THE GREAT CONVERGENCE OF MEDICINE

Rose Nguyen, Investment Manager. Third Quarter 2018

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Convergence of Medicine 41904 0918.indd
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PROLOGUE – PRESIDENTIAL TREATMENT

On 12 December 1799, President George Washington, still physically fit at age 68, went horse riding near Mount Vernon. The next day he had a sore throat and the pain got worse over night. The following morning he had significant difficulty speaking and breathing. In hope of a cure, his physicians decided to drain about four litres of his blood (more than half of his total blood volume) over a short period of 9–10 hours. Just after 10pm on 14 December 1799, President Washington exhaled his last breath.

George Washington, c.1797

Blood letting, 1700s.

Most likely, President Washington had acute epiglottitis – a bacterial infection that causes swelling of the throat, blocking the airway. Nowadays, doctors can secure the airway by either placing a tube in the patient's mouth or making a small cut in the throat, and then give the patient antibiotics. Better still, we can avoid the disease by giving children the Hib vaccine (against haemophilus influenza type B bacteria). Unfortunately, neither antibiotics nor vaccines were discovered at the time.

How shocking, nonetheless. Who would have thought that bloodletting – a medical practice dating back to before the Common Era – continued to be a treatment fit for a president as late as the 18th century? The truth is that bloodletting had been the 'standard of care' for more than 2,000 years. Although less commonly employed than before, it persisted well into the 20th century, even as to be recommended in the 1923 edition of *The Principles and Practice of Medicine* by Sir William Osler, one of the four founding professors of The Johns Hopkins Hospital.

Fast forward a century and the face of medicine has changed completely. We have conquered many deadly infectious diseases, some of which are on the verge of being eradicated globally, such as smallpox and polio. We have gone from savagely brutal trepanning to almost pain-free, minimally invasive, surgeries. Once considered a death sentence, with the rise of gene therapy, cancer is now deemed curable.

THE GREAT CONVERGENCE OF MEDICINE

BY ROSE NGUYEN

If we condensed the last 200,000 years of the relatively short history of us, homo sapiens, into a single calendar year, then most of the medicine we came to know today would have only been discovered or invented during the past four hours.

However, over the final hour, innovation appears to be happening faster than ever. From gene editing to robotic surgeries to mind-controlled bionic limbs, reality has never sounded so much like science fiction. But why only now? It appears that millennia of cumulative knowledge are bearing fruit. However, there is also something else going on. We are witnessing an unprecedented level of convergence among various fields of science and technology. This era of Great Convergence is likely to transform life science and redefine what medicine is about. The future is likely to be fundamentally different from what we have today. But before considering what the Great Convergence might mean for medicine and how it will redefine healthcare in the decades ahead, it is worth taking a step back to reflect briefly on just how far medicine has come over the course of those last four hours.

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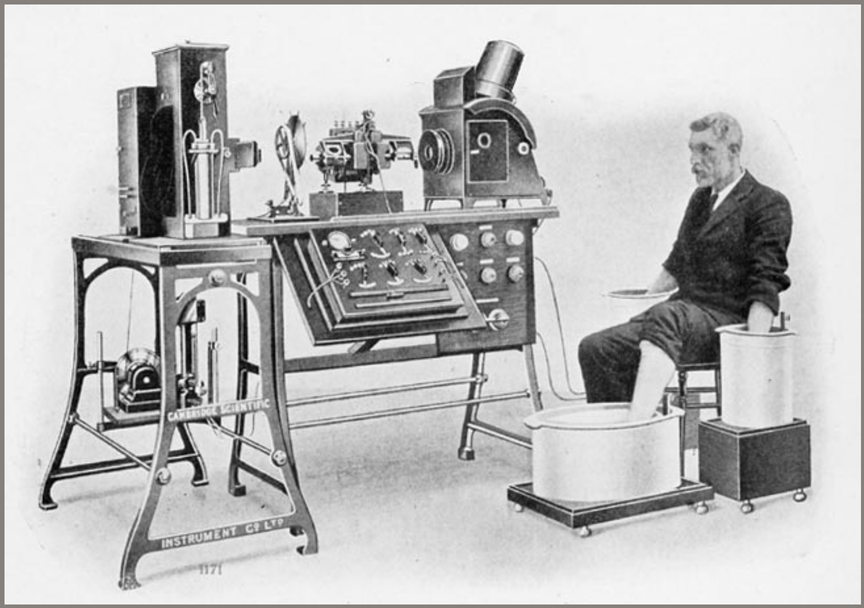
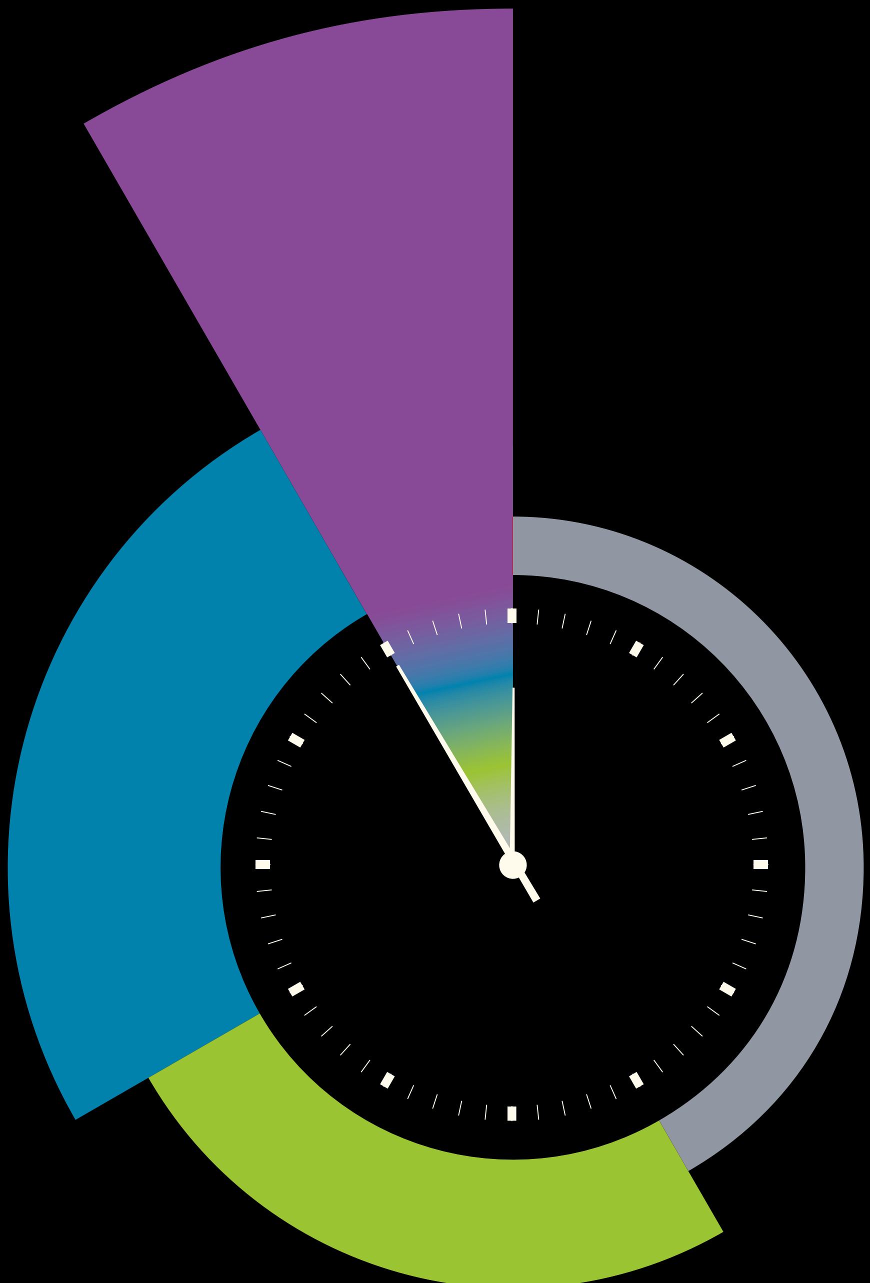


