Cite as: Megan Townsend, Illumina: Improving human health by unlocking the power of the genome, Innovation & Impact, 2021
URL: iai.digital/2021/illumina

Illumina: Improving human health by unlocking the power of the genome

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Abstract: Today, Illumina is a global leader in genomics – an industry at the intersection of biology and technology. The initial line of Illumina products enabled researchers to explore DNA at an entirely new scale, helping them create the first map of gene variations associated with health, disease, and drug response. Today, Illumina offers a comprehensive portfolio of leading-edge sequencing and array-based solutions that are empowering scientists to sequence and understand genetic variation and function at an unprecedented scale and, as a result, discoveries that were unimaginable even a few years ago are now becoming routine. Collectively, this will provide a much deeper understanding of genetics than ever before.

Keywords: Genomics, DNA, Sequencing, NGS, Illumina, Solexa, Illumina Accelerator, Precision Medicine

1. The success story

As a global leader in DNA sequencing and array-based technologies, Illumina is applying innovative technologies to the analysis of genetic variation and function, making studies possible that were not even imaginable just a few years ago. Currently, these technologies are empowering ground-breaking advancements in life sciences, oncology, reproductive health, genetic disease, agriculture, microbiology, and other emerging segments, through the power of genomics. The rate of progress is now accelerating exponentially, enabling scientists across the globe to advance disease research, drug development, and the development of molecular tests. As such, Illumina is realising its mission: To improve human health by unlocking the power of the genome.

> *"Genomic analysis tools are now more accessible than ever, and human genomes are being sequenced at an unprecedented scale. The resulting discoveries are now making*

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their way into patient treatment and are poised to trigger a fundamental shift in healthcare to realise the huge potential of personalised medicine for everyone. Illumina continues its global commitment to improve human health by unlocking the power of the genome."

David Bentley, VP & Chief Scientist at Illumina. Formerly Scientific Advisor, then Chief Scientist, Solexa.

Figure 1. Illumina market segments and genomic-driven applications.

2. Where did we start

Twenty-four years ago, during a visit to a local pub, The Panton Arms, four Cambridge University scientists engaged in a creative discussion. Unbeknown to them, at least until the next morning, that discussion was the beginning of a chain reaction that would eventually lead to a new DNA sequencing approach and the birth of Solexa.

The idea was built on Sir Shankar Balasubramanian and Sir David Klenerman's previous work using fluorescently labelled nucleotides to observe, at a single molecule level, the activity of a polymerase enzyme as it synthesised DNA. The contributions of previous Cambridge scientists to the first draft of the human genome, and Cambridge University's rich history of DNA research by Alexander Todd, James Watson, Francis Crick, and Fred Sanger, inspired Balasubramanian and Klenerman to theorise how this approach might be used to sequence DNA. The result was a theoretical approach using massively parallel sequencing of short DNA fragments, previously referred to as sequencing by synthesis (SBS) and now known as Next Generation Sequencing (NGS). Their calculations hypothesised a potential of a 100,000-fold improvement in costs compared to existing DNA sequencing technologies at the time.

In 1998, the small start-up was founded under the name Solexa and in the years that ensued, Solexa received their first funding round of $3 million from the venture capitalist firm, Abingworth; raising a further $20 million shortly after.

At the same time, another breakthrough in genomic technology was happening on the other side of the world. A company was being founded in San Diego by David Walt, Mark Chee and colleagues, with the vision to develop genotyping array technology using fibre optic imaging of fluorescently labelled DNA on microbeads. This vision was built on the basis of pioneering research at Tufts University. This led to the establishment of a global organisation providing technology for DNA genotyping: Illumina. This would prove significant for Solexa in the coming years.

Back in the UK, in 2001, Solexa moved into a basic research facility on Chesterford Research Park, Cambridge. The site, previously a World War 2 ammunition dump, came with its own set of challenges. A regular part of the workday became controlled explosions following the unearthing of a remnant explosive. Coupled with the desultory drifting of pungent smells culminating from residing agrochemical research laboratories; the building did not offer much in the way of increased productivity.

