

CRISPR & Gene Editing – 2023 Next Industrial Revolution

- CRISPR & Gene Editing
- Future of Healthcare & Gene Editing
- Portfolio Implementation
- Upcoming Catalysts
- CRISPR & Gene Editing Sub-Sectors:
 - CRISPR & Gene Editing Technology
 - Gene Editing Development Solutions
 - Gene Editing Sequencing Solutions
- Portfolio Implementation

January 2023



XDNA | Nasdaq Listed

This is a very different environment than what most investors have ever seen, or in a very long time...

We believe the need for diversification, and in particular, next generation healthcare, has never been more important.

Backdrop

- Growth outlook has deteriorated which puts current earnings estimates at risk
 - Continuing war in Europe which could lead to recessionary pressures
- Corporate earnings concerns in 2023
 - Tech sector has roughly 60% international revenue exposure denominated in dollars
 - S&P 500 roughly 40% international revenue exposure denominated in dollars
- Inflation outlook, commodity surge, and supply chain challenges
 - Oil, palladium, etc.
 - China factory shut down / zero covid policy

What is CRISPR & Gene Editing?



Clustered Regularly Interspaced Short Palindromic Repeats

At its core, CRISPR & Gene Editing is a pair of biological scissors that cuts and replaces genes in living organisms' cells. It has the potential to disrupt virtually every facet of our lives, from curing genetic diseases, detecting and treating cancers, treating HIV, to even bioengineering new crops and plants to feed the world's growing population.

- CRISPR is based on a rudimentary bacterial immune system that Japanese scientists first noticed more than 30 years ago. The system destroys pathogens by cutting the DNA of invaders using enzymes called CAS nucleases, Cas9 being the most widely studied.
- In recent years, the term CRISPR has entered the popular lexicon. CRISPR — more precisely known as CRISPR-Cas9 — is a powerful genome editing technique that allows scientists to make changes to specific DNA sequences and thereby alter gene function.
- Gene editing is much newer technology and builds on the gains of gene therapy.
 - Instead of using a virus, however, gene editing relies on a molecular machine called CRISPR, which can be instructed to repair a mutation in a gene in nearly any organism, right where that “typo” occurs.

Types of gene editing that are being explored:

- CRISPR variations including Cas12/14/Clover
- Transcription activator-like effector nucleases (TALENs)
- Zinc Finger Nucleases (ZFNs)
- Base Editing
- Prime Editing



Types of CRISPR Human Editing Applications

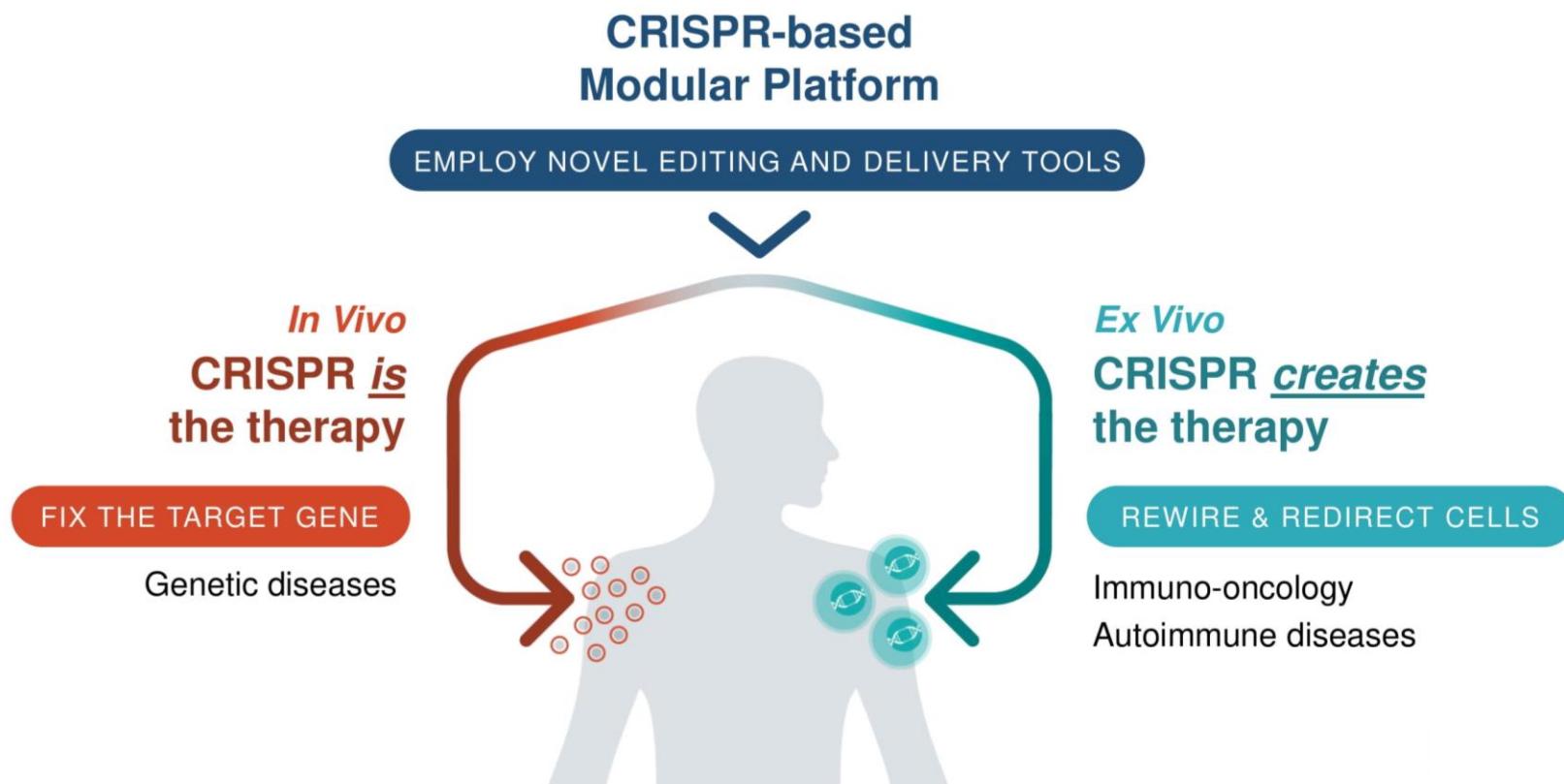


IN VIVO: Direct Injection, ultrasound

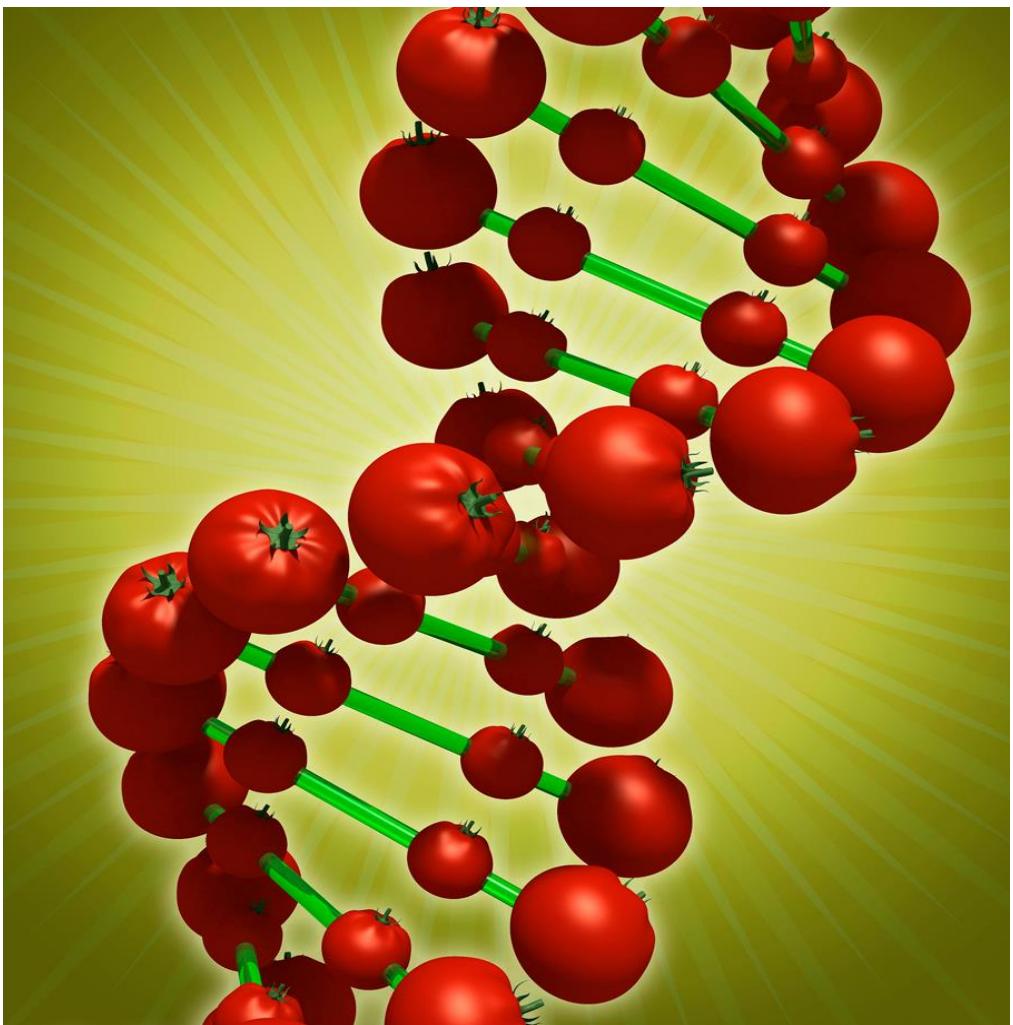
- Transient expression
- Treatment of systemic diseases through skin
- DNA vaccination

EX VIVO: Biopsy, gene transfer – cell culture

- Cells are collected and stem cells are isolated
- Therapeutic gene is inserted in an inactivated virus
- Viruses are mixed with patients stem cells, restoring healthy genotype and transduced stem cells are re-introduced into patient



Japanese Pizza Will Not Be the Same



Two of the researchers behind CRISPR were awarded the 2020 Nobel Prize in chemistry in an aptly titled press release, *Genetic scissors: a tool for rewriting the code of life*. The Royal Swedish Academy of Sciences stated, “Using these, researchers can change the DNA of animals, plants and microorganisms with extremely high precision. This technology has had a revolutionary impact on the life sciences, is contributing to new cancer therapies and may make the dream of curing inherited diseases come true.”

- In Japan, a **new tomato using CRISPR-Cas9 gene editing** technology, includes higher levels of an amino acid that is believed to aid relaxation and help lower blood pressure. **The tomato was engineered using the Crispr gene-editing technology so that vitamin accumulates in the fruit's peel and flesh.**
- The next five to ten years might deliver tremendous advances as CRISPR and gene editing reach a tipping point, where the preclinical work of the past decade is leveraged by a rapidly growing number of clinical trials.
- In medicine, CRISPR gene editing allows physicians to directly fix typos in the patients' DNA. **The first successful human application for CRISPR base editing was announced in England on December 10 (page 16).**

XDNA ETF - Overview



XDNA

Kelly CRISPR & Gene Editing Technology ETF

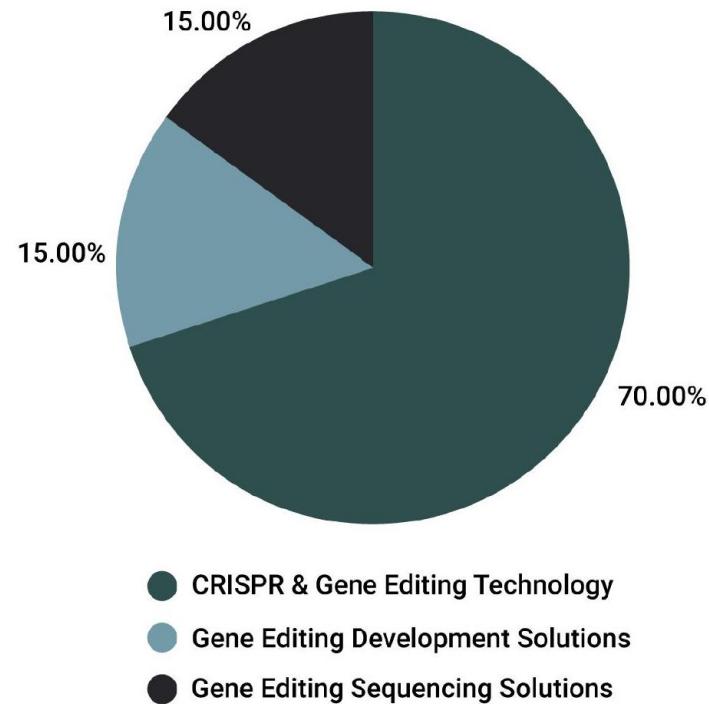
Top 10 Holdings

PERCENTAGE OF NET ASSETS	NAME	IDENTIFIER
10.66%	THERMO FISHER SCIENTIFIC INC COM	TMO
10.20%	BEAM THERAPEUTICS INC	BEAM
9.37%	CRISPR THERAPEUTICS AG	CRSP
7.92%	INTELLIA THERAPEUTICS INC	NTLA
6.46%	POSEIDA THERAPEUTICS INC	PSTX
4.97%	ABBVIE INC	ABBV
4.88%	PRIME MEDICINE INC	PRME
4.83%	EDITAS MEDICINE INC	EDIT
4.68%	SANGAMO THERAPEUTICS INC	SGMO
4.15%	CARIBOU BIOSCIENCES INC	CRBU

Date: 12/19/2022
Subject to Change

XDNA seeks to track the total return performance, before fees and expenses, of the [Strategic CRISPR & Gene Editing Technology Index](#), which measures the performance of companies that specialize in CRISPR & DNA modification systems, and technologies, for variety of applications including basic biological research, development of biotechnological products, and treatment of diseases as well as next-generation sequencing that may be used at various stages of a genome editing workflow.