Some new smartwatches include an electrocardiogram sensor for heart rhythms. The technology has come a long way since Willem Eithoven invented the ECG machine in 1903, when the patient's hands and feet had to be immersed in jars of salt solution.



The clock represents the development of healthcare from 1746 to 2020

Each hour equals ~23 years

1746 – 1860

Bloodletting still the 'standard of care'

1861 – 1929

Fundamental basic discoveries

- Germ theory
- Antiseptic
- First-lab developed vaccine
- Penicillin
- X-ray

1930 – 1998

Golden Age of Pharma

DNA's double helix discovery

Biotech industry emerged

Human Genome Project began

1999 – 2020

Human Genome Project completed

Discovery of induced pluripotent stem cells

Breakthrough in genome sequencing technology

First living bacterium successfully synthesized

Breakthrough in CRISPR gene-editing technology

First functional human liver was created from stem cells

First 'mind-controlled' prosthetic limb was introduced

Genome Project-Write began

Three gene therapies were approved

THE LAST FOUR HOURS

The journey of medicine has been arduous, often epitomised by a resistance to change. Prior to the 20th century, new discoveries were so rare that when they did occur, the medical community were reluctant to assimilate them into medical practice, so it took a very long time for medicine to progress. For example, it took more than 300 years to get rid of bloodletting after the theory was contested in the 16th century. Even something as simple as handwashing was met with resistance. It took over 40 years, from the publication of Ignaz Semmelweis' 1847 study showing that physicians washing their hands dramatically cuts hospital infection rates, for handwashing to become standard practice.

Medicine has begun to adapt to new discoveries and treatment approaches, slowly at first but, over time, this adaptability has snowballed. In 2017, it only took six months for the US Food and Drug Administration (FDA) to approve the first gene therapy – Kymriah – which offers a completely new approach for treating cancer. The greater willingness to accept novel treatment approaches is a function of the rate of change itself – as breakthroughs occur more frequently, human minds become more accustomed to change being the norm and more open to new ideas. The pace of medical intervention began to pick up speed in the 20th century. Let's take a brief look at three areas that saw tremendous progress over that period, which help to set the context for the most recent changes: vaccination, surgery and drug development.

VACCINATION

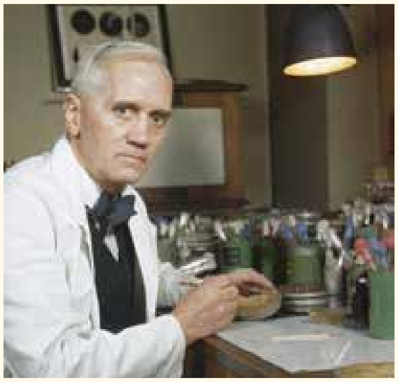
Edward Jenner first discovered vaccination in the 1790s after observing that milkmaids who were exposed to cowpox later became immune to smallpox. He began injecting people with fluid from cowpox lesions, however, his idea seemed so strange at the time that he was ridiculed by the medical community. It only became widely accepted in the late 19th century that injecting a weakened form of a bacterium or virus could help the body to produce antibodies that prevent or ameliorate any later infection. During the 20th century, scientists developed more than 20 vaccines, bringing many severe, infectious, life-threatening diseases such as smallpox, tuberculosis, polio, pneumonia, and so on, under control.

