The following is a redacted version of the original report. See inside for details.

Goldman Sachs

The genome medicine revolution is front and center for investors in healthcare. The long-awaited optimization of science coupled with encouraging clinical trial results and regulatory approvals have resulted in gene/cell therapies entering the market with the potential to create new and address existing markets at a rapid pace. M&A activity is rising as large biopharma companies look for entry and critical catalysts are stacking up on the calendar. In the latest report in our **Profiles in Innovation** series, we examine the drivers behind surging momentum for three inter-related technologies — gene therapy, genetically-engineered cell therapy and gene editing — and argue investors still do not fully recognize their potential to create new profit pools and disrupt the existing $1tn annual biopharmaceutical market. We see a 'one-time' total addressable market of $5tn for genome medicine, with the potential to expand further.

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PROFILES IN INNOVATION

The Genome Revolution

Sizing the genome medicine opportunity

The Goldman Sachs Group, Inc.

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Note: The following is a redacted version of "Profiles in Innovation: The Genome Revolution" originally published April 10, 2018 [71pgs]. All company references in this note are for illustrative purposes only and should not be interpreted as investment recommendations.

PM Summary

Genome medicine represents a new era. The manipulation of genes, the 'blueprint' of life that determines human attributes from our eye color to the risk of developing heart disease, has become a reality. Driven by advances in scientific knowledge (such as the discovery of the CRISPR/Cas9 gene editing system) and exponential declines in genome sequencing costs, scientists are increasingly able to target the genetic cause of a disease and repair it at the source by replacing or editing genes or introducing genetically-engineered cells. Given genes are the foundation of all biological activity, we believe genome medicine has transformative potential across the entire spectrum of disease categories (cancer, neurology, ophthalmology, liver, etc) and represents a $4.8tn total addressable market (TAM), derived from the creation of new profit pools as well as disruption of the $1tn (annual sales) biopharmaceutical industry. Its emergence may also have profound implications for the current healthcare and payor system, which is not designed to accommodate high costs for therapies that may prove to be potentially 'one-time curative' treatments (€1mn for the first EU-approved gene therapy drug Glybera). However, the nature of genome medicines also introduces a new dynamic where the prevalent patient population gradually becomes smaller. Further, this could result in an increase in "diseases of aging."

We believe investors underappreciate the potential for genome medicine to not only address rare diseases with no existing or limited treatments but also the much larger markets for common diseases. For example, success in CAR T cell therapy is raising the possibility that gene therapies could initially serve as last-line treatments in cancer, opening new markets, but then progress to front-line settings with potential repercussions for incumbents.

We interview leading scientists in the field and discuss how gene editing offers the potential to further the progress of genome medicine. As the pace of discovery and development in genome medicine accelerates, we expect companies that innovate to advance next-generation technologies will gain a competitive advantage.

The age of genome medicine

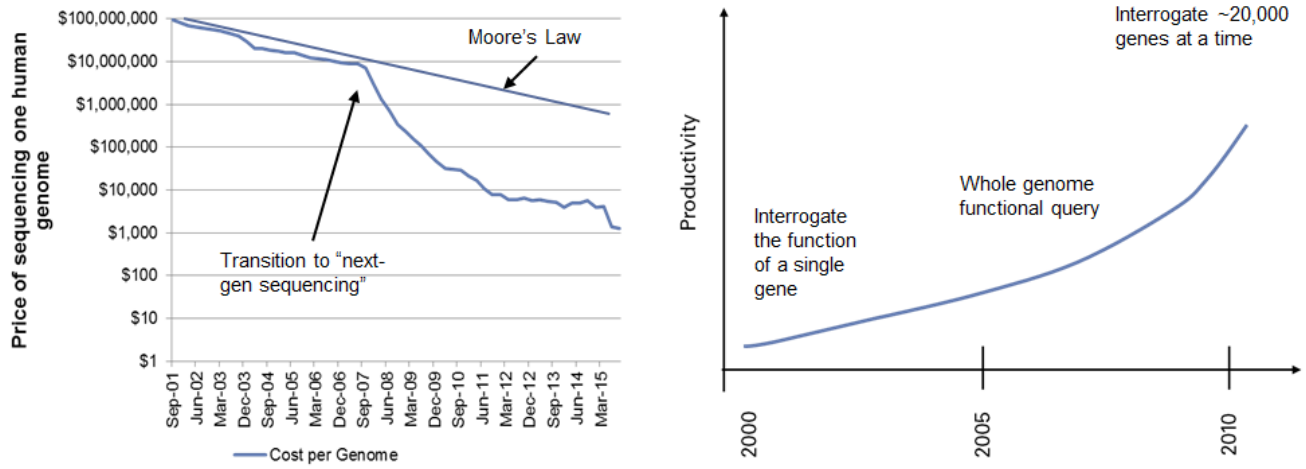
Gene therapy: 2.0 (vs. 1.0 - a false start)

Gene therapy emerged as a concept in the 1970s following the publication of a paper in *Science* titled "Gene therapy for human genetic disease," which proposed the use of healthy DNA to replace defective DNA (typically inherited from parents or developed in utero due to outside factors such as stress, physical or chemical injury) in patients with genetic disorders. The severity of a genetic disease is correlated with the number and role of the genes encompassed in the defective DNA portion. For example, defects in a gene involved in key cellular mechanisms of growth and development may have widespread effect, often impacting multiple organs. While genetic disorders tend to impact small patient populations (rare diseases are defined as fewer than 200k patients in the U.S. or 1 in 2k in the E.U.), only a minority of these diseases have approved therapies. Of these drugs, most do not address the underlying disease cause and instead serve to manage symptoms. Thus, the prospect of addressing the underlying cause of disease with a potential "one-time cure" has always been appealing. Early clinical studies at the National Institute of Health (NIH) Clinical Center revolved around developing a gene therapy in enzyme (ADA)-deficient patients with severe combined immunodeficiency (SCID), which delivered a functional copy of the gene into cells ex vivo (outside the body) using a lentiviral approach and then transferred the cells back into the body. However, an experimental gene therapy developed at the University of Pennsylvania to treat ornithine transcarbamylase (OTC) deficiency resulted in the death of an 18-year old in 1999 and led to a significant setback to clinical research in gene therapy.

The birth of the genome revolution

Drug development in biotechnology has greatly accelerated due to the Human Genome Project, which resulted in sequencing of the human genome in 2003 enabling scientists to identify novel genetic targets that cause disease. In addition, since 2001, the cost of sequencing the human genome has declined faster than Moore's law would predict, to ~$1k from $100mn. As the cost of sequencing a single genome improves, so does the drug developer's ability to 1) identify key biological genetic targets to address underlying disease, 2) generate animal models with predictive potential to ascertain clinical benefit in humans, and 3) identify biomarkers that are early indicators of drug activity and safety. These, combined with advances in the understanding and development of delivery platforms (such as lipid nanoparticles and viral vectors), more rigorous regulatory oversight, higher clinical safety standards, and ethical questions, have spurred a re-emergence of interest and efforts to develop safer and more efficacious genome therapies.

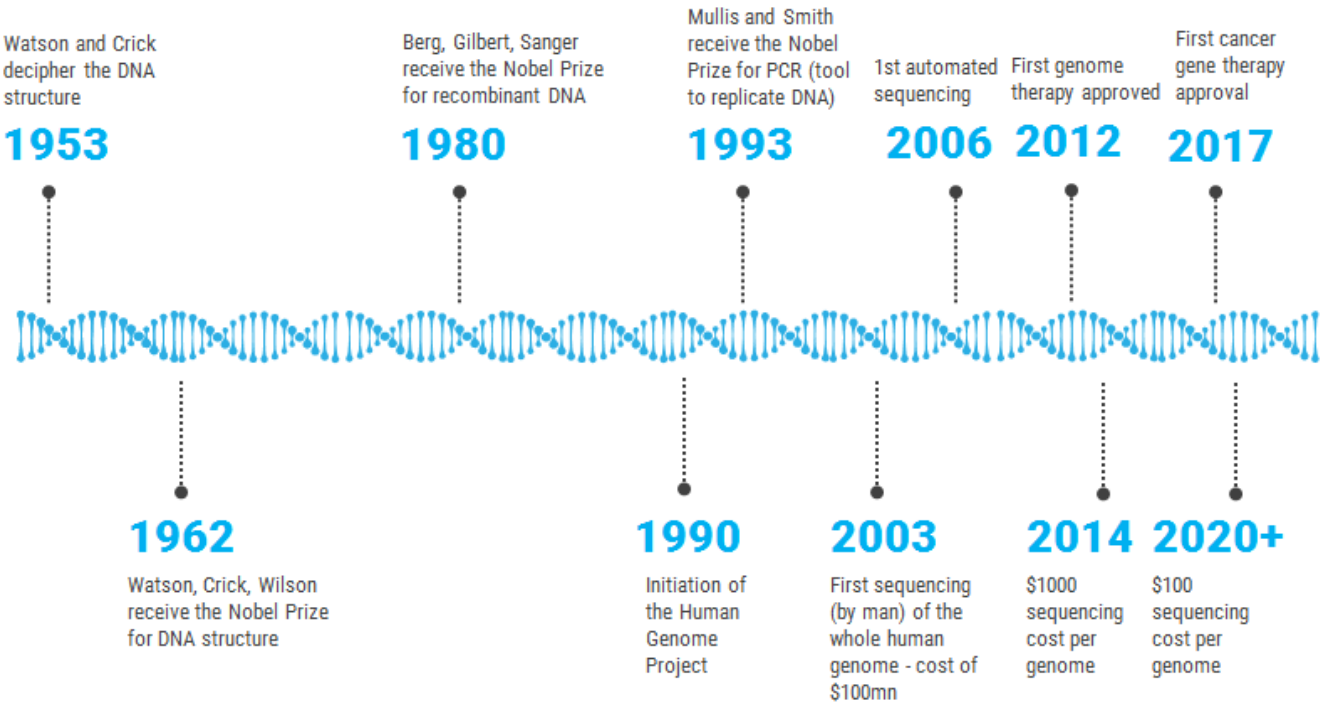
Exhibit 1: The decline in cost of human genome sequencing has outpaced Moore's law and boosted R&D



"Considering we are analyzing more reads now in one afternoon than in the first five years of doing this, we could have spent the last six years sitting on the beach"- von Kalle et al, Human Gene Therapy, 2014 – on evaluating the safety of gene therapy

Source: National Human Genome Institute, Goldman Sachs Global Investment Research

Exhibit 2: Key events in the evolution of genome medicine



Source: Goldman Sachs Global Investment Research

The promise of genome medicine

It is difficult to overstate the promise of genome medicine, which includes three distinct but inter-related technologies: gene therapy, genetically-engineered cell therapy, and gene editing—they hold the potential to be life-changers for patients, game-changers for healthcare investors, and game-enders for incumbents who fail to respond to the pressure to innovate. Understanding the science behind these technologies puts this

into perspective. That said, while genome medicines are emerging with compelling efficacy and safety profiles, we are still in early stages and optimization is occurring on multiple fronts.

Today, most chronic disorders require lifelong treatment. For example, severe hemophiliacs require 50+ infusions a year, while patients administered immuno-oncology drug Keytruda typically visit their physician every three weeks. In contrast, gene and cell therapies have the potential to be "one shot cures" or at the very least less-frequent treatments, targeting diseases at the genetic level. While they are being tested (and proven effective) as treatments of "last resort," these therapies could next move into earlier stages of disease progression, which would disrupt existing therapeutic markets. In diseases where there are no current treatment options (many rare diseases), new profit pools are formed.

Exhibit 3: Genome medicine: Three inter-related technologies

	Approach	Delivery	Examples	Pros/Cons	Current Uses	Future Enhancements
Gene Therapy	inject corrected gene	viral vector	AAV	(+): produces missing or fixed protein (-): virus supply	severe diseases	repeat dosing
Cell Therapy	reinfuse enhanced cells	viral vector + cell infusion	CAR T TCR	(+): efficacy in last line cancer setting (-): virus supply; manufacturing time	cancer	allogeneic (off the shelf)
Gene Editing	"molecular scissors"	viral vector or fat-lined capsule	ZFN TALEN CRISPR meganucleases	(+): permanent change in genome (-): virus supply; no clinical data	severe diseases agriculture	multiple gene targeting

Source: Goldman Sachs Global Investment Research

How does gene therapy work?

Many diseases — from heart disease to Parkinson's disease — can be traced back to differences in the body's genetic code. Gene therapy is designed to fix these problems at the source by inserting or editing a corrected DNA sequence that can override the existing error.

While it may seem counterintuitive, viruses are uniquely suited to deliver the corrected gene into the body. A disease-causing virus, e.g. influenza virus, consists of a protein shell (capsid) that hones in on a specific cell type, e.g. respiratory tract mucosa, and injects its genetic payload into the host cell which then replicates and releases more virus particles to infect other cells in the body. Gene therapy co-opts this ability, stripping the virus of its pathogenic properties (at which point it is defined as a vector) and leveraging its ability to inject (in this case corrected) genetic material into target tissues and cells. Gene therapy can be used to deliver genetic material to both replace defective/deficient genes, e.g. replace SMN1 protein in spinal muscular atrophy, or to 'silence' defective disease-causing genes, e.g. tau protein knockdown in Alzheimer's disease.

