UBS

Longer Term Investments

Genetic therapies

Chief Investment Office GWM | **07 March 2019** 3:10 pm GMT
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- Genetic therapies use genes and cells to treat serious diseases. They could revolutionize medicine by removing the fundamental causes of inherited genetic conditions like hemophilia.
- If shown to be successful in treating more common illnesses, such as diabetes or Alzheimer's disease, they could profoundly disrupt the existing pharmaceutical industry. Much more clinical data is needed to determine their efficacy in such applications, and other practical challenges have to be resolved. But advances here could change how healthcare resources are allocated.
- The first treatments to reach the market could achieve combined sales exceeding USD 20bn, we estimate. The longer-term potential is large but currently difficult to quantify.
- We recommend a diversified portfolio of companies exposed to the theme given the idiosyncratic risks of drug development.

Our view

Genetic therapies modify genetic information with the intent of curing disease. Replacing defective DNA can remove the cause of an illness and restore health. The technology represents a paradigm shift in medical care compared to traditional drug treatment, which usually just slows disease progression or relieves symptoms.

In the last two years gene therapies have achieved scientific proof-of-concept and gained regulatory clarity. They are now receiving the backing and capital of big pharma and biotech companies. Clinical data to come will likely reveal which companies' products are most promising, while more comprehensive coverage by insurers and governments should help these new products achieve commercial viability.

We expect improvements in technology to spur development of new genetic therapies as the pipeline evolves. Clinical success, unmet need and the resolution of complex economic issues will determine which therapies are ultimately successful. Population growth and aging provide a supportive backdrop for the theme.

Much remains to be proven but we see sufficient evidence that gene therapies have a key role to play in treating certain rare diseases. Should new data demonstrate their efficacy in treating more common illnesses, they could profoundly disrupt the existing biopharma industry.

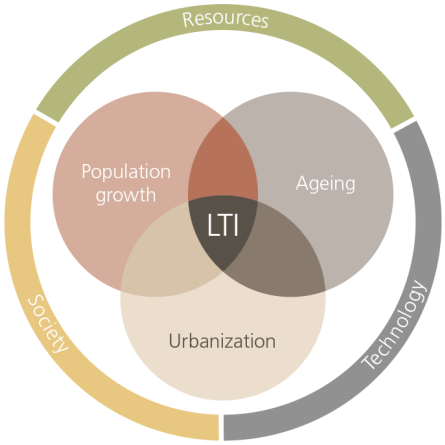
Introduction to the Longer Term Investments (LTI) series

– **The Longer Term Investments (LTI)** series contains thematic investment ideas based on long term structural developments.

– Secular trends such as population growth, ageing, and increased urbanization create a variety of longer term investment opportunities.

– These investment opportunities are influenced by the interplay of technological advancement, resource scarcity, and the societal changes.

– Investors willing to invest over multiple business cycles can benefit from potential mispricings created by the typically shorter term focus of stock markets.



We recommend taking a diversified approach to investing in the theme given the high idiosyncratic risks of new technologies and drug development.

Genetic therapies – toward a new treatment paradigm

Genetic therapies appear to be at a crucial inflection point: after years of investment and a number of false starts, the first of a new generation of gene therapies has now reached the market. We expect both continued scientific innovation and signs of commercial acceptance to support the theme. Longer term, genetic therapies could cause major disruption to the existing biopharma industry, although scientific, technological and economic hurdles still need to be overcome.

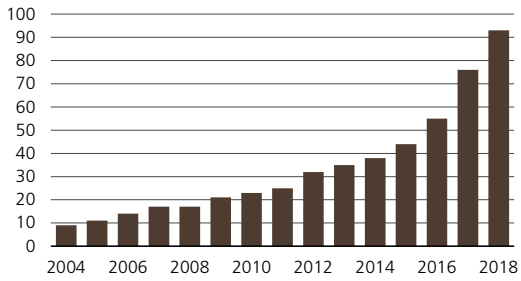
Moving from pipeline to commercial reality

While the number of genetic therapies in development has been steadily growing for over a decade (Fig. 1), numerous key milestones have been reached within the last two years that place the field at the cusp of commercial acceptance.

- **Scientific proof-of-concept**: In late 2017 the first gene therapy for an inherited genetic disease received US approval, and a second is currently filed with approval expected this year. Two cell therapy products (CAR-T for cancer) were also approved the same year.
- **Regulatory clarity**. While existing approvals set precedents and established the approval requirements for genetic therapies, the US Food and Drug Administration (FDA) has gone further and recently published guidelines about their future development. It has stated it expects to approve 10-20 new cell and gene therapies per year by 2025.
- **Big pharma interest**. As the industry has matured, large-cap pharma and biotech companies have begun to invest in the technology. We estimate that, since 2017, big pharma has spent over USD 35bn on acquisitions of cell therapy and gene therapy companies. These deeper-pocketed groups can provide capital for further development, manufacturing capacity and building out commercial infrastructure.