> *"I worked in a windowless office shared by six people, which was so small that one of us had to get up for the person in the corner to get out. Despite the limited facilities, there was a strong spirit of teamwork and innovation."*
>
> Klaus Maisinger, Director of Bioinformatics at Illumina, formerly Research Leader at Solexa

The true value of this site was its proximity to both the Cambridge ecosystem and the Sanger Institute. The Sanger Institute at the time was working on the revolutionary Human Genome Project and several of the scientists working on this project became close scientific advisors to Solexa.

Here, at Chesterford, Solexa set out to embrace all the requirements to make their sequencing hypothesis work; reinventing and substituting every chemical, biological and physical process behind their technology from enzymes to surface chemistry, optics to bioinformatics.

> *"Although we didn't know whether we would ultimately succeed, the multi-disciplinary teams were working towards one single goal and making continuous and rapid progress."*
>
> Klaus Maisinger

Nonetheless, the characteristics of DNA strands became a critical barrier in the ability to inexpensively detect single DNA molecules through fluorescent tagging. Fortunes changed in 2004 following the acquisition of Manteia, a sequencing company specialising in cluster chemistry, which heralded the solution to Solexa's problem. Solexa utilised Manteia's cluster chemistry methods to amplify single DNA strands to form clusters of duplicate copies, providing a much larger signal for the sequencer optics to accurately identify the bases in the DNA. Their sequencing technology rapidly advanced overnight.

The next major breakthrough came on a Sunday afternoon in February 2005. After spending a great deal of time double-checking the results and their statistical significance, the Solexa team

realised that they had sequenced their first ever genome with short reads. The complete genome of bacteriophage phiX-174, the very same genome first sequenced by Fred Sanger.

> *"The sequencing quality and coverage were poor by modern standards but following this breakthrough we rapidly moved on to sequencing larger and larger samples."*
>
> Klaus Maisinger

Solexa acquired a further instrumentation company, Lynx Therapeutics, in 2005 through a reverse merger, becoming an international public company (NASDAQ), with offices in Chesterford, UK and Hayward, CA. The engineering and software teams based in Hayward immediately went to work transforming the successful Solexa prototype into a commercial sequencing instrument. In 2006, the first Solexa sequencer, the Genome Analyzer, was developed and by that December, the sequencer was able to deliver one gigabase (Gb) of data in a single run.

Solexa's well-timed and opportunistic acquisitions and continued success meant that in 2007, Solexa arrived at the door to a new opportunity. Following a $650 million acquisition offer from Illumina, they opened a new chapter. Solexa's sequencing technology was the perfect marriage to the predominantly genotyping and gene expression portfolio of Illumina. Meanwhile, the commercial capabilities and experience possessed by Illumina facilitated the uptake of sequencing technologies into scientific institutions at an unprecedented speed, which could not be achieved by Solexa alone.

In the years that followed numerous microbe, plant, animal and human genomes had been sequenced, and Illumina accomplished the highly ambitious milestone that Solexa initially set out to achieve: to sequence a human genome within one week.

Illumina did not stop there. Its mission to improve human health by unlocking the power of the genome meant that driving down the cost and duration of sequencing even further was a top priority. Today, a human genome can be sequenced in less than 24-hours, for under $600 (Figure 2) and Next Generation Sequencing (NGS) data output has increased dramatically.