The type of virus and how it is engineered depends on the target condition:

1. **Lentiviral vectors**: Derived from the HIV-1 virus, these vectors inject the corrected gene which is then incorporated into the target cell's DNA, ensuring the fix will be passed on to all future daughter cells when the host cell divides. This makes lentiviral vectors ideal for treating diseases involving frequently dividing cells, such as blood cancers.
2. **Adeno-associated virus vectors**: Unlike lentiviral vectors, adeno-associated or "AAV" vectors do not insert their DNA cargo into the host DNA; instead, these vectors deposit the corrected gene just outside the genome in the host cell's nucleus. When the host cell divides, only one of the daughter cells will inherit the "fix"—thus AAV is best suited for tissues that do not divide rapidly, such as the liver, eye, muscle, or nerve cells.

The resurgence of interest in developing genome medicines (gene and CAR T therapies), by commercial biotechnology companies as well as academic centers, has resulted in significant demand for viral vectors. Given just five years ago, virus engineering was confined to a handful of labs, current commercial scale needs have outpaced supply due to the complexity and rigorous specifications of manufacturing. Some companies are also targeting gene therapy platform construction more broadly, equipping themselves with not only the required virus supply but also the tools to build vectors capable of venturing into new tissues and thus new disease areas.

Exhibit 4: Vector selection is key for target tissue/organ specificity

Target organ	Vector type
Eye	AAV2, rAAV2, AAV2.7m8 AAV4, AAV5, AAV6, AAV8, AAV-ChR2
Liver	AAV3, AAV8, AAV9, AAVrh10, SPK-200
Blood (bone marrow)	Lentivirus, AAV5
Muscle	AAV1, AAV5, AAV8, AAV9, rAAVrh74
Central nervous system (brain)	AAV2, AAV4, AAV5, rAAV6, AAV9, AAVrh10
Heart	AAV1, AAV2i8, AAV9
Pancreas	AAV8

Source: Goldman Sachs Global Investment Research

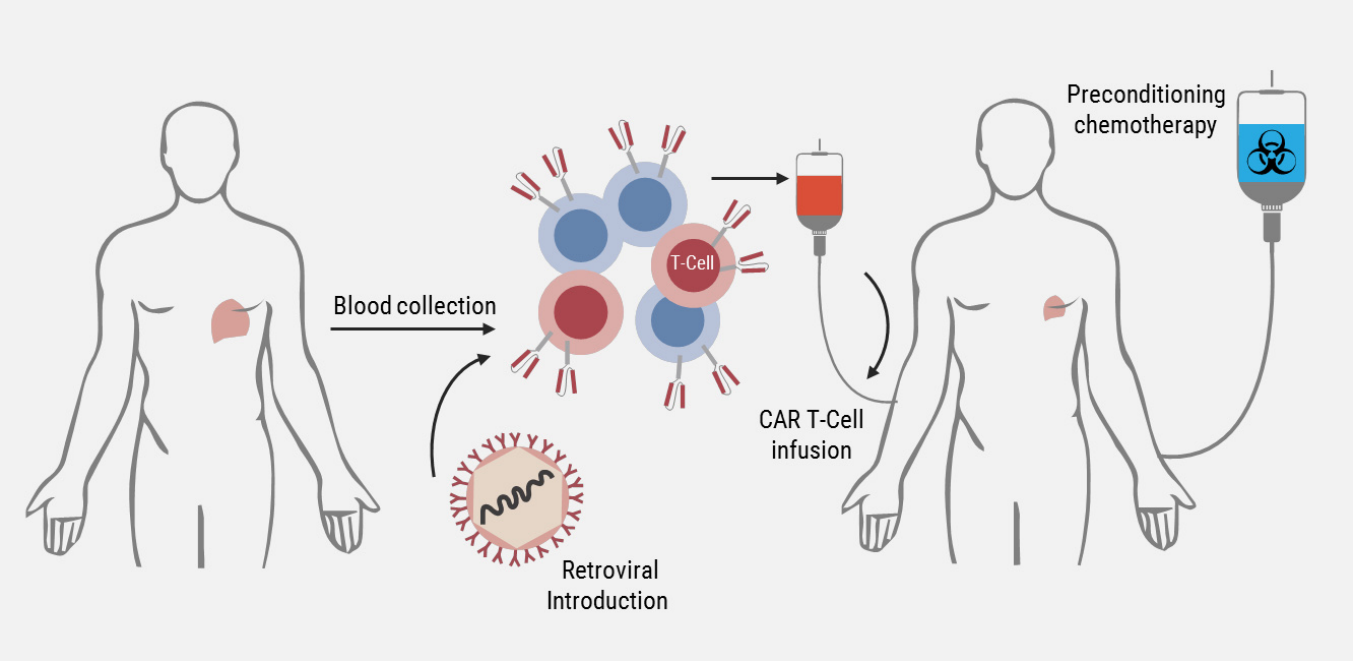
Cell therapy: Cells engineered to fight cancer (CAR T and TCR)

Cell therapy is a technology that leverages the ability of gene therapy to insert a desired gene into a cell (which is then translated into a protein to serve a specific function) and works at a cellular level to infuse enhanced cells into the body to fight disease. In cancer specifically, engineered immune cells (T cells) have made notable advances, with CAR T and TCR as two of the most advanced cell therapies. In the case of chimeric antigen receptor (CAR) T or T-cell receptor (TCR) therapies, T cells from patients are harvested and a lentiviral gene therapy is used to insert a CAR directed to a specific antigen protein on cancer cells. These T cells are then grown and re-infused into patients so that these 'enhanced' T cells have a new ability to recognize and clear specific cancer cells in the body. Although multiple CAR T candidates are being developed for blood cancers

(CD19+, BCMA+, etc), we do not believe that all genome medicines are created equal, and there is room for the players to differentiate themselves.

Like immuno-oncology, cell therapy leverages the body's natural disease-fighting T cells to attack cancer; however, unlike immuno-oncology treatments (such as checkpoint inhibitors Opdivo and Keytruda), which support the body's natural immune T cells to fight cancer by removing local tumor immunosuppression or 'brakes,' CAR T therapies are 'enhanced' immune cells that have shown impressive efficacy where checkpoint inhibitors have failed. In CAR T treatment, a patient's T cells are collected through a blood draw and then fitted with a CAR designed to hone in on targets on the surface of tumor cells. When these engineered CAR T cells are reinserted into the blood, the CAR directs the T cell to the tumor site where it can then release toxic chemicals and kill cancer cells locally.

Exhibit 5: Gene therapy for cancer (CAR T)



Source: Goldman Sachs Global Investment Research

Because CARs can detect targets only on the surface of tumor cells, they are not as well suited for treating solid tumors (versus blood cancers), where the receptor's target is found inside the cells. As CELG/Juno noted at December's American Society of Hematology (ASH) , 60% of the top 50 cancer antigens are found inside cells, rendering the CAR T strategy less effective or ineffective for the majority of cancer types. This has led companies like CELG/Juno, GILD/Kite, ADAP, BLUE, and BLCM to invest in a different form of T cell engineering that has the potential to detect targets inside tumor cells.

The therapy, known as "TCR," equips the T cells with the ability to recognize unique proteins (antigens) that are found in specific cancer cells. So far, early clinical proof-of-concept data suggest activity of TCRs in solid tumors. Should TCRs prove effective in treating solid tumors, cell therapy's reach would expand by several orders of

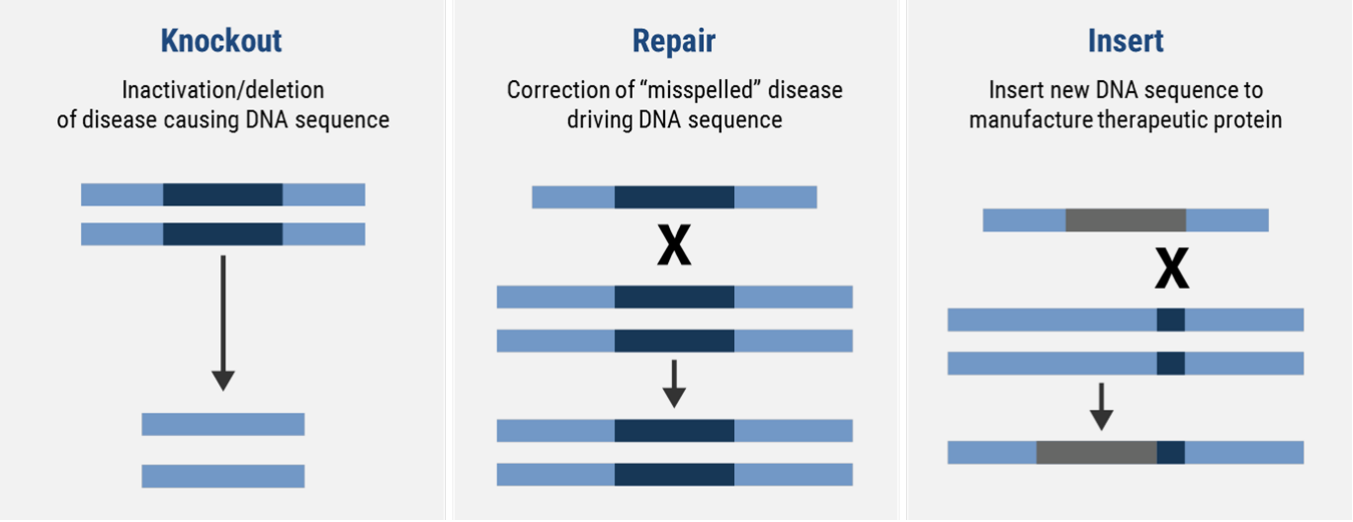
magnitude given the most common cancers — lung, breast, prostate, colon and skin cancer — are all solid tumors.

Gene editing: The next frontier

For all its promise, gene therapy 2.0 has its own limitations ranging from viral vector manufacturing supply to the potential need for re-dosing and the ability to re-dose. Gene editing, a related but more nascent technology, has the potential to address some of these challenges and expand the addressable pool of disease areas. However, the technology is still in its infancy and drug candidates are just beginning to enter the clinic.

Gene editing leverages specific enzymes/proteins to directly modify a cell's DNA. There are four distinct systems: CRISPR/Cas9, TALEN, zinc finger nucleases (ZFN) and meganucleases (although some experts classify meganucleases as TALENs). Other related gene editing techniques include MegaTAL (combination of meganuclease and TALEN) and homologous recombination gene correction. CRISPR/Cas9 has emerged as the most versatile, affordable and simple gene editing system, although biotechnology companies are also developing alternative editing systems, which could be differentiated by target DNA sequence specificity, off-target editing events, and specificity (extent of match to intended DNA target). Unlike gene therapy, which can only insert a corrected sequence to override an errant or missing one, gene editing technology can function like 'molecular scissors,' cutting out or repairing a disease-causing segment and/or inserting 'corrected' ones. Gene editing also has the potential to target diseases where multiple genes may be implicated through multiplexing (introduction of several gene edits simultaneously), which cannot be achieved by gene therapy.

Exhibit 6: Gene editing can knockout, repair, or insert DNA



Source: Goldman Sachs Global Investment Research

CRISPR/Cas9 is currently limited to a handful of diseases because of limitations in delivery, but should move into more conditions as the technology advances (see takeaways from our Innovation Symposium panel on CRISPR later in this report). The current delivery approach utilizes fat-lined capsules (lipid nanoparticles, LNPs) as well as viral vectors (e.g. AAV) to deliver the CRISPR/Cas9 editing machinery and guide RNAs

(gRNAs, which guide CRISPR/Cas9 to a specific DNA site for editing) preferentially to the liver. Different LNPs and platforms are being explored to deliver CRISPR/Cas9 into other cells, including use of viral vectors similar to gene therapy.

However, there is still significant room for optimization to develop next-generation gene editing drugs with improved tissue targeting and greater specificity to minimize potential off-target edits, improve persistence/engraftment of cells and treat polygenic disorders.

We spoke with leading scientists in the field of gene editing, including Andrew May, Senior Director of Genome Engineering, Chan-Zuckerberg (CZ) Biohub (independent nonprofit research center focused on driving cooperation between scientists and major academic institutions across geographies to bring together science and technology to explore "blue-sky" areas and high risk, high reward projects to solve the world's health problems). One KOL viewed the CRISPR/Cas9 as a robust but easy-to-use system with a very high editing efficiency level, but cited specificity (extent of match to intended DNA target) as one of the main disadvantages of CRISPR/Cas9 vs. other gene editing systems. However, he noted that these gene editing technologies can all be engineered/optimized and thus does not view specificity as a concern. Another KOL sees this as a theoretical concern but one that could result in permanent edits that arise years or decades later. Because gRNAs are used in CRISPR/Cas9 editing and do not bind to target DNA as tightly as other systems, there is a potential for the gene editing system to make off-target cuts. However, our KOL believes this can be addressed through: (1) careful screening and selection of gRNA or mRNA to eliminate off-target binding; (2) utilizing an appropriate method of delivery, e.g. ex vivo where the Cas9 protein only persists for a day so that they do not persist in the body to potentially cause off-target edits; and (3) development of novel Cas9 endonucleases that do not bind wild-type DNA. They noted that CRISPR/Cas9 is able to edit 80%+ of cells ex vivo with one dose. However, given safety concerns (theoretical risk of off-target editing), the technology is entering the clinic in a targeted way. They anticipate an initial focus on treating severe genetic diseases with significant morbidity/mortality, where the benefit/risk is very clear, and advances will be made in the future to enable even broader development. Another area of optimization is the technology needed to deliver CRISPR into a variety of human tissues as this differs by disease. Existing technology (AAVs and LNPs developed with gene therapy approaches) allows delivery of CRISPR to the eye, liver, and certain blood cells and hence diseases that affect these organs have been a near-term focus. Per our KOLs, conceptually, gene editing appears to be attractive and revolutionary as a biological tool. While the genomic revolution has just begun, the potential of gene editing has barely scratched the surface. Dr. May sees a future where gene therapy and gene editing will likely co-exist as there are certain areas where gene therapy will work better than gene editing, though he believes the technology will have an impact on less versatile platforms such as RNAi. The versatility of gene editing will enable its use in ex-therapeutic areas such as in agriculture to genetically engineer crops and food. Given plants could be genetically modified with no traces of foreign DNA, it is possible they could be outside the scope of regulators, making its impact that much quicker and stronger. When asked about germ line editing and "designer babies", he acknowledged the ethical considerations and that there should be some concern about people pursuing enhancements, but the frequency is likely to be limited.