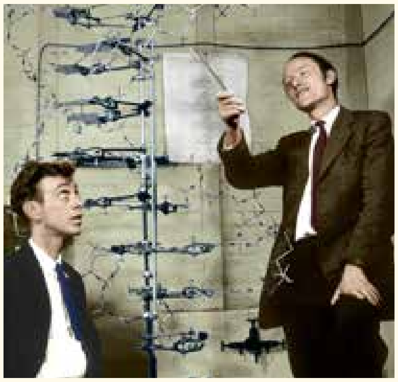
A cartoon ridiculing Edward Jenner's use of cowpox to vaccinate against smallpox, depicting his patients developing cow heads.

SURGERY

The discovery of anaesthetics in the mid-19th century transformed surgery. Until then, alcohol or even poisons were used to knock patients out so that surgeons could perform painful operations. The next big advance was in the early 20th century, when minimally invasive surgeries became a reality thanks to significant developments in imaging and surgical techniques. The invention of the endoscope – a long, thin, flexible tube attached to an optical system – helped us to look inside the body for the first time without significantly opening it up. Yet, that invention was only possible thanks to the invention of the microscopic lens to magnify images and the light bulb to illuminate the inside of the body. This was an early example of a breakthrough brought about by combining different technologies. In the later half of the 20th century we entered a new age of medical imaging, with the development of a variety of scanning technologies, including X-ray, CT (computerised tomography), MRI (magnetic resonance imaging) and ultrasound, which again were helped by advances in physical science.

An early chloroform machine.





DRUG DEVELOPMENT

The early 20th century saw the birth of the pharmaceutical industry out of the nascent chemical sector. The discovery of penicillin by Alexander Fleming in 1928 and the governments' efforts to manufacture penicillin at a mass scale during World War II sparked the so-called 'Golden Age' of the pharmaceutical industry in the 1940s–1970s. This period was characterised by a blossoming of new drugs, including antibiotics, antihistamines and antidepressants. Similar to Fleming's chance discovery of penicillin from an already discarded, contaminated petri dish, serendipity played a major role in the early pharmaceutical companies' success. With little prior knowledge of what might work and why, drug companies screened thousands of chemical compounds, either found in nature or synthetically made, in the hope of finding potential therapeutic activity. With very few drugs in existence at the time, their hit rate was high simply because the space left for exploration was immense. This allowed firms to build competitive advantages around scale. The bigger they were, the more compounds they could screen, and the higher their chances of success. The big pharmaceutical companies came out of this era, including Pfizer, Merck, GSK, and Johnson & Johnson.

The problem with this random paradigm is that it is difficult to leverage past successes or to gain any insight from failure. The first paradigm shift began with the discovery of the structure of DNA by James Watson and Francis Crick in 1953. This led to the development of molecular and cell biology, which formed the basis of the emerging biotechnology industry in the 1970s. Instead of pure random screening, biotech companies endeavoured to use science and new technologies, such as recombinant DNA, to produce new drugs. In doing so, they were able to bring about some spectacular treatments for cancer, multiple sclerosis and hepatitis. The 20th century drew to a close with the launch of the Human Genome Project in 1990, an enormous and ambitious project that aimed to map all the genes found in humans. This would propel our understanding of the human blueprint to a level previously deemed unattainable.

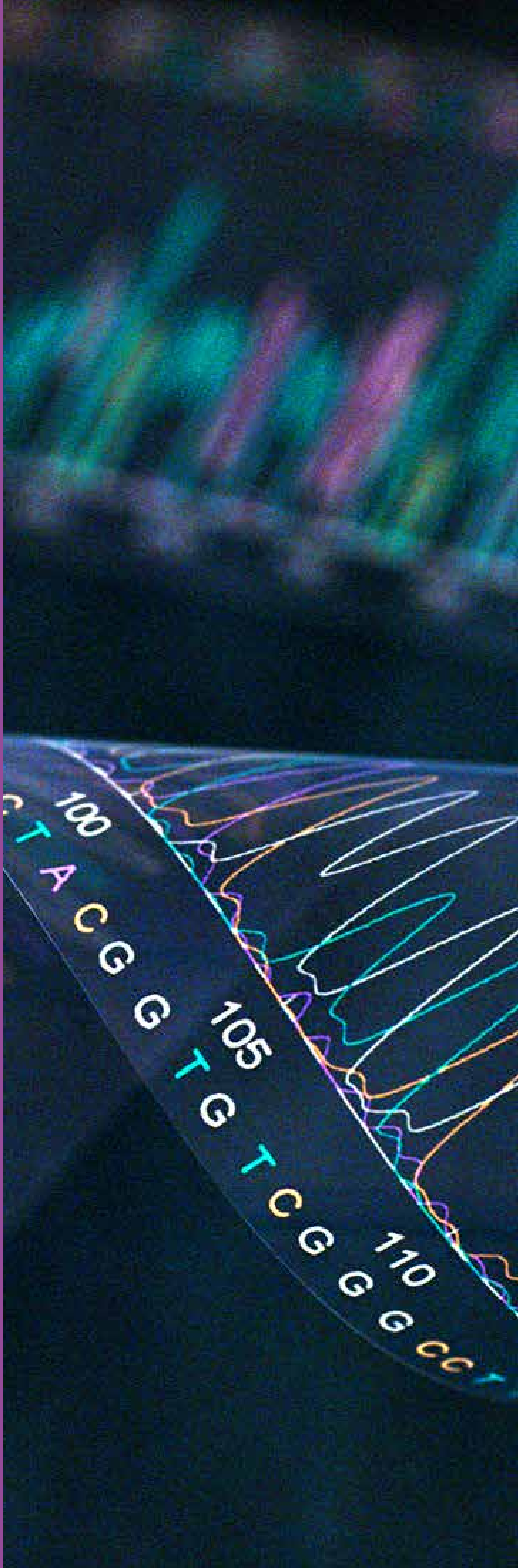
Sir Alexander Fleming sits next to a collection of test-tubes and dishes, in his laboratory. Discovered penicillin.

The discoverers of the structure of DNA. James Watson (left) and Francis Crick, with their model of part of a DNA (deoxyribonucleic acid) molecule in 1953.