Fig. 1: Large number of gene-therapy products in development

Active trials for gene therapy products



Source: Bernstein research, clinicaltrials.gov. Note: trials for gene therapy products using adeno-associated virus (AAV) vectors, the most common type of vector used for *in vivo* gene therapy.

Box 1: Defining genetic therapies

"Genetic therapy" serves as an umbrella term we use for a class of treatments that modify human genetic information with the intent of curing disease. The premise is simple and elegant: replacing defective DNA can remove the cause of an illness and restore health. Conceptually, this approach represents a paradigm shift in medical care relative to traditional drugs, which act on proteins and usually just slow disease progression or relieve its symptoms.

We identify three distinct approaches to treatment, according to the technology used:
- **Gene therapy** introduces a copy of a missing gene into cells where it is absent or damaged, restoring the correct gene and protein function.
- **Gene editing** precisely alters the genetic material in a cell by inserting, deleting or correcting an existing gene. The change is permanent.
- **Cell therapy** administers entire cells that have been modified to achieve a specific therapeutic aim, such as targeting cancer.

Each technology is described in more detail in the Appendix, along with an overview of the science of genetics.

In our view, these milestones have reduced the technological risk of the industry. Given the number of products in development, we expect new clinical data to emerge in the coming years that will expand their applications to new and more prevalent diseases. Commercial considerations are also now becoming important.

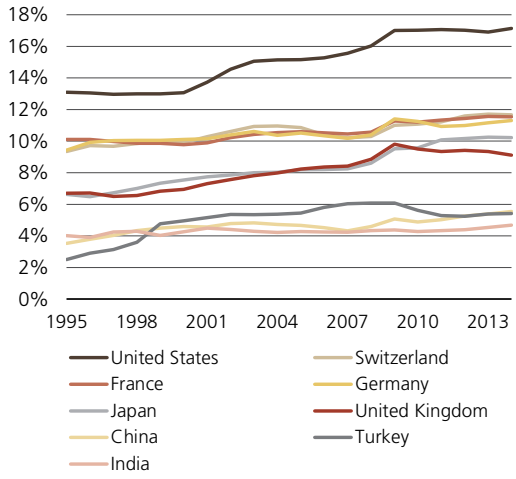
Major disruptive impact possible, but yet to be demonstrated

Genetic therapies that could cure chronic diseases with a single treatment would revolutionize healthcare, improving patient outcomes while reducing or even eliminating much of the on-going cost of managing these patients. The existing biopharma industry would face major disruption. But this blue-sky scenario for gene therapy companies is not yet supported by the clinical data. Remarkable efficacy has been observed in the treatment of several monogenic diseases (i.e. those linked to a single defective gene), including spinal muscular atrophy and some forms of inherited blindness. Others like hemophilia have also responded well to genetic therapies, though the hope that they can be used to treat widespread, chronic diseases remains a hypothesis.

For them to achieve their full disruptive potential further progress will need to be made on a number of fronts:

- **Evidence of efficacy in chronic disease**. Gene therapies have shown proof-of-concept in monogenic diseases. But the chronic illnesses like diabetes and cardiovascular disease that consume the majority of healthcare spending have more complex causes, with genetic mutations often representing risk factors rather than direct disease triggers. A number of genetic therapies are in studies to address widespread diseases such as Alzheimer's and Parkinson's disease, but we are unaware of any imminent data that might confirm their effectiveness. Doctors and patients will also want assurance regarding their safety before using gene therapies instead of well-understood drugs.

Fig. 2: Healthcare spending rising worldwide
Healthcare spending as a % of GDP



Source: World Bank. As of September 2017

- **More cost-effective manufacturing at scale**. Genetic therapies are difficult to manufacture, and current technology does not scale well. For example, according to one estimate, manufacturing a single dose of gene therapy to treat hemophilia using current technology could exceed USD 200,000. Wider adoption will require significant investment in capacity and, potentially, the development of more efficient manufacturing processes.
- **Supportive reimbursement and payment models**. Even assuming manufacturing costs can be reduced, genetic therapies are likely to command high prices given their potential to offer long-term or permanent cures. Economically, high upfront prices can be justified by future savings on drug and clinical costs. But the initial cash outlay may present a major hurdle to healthcare systems already facing significant financial pressure (Fig. 2). Potential solutions include staggered payments, or rebates in the event that patients fail to respond to treatment; some have even proposed an annuity-like payment model, tying total payment to how long an effective treatment lasts.

