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James Sanders – Portfolio Manager
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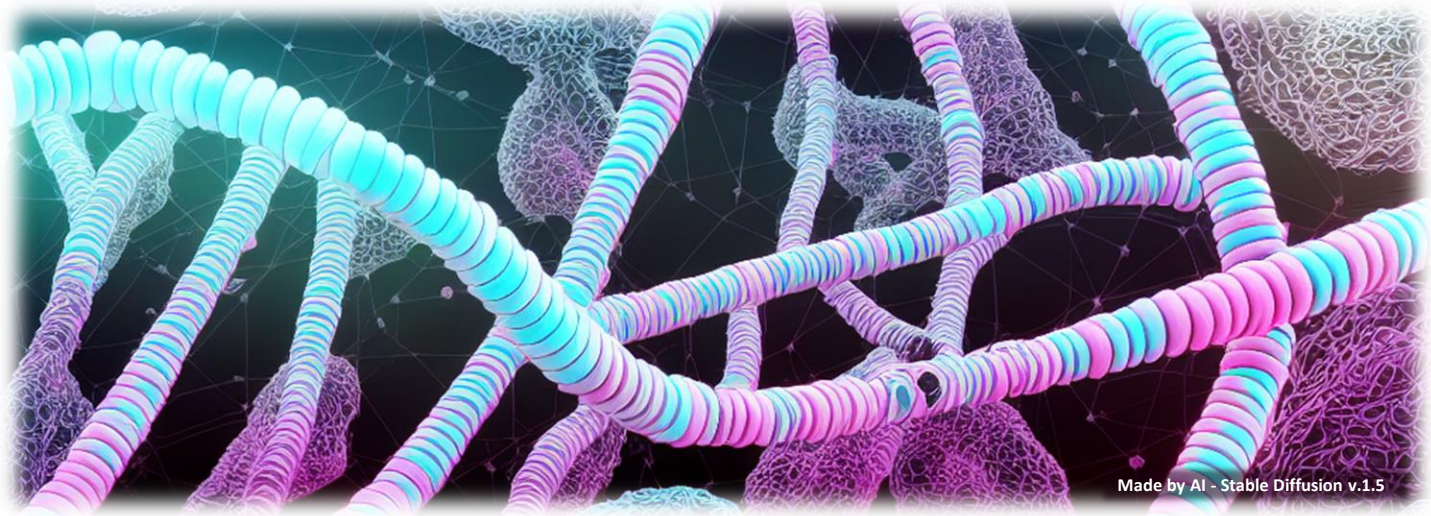
On the Horizon #4 – Genomics



Excitement about genomics is not new. The Human Genomic project, which ran from 1990-2003 for an estimated cost of $3BN, attracted a great deal of interest amongst financial types in both private and public markets, creating a 'Genomic Bubble' whose bursting came about a year after the Dot-com bust of 2000. Ahead of the first draft of the human genome, IHGSC head Francis Collins claimed the results would "eventually allow clinicians to subclassify diseases and adapt therapies to the individual patient" and that "gene-based designer drugs will be introduced to the market for diabetes mellitus, hypertension, mental illness and many other conditions".

Revolutionary new genomic treatments in the years since have been few and far between, and investor enthusiasm waned in the absence of headline grabbing breakthroughs (similar to artificial intelligence in the noughties). Twenty years later, genomics may finally start to deliver on its promise. What has changed? A convergence of exponential technologies, falling costs and new tools have energised the industry, catalysing a leap from scientific research labs to commercial applications.

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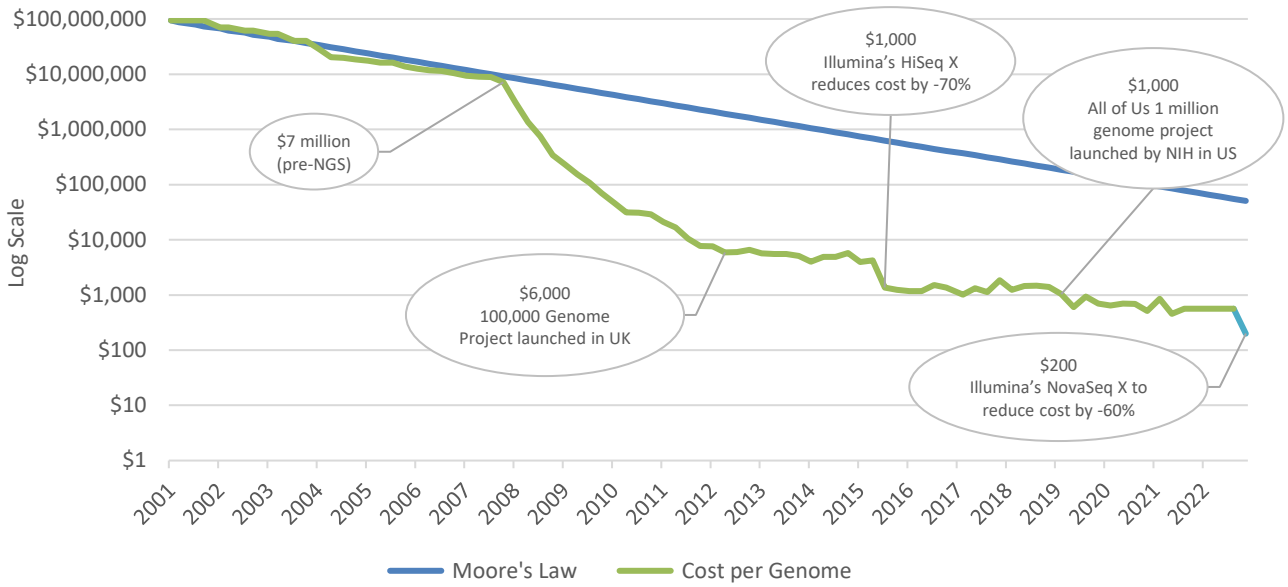
Gene Sequencing

One such catalyst was the arrival of next-generation sequencing in 2007, which replaced the Sanger method that had been standard practice for 30 years. This allowed for automation and massive parallelisation of the gene sequencing process, greatly expanding accessibility to academia and the life sciences industry. Today a typical lab can sequence many terabases in a day – volumes that would take a similarly-sized lab hundreds of years using the Sanger method[1]. The market has been dominated by Illumina, however several interesting new technologies emerged recently to provide alternatives to Illumina's platform.

This chart shows the amazing decline in sequencing costs since high throughput next-generation sequencing (NGS) arrived in 2007



Source: National Human Genome Research Institute; Green Ash Partners

The majority of NGS instruments in use today employ short reads. This involves breaking DNA into billions of short fragments (150-300 base pairs) which are amplified (copied) and then reassembled by a computer into a continuous genomic sequence. To put this into context, the human genome has around 3 billion base pairs spread across 23 pairs of chromosomes. The main advantage of this approach, technically called sequencing by synthesis (SBS), is the massive parallelisation that has steadily driven costs lower with each new generation of instrument. It is also very accurate, achieving Q30 read accuracy (99.9%).

