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THE BIOLOGICAL REVOLUTION

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What do Grail, Verve and Denali have in common? The ability to turn biology into information science and put it to revolutionary use transforming our health and wellbeing.



Throughout modern human history, there have been periods of great technological innovations that have radically disrupted and changed the ways in which societies and economies work. From the steam engine to electricity to computing, these incredible inventions which were the hallmarks of the previous industrial revolutions have completely transformed our lives over the past two centuries. We believe that another revolution is underway – this time in relation to biology. If the previous industrial revolutions were about inventing new things to make our lives better, then the biological revolution is about pushing our understanding of biology and unpacking millions of years of evolution, the insights from which will transform healthcare and redefine our health and wellbeing.

The facts of life

For millennia, much of biology has remained a black box. The complexity, sophistication, and intricacy of the human body has prevented us from making significant inroads into reducing the number of deaths from cancers, heart diseases, Alzheimer's and so on. Cardiovascular disease remains the number one killer globally, claiming approximately 18 million lives per year. One in two people in the UK will develop cancer over their lifetime. And if we are lucky enough to live beyond 80 years, one in six of us in the UK will develop dementia.

These are grim statistics, but our hope is that the figures will dramatically reduce as the biological revolution unfolds, and we will return to specific examples of

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companies radically improving the outcomes in these areas later in the paper. Before exploring where a biological revolution could lead, it is helpful first to understand where it has come from.

The study of life

The biological revolution has been in the making for a long time. Biology in Greek means “the study of life”, and this subject has always been at the centre of human interests. However, there have been many false premises and setbacks along the way.

An example is Pythagoras’ theory of ‘spermism’. His hypothesis was that babies were created purely from male sperms, which circulated around the male body to gather instructions about making different body parts. From there the sperms were nurtured and matured in the woman’s womb. The problem with this theory, as Aristotle identified two centuries later, was that the sperms couldn’t possibly produce female babies simply because men don’t have female parts. Looking back, such theories might sound absurd, but it is hard to blame the thinkers when they lacked the proper tools and technologies we now have to study life.

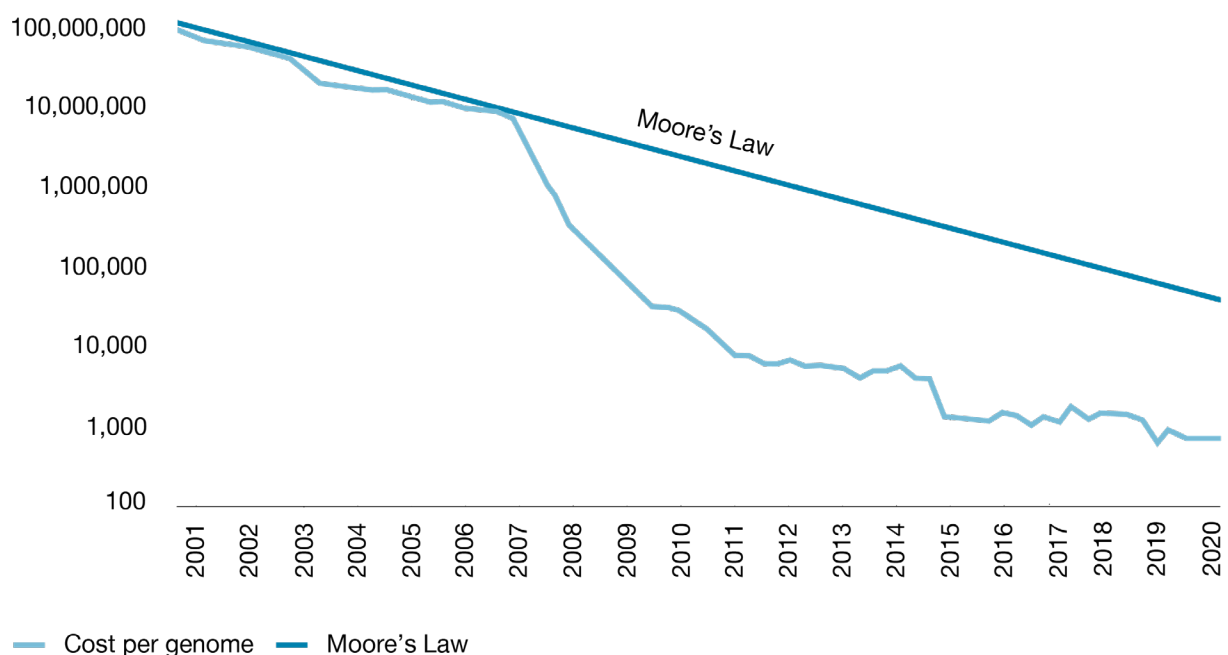
Things began to change with the invention of the microscope. For the first time, we were able to see the components of life and other microorganisms which we didn’t know existed. This led to a burst of new knowledge, the ‘Cambrian explosion’ moment of biology. As the technologies have improved over time, it is now possible to observe the cellular machinery, how different proteins interact with each other, leading to a much better understanding of biology and how to manipulate it.