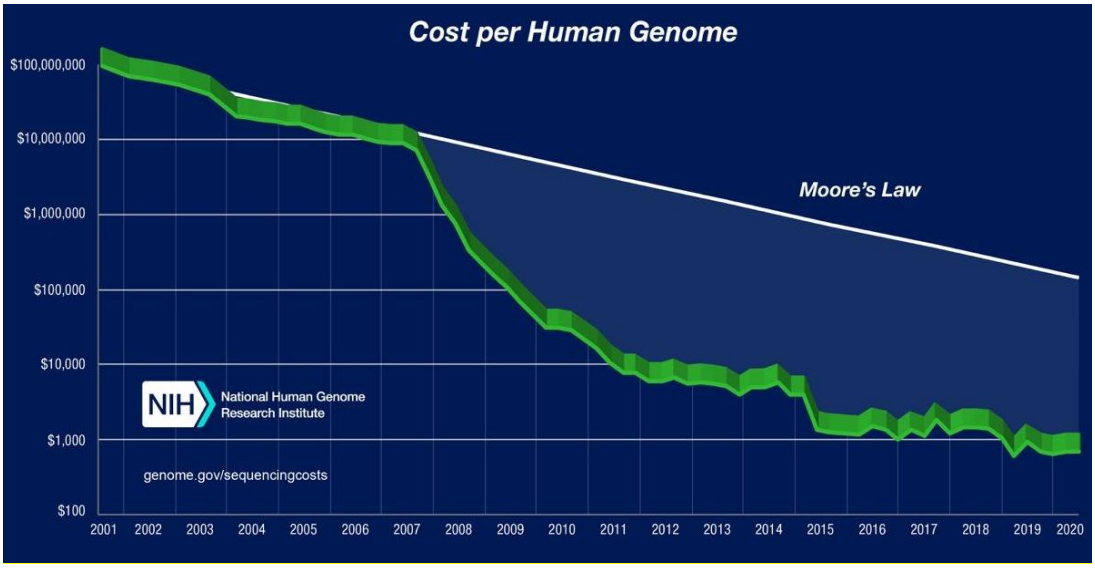

Figure 2. The Cost of Sequencing a Human Genome [1].

3. Our technology

Illumina sequencing technology, sequencing by synthesis (SBS), is now a widely adopted next-generation sequencing (NGS) technology worldwide. To describe the key concepts of sequencing by synthesis (SBS) technology it is helpful to describe the sequencing process in context of the four-step Illumina sequencing workflow: library preparation, cluster generation, sequencing and data analysis.

Library preparation, the first step in the workflow, is the process of readying the DNA inside of a sample for cluster generation and sequencing. This process includes breaking the DNA up into small, random fragments, adding adaptors onto the end of the DNA strands and concludes with the amplification of the DNA, producing millions of copies: a DNA library.

In cluster generation the DNA library, is loaded into an Illumina flow cell. The flow cell is a glass slide with lanes, each coated in a lawn of two types of surface-bound oligos. The oligos are complimentary to the adaptors on the end of the DNA fragments and work to attract the DNA to the flow cell which is then fixed in place through hybridisation. Each hybridised DNA strand is then replicated through a process called bridge amplification (Figure 3). In bridge amplification the DNA bends over and binds to the second type of oligo forming a bridge. An enzyme called polymerase then copies the DNA template to form a duplicate. This process is then repeated over and over and occurs simultaneously forming millions of distinct clusters of DNA fragments. When cluster generation is complete, the DNA fragments are ready for sequencing.

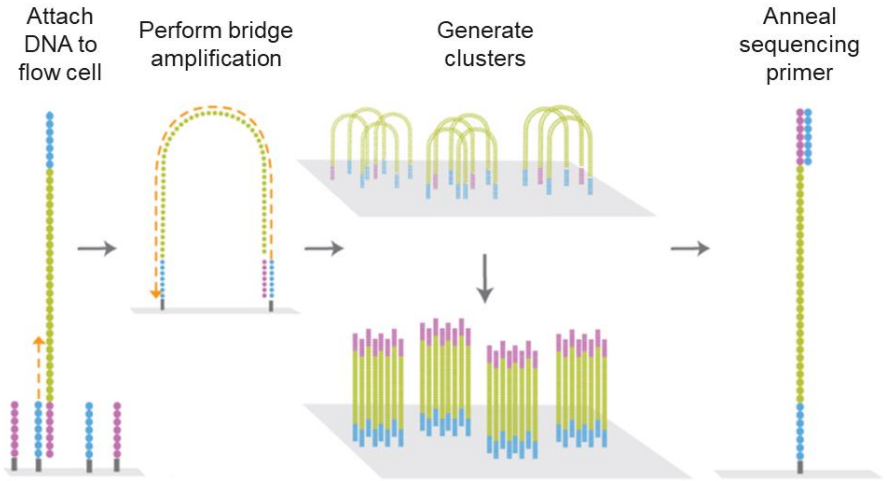

Figure 3. Cluster Generation.

