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Decades of discovery science set to revolutionise healthcare

A case study of the impact of discovery science on public health and wellbeing

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The development of successful innovations that transform healthcare often rely on the knowledge derived from decades of discovery science and the substantial investment and research expertise of industry to bring products to market. Curiosity-driven discovery science provides the fertile ground upon which novel technologies for improving human health are developed; historical examples include the development of MRI for imaging, or radiotherapy for treating cancer. Similarly, the foundations of nanopore sequencing – a novel technology with applications in healthcare -- were established via decades of interdisciplinary discovery science and now have been successfully translated into practice through industry R&D. The commercial sequencing device that has been launched literally brings the power of modern genomics to the palm of your hand.

This report presents a case study showcasing the impact of discovery science on public health and well-being using nanopore sequencing as an example.

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Section 1: Introduction

The development of nanopore sequencing is a world-leading example of how discovery science funded by the MRC and others was successfully translated through industry R&D into a novel technology poised to deliver widespread societal impact. This technology enables hospitals, GP surgeries, or rural clinics to offer genetic sequencing 'by the bedside'. Nanopore sequencing represents a paradigm shift in genomics and biotechnology.

The applications of nanopore sequencing are vast and ever-increasing.

What is nanopore sequencing?

Nanopore sequencing is a 'next generation' DNA sequencing technique that uses a doughnut shaped protein whose hole is just a millionth of a meter wide – a nanopore.

These tiny pore proteins are embedded in cell membranes, perforating it; nanopore sequencing detects the molecules that go through its inside channel. When the pore is open, ions can flow freely through it, creating a tiny but measurable current. But if something blocks the pore – for example a strand of DNA - that current collapses. The four bases of DNA - A, C, G, and T- each change the current through the pore in unique ways. So, as a DNA strand threads its way through the pore, the rising and falling current reveals its sequence.

Over the recent years, advances in technology have allowed many more diagnostic tests to be carried out at the patient's bedside rather than the laboratory bench. Known as point-of-care testing, these technologies confer obvious advantages to both the patient and healthcare professionals; quicker results mean faster treatment, and less cost to the health service.

Until recently, routine point-of-care testing has been limited to biochemical tests such as the measurement of glucose or blood cell counts. But within the last decade, point of care diagnostic development has been expanding into the fields of infectious diseases and personalised medicine. The MinION sequencer, developed by Oxford Nanopore Technologies, is a tiny pocket-sized DNA sequencer that performs nanopore-based sequencing in just a few hours. Launched in 2005, Oxford Nanopore Technologies was valued at £1.5 billion in May 2018 thanks to investment and expansion into the Asia Pacific region.

Section 2: Enabling discoveries and advancements

Nanopore sequencing would not be possible were it not for a multitude of discoveries and advancements that developed the fields of genetics, genomics, and molecular biology over the past several decades. These advancements funded through the MRC, other research councils, and academic research funders around the world, together with significant private sector R&D investment, have made nanopore sequencing a reality.

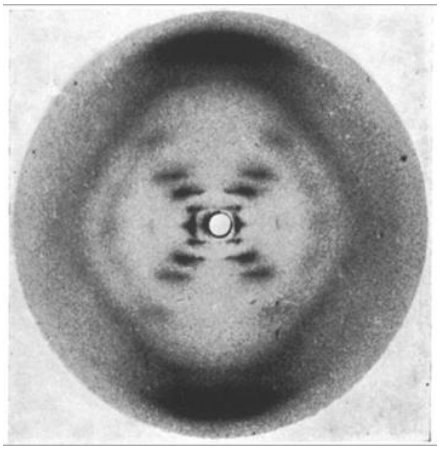
These key milestones include;

X ray crystallography and discovering the structure of DNA

MRC-funded researchers identified the potential applications of **X ray crystallography** in the developing field of structural biology. Early strategic investment by the MRC led to the setting up of two new research units in London and Cambridge to study the structure of biological molecules. Scientists at these research units discovered the structure of DNA and were awarded the Nobel Prize in 1962.