THE CURRENT HOUR

The 21st century dawned with an extraordinary event that took place on 26 June 2000 at the White House. President Bill Clinton announced:

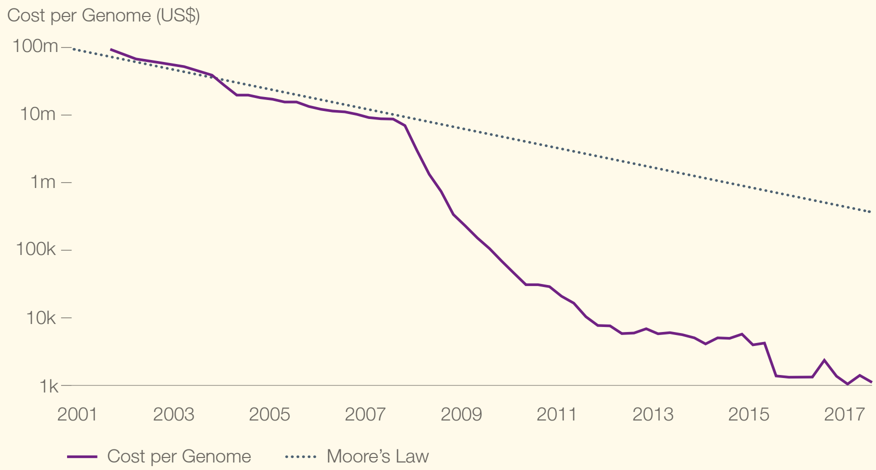
We are here to celebrate the completion of the first survey of the entire human genome. Without a doubt, this is the most important, most wondrous map ever produced by humankind… We have pooled the combined wisdom of biology, chemistry, physics, engineering, mathematics and computer science, tapped the great strengths and insights of the public and private sectors. More than 1,000 researchers across six nations have revealed nearly all 3 billion letters of our miraculous genetic code… [genome science will] revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases.



The sequencing of the human genome was undoubtedly one of the greatest achievements of humankind, all the more impressive when considered in the context of history. Scientists first knew about the existence of DNA in 1869, yet it took 84 years to discover DNA's double-helix structure. Another 42 years passed before we could sequence the genome of a bacterium in 1995. Five years later, we had completed the first draft of the human genome, which is almost 2,000 times larger than the bacterium. The project took more than 10 years and $3 billion to complete. In the early years, the cost of genomic sequencing meant it was too prohibitive to be more than just a scientific curiosity. Then in 2007 a California-based genomics company achieved a breakthrough in gene sequencing. Next generation sequencing has dramatically truncated the time needed to sequence the genome from over a decade to less than a day, and has enabled costs to go down by a factor of 10 almost every year since. Today, genome sequencing costs only $1,000, and the company is working hard to reduce costs even further to just $100 per genome.

The human genome project achieved another feat that was perhaps equally important as the gene map itself – that was the profound collaboration among scientists across disciplines, countries and sectors as President Clinton alluded to in his speech. This is the foundation for the new era of medicine – the era of Great Convergence – as molecular biology and genomics combined with advances in engineering, information technology, computing, materials, imaging, nanotechnology, and optics will transform life science.