Gene editing is also a platform technology for the development of cancer therapies. We view allogeneic T cell therapy as the future given the immediate availability following diagnosis and the lower rate of drug variability and manufacturing failure.

Interview with Dr. Daniel Rader

Chair of Genetics, University of Pennsylvania School of Medicine

Daniel J. Rader, MD, is a widely recognized international leader in human genetics, Chair of the Department of Genetics in the Perelman School of Medicine at the University of Pennsylvania. As a prominent physician-scientist in the field of lipid and cardiovascular disease, Dr. Rader has been a faculty member at the University for over 20 years and is the Seymour Gray Professor of Molecular Medicine.

What is gene therapy? How disruptive is this technology?

Gene therapy provides expression of a gene where it is absent or defective due to mutations (which has resulted in disease). The technology is disruptive if it can significantly displace existing approaches. The early phase of gene therapies are being developed for conditions where there is a high unmet need and a lack of existing treatment options. Thus, this treatment modality is important and success in the field will likely have a transformational impact on patients with rare genetic diseases.

Where do we currently stand in terms of the scientific evolution of this field?

We are still in the early days of gene therapy drug development with therapies just beginning to gain approval. There is still significant room for further optimization in terms of vector selection, promoter design, gene expression and regulation of expression. Based on clinical and, more importantly, preclinical data, adeno-associated viruses (AAV) are not believed to be associated with risk of carcinogenesis, and lentivirus, where there is potentially more concern based on biology, have shown no major signal/risk of cancer either. While AAV-based vectors are the most widely used vectors in the clinic, I expect breakthroughs in the field to result in development of other vector types.

Are there low-hanging fruit in terms of target diseases? Can we think broader than monogenic diseases?

I see diseases such as hemophilia as low-hanging fruit, where restoration of a fraction of gene/protein expression leads to significant improvement in symptoms. Hemophilia is also unique as an early gene therapy disease target given the large size of the market. Rare diseases, e.g. metabolic liver disorders, are a good target given most of these are recessive diseases that result in a lack of a specific protein/enzyme expression. I expect gene therapy to have a significant impact in rare diseases in the next 5-10 years. Beyond monogenic disorders, gene therapy has significant potential in more common disorders where regulation of gene expression levels can have a therapeutic effect. For example, the regulation of adiponectin levels, an insulin sensitizing protein, in Type I diabetes patients could potentially restore insulin sensitivity in patients and also mitigate the effects of obesity on diabetes, and be truly disruptive. As the technology matures, I see gene augmentation becoming a possibility, which would enable expansion into much larger markets.

Should we expect "curative" gene therapy? How far away are they?

While questions regarding durability of AAV gene therapy remain to be answered, the preclinical/clinical data so far is good and encouraging. Whether this first generation of gene therapies can offer lifelong gene expression or a "cure" is hard to say, and we may be setting unrealistic expectations for a single shot with

the current AAV vectors. However, I am optimistic that they will provide therapeutic benefit for years and possibly more than a decade, and as science progresses, I believe loss of gene expression could be addressed in the future by re-dosing, potentially with a different serotype, or through a different approach.

What are the challenges in gene therapy?

One important issue in gene therapy is the ability to re-dose patients, but I have a high level of confidence that this will be successfully addressed in the future. Another challenge is treating patients that have pre-existing neutralizing antibodies to the AAV vector, which renders the drug less effective. Achieving a sufficient level of gene expression for therapeutic benefit may be achievable in some diseases such as hemophilia, but other conditions such as homozygous familial hypercholesterolemia (HoFH) require much higher expression levels. Targeting the appropriate tissue/cell type is also an important goal of gene therapy. While the liver has been an easy target, other targets are more challenging, such as the central nervous system due to the need for sufficient dissemination in the brain (although there has been some good clinical data in diseases such as spinal muscular atrophy), skeletal muscle and the heart. The key issues to address include targeting tissues/organs in multisystem diseases, delivering sufficient doses safely and developing better viral vectors. One approach could be to target liver expression of enzymes/proteins, which then leaks into the blood and mimics the function of enzyme replacement therapies.

Could you describe gene therapy in the context of cancer (CAR T and TCR)?

Gene therapy can also be used to modify a patient's own cells ex vivo (outside the body) and then re-infuse them in order to more effectively target and kill cancer cells. While this is different from gene therapy replacement of a defective or missing gene, CAR T and TCR cell therapy fit under a broader definition of gene therapy.

What do you see as the impact from CAR T cancer gene therapy in 10 years?

CAR T therapies have been transformational so far in terms of their efficacy, and I expect further refinement and optimization of the technology to result in safer and more efficacious drugs that move into earlier-line cancer settings. However, targeting solid tumors will be more challenging. I believe there are only a few attractive targets for this technology and thus expect a long road for development where success is likely limited to these few specific solid tumors. However, in the next decade, CAR T technology will likely expand to other cells like macrophages and be used to treat non-cancer diseases such as auto-immune diseases.

What is gene editing? Why and where do we want to utilize this tool? Will it render gene therapy obsolete?

Conceptually, gene editing appears to be attractive and revolutionary as a biological tool. However given safety concerns and the theoretical risk of off-target editing, the technology is entering the clinic in a targeted way. It will likely be initially employed in diseases of very high unmet need with high risk of mortality in patients where the potential risk of gene editing is diminished in the context of untreated disease. As safety is established, gene editing could eventually be applied more widely in people with less severe disease or in a prophylactic setting. While gene editing could theoretically replace gene therapy in 20-30 years, I believe gene therapy is here to stay for the near-term and editing is more likely to augment

and expand the total addressable market.

What is unique about CRISPR (vs. the others) that has driven such rapid advancement of the gene editing field?

CRISPR emerged as the preferred gene editing system ("swept others as a biological tool") given its affordability, specificity, and flexibility (and clinical applications) compared to other technologies such as ZFNs (zinc finger nucleases) and TALENs, although meganucleases are an exception and being used in some clinical trials. However, one common challenge is delivering all the components of the gene editing machinery into the target tissues/cells at sufficient levels to provide clinical benefit. In terms of safety, although CRISPR/Cas9 is able to make very specific nucleotide base edits, specificity and off-target editing is an important concern.

What are the industries where CRISPR is likely to have the biggest impact?

I see widespread application across therapeutics, agriculture (large impact), veterinary treatment, and modifying livestock. Therapeutic applications will take more time to develop given the challenge and rigor of human clinical drug development. I am also optimistic on using gene drives in a controlled manner.

What will gene editing and CRISPR look like in 10 years? Will today's tools be replaced by next-generation technology?

I believe the fundamental concept and machinery of gene editing and the CRISPR system are here to stay. However, advances and new discoveries in the technology could result in improvements in how the enzyme (Cas9) edits DNA, e.g. replacing DNA bases without cuts.

What are some other important issues to keep in mind as the field of gene editing evolves?

Conceptually, gene editing could be used as prophylaxis in patients at risk of developing a disease, e.g. heart disease, breast cancer, etc. This could become possible in a decade with gene therapy/editing, but safety will need to be very well established. This would represent a shift from gene therapy/editing use from treatment to prevention of disease.

The ethical implications of gene editing are profound when it comes to use in people without disease, such as the embryo, fetus, egg or sperm. While the prospect of pre-implantation genome editing to ensure a child does not develop a fatal disease may be justified, it could set up a slippery slope for other applications.

Regarding RNA approaches to target genetic diseases, the safety issues seen in the therapeutic class could be justified in certain diseases with high unmet need. However, as gene editing matures, RNA therapies could be rendered obsolete in the next 10-20 years.

10 things you may not know about genome medicine...

1) The **Human Genome Project cost $2.7bn** and took **15 years** to complete. Today, it costs less than $1k to sequence the human genome.

2) **Genome medicines** have been in development since the **1990s**. However, a patient death in a clinical trial in 1999 led to a long pause on further gene therapy clinical development.

3) The **first approved genome medicine** in the **EU** was QURE's **Glybera** in November 2012 for the treatment of lipoprotein lipase (LPL) deficiency, while in the **US**, it was NVS' **Kymriah** to treat pediatric acute lymphoblastic leukemia, a type of blood cancer.

4) Genome medicines can be **delivered by** various means including **lipid nanoparticles** (LNPs - small lipid-lined capsules) or **viral vectors**.

5) It takes **~17 days to turn around/manufacture** GILD/Kite's Yescarta CAR T drug for diffuse large B-cell lymphoma.

6) When measured by numbers, **China is one of the leaders in CAR T** therapy development with 164 of 466 trials currently being conducted in the country.

7) Genome medicine has **potential applications in agriculture** — There is potential to develop crops with new traits such as disease resistance, increased yield and drought tolerance.

8) **CRISPR** is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats while Cas9 is CRISPR associated protein 9.

9) The **CRISPR/Cas9 system evolved in bacteria** as a defense mechanism against viruses and is widely distributed across bacterial species.

10) In **2017, the first human embryo successfully underwent gene editing** with CRISPR/Cas9 in the US. However, three prior reports of editing human embryos have been reported by scientists in China.

Sizing the genome medicine opportunity

We see a $4.8tn+ potential TAM for genome medicine

We see a significant market opportunity for genome medicines that will both disrupt existing biopharma markets as well as create new profit pools (e.g. genetic inherited blindness, last-line cancer). In this section, we size the potential total addressable market of genome medicine in a 'blue sky' scenario and identify therapeutic areas with high growth potential, although these could expand on technology advancement. We estimate that the total addressable market for genome medicines could reach $4.8tn+, which reflects a 'blue sky' scenario based on various assumptions (see details below) and where genome medicines are successfully commercialized across a wide spectrum of common and rare genetic diseases.

Our calculation of TAM for genome medicines is based on the following methodology and key assumptions:

(1) Pricing for gene therapy/editing at $1mn per treatment and cell therapy at $375k, and a one-time upfront full payment for treatment.

(2) 100% penetration into all patients — both the incident and prevalent patient pools — given the appeal of a one-shot cure. However, in practice, penetration will be lower in both populations.

(3) TAM only captures US and EU5 patients — therefore the global TAM opportunity exceeds $4.8tn.

(4) Our TAM includes ~$3.6tn derived from the prevalent pool, which we assume will be exhausted over time as patients are "cured".

Based on our assumptions, the global cumulative TAM for genome medicine across all disease areas based on the current generation of technology platforms (gene therapy, editing and cell therapy) could reach $4.8tn, driven by oncology (>$1tn), neurology (>$1.5tn) and eye disorders (>$0.5tn). This compares with annual global prescription sales of $1.01tn projected in 2022 per independent third party estimates (EvaluatePharma). We see the commercial opportunity driven by both the creation of new profit pools, e.g. orphan disorders, as well as disruption to current therapies/markets, e.g. cancer, heart, neurology and viral infections. We note that a significant proportion of our estimated revenue pool is derived from prevalent patients, i.e. patients who already have the condition ($3.6tn), and once these are treated they are essentially "cured". Therefore, in the long term, disease incidence, i.e. number of new patients born with or developing the disease, will be the primary driver of recurring sales, with oncology ($1.2tn) as the largest source. In addition, this scenario is also contingent on the continued optimization of gene therapy efficacy/safety, movement to earlier-line settings in cancer, and standardization and successful scaling of manufacturing of viral vectors to meet commercial demand.

We view several current large opportunities in genome medicine: targeted cancer therapy with genetically engineered immune cells and large market disorders with a

single-gene defect. Given gene therapy and editing are initially being developed to replace, knock out or modify a single gene / mutation site, we see the near-term therapeutic potential of the technology revolving around orphan disorders (e.g. spinal muscular atrophy, Duchenne muscular dystrophy and sickle cell disease) and blood cancers. However, given the potential for CRISPR/Cas9 multiplexing (modification of several genes / mutations simultaneously) and improving understanding of the various genetic drivers in diseases such as cardiovascular disorders (e.g. stroke) and diabetes, we see room for upside as the technology is optimized - we do not include these diseases in our global TAM estimate of $4.8tn.

As gene therapy / editing matures, we see the technology expanding into larger markets including potentially gene augmentation, in utero gene editing for fatal congenital diseases or even modification of germline cells (sperm and egg) to eliminate a disease-causing mutation in a population. We also view infectious diseases, particularly HIV, as amenable to gene editing as these viruses express specific DNA sequences that can be targeted by CRISPR/Cas9. Below, we conduct a deep dive on the genome medicine opportunities across multiple therapeutic areas.

