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October 2019 – Revisiting Genetic Medicine Investments

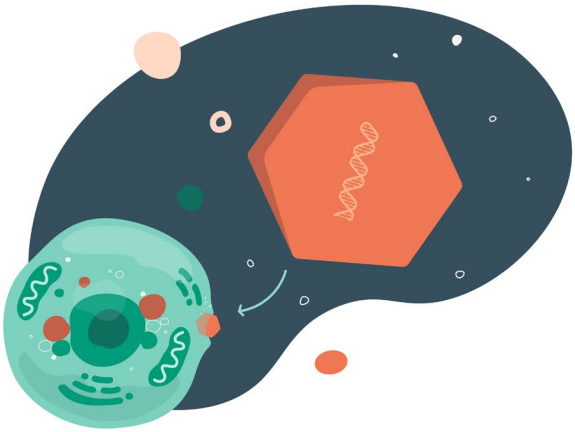
Almost two years ago we wrote about the scientific promise of genetic medicine. Since then, the science has accelerated as investors, companies and academic labs in the space have deployed significant capital and resources into groundbreaking research and advancing in-human clinical trials. Several gene therapies have even received commercial approval from the FDA and European Medicines Agency (EMA). These are life changing therapies for patients who often face debilitating chronic conditions that are a drain on quality and duration of life, as well as a financial drain on the healthcare system. Despite significant scientific and clinical progress, many public companies focusing on genetic medicine have seen their share prices halved over the last six months due to external factors that we think are unlikely to impact the long-term promise of the investment opportunity. In light of the sell-off and, in our view, attractive opportunity, we wanted to revisit the space. While these are high-risk investments, we think some exposure could make sense for many portfolios so long as investors have a multi-year investment horizon and are willing to sit through periods of elevated volatility.

As a brief, 10,000-foot refresher, we have included a simple graphic on the following page explaining the three main approaches to genetic medicine: gene therapy, cell therapy and gene editing. We would be happy to discuss the science behind genetic medicine in more detail if interested.[1]

To get a better sense on the investment opportunity and landscape, Stuart attended the largest Wall Street investment conference focused on genetic medicine two weeks ago in New York, where more than 80 public and private companies, as well as key opinion leaders, presented their latest data and provided insights on key scientific developments and investment trends in the sector. The key takeaway for investors is that companies involved in genetic medicine development represent a transformational shift in the approach to healthcare in the U.S. and globally: **from chronic treatments** designed to keep patient's symptoms in check **to curative treatments** that are administered once. While this shift will require a new approach to insurance reimbursement models, the new treatment paradigm has the potential to significantly lower healthcare costs as even a therapy priced at $1m has the potential to drastically reduce systemic costs of chronic treatments (for example, a $1m Hemophilia treatment administered one time would in four years represent net savings to the healthcare system as the average annual patient cost in the U.S. is $270,000).[2]

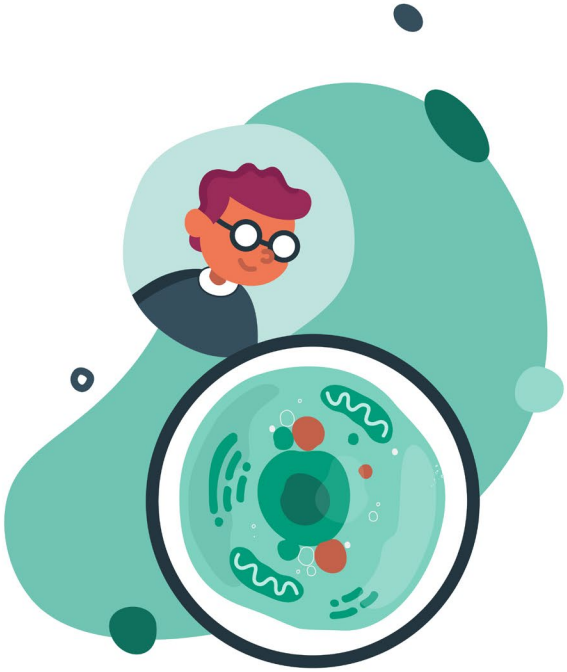
The other key takeaway is that scientific advances in the field are much farther along than appreciated by the investment community and general public. Aside from compelling clinical data generated in many of the 300+ genetic medicine trials in progress (ranging from cancer treatments, neurological disorders, vision loss, blood diseases and rare skin conditions),[3] there is widespread optimism about the potential for genetic medicine to soon target conditions caused by more than one genetic mutation. Currently, most genetic medicine is aimed at treating some of the 10,000 or so monogenic diseases caused by a single mutation in a patient's genome.[4] This is accomplished through replacing, silencing or editing a patient's single genetic mutation. In the medium-to-longer-term future, leading scientists (such as Jim Wilson from the University of Pennsylvania and George Church from Harvard)[5] are optimistic that genetic medicine can be used to treat the majority of diseases caused by polygenic mutations – or multiple defects in a patient's genome – including common diseases of aging.

