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Insights

Genomic testing and the future of medicine

Key highlights:

- Genomic testing could become the standard of care, with more sequencing at birth, for cancer patients, and even for healthy adults, among other uses
- The significant number of gene therapy drugs currently in biotech and pharma pipelines could drive a proliferation of gene therapy treatments over the next 10 years, offering long-overdue hope for many patient populations and driving numerous investment opportunities
- These innovations could cause substantial changes to the cost structure and timeline for treatments, potentially transforming global health care systems

The growth of genomic testing could signal a new chapter in the future of medicine.

Progress in genetic screening, testing, and analytics has the potential to revolutionise the treatment of countless diseases. In particular, we believe these advancements have significant potential to create gene therapies for rare diseases[1]. Many of these innovations could replace ongoing treatments with long-term cures. The increased power of genomic testing could therefore be enormously impactful to society. Importantly, it will also have substantial cost implications that could transform the global health care system.

[1] Rare diseases are defined as affecting fewer than 200,000 people in the US. However, there are more than 10,000 known rare diseases (affecting nearly 10% of the population).

A revolution in genomic testing

The Genome Project was groundbreaking and unlocked tremendous innovation potential. In the last few decades, the cost of gene mapping has reduced from millions of dollars per genome to now only hundreds of dollars per genome. It may soon fall to US$100. The falling cost of gene mapping has drastically increased our understanding of the genome and now allows us to focus on the downstream developments from this knowledge to unlock its power for drug discovery, including treatments for rare diseases.

Notably, innovation in genome sequencing technologies and strategies does not appear to be slowing down. We believe there is significant elasticity of demand as sequencing costs decline and as new clinical sequencing applications become viable. We see several new categories that have the

potential to become the standard of care during our lifetime, such as more sequencing at birth, for cancer patients, and even for healthy adults, among other uses.

- Sequencing at birth: This can help identify mutations in newborn infants that could affect their health and have implications for their family members and future generations. An estimated 6% of children are born with a genetic variation that presents as a disease.[2] Progress in this space is critical as many of these diseases are not identified until it is too late for treatment or cure. In these cases, an ounce of prevention may be worth a pound of cure. In addition, this could enable long-term studies for future research. Already, we have seen testing's significant impact on rare unknown genetic diseases (RUGD) sequencing, which helps eliminate the diagnostic odyssey for newborns and allow more appropriate treatments earlier than before.

- Sequencing cancer patients: Over the next few years, we believe commercial tests will be available for sequencing cancer patients across every stage. In our view, we will have symptomatic pan-cancer screening tests (in healthy individuals), germline sequencing to test for hereditary cancer risk (in healthy, but higher-risk individuals), somatic tumor sequencing to direct targeted therapies (for newly diagnosed cancer patients), and cancer recurrence monitoring tests (for cancer patients in recovery). Continued advancements here could detect cancer early, identify how specific patients will react to certain drugs, and help change the course of treatment. The number of known sub-types of cancer has increased dramatically and, consequently, the number of targeted treatments has grown substantially as well.

- Sequencing adults: There are numerous population studies underway with the potential to aid future research by creating a repository that combines genetic data with phenotypic information and medical records. The large population sequencing efforts of the last decade should start to yield important insights that will drive pharmaceutical R&D forward. These broad sequencing efforts also raise ethical and inequality concerns as standards for data sharing are still evolving.

We have already seen the benefits of this type of innovation in cancer treatment. The impact of this progress can be enormous. For example, a 1% reduction in cancer mortality equals an estimated US$695 billion in increased quality of life, productivity, and survival.[3] This is just the beginning.

We believe this huge increase in the categorisation of sub-types of disease will likely happen with all types of diseases, enabling new, targeted therapies. These targeted therapies also span multiple different technologies, including cell and gene therapy, mRNA-focused therapeutics, and more. The mRNA technology is particularly relevant in the wake of recent vaccine developments. Importantly, developments in pharmacogenomics can also increase our ability to understand how a patient will metabolise and react to drugs.

