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RESEARCH

CRISPR GENOME-EDITING **MARKET OPPORTUNITY AND KEY PLAYERS**

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RESEARCH WHITE PAPER BY
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EXECUTIVE SUMMARY

In fewer than five years, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-genome-editing technology has taken the scientific community by storm and has revolutionized the pace of modern biology, promising an era of curative medicine and rapid biotechnological breakthroughs. Thanks to its accessible cost and ease-of-use, CRISPR has democratized genome-editing. Many companies are deploying the CRISPR platform to commercialize novel therapies and to increase research and development productivity across the drug discovery process, agriculture, diagnostics, chemicals, and material sciences.

ARK believes that CRISPR is biotech's breakthrough of the century and that it will have a profound impact on the world's most salient issues, especially as its toolbox expands. In the near-term, ARK expects the first commercial CRISPR products will be for agricultural purposes, as it increases global food supply and enhances sustainability measures. In medicine, CRISPR's addressable market in the monogenic disease space totals more than \$75 billion annually with nearly \$2 trillion in latent demand from unaddressed populations. When juxtaposed with the fact that monogenic diseases only account for an estimated 2% of all genetic diseases, it is evident that CRISPR technology is still in its infancy. This is a platform in its earliest stages.

This paper will elucidate the significance of genome-editing, the origins of CRISPR, how it works and how it compares to legacy genome-editing technologies. Then, it will examine CRISPR's market opportunity across application areas and extrapolate the direct and indirect investable opportunities as a result of CRISPR technology.

RESEARCH HIGHLIGHTS

- | \$250 billion annual global CRISPR-enabled CAR-T addressable market
- | \$75 billion in annual global revenue potential for addressing all 10,000 monogenic diseases
- | \$1.9 trillion global addressable market for monogenic diseases on a prevalence basis
- | \$170 billion in agriculture-crops, livestock, and aquaculture—value creation by 2025
- | 585 trillion increase in calorie production, feeding an additional 800 million people by 2025
- | 35% Aquaculture global market expansion by 2025
- | Emerging trends in CRISPR-based diagnostics, antibiotic resistance, drug discovery, data storage,



1 THE RISE OF CRISPR

What is CRISPR?

CRISPR is a simple, powerful and programmable genome-editing tool. An acronym for Clustered Regularly Interspaced Short Palindromic Repeats, CRISPR is the equivalent of a “molecular Swiss Army Knife” composed of two parts: first, the body, or the ‘guide RNA’, that isolates the portion of the DNA that a researcher wishes to manipulate and, second, the tool, or ‘nuclease’, that performs an operation on that stretch of DNA. In a simple example of today’s most popular guide-nuclease pairing, CRISPR-Cas9, CRISPR guides the molecular Swiss Army Knife to a targeted spot in the genome and uses Cas9 as “molecular scissors” to cut the double-strand of DNA. Other nucleases can alter the specificity and cutting efficiency/patterns, target RNA and address different stretches of the genome. In this paper, “CRISPR” will encompass all CRISPR editing systems and mechanisms of action.

Why CRISPR? It’s Cheaper, Faster, Easier

CRISPR makes genome-editing relatively simple. Compared to other editing techniques, CRISPR is much faster and cheaper, as shown in the chart below. An answer to funding constraints, it is increasing the productivity of research by lowering the cost per experiment. CRISPR is democratizing science by lowering the level of sophistication required to carry out meaningful scientific experiments so that even high school students are experimenting with the technology.

	ZFNs ¹	TALENs ²	CRISPR
First Human Cell Modification	2003	2009	2012
Time to Manufacture (days)	22	10	5
Cost (per pair of nucleases)	~\$5,500	~\$360	~\$30

Source: ARK Investment Management LLC

————— **Newer Genome-Editing Technique** —————>

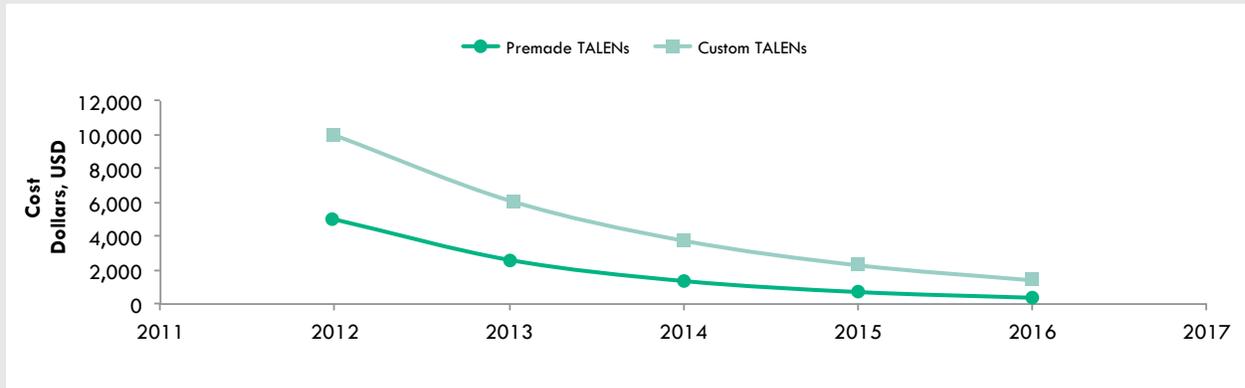
ARK expects that CRISPR gene-editing costs will decline at a rate similar to that of TALENs-based editing. Targeting a customized stretch of DNA, the cost of a TALENs experiment dropped from \$10,000 to roughly \$1,400 in the 4 years from 2012 to 2016, and almost 10-fold in the eight years since its discovery, as shown in Figure 1.