Demand supported by demographics and potential healthcare cost savings

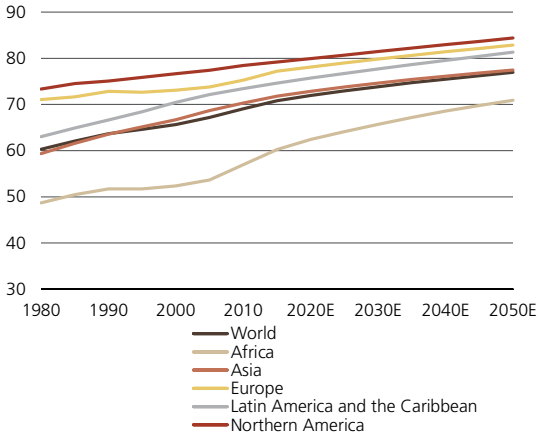
Demographic trends favor rising genetic therapy demand. World population will approach 10 billion by 2050, up from 7.3 billion currently. Global life expectancy is expected to reach 77 by the same year, compared to 70 in 2015 (Fig. 3). An older population increases demand for healthcare and drugs in general, and age-related diseases in particular. Cancer is an important early market opportunity for cell therapy treatments such as CAR-Ts, and gene therapies are being developed for many other diseases associated with aging, including Parkinson's and Alzheimer's disease. However, many of the initial applications of gene therapy and gene editing currently occur in hereditary diseases where aging plays little to no role.

The need to better allocate scarce health system financial resources could also underpin broader use of genetic therapies. They will almost certainly gain a place in disease management if they can demonstrate lower total expenditure than chronic drug therapy. We believe healthcare reimbursement is in the early stages of shifting toward new systems that reward quality and value of care over volume. This backdrop is likely to support treatments that, while individually expensive, can save costs elsewhere in the system.

Building the market

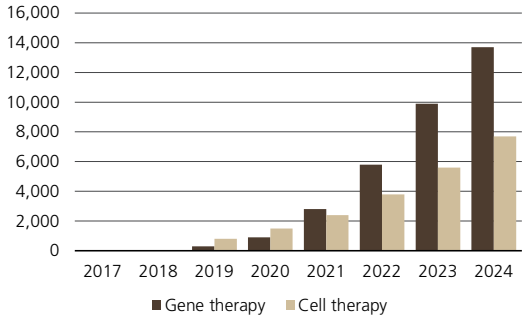
Beyond achieving further clinical success, the genetic therapies industry, in our view, needs to take further crucial steps to demonstrate its commercial viability. The initial market opportunity for it, we estimate based on approved treatments and the current late-stage pipeline, exceeds USD 20bn (Fig. 4). This figure captures likely markets for gene therapies that treat hereditary diseases, with known late-stage pipeline candidates, as well as cell therapies for blood-borne cancers whose efficacy has been demonstrated. There is substantial uncertainty about the therapies' use in larger indications, so the estimates of the total market opportunity vary widely.

Fig. 3: Life expectancy climbing worldwide
Life expectancy at birth, years



Source: United Nations, Department of Economic and Social Affairs, Population Division (2017); World Population Prospects: The 2017 Revision, UBS, as of July 2018

Fig. 4: Early indications of market potential in the area of USD 20bn
Consensus forecasts for late-stage gene and cell therapy products, USD billion



Source: Bernstein research, UBS

For context, our initial USD 20bn estimate represented 2% of global pharma and biotech revenues in 2018, and we would expect the opportunity to increase substantially as positive clinical data emerges in new indications.

With two cell therapies and one gene therapy commercially available at the end of 2018, cumulative sales have reached USD 350m (Fig. 5). We think the issue of reimbursement has held back early sales, in particular for government-funded patients. But new coverage rates to be published later this year could offer relief by raising payments to hospitals for CAR-T therapies, which could help boost uptake.

More evidence of the durability of gene therapy treatment, provided it is favorable, will also bolster its use. In mid-2019, for example, Biomarin is expected to publish data for its ValRox gene therapy for hemophilia that could demonstrate the treatment is effective for up to three years. While three years is not a lifetime cure, it would represent a major upgrade over the current three-times-a-week factor VIII infusions.