There are some limitations of the short read approach, especially when it comes to whole genome sequencing (WGS):

- The process of amplification can introduce a bias whereby sections of the genome are underrepresented in the reads (where there is high guanine-cytosine content)
- Repetitive or duplicated sequences may be poorly detected or missed entirely
- Structural variants (insertions/deletions or inversions >1 kilobase) cannot be detected
- Copy number variants (CNVs) where genetic traits involving the number of copies of a particular gene are mostly undetectable

[1] *Dr Robert Fulton, Professor of Genetics at the Washington University School of Medicine on the Illumina Genomics Podcast – "The Human Genome and What Are Missing"*

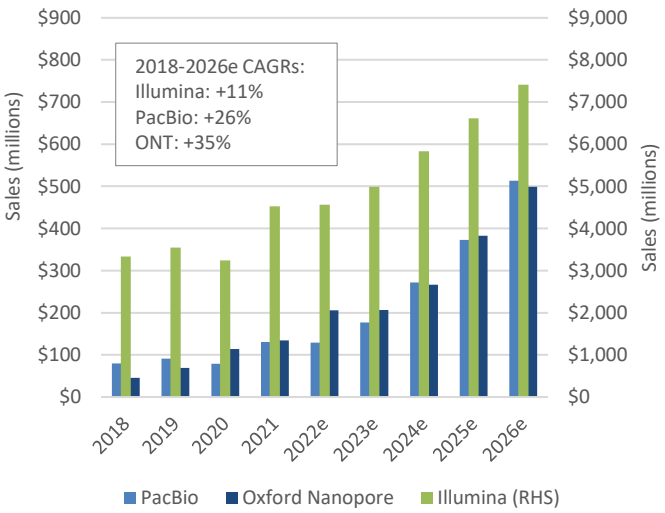
It has become increasingly clear that structural variants in their many forms play an important role in gene expression, though their functional effect are still not well understood. For this reason, there has been growing interest in long read sequencing technologies.

- **Pacific Biosciences of California (PacBio)** – listed in 2010, and Illumina attempted to acquire them in 2018 though this was blocked by the FTC. PacBio uses the same SBS approach as Illumina, however instead of breaking DNA into short fragments, they use a method that creates large, circular DNA molecules that can then be sequenced continuously. This results in a much longer read length of 25 kilobases (can go up to 50kb). The trade off used to be lower accuracy, however this has recently been improved, with Q30 now achievable

- **Oxford Nanopore Technologies (ONT)** – listed in 2021. ONT uses a different technology, whereby DNA is passed through a nanopore, a tiny hole made of protein, and variations in an electric current can be decoded by a computer to identify the A,G,C, T bases. This approach can yield reads of up to a millions bases, however 5-20 kilobases is more typical. It can also produce sequencing results in real time, and instruments come in all sizes, from machines outputting 14TB per run to portable 50Gb instruments that can be used in the field with a laptop. Again, this versatility can come at the expense of accuracy, though this has been improving, and >Q20 (99.3%) is possible using the latest chemistry kit and flow cells

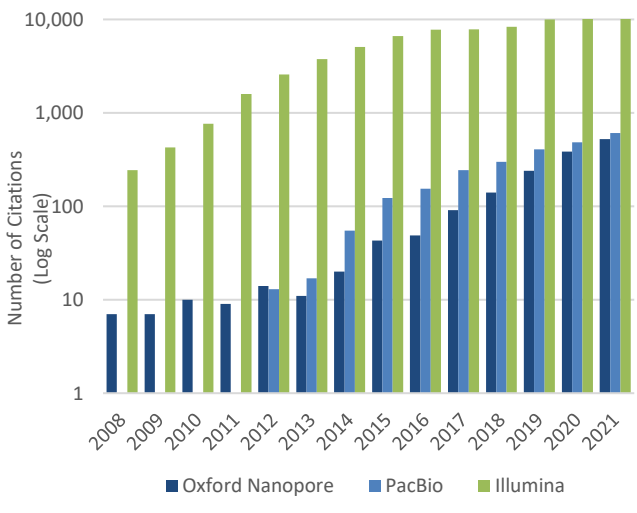
Both long read approaches are better at detecting structural variants, and can also pick up epigenetic features such as DNA methylation, which provides information on gene expression. The main disadvantages to these approaches are higher costs and lower throughput, however as with accuracy, these limitations are diminishing as the technologies mature. Illumina is working on their own long read technology called Infinity, however this is a synthetic form of long read, and only go up to 10 kilobases (the advantage is that it will run on existing Illumina machines).

Illumina sales are an order of magnitude larger than the long read peers, but peers are growing much faster



Source: Bloomberg, street estimates, company reports; Green Ash Partners

Adoption of long read technology is accelerating, as shown here by PubMed citations (Log Scale)



Source: PubMed – National Library of Medicine; Green Ash Partners

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Using data from Vilella Genomics, a bioinformatics consultancy, the global installed base of gene sequencing instruments has the capacity to generate around 7 million GB/day of data, or 29 million human genomes per year. While this seems like a lot, it would take today's installed base 274 years to sequence every person on the planet (if used exclusively for human WGS). If a goal was set to sequence every new born, we would need a six-fold increase in capacity. Of course, in practice, gene sequencing instruments are used for many other things aside from human WGS, in animal, plant and microbial domains.

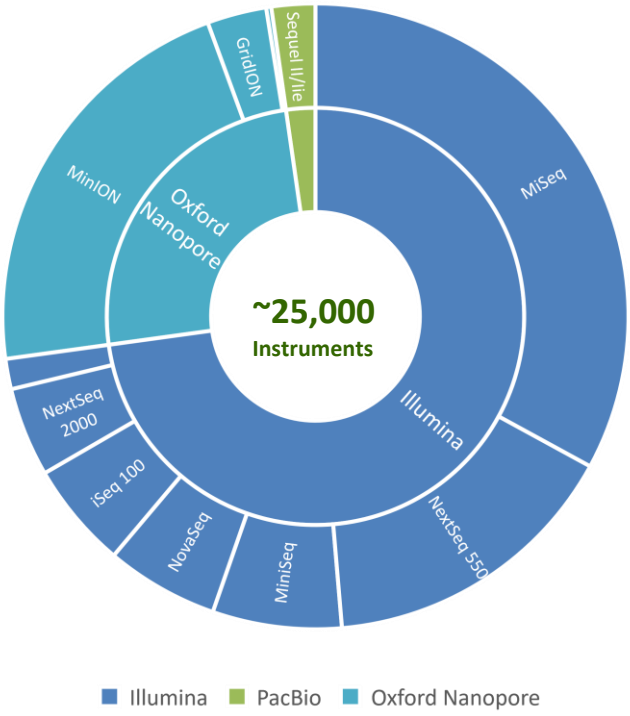
Why Would We Want to Sequence Everyone?

There a several proven and potential benefits to widespread genome sequencing in the population. In 2013, the UK showed some leadership in this with the launch of the 100,000 Genomes Project which completed in July 2019. Initially, the project focused on two main areas:

Cancer – as part of the project, a study was conducted on children with cancer, whereby WGS was applied to blood and solid tumour samples to uncover mutations and gene variants that were causing the cancers. As a result of the findings from WGS, 17% of those enrolled had their diagnosis changed or refined, 22% had their prognosis re-evaluated and 19% had a new treatment option identified that would not otherwise have been considered.