Sector Breakdown



Every Rebalance
Date 12-16-2022

XDNA Index - Sector Constituents



CRISPR & Gene Editing Technology - 67.98%		
Security RIC	Security Name	Weights
BEAM	BEAM THERAPEUTICS INC	9.74%
CRSP	CRISPR THERAPEUTICS AG NAMEN AKT	9.55%
NTLA	INTELLIA THERAPEUTICS INC	7.88%
PSTX	POSEIDA THERAPEUTICS INC	6.01%
PRME	PRIME MEDICINE INC	4.72%
CRBU	CARIBOU BIOSCIENCES INC	4.63%
SGMO	SANGAMO THERAPEUTICS INC	4.53%
VERV	VERVE THERAPEUTICS INC	4.48%
EDIT	EDITAS MEDICINE INC	4.29%
ALLO	ALLOGENE THERAPEUTICS INC	4.27%
TSVT	2SEVENTY BIO INC COMMON STOCK	4.17%
DTIL	PRECISION BIOSCIENCES INC	3.71%

CRISPR & Gene Editing Technology Description:

Includes companies that specialize in DNA modification systems, and technologies, for a variety of applications including basic biological research, development of biotechnological products, and for the treatment of diseases.

CRISPR & gene editing technology enables genetic elements to be mutated, silenced, induced or replaced. The most common use of DNA modification technology is the targeting of cells within the body to treat genetic disease.

Gene Editing Development Solutions - 16.17%		
Security RIC	Security Name	Weights
ABBV	ABBVIE INC	4.86%
NOVN.SW	NOVARTIS N	3.23%
BMY	BRISTOL-MYERS SQUIBB CO	2.87%
SAN.FP	SANOFI	1.78%
VRTX	VERTEX PHARMACEUTICALS INC	1.37%
REGN	REGENERON PHARMACEUTICALS	1.36%
BIIB	BIOGEN INC	0.70%

Gene Editing Development Solutions Description:

Includes companies that have deep scientific, technical and clinical development experience, potentially along with an intellectual property portfolio, that have rights to develop CRISPR or gene-editing based therapeutic products or targets and/or jointly develop potential products with CRISPR & gene editing technology companies to create a new class of therapeutic products.

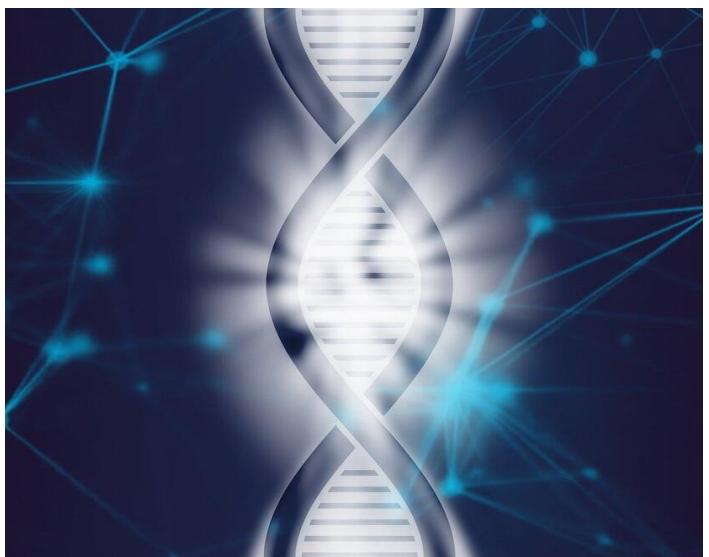
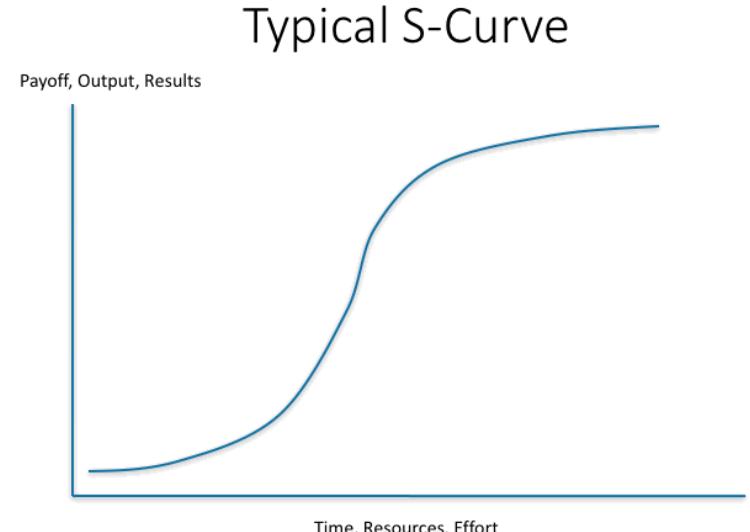
Gene Editing Sequencing Solutions - 15.86%		
Security RIC	Security Name	Weights
TMO	THERMO FISHER SCIENTIFIC INC	10.68%
A	AGILENT TECHNOLOGIES INC	2.58%
ILMN	ILLUMINA INC	1.85%
QGEN	QIAGEN NV SHS NEW	0.64%
PACB	PACIFIC BIOSCIENCES CALIF INC	0.11%

Gene Editing Sequencing Solutions Description:

Includes companies that specialize in next-generation sequencing that may be used at various stages of a genome editing workflow. The companies provide sequencing methods to determine the impact of an edited sequence on the structured function of genes and analysis tools for CRISPR and gene splicing and editing.

XDNA ETF INVESTMENT CASE

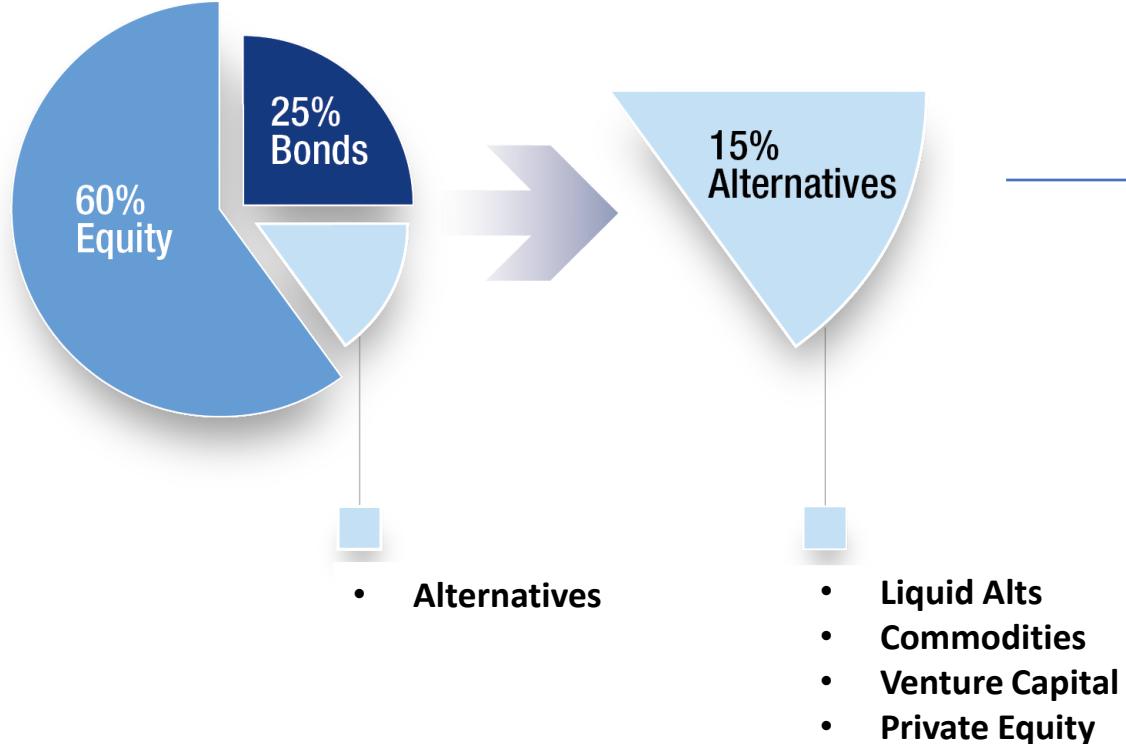
- **Exposure to Innovation:** Aims for thematic multi-cap exposure to innovative companies focusing on CRISPR and gene editing technology.
- **High Growth Potential:** Aims to capture long-term growth with low correlation to traditional growth and healthcare strategies. Enables investors to access growth potential through companies that we believe are positioned to benefit from disrupting the genomic and life science industries.
- **Tool for Diversification:** Offers a tool for diversification due to little overlap with traditional indices. XDNA can be a complement to traditional healthcare and growth strategies.
- **Targeted Exposure:** XDNA is a concentrated portfolio that provides access to emerging areas within the healthcare sector at the intersection of science and technology.
- **Cost Effective:** In a single trade, XDNA delivers access to dozens of companies with exposure to the emerging CRISPR and gene editing theme, seeking to provide a lower cost alternative to mutual funds, private equity funds, and venture capital management in an Exchange Traded Fund (ETF).



Venture Capital Compliment to an Existing Equity Portfolio

As an alternative strategy alongside alpha and beta equities, investors may experience reduced volatility and downside risk.

SAMPLE PORTFOLIO ALLOCATION



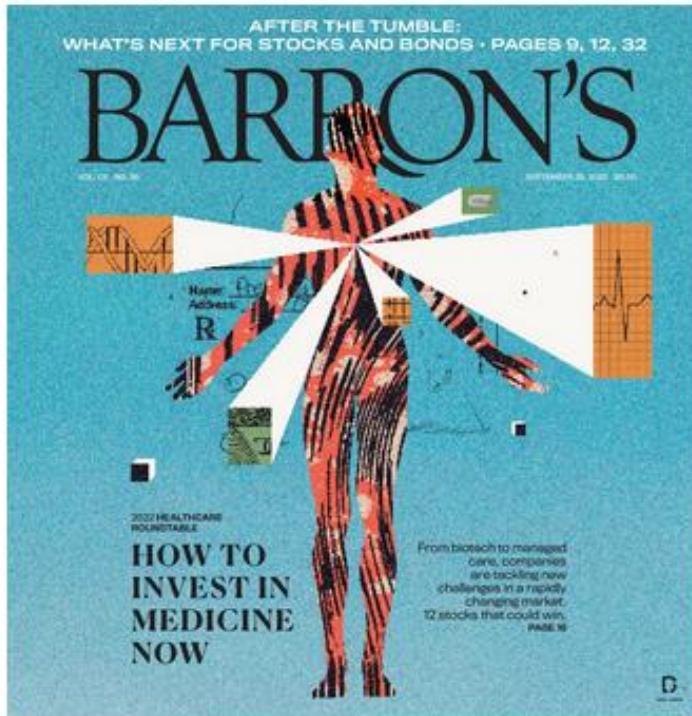
XDNA

Kelly CRISPR & Gene Editing Technology ETF

Publicly Traded Venture Capital Exposure Attributes:

- Daily liquidity
- Longer-term holding period / investment horizon
- Qualities of startups, early-stage, and emerging companies that have been deemed to have high growth potential or which have demonstrated high growth
- Companies are at the next stage of the innovation life cycle—the period in a company's life when it begins to commercialize its innovation

Venture Capital investing in publicly traded CRISPR companies



September 26, 2022

What's Next for the Healthcare Industry, and How to Invest

Barron's: “Jorge, do you see bargains among broken initial public offerings?”

Conde: “The main opportunity is in areas where we are starting to see concrete proof that a new modality, a new form of medicine, can work. Gene editing is one such area. Companies such as **Verve Therapeutics** and **Intellia Therapeutics** have been able to advance into clinical trials to bring these therapies closer to patients.”

* **Verve Therapeutics & Intellia Therapeutics are constituents of the XDNA Index**

Jorge Conde is a General Partner at Andreessen Horowitz, where he leads investments at the cross section of biology, computer science, and engineering.

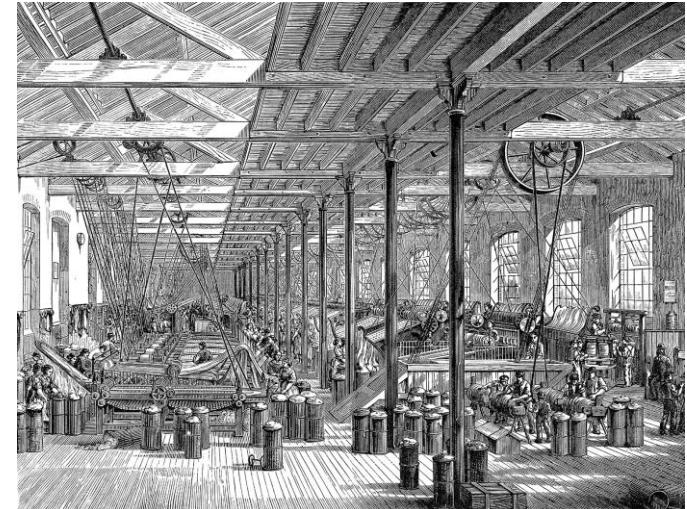
Founded in Silicon Valley in 2009 by Marc Andreessen and Ben Horowitz, Andreessen Horowitz is a venture capital firm, “We are stage agnostic: We invest in seed to venture to late-stage technology companies, across bio + healthcare, consumer, crypto, enterprise, fintech, games, and companies building toward American dynamism.” Source: a16z.com



The Next Industrial Revolution – Life Sciences

Impact of Technology on the Genome

- Throughout history, society has been transformed through the industrial revolutions. The previous industrial revolutions focused on the impact that technology has on our resources: Agriculture, Energy, Metallurgy, Textiles, Chemicals, Transportation, Communications
- The Industrial Revolution took place over more than a century, as production of goods moved from home businesses, where products were generally crafted by hand, to machine-aided production in factories. This revolution, which involved major changes in transportation, manufacturing, and communications, transformed the daily lives of Americans as much as— and arguably more than—any single event in U.S. history.
- **What distinguishes this industrial revolution, from the previous, is that it will transform the daily lives of people because it will impact changes to their health due to CRISPR and genomic editing.**
- In-Q-Tel (The CIA registered nonprofit venture capital firm) in September 2022 invested in a CRISPR start-up and the White House issued an Executive Order “to develop genetic engineering technologies and techniques” as the Fourth Industrial Revolution is starting to take hold.