One of the key techniques that was essential for revealing the structure of DNA was known as ‘X ray crystallography’. By passing a beam of X rays through a crystal, scientists can analyse the resulting diffraction pattern to work out what the structure of that crystal is. It’s like shining a torch at a hidden chandelier, and then working out its shape from the pattern of spots it makes on the wall.

Realising the potential applications of X ray crystallography, in 1946 we set up a new Biophysics Research Unit at Kings College London. A year later, in 1947 we also set up a Unit for Research on the Molecular Structure of Biological Systems in Cambridge (later renamed as the MRC Laboratory of Molecular Biology) to enable the study of proteins using X-ray diffraction to study proteins.



This early strategic investment into the newly developing field of structural biology paid off within a few years; scientists **Dr James Watson** and **Professor Francis Crick** were recruited to the MRC Molecular Structure of Biological Systems Unit while **Professor Maurice Wilkins** and **Dr Rosalind Franklin** began work at the MRC Biophysics Research Unit. Together, the work of these four scientists showed how four chemical letters A, T, C and G interact in three dimensions to form a long spiralling molecule with a double ‘backbone’ made up of sugar and phosphate blocks. Nitrogen-containing compounds, called bases, protrude from the two halves of the backbone and link together in pairs, so the whole molecule is like a zip.

The insights and new technologies spawned from the now famous double helix structure of DNA fundamentally changed the landscape of cellular biology and heralded the golden age

of molecular biology. The double helix has even become pervasive in art and design, a testament to its assimilation into the public consciousness.

Single ion channel recordings

In 1970, two scientists at the University of Cambridge **Dr Steve Hladky** and Professor **Denis Haydon** recorded the current flow through a single ion channel in an artificial membrane. In 1976, two German cell physiologists **Professor Erwin Neher** and **Dr Bert Sakmann** developed a technique, called patch-clamp, to record the incredibly small electrical current (amounting to a picoampere - 10-12A) that passes through a single ion channel on a biological cell membrane. The ability to measure this current flow and quantify it was instrumental for enabling the development of nanopore sequencing over three decades later.

Each living cell is surrounded by a membrane and embedded into this membrane are protein channels through which the cell interacts with its external environment. Some of these channels can open and close to selectively allow the passage of molecules which are made up of charged atoms, or ions. Some membrane proteins - like α-hemolysin used in nanopore sequencing - are open all the time, allowing a continuous flow of ions through the pore. The flow of ions through a membrane pore can be read as a current flow, much like how an electric current through a wire is a flow of electric charge. These discoveries and techniques revolutionised molecular biology and electrophysiology, and decades later, aided the development of a single-molecule detection technology known as stochastic sensing, which was instrumental for the development of nanopore sequencing.

The first quantitative description of a current through a cell membrane channel was reported in 1970 by Dr Hladky and Professor Haydon. They reconstituted a bacterial ion channel into an artificial membrane and measured the current produced when the channel spontaneously opened. Six years later in 1976, Professor Neher and Dr Sakmann developed a technique known as the patch-clamp and successfully recorded the current flowing through a single channel in a biological membrane, and were awarded the 1991 Nobel Prize for Physiology.

Development of DNA sequencing

In 1975 **Dr Fred Sanger** and colleagues at the MRC Laboratory of Molecular Biology developed a new method for rapid sequencing of DNA. Using this method, the team sequenced a bacteriophage virus, which was the first fully sequenced DNA based genome. In 1977 the team developed an improved method known as the ‘Sanger method’ which won a Nobel Prize in 1980. The Sanger method for DNA sequencing was instrumental to the successful progress of the Human Genome Project.