Rare Disease – it is estimated there are 10,000 rare disorders affecting 6% of the population in Western societies, more than 80% of which have a genetic component[1,2]. A third of children with a rare disease die before their fifth birthday. Diagnosing and treating these conditions is extremely difficult and expensive. The UK 100,000 Genomes Project enabled a pilot study of 4,660 participants in 2,183 families, encompassing 161 disorders. 25% of patients in the study received a new diagnosis as a result of genetic testing (40-55% for those with intellectual disability, hearing or vision disorders). 14% of diagnoses were based on gene variants that were only discovered due to WGS. One participant, a ten year old girl, had spent seven years and 307 hospital visits searching for a diagnosis, at a cost of £356k to the healthcare system.

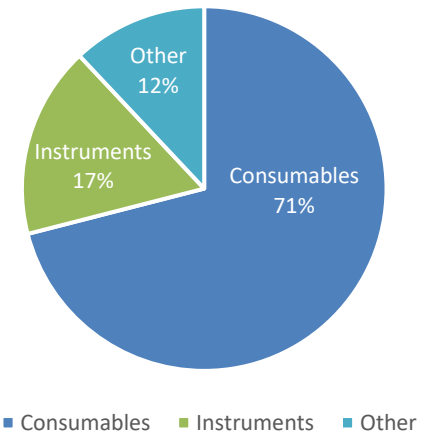
Installed based of gene sequencing instruments for Illumina, PacBio and Oxford Nanopore



Source: Vilella Genomics; cavers ~90% of total installed base -'other' platforms excluded; Green Ash Partners

Growing an installed based is important for sequencing companies, as it grows recurring revenues from consumables, which are higher margin than the instruments themselves

Illumina Revenue Split by Segment FY21



Source: Bloomberg; Green Ash Partners

[1] Generation Genome. Annual report of the chief medical officer. 2016 ; [2] Ferreira CR. The burden of rare diseases. Am J Med Genet A 2019;179:885-892

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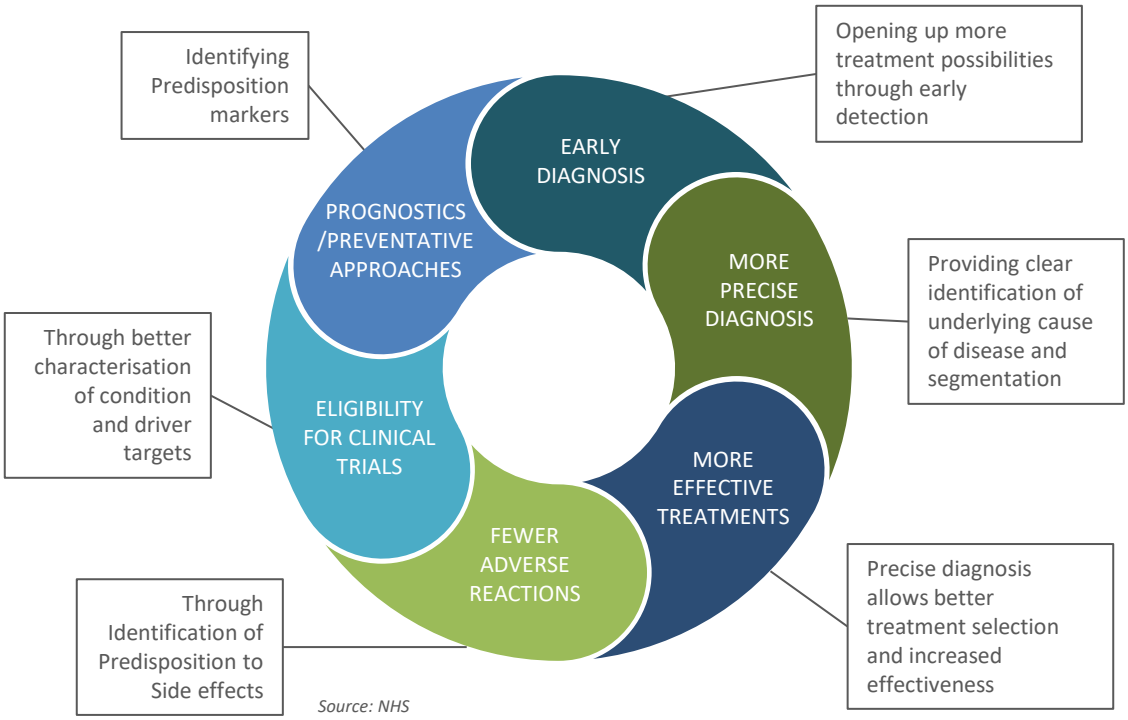
The success of the 100,000 Genomes Project in the UK has brought genomics to the forefront of the UK's healthcare strategy. The NHS is uniquely positioned to form the vanguard of this new frontier, as one of the largest single-payer universal healthcare system in the world. This ambitious strategy has been laid out at length in the recently published Accelerating Genomic Medicine in the NHS.

Potential Benefits of Embedding the Use of Genomic Medicine into the Healthcare System



Source: NHS

New initiatives include:

Cancer 2.0 – since the completion of the 100,000 Genomes Project, researchers and clinicians are partnering with Genomics England to connect genomic and long-term clinical data from health records.

- **Multi-modal Data** is the next stage in this process, whereby the markers and characteristics of cancers are cross-referenced at all resolutions, from genomics at a molecular scale, through to pathology (tissue samples), MRI and CT scans. Machine learning will play a role in finding patterns in the data, through partnerships with AI-first start ups like Insitro

- **Long Read Sequencing** is being explored as a novel technology with the potential to capture large regions and structural features of the genome that are missed by short read sequencing

Diverse Data Vision – there is a significant ethnic bias to the genomic data collected to date (Europeans represent 78% of people in genome-wide association studies). The NHS is in a position to remedy this, which is an important step in ensuring all patients receive the same quality of personalised medicine – at the moment, polygenic risk scores are 4.5x more accurate for those of European ancestry than of African ancestry.

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New Born Genomes Program – the NHS is currently evaluating the feasibility and merits of conducting WGS to every baby born through the NHS (starting with 100,000). The goal is provide early diagnosis and care for rare genetic conditions, and will allow screening to be expanded into the universe of ~8,000 rare diseases with a genetic component, versus just 9 conditions that are screened for today.

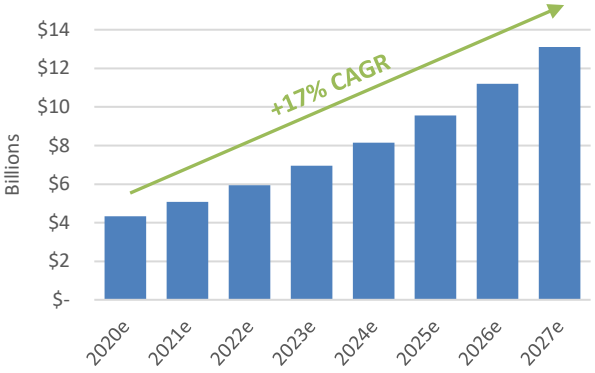
Pharmacogenomics – one of the potential benefits of WGS that spans cancer, rare disease, clinical trials and even routine care is the ability to identify patients that may have adverse reactions to certain drugs or antibiotics. For example, there is an antibiotic called gentamicin that is administered as standard procedure to any new born entering ICU, but results in irreversible hearing loss for 1 in 500 babies. The NHS is trialling a rapid gene sequencing test that can inform clinicians to administer an alternative vaccine if the baby has this genetic predisposition. In a recent study, the test was used on 750 babies and saved 3 from permanent hearing loss. As well as providing a huge benefit to the susceptible babies and their families, the test costs just £114 versus an estimated cost of £57k to treat permanent hearing loss over a patient's life time (savings to the NHS of £5-7MM per annum). If this were rolled out worldwide, it could save 14,000 infants per year from aminoglycide-induced hearing loss.