Government Funding Plays Key Role in Industrial Revolution for Societal Returns

Rise in government funding and growth in the number of genomics projects

In recent years, governments in various countries across the globe have made significant investments in the field of genomics, which have played a major role in the development of new technologies in genome editing. The availability of government funding has enabled academic and government institutes to carry out in-depth research related to genome editing/engineering.



- In the previous industrial revolution, the U.S. government adopted policies that supported industrial development such as providing land for the construction of railroads and maintaining high tariffs to protect American industry from foreign competition.
- The CIA investment and White House's executive order are reminiscent of JFK's Moonshot Speech where the moon was just the beginning of the government's investment into science and technology.
- The U.S. government launched the Cancer Moonshot in 2016. To date, National Cancer Institute "NCI" has supported over 70 programs and consortia and more than 250 research projects.

The
Intercept_



THE CIA JUST INVESTED IN WOOLLY MAMMOTH RESURRECTION TECHNOLOGY

While skeptics doubt the prospects for de-extinction, the CIA's venture capital firm deems powerful genetic manipulation tools worth the money.



Daniel Boguslaw

September 28 2022, 9:03 a.m.

- Colossal uses CRISPR gene editing, a method of genetic engineering based on a naturally occurring type of DNA sequence.
- The embrace of this technology, according to In-Q-Tel's blog post, will help allow U.S. government agencies to read, write, and edit genetic material, and, importantly, to steer global biological phenomena that impact "nation-to-nation competition" while enabling the United States "to help set the ethical, as well as the technological, standards" for its use.
- The size of In-Q-Tel's stake in Colossal won't be known until the nonprofit releases its financial statements next year.

The C.I.A. Blog on Investing in CRISPR



In-Q-Tel is the Central Intelligence Agency's registered nonprofit venture capital firm

- Crispr-Cas9 is the second generation of technologies that seek to repair thousands of inherited genetic disorders and battle cancer in new ways.
- **The revolution rolls onward.** Understanding the code, and learning to read it (DNA sequencing), write it (DNA synthesis), and edit it (using tools like CRISPR/Cas) is work that is ongoing all over the world and generating enormous amounts of both raw DNA sequence data and information on how that data works inside cells to produce useful functions and goods.
- Why the interest in a company like Colossal, which was founded with a mission to “de-extinct” the wooly mammoth and other species? Strategically, it’s less about the mammoths and more about the capability [...] Solving the challenges that must be overcome in engineering animals and plants (making massively parallel and highly accurate genome edits, making healthy sperm and eggs from edited stem cells, and gestating large animals to term) will unlock such capabilities as programming the physical properties of wood to improve building materials, preventing the extinction of not-yet-extinct but endangered animal species, sequestering carbon from the atmosphere, further enhancing crop species to tolerate increasingly severe climatic changes, and curing human diseases such as sickle-cell anemia, beta thalassemia, Duchenne muscular dystrophy, and many kinds of cancer.
- **Why is this a big deal?** We now sit at a pivotal point in history, where transnational issues (pandemics, climate change, population growth, human migration) intersect with nation-to-nation competition that will increase the potential for global conflict in coming decades, a reality that was formally recognized this week by the Biden administration in the release of the Executive Order (EO) on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy.



How Can We Use Biology to Solve Global Issues?

SEPT. 20, 2022

Kevin O'Connell
SENIOR VICE PRESIDENT, TECHNOLOGY • IN-Q-TEL

Eugene Chiu
SENIOR PARTNER • IN-Q-TEL

BIOTECHNOLOGY



SEPTEMBER 12, 2022

Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy

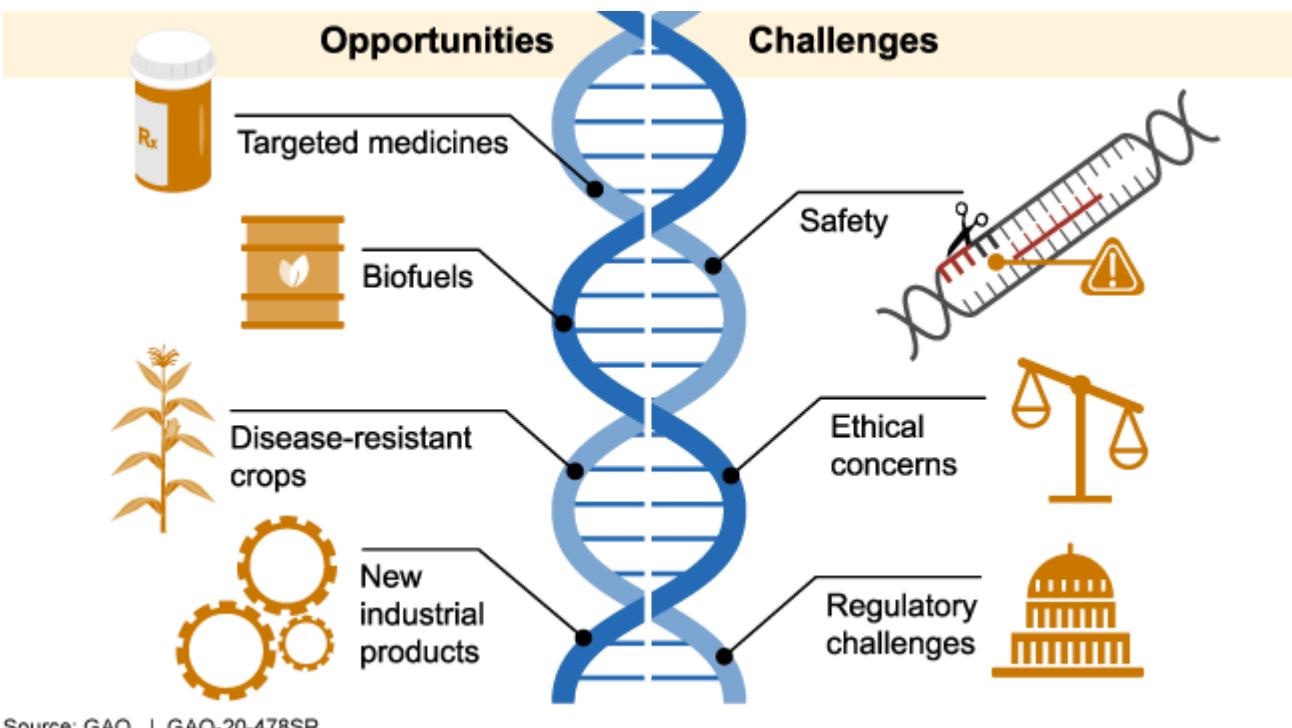
THE WHITE HOUSE



BRIEFING ROOM

PRESIDENTIAL ACTIONS

- We need to develop genetic engineering technologies and techniques to be able to write circuitry for cells and predictably program biology in the same way in which we write software and program computers.
- For biotechnology and biomanufacturing to help us achieve our societal goals, the United States needs to invest in foundational scientific capabilities. We need to develop genetic engineering technologies and techniques to be able to write circuitry for cells and predictably program biology in the same way in which we write software and program computers.”
- Advance the science of scale-up production while reducing the obstacles for commercialization so that innovative technologies and products can reach markets faster.

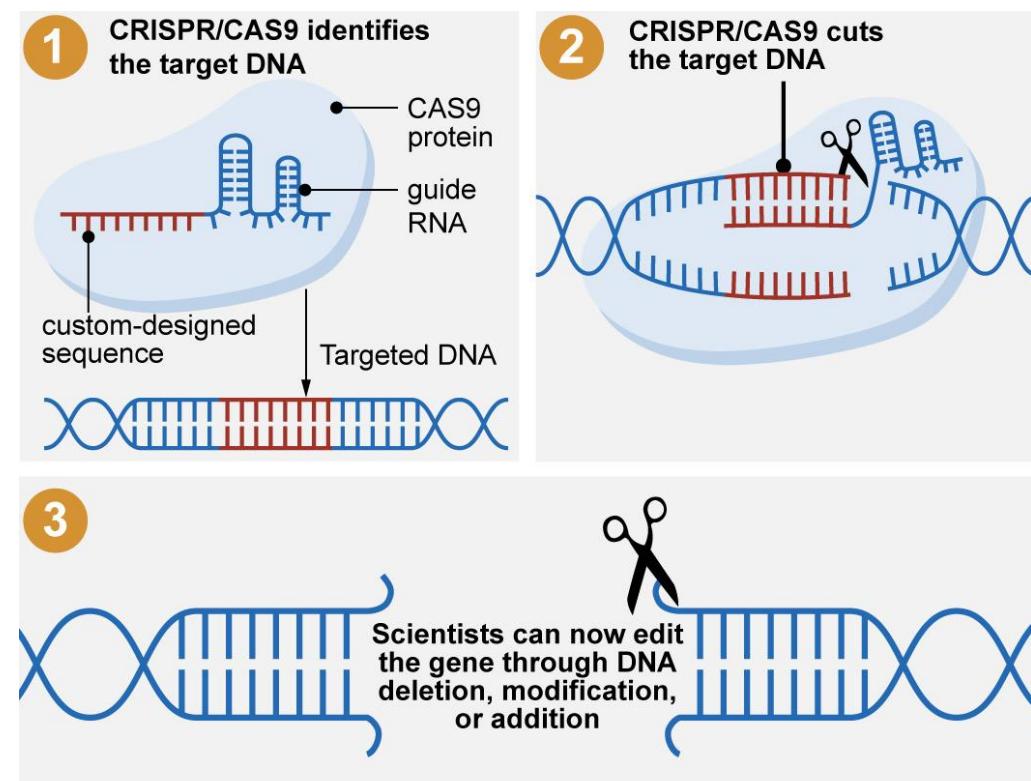


Source: GAO. | GAO-20-478SP

CRISPR leverages a natural defense mechanism of bacteria to cut DNA at a specific location. Specifically, when bacteria are attacked by a virus, they record a section of the virus's DNA in their own DNA, bookending it with a repeating sequence called Clustered Regularly Interspaced Palindromic Repeats (CRISPR). Storing part of the virus's genetic code allows the bacteria to "remember" it. When the same type of virus attacks again, the bacteria use a specific CRISPR-associated protein number 9 (CAS9) to cut the virus's DNA, destroying the virus.

Published: Apr 07, 2020.

Researchers are already building on CRISPR to create new gene editing systems. For example, a system known as prime editing builds on the knowledge of CRISPR/CAS9 to directly exchange one piece of the DNA with another, which is known as base editing ([next page](#)).



Source: GAO. | GAO-20-478SP



CRISPR & Gene Editing: Accelerating Technology Platforms

Key Aspect of Industrial Revolutions – Accelerating Technology

First-generation tools such as CRISPR – CAS9 can precisely hone in on specific parts of a genome.

- These tools also require breaking apart both strands of the double-stranded genome.

Second-generation tools such as CRISPR Base Editing can precisely hone in on specific parts of a genome down to a single base pair.

- These tools do not require making any breaks to the double-stranded genome, which avoids many risks of earlier tools now in clinical development.

Third-generation tools such as CRISPR Prime Editing can do everything prior-generation tools promise but with more precision.

- Prime editing theoretically can remove faulty genetic material, insert new genetic material, change genetic material, and any combination of these tasks.

- While not all diseases have a single-gene basis, most have a genetic component. Early studies suggest that conditions like heart disease, chronic pain and Alzheimer's disease could all be treated with CRISPR.
- The first person to be gene-edited with CRISPR was treated only three years ago for a disorder of red blood cell production.
- Since then, the technology has been used to treat:
 - congenital blindness
 - sickle cell disease
 - heart disease
 - nerve disease
 - cancer
 - H.I.V.