The code of life

One of the most important technologies in life sciences, the one that propelled our knowledge of biology to a new height, is gene sequencing. Gene sequencing allows us to read the code of life. It’s fascinating that despite the complexity of biology, the code of life is written with just 4 DNA letters – A, T, C and G. Hidden behind what seems to be the chaos and unpredictable emergent properties of biology is in fact a rather orderly information system. There is great potential to turn the anarchy of biology into an information science. By using experimental observations, machine learning, gene editing and other advanced techniques, we can start mapping out the genetic circuits within a cell and understand how different genes relate to each other at the tissue level, organ level, and eventually for the whole organism.

Over the past 20 years, the cost of sequencing a whole human genome has declined dramatically from over \$100m to under \$1000 today. If Illumina has led the charge in bringing down the costs of sequencing, then younger companies, such as 10X Genomics, have been striving to increase the resolution of sequencing. Now we can sequence at the individual cell level, and compare the genomes of healthy cells versus diseased cells to figure out what genes are responsible for the disease. Using single cell sequencing, we can also start to build a map of cell-to-cell interaction. Imagine for a moment if we were to master human biology and learn to configure it like we would a computer. If a part goes awry, we know exactly what’s wrong and how to fix it. Developing a drug to treat a disease could be as simple as writing a new software to fix a computer virus.

Cost per Raw Megabase of DNA Sequence



The Bright Side of Life

Whereas we normally associate revolutions with a big and transformative change, sometimes they are generated by the accumulation of gradual changes, imperceptible at the time. We believe that the life science industry is building momentum for a transformational change in the same spirit, with the biological revolution having been quietly gathering pace over the past decades.

During 2020, we witnessed this radical shift first-hand. The reason we could develop the vaccine against Covid-19 so rapidly was due to the accumulation of lots of tiny changes that have taken place across many different industries over the past few decades. These include material science, chemistry, biology, genomics and data science. On its own, each improvement would have been insufficient to move the dial, but in combination, it allowed companies to create effective vaccines at an unprecedented speed. Let's explore a few other examples where we see the potential for transformational change in healthcare.

Cardiovascular (Verve Therapeutics)