Genetic Testing

Non-invasive Prenatal Testing (NIPT) is one of the first genetic tests that takes advantage of NGS to offer a widely available product that is both more accurate and less disagreeable than previous prenatal screening methods. NIPTs such as the Harmony Test are estimated to be performed on 10 million expecting mothers per annum[1], covering about 7% of babies born globally each year. The tests analyse cell-free DNA (cfDNA) in a pregnant woman's blood of which a portion will come from the foetus (3-30% when measured between weeks 10-20 of pregnancy[2]). There are several different test providers, including Illumina and Roche, and tests can screen for up to 16 disorders, including Down's Syndrome.

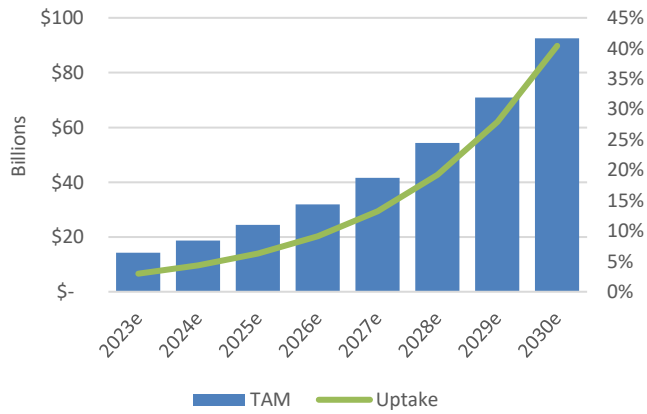
Liquid Biopsy Cancer Screening is a potentially huge market. GRAIL is currently working with the NHS on a 140,000 participant study to evaluate their Galleri test, a multi-cancer early detection test (MCED) which aims to detect circulating tumour DNA (ctDNA) from a blood sample. This approach has the potential to detect the onset of cancer before a patient is symptomatic, which both increases the efficacy and decreases the cost of treatment (pancreatic cancer isn't normally detected until stage II or IV and consequently has a one year survival rate of just 5%). The relative ease of a blood test versus other regular screens such as colonoscopies or a mammogram also helps encourage at-risk groups to

Estimated revenues and growth forecasts for the NIPT market globally



Source: Meticulous Research; Green Ash Partners

Estimated TAM for liquid biopsy cancer screening



Source: Census population data; Green Ash Partners

1 Samura O. 2020. Update on noninvasive prenatal testing: a review based on current worldwide research. J. Obstet. Gynaecol. Res. 46:1246–54
2 Canick JA, Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE. 2013. The impact of maternal plasma DNA fetal fraction on next generation sequencing tests for common fetal aneuploidies. Prenat. Diagn. 33:667–74

attend check ups. For those already diagnosed with cancer, blood tests may be able to replace solid tumour biopsies in some cases. This has the advantage of capturing the ctDNA from multiple tumours, which can give a fuller picture of genetic mutations and inform a personalised and targeted treatment regime. Once in remission, liquid biopsy tests can be used to monitor minimum residual disease (MRD), to ensure the cancer has not returned. Combining these tests with existing standard of care screening could materially improve quality-adjusted life years (QALYs) and reduce healthcare costs. The NHS aims to detect 75% of cancers at stage I or II by 2028, versus 55% in 2028 – MCED tests are expected to do a lot of the heavy lifting to achieve this goal.

CRISPR-based Gene Editing

In parallel to the exponential improvements in gene sequencing capability, there has been a revolution in molecular tools to alter DNA and gene expression. The big inflection came with the seminal paper by Jennifer Doudna, Emmanuel Charpentier et al published in 2012 that found bacteria and archaea use an assembly of RNA-based guides (gRNA) and CRISPR-associated (Cas) nuclease 'scissors' as part of their immune response to viruses. This CRISPR-Cas9 system can be adapted to disrupt, delete or correct/insert DNA at specific locations in the genome.

Doudna and Charpentier's paper has been cited >9,000 times and referenced in >1,300 patents since its publication, and the authors have shared a Nobel Prize for their discovery. CRISPR essentially leap-frogged older tools for manipulating DNA, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), before they achieved commercialisation, condemning them to an early obsolescence. This is due to CRISPR embodying all three hallmarks of disruptive innovation: Faster, Better, Cheaper.

By the end of 2016, three companies had raised money in the public markets to develop one-time cures for genetic diseases based on CRISPR-Cas9 (Intellia Therapeutics, CRISPR Therapeutics and Editas Medicine). Six years later, we are on the cusp of approved treatments for Sickle Cell Disease and Beta Thalassemia, and there are human trials underway evaluating potential cures for certain liver disorders and blood cancers.

Editing genes in humans using CRISPR-Cas9 isn't without risk. Off target effects are a big concern, especially in vivo (where edits to cells are made inside the body, rather than outside/ex vivo). Also, Cas9 edits DNA by causing a double strand break – while cells have innate machinery to repair these afterwards, there is a risk of chromothripsis, which can lead to cell death, or worse, cancer.

gRNA (yellow) directs Cas9 protein (purple) to specific location, where it acts as molecular scissors and cuts the DNA strand (turquoise)

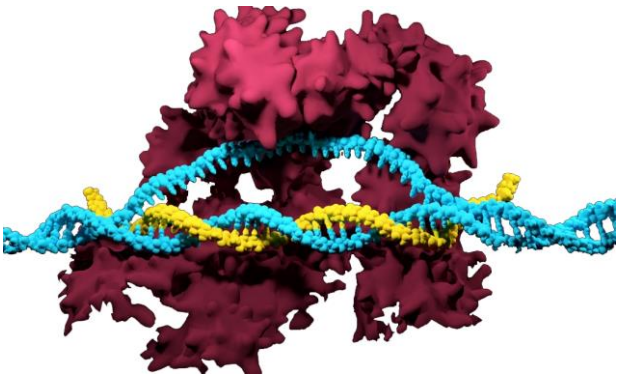


Image Credit: Synthego

CRISPR-Cas9 enables three types of edit

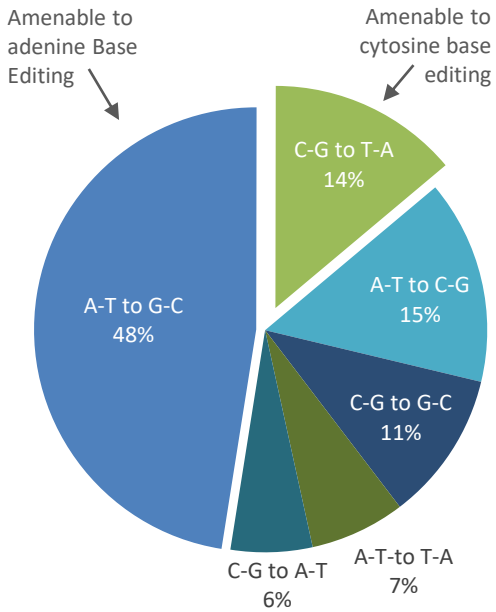
Disrupt	Delete	Correct or Insert
If a single cut is made, a process called non-homologous end joining can result in the addition or deletion of base pairs, disrupting the original DNA sequence and causing gene inactivation	A larger fragment of DNA can be deleted by using two guide RNAs that target separate sites. After cleavage at each site, non-homologous end joining unites the separate ends, deleting the intervening sequence	Adding a DNA template alongside the CRISPR/Cas9 machinery allows the cell to correct a gene, or even insert a new gene, using a process called homology directed repair

Source: CRISPR Therapeutics

In recent years, next-generation CRISPR-based gene editing systems have started to appear, aiming to both broaden the universe of genetic diseases that can be tackled by gene editing and mitigate some of the potential risks inherent to CRISPR-Cas9 edits.