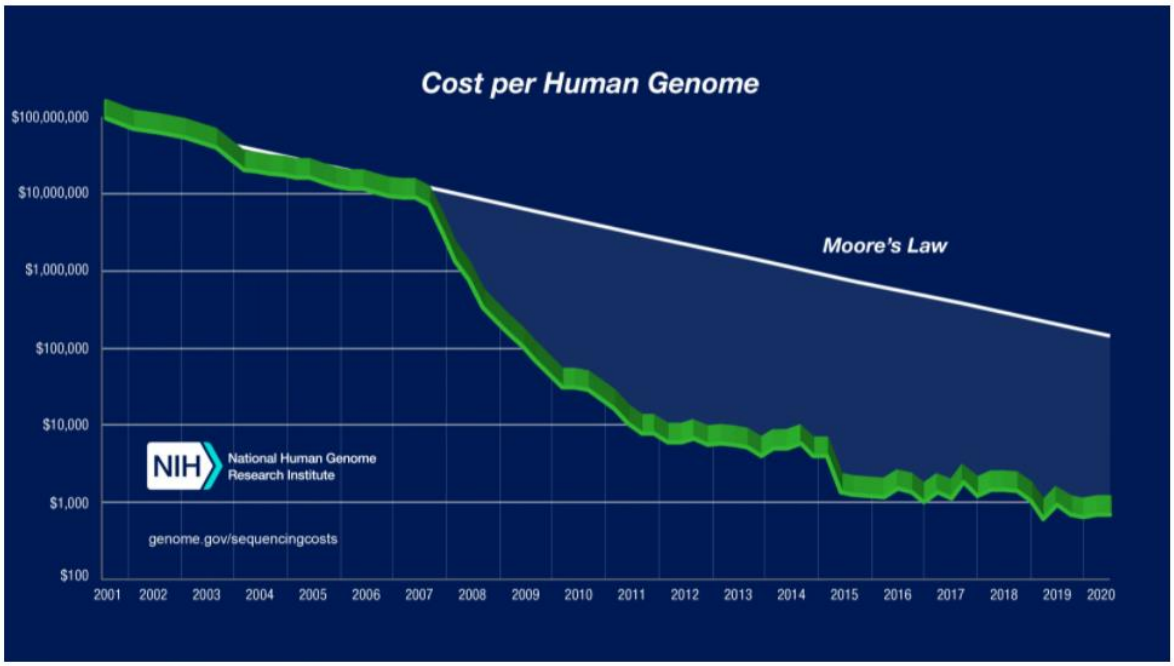
Dr. Bobby Gaspar, MD, PhD, an expert in gene therapy, feels strongly that this is the right way to treat a whole series of diseases because it can enhance safety and improve efficacy. He believes the ability to identify the specific genes associated with a disease opens up a whole new world of treatments.

Rapid innovation in therapeutics

There has been significant progress in key areas such as eye diseases, muscle atrophy disease, and sickle-cell disease. In some cases, no progress had been made in treating these diseases in years but there is now renewed hope with gene therapy. By finding the root cause of a disease, we are better able to target it directly instead of simply treating symptoms. Critically, the scope of the opportunity is rapidly expanding.

In 2007, there were 2,000 human genes associated with rare diseases, when the cost to sequence a genome was US$10 million.[4] In the next seven years (until 2014), as the sequencing costs came

down, the number of genes discovered associated with rare diseases doubled to more than 4,000. This implies that more genes were discovered in seven years than in the previous century.[5]



Cost per genome data - August 2020

Source: National Human Genome Research Institute
https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

This process takes time to transition to real-world treatments. For example, the development of a revolutionary treatment for a rare eye disease took two decades from gene identification (RPE65) in 1997 to a new drug approval in 2017.