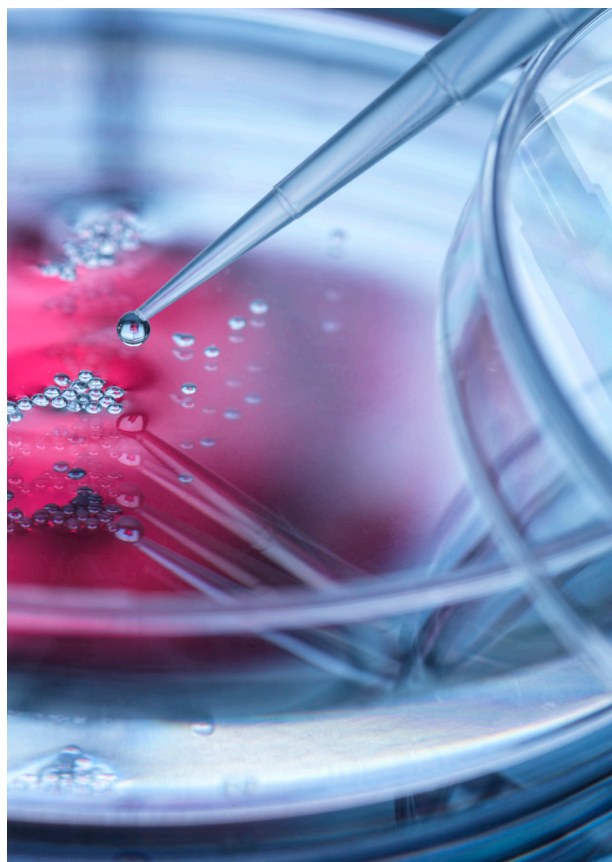
Cardiovascular diseases are diseases of the heart and blood vessels, with lifestyle being a major risk factor. What if biotech companies could mitigate the risks of suffering from heart diseases regardless of lifestyle? Or better still prevent heart diseases altogether?

Verve Therapeutics hopes to find out. It is developing a single-course gene-editing medicine to lower the risk of cardiovascular diseases. The company's technology is based on advances in several areas.

First, large population genomic studies have revealed new insight that there are certain genetic variants that confer natural protection against cardiovascular diseases for some people. By manipulating the genes we've discovered that can lower or raise cholesterol, it is possible to provide a natural protection for those who are less fortunate.

Second, ground-breaking gene editing tools, so-called base editing technology, enable us to manipulate genes precisely and efficiently.

And finally, biotech companies have made a lot of progress on how we deliver gene editing tools and other medicines to cells. Packaged within a lipid nanoparticle, mRNA (as used in some Covid-19 vaccines) codes the production of a gene editing tool: human cells have literally become the manufacturers of the gene-editing tool that then goes and modifies the targeted cells within their own body.