Cancer represents a $1.2tn recurring profit pool

We believe the oncology therapeutic market could reach an incident (annual recurring) TAM of $1.2tn compared to the $200bn in incident sales projected in 2022 for approved therapies, primarily driven by lung (~222.5K US cases/year) and breast (~25.7K US cases/year) cancers. While use of genetically engineered CAR T cells targeting specific antigens has shown impressive efficacy in blood cancers such as non-Hodgkin B cell lymphoma, acute lymphoblastic leukemia and multiple myeloma, progress in solid tumors has been slower, although recent early clinical data suggests activity of TCR cell therapies in solid tumors.

We believe CAR T cell therapies have been particularly effective against blood cancers given their accessibility in the circulatory system and the specificity of antigens expressed on cell surface, e.g. BCMA in multiple myeloma (MM) and CD19 in lymphomas and leukemias. Recently approved cell therapies Kymriah and Yescarta in pediatric ALL and adult B-cell lymphoma, respectively, target last-line settings but we believe optimization of the technology in terms of efficacy, durability, safety, antigen targeting and resistance to immunosuppression will lead to use in earlier-line settings.

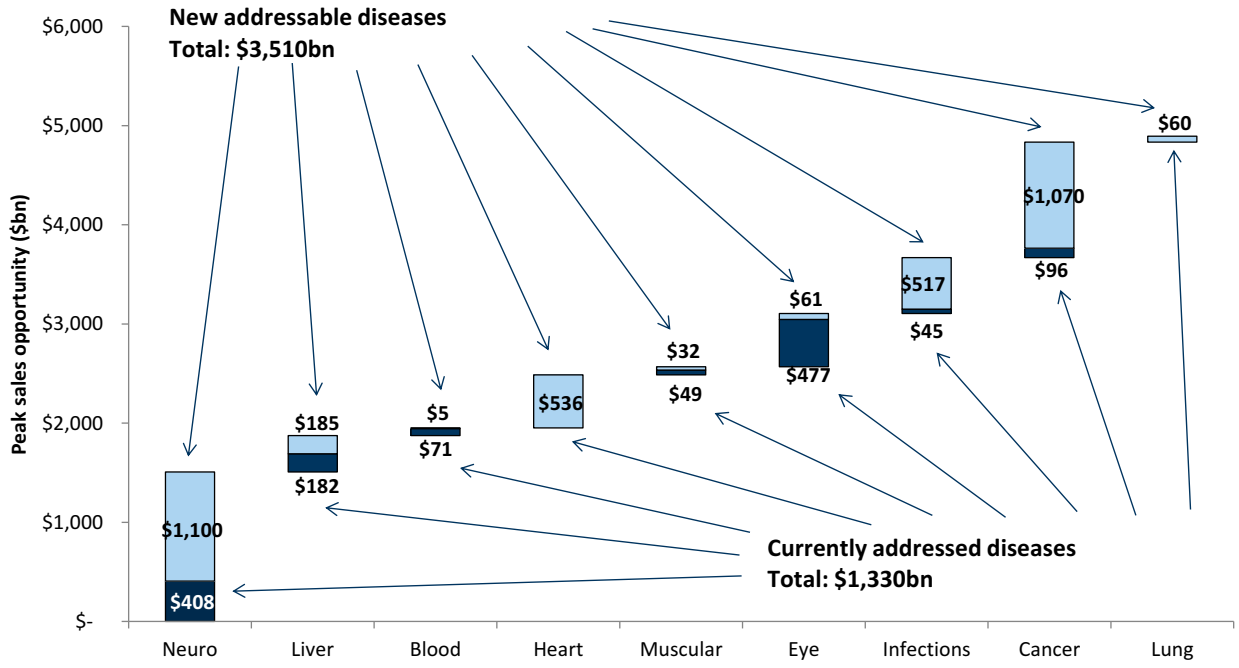
We believe TCRs may be more promising than the CAR T approach in solid tumors given the biologic rationale that there are fewer surface antigen targets but more intracellular antigen targets in solid tumors. While there are promising early signs of efficacy, cell therapy in solid tumors is associated with several difficulties that need to be overcome: heterogeneity of antigen expression in solid tumors, the immunosuppressive tumor microenvironment and cell persistence in the tumor, amongst others. Given solid tumors are much more common than blood cancers, we view clinical success in solid tumors as key to realizing the incident $1.2tn potential market opportunity for genetically engineered cell therapies. However, key opinion leaders do not see cell therapy applied widely for solid tumors given the limited number of effective solid tumor antigen targets.

The next growth opportunity in this space will likely come from optimization of cell therapies leading to use in earlier lines of treatment in CD19+ and BCMA-expressing blood cancers, and new blood cancers, e.g. AML. The genetic engineering of other immune cells such as macrophages or use in auto-immune diseases can also lead to new therapeutic uses.

We are in the first wave of genome medicine

We view the current generation of genome medicine as the 'first wave' and anticipate a next generation of optimized therapies will emerge in the coming years with better efficacy, safety, targeting and specificity. We believe these improvements will expand the range of addressable diseases to include solid tumors, multigenic disorders and others. We see ~$3.5tn in upside from new TAMs (diseases with no existing treatments) addressable by next-generation genome medicines.

Exhibit 7: First wave: Genome medicine represents a potential $4.8tn total addressable market



Source: Goldman Sachs Global Investment Research

Neurology represents a large market amenable to genome medicine

Companies such as AVXS and ABEO are developing gene therapies targeting orphan neurology disorders, but we also see significant potential in large-market indications such as Alzheimer's disease (AD, ~5.4mn US affected) and Parkinson's disease (PD, ~1mn US affected). VYGR is developing AAV-directed gene therapies for PD through restoration of the AADC enzyme and AD by tau protein knockdown. Approximately one-third of people aged 85 and older develop AD. By 2050, one new case of AD is expected to develop every 33 seconds in the US, or nearly 1mn new cases per year. The global costs of dementia have increased from $604bn in 2010 to $818bn in 2016 (+35%) and are projected to exceed $1tn in 2018 (World Alzheimer Report 2016 - most recent

report as of March 29). We believe the market potential for an AD gene therapy could exceed $1tn. In PD, we see $200bn market opportunity.

$500bn+ opportunity in heart failure gene therapy could be on the horizon

Heart failure is a progressive and fatal condition affecting ~5.8mn patients in the US. Standard of care revolves around prevention of exacerbations and symptomatic relief, but there are no available therapies to reverse disease or extend survival. While efforts to develop gene therapy in the past decade have been unsuccessful, recent progress in the field including optimization of delivery and targeting has been promising. Investigators at Mount Sinai Hospital have recently successfully treated porcine models of heart failure showing improvements in heart function and reduction in heart size. The data is particularly encouraging given pig hearts are similarly sized to those of humans. The gene therapy being tested targets the protein phosphatase-1 which is found across all patients with heart failure and thus the treatment is able to target a broad population rather than subsets of patients with specific mutations. We believe the successful development of a gene therapy for heart failure could create a new profit pool of $500bn+, which assumes a pricing of $100K for a one-time treatment.

Infectious diseases, particularly HIV, could be next frontier for gene editing

Viruses are composed of a protein capsid (shell) designed to deliver genetic material into a host cell, co-opt the cellular machinery to replicate DNA and synthesize capsid proteins, which are then assembled/released to infect other cells. Gene editing is ideally suited to eliminate viruses as they target the DNA blueprint that is required for viruses to replicate. Additionally, CRISPR/Cas9 is able to 'cut' out specific pieces of DNA that may have integrated into the host DNA as is seen with the HIV virus and address the lack of current therapies to remove integrated DNA. The CDC estimates that the lifetime cost of HIV therapy is $379k, which does not include the costs associated with complications and hospitalizations. We believe the one-shot curative potential of gene editing is particularly appealing in HIV. Hepatitis B and C are also chronic infections where gene editing could be developed to eliminate dormant DNA in liver cells, but we note that current antiviral treatments have shown high cure rates and have significantly reduced the prevalent pool and incidence of these infections. As the pool of HIV and hepatitis patients depends on continual transmission, we note that the gradual elimination of carriers would not only decrease disease prevalence but also incidence.

Game-changing gene therapies for orphan disorders

Initial efforts of gene therapy focused on orphan disorders with high unmet need where a single gene defect is known to contribute to disease. Proof-of-concept clinical and efficacy data has thus far been compelling and durability has been seen in patients treated ~8 years out in hemophilia. We see a ~$680bn market opportunity in orphan disease gene therapy. We view gene therapy/editing as a potential threat to the orphan disease franchises of companies that do not own these technology platforms. We view gene therapy as currently ideally suited for orphan diseases given many of them are caused by a mutation in a single gene that can thus be replaced.

Sustainability and pricing...

The potential to deliver "one shot cures" is one of the most attractive aspects of gene therapy, genetically-engineered cell therapy and gene editing. However, such treatments offer a very different outlook with regard to recurring revenue versus chronic therapies, particularly in certain diseases where it is possible to cure a large proportion of the prevalent patient pool (or at least prevent an additional dose from being required for an extended period). While this proposition carries tremendous value for patients and society, it could represent a challenge for genome medicine developers looking for sustained cash flow. GILD is a case in point, where the success of its hepatitis C franchise has gradually exhausted the available pool of treatable patients.

We highlight several potential solutions for these genome medicine companies to sustain an attractive profile.

Solution 1: Address large markets: Hemophilia is a $9-10bn WW market (hemophilia A, B), growing at ~6-7% annually. We estimate that the hemophilia A market currently represents ~$6.5bn, while hemophilia B is ~$1.2bn.

Solution 2: Address disorders with high incidence: Spinal muscular atrophy (SMA) affects the cells (neurons) in the spinal cord, impacting the ability to walk, eat, or breathe. It is the leading genetic cause of death in infants. SMA affects ~1 in 11k babies, and 1 in 50 individuals in the US is a genetic carrier. Cancer is also a sustainable market given the patient population is almost entirely incident driven.

Solution 3: Constant innovation and portfolio expansion: There are hundreds of inherited retinal diseases (genetics forms of blindness). Once a gene therapy is approved for a genetic eye disease, the validated platform could be used to quickly develop many more eye-based gene therapies. Pace of innovation will also play a role as future programs can offset the declining revenue trajectory of prior assets.

Case Study

The impact of curative therapies on the hepatitis C market

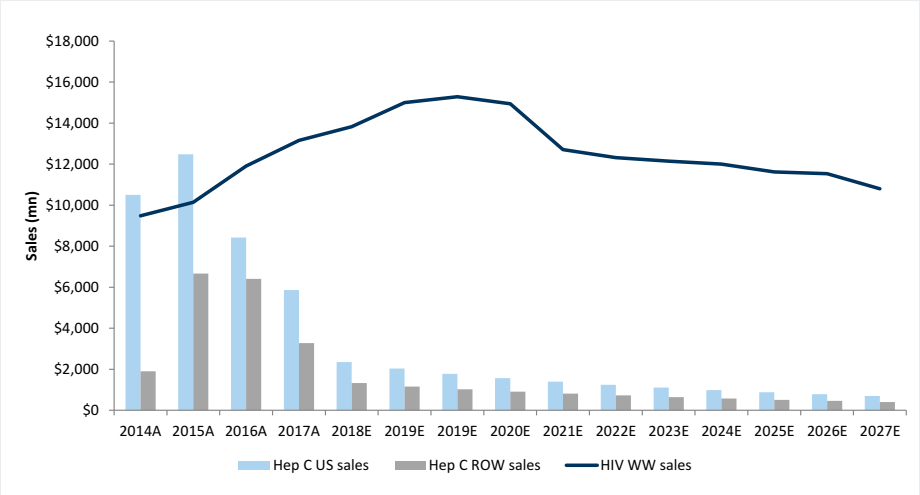
A recent study conducted by researchers at Yale University and funded by Merck (MRK) explores the impact of increased screening and treatment of hepatitis C (HCV) on its future prevalence in the US. More than 5mn individuals in the US are infected with HCV, making it the most common blood-borne infection and leading cause of cirrhosis in the US. The advent of new antiviral drugs such as Sovaldi and Harvoni, both developed by GILD (other HCV players such as ABBV, MRK are also developing other similar therapies), has led to cure rates of >90% with minimal side effects, and raises the possibility of eliminating HCV through reducing the carrier pool and thus reducing future spread.

Using a compartment model and calibration with historical HCV epidemiological data, the future prevalence, incidence and HCV-related morbidity/mortality events were projected out to 2040. Based on the data, the total HCV prevalence could fall by more than 80% within the next 10-20 years through use of curative therapies alone. With increased HCV screening, an additional 150k infections could be identified over 10-20 years, and essentially eliminate HCV from non-intravenous drug users (IVDUs). The decline in HCV prevalence also has downstream benefits including reduced cases of cirrhosis, liver transplants and deaths.

Following FDA approvals of Sovaldi in December 2013 and Harvoni in April 2014, GILD reported >$10bn in net sales in 2014, making it one of the most successful drug launches in history. However, Sovaldi/Harvoni eliminate the underlying cause of HCV and thus cure patients. Unlike chronic therapies such as hemophilia where there is a recurring revenue stream, Sovaldi/Harvoni are one-time treatment regimens that result in a lump sum payment. Revenue from GILD's US HCV franchise peaked at $12.5bn in 2015 and has been declining as the pool of prevalent and addressable HCV patients continues to decline, with screening and identification of new patients sustaining new scripts.

GILD's rapid rise and fall of its hepatitis C franchise highlights one of the dynamics of an effective drug that permanently cures a disease, resulting in a gradual exhaustion of the prevalent pool of patients. In the case of infectious diseases such as hepatitis C, curing existing patients also decreases the number of carriers able to transmit the virus to new patients, thus the incident pool also declines. In the face of exhaustion of prevalent and incident patient pools, companies require further innovation to sustain revenue growth. Where an incident pool remains stable (eg, in cancer) the potential for a cure poses less risk to the sustainability of a franchise.