Investment conclusion

Genetic therapies represent a paradigm shift in medicine that has the potential to revolutionize healthcare delivery and disrupt the biopharma industry. While the initial dent they make in the market will be modest, they still represent life-changing breakthroughs for a limited number of patients with serious inherited diseases.

The field currently stands at an inflection point as recently approved therapies should begin to demonstrate their commercial potential. We expect new approvals, clarity on the duration of treatment and more favorable reimbursement terms to spur sales growth and support the theme. Despite previous setbacks, if genetic therapies take off this time we think they could be here to stay.

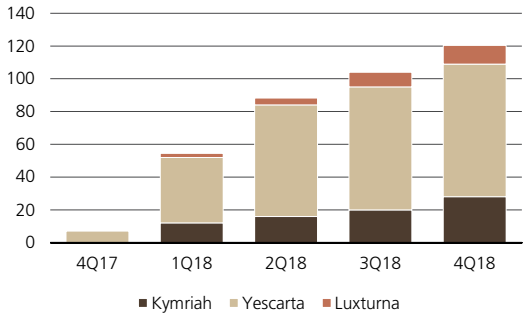
We anticipate pharma and biotech companies taking genetic therapies increasingly seriously, both as new opportunities and as potential competitive threats. More acquisitions of genetic therapy companies are likely.

Our estimate of the initial market potential the therapies represent translates into just 2% of global biopharma sales. We see the chance for marked capital appreciation of the theme should clinical trials and commercial rollouts meet our expectations. However, as ever in drug development, not all companies will succeed and idiosyncratic risk is high. We recommend investing in the genetic therapies theme through a diversified portfolio of firms exposed to it to manage the risks associated with clinical failure.

Ethical debates about genetic therapies

The ability to alter genetic information that may lead to permanent, or inheritable, changes in an individual's genome raises a number of ethical questions. It invites comparison to eugenics and raises concerns that wealthy parents will be able to selectively improve their children's physical and mental characteristics to the detriment of those less able to afford to.

Fig. 5: Genetic therapies sales
Quarterly sales of approved gene and cell therapy products (USD millions)



Source: Company filings, UBS analysis.

Further reading:

- "Shifting Asia – China's biotech revolution," August 2018
- "Longer Term Investments – HealthTech," 28 June 2018
- "Longer Term Investments – Oncology," 25 January 2018

Our theme focuses on companies that use gene therapy and gene editing techniques in human health applications with the intent of treating or curing disease. We think genetic therapies can play a key role in these cases, as illustrated by the remarkable efficacy results seen in the limited number of patients who have benefited from the treatments so far.

It is important to distinguish between somatic modifications, undertaken after birth, and germline editing carried out on embryos. Somatic modifications only affect the treated individual and cannot be passed on to future generations. Modification to the germline, on the other hand, will be present in every cell of an individual's body and, more importantly, can be passed on. Most scientific bodies support the former but not the latter, following the recommendation of the 2015 International Summit on Human Gene Editing.

The widely publicized case of gene-edited babies born in China in November 2018, which led to international condemnation of the scientist responsible, was a case of germline editing. The embryos had been altered using CRISPR gene editing intended to make them resistant to the HIV virus. More recent reports, however, have suggested that the alterations to the HIV-resistance gene, known as CCR5, may also improve the girls' cognitive abilities. Following the incident, China recently announced it will tighten regulations pertaining to gene editing.

Risks of investing in genetic therapies

Major risks to investing in the *Genetic therapies* theme include:

- **Technology failure**. The science behind genetic therapies is relatively new and the number of patients treated small. Despite several treatments having been approved, the technology could ultimately fail due to as-yet unidentified safety issues. This risk is more acute for gene editing, where even fewer clinical datapoints exist and the permanent alteration of the genome means side-effects could still surface many years after a treatment is approved.
- **Commercial failure**. Genetic therapies could be commercially unsuccessful despite technical success. Indeed, first-generation gene therapy products (Glybera from uniQure and Glaxo's Strimvelis) flopped in the marketplace as their use was restricted by a lack of patients and manufacturing challenges. We believe these factors are understood by current gene therapy sponsors, reducing the risk.
- **Product failure**. As with all drugs, each individual project carries idiosyncratic risks of product failure. This risk typically diminishes as products progress through the clinic, although the financial consequences of failure increase. This risk is best mitigated by investing in a broad portfolio of companies.
- **Competition**. Genetic therapies will be subject to the usual competitive risks of drug development: even a curative gene therapy could be rendered effectively obsolete by the availability of a better treatment with fewer side-effects, less dangerous administration or a lower cost. Another consideration for curative gene

therapy products is that they will reduce the size of their own market over time. In other words, the first treatment to market may be the most commercially successful even if it is inferior to a later product.