Fortunately, we are now seeing this process from discovery to trial to potential approval accelerating massively. The US Food and Drug Administration (FDA) expects progress in trials related to this innovation to culminate in 10 to 25 new gene therapy approvals annually by 2025 and we believe that number will continue to grow over time.[6]

Dr. Gaspar also believes the understandings gained in rare diseases can translate to treatments for larger populations. For example, his team has identified a treatment for a rare disease that has a symptom that looks like Crohn's disease. He thinks this knowledge can be leveraged to treat a subset of the large population with Crohn's.

We expect to see gene therapies increasingly approved for large patient populations. For example, sickle-cell anaemia will likely be one of the first diseases to have gene therapies approved that impact tens of thousands of patients in the US in the early 2020s.[7] In our view, this will be a landmark achievement for science and a dramatic improvement in the quality and quantity of life for tens of thousands of African Americans.

The significant number of gene therapy drugs currently in biotech and pharma pipelines could drive a proliferation of gene therapy treatments across a number of diseases over the next 10 years. Progress on these revolutionary therapeutics provides long-overdue hope for many patient populations. But it will also present tremendous costs for the entire health care system.

Significant impacts on the global health care system

The one-time cost for the eye treatment mentioned above is US$425,000 per eye and the price for the sickle-cell treatment could be greater than US$1 million.[8] While the cost of new therapies such

as these can be high, that cost should be weighed against potentially a lifetime of benefits. After all, many of these innovations could cure diseases that previously required lifelong treatment.

But the changes in cost structure and timeline for treatment raise significant questions for health care systems built on the previous model. The system is now built around chronic care, but the future may move away from repeated annual costs. This is particularly relevant in places without a single-payer model, such as the US, where many questions are left to be resolved. Who will ultimately be responsible for one-time, high-priced treatments? What is the duration and sustainability of these treatments? Can we maintain current payment models with treatments that have such high upfront costs?

These innovations have the potential to transform every aspect of the system from research, clinical trials, and approval to manufacturing. In our view, if the system changes from chronic therapy to one-time treatments that cure patients, the reimbursement landscape will need to adapt.

Furthermore, as these gene therapies expand into diseases that address larger populations, we believe the current payment model will indeed evolve, with three key potential models:

- We expect to see the direct government negotiation model become most prevalent in single-payer systems, such as those in Europe. Although it isn't our base case, if this model were implemented in the US, government programs would negotiate directly with the pharmaceutical industry to set prices for therapies. Gene therapy prices are likely to be heavily pressured in this model.

- In a model driven by treatment outcomes, therapy prices are directly related to quality-of-life improvements and cost savings versus the current standard of care, and are also based on the duration of effect. This model justifies high prices for gene therapies and is supported by many biotech and pharma companies.

- In a free-market model, payers will negotiate directly with the pharma companies to determine an appropriate price for the therapy dependent on many factors. These include the patient population, the disease, and the right treatment for each specific patient (instead of choosing gene therapy for all or none of the patients).

Rapid progress in this space is creating exciting opportunities but companies and investors are grappling with how to understand the investment potential created by these innovations. As noted above, the system is currently built around multiples of annual costs for long-term treatments. But it may be difficult to understand how to evaluate the market for a high-cost, one-time cure.

In many spaces, we expect the first-mover advantage for a new gene therapy will be large. In our view, this will be particularly true in targeted rare diseases where the first gene therapy treatment can reach the majority of patients. But with more mainstream diseases, there may be competition that makes it challenging to maintain the high prices to warrant significant development costs.

In addition, these innovations will have major ramifications for manufacturing processes. These treatments are often much more complex to manufacture and will require companies to make substantial investments to adapt new manufacturing capabilities. This is particularly relevant as companies look to automate manual processes and reach scale while trying to comply with regulators and quality standards. For smaller gene therapy companies looking to reach scale and commercialise over time, this raises questions of whether it makes sense to have in-house manufacturing or to partner with larger players.