Nobel-Prize Winning Genome Editing Technology



Precise and modular approach
for editing the genome



Potential for life-long effect
following one-time treatment



Locates a genetic sequence
to make a permanent change



Overcomes key limitations of
gene and RNAi therapies



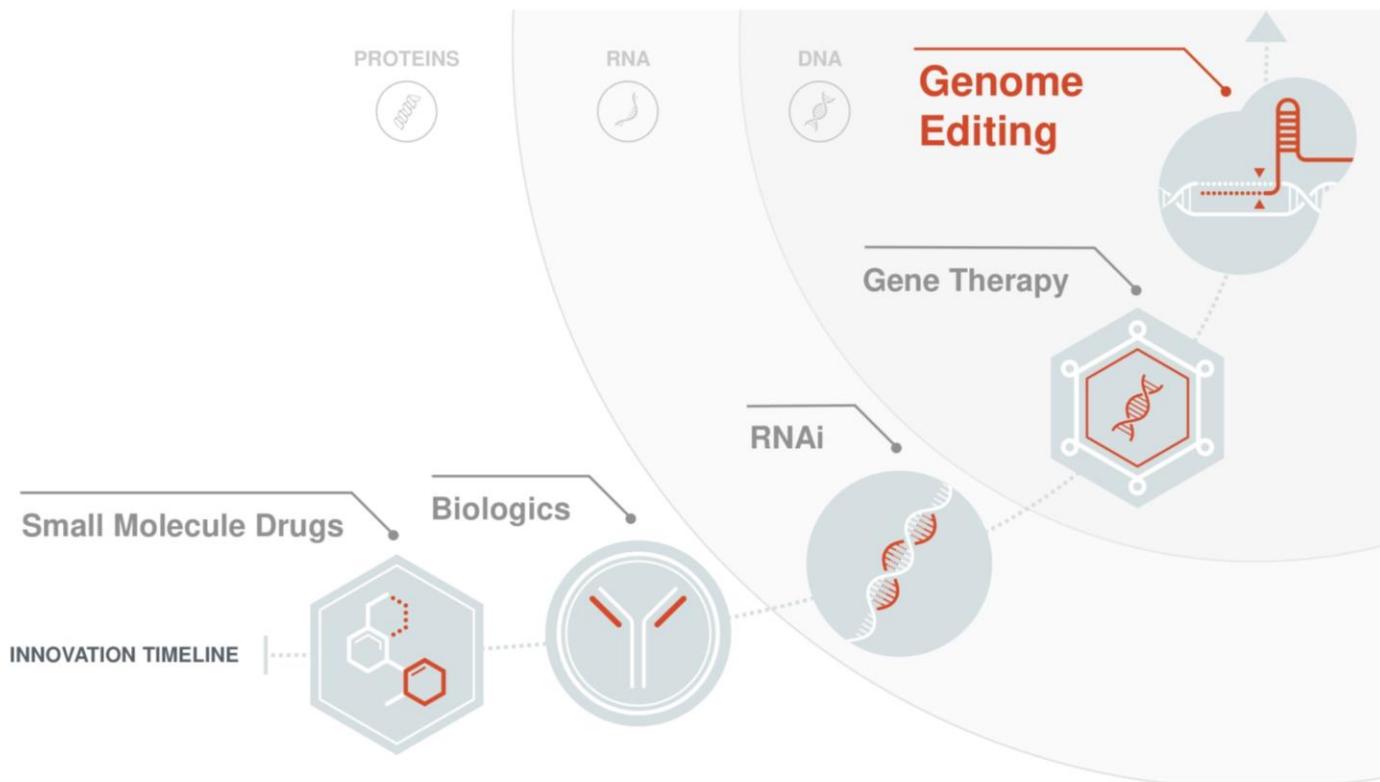
High level of specificity to
make one or multiple edits



Provides foundational
capabilities for derivative tools

Therapeutics Over Time

Therapeutic Strategies to Treat Life-Threatening Diseases Have Advanced Over Time



- **Genomic medicine** is a developing field of medical research that harnesses recent advances in genetics to develop new medicines for diseases. Advances in the scientific fields of cell therapy and gene therapy have paved the way for the success of gene editing, which in turn is now expanding and accelerating the development of a new class of genomic medicines.
- **Gene editing** and **gene therapy** technologies are different in a few important ways.
- Gene editing is the next evolution of healthcare where the goal is to have a one-time treatment as opposed to multiple treatments.
- In gene editing, a mutated gene is revised, removed, or replaced at the DNA level.



Base editing: Revolutionary therapy clears girl's incurable cancer

December 10, 2022



- A teenage girl's incurable cancer has been cleared from her body in the first use of a revolutionary new type of medicine.
- Alyssa, who is 13 and from Leicester, was diagnosed with T-cell acute lymphoblastic leukemia in May last year.
- All other treatments for Alyssa's leukemia had failed.
- Her cancer was aggressive. Chemotherapy, and then a bone-marrow transplant, were unable to rid it from her body.
- Doctors at Great Ormond Street Hospital used "base editing" to perform a feat of biological engineering to build her a new living drug.
- Six months later the cancer is undetectable, but Alyssa is still being monitored in case it comes back.

The Largest Biotech IPO – 2022 (3RD GEN CRISPR)

Prime Medicine IPO: The Largest Biotech IPO in 2022



20.10.2022 Date	NASDAQ Platform	PRME Ticker	10.29 million shares Allocation volume
17 USD Share price	175 million USD Gross proceeds from the sale of securities*	1.43 billion USD Estimated value of the company*	

* – excluding the sale of ordinary options by the underwriter.

- Prime is a “platform” biotech, built around a gene editing technology it will use to develop several medicines, rather than a “product” biotech concentrated more closely on a single drug.
- Prime’s IPO is the 19th in the biotech industry this year, compared to more than 90 this time last year, according to data from BioPharma Dive
- The company has 18 research programs across diseases of the blood, liver, ear, eye and lung.
- None are in human trials.

Gene Editing Capital Raises: 2012 - 2022 YTD

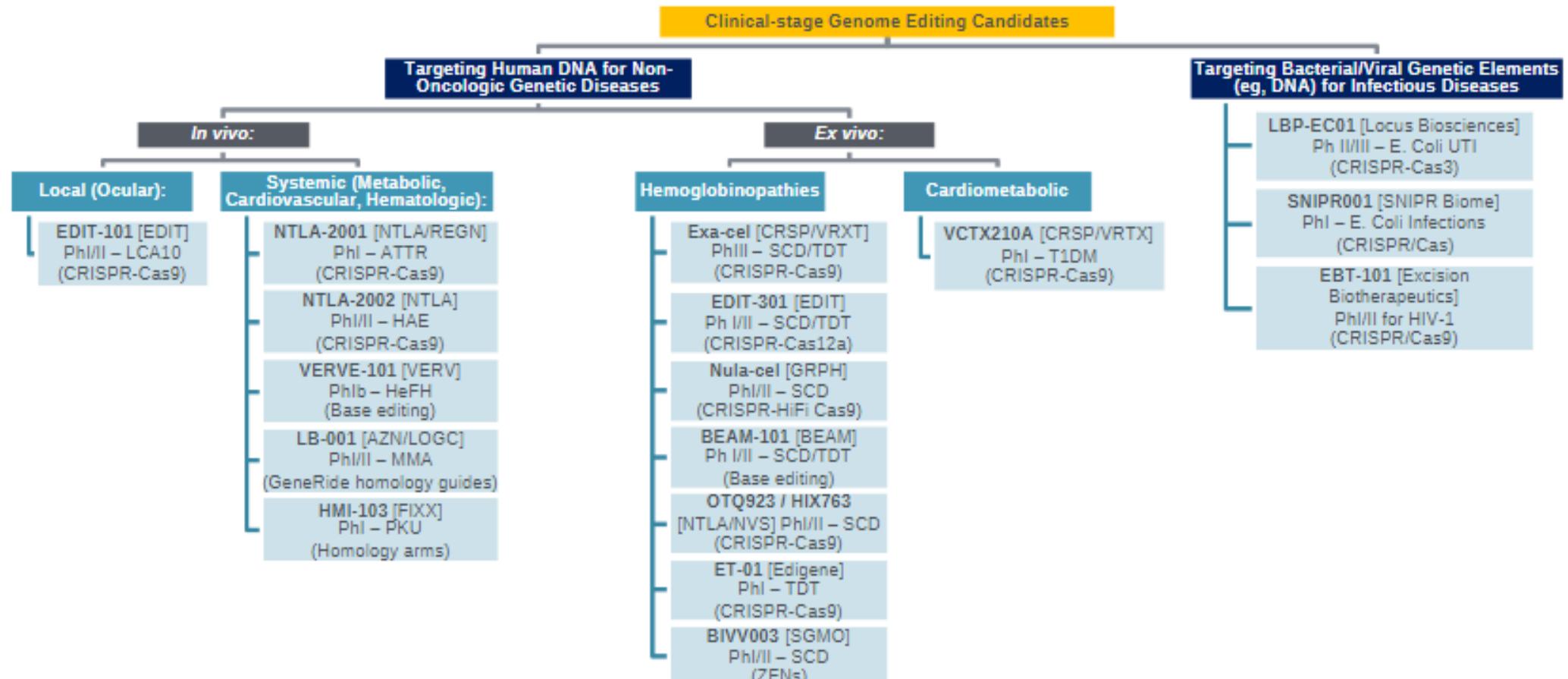


10 Years of Accelerating Investment in CRISPR Technology



Source: Company Filings, Piper Sandler Research
Date: November 2022

CRISPR Technology in Clinical Phases – Road to Commercialization



Date: December 2022

Source: Company Filings, Piper Sandler

The Gene Editing Market – The Possibilities



- There are up to 400 million people worldwide affected by one of the 7,000 diseases caused by mutations in single genes.
- Physicians are using CRISPR to test a treatment for people who carry H.I.V. by cutting out the virus's DNA from their immune system. If they succeed, it's possible that about 40 million people could benefit.
- Recent examples illustrate the possibilities of what CRISPR can accomplish:
 - In China, CRISPR was recently used to treat two children ages 7 and 8 with a genetic condition related to sickle cell disease called beta-thalassemia.
 - Before treatment, the children were unable to create normal red blood cells and required blood transfusions every two to three weeks.
 - Within a month after they received gene-edited cells, the transfusions ended.
 - Eighteen months later, the children remained free of disease symptoms.

XDNA Index Constituents:

- CRISPR Therapeutics and Vertex have cured 31 people with sickle cell disease, who no longer experience the debilitating episodes of pain that characterized their condition.
- Intellia Therapeutics teamed up with Regeneron and used CRISPR to inactivate a typo-laden toxic gene in the livers of 15 people. A mere month after this injection, 93 percent of the toxin was gone from the bloodstreams of patients who received the highest dose of CRISPR medicine.
- Verve Therapeutics is developing a CRISPR treatment for heart disease, with an initial focus on a severe genetic form. Should Verve meet its ambitious goal of expanding this approach to patients with the common type of heart disease, one gene edit could replace daily medications such as statins.



Future of Healthcare & Gene Editing

BARRON'S

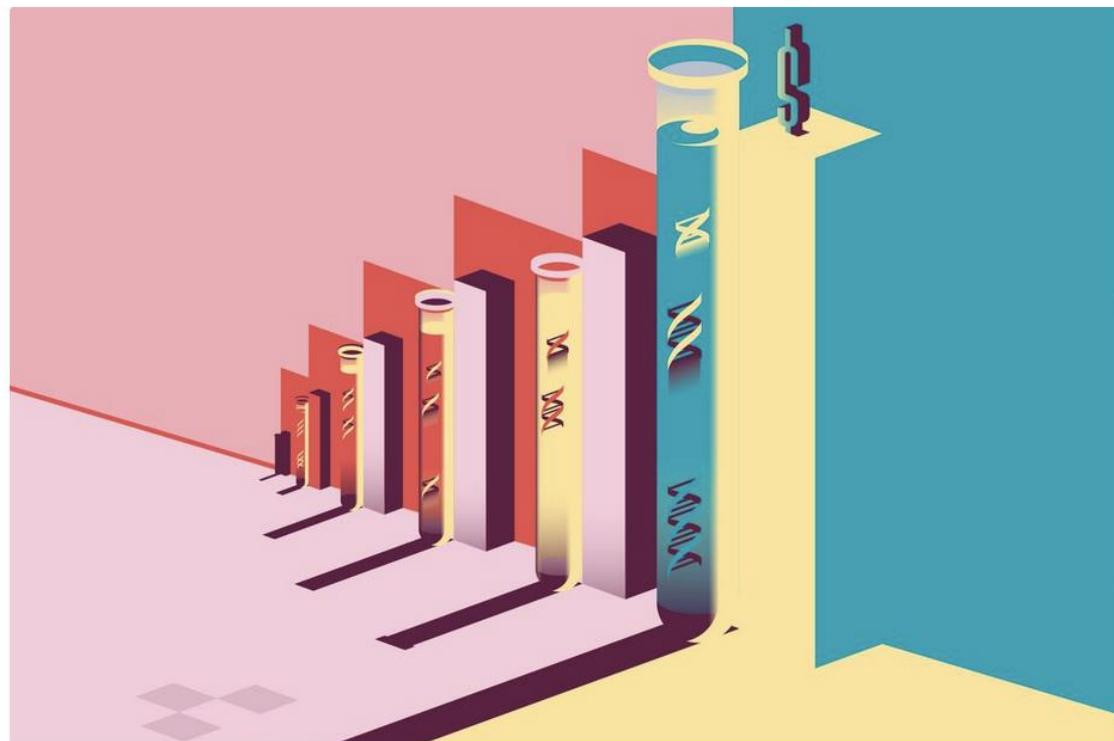
January 14, 2021

- Crispr-Cas9 is the second generation of technologies that seek to repair thousands of inherited genetic disorders and battle cancer in new ways.
- Gene editing is advancing so quickly that next-generation technologies are already on the heels of Crispr-Cas9, including a more-precise tool called base editing.
- While gene-editing start-ups will lose money during years of clinical trials, it's hard to say the stocks are overvalued.
- If their one-time interventions can cure diseases that otherwise require chronic treatment—or lack any treatment at all—then the stocks will fly. Patent rights and know-how also make them desirable partners or acquisition targets for Big Pharma.

BIOTECH AND PHARMA | FEATURE

With Rare Speed, Gene Editing Emerges as Biotech's New Cutting Edge

By [Bill Alpert](#) Jan. 14, 2021 3:11 pm ET



Intellia Therapeutics NTLA -2001 Proved that Gene Editing Can Work in Humans

Intellia hits a 'home run' with gene-editing results, setting up entire field for a grand slam

By Annalee Armstrong • Jun 29, 2021 10:05am

clinical research CRISPR gene editing stock market



June 29, 2021

- Intellia and partner Regeneron showed for the first time that gene editing can work in a human.
- NTLA-2001 reduced serum levels of transthyretin, a key biomarker in the rare disease transthyretin (ATTR) amyloidosis, by 87%, besting standard-of-care therapies that typically reach 80%.
- Intellia was surprised at the strength of the data as well; David Lebwohl, M.D., Intellia's chief medical officer, told Fierce Biotech that the serum reduction was "beyond what we expected."
- Intellia hopes the results will ultimately stick, offering patients a one-and-done treatment.