Exhibit 8: GSe GILD hepatitis C vs. HIV franchise sales



Source: Goldman Sachs Global Investment Research

A myriad of pricing/reimbursement models for one-time treatments

Given the possible one-time curative nature of gene therapy, we believe price tags of $1mn+ are likely, depending on the size and severity of the addressed disease and the benefit of treatment.

In terms of pricing/reimbursement models, we view three possibilities: 1) a one-time fixed payment; 2) a fixed/variable payment amortized over several years; 3) a pay for performance model over time (payment per efficacy). In the U.S., we believe pay for performance models could be difficult to institute given the ability to switch healthcare plans and need to track patients over time. However, we acknowledge multiple and varied pricing/reimbursement models may be instituted across geographies. The following represent examples of the different pricing strategies used in genome medicine:

1. One-time: In 2012, the first gene therapy, UniQure's (QURE) Glybera for the treatment of a rare disease, familial lipoprotein lipase deficiency (LPLD – individual lacks the protein required to break down fat), was approved in the EU and priced at €1mn. However, Glybera is no longer marketed due to lack of clinical durability in the face of existing standard of care (a strict low fat diet). A second gene therapy, GlaxoSmithKline's (GSK) Strimvelis was approved in the EU in 2016 to treat ultra-rare immune disorder ADA-SCID. The drug was priced at €594,000. Since ADA-SCID affects only ~15 children per year in the EU, pricing is likely uncomparable. Strimvelis also only offers the treatment at the Ospedale San Raffaele in Milan, Italy.
2. One-time with performance contingency: The first approved CAR-T cancer gene therapy, NVS' Kymriah was approved by the FDA in August 2017 in relapsed or refractory pediatric/adolescent acute lymphoblastic leukemia (ALL), a $1.1bn market. Approximately 3k patients aged 20 and younger in the US are diagnosed annually,

making it the most common childhood cancer, according to the National Cancer Institute. Current treatment options include chemotherapy and stem-cell transplants, but ~600 relapse annually. The one time treatment was priced at $475k, however payment is contingent on a successful outcome one month post administration. For context, a Phase 1/2 clinical trial in 63 ALL patients resulted in a 83% remission rate within three months – at 12 months, 79% of treated patients were alive.

3. One-time: Gilead (GILD)/Kite's Yescarta became the first commercial cancer gene therapy for relapsed or refractory large B-cell lymphoma in October 2017. In a Phase1/2 clinical trial, 72% of patients treated with a single infusion of Yescarta responded to therapy (overall response rate) including 51% of patients who had no detectable cancer at median follow up of 7.9 months. Yescarta pricing is at $373k for this larger market opportunity versus pediatric ALL, but is not outcome based.
4. Outcome-based:-Luxturna's one time US gross price is $425k per eye and translates to $850K for two eyes. By pricing below $1mn, Luxturna would not be affected by a 23% rebate to 340B Drug Discount Program eligible hospitals. The outcome based pricing model, supported by Harvard Pilgrim and affiliates of Express Scripts (covering 2mn lives), ensures payor rebates if 1) short term efficacy is not seen in 30-90 days post-treatment and 2) long term durability (30 months) is not maintained. ONCE's Luxturna pivotal data showed ~5 lux improvement in light perception in patients at 30-90 days, which was durable out to 30 months of follow-up. The second model, focusing on innovative contracting, aims to avoid the markup usually charged by treatment centers through ONCE directly selling Luxturna to the payor or the payor's specialty pharmacy. The final plan under negotiation with CMS is an installment model to spread payments out over multiple years with an outcomes-based rebate component initially tested as a demonstration project. Management expects CMS to begin coverage of Luxturna within a year. EU approval is on track for 3Q18 based on the receipt of Luxturna's day 120 list of questions, and we expect ONCE to demonstrate global flexibility in regards to drug pricing/reimbursement with multiple models to suit particular commercial territories.

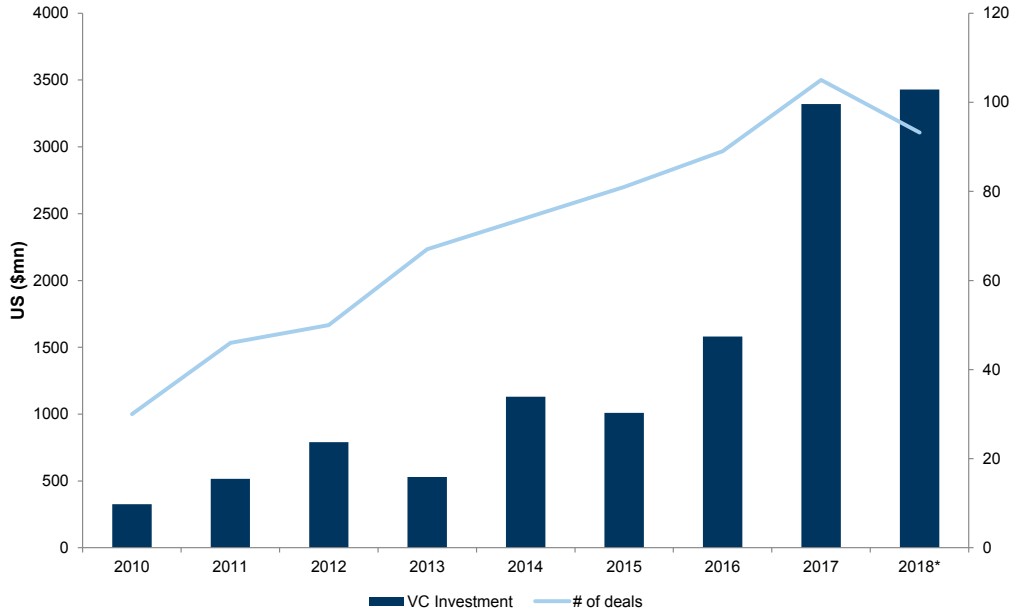
The venture landscape

VENTURE CAPITAL HORIZONS

Venture capital has played a key role in the healthcare sector by providing capital and an incubation period for early biotechnology startups with innovative but unproven platforms to develop their technology, build expertise, gain intellectual property, generate proof-of-concept data and allow treatments to advance to the clinical or commercial stage. Alongside traditional venture capital, we note that many public biopharmaceutical companies have also established venture capital arms, e.g. RocheVentures, Novo Ventures, Bayer Lifescience Center, Pfizer Incubator, leveraging their extensive resources to develop technologies.

Venture capital investment into the genomics space has accelerated over the past five years from $529mn to $3.32bn between 2013 and 2017, representing a ~60% 4-year growth CAGR. Notably, the number of deals has not increased in tandem with funding volumes, suggesting companies with novel genomic platform technologies are attracting larger investments per deal over time from venture capital firms.

Exhibit 9: Venture capital investment in genomics since 2010



Source: CB Insights, Goldman Sachs Global Investment Research, *YTD

Nuance within Genome Medicine: Platforms in focus

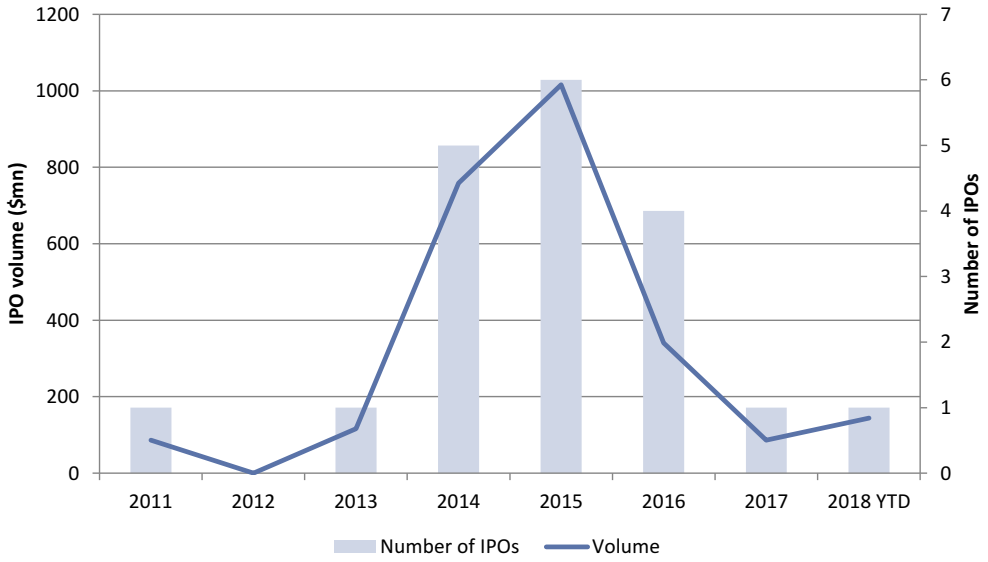
The vast potential of genome medicine to cure almost any diseased tissue means that successful therapies will lead to a sea change in the therapeutics industry. Clinicians and researchers are advancing programs in rare diseases, and it is likely that the scope of addressable therapeutic areas will expand over time.

The outlook for IPOs and M&A

The increase in venture capital flowing into genome medicine companies has also resulted in a slew of exits in the form of IPOs as well interest from a M&A standpoint. The peak of genome medicine IPO activity occurred in 2015, when six genome medicine companies tapped the public markets and raised more than $1bn in capital, although volumes declined in the subsequent years amid drug pricing pressure and market volatility. We note the first of the next-generation wave of genome medicine companies, BLUE, went public (IPO) in 2013. However, we expect IPO activity in genome medicine companies and biotechnology to pick up in 2018, driven by a confluence of market conditions, R&D productivity resulting in more genome medicines entering the clinic, and favorable valuations (supported by drug development successes

in this field and the regulatory environment) — we note that YTD, genome medicine companies have raised more capital than in 2017. Furthermore, some of the early wave of next-generation genome medicine companies have seen significant valuation gains as platforms have matured, pipelines progressed from the clinic to launch, and acquisitions have fueled premiums.

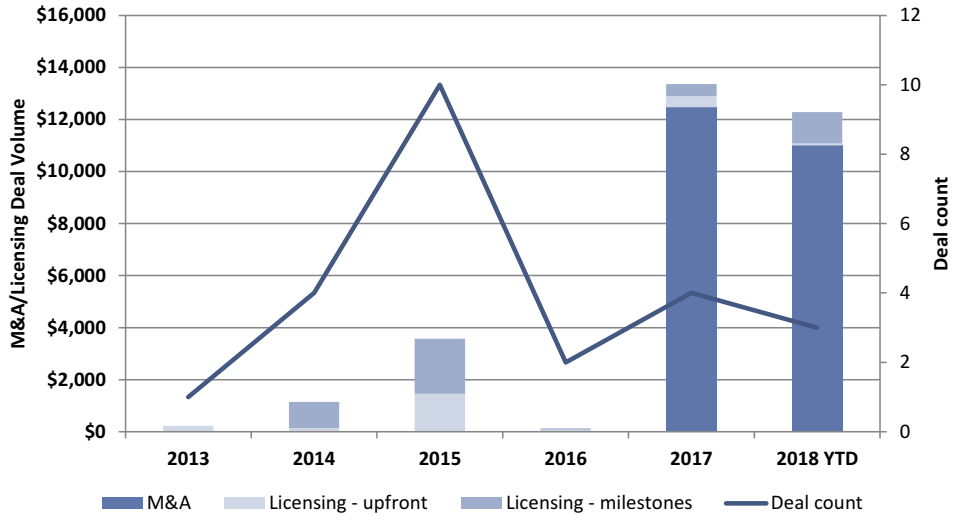
Exhibit 10: Genome Medicine IPO activity 2011-2018



Source: FactSet, Goldman Sachs Global Investment Research

Given their potential to disrupt the therapeutics market, genome medicine companies have also attracted the attention of large biopharma. Earlier business development activity in this space was limited to early and/or smaller R&D licensing and collaboration agreements (mean licensing upfront of $126mn and milestones of $346mn) rather than outright acquisitions.