Defining the Approaches



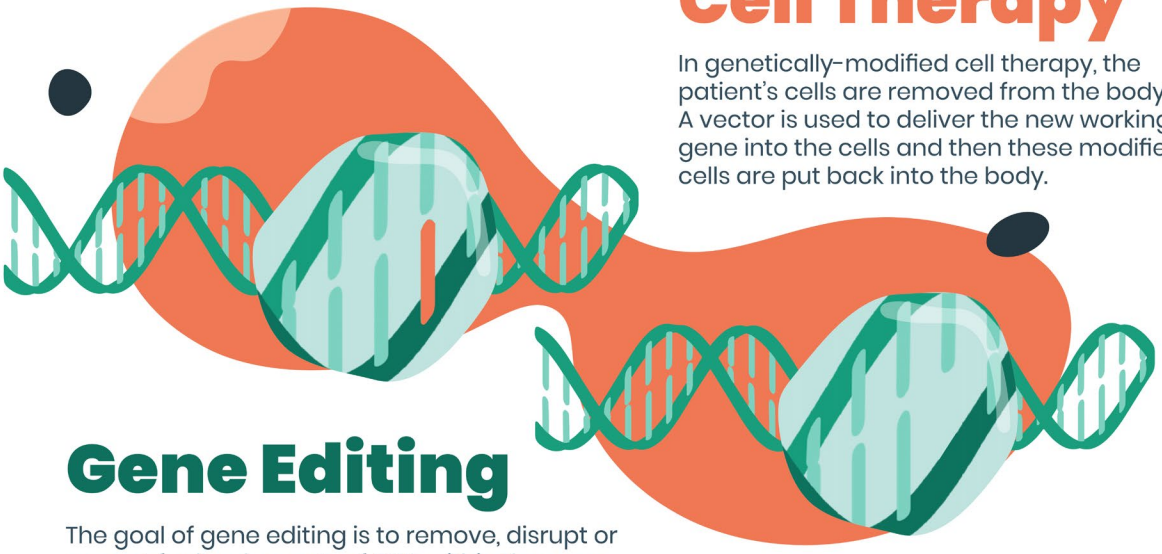
Gene Therapy

It is the introduction, removal or change in genetic material - DNA or RNA. A vector, often a virus, delivers a new working gene or genetic material into the cell. Don't worry the genes in the virus that could cause disease have been removed.



Cell Therapy

In genetically-modified cell therapy, the patient's cells are removed from the body. A vector is used to deliver the new working gene into the cells and then these modified cells are put back into the body.



Gene Editing

The goal of gene editing is to remove, disrupt or correct faulty elements of DNA within the gene. Gene editing uses systems that are highly precise to make this change inside the cell.

AMERICAN SOCIETY of GENE & CELL THERAPY

According to a recent Goldman Sachs analysis, the U.S. and European market opportunity for genetic medicines may be as large as $4.8 trillion – yes, trillion – based on current treatment costs for the range of indications for which genetic medicine holds the most commercial promise (oncology, neurology and eye disorders).[6] For as much political flak that pharmaceutical companies receive today on drug pricing behavior, their true long-term threat is not from a changing regulatory environment, but from the new generation of genetic medicines under development that threaten to disrupt the primarily chronic treatment paradigm of the global pharma industry, whose sales amount to an estimated $1 trillion annually.[7]

In assessing potential investments in the genetic medicines space, we think its important investors focus on the following factors:

1) Attractive valuation relative to a company's cash balance, breadth of clinical assets/intellectual property and internal manufacturing capabilities. Recent M&A transactions also provide guidance as to valuation.

2) Ample cash on balance sheet to support companies in costly clinical development. We especially like companies trading at low multiples to their cash balance, as that reflects over-pessimism about the underlying science.

3) Internal manufacturing capabilities that enable companies to design and manufacture highly engineered viruses (typically adeno associated viruses) that deliver therapies into the target patients' bodily tissue. Manufacturing is a bottleneck issue for genetic medicine firms, so companies that have FDA or EMA approved facilities have a relative competitive advantage (manufacturing expertise is also attractive to potential strategic acquirors).