Base Editing is a promising approach, developed by David Liu's lab at the Broad Institute of MIT and Harvard. This still uses gRNA to target a specific part of the genome, and then an enzyme is used to chemically change a base and achieve a desired edit. This has the advantage of avoiding double stranded breaks, but also potentially create fewer off-target effects (insertions/deletions). It does have its own set of limitations – currently only A-T to G-C or C-G to T-A edits can be made with base editors, and the molecular package is much larger than CRISPR-Cas9, which makes it challenging to deliver via adeno-associated viral (AAV) vectors – these are effective delivery vehicles that can specifically target multiple types of tissue (lung, heart, neurons and skeletal muscles), but limited in their capacity to around 4.7kb which is too small for base editors (but just about ok for CRISPR-Cas9). Liu founded Beam Therapeutics to commercialise base editing, and has also licensed the use of base editing to Verve Therapeutics who are focused on cardiovascular disease. Intellia Therapeutics is also developing its own base editors.

There are more than 37,000 known point mutations linked to disease – 62% of these could potentially be corrected by either adenine or cytosine base editors



Source: Dr. David Liu, Howard Hughes Medical Institute; Green Ash Partners

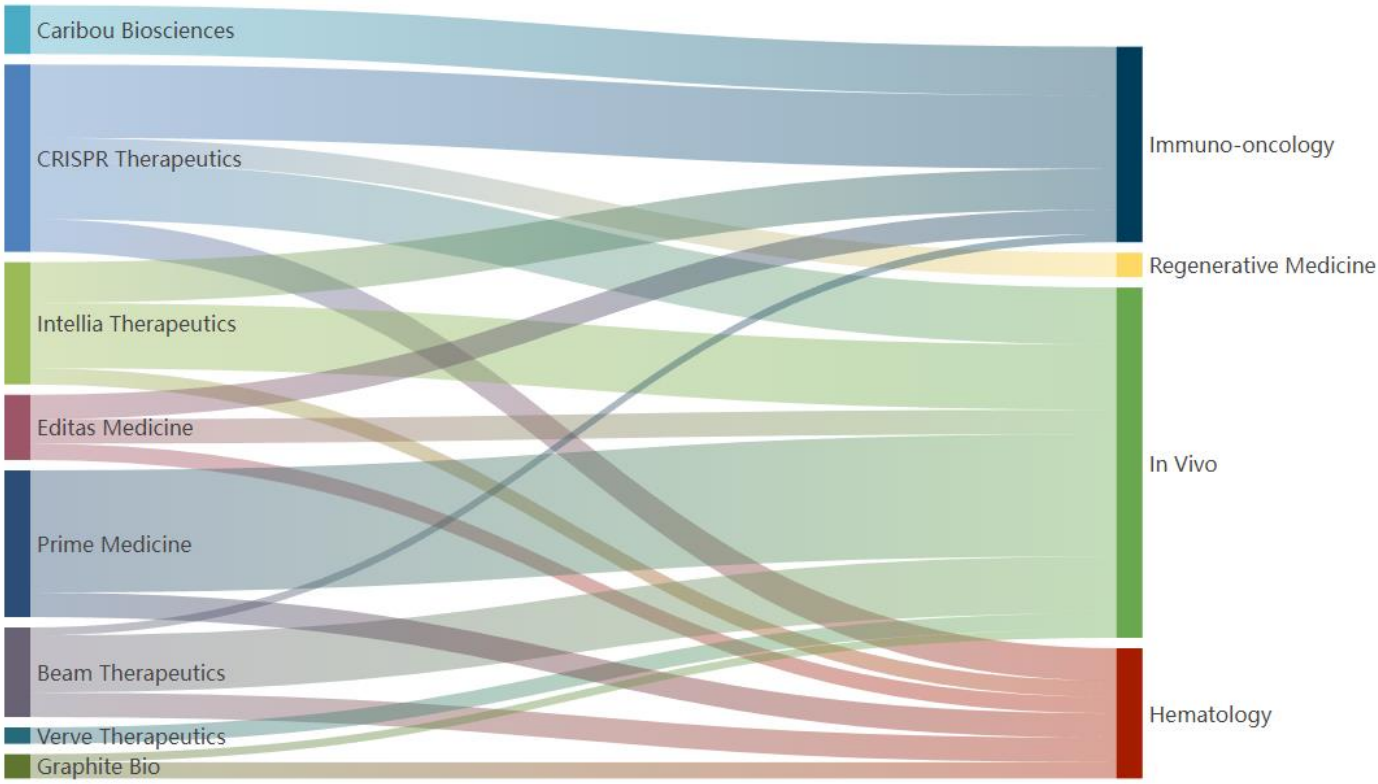
Prime Editing is the latest innovation, hailed as a word processor for the genome. It can effect all 12 of the possible letter changes in DNA, versus only 4 for based editing, while also avoiding the double stranded breaks cause by CRISPR-Cas9 edits. In theory it can also be more precise, and can perform edits on longer chunks of DNA (>5,000 base pairs) expanding its target universe to 89% of the ~75,000 human disease-causing mutations listed in the US NIH Clinvar database. A key limitation is its size, which is even larger than base editors (the pegRNA guide alone is 5x larger than the gRNA used in based editing). This will require progress on delivery vectors for in vivo targets. It is also relatively new (paper published in 2019), so there is currently only efficacy data in animal models and non-human primates.

Meanwhile, CRISPR-Cas is not standing still. Companies like Caribou Biosciences, another gene editing biotech founded by Doudna, are building platforms based on newer CRISPR-associated proteins (in their case Cas12a) which have different or more effective editing capabilities and have also innovated on the guide molecule, developing a CRISPR-hybrid RNA-DNA guide (chRDNA) which reduces off target edits. This package is smaller than CRISPR-Cas9 and the base editors, making it easier to use AAV vectors. At the moment the focus is on ex vivo edits to T Cells/NK Cells to treat cancers.

Each new approach advances the field and enlarges the tool kit available to researchers. So far we have focused on potential therapies for genetic disease and cancer in humans, for which there is significant unmet need, however there are parallel projects underway to explore potential applications in many other areas, from agriculture to diagnostics.

We are in the early days of curative medicine, whereby one-time edits to the genome can permanently cure diseases – by some estimates 10,000 human disorders caused by the mutation of a single gene, affecting 1% of the population. When thinking about the total addressable market (TAM) for these treatments, it is easy to come up with huge numbers – if just 10% of the 86 candidates in the pipeline below reached commercialisation, and each treated 30,000 patients per year at a cost of $1 million, the TAM is over $250 billion (many expect early gene editing treatments to fetch up to $2.5 million). This compares to today's combined market cap of $16BN for these eight public companies.

