believes the sector has been held back by products of dubious quality not underpinned by proper academic research. "This is a murky field, so we have to focus on high science," he says. "Most folks build something that they hope will work and leave it at that."

One way of improving the sector's image is through the creation of tougher rules, he argues. "I believe appropriate regulation is important for the development of the field, because there are a lot of snake oil salesmen."

Posit plans to submit the Active study to the US Food and Drug Administration to win approval to market its BrainHQ product for dementia.

The company also plans to provide separate research to support its intention to market to sufferers of "chemo brain", which refers to memory loss that afflicts cancer patients after treatment.

Another company hoping to set itself apart from the bevy of questionable brain apps is Akili Interactive, a start-up founded by Boston-based Pure Tech, developing mobile video games to treat neurological conditions.

In July, the group secured $11.9m of funding from the venture capital arms of Amgen, the large US biotech group, and Merck, the German drugmaker, taking the total amount it has raised this year to more than $42m.

The company's lead product, Project Evo, aims to train the brains of children with attention deficit hyperactivity disorder (ADHD) by asking them to prioritise amid a blizzard of information.

"There is a consumer industry known as 'brain training' with a mix of semi- or unvalidated products that have come under scrutiny," says Akili chief Eddie Martucci. "This is quite different from our digital medicine approach."

Mr Martucci says Akili wants to prove its technology works in bona fide clinical trials. The company has no plans to release any of its products until the studies are complete and it has secured regulatory clearance.

If Akili is successful, it could take business from drugmakers that produce medicines for children with ADHD, such as Shire, the Anglo-Irish pharmaceuticals group. "This is a $7bn drug market and there are lots of parents who don't necessarily want to put their kids on Ritalin," says Zack Lynch, of Jazz Venture Partners, an investor in Akili.

Jazz is also backing Pear Therapeutics, which hopes to use digital technologies to augment existing medicines. Pear's first target are patients suffering from addiction or substance abuse disorder, who number almost 22m in the US.

If companies such as Akili, Pear and Posit can provide data that proves their products work, they could be part of a flourishing new industry. The global market for cognitive assessment and training is worth $2.4bn, according to MM, the research company, and is expected to triple to $7.5bn by 2020.

DNA editing accelerates along its controversial path

Gene editing

New techniques widen scope of genetic manipulation, reports *Clive Cookson*

Biotechnologists are racing to exploit the biggest advance in their field since the dawn of genetic engineering in the 1970s. The innovation, which usually goes by the name of genome editing, vastly increases the speed and efficiency with which scientists can cut and paste DNA in living cells — making it possible to add or remove genes in ways that were impractical with the previous hit-or-miss "recombinant DNA" methods.

Genome editing — and particularly the technique called Crispr (clustered regularly interspaced short palindromic repeats, pronounced "crisper") — can be applied through routine bioscience laboratory procedures to all life from microbes and plants to humans.

Agriculture is likely to experience the first practical applications, as breeders use Crispr to speed development of new plant and animal varieties with improved traits. Yet public attention focuses on human biology and medicine. The most controversial possibility is to use genome editing to eradicate inherited disease, starting with single-gene conditions.

"Genome engineering may offer the possibility of avoiding the transmission of such diseases by making genetic changes in the early stage embryo," says Professor Karen Yeung of King's College London, who chairs a new working group looking into genome editing and human reproduction for the Nuffield Council on Bioethics.

The technology would for the first time enable irreversible genetic changes to be passed on to future generations, so particular care must be taken to prevent unintended genetic consequences, the Nuffield Council says. But the greatest ethical concern is deliberate "research toward genetic enhancement, going beyond disease prevention into the engineering of 'desirable' genetic characteristics".

Experimental genome editing of non-viable human embryos for research purposes has taken place in China. Scientists in western countries are preparing for similar projects. The UK Human Fertilisation and Embryology Authority has allowed Kathy Niakan and colleagues at the Francis Crick Institute in London to use Crispr to switch genes on and off in a newly fertilised egg, in order to gain better understanding of early embryonic development.

However "germline" genome engineering to prevent the transmission of inherited diseases to future generations is unlikely to take place for several years, until legal and scientific barriers have been overcome. Medical applications that make genetic changes to patients' non-reproductive cells may reach the clinic more quickly.

This month the journal Nature reported the first case of someone being injected with cells edited by Crispr. A Chinese team led by Lu You at Sichuan university removed cells from the blood of a patient with lung cancer, made a genetic change to boost their immune activity and injected them back into the patient — hoping that this would enhance their anticancer properties.

Genetic changes in the early-stage embryo may help avoid inherited diseases, suggests Prof Karen Yeung

The University of Pennsylvania's Carl June — involved in a similar Crispr cancer trial to start in the US next year — says this could "trigger 'Sputnik 2.0', a biomedical duel" between China and the US, with the contest likely to improve the final product.