4) Broad clinical trial pipeline based on platform approach to therapies (meaning that the science underlying one set of trials can support expanded therapeutic indications should initial trials prove effective). Relatedly, we prefer companies with a solid intellectual property position either via internally developed patents or exclusive licensing.

5) Viable path to commercialization and sound business development activity. These companies eventually need to generate substantial cash flows from their therapies to generate long-term returns (unless acquired via an M&A transaction). We like firms whose clinical assets would provide a meaningful improvement to current treatment options should trials prove successful. We also scrutinize the competitive landscape amongst genetic medicine firms and prefer firms that either may be first to market in their therapeutic indication, or best to market in their treatment's safety, efficacy and duration. Business development activity, such as licensing agreements with larger pharma firms that provides immediate revenue and longer-term royalties are generally a plus and serve as validation of the science.

6) Sound management.

There are more than 100 small-to-medium-sized firms operating in this space and we have narrowed our preferred investment universe down to roughly 10-15 firms, which we would be happy to discuss with you in more detail if interested. While we are firm believers that returns over the next 3-5 years will be substantial for companies whose science proves effective, there are several near-term headwinds worth noting that may keep stock prices down and result in continued volatility:

1) Political discussions around drug pricing as election season heats up in the U.S. While these companies ultimately are disruptive innovators who can lower the total cost of current treatments, the sticker price of $1m plus therapies may serve as ripe targets for politicians. Note that over time, companies in the space anticipate costs to decline as they become more efficient at manufacturing and new treatment methods come to market such as gene switching/control (which would essentially allow for a relatively low cost orally-delivered medicine that can regulate gene protein expression to be administered as opposed to costly viral delivery).

2) The continued exodus of capital from small caps stocks into large cap stocks. As discussed last month, we think fund flows leaving small cap firms and heading into large cap firms is overdone, but it is impossible to predict when this may reverse.

3) General economic and policy uncertainty. Related to point #2, at times of heightened market volatility, investor capital tends to leave small cap stocks – as they are perceived as risky – and move into large cap and defensive stocks – which, are perceived (wrongly we often think) as safer.

4) Slowdown in M&A activity. Large cap pharmaceutical and biotech firms have been aggressive acquirors of promising genetic medicine companies over the last several years, as acquiring promising science is often a safer way to deploy capital than investing from scratch in risky research and development. M&A activity has largely ground to a halt since the early spring after the Federal Trade Commission (FTC) decided to scrutinize Roche's proposed takeover of gene therapy firm Spark. We expect M&A activity to resume at a rapid pace once the Roche / Spark deal is approved and that companies will engineer deals to fit whatever framework the FTC outlines as acceptable for the Roche/Spark deal to close.

Despite these headwinds, we think that promising scientific results and commercialization of genetic therapies will prove far more consequential in driving stock returns – especially over a medium-to-longer-term period. Please let us know if you would like to discuss specific investment opportunities. We think the recent pullback is providing an attractive long-term entry point for patient investors who have a relatively high-risk tolerance. On a related note, our associate Alissa Hirsh has been researching opportunities more generally related to improvements in human longevity – though similar, investing in that theme is likely a more conservative way to get exposure to some of the scientific advances discussed in this letter. We hope to be able to share her presentation on the subject next month.

Lastly, we want to thank and highlight Lisa Schneider who earlier this month celebrated her 15-year anniversary with us. We are quite grateful for everything Lisa has done.

As always, please feel free to reach out with any questions on this letter, the markets generally or your portfolio. Many thanks.

Sincerely,

Peter Karmin
Managing Member

Stuart Loren
Director

Citations and Disclosures

[1] American Society of Gene & Cell Therapy, *Different Approaches*: https://www.asgct.org/education/different-approaches (accessed on Oct. 21, 2019).
[2] BioSpace, *A Look at Hemophilia Drug Prices and the Market* (July 3, 2018).
[3] Genetic Engineering & Biotechnology News, *25 Up-and-Coming Gene Therapies of 2019* (May 20, 2019).
[4] National Center for Biotechnology Information, Giulliana Augusta Rangel Gonçalves and Raquel de Melo Alves Paiva, *Gene therapy: advances, challenges and perspectives* (2017).
[5] Notes from Chardan's 3rd Annual Genetic Medicines Conference (Oct. 7-8, 2019).
[6] Goldman Sachs, *The Genome Revolution* (April 2018).
[7] Goldman Sachs, *The Genome Revolution* (April 2018).

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