In Vivo Leader: First to Demonstrate Systemic CRISPR Gene Editing in Humans



The NEW ENGLAND
JOURNAL of MEDICINE

August 5, 2021

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyrtasou, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

Science
JOURNALS AAAS

"CRISPR injected into the blood treats a genetic disease for the first time"

FT
FINANCIAL TIMES

"CRISPR gene-editing 'revolution' treats internal organ for first time"

USA
TODAY

"It's a wow': New CRISPR gene-editing success holds promise for treating many genetic diseases with a single dose"

nature

"Landmark CRISPR trial shows promise against deadly disease"

Intellia Therapeutics Updated Data Proves that Gene Editing Sustained

February 28, 2022

Jun 24, 2022

Updated clinical data demonstrates that the experimental in vivo CRISPR therapy resulted in rapid, deep and sustained responses in 15 patients.

- June 2021, Intellia offered early data on the first six people who were given the drug. Among those who got the highest dose, blood levels of the errant protein dropped on average by 87%.
- By June 2022, All doses tested led to reductions in levels of a disease-causing protein, a benefit that is sustained 12 months in the patients followed the longest.
- Intellia's data show that protein levels stay low for at least 12 months after the CRISPR therapy.
- The New Data: Nine more people added to the trial received one of two higher doses of the drug. It appears that the higher the dose, the better it knocks out the gene.
- The Phase 1 clinical trial is continuing - Intellia says it now plans to speak with the FDA and other agencies about a pivotal study that could support regulatory approval.
- Although it will take years to learn whether this will be a lifelong fix, the data suggest that a one-and-done treatment is at least a possibility.

In the gene-editing world, the new data have brought “not just a collective sigh of relief that nothing bad happened, but also a fairly audible ‘Woohoo!’” - Fyodor Urnov, director of the Center for Translational Genomics at the Innovative Genomics Institute according to Bloomberg.



First Sickle Cell Patient Treated with CRISPR Gene-Editing Still Thriving

December 31, 2021



SPECIAL SERIES

The CRISPR Revolution

HOW DOCTORS ARE EDITING GENES TO FIGHT DISEASE



Victoria Gray, who has sickle cell disease, volunteered for one of the most anticipated medical experiments in decades: the first attempt to use the gene-editing technique CRISPR to treat a genetic disorder in the United States.

Meredith Rizzo/NPR

- For more than a year, Victoria Gray's life had been transformed. Gone were the sudden attacks of horrible pain that had tortured her all her life. Gone was the devastating fatigue that had left her helpless to care for herself or her kids. Gone were the nightmarish nights in the emergency room getting blood transfusions and powerful pain medication.
- **She's doing so well for so long that she's officially no longer in the landmark study she volunteered for.** That involved doctors taking cells out of her bone marrow, and editing a gene in the cells in their lab, using the revolutionary gene-editing technique known as CRISPR. CRISPR allows scientists to make very precise changes in DNA much more easily than ever before. Many think it will revolutionize medicine.
- Doctors then infused billions of the modified cells back into Gray's body. The hope was the edited cells would produce a protein known as fetal hemoglobin, alleviating the symptoms of sickle cell.
- Vertex Pharmaceuticals in Boston, which is developing the treatment with CRISPR Therapeutics in Cambridge, hopes to seek Food and Drug Administration approval sometime in the next 18 to 24 months.
- Doctors will still follow her for 15 years to make sure the treatment keeps working and continues to be safe.

CRISPR at a Tipping Point

October 21, 2021



Can you briefly describe how CRISPR is being used today, what its potential is in the next 5-10 years, and how we can expect it to change our world?

Doudna:

- Given that CRISPR genome editing as we know it hasn't quite hit its tenth birthday, it's always astonishing to see how much has been accomplished in that time.
- There is always a lot of focus on the development of genome-editing therapeutics, but the greatest effect so far has been on life science research and our ability to understand the genetic basis for diseases and other genetic traits, whether it's health related, or how a butterfly gets its colors.
- The next 5-10 years will also bring surprises, but we're at a tipping point right now where the preclinical work of the past nine years is transitioning into clinical trials, and the number is growing quickly.
- From just one or two in the past few years, we're now seeing trials for congenital blindness, chronic infection, cancers, and more, not to mention a number of new rapid point-of-care diagnostics.
- The first CRISPR-edited crop just hit the market in Japan, and while the development of agricultural applications may take longer, their effect on hunger, malnutrition, climate change adaptation, and carbon capture will have a far greater impact on human health than any single new therapy.
- Take the example of sickle cell disease: the first wave of clinical trials on CRISPR-based therapies is looking quite promising in terms of safety and efficacy, but right now the procedure costs in excess of \$2 million per patient. The procedure itself can only be performed by a small number of experts at a handful of hospitals worldwide. So I'm thrilled about the progress, but we don't yet have a cure that meets the needs of the vast majority of people in the world who suffer from this disease.

CRISPR Edits Seeking to Lower Cholesterol & Prevent Heart Attacks

July 12, 2022



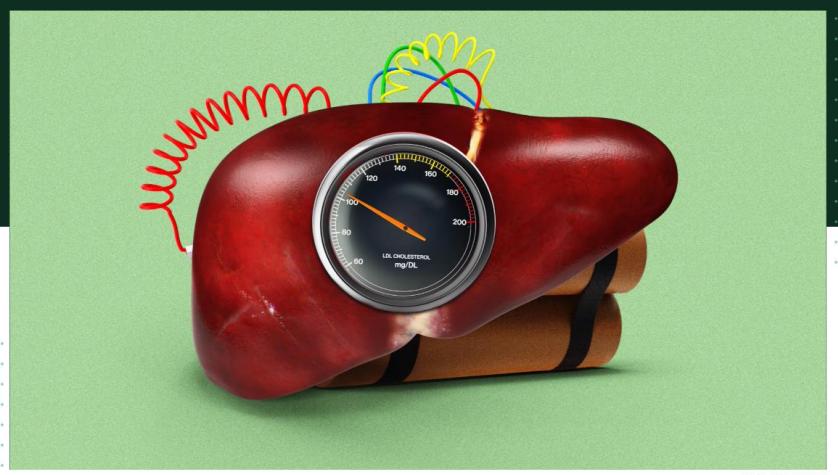
BIOTECHNOLOGY

Edits to a cholesterol gene could stop the biggest killer on earth

In a first, a patient in New Zealand has undergone gene-editing to lower their cholesterol. It could be the beginning of new era in disease prevention.

By Antonio Regalado

July 12, 2022



- Crispr is already moving out of the realm of rare diseases and into a common one is a significant development.
- This trial also comes when new types of gene editors are proliferating.
- A team of researchers from US biotech company Verve Therapeutics (7.85% of XDNA as of 7-21-22) have injected a gene-editing serum into a live patient's liver with the goal of lowering their cholesterol
- Watershed moment in the history of gene editing that could potentially save millions from cardiovascular disease and heart attacks, *MIT Technology Review* reports.
- The company claims that these genetic edits will be able to permanently lower levels of "bad" LDL cholesterol, a fatty molecule that at excessive levels can lead to clogged arteries.
- Many drugs have also remained wildly expensive, with insurers refusing to pay for them, according to *MIT Tech*. "If this works and is safe, this is the answer to heart attack — this is the cure," Kathiresan (CEO of Verve) told *MIT Tech*.
- The trial is starting in New Zealand with 40 subjects, but Verve hopes to eventually receive permission to enroll people in the UK and the US.

CRISPR Edits Seeking to Lower Cholesterol & Prevent Heart Attacks

July 12, 2022

MIT
Technology
Review

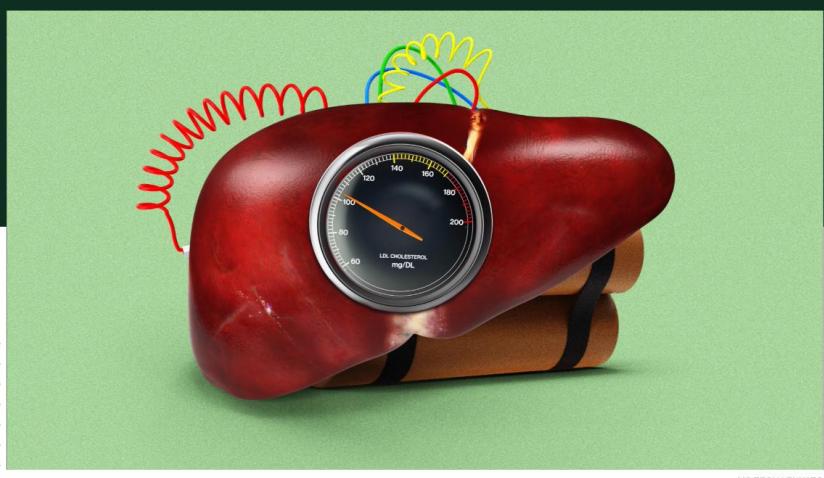
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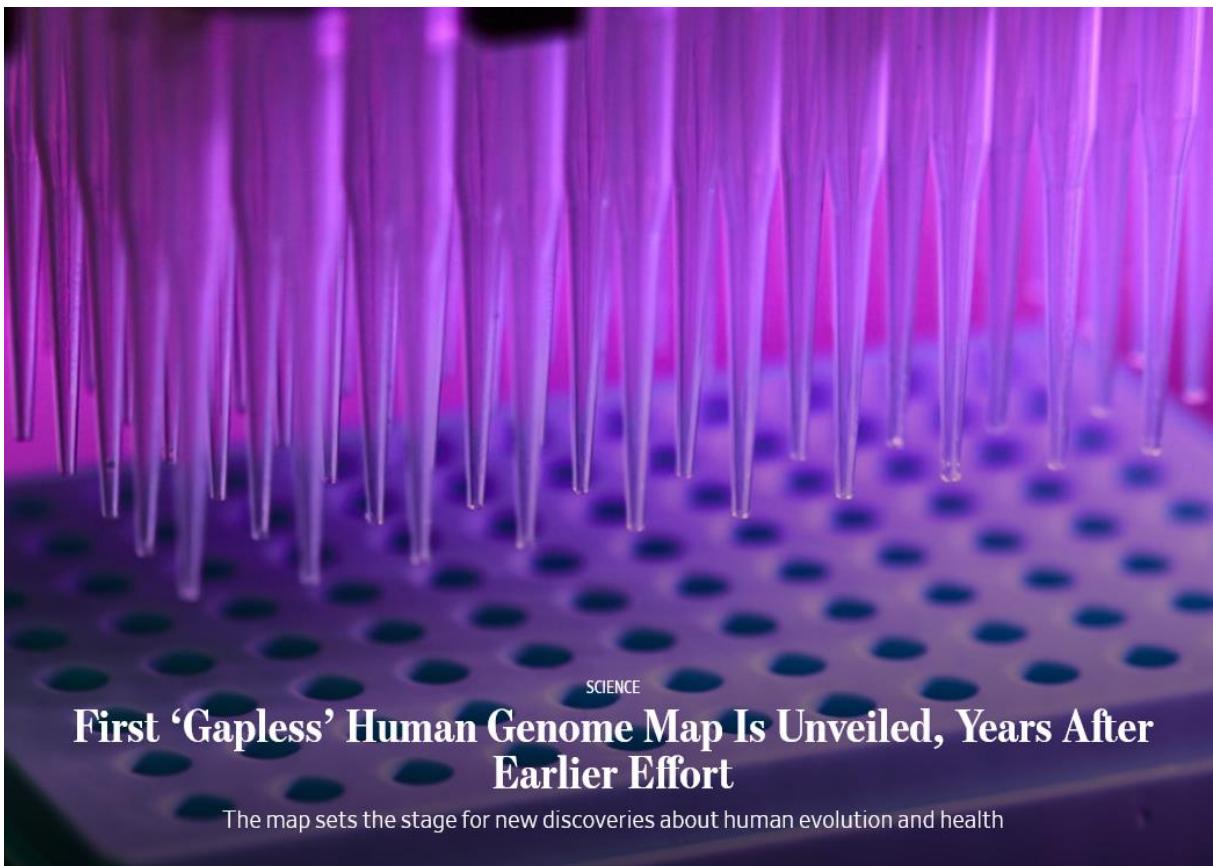
- The company's one-time injection changes a single letter of DNA in the instructions for building a protein called PCSK9, which is known to drive up levels of LDL, or "bad" cholesterol.
- Verve plans to aim the drug at the roughly 1 million people in the US with an inherited form of dangerously high cholesterol called familial hypercholesterolemia. Long term, however, the company thinks its therapy could offer a permanent, potentially more effective alternative to the statins that millions of Americans take every day. In that distant and still theoretical future, the average person could get Verve's one-time shot to keep cholesterol low enough to avoid heart attacks altogether.
- Verve licensed the technology from Beam Therapeutics, which was founded in 2017 based on discoveries made by Broad Institute scientist David Liu.
- If Verve's drug works, it will also raise a host of other not insignificant commercial issues, such as whether a one-and-done therapy can ever be made affordable for the masses and whether consumers will be willing to give up their statin pills for a drug that tinkers with their genes.

First “Gapless” Human Genome Mapped



THE WALL STREET JOURNAL.