In sequencing by synthesis (SBS), nucleotides, the building blocks of DNA, are modified to comprise a terminator which blocks the addition of any further nucleotides once it is bound to the DNA strand. This terminator also contains a fluorescent label. Sequencing begins with the binding of the first nucleotide to a DNA strand. After the addition of the nucleotide the clusters are excited by a light source and the fluorescent label emits a light signal. The emission wavelength in conjunction with the signal intensity determines the nucleotide call. The sequencer captures this light source and records it (Figure 4).

For a given cluster all identical strands are read simultaneously and hundreds of millions of clusters are sequenced in a massively parallel process. The terminator is then removed, and a second nucleotide can bind to the DNA fragment. This process continues until millions of reads representing all the fragments are recorded. The end result is true base-by-base sequencing that enables accurate data for a broad range of applications.

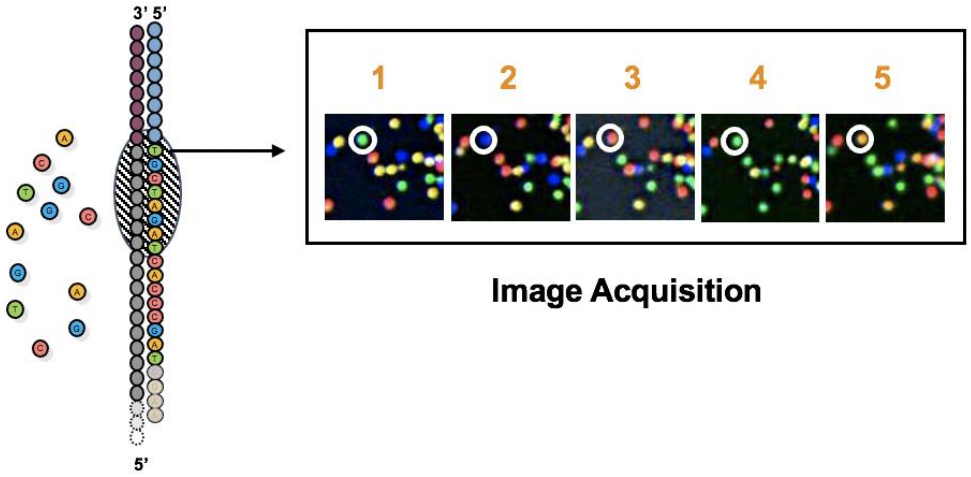

Figure 4. Sequencing by Synthesis (SBS).

Continuous innovative iterations of this technology, to improve and drive down the costs of sequencing, has led to the first-in-class sequencing technology we know of today.

Next Generation Sequencing (NGS) is now at the forefront of innovative change as we move forward in the 21st century. One prime example is in oncology. As genomics-focused pharmacology begins to play a greater role in cancer treatment, Next Generation Sequencing (NGS) has emerged as a valuable method for obtaining a deeper and more accurate look into the molecular underpinnings of individual tumours. With targeted therapies becoming the new standard of care in oncology, NGS-driven companion diagnostics are widely seen as driving the selection of treatments to optimize patient outcomes in the future.

The opportunity for innovation does not stop there. Next Generation Sequencing (NGS) has empowered the identification of genetic sequence variations and alleles which play causal roles in other diseases, including complex disease such as cardiovascular and neurological diseases. This in turn, has led to a new foundation of biological knowledge to apply in disease and drug development research.