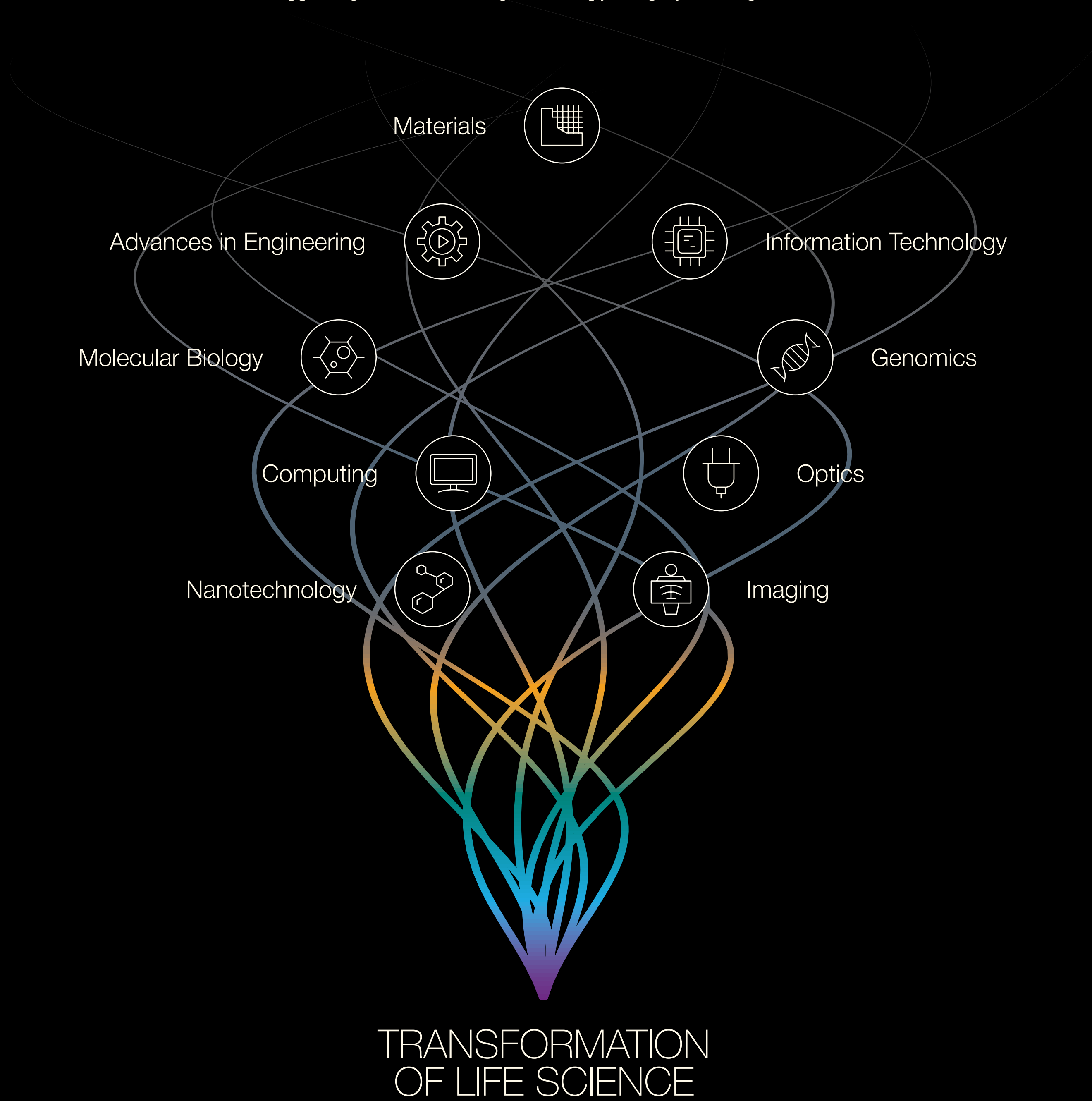
Gene Sequencing Costs



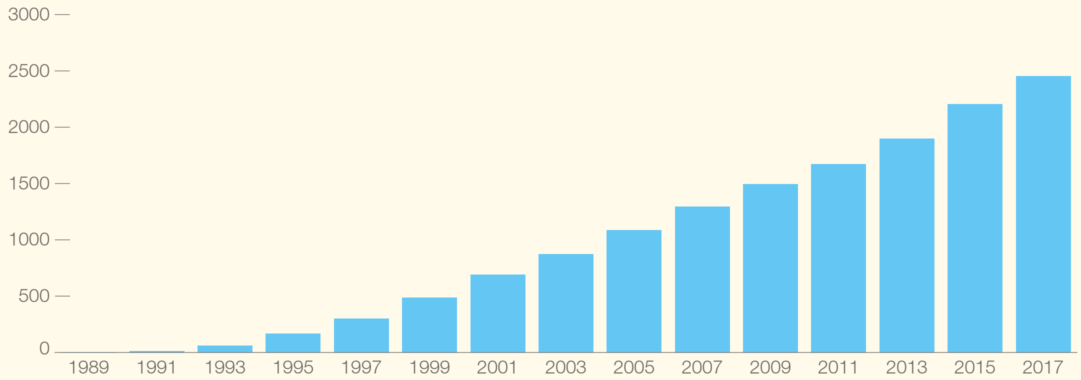
Source: National Human Genome Research Institute.

THE GREAT CONVERGENCE – WHERE TO FROM HERE?

The Great Convergence is likely to transform every aspect of medicine, from treating diseases to preventing illnesses. Some of the greatest developments are happening in the fields of gene therapy, surgery and digital health.



Cumulative Number of Gene Therapy Trials Approved Worldwide



Source: The Journal of Gene Medicine, 2017.

GENE THERAPY

In the 1990s, the idea of interfering with human genetics to treat a disease at its source seemed unimaginable. To date, almost 2,600 gene therapy clinical trials have been completed or are ongoing in almost 40 countries. In particular, over the past five years, more than 750 gene therapy trials have been initiated globally. The field achieved a significant milestone in 2017 when the US FDA approved three groundbreaking gene therapies for blood cancer and hereditary vision loss: Kymriah, Yescarta, and Luxturna. The results are striking. A large proportion of patients in the trials have seen a complete remission of cancer or a significant improvement in vision. The capacity for gene therapy to cure many genetic diseases is now an established reality.

A terrific example of how technological convergence can generate medical breakthroughs is RNA interference (RNAi). RNAi is a natural biological process that turns off genes to prevent damage to our body when genes go awry. It does so by destroying the messenger RNA, which carries the DNA instructions for protein making, without changing the core DNA code. For the past 15 years, we have struggled to turn RNAi into a treatment option mostly due to the delivery mechanism. We need to deliver short-interfering RNA (siRNA) strands into the cells to destroy the messenger RNA, but they are easily broken down by enzymes in the blood and cannot pass the cell membranes to get inside the cells. This is where nanotechnology comes in. Nanoparticles made of materials such as lipid or polymer can be engineered to act like smart bomb shells that protect and transport siRNA strands to the destination and only then release them. One innovative US biotech company is using lipid nanoparticles as a delivery vehicle for its RNAi drug Patisiran for the treatment of hereditary ATTR amyloidosis – a genetic disease stemming from the liver that can affect other organs and tissues including the legs, heart, eye, kidney and thyroid. Patisiran is considered a breakthrough therapy – a designation that expedited its review by the US FDA and led to the drug being approved in August 2018.