Although the structure of DNA was revealed by Dr James Watson and Professor Francis Crick in the early 1950s, sequencing DNA molecules (i.e. determining the order of the four chemical letters A, T, C and G within the long spiralling molecule of DNA) was not yet a reality by the early 1970s. This was because DNA molecules are extremely long, and

researchers had not yet found an enzyme capable of cleaving the DNA into smaller, more manageable pieces.

In 1962 Dr Sanger joined the MRC Laboratory of Molecular Biology as the Head of the Protein and Nucleic Acid Chemistry Division and soon turned his attention to the problem of sequencing nucleic acids such as DNA. In 1977, Dr Sanger and his team introduced an improved method for sequencing DNA, known as the ‘dideoxy chain termination method’ or the ‘Sanger method’. The importance of this work was recognised a short time later in 1980, when he was awarded the Nobel Prize in Chemistry. The Sanger method would go on to shape the fledgling field of genomics, and was instrumental to the Human Genome Project, the international collaboration to identify all the approximately 20,000-25,000 genes in human DNA.

Protein engineering

Protein engineering has been applied to enzymes and antibodies for applications in biotechnology, and notably for membrane proteins in the development of nanopore sequencing. This important enabling technology was developed in the late 1970s by **Dr Michael Smith** at the University of British Columbia in Canada. Together with collaborator **Professor Clyde Hutchison**, the team developed a technique known as site-directed mutagenesis. Site-directed mutagenesis allows scientists to re-programme the genetic code by replacing specific amino acids, and thus construct proteins with desirable properties for applications in biotechnology.

The ‘central dogma of molecular biology’, as postulated by Professor Francis Crick in 1957 outlined how genetic information flows from DNA to proteins. This genetic code - programmed into the DNA molecule - determines the number and sequence of amino acids in a protein, and therefore the functional properties of that protein. By reprogramming the code of a DNA molecule, for example changing the word CAC to GAC, it would be possible to obtain a protein in which the amino acid histidine is replaced by the amino acid aspartic acid. In doing so, the shape and structure of the entire protein molecule can potentially be affected, because histidine carries a positive charge while aspartic acid is negatively charged. This can in turn result in the construction of a protein with desirable properties such as solubility or membrane binding.

In 1975, Dr Smith undertook a sabbatical year at the MRC Laboratory of Molecular Biology (MRC LMB) in Dr Fred Sanger’s lab. Sabbaticals allow scientists the opportunity to work in intellectually stimulating new environments while developing new techniques and collaborations. The MRC LMB was considered one of the leading institutions in the rapidly developing field of molecular biology, and the free-flow of ideas and people was characteristic of the time. The sabbatical at the MRC LMB provided Dr Smith with the background and inspiration that led him to the recognise that changing a single base in a gene could lead to a protein substituted amino acid. In 1978, in collaboration with another former Sanger lab sabbatical colleague Professor Hutchison, he introduced a new technique known as "site-directed mutagenesis" into molecular biology.

Over 20 years later, Professor Hagan Bayley used site directed mutagenesis techniques to modify membrane proteins for the application of nanopore sequencing. Site-directed mutagenesis presented an invaluable opportunity to manipulate the fundamental building blocks of DNA and proteins, and in recognition of this contribution, Dr Smith was awarded the 1993 Nobel Prize for chemistry.

Development of nanopore sequencing

The development of a commercial nanopore sequencing device can be traced to discovery science in the 1980s, particularly **Professor Hagan Bayley**'s work, when the movement of nucleic acids such DNA through pore proteins (a protein embedded in the cell membrane) was first observed. At that time nanopore sequencing was not on the research agenda. However, a series of enabling technologies led to the founding of the spin-out company Oxford Nanopore Technologies in 2005 and, nine years later thanks to extensive in-house R&D, its first product, the MinION sequencer.