- **Pricing & reimbursement**. Unfavorable reimbursement has hampered the uptake of CAR-T therapies, as hospitals may not be covered for the non-drug costs associated with managing the complications of these treatments. We expect both the amount and the availability of government reimbursement to increase, and new US Medicare reimbursement rates should be announced in 2019.
- **Intellectual Property**. Much of the intellectual property (IP) related to gene therapy products is closely controlled by a few institutions. Lack of access to it could prevent a company from launching a product, or expose it to significant liabilities for infringement. We expect companies to be able to pay to license necessary IP, in line with industry practice.
- **Ethical concerns**. Gene therapy and gene editing are subject to a number of ethical risks. In November 2018 a Chinese scientist created the world's first gene-edited human babies to widespread international condemnation. Most countries currently prohibit gene editing of germline cells (i.e. those that can develop into functional embryos). Further ethical malpractice could lead to wider restrictions on the use of the technology, which may ultimately constrain its use for disease treatment.

Link to sustainable investing

In our view, genetic therapy can be considered an SI topic. It aligns to Sustainable Development Goal (SDG) 3 "Good Health and Well-Being" due to its aim to cure diseases by addressing their underlying cause rather than reactively treating symptoms. Targeting genetic mistakes that occur early in the disease cycle reduces the need for lifelong disease management and can considerably improve the quality of life for sufferers. This is especially true for monogenic diseases that could be cured with relatively simple gene modifications.

While the initial impact of the theme may be limited given expectations that treatment prices will be high, technological advances tend to reduce drug-manufacturing costs over time, which could make such treatments more widely accessible. In a bullish scenario, the potential of genetic therapies to disrupt traditional drug treatments could result in the practical elimination of some diseases with no existing treatment and of genetic diseases currently treated chronically. The main sustainability risk, however, is that such therapies will be misused or ineffectively regulated. That could lead to a slippery slope where gene-editing technologies are applied to achieve unethical goals. For this reason, we support companies that enforce policies compliant with current regulatory frameworks across their value chain and that enforce strict management of research processes.

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Melissa Spinoso, Sustainable Investing Analyst
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Appendix: Understanding genetic therapies

"Genetic therapy" serves as an umbrella term we use for a class of treatments that modify human genetic information with the intent of curing disease. The premise is simple and elegant: replacing defective DNA can remove the cause of an illness and restore health. Conceptually, this approach represents a paradigm shift in medical care relative to traditional drugs, which act on proteins and usually just slow disease progression or relieve its symptoms.

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Each is described in more detail below.

Genetic therapies - history and background

While the concept of gene therapy dates to the 1970s, it took until the early 1990s for the technology to reach the stage where patients could be treated. The field suffered a number of early setbacks, including the high-profile death of a patient in a 1999 trial and the commercial failure of two products launched in the first half of this decade. However, the field has survived these impediments and gene therapy techniques have continued to advance: the human genome was sequenced in the early 2000s and the cost of sequencing has plummeted in the last decade, which has improved our understanding of the genetic basis of many diseases. Progress has also been made in how to deliver gene therapies to patient cells, reducing the risk of significant side-effects. The latest generation of therapies has demonstrated evidence of remarkable efficacy in selected patient groups, with an acceptable safety profile. More recently, new technologies like CRISPR (see below) have enabled therapies based on gene editing to reach the clinic.

The first in vivo gene therapy to be commercially approved was launched in 2012 to treat an extremely rare hereditary condition leading to pancreatitis. The product was a disaster commercially, however,with reports suggesting just one commercial sale in five years. The next product followed in 2016, using an ex vivo approach to treat severe immunodeficiency ADA-SCID (also known as "bubble boy syndrome"). However, manufacturing constraints led to availability being limited to a single hospital in Milan and it, too, disappointed financially.

After these false starts, the last three years has seen a number of milestones for genetic therapy development. The first products of the current generation of genetic therapies to reach the market were two CAR-T (cell therapy) treatments for cancer approved in the US in 2017.

Later in 2017, a product for gene therapy treatment for blindness received FDA approval. More recently, in February 2019, the first use of an eponymous gene editing platform in a human clinical trial was announced. While in vivo gene editing treatments remain some years from commercial availability, we view this as an important milestone for the industry.