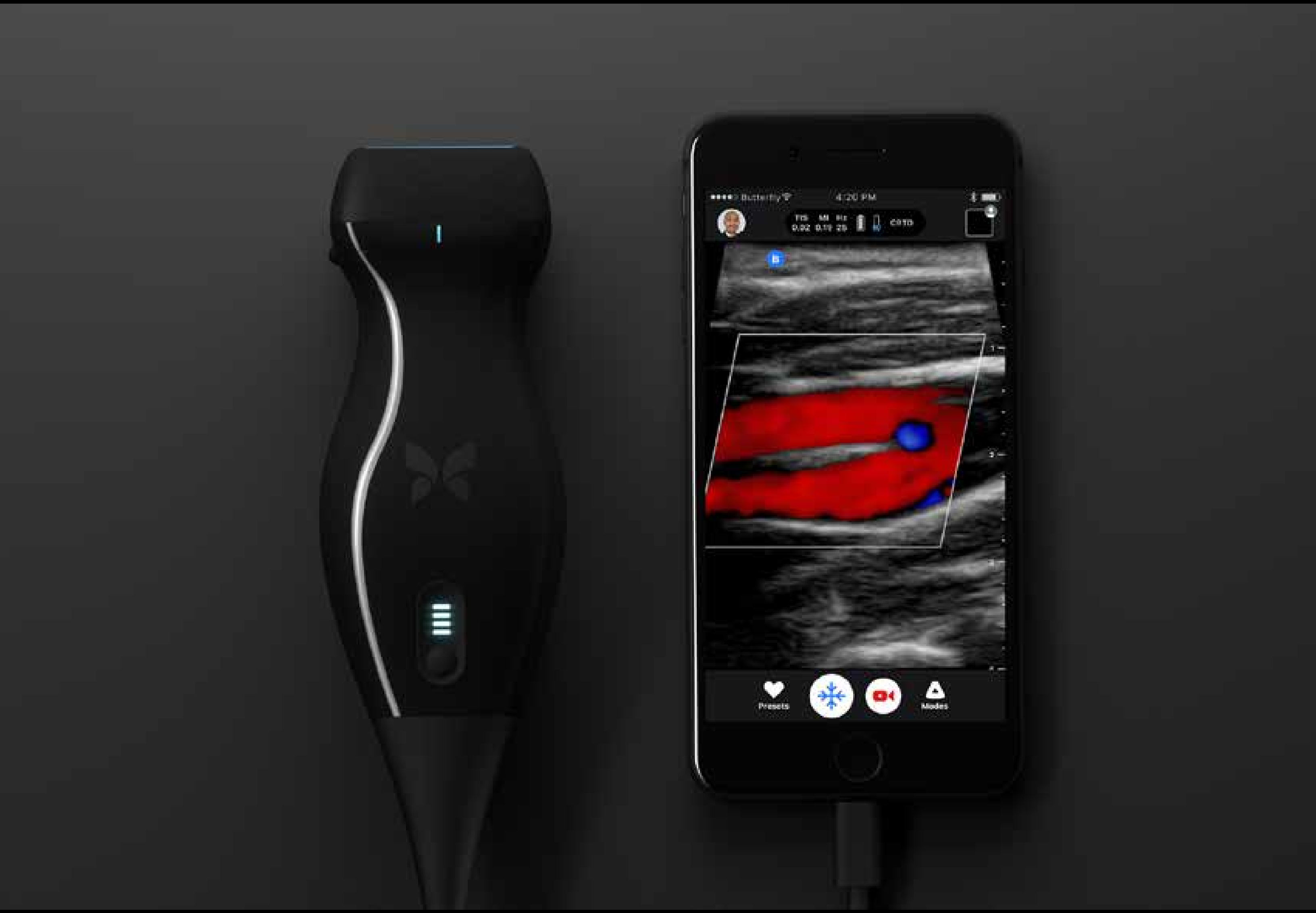
SURGERY

Advances in imaging, biomaterials, robotics, virtual reality, augmented reality and 3D printing have transformed modern surgery. Nowadays, surgeons can take detailed images of the patient's heart, for example, print a 3D model of it to study, plan the procedure using computer-assisted software, and practice the surgery beforehand through a virtual reality simulation. Surgeries have also become increasingly less invasive, less complex and less expensive.

Take aortic stenosis as an example. It is a serious disease in which the aortic valve of the heart becomes narrow due to calcium build-up, which restricts blood flow to the body. Fifty per cent of patients will die within two years of showing symptoms such as breathlessness, fatigue or chest pain. Until recently, open heart surgery was the only option for replacing the valve. This requires cutting open the breastbone, stopping the heart and putting the patient on an artificial heart machine. The surgery can take two to four hours, after which a complete recovery will take at least four to six weeks. However, a new minimally invasive procedure called TAVR (transcatheter aortic valve replacement) is transforming heart surgery. All the procedure requires is a small cut in the thigh to insert a tiny catheter into the femoral artery, from where it goes all the way up to the heart and puts a new valve in the place of the old valve. The whole procedure takes less than an hour, with the heart beating throughout. In some advanced clinical sites, the patient can even stay conscious the whole time, begin walking within a few hours, and return home the next day. Such results would be unimaginable ten years ago.

To some people, the idea of a robotic surgeon may sound like science fiction, but robot-assisted surgery is already being performed with the da Vinci system. To date, da Vinci has performed 5 million procedures worldwide, which benefits patients in terms of a lower chance of infection, less pain, reduced blood loss and quicker recovery. However, the da Vinci is still quite big and bulky. What if we could minimise it to the point that we could put it inside the patient's body? In his 1959 provocative talk, the Nobel Prize-winning physicist Richard Feynman suggested that one day we could "swallow the surgeon". "You put the mechanical surgeon inside the blood vessel and it goes into the heart and looks around", Feynman said. "It finds out which valve is the faulty one and takes a little knife and slices it out". Surreal as this sounds, it might one day become reality. At Drexel University, a research team is developing nanorobots – groups of tiny nanoparticles – that can be guided by MRI to march through our bloodstream and break up clogged blood arteries. TAVR itself might be obsolete one day. The future of surgery might be completely non-invasive.

An operating theatre using the da Vinci robot.



The integration of digital technologies into healthcare will give us plenty of new tools to monitor our health, empowering us to be proactive in preventing diseases or in seeking early treatment.

DIGITAL HEALTH

The digital revolution began in the mid-20th century and mushroomed in the early 2000s, transforming many aspects of our life – from reading, communication, entertainment and so on, but until lately has had little impact on how we take care of our health. The integration of digital technologies into healthcare will give us plenty of new tools to monitor our health, empowering us to be proactive in preventing diseases or in seeking early treatment.