March 31, 2022



First ‘Gapless’ Human Genome Map Is Unveiled, Years After Earlier Effort

The map sets the stage for new discoveries about human evolution and health

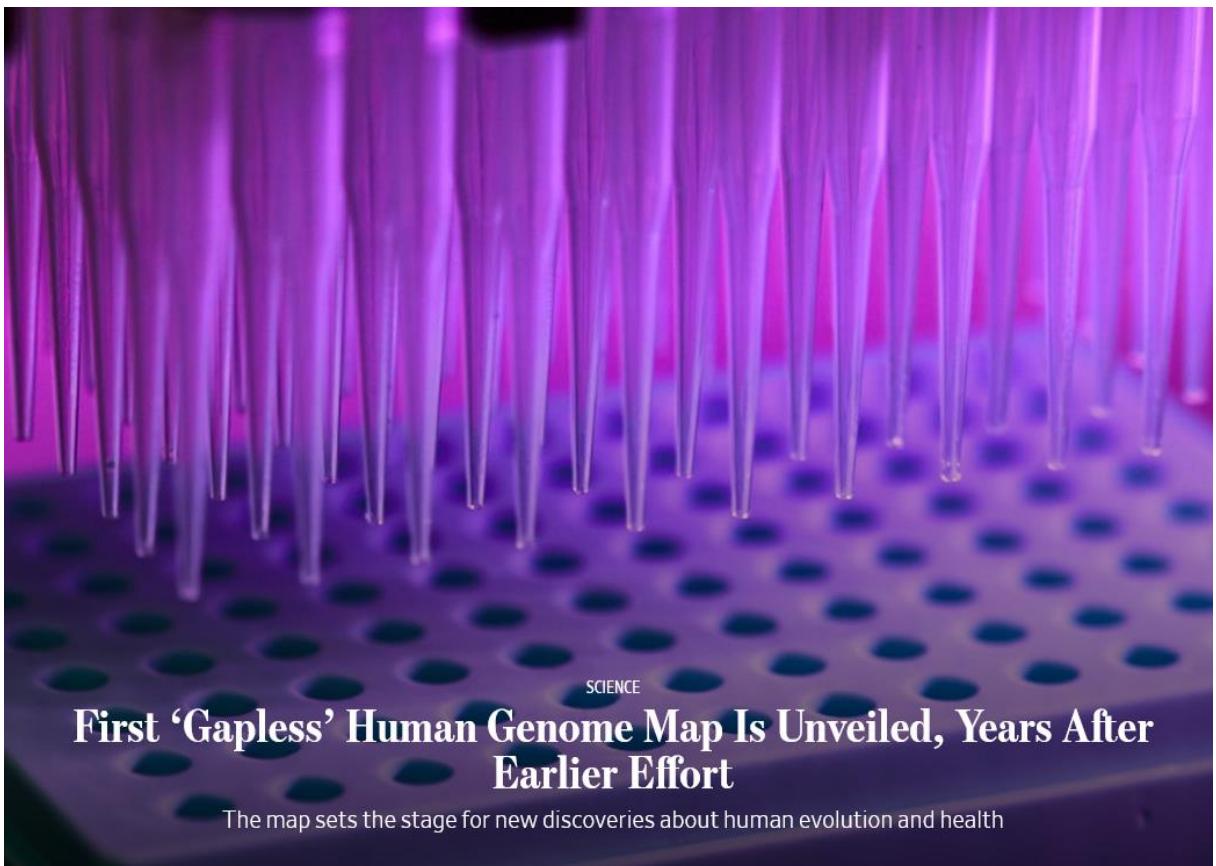
- Scientists have unveiled what they call the first truly complete map of a human genome, filling in significant gaps that persisted for almost 20 years
- Setting the stage for new discoveries about human evolution and fresh insights into cancer, birth defects and aging.
- The newly mapped regions, described in six papers published this week in the journal Science, include parts of the genome that had long been uncharacterized because of the limits of DNA-sequencing technology. [...]

First “Gapless” Human Genome Mapped



THE WALL STREET JOURNAL.

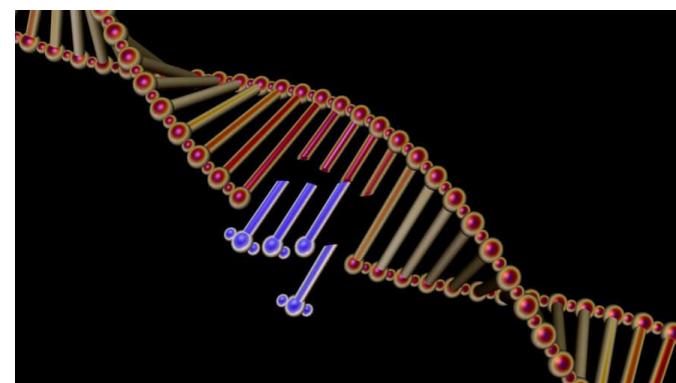
March 31, 2022



- The scientists behind the research identified 99 new genes that likely code for proteins essential to human life, along with 2,000 more whose function is unclear.
- Exploiting the new map for medical care would likely take years of additional research, said Wendy Chung, a Columbia University geneticist who wasn't involved in the effort. But the map "gets us to the starting line," she said, adding, "We have patients with diseases that we know are genetic but we haven't been able to identify. I hope this map will help us fill in some of the gaps in our knowledge."

Recent Impact of Technology on the Genome Q4-2022

- Investor's Business Daily [*Crispr Stock Jumps After Unveiling Timeline For FDA Submission Of First-Ever CRISPR Drug*](#), "Crispr Therapeutics (CRSP) said it will begin asking the Food and Drug Administration to approve what would be the first-ever gene-editing treatment to hit the market using the CRISPR technology from where it gets its company name."
- Wired reported on [*There's New Proof Crispr Can Edit Genes Inside Human Bodies*](#), "The diseases involve two different genes, and in both cases Crispr was able to safely and successfully edit them. 'This shows us that we can have exactly the same kind of results in a totally different gene,' says John Leonard, Intellia's CEO."
- The life sciences revolution has grown out of the realm of rare diseases and into common ones when MIT Technology Review [*Edits to a cholesterol gene could stop the biggest killer on earth*](#) reported, "A volunteer in New Zealand has become the first person to undergo DNA editing in order to lower their blood cholesterol, a step that may foreshadow wide use of the technology to prevent heart attacks."





KELLY
ETFS

CRISPR & Gene Editing Sector Examples



Foundational Partnerships Provided Access to R&D Capabilities

REGENERON

- Up to 15 *in vivo* targets with a mix of co-developed and licensed programs
 - Liver-centric product development
- **ATTR:** First selected Co/Co program
 - Intellia is lead party; Regeneron will share 25% of costs and profits
- **Hemophilia A and B:** Co/Co agreements based on targeted insertion capabilities
 - Regeneron is lead party; Regeneron will share 65% of costs and profits
- *In vivo* targets exclusively developed by Regeneron:
 - Up to \$320M in milestones per target
 - High single-to-low-double-digit royalties
- Non-exclusive license to certain platform IP on up to 10 *ex vivo* CRISPR products in defined cell types

NOVARTIS

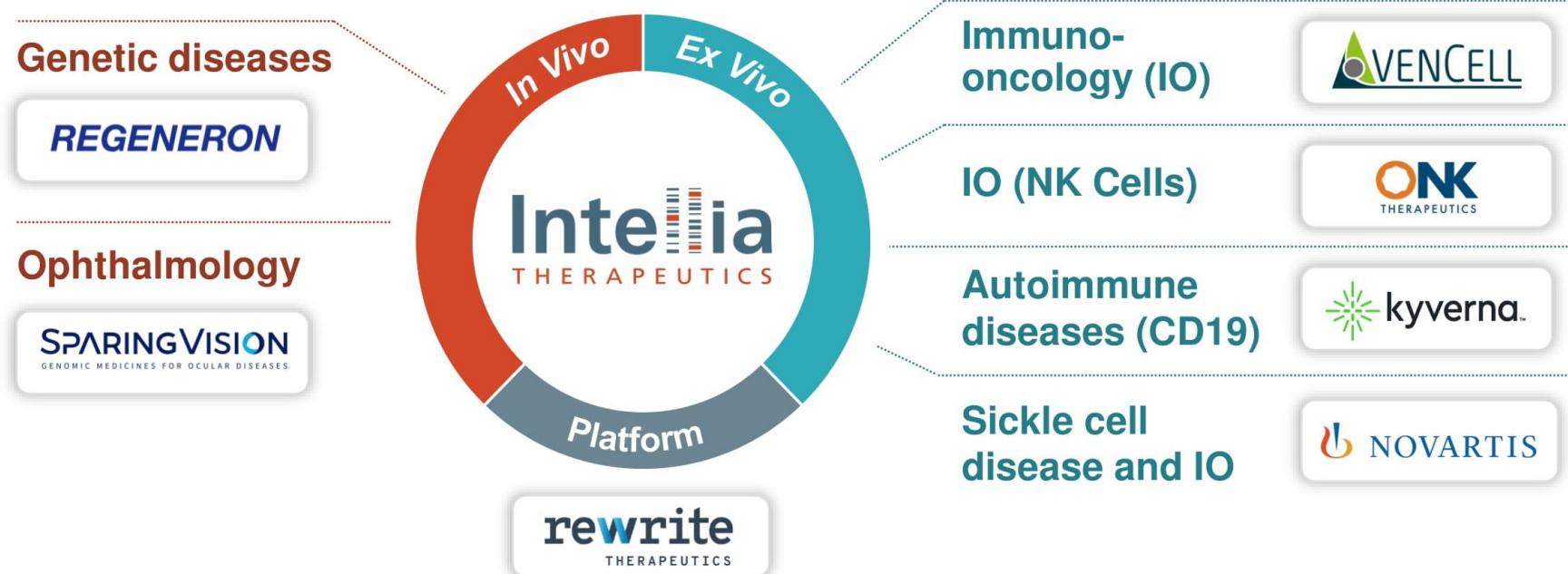
- Advancing Phase 1/2 study for sickle cell disease based on CRISPR/Cas9-edited HSCs
- Research collaboration term concluded in December 2019
- Novartis selected various CAR-T, HSC and OSC targets for development
 - Up to \$230M in milestone payments per product
 - Mid single-digit royalties
 - All non-selected targets revert to Intellia



Growing Intellia's Impact on Patients Through Strategic Collaborations and Business Development

Increasing shareholder value:

- Leveraging our technology while retaining rights to key areas of focus
- Accelerate development of programs outside key areas of focus
- Expand our pipeline with valuable rights in future commercial success
- Access external expertise to enhance our platform





Creating and Capturing Value

Advancing Wholly-Owned Programs and Through Business Development Collaborations

Adding Capabilities Through Partnerships



Current



Potential Future Partnerships

Oncology indications / cell therapy
e.g., gamma-delta T cells

Regenerative medicine
e.g., iPSCs

International expansion
e.g., SCD in Europe

Add Complementary Technology



Current

iPSC from



Potential Future In-Licensed Technology

Advanced delivery technologies

Emerging advances in editing enzymes

Technology That We Out-license



Current

Cas9, AsCas12a

Potential Future Out-Licensed Technology

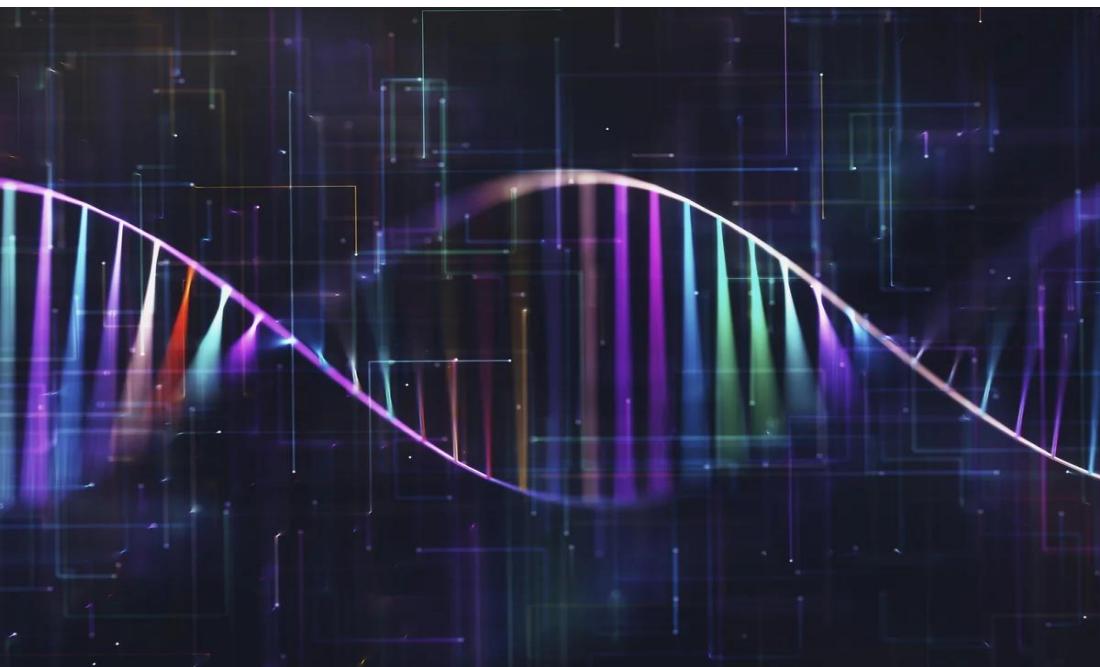
Cas9, AsCas12a, SLEEK

BARRON'S

January 10, 2022

BIOTECH AND PHARMA

Pfizer and Beam Partner to Develop Treatments for 3 Genetic Diseases



- Gene editing is the next phase of genetic medicine, and another big step was just announced.
- Pfizer unveiled a \$1.3 billion partnership with Beam Therapeutics to develop three treatments for genetic disease in the next four years. They'll use Beam's leading-edge technology that makes precise corrections to typographical errors in our genes—a technology called "base editing."
- "They called us over the summer and we immediately hit it off," Beam chief executive John Evans told *Barron's*. "The strategic vision of both sides was clear right away."
- Pfizer (ticker: PFE) will pay Beam (BEAM) \$300 million up front, and more than \$1 billion in potential milestone payments, to collaborate on three treatments for rare genetic diseases of the liver, muscle, and central nervous system. Beam also stands to get royalties on the products' commercial sales, which will be handled by Pfizer—although Beam can choose to join in the clinical testing and sales of one of the products.