Exhibit 11: Genome medicine licensing and M&A deals



Source: Goldman Sachs Global Investment Research

We anticipate further M&A activity in the genome medicine space as assets mature

The clinical success and regulatory approvals of a number of genome medicines (albeit in last-line cancer and severe orphan diseases) serve as compelling proof-of-concept that has attracted increasing attention from large biopharma facing slowing top-line growth and upcoming patent cliffs and looking to replenish R&D pipelines with these disruptive technologies/assets. The two largest M&A transactions in genome medicine occurred in 2017 and 2018 and were concentrated solely on oncology assets in late-stage clinical development (GILD/Kite and CELG/Juno), in line with historical interest in the space. In terms of M&A, our prior analysis suggests that in the oncology space acquirers prefer either: (1) commercial or regulatory-stage companies — however these are scarce and attract significant premiums; or (2) early clinical stage companies — a high-risk, high-reward approach (given the possibility of a negative return on investment in the case of failure but potentially higher returns than commercial stage investments if successful)

Genome medicine: the next wave

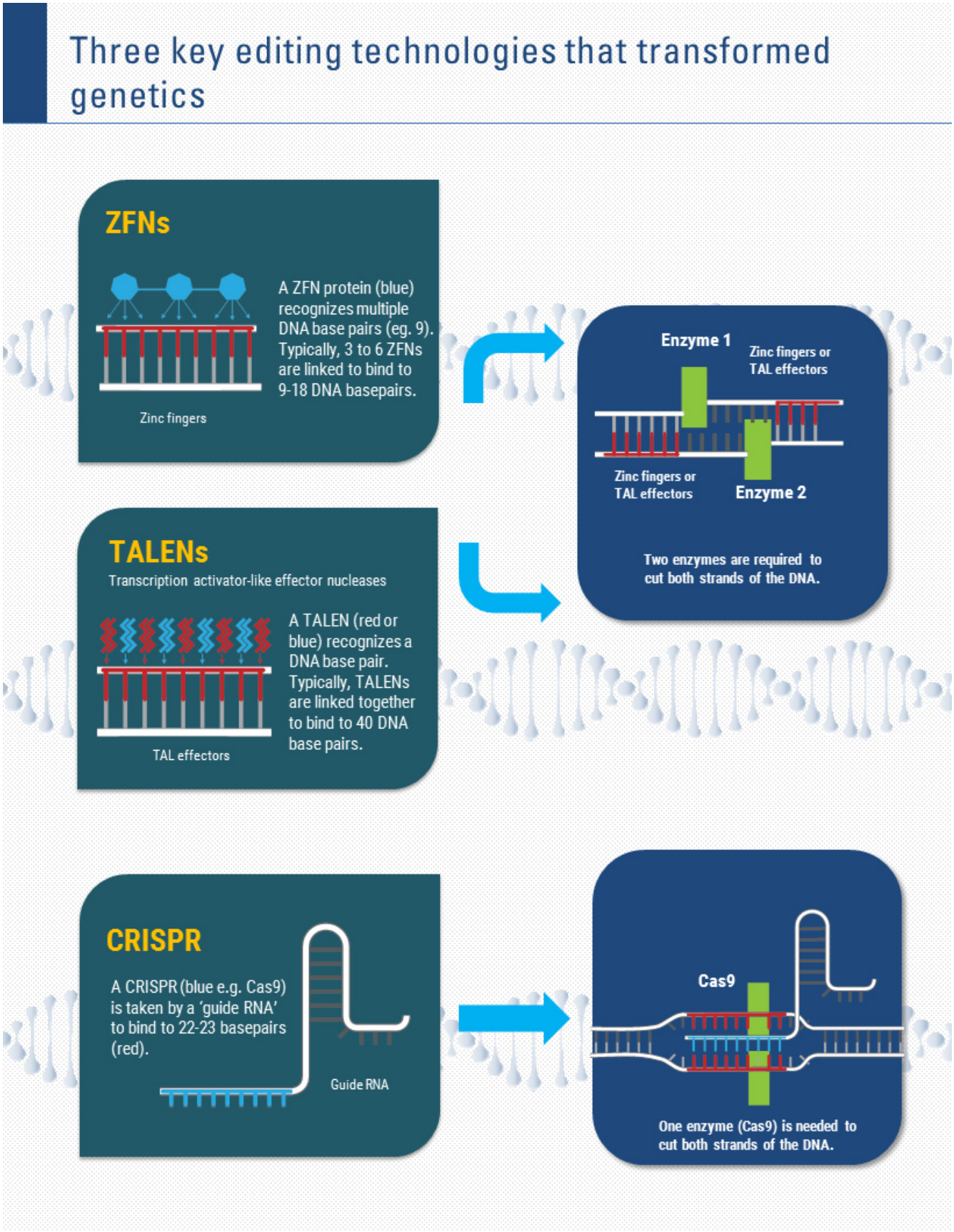
While the current wave of genome medicines is bearing fruit, efforts are underway to develop the next generation of therapies with enhanced efficacy, safety and/or durability. Some of the developments include: allogeneic ("off-the-shelf") cell therapies, next-generation TCR cell therapies targeting solid tumors, enhanced T cell therapies (e.g. kill switches; incorporating gene editing), gene therapy to knock down mutant proteins, gene editing that does not require nucleases but leverages existing cellular machinery and novel technologies that can efficiently insert genes ex vivo without a viral vector. Other possibilities include gene editing of germline cells (sperm/egg) or embryos, treating multigenic chronic disorders through multiplexing of CRISPR/Cas9 and creating compatible animals for human transplantation to provide a more abundant organ supply.

However, as genome medicine and its capabilities continue to advance, numerous ethical issues will need to be considered and addressed.

Gene editing is the next frontier

Gene editing is a form of genetic engineering where the chemical sequence of an organism's DNA is altered using engineered nucleases, a type of "molecular scissors". These nucleases can be programmed to create highly precise cuts at any site in DNA, allowing scientists to edit the genetic blueprints of living cells. As depicted in , the ability to precisely cut DNA allows several different types of edits to be accomplished. First, gene editing can be used to physically remove a disease causing fragment of DNA. Second, it can serve to repair disease-causing regions of DNA (in the case of inherited genetic disorders, the diseased DNA would be excised and replaced with normal healthy sequences of DNA). Third, it can insert a new DNA fragment into a patient's genome to produce a therapeutic effect. This third option could include insertion of synthetic DNA fragments, such as those used in cellular immunotherapy treatments (CAR Ts). The ability to "correct" defective DNA that is the root cause of a disease can be considered the ultimate form of precision medicine.

Exhibit 12: The three main tools for gene editing



Source: Goldman Sachs Global Investment Research

Gene therapy versus gene editing?

Gene therapy delivers a "functional" gene to fix or replace a missing or defective gene. Gene editing is a type of genome medicine where the chemical sequence of an organism's DNA is directly altered using "genetic scissors" that can knockout, repair or replace defective gene(s). Both therapies restore a reservoir of normal genes into target cells, although the genetic material will only be passed down if integrated into the host cells' genome, e.g. by gene editing or by lentiviruses (not AAV) in the case of gene therapy.

Gene editing technology's versatility is such that it is also being studied for a large range of other ex-therapeutic uses, including genetically engineering food and animals (eg. creating mosquitoes that resist malaria) as well as providing a highly portable and inexpensive diagnostic test platform, and could address a wider range of diseases than gene therapy.

Exhibit 13: Comparing different gene editing platforms

Gene Editing Technology	Advantages	Limitations
Zinc finger nuclease	Low immunogenicity Modular design and specificity	Relies on difficult to engineer proteins Expensive Off target cuts (effects) occur
TALEN	Cheaper to design than ZFN	Difficult to produce proteins Difficult to deliver Off target cuts (effects) occur
CRISPR	Easy to use Affordable to produce High editing efficiency – up to 80%+ cutting	Delivery is challenging Off target cuts (effects) occur
Meganucleases	High specificity and very low off-target cuts Induces homologous recombination	Very limited range of DNA sequences that can be recognized for editing Complex to design and engineer

Source: Goldman Sachs Global Investment Research

Delivery of the gene editing machinery remains a key hurdle

Companies are developing different delivery techniques to ensure gene editing tools reach the correct cells. The first method is modifying patient' cells outside the body — or ex-vivo — and infusing them back into the body. Ex vivo gene editing enables researchers to remove cells and apply the blueprint and machinery. The method ensures optimal gene editing has occurred before returning the edited cells back into the body. A second method is using engineered viruses like the AAV capsid (also LPNs) used in gene therapy to package and deliver the gene construct and promoter and edit in the body.

What is inside the gene editing toolbox?

There are multiple gene editing tools in clinical development. For example, zinc Finger Nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) both consist of a protein that serves as a DNA cutting enzyme and a DNA template that recognizes and binds the specific target gene segment. Both ZFNs and TALENs rely on proteins that can be difficult to engineer for each gene target but could potentially offer

greater specificity and clear IP ownership. CRISPR consists of a DNA cutting protein guided by an RNA molecule that is able to find the specific gene of interest. RNA molecules are easier to engineer thus resulting in a more affordable and easy to use tool to edit the genome.

mRNA editing adds to the genome medicine toolkit

Scientists at the Salk Institute recently published research relating to the use of a newly-discovered Type VI-D CRISPR/Cas13d system that targets RNA molecules for editing. RNA is the intermediate template derived from DNA, which is then translated into functional protein. Targeting RNA could be an advantage given RNA is transient and intermediary, and thus editing RNA molecules does not result in permanent changes to the genetic code as in the case of DNA gene editing with the CRISPR/Cas9 system. However, RNA gene editing medicines will likely need to be given chronically as the effects are not permanent.

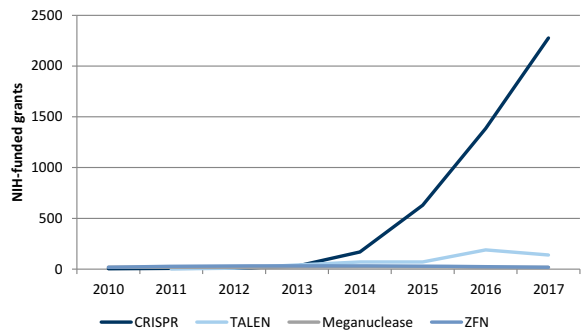
Gene drives could eradicate Zika, malaria, and other viral diseases

Scientists are able to weave gene-editing machinery directly into an insect's DNA. That way, instead of a given gene passing to half of a mosquito's offspring, as would normally occur, it spreads to all of them — resulting in "a gene drive." Depending on the genetic payload scientists choose to spread, they could modify insects to be incapable of spreading disease. Currently in three labs across the United States, a drive is spreading a gene among mosquitoes which blocks the malaria parasite from developing, thus eradicating it. Since there is significant interconnectedness between species, concerns over unforeseen ecological consequences have been raised, and regulators are stepping in.

Gene editing could sidestep concerns over GMOs

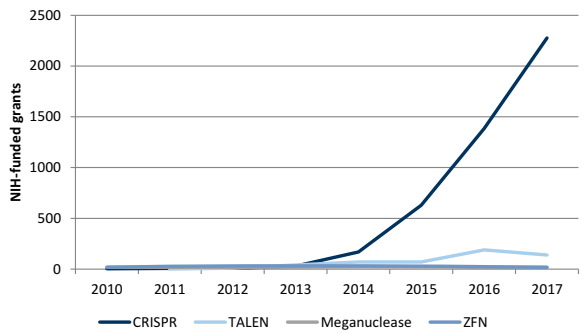
The gene-editing technology provides a way to modify crops in hopes of making them yield more food and resist drought and disease more effectively. Research has shown that gene edited plants could have no traces of foreign DNA, making it possible that they will not fall under existing regulations governing genetically modified organisms and could sidestep many of the consumer concerns over these GMOs.

Exhibit 14: NIH grants mentioning CRISPR have exceeded other editing platforms in recent years



Source: NIH RePORT

Exhibit 15: CRISPR publications have grown exponentially since 2010



Source: PubMed

"Off-the-shelf" allogeneic cell therapies

While the current generation of autologous ("personalized" medicine through the use of one's own T cells) CAR Ts have shown compelling efficacy in last-line blood cancers, companies are continuing to optimize the technology and address certain limitations, including the need to use patients' own T cells, manufacturing time (which can take several weeks) and failure to manufacture CAR T cells. The next wave of T-cell technology employs an allogeneic "off the shelf" approach which would overcome these limitations and represent a major advancement in the field of cell therapy. Allogeneic cell therapy offers the possibility of harvesting T cells from a healthy donor so that they are ready to administer when the patient needs it, as opposed to engineering each patient's T cells individually (autologous). The allogeneic product can be expanded in quantities that may be unattainable from the autologous source, undergo cryopreservation, and be readily available for delivery shortly following diagnosis, thus saving precious time in the setting of a rapidly progressive and fatal disease. In comparison, the manufacture of the autologous product may require several weeks to reach sufficient numbers for administration, and the ability of the patient's cells to expand is unpredictable.

The safety and efficacy of off-the-shelf products remains to be systematically tested and methods are required to minimize the potential for donor cell rejection by the recipient and reduce the alloreactivity potential of the product. Approaches to address these concerns are underway, seen specifically in the manufacturing process. The allogeneic process is similar to traditional CAR-T therapies, however once the donor cells are harvested, they are modified with gene editing to knock out the native T-cell receptor thereby avoiding rejection by the person's immune system in the form of graft-versus-host disease (GVHD) that would be expected on administration of an allogeneic product into a non-matched patient. Another approach would be to include a gene such as caspase 9, an intrinsic activator of apoptosis (programmed cell death), into the CAR construct to minimize the risk of GVHD after allogeneic CAR T cell infusion. Allogenic T-cells represent the next wave of adaptive immunotherapy and multiple trials are underway, which will serve as proof-of-concept to pave the way for off-the-shelf universal CAR T cell therapy.

Targeting solid tumors

CAR-T therapies have shown impressive activity in blood cancers, which target proteins on the surface of cancer cells. However, treatment in solid tumors (i.e. breast, lung, liver cancer) is a challenge given the difficulty of enabling CAR T cells to penetrate and function in the tumor microenvironment. Multiple companies (e.g. GILD/Kite, CELG/Juno, BLUE, ADAP) are utilizing T cell Receptors (TCRs) technology which can recognize tumor-specific proteins on the inside of cells. Thus, TCR therapies could expand potential cancer cures from just blood cancers to solid tumors as well.

Gene editing for viral infections

There are currently limited curative options for many viral infections given they are intra-cellular and can remain dormant and undetectable in cells. Viruses such as HIV integrate their DNA into the hosts' cells and can remain dormant for long periods of

time and thus evade immune detection and clearance. Gene editing technologies such as CRISPR/Cas9, ZFNs and TALENs provide a potentially effective, highly specific, and versatile therapy applicable to human viruses, including HIV, papillomaviruses HPV16 and HPV18, hepatitis B virus (HBV), Epstein-Barr virus (EBV), polyomavirus JC (JCV), Herpes simplex virus, and other Herpesviruses. CRISPR/Cas9 is a simple but powerful tool that can be harnessed to 'cut out' viral DNA in host cells — a specific guide RNA (gRNA) complementary to the viral DNA sequence can be introduced, which then directs the CRISPR/Cas9 complex to the relevant section.