On November 16 a team from Salk Institute in California announced in the journal Nature that it had partially restored vision to rats suffering a form of retinitis pigmentosa, an important cause of human blindness, by introducing a correct version of a defective gene.

The Salk scientists were able efficiently to edit non-dividing cells in the eye. Crispr has previously been most effective in dividing cells such as those in the skin and gut but most cells in an adult mammal are non-dividing.

Silence Therapeutics, a UK company, has used Crispr to add genes to living mice, which produced new proteins in their liver for 200 days with no apparent side-effects. Ali Mortazavi, chief executive, said the study showed that "in vivo" gene editing would be possible, as well as the "ex vivo" applications in which target cells are extracted, edited and put back into the body. Clinicians would use genome editing to make permanent genetic changes in patients, while reserving alternative RNA-based technologies for transient treatments.

A complex patent dispute overshadows Crispr and its associated biochemistry, pitting the Massachusetts Institute of Technology against the University of California, Berkeley.

"In the end they are going to shake hands and agree a settlement," forecasts Mr Mortazavi. "The prize is too big for either side to win everything."

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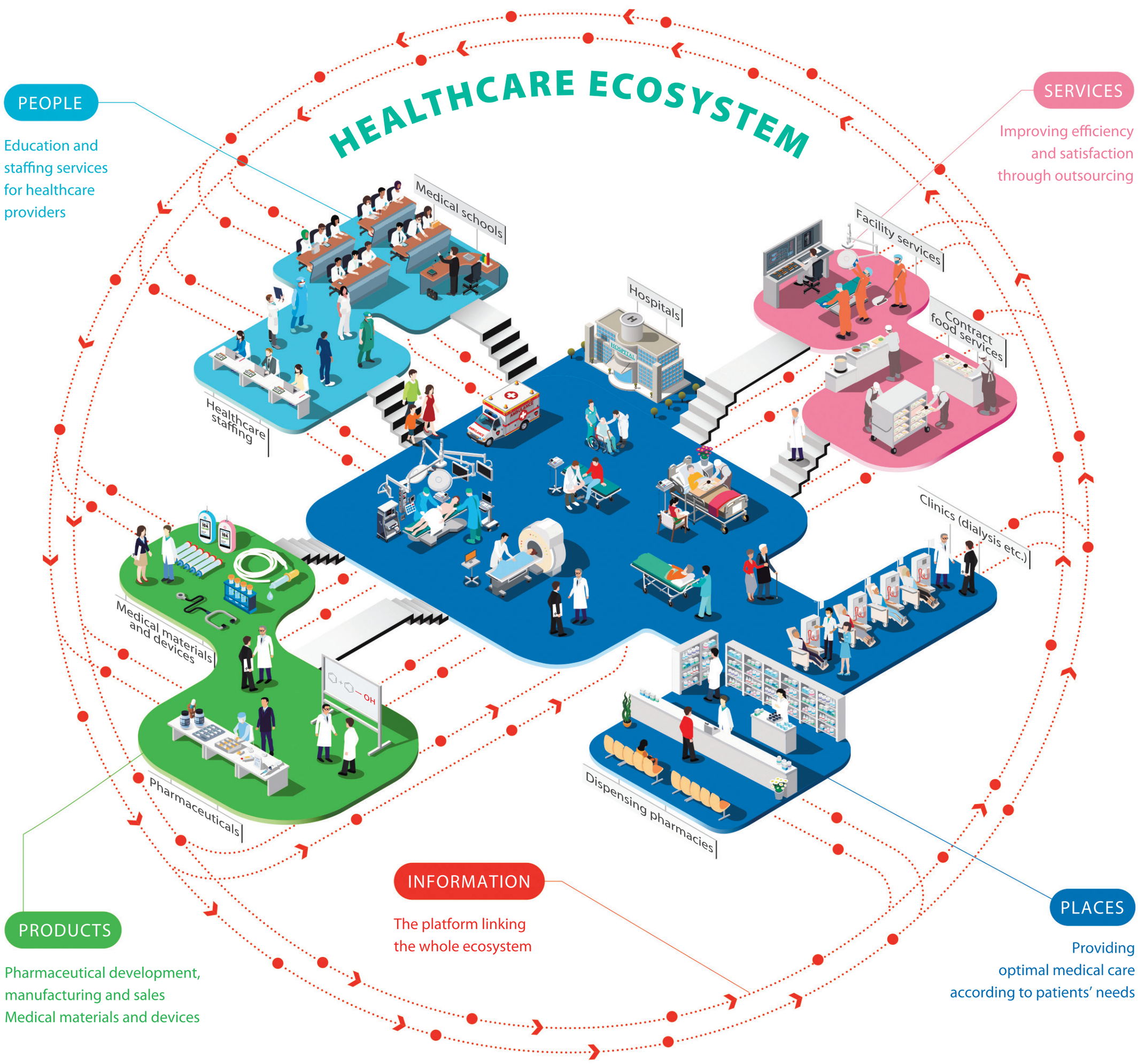

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