1 ZFNs: Zinc Finger Nucleases

2 TALENs: Transcription activator-like effector nuclease



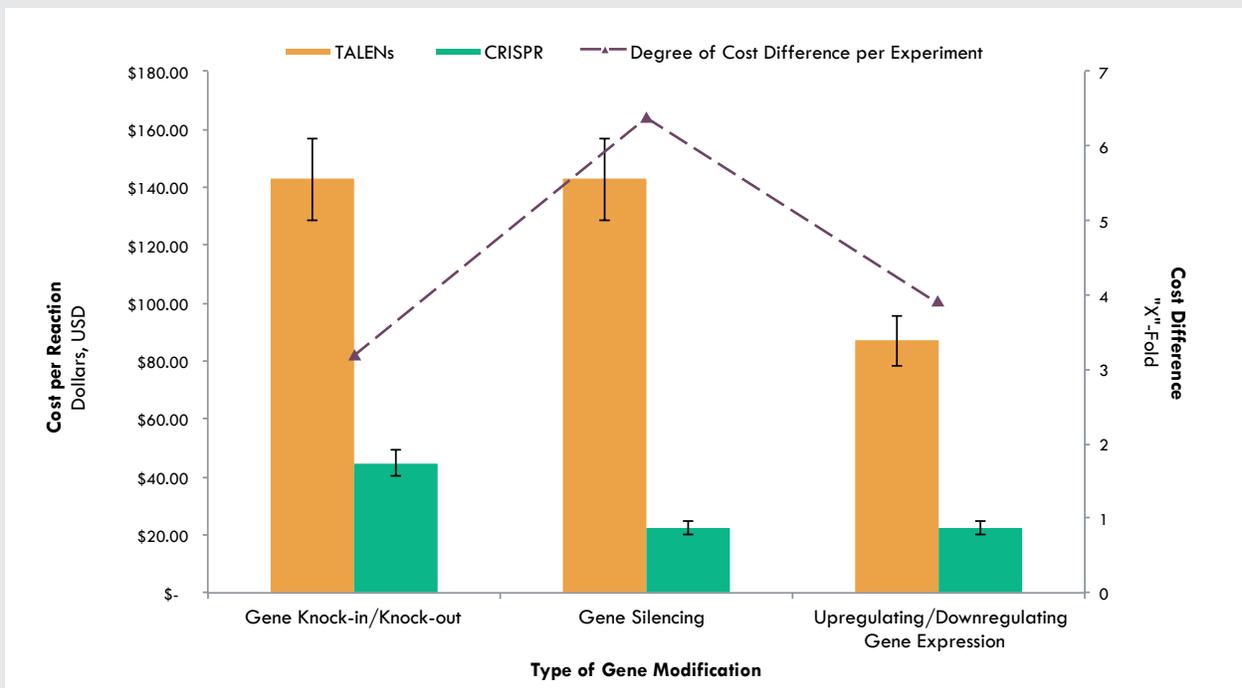
FIGURE 1
TALENs gene editing cost decline



Source: ARK Investment Management LLC, 2018

In the 6 years since its discovery, CRISPR's costs per reaction already are 3- to 6-fold below those for TALENs, depending on the type of modification, as shown in the chart below.

FIGURE 2
CRISPR: 3-6x cheaper based on gene modification (Per Reaction)