The story of nanopore sequencing, starts in the early 1980s with work on the structure of a doughnut shaped protein called α-hemolysin in *Staphylococcus aureus* bacteria. *S. aureus* is a common bacterium responsible for causing a wide range of infections by destroying red blood cells via the α-hemolysin protein; α-hemolysin forms a pore on the red blood cell's membrane and perforates it, causing it to leak its contents. At the time when Professor Hagan Bayley and his team were studying the structure of α-hemolysin, the possibility of nanopore sequencing was not on their agenda. However, by the late 1980s thanks to nearly 40 years of DNA research and the development of techniques such as single ion channel recording, it was clear that an artificial membrane with embedded α-hemolysin nanopores could be used for sequencing DNA.

As the team of scientists observed these membranes containing pore proteins, they noticed that it was possible to measure and identify the molecules that pass through the nanopore. All cells have a membrane that separates the interior of the cell from the external environment. Given that many biological molecules carry small electrical charges, there is a difference in electrical potential between the inside and the outside of the cell. This membrane potential can be used by pore proteins that span the cell membrane to allow the flow of charged molecules from one side to the other. In the case of the α-hemolysin pore, it allows a steady measurable ionic current through its inside channel. Because DNA is a charged molecule, it is drawn through this open channel due to the difference in membrane potential. The entry of the DNA molecule into the pore gives rise to temporary, measurable variations in the current that are characteristic of the molecule passing through; these can be measured and used to identify the molecules involved.

In 2003 Professor Bayley moved to the UK and joined the Department of Chemistry at the University of Oxford. Supported by funding from the MRC, BBSRC and EPSRC, his work on nanopore technology continued to thrive alongside a rapidly expanding research team. Building on techniques and discoveries made by fellow scientists, his research led to many breakthrough developments, particularly in techniques that allowed the 'sensing' of individual molecules passing through a pore. In 2005, a spin-out company was formed to support and further translate this research into applications in sequencing.

Ratchetting DNA molecules

Early experiments during the development of nanopore sequencing showed that a single DNA molecule moved too fast through the membrane pore for accurate measurements of its DNA sequence. An inspired modification using an enzyme to slow down the DNA molecule as it moved through the membrane pore helped address this problem. Ratchetting a DNA molecule base by base in this manner through the membrane pore was crucial for subsequently developing nanopore sequencing devices.

In 1996 scientists showed that a single DNA molecule could move through a protein nanopore embedded within a biological membrane. However, the DNA molecule moved through the protein nanopore extremely fast; in the range of 1-10 microseconds per DNA base. This speed was too fast to accurately and reliably identify the sequence of the bases forming the DNA molecule as it moved through the pore; it was like trying to identify the passengers on a high-speed train by standing near the entrance of a tunnel as the train rushed past. In 2008, **Professor Mohammed Reza Ghadiri's** team at the Scripps Research Institute in the US, in collaboration with Professor Hagan Bayley, solved this problem by using an enzyme called DNA polymerase to slow down the DNA molecule as it passed through the protein nanopore. In 2010 this method was improved by scientists at University of California Santa Cruz, and the ratcheting approach was then further refined by in-house scientists at Oxford Nanopore Technologies. The DNA molecule now moved through the protein pore at a much slower speed of around 2 milliseconds, a single base at a time. The single-base resolution of this approach and the ability to control the passage of DNA in single-base steps had laid the foundation for nanopore sequencing, but many technical challenges remained to deliver a device that could routinely be used in the laboratory or in the field.

Genome sequencing projects

The ability to sequence the entire repertoire of genetic material within an organism thanks to Dr Fred Sanger's breakthrough heralded the age of the genome. It led to numerous genome sequencing projects of various organisms relevant to human health, ranging from the humble nematode worm to the human genome. These projects provided invaluable insights into the fundamental nature of life and led to a new understanding of diseases such as heart disease, diabetes, and cancer.

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- In 1998, US and UK researchers including **Dr Sydney Brenner** and **Sir John Sulston** finished sequencing the genome of a tiny transparent nematode worm called *Caenorhabditis elegans.* The *C. elegans* genome project was the first complete genome of a multicellular organism.