We expect further clinical and commercial developments in the coming months and years, as a number of other treatments are in late-stage development or filed for approval. The next major milestone is likely to be approval of spinal muscular atrophy (SMA) gene therapy in mid-2019. SMA is a rare neuromuscular disorder afflicting newborn babies. While gene therapy treatment allowed the ability to treat a previously-untreatable disease, SMA gene therapy may be more disruptive since treatments for SMA already exist. How the product is priced and its success with reimbursement will, therefore, be an important indicator of how payers view genetic therapies in conditions with alternative treatments.

The science behind gene therapy: The role of genes and proteins

Genes and proteins are both essential parts of our cells: genes contain our genetic information, while proteins are larger molecules that perform the physical functions required to build, maintain and regulate our bodies. Each gene is a specific sequence of DNA that consists of anywhere from hundreds to millions of base pairs and contains the instructions the cell needs to manufacture proteins.

In a process known as transcription, the genetic "code" in our DNA is "read" by RNA, an intermediate molecule that assembles sequences of amino acids into proteins. Collectively, all of an individual's genes are known as their genome. The Human Genome Project estimated that the human genome contains around 20,000 genes that code for proteins.

Mutations in a gene, or mistakes in DNA transcription, can lead to defective proteins. Mutations can either be inherited or acquired due to environmental factors. While some mutations are harmless, others cause potentially serious illness as key proteins required for the proper functioning of our bodies are either absent, malfunctioning, or occasionally over-produced. This linkage is clearest in the case of hereditary diseases. For example, spinal muscular atrophy (SMA) is a monogenic hereditary disease caused by the mutation of a gene known as SMN1 in an otherwise healthy baby. The defective gene leads to a deficiency of a protein called SMN that promotes the function of nerve cells in the spinal cord. A lack of SMN prevents the muscles in the chest and back from developing properly, leading to a curved spine, an inability to walk and even breathing difficulties in severe cases.

Not all diseases have such a clear link to genetic defects: some mutations are thought to increase the risk of developing certain conditions, but additional triggers, such as environmental conditions, also contribute. For example, at least seven genes have been identified in playing a part in a person developing Parkinson's disease, but none are currently believed to directly cause the condition, and a person

may carry mutations in one or more of these genes yet never develop Parkinson's.

The core idea behind genetic therapy is to fix the damaged genetic material and restore correct protein function. Doing so removes the underlying cause of the disease. By contrast, traditional drugs act by blocking or promoting the interactions of proteins. While this can effectively treat the symptoms of a disease as long as the drug is present, it does not address the underlying cause of defective proteins in the first place.

What is gene therapy?
Gene therapy introduces a copy of a missing gene into cells where it is absent or damaged. Once the missing gene is replaced, the cell can express related proteins correctly, removing the cause of disease.

The biggest technological challenge of gene therapy is getting the corrected gene (known as a "transgene") into the cell. This is achieved by attaching the transgene to an inactivated virus ("vector") that carries it into the cell nucleus. Viruses used as gene therapy vectors have been modified so that they cannot replicate or release their own genetic material into the body.

An important unanswered question about gene therapy is its durability. Because neither the transgene nor the vector integrates into the genome, it is not clear how long the cell will continue to express it, or how long the treatment will last. A key datapoint for this debate, we believe, will be the publication in mid-2019 of three-year efficacy data for Biomarin's ValRox, a gene therapy product in Phase III for hemophilia. This disease is treatable today but at the cost of significant inconvenience for patients: many must undergo preventative injections of factor VIII three times a week A significant number of patients develop inhibitors to factor VIII that reduce its efficacy and necessitate treatment with bypassing agents at a cost that can exceed USD 500,000 annually. A long-lasting gene therapy would constitute an attractive option for many hemophilia patients, even if the effect was not permanent.

What is gene editing?
Gene editing is a more complex and potentially much more powerful technique that facilitates the permanent correction of defective genes. It requires three steps:

1. Identify the damaged section of DNA
2. Cut it out using an enzyme (often referred to as "molecular scissors") to remove the damaged base pairs
3. Repair the gene by inserting new genetic material or closing the gap

Gene editing results in a permanent change to the patient's genome. It is more versatile than gene therapy, since it is possible to insert new genes, or to correct or delete defective ones. Gene editing is also believed likelier to provide a durable treatment effect than gene therapy, since the corrected genetic material is integrated into the patient's genome. But the technology is at a nascent stage of development with little clinical data in the public domain. For example, the

first treatment of a patient with a gene-editing treatment using the popular CRISPR/Cas9 system was announced only in February 2019.

The primary side-effect associated with gene editing is the risk of "off-target" effects, where a gene-editing treatment cuts unintended pieces of genetic material that could result in such consequences as carcinogenicity. Also, intended modifications may also have long-term effects undetected during limited clinical trials.