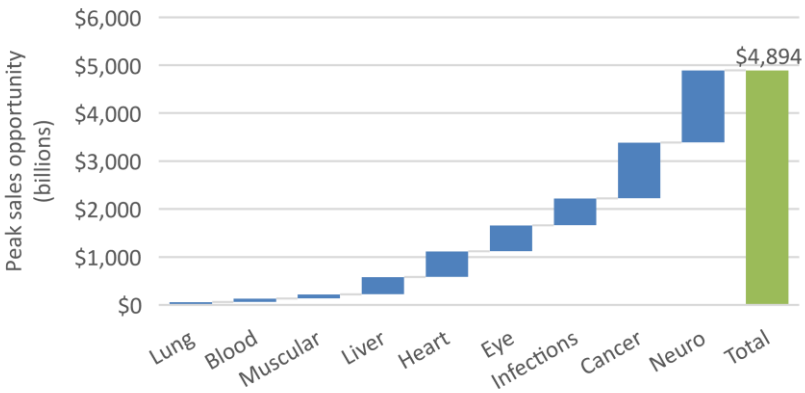
CRISPR-based Development Pipeline of Publicly Listed Companies by Therapeutic Area



Source: Green Ash Partners

Looking beyond the current development pipeline of the CRISPR companies, the numbers become even larger: Goldman estimated a total addressable market size of nearly $5 trillion in a 'blue sky scenario' when they initiated on the theme back in April 2018. This would equate to about 3.5x the value of prescription drug sales globally in 2021[1].

Global TAM for Genomic Medicine in a 'Blue Sky Scenario'



[1] *IQVIA Market Prognosis, Sep 2021; IQVIA Institute, Nov 2021*

Source: Goldman Sachs Investment Research; Green Ash Partners

RNA-based Therapeutics

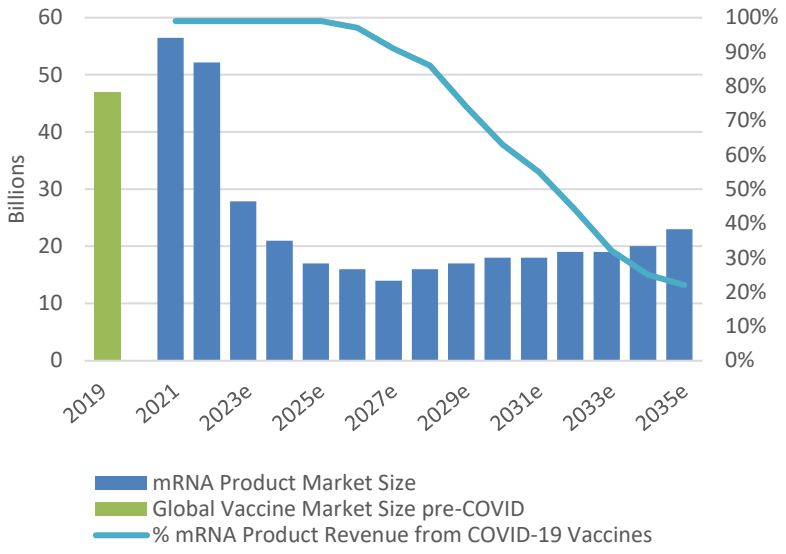
The idea of using RNA molecules to manipulate biological pathways and treat disease has been around for years. The are three main types of RNA – Messenger RNA (mRNA) which provides a template for protein synthesis, transfer RNA (tRNA) which brings amino acids to the ribosome, and ribosomal RNA (rRNA) which binds the amino acids together to form an protein.

Messenger RNA was used to create proteins in mice as early as 1990, but didn't become famous until 2020, as the molecule behind the most widely-used and effective COVID-19 vaccines. It was also the developed in record time - the Chinese health authorities first announced the discovery of a novel coronavirus on the 9th of January, 2020 and the whole genome of the virus was published two days later. By the end of that weekend, Moderna had produced an mRNA sequence encoding the virus' spike protein, designed to 'teach' the immune system to create binding antibodies as a defence. A few weeks later, the first doses of their COVID-19 vaccine were sent to the NIH for testing. The development of BioNTech's mRNA-based COVID-19 vaccine (in partnership with Pfizer) was similarly rapid, and this feat has been shown to be repeatable, with the development of several variant-specific COVID vaccines since.

Two years on from the approval for the first mRNA vaccines, there are now dozens more in the pipeline. Targets range from diseases like Malaria and TB, two of the biggest killers globally and both currently without vaccines, to seasonal flu, for which vaccines exist, but with just 40-60% efficacy at preventing illness (versus >90% for the original COVID-19 mRNA vaccines). Beyond infectious diseases, the mRNA approach is also being applied to oncology, with several cancer vaccines already in clinical trials.

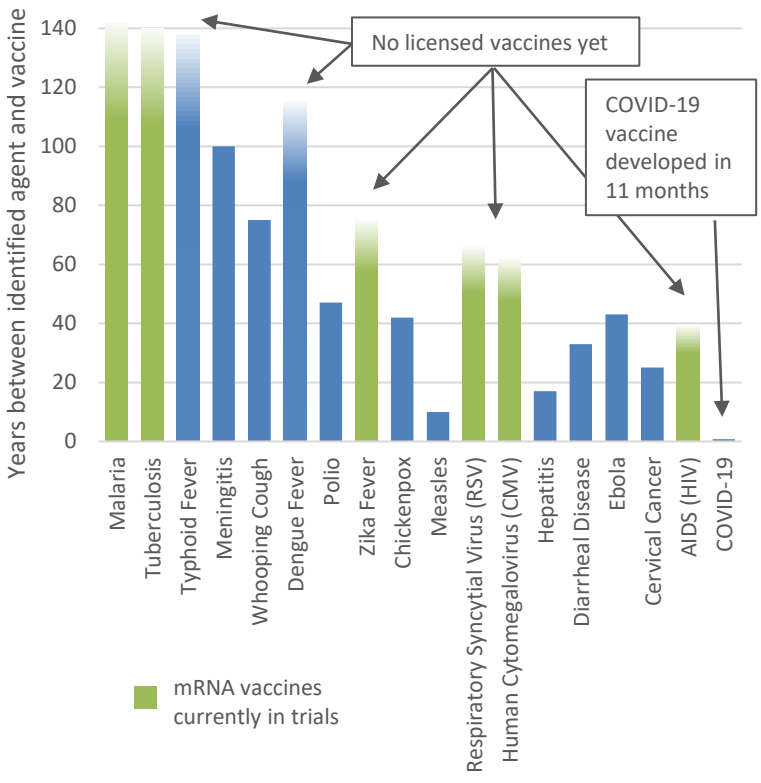
Developing new mRNA vaccines is akin to writing software, designing mRNA sequences to instruct the machinery of a cell to encode

In 2021, revenues from mRNA-based COVID vaccines exceeded revenues from 2019's entire global vaccine market by +19%