In HIV, using CRISPR/Cas9 combined with multiple gRNAs flanking the provirus section allows for the excision of integrated proviral DNA, which is then broken down in the cell. This leads to inactivation or complete excision of the HIV provirus from the host DNA so that the affected cell is no longer infected. CRISPR/Cas9 is uniquely suited to remove viral infections given multiplexing enables multiple breaks in the DNA strand. An approach that only makes one cut in the DNA could create escape mutations or substitutions that then rejoin and remain viable reservoirs of viral infection. While the power of these tools continues to be tested and studied in multiple trials to help us better understand the potential impact of gene editing in broader context of the patient, we believe gene editing holds tremendous promise in being able to deliver a one-shot cure for viral infections such as HIV, hepatitis B/C, and herpesviruses.

Treating chronic disorders by gene editing

While gene therapy and editing are currently tested in rare diseases like sickle cell and spinal muscular atrophy, creating treatments for more common diseases could transform the therapeutics landscape. According to the World Health Organization, about 17.7 million people died from cardiovascular disease in 2015. Current management of patients with chronic disease, e.g. cardiovascular disease, is to administer life-long treatments such as cholesterol-lowering drugs like statins. However, a one-time approach — like genome medicine — would be attractive in addressing chronic diseases. In a mouse containing human liver cells, researchers recently disabled a human gene PCSK9 through gene editing, reducing blood LDL cholesterol by 35-40%, and potentially cutting the risk of heart attack by 27% and stroke by 21%. The data show the therapeutic approach is feasible and could be given to humans.

The WHO projects diabetes will be the seventh leading cause of death in 2030 with Type 2 comprising the majority of affected patients. Type 2 diabetes results when the body becomes resistant to insulin, which leads to elevated blood glucose, which damages the heart, blood vessels, eyes, kidneys, and nerves. Researchers have delivered adiponectin, a protein that increases insulin sensitivity, into mice via gene therapy, and this could be developed in the future to reduce disease burden in Type 2 diabetes.

Opening the door to xenotransplantation

More than 30k patients undergo transplant surgery each year, and according to UNOS one patient is added to the U.S. transplant waiting list every 10 minutes while 20 people on the list die each day waiting for vital transplants. As the number of people added to the transplant list grows each year, the organ shortage continues to increase creating a

need to innovate and find novel ways to address the shortage. Gene editing is now being seen as the means to potentially solve this shortage by addressing the shortcomings of xenotransplantation from porcine donors to ease the shortage of human tissues and organs. Gene editing is being studied to disable the genes responsible for eliciting a rejection response mounted by the host. Researchers from Harvard Medical School have taken the first step using CRISPR/Cas9 to successfully disable the genes coding for Porcine Endogenous Retroviruses (PERV), which could infect a recipient on immunosuppressant drugs, from swine embryos to create litters of healthy swine without PERV. The potential for gene editing to generate pigs carrying xenoprotective modifications designed to inhibit rejection is another promising area of research. While many challenges remain, future advances in the field may make it possible to engineer pigs to supply compatible organs for human transplant.

Ethical issues to consider

As the field of genome medicine advances with an increase in potential applications, ethical issues and debates will further come to the forefront. Gene editing drugs are beginning to enter the clinic — so far these studies have been in patients with established disease and target body (somatic) cells. However, current gene editing technology is also capable of modifying DNA in germline cells such as sperm/egg and embryos. While the potential to eliminate a disease-causing mutation in an embryo and future generations is appealing, gene editing could leave some cells uncorrected (resulting in mosaicism) or introduce unintended off-target edits which are then introduced into the human gene pool. As it becomes possible to modify (replace or delete) genes, the question of whether it is ethical to perform gene augmentation to improve traits such as height or intelligence also becomes relevant. Unequal access to such gene therapy — given high costs — could also raise concerns about widening socioeconomic inequalities. While some genes clearly cause disease, there is no commonly accepted definition of what constitutes "good" vs. "bad" genes. The rise in genome medicines could also lead to increased genetic testing, the results of which could have implications for health insurance coverage.

GS Innovation Symposium

Interview with UC-San Francisco, Intellia Therapeutics, & Editas Medicine

Featuring Dr. Jonathan Weissman, Professor of Cellular Molecular Pharmacology at the University of California, San Francisco; Nessan Bermingham, PhD, Chief Executive Officer (former), Intellia Therapeutics; and Katrine Bosley, Chief Executive Officer, Editas Medicine

The discovery of the gene-editing technology CRISPR-CAS9 in 2013 came from bacteria in academic research labs. CRISPR is now being explored as a way to precisely edit human genes to cure diseases. But, the technology's versatility is such that it is being studied for a large range of other uses as well. Below we hosted a panel, with experts in the field from University of California-San Francisco, Intellia Therapeutics, & Editas Medicine to assess possibilities and challenges of CRISPR technology.

What is CRISPR? CRISPR is a robust tool/platform that allows for efficient editing of genes/DNA (blueprint for living organisms). The Human Genome Project enabled us to "read" the genome, but CRISPR allows the capability to "write" as well. Earlier technologies required assembly of very complex and cumbersome components to edit DNA. CRISPR has made it much easier to make changes in an "off-the-shelf" manner. Within the therapeutics space, CRISPR is being developed as a way to precisely edit human genes to hopefully cure diseases and discover new drug targets.

Benefit/risk is key in early adoption areas: With respect to therapeutics, there are theoretical concerns with permanent editing of the genome and unintended effects that could arise years or decades later. However, panelists noted that there's been a significant amount of work to understand the specificity of CRISPR and regulatory bodies also want the science/medicine to advance. Furthermore, companies are initially focusing on treating severe genetic diseases with significant morbidity/mortality, where the benefit/risk is very clear. Companies are also working on advancing the technology needed to deliver CRISPR into a variety of human tissues as this differs by disease. Existing technology (developed with gene therapy approaches) allows delivery of CRISPR to the eye, liver, and certain blood cells and hence diseases that affect these organs have been a near-term focus. Companies are also able to extract cells from patients, edit multiple genes, and return them into patients, to treat resistant cancers for example. Our panelists noted these approaches are only the beginning of gene editing and many more advances will likely be made within the next 5 years to enable even broader development.

Enormous potential, but societal/ethical questions must be addressed in parallel: Panelists discussed some of the theoretical longer-term exciting prospects for the technology, including editing out from an embryo the BRCA gene that increases the risk of breast cancer, or using "gene drives" to develop mosquitos that resist malaria. However, there are clearly societal/ethical questions that must be addressed in parallel as the technology evolves and, importantly, panelists noted that these conversations are happening. The National Academy of Sciences and the National Academy of Medicine recently outlined criteria allowing germ-line editing clinical trials to go forward only for serious diseases with stringent oversight. Experiments to develop strains of mosquitos that resist malaria are ongoing, although only in a highly controlled environment.

Gene Therapy in China

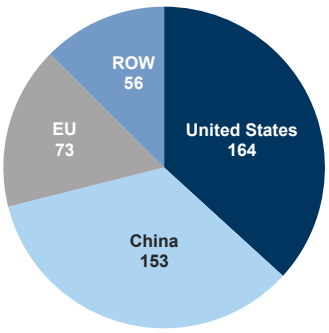
The field of genome medicine is flourishing in China, with heavy investment from both the government and private sectors, following the former's 15-year China Precision Medicine initiative launched in March 2016 (target funding of US$9.2bn). While China's efforts in genome medicine remain at an early stage, China is reframing its regulatory framework to drive drug development in this field.

The emergence of genomics was initially evident through DNA sequencing and non-invasive prenatal testing (NIPT); the focus then shifted to early cancer diagnosis, and over the past three years to gene editing, gene therapy and cell therapy, particularly CAR T cells.

CAR Ts in China – a local focus amidst a growing global presence

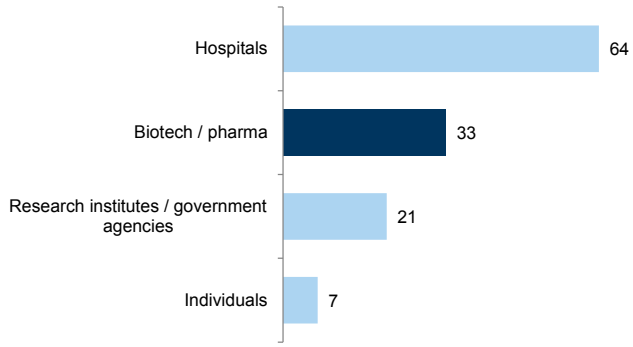
As of February 2018, a total of 153 CAR T trials (or about 1/3 of global CAR T trials) were conducted in China, similar to the US and ahead of EU and Japan. Some clinical trials have shown promising early results. Importantly, CAR T therapies, if successfully developed and approved in China, are likely to be substantially cheaper in China versus the U.S. , with the potential to result in medical tourism.

Exhibit 16: ~1/3 of global CAR T trials are in China
Number of ongoing trials by country / region (as of Feb 2018)



Source: Clinicaltrials.gov, Goldman Sachs Global Investment Research

Exhibit 17: 30+ companies involved in CAR T development
Sponsors / collaborators of CAR T studies in China



Source: Clinicaltrials.gov, Goldman Sachs Global Investment Research

We note several trends and important developments regarding genome medicine in China:

- Significant unmet medical needs in cancer patients: There are >80k new cases of lymphoma in China annually with a prevalence of >200-300k. This exemplifies the large market opportunity for CAR Ts, albeit in one blood cancer — with solid tumors representing a greater proportion of the cancer market. As a result of significant demand, hospitals, which are mostly government-owned, are conducting in-house CAR T studies (>60 of the sponsors / collaborators of CAR T studies in China are hospitals).
- Government's establishment of a regulatory framework: CFDA released the first guideline for development and evaluation of cell therapies on December 22, 2018,

officially paving the way for INDs for CAR Ts. Since, a total of nine Chinese companies have filed INDs with the CFDA..

- Collaborations with global partners: The emergence of CAR Ts in China also triggered the growing interest of global biotech / pharma on collaborations in the space, through in-licensing and out-licensing .

Gene editing in China – taking the lead in clinical studies

The application of gene editing in a clinical setting has resulted in significant debate since the technology (e.g. CRISPR/Cas9) is fast-evolving and safety remains a concern — also given ethical concerns on future pursuits (e.g. "designer babies"). While global peers and regulators in the US and EU remain cautious on the initiations of human studies using CRISPR/Cas9, China has taken the lead. As of the end of February 2018, there were nine registered clinical studies testing CRISPR-edited cells to treat various cancers and HIV infection in China, vs. only one study in the U.S. All of the studies were initiated / sponsored by top-tier public hospitals across China, and >80 patients were reported as being treated by these investigational genome medicines.

China's early move in the space was largely due to the government's support for CRISPR /Cas9 research and limited regulation thus far in this field:

- Government support: In 2017, the National Natural Science Foundation of China, the key government-run fund that provides capital to natural science research in China, granted funding to >90 projects on CRISPR research, and cumulatively in the past four years, >270 projects on CRISPR have received government funding.
- Limited regulation: China has not established specific regulations on the clinical applications of gene editing, particularly for hospital-initiated projects. Most of the ongoing studies were approved by the hospitals' internal committee assessing patients who failed all available therapies. However, with more studies entering development, we see national level regulators, e.g. CFDA, as likely to step in to place more stringent controls on these investigational therapies.

Manufacturing genome medicines

The manufacturing of genome medicines is highly complex and is an integral process that determines the efficacy and safety of the final drug product. The choice of viral vector, gene construct and promoter will determine how the drug product is manufactured. Multiple manufacturing parameters such as yield, manufacturing scale, empty capsid ratio, manufacturing cell line, and efficacy assays need to be optimized in order to produce a final drug product. Due to the proliferation in the number of gene therapy companies, the demand for genome medicine manufacturing capacity has exceeded supply growth, thus leading to competition between gene therapy players for viral vector manufacturing capacity. Nevertheless, over time, as the field advances, we expect sufficient manufacturing capacity to meet demand, and optimization to increase yield and purity to continue. Below we examine the various components and options in the manufacture of gene therapy.

What goes into making an AAV and lentivirus gene therapy?

Select the appropriate AAV vector

The specificity of an AAV for a particular tissue is determined by the interaction of viral surface structures with receptors present on the surface of the cell type. Beyond tissue specificity, other factors are also important in selecting an appropriate vector: seroprevalence (proportion of people with pre-existing antibodies), immunogenicity, safety, manufacturing ease, and licensing rights.

Select the appropriate gene construct for the disease

Once a tissue-specific vector is selected, the next step is to design the appropriate gene construct — the genetic material that will be inserted into cells and translated into a protein product. Some of the factors influencing construct selection include the gene defect in the target disease, the size of the gene itself, the need for any modifications, e.g. truncation, and finally use of an appropriate promoter to drive the gene expression and activity. Where gene therapy is used to replace a single defective gene, the ideal situation would be to use the defective/deficient gene as the construct. However, in some disorders, e.g. hemophilia B or Duchenne muscular dystrophy, the Factor IX and dystrophin genes are too large to fit into an AAV capsid. Thus, companies have engineered variants (e.g. Padua for hemophilia B) with an 8-fold increase in activity or designed shortened/truncated version of proteins (e.g. dystrophin) to fit in an AV capsid. Where a gene therapy is designed to neutralize a disease-causing gene/protein, a gene template is created which 'silences' the target — for example, VYGR is developing a gene therapy to silence genes related to chronic pain, Huntington's disease and Alzheimer's disease.