BARRON'S

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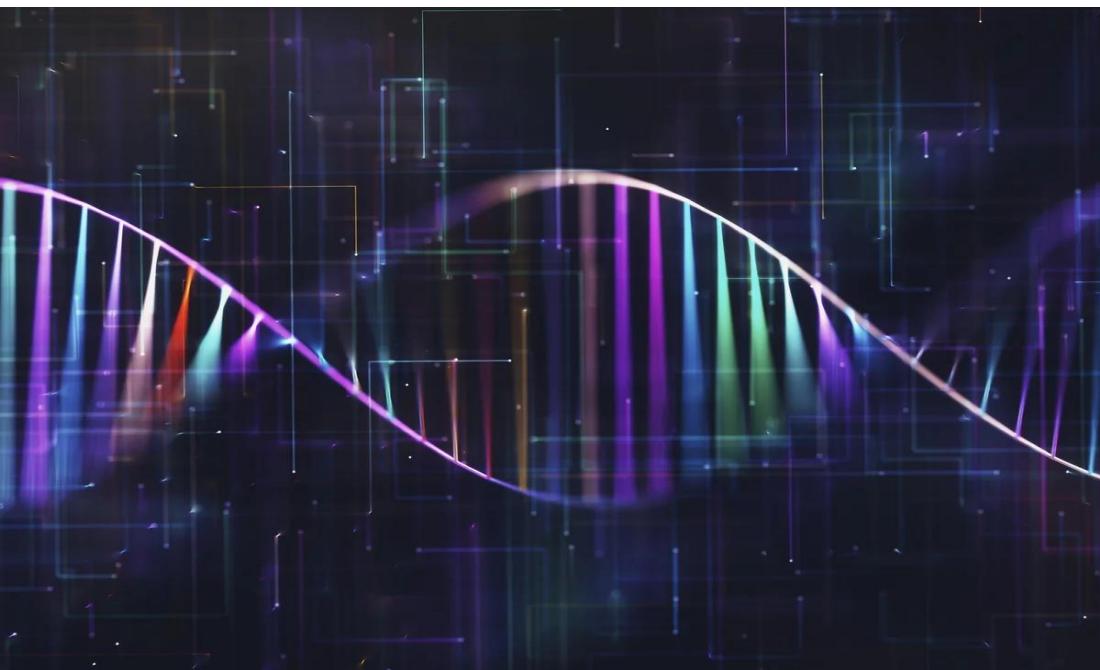
- The stock market's enthusiasm for replacement gene therapy has slowed since 2018, when Novartis and Roche jumped in with pricey acquisitions. Since then, gene therapy has encountered obstacles and delays.
- Next came gene editing—a more profound technology. Whereas gene therapy adds healthy genes alongside a defective one, gene editing actually doctors the problematic gene.
- Beam's base editing evolved from the Nobel Prize-winning discovery of Crispr-Cas9 technology in 2012, by scientists Jennifer Doudna and Emmanuelle Charpentier. Crispr molecules can be programmed to find precise locations in the 3 billion links of our genome's DNA code, allowing the Cas9 enzyme to then make a cut through the DNA's double strands.
- The permanent changes of a Crispr-Cas edit avoid certain shortfalls of replacement gene therapy—whose changes sometimes don't last, and whose randomly-inserted genes can potentially trigger cancer. Crispr-Cas editing is now in clinical trials to treat sickle-cell disease, cancer, and liver disorders, as it's being commercialized by companies such as Crispr Therapeutics (CRSP), Intellia Therapeutics (NTLA), Editas Medicine (EDIT) and Caribou Biosciences (CRBU). The pharma companies Vertex Pharmaceuticals (VRTX) and Regeneron Pharmaceuticals (REGN) have partnered with Crispr-Cas specialists. The Crispr companies' stocks rose to peaks of excitement about a year ago, before their valuations subsided with much of the biotech sector.
- Some 60% of known genetic diseases arise from a single-letter typographical error in our genome, so the opportunities open to Beam and its partners are large.

BARRON'S

January 10, 2022

BIOTECH AND PHARMA

Pfizer and Beam Partner to Develop Treatments for 3 Genetic Diseases



- The U.S. Food and Drug Administration recently cleared Beam to do a clinical trial of a sickle cell therapy which the company expects to put in its first patient in 2022's second half. It will seek permission this year to test a second sickle cell therapy, as well as a cell therapy for leukemia.
- Last year, Beam showed that it could encode base-editing instructions in easy-to-administer messenger-RNA molecules encapsulated in the non-immunogenic vehicles known as lipid-nanoparticles. This is similar to the mRNA vaccines developed by Pfizer-BioNTech and their rival Moderna (MRNA).
- That made the base-editing team-up a natural follow-on for Pfizer, says Beam CEO Evans. "We were heading in the exact same direction," he said.

Novartis In Vivo Deal with Precision BioSciences

BIOTECH

Novartis plots Precision attack on sickle cell, paying \$75M and putting up \$1.4B in biobucks to form in vivo gene editing pact

By Nick Paul Taylor • Jun 22, 2022 03:40am



The Novartis deal extends Precision's cash runway out to the second quarter of 2024. (Novartis)



June 22, 2022

- One year after Intellia's landmark data, Novartis is making a play for the in vivo gene editing market.
- The move sees the Swiss pharma pay Precision BioSciences:
 - \$75 million upfront in a combination of cash and equity investment
 - Up to \$1.4 billion in milestones to secure rights to a potential treatment for sickle cell disease and beta thalassemia.
- The Novartis deal extends Precision's cash runway out to the second quarter of 2024, versus mid-2023 prior to the agreement. Precision expects three of its wholly owned preclinical in vivo programs to get to the clinical trial submission stage over the next three years, with a filing for a candidate designed to reduce expression of the PCSK9 gene penciled in for as early as the end of this year.



Risks & Regulation

The most-discussed safety risk with CRISPR is that **the Cas9 enzyme, which is supposed to slice a specific DNA sequence, will also make cuts in other parts of the genome that could result in mutations that raise other health risks.**

DNA Modification Technology Company Risk. DNA modification technology companies face intense competition, and products and services with a potentially short product life. These companies will generally require large amounts of capital expenditures on research and development, with no guarantee that the product or service would be successful. They may be heavily dependent on intellectual property rights. The laws related to these rights can vary and there is no guarantee that a company will be able to successfully protect their intellectual property rights. These companies, like other healthcare companies, are subject to various government and regulator oversight that could hamper or impede their operations.

Foreign Securities Risk. Investments in non-U.S. securities involve certain risks that may not be present with investments in U.S. securities. For example, investments in non-U.S. securities may be subject to risk of loss due to foreign currency fluctuations or to political or economic instability.

Company Risks

- Clinical Trial Risk
- Interest Rate Sensitivity
- Supply / Demand Conditions
- Competition
- Financing and Capitalization

Market & Regulatory Risks

- Regulator Approval
- Technology
- Consolidation
- International & Currency Risks

- Visit: KellyETFs.com and KellyIntel.com
- Email: Kevin@KellyIntel.com
- Please add XDNA, HOTL, RESI to your stock quotes



KEVIN KELLY

Founder, Chief Executive Officer
Kelly Intelligence
Kelly ETFs



Appendix



KEVIN KELLY

Founder, Chief Executive Officer, Kelly ETFS

At Kelly ETFS, Kevin is responsible for ETF product design, structuring, and managing retail and institutional investment research. Kevin is the Founder and CEO of Kelly Intelligence, an investment management and intelligence firm that seeks to bring cutting-edge products, with forward-looking exposure. Its growing suite of indexes provide highly liquid, pure-play access to innovative business models, emerging industries, and disruptive technologies. Mr. Kelly is also the creator and sponsor of the SRVR and INDS ETFs. In September 2014, Nasdaq named Kevin an 'ETF Insider,' and he is a recognized leader in ETF design, distribution and growth with his extensive track record of launching multi-billion dollar ETFs including the Nasdaq 100 Covered Call ETF (Nasdaq:QYLD). Mr. Kelly's thought leadership on markets, derivatives, e-commerce, and technology can be found weekly in top media outlets.

ABOUT KELLY ETFS

Kelly ETFS strives to create disruptive exchange-traded funds (ETFs) that offers investors the opportunity to capture highly liquid, pure-play exposure to the best-in-class companies identified in each emerging theme or sector, regardless of geographical location. Based in Denver, the team is committed to building investment products with exposure to the world's most transformative companies and industries.

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LISTED LISTED
NYSE ARCA NYSE ARCA

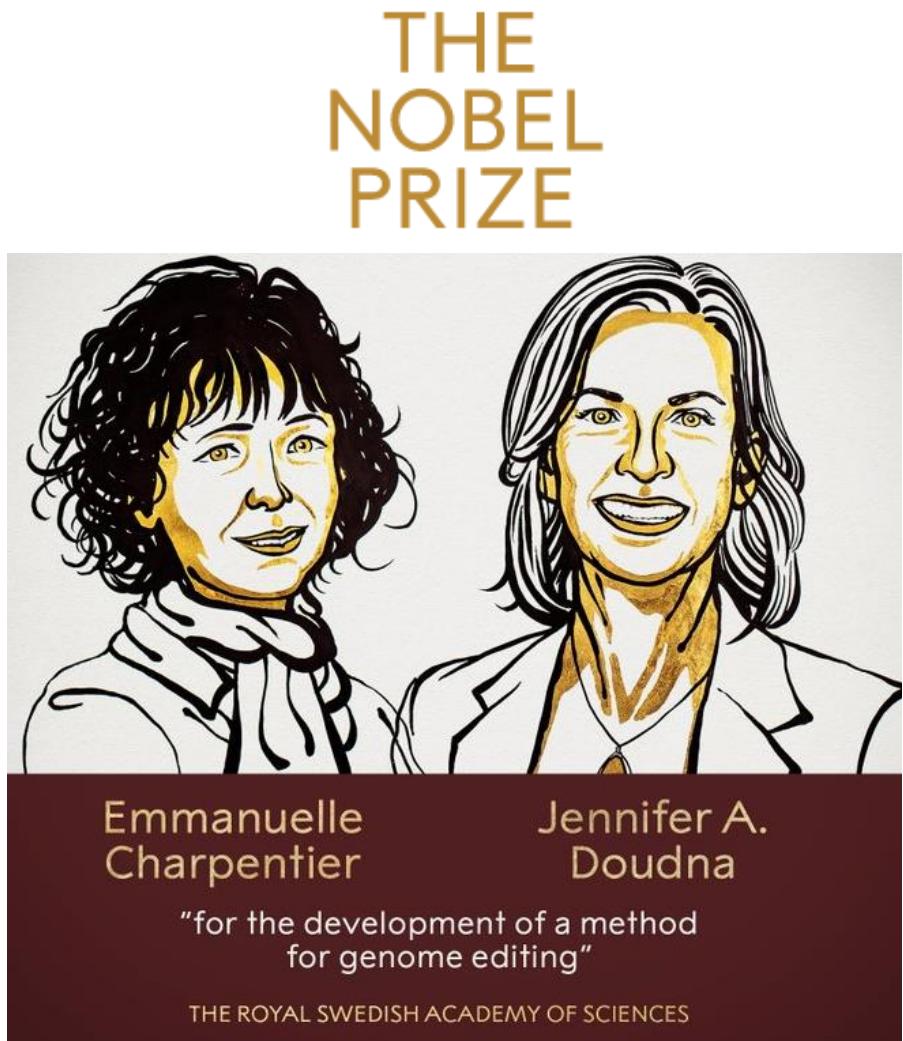
Genome Editing Breakthrough Awarded Chemistry Nobel Prize

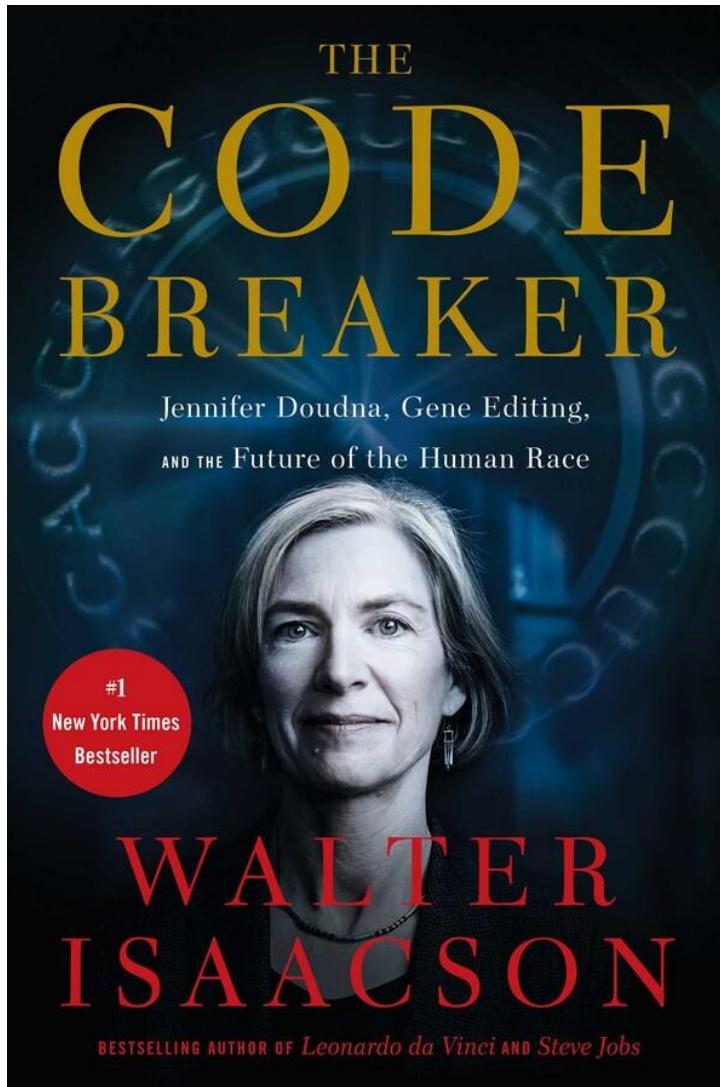
October 7, 2020 - The Royal Swedish Academy of Sciences

- **Emmanuelle Charpentier**
Max Planck Unit for the Science of Pathogens, Berlin, Germany
- **Jennifer A. Doudna**
University of California, Berkeley, USA

“Emmanuelle Charpentier and Jennifer A. Doudna have discovered one of gene technology’s sharpest tools: the CRISPR/Cas9 genetic scissors. Using these, researchers can change the DNA of animals, plants and microorganisms with extremely high precision. This technology has had a revolutionary impact on the life sciences, is contributing to new cancer therapies and may make the dream of curing inherited diseases come true.