Source: Nature Reviews – Drug Discovery, Statista, Bloomberg; Green Ash Partners

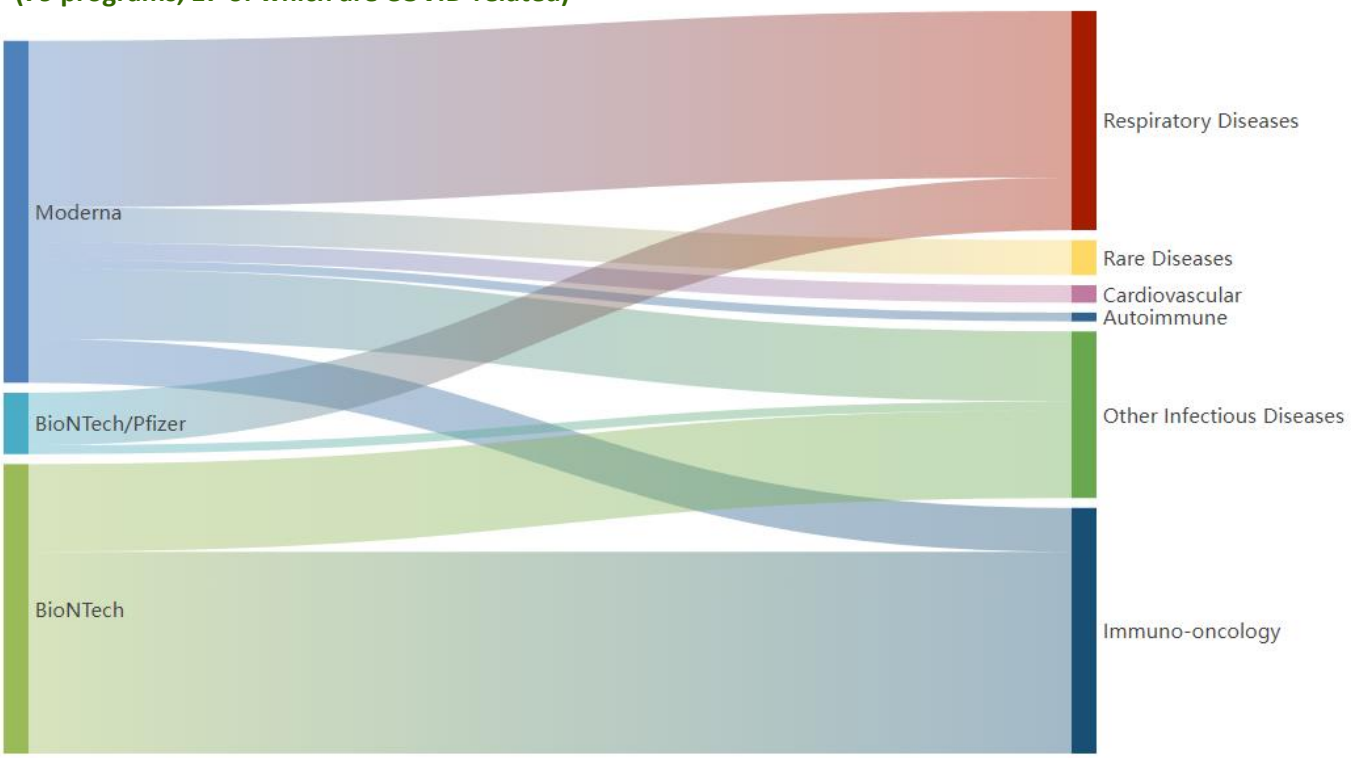
Moderna and BioNTech have vaccine candidates in trials for six of the eight diseases with no vaccine shown below



Source: Our World in Data; Green Ash Partners

a desired protein. The delivery method of mRNA vaccines has advantages over traditional vaccines, which rely on cultured animal cells to produce inactivated or adapted viruses as vectors. MRNA vaccines use liquid nanoparticles, which are easier to produce and are less likely to trigger an immune response.

MRNA-based Development Pipeline of Moderna and BioNTech Therapeutic Area (79 programs, 17 of which are COVID-related)



Source: Green Ash Partners

One of the attractions of using RNA to give instructions to cells is that it is quickly broken down by the body, like a message written in disappearing ink. By contrast, CRISPR-based gene edits are permanent (though not heritable in the cases of the therapeutic applications discussed previously).

RNA interference (RNAi) is another RNA-based tool that can be deployed in cases where a disease is caused by a malformed or over-produced protein. Small pieces of RNA (~22 nucleotides long) are introduced to bind to messenger RNA in a cell, preventing them from instructing the production of proteins. There are two varieties: small interfering RNA (siRNA) which targets a specific mRNA, and microRNA (miRNA) which suppresses mRNA generally, regulating gene expression. Currently four siRNA-based therapeutics have been approved to treat chronic conditions such as hereditary transthyretin amyloidosis (hATTR) and heterozygous familial hypercholesterolemia (HeFH). These targets are in the sights of CRISPR-Cas9 and base editing companies who are in the process of developing one time cures – Intellia's in vivo treatment for hATTR is currently showing encouraging data in clinical trials and Verve started dosing the first patient for their HeFH treatment in July. The cost per patient of Patisiran, the siRNA treatment for hATTR, can be up to $680k per year, which explains the potential $2-2.5 million price tag of the first approved gene editing treatments, given they result in permanent cures.

DNA Synthesis

Like DNA sequencing, we have had the ability to synthesise DNA for forty years, however back in the '80s this was highly manual and low throughput. Since then, the field has followed a similar path of technological improvements, however while the cost to read DNA has fallen by seven orders of magnitude, the cost to write DNA has only fallen by three or four (this varies by method, and there is also a cost/accuracy trade off). By some accounts, cost/base pair has fallen by around -10x in the last decade or so, to less than $0.07/bp.

To be useful, bases (also called nucleotides) have to be strung together into a sequence (oligonucleotides); Twist Biosciences offers oligonucleotides of up to 300 nucleotides in length with an error rate of 1:2000. They can manufacture genes of up to 5,000 base pairs. Oligo synthesis still employs a technique based on phosphoramidite chemistry which was developed in the '80s. Like gene sequencing, there have been some 'next generation' improvements which have reduced costs and increased accuracy and throughput. Computer-controlled lab instruments have automated the process, and more recently, microreactors have been developed that fit on a chip, and allow DNA synthesis to benefit from some of the massive parallelisation advantages realised by NGS. Looking ahead, there are pre-commercial enzyme-based approaches to oligo synthesis in development. The attraction of these methods versus phosphoramidite chemistry is they could provide faster and higher yield results, and the process doesn't require the use of hazardous chemicals.

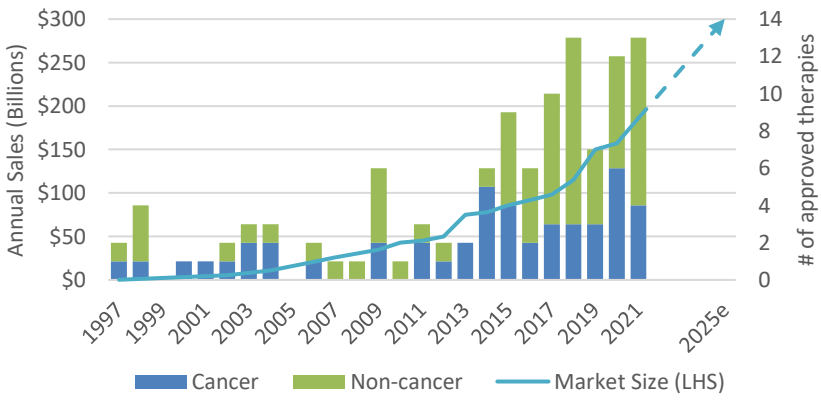
Today, DNA synthesis is about half the size of the DNA sequencing market. The latter benefits from the prospect of offering benefits to individual consumers, through personalised healthcare, while use cases for DNA synthesis remain confined to specialised labs for the time being.