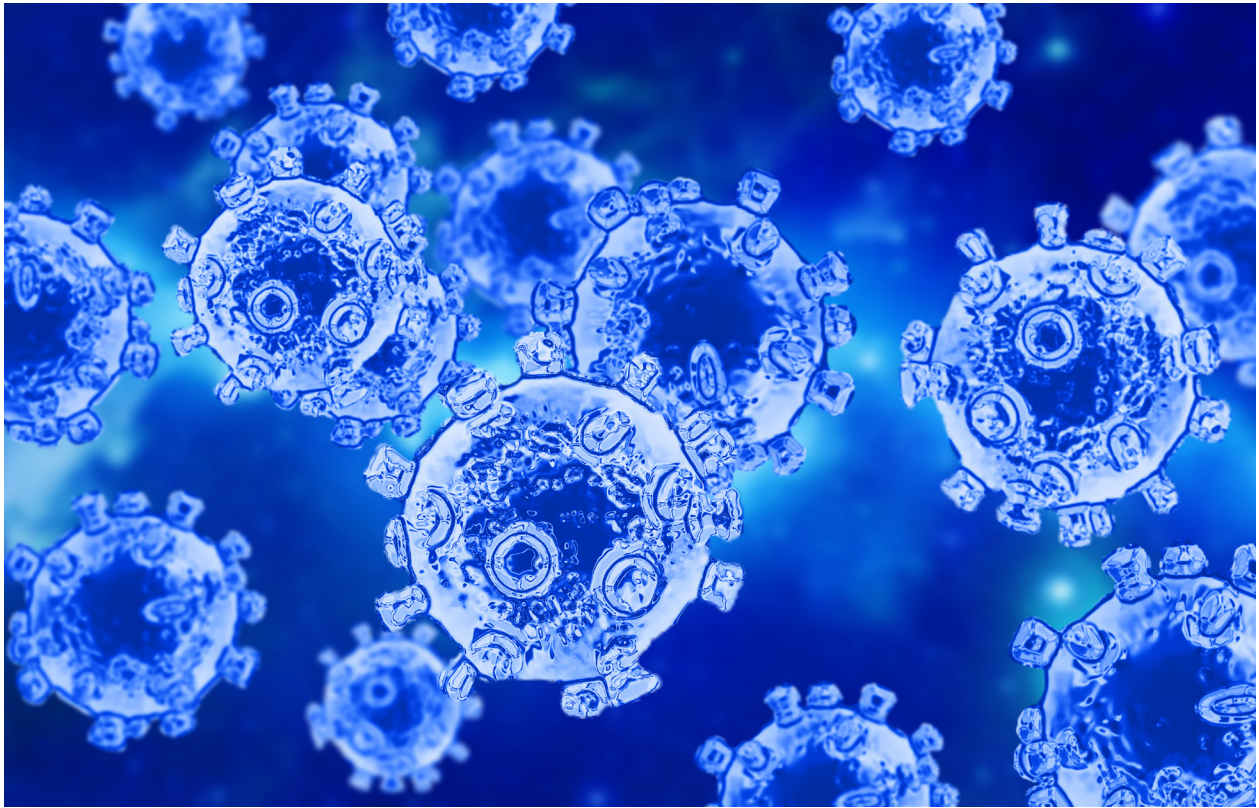


In isolation, each of these advances might not solve the enormous problem of cardiovascular diseases. However, when combined, they offer a step change in the way we can prevent and treat these diseases.

Alzheimer's (Denali Therapeutics)

Advances in many different sciences have enabled Denali Therapeutics to develop new approaches to the treatment of neurodegenerative diseases. One of the longstanding challenges in addressing neurodegenerative diseases has been our inability to find a way to deliver large molecular drugs through the blood brain barrier (BBB). While the BBB helpfully stops harmful substances getting into the brain, it also unhelpfully prevents many drugs getting into the brain and therefore limits our abilities to treat and prevent Alzheimer's and other conditions.

Denali is making great progress in addressing this challenge and the company has already demonstrated its ability to get complex molecules into the brain. In addition to unlocking access to the brain, Denali is also leveraging on advances in genetics, pathology and cell biology to identify pathways that trigger neurodegeneration. This brings us closer to establishing what the underlying causes of diseases are and therefore increasing the chances of developing effective drugs.



Cancer (Illumina/Grail)

Unfortunately, despite many decades of cancer research, the disease remains the second largest killer in the world. If we were able to diagnose cancer at an early stage, it could substantially improve the outcomes for patients and provide an opportunity to turn cancer into a chronic disease, rather than a killer.

Grail is one of the leaders in the early diagnosis of cancer. The company provides a test, based on a single blood draw, that can diagnose dozens of cancers in their early stages. This test can be performed in the doctor's office, possibly annually as part of the general health check-up for seniors.

Grail's achievement so far is already nothing short of transformational. What many have failed to appreciate is how powerful different technologies can be when they are brought together, leading to even more radical change than the sum of parts. In Grail's case it has combined breakthroughs in genome sequencing and AI to great effect.

A New Phase of Life

While we have only highlighted a few disease areas, it is important to note that the biological revolution is impacting the entire spectrum of health. As investors in transformational health companies, we are excited about identifying and supporting innovative companies through the biological revolution.

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Service Provider Risk, Small-and Medium-Capitalization Securities Risk and Valuation Risk.

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Top Ten Holdings – The Baillie Gifford Health Innovation Equities Fund

Holdings	Fund %
1. Moderna Inc.	6.23
2. Sartorius Pref.	5.89
3. 10X Genomics Inc Class A	5.63
4. M3	5.29
5. Argenx	5.16
6. Illumina	5.12
7. Genmab	4.83
8. Edwards Lifesciences Corp	4.79
9. Ambu	4.68
10. ShockWave Medical Inc	4.67

As at 30 December 2021. It should not be assumed that recommendations/ transactions made in the future will be profitable or will equal performance of the securities mentioned. A full list of holdings is available on request. The composition of the Fund's holdings is subject to change. Percentages are based on securities at market value.

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