‘There is enormous power in this genetic tool, which affects us all. It has not only revolutionised basic science, but also resulted in innovative crops and will lead to ground-breaking new medical treatments,’ says Claes Gustafsson, chair of the Nobel Committee for Chemistry.”





Simon & Schuster

A Best Book of 2021 by *Bloomberg BusinessWeek*, *Time*, and *The Washington Post*

The bestselling author of *Leonardo da Vinci* and *Steve Jobs* returns with a “compelling” (*The Washington Post*) account of how Nobel Prize winner Jennifer Doudna and her colleagues launched a revolution that will allow us to cure diseases, fend off viruses, and have healthier babies.

Coming in at nearly 500 pages, the book dives into the essence of life and the heady world of genomes and genetic coding, or what Isaacson calls “the third great revolution of modern times,” following the atom, and the bit which led to the digital revolution.

Source: Simon & Schuster Website

In Vivo **CRISPR is the therapy**

GENETIC DISEASES

Strategic Advantages:

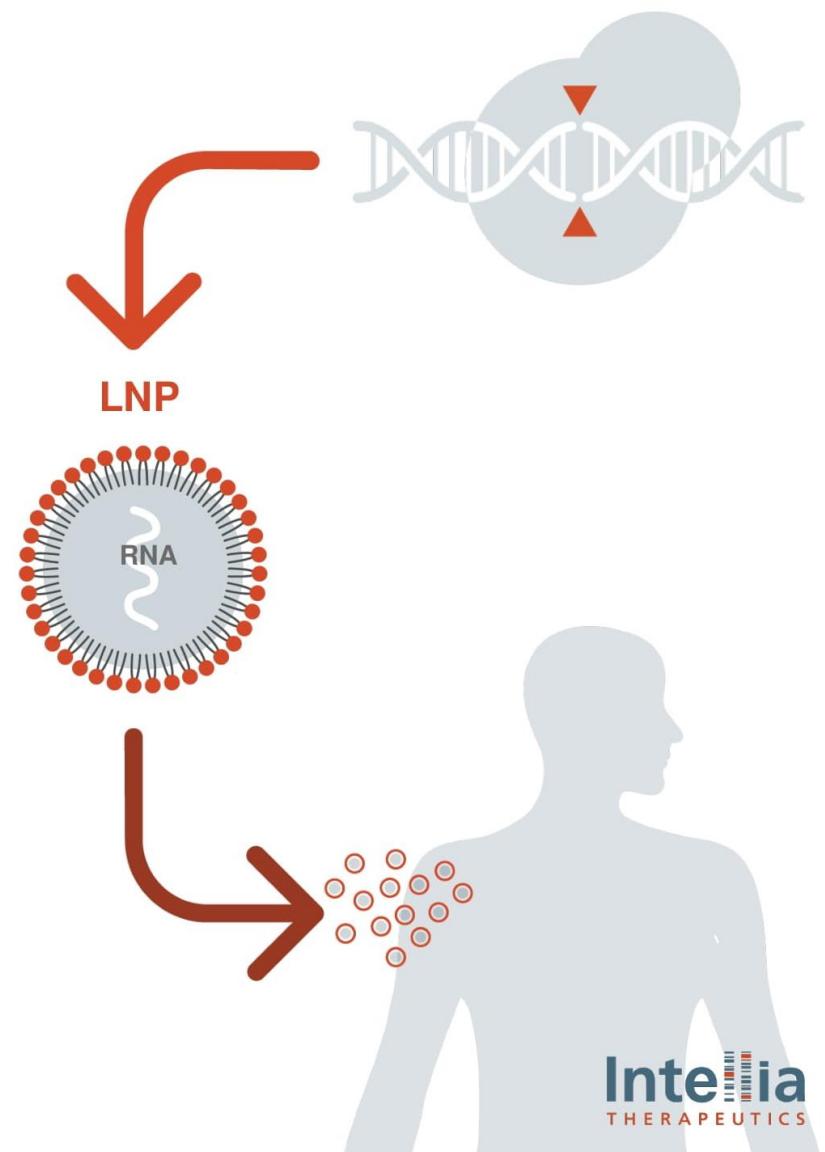
Potential curative therapy from single dose

Systemic non-viral delivery of CRISPR/Cas9 provides transient expression and potential safety advantages

Permanent gain of function with targeted gene insertion

Capable of delivering to multiple tissue types for various therapeutic applications

LNP: Lipid Nanoparticle



Intellia
THERAPEUTICS

Ex Vivo

CRISPR creates the therapy

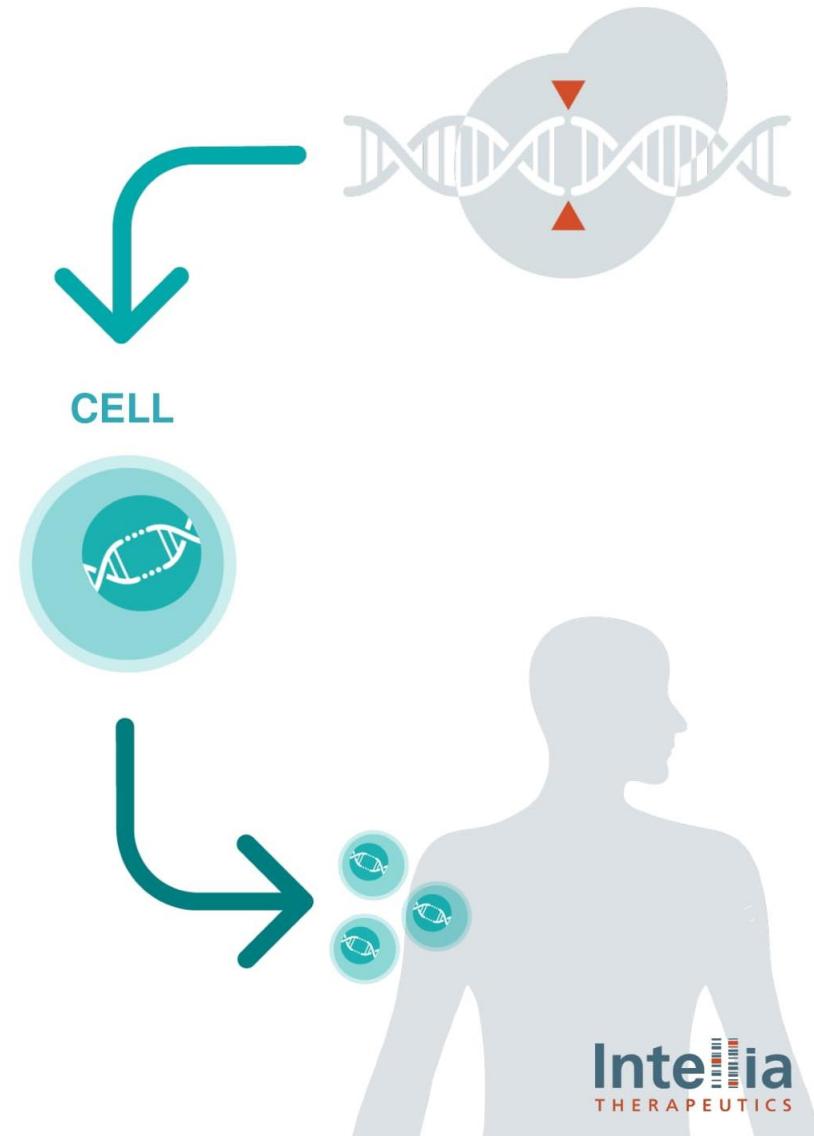
IMMUNO-ONCOLOGY / AUTOIMMUNE DISEASES

Strategic Advantages:

Utilizing proprietary CRISPR engineering platform to create differentiated cell therapies for IO and AI diseases

Targeting modalities, such as TCR, with broad potential in multiple indications

Focused on reproducing natural cell physiology for potential improvements to safety and efficacy in immuno-oncology



Intellia
THERAPEUTICS



Bristol Myers Squibb αβ T Cell Program Partnership

Spanning CAR-T and Allogeneic Cell Therapies

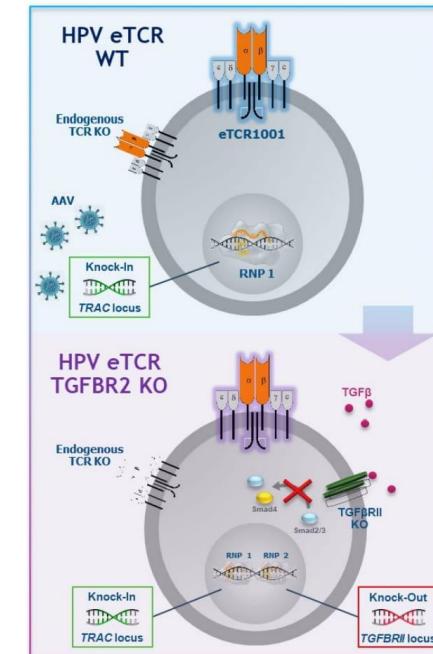
- ☑ Longstanding collaboration since 2015
- ☑ Opted into 7 programs (RNPs)
- ☑ One declared development candidate
- ☑ Leveraging unique Editas platform technologies (Cas9, AsCas12a)
- ☑ Received over \$125 million in payments to date, plus potential for additional milestones and tiered royalties



| Source: Abstract #200 at Society for Immunotherapy of Cancer's (SITC) 36th Annual Meeting
eTCR: Engineered T cell receptor
TME: Tumor microenvironment

Example of Editas Technology Used by BMS

HPV eTCR TGFBR2 Knockout Engineering Strategy



TCR alpha (TRAC) knockout:

- Disrupt endogenous TCR expression
- Prevent potential autoreactivity

eTCR knock-in at the TRAC locus:

- Delivered using AAV for controlled gene delivery

TGF β R2 knockout:

- Armoring strategy to prevent TME-mediated immune suppression

Liquidity - Liquidity refers to the ease with which an asset, or security, can be converted into ready cash without affecting its market price

Correlation - Correlation, in the finance and investment industries, is a statistic that measures the degree to which two securities move in relation to each other.

Sharpe Ratio: The Sharpe ratio adjusts a portfolio's past performance—or expected future performance—for the excess risk that was taken by the investor. A high Sharpe ratio is considered good when compared to similar portfolios or funds with lower returns.

Beta - Beta is a measure of a strategy's sensitivity to market movements. It measures the relationship between a fund's excess return over T-bills and the excess return of the benchmark index. Equity funds are compared with the S&P 500 index. Morningstar calculates beta using the same regression equation as the one used for alpha, which regresses excess return for the fund against excess return for the index. This approach differs slightly from other methodologies that rely on a regression of raw returns.

Alpha - A measure of the difference between a strategy's actual returns and its expected performance, given its level of risk as measured by beta. A positive alpha figure indicates the strategy has performed better than its beta would predict. In contrast, a negative alpha indicates the strategy's underperformance, given the expectations established by the strategy's beta.

Standard Deviation - Standard deviation measures the dispersion around an average. For an index portfolio, it represents return variability. Investors can use standard deviation to predict a portfolio's volatility. A higher standard deviation implies a wider predicted performance range and greater volatility.

Disclaimers

Investors should carefully consider the investment objectives, risks, and charges and expenses of the fund before investing. The prospectus contains this and other information about the fund, and it should be read carefully before investing. Investors may obtain a copy of the prospectus by visiting KellyETFs.com or calling (800) 658-1070.

The funds are distributed by Foreside Fund Services, LLC.

Limited Operating History Risk. The Fund is a recently organized investment company with a limited operating history. As a result, prospective investors have a limited track record or history on which to base their investment decision.

DNA Modification Technology Company Risk. DNA modification technology companies face intense competition, and products and services with a potentially short product life. These companies will generally require large amounts of capital expenditures on research and development, with no guarantee that the product or service would be successful. They may be heavily dependent on intellectual property rights. The laws related to these rights can vary and there is no guarantee that a company will be able to successfully protect their intellectual property rights. These companies, like other health care companies, are subject to various government and regulator oversight that could hamper or impede their operations.

Foreign Securities Risk. Investments in non-U.S. securities involve certain risks that may not be present with investments in U.S. securities. For example, investments in non-U.S. securities may be subject to risk of loss due to foreign currency fluctuations or to political or economic instability.

NOT FDIC INSURED | MAY LOSE VALUE | NOT BANK GUARANTEED

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