- In 2001 an international team of scientists including researchers funded by the MRC and the Wellcome Trust published an initial draft sequence of the human genome.

The cost of sequencing genomes has fallen dramatically, while the speed and accuracy of the next generation of sequencing technologies has increased.

Section 3: Applications of combined discovery science knowledge in healthcare

An inexpensive handheld sequencing device confers obvious advantages when considering the expanding potential applications for nanopore sequencing. Indeed, as illustrated by the examples described below, nanopore sequencing is set to impact healthcare thanks to the exciting possibility of routine point-of-care gene sequencing in a variety of settings.

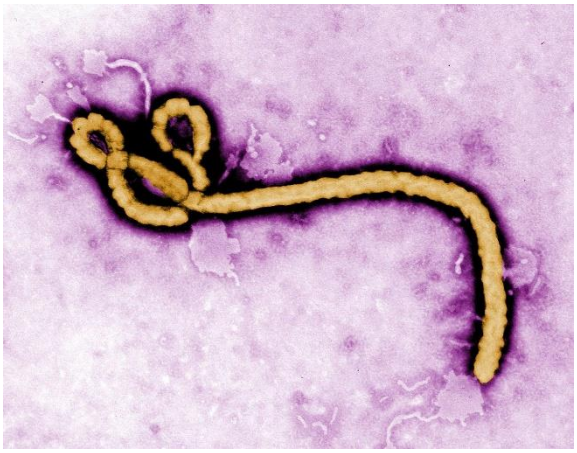
The MinION DNA sequencer is tiny, portable and relatively cheap thanks to being the size and weight of a chocolate bar, powered by a laptop USB cable, and costing $1,000. For comparison, a DNA sequencing machine produced by a rival company using different technology, is the size of a washing machine and costs about $750,000. The MinION DNA sequencer quite literally brings the power of modern genomics to the palm of your hand; it's small size and low cost means that it can be used in a variety of settings, ranging from small clinics to the field.

A study published in 2016 assessed the MinION's sequencing performance against two machines currently available on the market and reported good agreement on accuracy across all three technologies. The MinION platform is constantly improving through a multi-million pound industry R&D programme and field-testing by academic researchers; sequencing data, software improvements and sample preparation protocols are being shared on the internet between researchers, forming a 'nanopore sequencing community'.

Tracking Ebola

In 2013 an outbreak of Ebola virus spread through West Africa causing tragic loss of life and economic disruption. The first cases were recorded in Guinea in December 2013; later, the disease spread to neighbouring Liberia and Sierra Leone, with minor outbreaks occurring elsewhere. Viral genome sequencing can play an important role in characterising the virus and monitoring its response to vaccines and treatment. A team of researchers, part-funded by the MRC, deployed handheld nanopore sequencers in the affected areas as part of a pilot genomic surveillance system. The project demonstrated that real-time genomic surveillance can thus be used to guide control measures in resource-limited settings

The West African Ebola virus outbreak in 2013 was the largest on record, responsible for nearly 30,000 infections and almost 12,000 deaths. Because the Ebola virus has a rapid but constant mutation rate, during a prolonged epidemic it is possible to identify distinct sub-



lineages of the virus. By sequencing Ebola genomes from newly diagnosed patients, the team could chart the source of new infections. If two people had identical strains of the virus, it was likely that they infected each other or at least they are nearby links on the same transmission chain. By attributing fresh diagnoses to existing clusters of the disease, the team could help local health workers identify the routes through which the virus was spreading and develop effective strategies for stopping it.

However, staying one step ahead of the Ebola virus meant that speed was of the essence. Until then, sequencing Ebola genomes required a laborious process of sending clinical samples to specialist labs with expensive sequencing equipment that took weeks or even months to produce results. In contrast, the handheld sequencers used by the team helped them produce results less than 24 hours after receiving an Ebola-positive sample, with the sequencing process taking as little as 15-60 minutes.