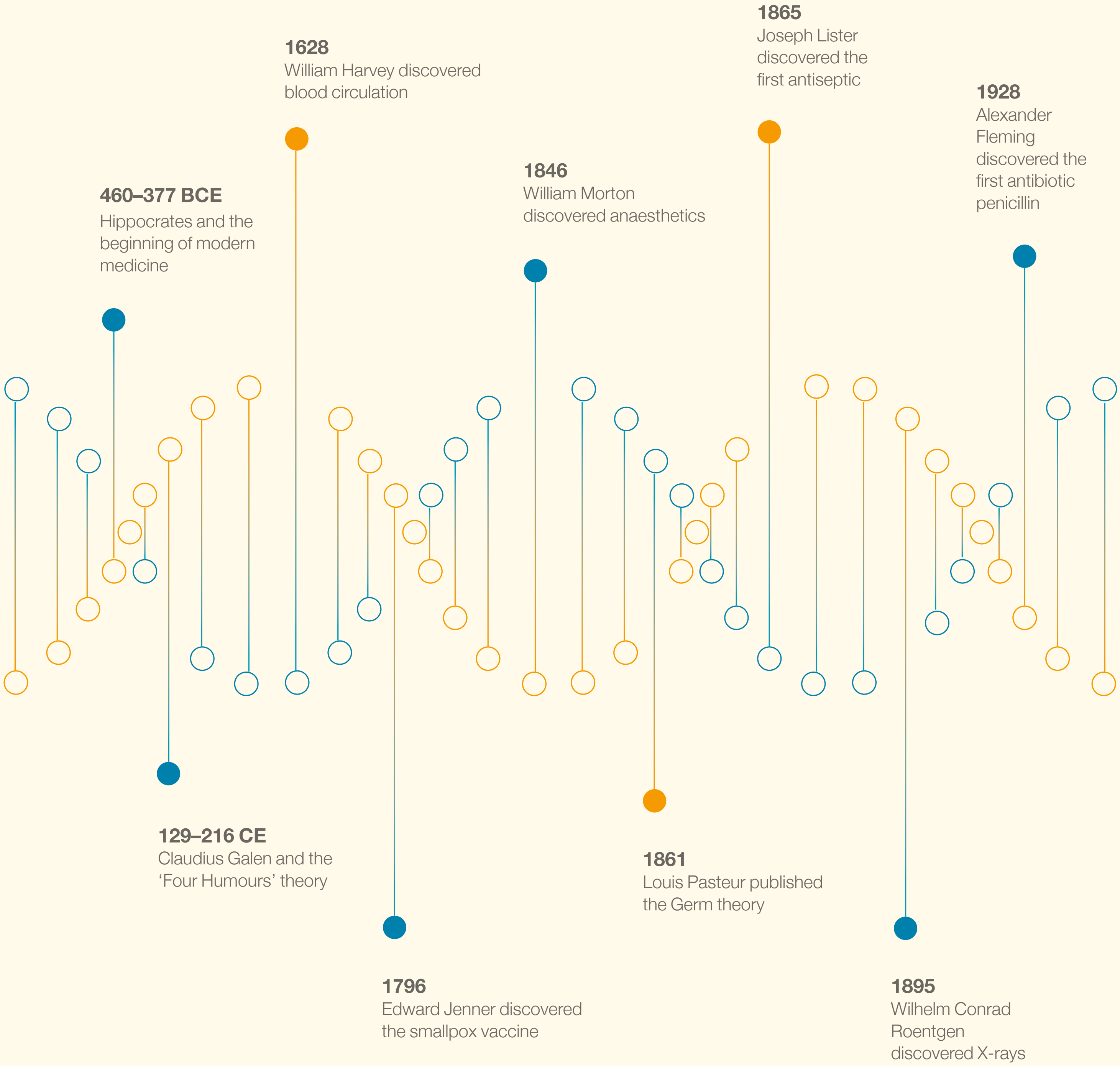
There has been a lot of innovation recently in terms of helping chronically-ill patients to manage their conditions better. An example is the continuous glucose monitoring system developed in the US for diabetic patients. However, monitoring is not just for the sick. To prevent diseases, we need to take pre-emptive measures. New affordable, medical-grade, pocket-sized devices, developed by private companies in the US, now allow us to measure heart rhythms anytime, anywhere. You simply place your fingers on the device and the electrocardiogram (ECG) reading is displayed directly on a smartphone app, alerting you to whether the reading is normal or not. Detecting abnormal heart rhythms early will thus help to prevent stroke or heart failure in the future. These devices are impressive, but you know what's even more striking? The latest smartwatches now include ECG sensors. If Willem Einthoven, the inventor of the first ECG machine in 1903, had lived until this day, he would surely be stunned by the lightning speed of innovation.