In rare disease, Next Generation Sequencing (NGS) technologies have empowered a turning point in both research and diagnoses, helping to deliver rapid, accurate and conclusive answers to individuals and their families, sometimes performing as the last stop in an agonizing diagnostic journey.

In non-invasive prenatal testing (NIPT), Next Generation Sequencing (NGS) has evolved pregnancy screening options, delivering a solution that provides high detection rates, low false-positive results, and no risk to mother and baby.

In agricultural genomics, Next Generation Sequencing (NGS) has and will continue to drive sustainable productivity and offer solutions to the mounting challenges of feeding the global population.

And Next Generation Sequencing's (NGS's) impact in infectious disease is most visible at present through its continued transformative role in the Coronavirus pandemic. NGS enabled the rapid sequencing of the virus's code which aided in the development of PCR testing kits and vaccine development, and has led to global surveillance methods using rapid genome testing to track viral mutations. In turn, supporting and informing regional decisions to respond to the pandemic in real time. Ultimately, leading to public health professionals changing the methods they use to research and monitor epidemics and pandemics in both the present and the future.

5. Looking to the future

While the rate of scientific progress is accelerating rapidly, genomics continues to play an essential part in delivering answers to important scientific questions and solutions to crucial challenges across the globe. What is the true clinical significance of the genome? What causes cancer cells to mutate? What is the origin of a puzzling disease? Can we safeguard the world's food supply? Is it possible to prevent the next infectious disease outbreak? These are just a few of the challenges that continue to inspire Illumina and drive innovative thinking, actions and investment for the future.

In the near future, our goals at Illumina are threefold: to continue to drive down the costs of sequencing to further improve accessibility to sequencing technologies; to continue to support population genomic initiatives across the world - building on the experience and success of the role Illumina played in the UK's 100,000 Genome Project; and, to continue to release innovative and diverse products that help expand the value of the genome - driving more genetic insights into precision medicine and helping transform healthcare practices.

Nevertheless, the Illumina mission to improve human health by unlocking the power of the genome cannot be realised by Illumina alone. By partnering with entrepreneurs, start-ups, and other innovative companies, Illumina looks to support their ambitions to become leading genomic breakthrough companies. Illumina has recently launched its second Illumina Accelerator in Cambridge, UK, which builds on the success of its first located in San Francisco, US. By providing extensive mentorship, financial support and access to sequencing systems, reagents, and lab space, Illumina is building a dynamic ecosystem to help genomics start-ups launch; creating a genomics community that supports the life science ecosystem as a whole. By working together, Illumina is looking to advance breakthrough applications in genomics, including therapeutics, diagnostics, agriculture, synthetic biology, forensics, and direct-to-consumer applications.

> *"Illumina Accelerator serves as a catalyst for innovation in genomics. We're excited to support the life sciences ecosystem and start-ups globally via various means such as infrastructure, sequencing capabilities, commercial and capital networks."*
>
> Anya Roy, Associate Director & Site Lead, Illumina Accelerator Cambridge

Acknowledgments

I would like to thank Dr David Bentley and Dr Klaus Maisinger for sharing their experiences and insights on the Solexa and Illumina Journey; and the Illumina Accelerator team for providing their thoughts and for their commitment to supporting breakthrough genomic companies.

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Megan Townsend after obtaining her B.Sc in Pharmacology and MBiol from Nottingham Trent University, moved to Cambridge to begin her internship with Illumina. Within this role Megan helped launch the Illumina Accelerator Cambridge, while leading and assisting further initiatives to support the Cambridge innovation ecosystem. During her internship Megan was offered a permanent position in the Pharmaceutical Development team at Illumina. Currently, she is working to deliver strategies to support Illumina's business development initiatives in creating exciting collaborations with key players across the life science ecosystem. Megan has a keen interest in the utility of precision medicine in therapeutic development and patient health and aims to continue to support early-stage innovation throughout her career.