Real-time genomic surveillance is an invaluable new tool in our arsenal as we battle global disease outbreaks such as Ebola virus. Swift and accurate genomic information helps improve resource allocation and the timeliness of epidemiological investigations. Rapid sequencing of viral genomes also helps identify previously unknown routes of transmission, for example through food vendors or frequent travellers across borders. The design of a genomic surveillance system using portable nanopore sequencers for infectious diseases can be easily adapted for other pathogens, and indeed the 2013 Ebola virus outbreak helped develop a blueprint for deploying the MinION sequencers for the 2016 Zika virus outbreak.

Zika surveillance

In 2016 the World Health Organisation declared the Zika virus, linked to brain damage in thousands of babies in South America, an international public health emergency. At the time, knowledge of the virus's spread and genomic epidemiology was limited due to challenges in obtaining and processing patient samples for genome sequencing. A UK-Brazil collaboration, part-funded by the MRC Zika Rapid Response Initiative, used the MinION sequencer to successfully sequence the Zika virus directly from clinical samples. The project demonstrates how portable nanopore sequencing can address emerging global epidemics through mobile real-time surveillance of the virus.

In early 2015, a widespread epidemic of Zika fever in Brazil spread to other parts of South and North America. In January 2016, the World Health Organization (WHO) said the virus was likely to spread throughout most of the Americas by the end of the year. Because Zika virus infection during pregnancy was linked to birth defects including brain damage in thousands of babies, addressing the Zika epidemic became a global priority.

Viral genomic sequencing is an important tool for tackling emerging epidemics, and sampling the viral genome allows researchers to quantify the genetic diversity of the virus, reconstruct its origins, estimate rates of transmission while providing background information for vaccine development and drug design. However, until July 2016 only 23 Zika virus genome sequences from Brazil were publicly available, despite over 190,000 suspected Zika cases being reported to the Brazilian Ministry of Health since 2015. This lack of Zika virus genome sequences resulted in an extremely fragmented picture of the diversity of Zika virus circulating within Brazil, and made it difficult for researchers to develop a vaccine or design new drugs for preventing or treating the infection.

A UK-Brazil collaboration, part funded by the MRC Zika Rapid Response Initiative successfully piloted the portable DNA sequencer in the field to directly sequence Zika virus from clinical samples. Previous work in 2013 by Professor Nick Loman and his team in monitoring the spread of the Ebola virus outbreak in West Africa was particularly useful for designing a genomic surveillance system for Zika virus in South America. During the project the researchers trained Brazilian fieldworkers to perform sequencing using the nanopore platform and sequenced over a thousand clinical samples. As part of the Zika Rapid Response Initiative's commitment to open science practices, both the protocol and materials used are freely available through the ZiBRA project website. These results provided a framework for reconstructing the trajectory of the Zika virus spread through the Americas and helped track its spread into other geographic regions. The handheld sequencer is ideally suited for developing a surveillance network capable of detecting and characterising viral spread in real-time during a public health emergency.

Bedside test for tuberculosis

Tuberculosis is one of the top ten causes of death worldwide. Scientists from the University of Oxford are developing a technique to gather diagnostic and surveillance data for tuberculosis via whole genome sequencing (WGS) of sputum samples. The team are testing a bedside-test that uses nanopore sequencing technology to determine the presence of Mycobacterium tuberculosis in a clinical sample in less than 24 hours. In 2017 the team won seed funding from the Longitude Prize Discovery Award for this diagnostic approach using the nanopore sequencer.