Finally, a specific promoter is selected which determines the tissues where the gene can be expressed.

Exhibit 18: Tissue specific promoters drive gene expression

Promoter	Cell Type
Alb, Alpha1-at, Gata4, Hnf1 alpha, Foxa3, Hnf4aplha, Foxa1/2/3	Hepatocyte (Liver)
Pdx1, Ngn3, Mafa	Beta-Cell (Pancreas)
T-aplha1, Brn2, Ascl1, Mytl1	Neuron
Mlc2, Gata4, Tbx5, Mef2c	Cardiomyocyte (heart)
Pitx3, MyoD	Muscle
C/ebp alpha, C/ebp beta	Macrophage
Oct4, Sox2, Klf4, Myc	Stem cell
Kap	Renal proximal tubular cell (kidney)

Source: Goldman Sachs Global Investment Research

Selecting a scalable manufacturing host cell line

There are several factors to take into consideration when developing a manufacturing strategy for gene therapies: cell species to use, risk of contamination, safety, purity (full

vs. empty capsids), and scaleability among others. In order to manufacture gene therapies, the gene construct along with the DNA for the AAV are introduced into host cell lines to produce AAVs with a gene construct. There are a variety of potential host cells, including human cell and insect cell lines, each with distinct characteristics and certain advantages and limitations. The sf9/baculovirus system originates from insect cells, and though it could potentially contain foreign insect-derived proteins, it is not known to carry cancer-causing genes and is at a lower risk of infection from contaminant viruses in the environment. The HEK293 is a human-derived cell line; however it is an adherent technology requiring growth in a container surface, making it difficult to scale up. As part of the production process, a quality control step is required to remove empty AAV capsids to ensure only full AAVs (AAVs with gene construct) are obtained and contamination is monitored at each step.

Determine manufacturing method

Most human cell lines grow adherently, with the exception of tumors of the blood and some insect derived cell lines. Thus AAV drugs used in clinical studies were initially produced in adherent cell lines. In order to decrease costs and increase scalability, companies have shifted AAV production to cell lines grown suspended in a liquid media (suspension-based). For suspension cultures, the size of the cell culture vessel can easily be scaled up to a stirred tank reactor with total volume of up to 30k liters.

Cell therapy: autologous approach

The currently approved CAR T therapies (NVS' Kymriah and GILD/Kite's Yescarta) utilize a patient's own immune cells to fight cancer, by inserting a chimeric antigen receptor (CAR) to guide the cells to target cancer cells. The following steps are involved in manufacturing CAR T cells: 1) T-cells are collected from cancer patients through a blood draw, 2) T-cells are engineered in a lab with a lentiviral vector to express a CAR or T cell receptor (TCR) that allows them to hone in on tumor cells, 3) the cells are then allowed to grow and expand, and 4) CAR or TCR expressing T-cells are re-infused into patients where they kill tumor cells. Companies' CAR T manufacturing times are variable as some of the processes are yet to be automated. However, the process can take up to several weeks excluding delivery time, and patients with severe disease may progress while waiting for the drug. Also, there is a small chance of manufacturing failure. Thus, there is increasing interest to develop 'off-the-shelf' or allogeneic CAR T cells that can be infused into patients at a moment's notice.

Allogeneic CAR T

Several companies are attempting to deliver an "off the shelf" CAR T therapy, where CAR T cells are manufactured in advance and stored for administration. There are several advantages to this approach. First, this can translate to better clinical outcomes as patients do not have to wait several weeks of precious time for their autologous T cells to be prepared, thus leading to improved clinical outcomes. Secondly, given allogeneic cells are not 'personalized,' automation would be possible and could lead to lower cost of goods and a lower failure rate. Allogeneic CAR T cells are manufactured *ex vivo* by making the appropriate edits. CRSP's approach to its allogeneic CAR T cell therapy

leverages CRISPR/Cas9's ability to multiplex and carry out multiple edits with the same drug: knocking out multiple genes in the cell that cause immune rejection in the host cell and insertion of a CAR that targets cancer cells.

Appendix: DNA - Life's blueprint

DNA (DeoxyriboNucleic Acid) is the most fundamental building block of life on earth. It consists of a code written in four chemical subunits (adenine, A; cytosine, C; guanine, G; thymine, T) referred to as nucleotides. These four chemical nucleotides are arranged in sequence to encode information in a manner analogous to the 0s and 1s that make up binary computer code. However, given its tetrad composition, the complexity of information stored in DNA (genetic information) is higher than computer code. We therefore conceptualize DNA as the ultimate coding language as it stores all the information needed to build the vast array of human, plant, animal and micro-organismal (bacteria) tissues and cells. Every organism has its own unique collection and sequence of DNA referred to as the genome. Fundamental differences between organisms are directly tied to underlying differences in their genetic makeup. In general, more complex organisms tend to have larger genomes comprised of a greater number of DNA bases but this is not correlated with body size.

Breaking down the genetic operating system

DNA serves the blueprint for all the cell and tissue types in the human body. Although the genome is a continuous string of A, C, G and T nucleotides, the genetic material is subdivided into discreet sets of instructions called genes. Each gene provides the recipe for a unique protein, which is the functional output of the genome. Proteins play essential structural and molecular roles in all tissues of the human body and are also the therapeutic targets of most modern medicines. The information stored in each gene (DNA) is converted into corresponding intermediary molecule called RNA (RiboNucleic Acid). RNA is chemically related to DNA but acts as a messenger, carrying the genetic instructions on how to make a particular protein to the cell's manufacturing center, called the ribosome.

Exhibit 19: DNA serves as a blueprint for RNA, the tool to make the "house" (protein)

Source: Goldman Sachs Global Investment Research

Exhibit 20: Need to know scientific terminology

Cell: The most basic unit of life. The human body is made up of trillions of cells that act in coordination as tissues and organs.

DNA: Short for deoxyribonucleic acid. DNA provides the blueprint for life.

Gene: A functional unit of DNA. Each gene provides instructions to make molecules called proteins

Genome: The collection of all an organism's genes and DNA. Each species has a unique genome.

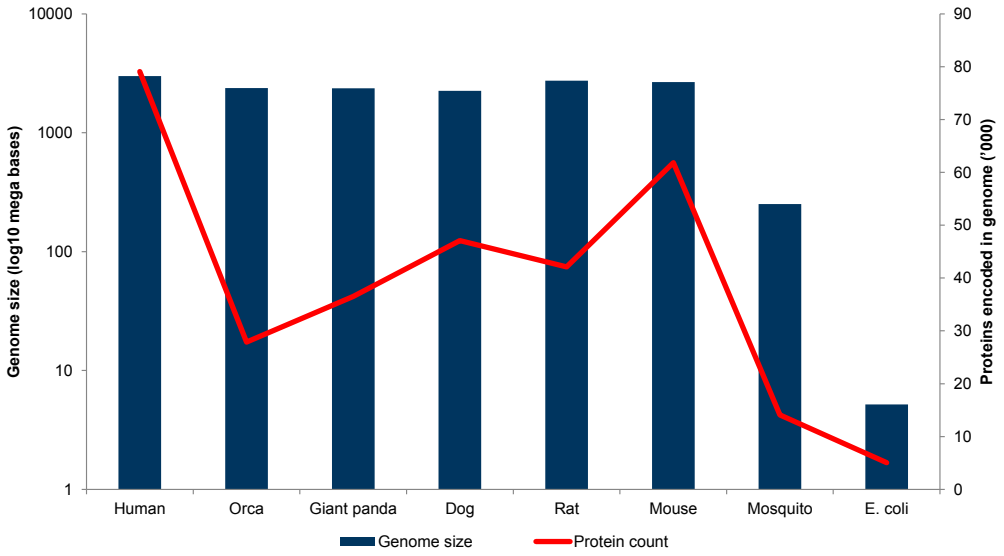
Genetics: The study of genes, heredity and the association between DNA and physical attributes.

RNA: An molecule chemically related to DNA that acts as a messenger of genetic information.

Protein: The functional output of genes. Proteins play many molecular and structural roles in the body.

Source: Goldman Sachs Global Investment Research

Exhibit 21: Human genome contains ~3 billion base pairs of DNA



Source: Goldman Sachs Global Investment Research

Interpreting the genetic code

The human genome encodes >20,000 genes, each of which corresponds to a unique protein. However, in any given cell or tissue type only a fraction of these genes are active or "on". The unique combination of genes in the "on" state vs. "off" state determines the makeup and identity of a cell, (e.g. skin, hair, blood). Since the discovery of DNA's structure in 1953, genetics researchers have focused on understanding the relationship between genes and their influence on cell identity. These efforts were advanced by several major technical milestones through history. In addition to the discovery of DNA's structure in 1953, we highlight the 1980 Nobel for "recombinant DNA" technology which allowed scientists to cut and paste fragments of genetic material and opened the door for genome engineering. The co-award of the 1980 Nobel prize was for the development of DNA sequencing technology which allowed researchers to read the genetic code for the first time in a highly efficient and accurate manner.

Game changer: Sequencing the human genome

The Human Genome Project (HGP) was an international scientific program aimed at determining the sequence of the human genome and mapping all of its constituent genes from both a physical and functional standpoint. The project launched in 1990 and was officially declared complete in 2003, however the initial sequence of the human genome was published in the top-tier scientific journal *Nature* in 2001 (Lander et al, 2001). The HGP was funded by the US government through the National Institutes of Health (NIH) as well as numerous other groups from around the world including the United Kingdom, Japan, France, Germany, Canada and China. When the US Congress established funding of the HGP in 1990 estimates suggested it would cost $3bn and complete in 2005. However, the project officially completed 2 years ahead of schedule

on April 14, 2003 and at a cost of $2.7bn, below the initial estimate. A parallel sequencing project was conducted in the private sector by Celera Genomics, which formally launched in 1998 and sparked a race to complete the human genome sequence. Celera completed their own human genome draft sequence around the same time as the HGP, at a cost of only $300mn. However, their sequencing method relied in part on data already generated and made public by the HGP which allowed a faster and more cost-effective path.

Biopharma companies are building in-house genome projects

The rapid drop in the cost of genome sequencing allowed an unprecedented advancement of the field of genetics and facilitated an understanding of the genetic basis of many rare disorders which in some cases resulted in development of novel treatments.

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Disclosure Appendix

Reg AC

We, Salveen Richter, CFA, Richard Yeh, Ross Weinreb, Ziyi Chen, Kevin Patel, Ph.D. and Alexana Astor, hereby certify that all of the views expressed in this report accurately reflect our personal views about the subject company or companies and its or their securities. We also certify that no part of our compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

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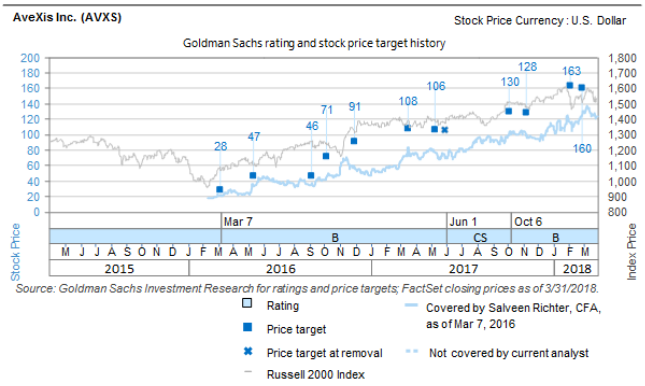

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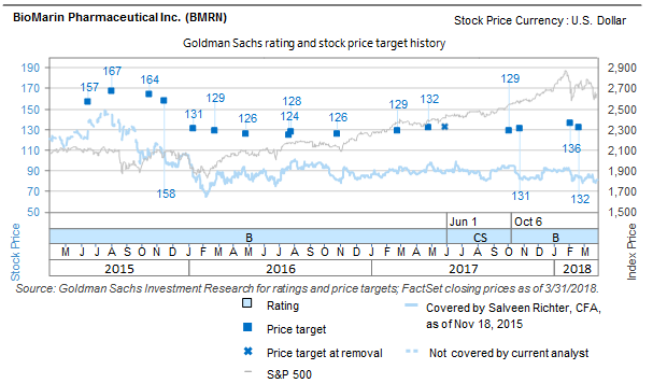

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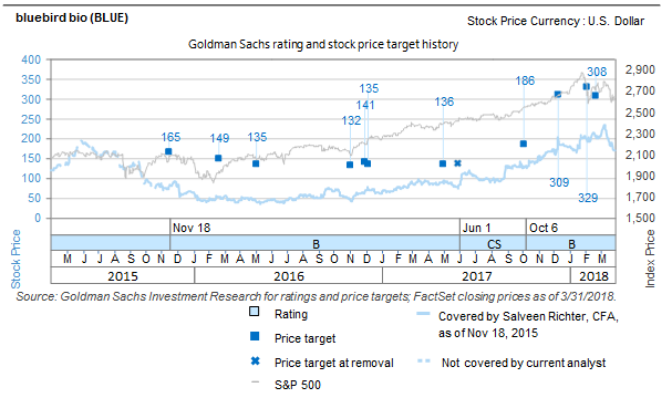

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