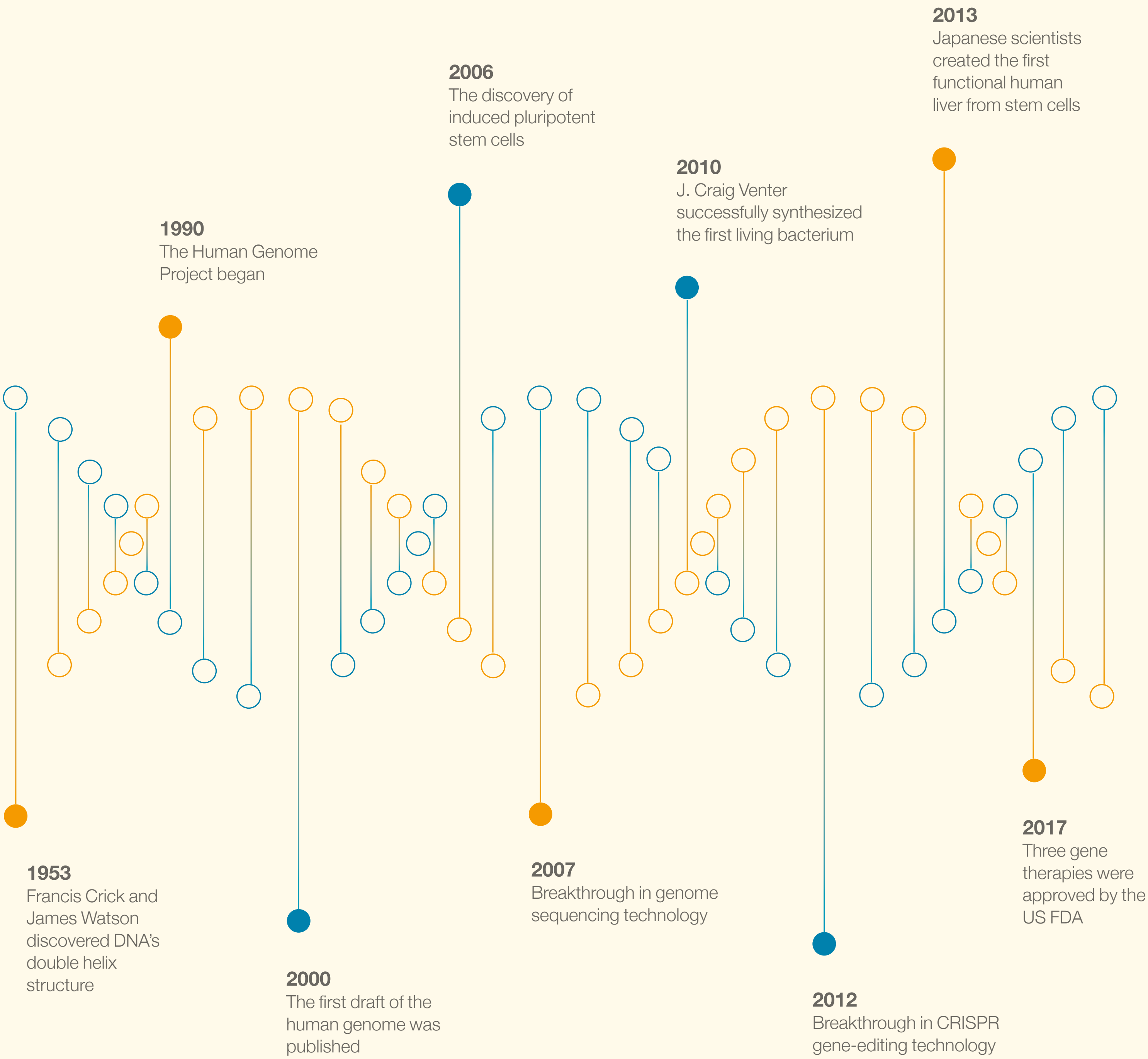
Another private US company manufactures an ultrasound-on-a-chip device, which is of similar quality to a professional ultrasound machine but at a fraction of the cost. The scanner connects to your smartphone and the AI software guides you to capture and interpret images of your body. The device currently costs under $2,000. It is mostly used by healthcare professionals, however, as prices fall and the software improves, it will ultimately end up in the hands of consumers. If you think this is too ambitious, then consider the case of the defibrillator, a device that gives an electric shock to someone in cardiac arrest. Used incorrectly, it can kill. But nowadays you come across defibrillators in many private and public places and these can be used by anyone without medical knowledge in an emergency.

A US start-up founded by the biologist Leroy Hood who helped develop the first DNA gene sequencer, is taking health monitoring and disease prevention to the next level. Hood's company offers a unique personalised wellness programme, based on your genetic profile and ongoing health conditions. The company is able to take a deep dive into your genetic makeup and other biomarkers based on a small blood sample that you send them. Using data analysis, its software program will evaluate your health conditions and calculate your predisposition to certain diseases. The company will then connect you with one of its trained healthcare professionals to create a plan of action and provide you with coaching sessions and ongoing support. The coaching could cover anything, from diet, to exercise, to mental health. This is personalised care right at the fingertips of the consumer. The whole programme currently costs $199 per month, which includes free blood testing, unlimited coaching, and new blood drawn every six months to update the data. As the company gets bigger and costs of testing decline further, we could expect the subscription cost to potentially drop to a level that might be on par with a gym membership. A holistic solution like this is perhaps the way forward to sustainably counteract the pandemic diseases of the 21st century such as diabetes, heart failure and cancer.

A low-cost, handheld scanner that generates clinical-quality ultrasounds on a smartphone. Ultrasounds are uploaded to the cloud, where any expert with permission can give second opinions or help analyse images.
© Butterfly Network.

A TIMELINE OF MEDICINE




1953
Francis Crick and James Watson discovered DNA's double helix structure
1990
The Human Genome Project began
2000
The first draft of the human genome was published
2006
The discovery of induced pluripotent stem cells
2007
Breakthrough in genome sequencing technology
2010
J. Craig Venter successfully synthesized the first living bacterium
2012
Breakthrough in CRISPR gene-editing technology
2013
Japanese scientists created the first functional human liver from stem cells
2017
Three gene therapies were approved by the US FDA

CONCLUSION

Hippocrates is said to have told physicians to "cure sometimes, treat often, comfort always". These six little words remind us that medicine is not only about treating the physical body, but also about understanding and caring for patients. On reading of the advances taking places across all fields of medicine and healthcare, it might seem that the future of healthcare will be so high tech and fast moving as to be cold and inhumane, but this is unlikely to be the case. Far from it. In this era of Great Convergence, the greater input from technology and science will actually make medicine more humane, as physicians will spend less time doing mundane tasks and will have more time to monitor and care for their patients in a meaningful way. Likewise, personalised medicine will mean that for the first time we can truly mould healthcare around an individual's needs, taking into account their unique living circumstances, values and beliefs. Leroy Hood's model, customised from individuals' biological data and their existing or potential healthcare needs, and delivered with ongoing professional support, may give a clue as to how tomorrow's standard of care will look. Building on the remarkable progress that we have made to date, we can be optimistic that the future of medicine – with a blend of sciences and technologies – will allow humans to effect cures, prevent diseases and live healthily in ways we could only previously have dreamed of.

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