In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease (including 400,000 among people with HIV) in the world. Over 95% of TB deaths occur in low- and middle-income countries. Although antibiotics to treat TB have been available since the 1950s, the drugs must be taken in complicated combinations for many months to be effective. First-line TB treatment includes four drugs (rifampin, isoniazid, ethambutol, and pyrazinamide), but with the spread of multidrug-resistant strains, there is a growing need for data on second-line drugs, including the fluoroquinolones and aminoglycosides. Thus,

forecasting whether a strain of TB could be killed by a certain drug, i.e. predicting its drug susceptibility by analysing whether a patient has a drug-resistant strain of TB is very important.

In 2017 a team led by **Dr Zamin Iqbal** at the University of Oxford published the results of their work developing a same-day diagnostic test by sequencing sputum samples from patients with TB using the nanopore sequencer. The test will also predict drug-susceptibility and inform disease surveillance by demonstrating the genomic relationships to previously seen strains. The team won seed funding from the Longitude Prize Discovery Award and are hoping to do a pilot study of their diagnostic in Ho Chi Minh City and Mumbai, two cities with a high level of multi-drug-resistant TB - therefore a large TB burden. The handheld MinION sequencer has already proven that it can get extremely accurate results, and if rapid comprehensive tests become widely available in these vulnerable regions of the world, it could drastically reduce the amount of undiagnosed drug resistant TB.

Currently the gold standard diagnostic method for TB diagnosis is through laboratory culture. However, as the *M. tuberculosis* bacteria grow and divide very slowly, this process can take up to 12 weeks to deliver results. In addition, a considerable proportion of the TB cases reported to WHO are still clinically diagnosed rather than bacteriologically confirmed. In 2016, for example, only 57% of the pulmonary cases reported to WHO were bacteriologically confirmed. All this highlights the urgent need for a rapid, portable, easy-to-use diagnostic method that can be used at the patient's bedside. The diagnostic method should be capable of identifying the presence, strain type, and any drug resistance of *M. tuberculosis* bacteria in patient samples, while also providing information on drug susceptibility and enabling disease surveillance. This is the first step in revolutionising the management of TB so that global eradication can become a reality.

Nanopore sequencing in personalised medicine

The speed, accuracy, and portability of nanopore sequencing is also positioned to transform personalised medicine, for example in the oncology field. Tumour samples can be routinely sequenced to identify key driver mutations and then targeted with treatments that can specifically kill the cancerous cells while leaving the healthy cells unharmed. Monitoring the evolution of cancer, from recurrence to metastasis, also becomes easier with the availability of cheaper, faster genomic sequencing.

In May 2018, researchers at the University of Nottingham and Queen Mary University of London achieved a new milestone in genomics by sequencing a single DNA strand more than two million bases (2 Mb) in length using nanopore sequencing. Other competing genome sequencing technologies have not been able to sequence DNA strands of this length and breaking the 1 Mb barrier is therefore considered a milestone. Sequencing a single DNA strand of more than 2 Mb is akin to running a 6.4-kilometre piece of rope through a fist, at a speed of about 1.5 meters per second. Another useful analogy to understand the vast quantity of data that resides within our genome is, if the genome were represented by the entire human population, then this 1 Mb long read would encompass the entire population of Birmingham and Manchester combined, while a single read from a traditional sequencing platform would correspond to the number of people in a busy train carriage. It's

easy to see why the speed and efficiency of nanopore sequencing distinguishes it from traditional sequencing methods.

Another advantage of nanopore sequencing technology is the ability to sequence epigenetic modifications. Epigenetic modifications are heritable markers that are not due to changes in DNA sequence. Rather, epigenetic modifications involve a chemical “tag” such as a methyl group being attached to bases in the DNA strand which alters the accessibility of the DNA, thereby regulating how and when genes are expressed. Traditional DNA sequencing technologies cannot directly distinguish between methylated and unmethylated bases in a DNA strand without specialised sample preparation. In 2017, scientists showed that nanopore sequencing can detect epigenetic modifications without this specialised preparation. This exciting development opens many research possibilities by allowing both the genome and the epigenome to be analysed from a single sequencing run.