There are two sides to the regulatory coin. As Dr. Gaspar notes: "Current regulations are designed for the existing medicine paradigm and don't have the flexibility for the medicines now coming along in gene therapy. As more applications become viable, companies and regulators will both need to adapt and evolve to move these drugs toward approval." Ultimately, for regulators to gain confidence

in the science, we think companies will need to demonstrate the long-term viability of these new treatments.

While there are still many questions outstanding, these technological innovations potentially offer even more than novel treatments. They also have the potential to drastically reduce the timeline and uncertainty of the research and approval process as we radically improve our understanding of these therapeutics. In our view, although there is a high cost to develop these treatments, as our knowledge increases, a pipeline of targeted treatments with increased accuracy, efficacy, and safety may offer companies a much higher chance of success and far fewer failures.

In addition, as with many areas of rapid innovation, this progress raises numerous interesting ESG questions. Will manufacturers face increasing pressure from investors to lower drug prices due to ESG considerations? Would companies be willing to lower the price of gene therapies for older patients who are unable to pay off the high prices over time? Will gene therapies be available in markets/countries that cannot pay their high costs?

We believe it is critical to watch how the system adapts to these new treatments. In our view, the current pace of innovation implies companies expect high profits per patient, but if prices go lower with increased competition or regulation, will that reduce the incentive for future innovation?

Bottom line: Investment implications

In our view, genomic sequencing is likely to fuel a revolution that drives the future of medicine. Many diseases, from the rare to the more common, will be increasingly treatable and even curable as a result of this innovation. We expect average prices for gene therapy to fall over time and competition to increase. Price pressures will, in our view, be most acute for those diseases with large patient populations and current treatment paradigms. However, we do not expect high levels of patient penetration across new gene therapy treatments in the short term.

The investment opportunities these innovations present span biopharma companies, genetics-based diagnostics firms, and sequencing equipment companies. There are now dozens of publicly traded companies that we find compelling in this space as well as more private companies that we frequently assess. This offers an investable opportunity set that is far greater in 2021 compared to even 10 years ago. Importantly, we believe this opportunity will continue to grow.

We think gene therapy proliferation also provides an opportunity for MCOs to demonstrate their value add to the system and their clients, as well as to create new products for self-insured customers.

Countries and regions are likely to see varying levels of adoption as these advancements continue. In our view, we should be looking to Europe to adopt these therapies more quickly given their single-payer model. In the US, many questions remain. Will states shift risks to new programs and private payers to manage cost? Should the federal government take the lead? Or is a state-by-state approach more likely?

We are entering a new frontier driven by genomic testing and the treatments it enables. In our view, this will improve health care and create opportunities for innovative treatments. But it will also have significant impacts on the system as a whole as the health care industry and countries alike adapt to new treatment and cost paradigms.

Source: Wellington Management, the sub-manager of the United Global Healthcare Fund.

Notes:
[1] US Food and Drug Administration, “Rare Diseases at FDA.” Data as of February 2020.
[2] US National Library of Medicine, National Institutes of Health, “Serious Birth Defects Kill At Least Three Million Children a Year,” John Zarocostas.
[3] Grail S-1, SEC filing. September 2020.
[4] National Human Genome Research Institute, “The Cost of Sequencing a Human Genome,” December 2020.
[5] US National Library of Medicine, National Institutesof Health, “NGS Technologies as a Turning Point in Rare Disease Research, Diagnosis, and Treatment,” Ana Fernandex-Marmiesse, Sofia Gouveia, Maria Couce.
[6] US Food and Drug Administration statement, January 2019.
[7] Endpoints News, November 2020.
[8] Fierce Pharma, January 2018, JAMA Pediatrics, “A Budget Impact Analysis of Gene Therapy for Sickle Cell Disease,” Patrick DeMartino, Meredith Haag, Alyssa Hersh, et al., March 2021.

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21 September 2021

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