Like gene therapy, the early uses of gene editing have been in inherited diseases. One example is Sangamo Therapeutics' SB-318 gene-editing approach to treating mucopolysaccharidosis type 1 (MPS-1). MPS-1 is one of a family of inherited disorders in which the lack of key enzymes allows the build-up of sugars in cells, leading to irreversible tissue damage over time. Some patients can be treated with enzyme-replacement therapy, or regular infusion of the missing enzyme, but replacing the gene that codes for production of the missing enzyme could provide a more permanent solution. Gene editing, with permanent correction of the genome, is likelier to offer long duration of effect in this situation, since the correction needs to be made in fast-dividing cells. SB-318 is currently in Phase I/II trials.

What is cell therapy?

Cell therapy is a related approach that differs from gene therapy and gene editing by administering entire cells instead of viral vectors. The cells, which may have been sourced from patients themselves, are often altered outside the body using techniques similar to gene editing to modify their genetic make-up to target a particular disease. They are then administered to the patient as whole cells.

Box 2: What is CRISPR?

There are at least four main gene-editing technologies in current development. The most well-known and widely used is known as CRISPR.

CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats) is a gene editing technology that uses guide RNA to locate the targeted DNA sequence, and an enzyme called Cas9 to cut the DNA. It is based on natural antiviral mechanisms found in bacteria.

Benefits of CRISPR include the flexibility to target different DNA sequences, as only the guide RNA portion of the molecule has to be altered, and the ability to multiplex (targeting multiple DNA sequences at once). This makes it an attractive solution for gene-editing treatments. It is currently being used as the basis of multiple pre-clinical gene-editing programs.

Conversely, some experts believe that CRISPR may be more susceptible to off-target effects than other gene-editing techniques, due to its use of RNA to identify binding sites.

Other gene-editing programs include Sangamo's ZFN platform, and TALENS. ZFN is a gene-editing platform that uses zinc finger DNA-binding proteins to recognize the individual necessary parts of the DNA, and enzymes to cut DNA.

So far the best-developed examples of cell therapy are T-cell treatments for cancer, including CAR-Ts such as Kymriah and Yescarta, both approved to treat leukemia. CAR-T is a form of personalized immunotherapy for cancer that combines the cytotoxic (i.e. cell-

killing) ability of T-cells (a type of white blood cell responsible for fighting infection) with the targeted nature of monoclonal antibodies. Treatment involves a three-step process:

1. T-cells are removed from the body
2. The T-cells are engineered to recognize the relevant cancer target
3. Engineered T-cells (CAR-Ts) are reintroduced to the patient, where they multiply and attack the targeted cancer cells

Like gene therapies, these treatments have shown impressive efficacy in limited patient populations but have yet to demonstrate their commercial potential. The cell therapy category is wider than just CAR-T treatment for cancer; for more background on CAR-T and cell therapies, please refer to our report *Longer-term Investments: Oncology*, published 25 January 2018.

How will gene therapy affect the existing biopharma market?
A major attraction of genetic therapies is their potential ability to effectively cure a patient with a single or small number of treatments. Removing the need for life-long treatment for patients with inherited or chronic disease would have a number of benefits. It would improve the quality of life and lead to less disruption for patients, drastically reduce the need for expensive physician time and eliminate spending on drugs. From a biopharma perspective, the latter point is a challenge to the existing drug industry's business model.

We expect genetic therapies to be used more modestly at first, however. Scientifically, the clearest case for their efficacy is in diseases with a direct link to a single genetic mutation (monogenic diseases). For more causally complex ones, where genetic mutations represent risk factors rather than specific causes, their efficacy has yet to be established. Moreover, treatments for widespread illnesses that can already be managed with cheap and safe drugs must meet a significantly higher safety bar than those for untreated rare diseases that are often terminal or severely debilitating.

Widespread use of gene therapies will also have a much larger budget impact on healthcare systems. This could be mitigated by one or more of the following: reducing manufacturing costs, demonstrating the long durability of treatment that reduces the need for re-treatment and/or explore innovative payment structures to ease the burden of high upfront treatment costs.

Considering the current gene therapy and gene editing pipeline, most projects in late-stage development target monogenic diseases with no satisfactory existing treatment or those necessitating chronic treatment that is inadequate (such as enzyme-replacement therapy or factor VIII prophylaxis for hemophilia). Treatments in the first group will effectively expand the existing biopharma market, while those in the second will compete for patients with existing treatments.