What's Next?

Gene Sequencing and Genetic Testing will continue to get cheaper, faster and more accurate. **Cheaper** sequencing expands the use cases, paving the way to mass population sequencing and regular genetic testing for cancer as a part of standard care. **Faster** enables genomic testing to move out of wet labs and into the clinic or the operating theatre - for example, so clinicians can include pharmacogenomic considerations in their decision-making or surgeons can determine whether a brain tumour is benign in the operating theatre in real time. Even sequencing of influenza strains could potentially save a lot of money, establishing whether antibiotics are required or not (in the case of pneumonia) and minimising ICU beds which cost £5,500 per night. **More accurate** sequencing, along with the ability to capture data on the epigenome, transcriptome, proteome, even the microbiome, will further our understanding of biological pathways. As well as advancing the field of bioinformatics and helping us realise the promise of personalised medicine, this goes far beyond human health. Whole genome sequencing is being applied to all branches of the Tree of Life, from the animal and plant kingdoms down to the level of bacteria and viruses, which could lead to all kinds of possibilities for synthetic biology.

Genetic Medicine is in its early innings. When trying to size the potential for a major new modality in medicine, it is perhaps instructive to look at the history of monoclonal antibodies which started to take off at the turn of the century. The chart on the right shows a +28% revenue CAGR over nearly three

Number of antibody therapeutics granted a first approval in either the US of EU each year, and annual sales (1997-2025e)



Source: Lu et al. Journal of Biomedical Science (2020) 27:1, The Antibody Society; Green Ash Partners

decades, as biologics have rapidly outpaced small molecule therapeutics (in 2018, eight out of ten of the best selling drugs worldwide were biologics); this market is expected to reach $300BN by 2025. We believe genomic medicine may be at a similar inflection point today, and the market opportunity is potentially much larger.

DNA Synthesis costs should continue to fall as throughput rises. This will open up opportunities as new applications emerge in medicine, as well as other large sectors such as agriculture, chemicals, and materials. If DNA synthesis can improve by similar orders of magnitude to gene sequencing, there is even potential to develop DNA read/write systems for computation and data storage.

Summary

The field of genomics is in a state of rapid change, driven by multiple inflections in disruptive technologies. Instruments for decoding and digitising the language of biology at ever higher resolutions and in real-time are becoming increasingly accessible, growing genomic databases of human populations, plants, animals, bacteria and viruses at an exponential rate. This has coincided with the rise of transformer models in AI, which, as it turns out, are uniquely suited to understanding connections in vast multi-modal data. As DeepMind's CEO Demis Hassibis puts it: "If you think of mathematics as the perfect descriptive language for physics, AI is perfect the descriptive language of biology because it's so messy, emergent, dynamic and complex". DeepMind's AlphaFold2 has unleashed a burst of innovation in proteomics, and most recently generative AI architectures such as diffusion models have been shown experimentally to be able to design proteins de novo. Meanwhile the emergence of molecular tools like CRISPR allow us to manipulate at the underlying letters in DNA and RNA with unprecedented precision.

The momentum in these fields is palpable, with new breakthroughs seemingly announced on a weekly basis. We may look back on this decade the Renaissance of genomics and synthetic biology.

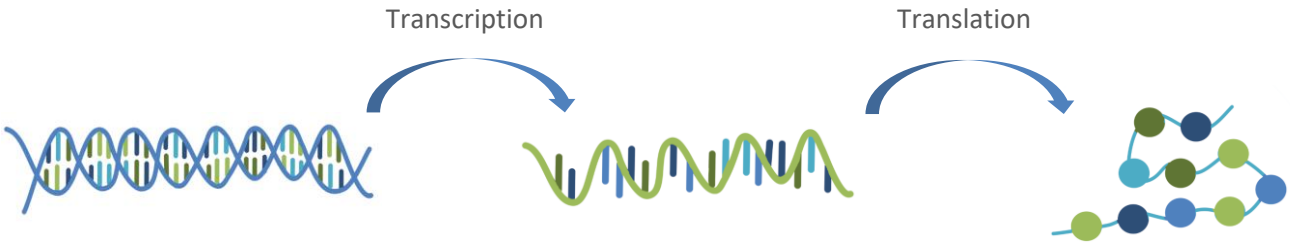
Further Reading

The Epigenetics Revolution: How Modern Biology is Rewriting Our Understanding of Genetics – *Nessa Carey (2011)*; Link

A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution – *Jennifer Doudna and Samuel H. Sternberg (2017)*; Link

The Next 500 Years: Engineering Life to Reach New Worlds – *Christopher E. Mason (2021)*; Link

The Genesis Machine: Our Quest to Rewrite Life in the Age of Synthetic Biology – *Amy Webb and Andrew Hessel (2022)*; Link



DNA

Deoxyribonucleic acid (DNA) is the source code of life. There are 3.2 billion base pairs in the haploid human **genome**, made up of adenine (A), cytosine (C), guanine (G), and thymine (T). Technically every person has the genomes of both parents within them; the diploid genome is therefore 6.4 billion bases long. The whole genome is contained within every cell, arranged in 23 haploid/46 diploid chromosomes tangled together in the cell nucleus. If stretched out as a single strand of DNA, the diploid genome would be over two metres long.

There are about 20-25,000 genes in the human genome, and each gene contains protein-coding regions called exons. There are ~180,000 exons which are collectively known as the **exome** and comprise about 1% of the genome. Genes are switched on and off either through chemical modifications to sections of DNA called methylation or by histones, protein spools that coil sections of DNA around them. This is known as the **epigenome**.

RNA

Ribonucleic acid (RNA) shares three of DNA's bases (A, C and G), but has uracil (U) instead of thymine (T) as its fourth. Messenger RNA 'reads' protein-coding exons and delivers the instructions to ribosomes outside of the cell's nucleus, which then synthesise proteins. These mRNAs, together with some varieties of non-coding RNA, are called the **transcriptome**.

RNA sequencing can be used to understand gene function, as every strand of mRNA is the mirror image of the exon from which it was transcribed. Unlike the genome, the transcriptome is ever changing, and varies between cells in different tissues or organs.

The impermanence of RNA also makes experimentation less risky when it comes to medicine. Therapies can target the output of genes, rather than making irreversible edits to the genes themselves. Of course this means the therapeutic benefits will also be temporary.

Protein

Proteins are incredibly versatile and complex molecules which underpin all aspects of biological function. There are 22 amino acids that form human proteins, though over 500 can be found in nature. The human **proteome** is yet to be fully mapped, however estimates of its size range from 20,000 different proteins to over 80,000. The Protein Data Bank contains nearly 200,000 proteins, whose structure has been painstakingly confirmed in the lab by x-ray crystallography, however DeepMind has since released structures for 200 million proteins, using their AlphaFold 2 AI model to predict their structures.

Proteins can make structural materials like cartilage, collagen or even spider silk. They can form enzymes, which act as catalysts to facilitate nearly all biochemical reactions in living organisms. They can even assemble into intricate nanomachinery – the nuclear pore complex controls the flow of molecules into and out of the cell nucleus and is comprised of over 450 individual protein molecules of 34 different kinds.

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