In our view, to become genuinely disruptive, genetic therapies must expand their application to treat more common, chronic diseases that may have genetic links. We think this is unlikely in the near term: while a large number of clinical trials are ongoing, we are not aware of any imminent clinical data that might confirm these hypotheses. Their ultimate disruption potential will also depend on the extent to

which they offer a complete "cure" or are part of a broader treatment program to reduce the risk or severity of disease.

Challenges for genetic therapies

In our view, recent scientific and regulatory milestones show that genetic therapies are likely to have a role treating rare diseases. But as outlined above, a number of challenges still need to be resolved for the technology to reach its full potential and become genuinely disruptive to the existing biopharma industry. We discuss the most relevant issues briefly below.

- **More cost-effective manufacturing**. Gene and cell therapies alike face major manufacturing hurdles. The viral vectors used in gene therapy products are incredibly large molecules that are technically challenging to manufacture. The current small scale of the industry makes this issue manageable still, but growth will require significant industry investment in capacity. Given the batch processes involved, the normal yield improvements seen when biotech products reach scale may not take place, which would limit the ability to reduce prices that promote wider adoption. Moreover, cell therapies are often tailored to each individual patient, a process that inherently lacks economies of scale. One solution may be so-called allogenic (i.e. off-the-shelf) cell therapies, but their development has progressed slowly.
- **Better government reimbursement**. Given their small patient populations and expensive manufacturing, all gene and cell therapies launched to date have high prices: CAR-Ts Kymriah and Yescarta cost USD 475,000 and USD 373,000, respectively, excluding administration costs, while Luxturna is priced at USD 850,000. High prices per se are not a problem for treatments with small patient populations, as their total budget impact is limited. But while commercial insurers cover these products, early experience suggests that poor reimbursement has limited their sales in government channels. For example, Medicare reimbursement for CAR-T treatments in the inpatient setting (accounting for the vast majority of use) is currently capped at USD 222,500, which does not cover the cost of the drug. In addition, emergency treatment for potential side-effects of CAR-T therapy can exceed USD 1m in extreme cases, exposing hospitals to high potential losses. In February, CMS announced a new nationwide coverage policy broadening the scope of eligibility for CAR-T treatment, but has yet to increase the amount paid for it. We expect a further announcement in 2Q19 with new coverage rates that could help alleviate the financial burdens for Medicare patients.
- **New payment models**. Currently, cell and gene therapy treatments are paid upfront as a single payment. Consistent with the general trend in the industry to tie reimbursement more closely to the value rather than volume of care, we expect to see alternative payment structures explored in time. But there is little agreement yet how to structure these payments, and the structure of the US insurance market in particular adds to the complexity.

Genetic therapies in China

While the US is the dominant player in developing genetic therapies, China has also made considerable leaps forward in the field, in part because of strong government support.

The USD 9.2bn China Precision Medicine Initiative was launched in 2016. Its early focus on gene sequencing and genomics for diagnostics, particularly pre-natal testing and cancer diagnosis, has quickly evolved into nascent capabilities in cell therapy and gene editing. China's high incidence of cancer and relatively large patient populations, even for blood cancers, makes it a natural market for genetic medicine. In 2018, 153 CAR-T trials, or one-third of the global total, were conducted in the country. Unsurprisingly, Chinese companies with genetic therapy capabilities have been quick to attract the attention of global biopharma companies for joint development.

Gene editing is also developing rapidly in China due to government funding and a more relaxed regulatory environment than in the US or EU. In 2018 the National Natural Science Foundation of China granted funding to over 90 CRISPR research projects, bringing the total to 270 government-funded projects since 2014. Although safety and ethics concerns surround some CRISPR/Cas9 uses in human studies, China has been active in trials, conducting at least nine registered clinical studies to treat cancer and HIV, with more than 80 patients tested as of February 2018. While there is no specific regulation on clinical applications using gene editing in China, the government has voiced support for international standards and guidelines regarding germline gene editing. Following the November incident it has recently announced that it will tighten regulations concerning gene-editing technology.

Appendix

Terms and Abbreviations

Term / Abbreviation	Description / Definition	Term / Abbreviation	Description / Definition
1Q, 2Q, etc. or 1Q11, 2Q11, etc.	First quarter, second quarter, etc. or first quarter 2011, second quarter 2011, etc.	A	actual i.e. 2010A
COM	Common shares	E	expected i.e. 2011E
GDP	Gross domestic product	Shares o/s	Shares outstanding
UP	Underperform: The stock is expected to underperform the sector benchmark	CIO	UBS WM Chief Investment Office

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Version 02/2019. CIO82652744