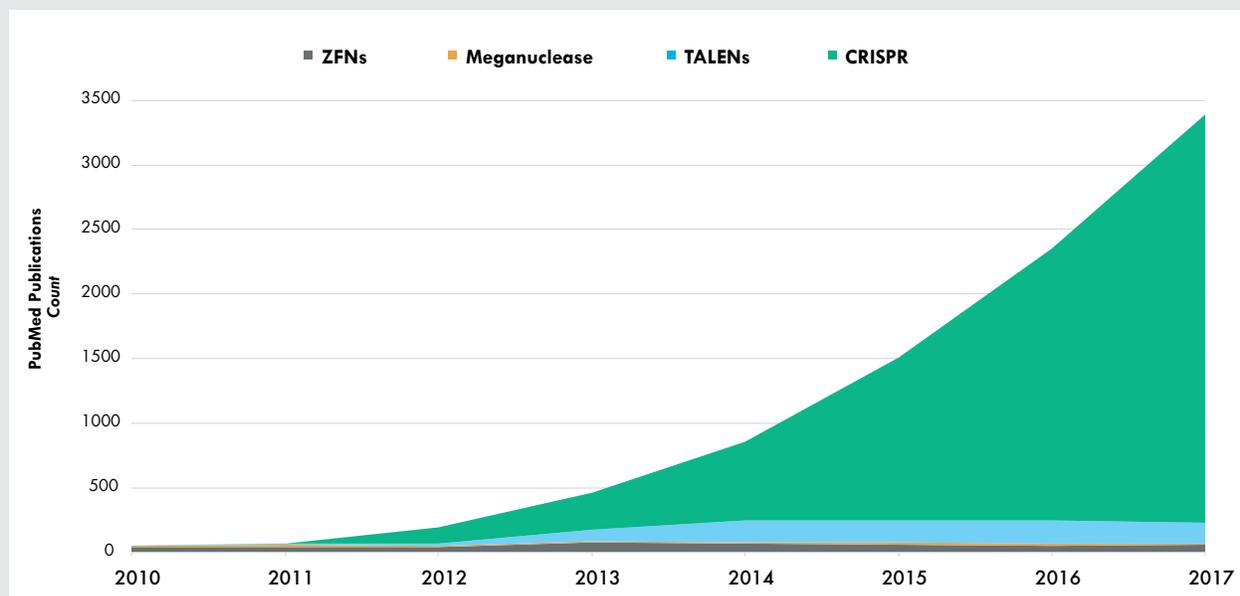
Source: ARK Investment Management LLC, 2018



In addition to its favorable cost-efficiency and manufacturing profile, CRISPR is orders of magnitude easier to use. Researchers can be trained in as little as a week,³ and middle school science classes already are experimenting with CRISPR.⁴ As a result, it is reinvigorating categories of research that have been dormant for years, importantly stem cells, while stimulating drug discovery and novel therapies like CAR-T.

Because of CRISPR's significant boost to their productivity, scientists are adopting CRISPR technology in droves, spending their valuable research and development (R&D) hours expanding its tool set. Illustrating its increasing importance to R&D efforts, the number of publications focused on CRISPR has risen dramatically relative to other gene-editing technologies, as shown below.

FIGURE 3
A 90% CRISPR PubMed publication growth rate from 2012-2017 highlights its rapid rise in popularity from initial discovery



ARK Investment Management LLC, 2017 | Data Source: PubMed

Demonstrating its profound impact on scientific research, more than 50% of all CRISPR publications are amongst the 10% most-cited papers, and roughly 20% are in the top 1%.⁵ Consequently, CRISPR is attracting a disproportionate amount of R&D dollars relative to other technologies in the space.

3 Using CRISPR to Edit Genes in Induced Pluripotent Stem Cells." The Scientist, www.the-scientist.com/lab-tools/using-crispr-to-edit-genes-in-induced-pluripotent-stem-cells-32927.
4 Yu, Alan. "How A Gene Editing Tool Went From Labs To A Middle-School Classroom." NPR, NPR, 27 May 2017, www.npr.org/sections/alltech-considered/2017/05/27/530210657/how-a-gene-editing-tool-went-from-labs-to-a-middle-school-classroom.
5 Elsevier. "CRISPR Infographic." 1st Edition, Butterworth-Heinemann, www.elsevier.com/research-intelligence/campaigns/crispr.



2 CRISPR MARKET OPPORTUNITY: HUMAN THERAPEUTICS

Transforming Health Care

Assuming “one size fits all”, medicine today treats symptoms rather than the underlying drivers of disease, a clearly suboptimal approach given the considerable genetic variation from person to person. As our understanding of human biology increases, medicine will become personalized, enough so that intractable diseases with a strong genetic basis, like cancer, might be cured.

Not only will genome editing correct mutations, but it also will enhance and accelerate our understanding of basic biology. The human body is more than the sum of its 3.2 billion DNA base pairs. CRISPR will help to identify the complex connections among gene sequences, gene synthesis, proteins, metabolism, organs, and disease.

Instead of treating symptoms, researchers now are focused on finding cures for once chronic and fatal diseases, potentially changing the reimbursement paradigm in place today. As additional gene therapies are approved, value-based pricing could become more commonplace, as novel treatments with large sticker prices require post-commercialization monitoring of not only initial efficacy, but ongoing durability and other safety metrics.

CAR-T: The First Application of CRISPR in a Commercial Therapeutic Setting

- | In the US, CAR-T has an annual addressable market of \$17 billion for late stage cancers, with the potential to expand 6-fold to more than \$100 billion once it is approved for early stage therapy.
- | CAR-T therapy is in its infancy, as the next generation will benefit from CRISPR gene-editing by increasing its potency, lowering cost of goods sold (COGS), and allowing allogeneic⁶ implementations.

The first application of CRISPR in a commercial therapeutic setting likely will occur in chimeric antigen receptor T-cell (CAR-T)⁷ therapy, a type of immunotherapy that harnesses an individual’s immune cells to target and kill cancerous cells while leaving healthy cells intact. According to ARK’s estimates, the global addressable market for CAR-T will be roughly \$40 billion annually if its applications remain limited to stage 3 and stage 4 metastatic cancers. If applied to all stages of cancer, the market could scale to \$250 billion. As a novel class of therapy, CAR-T will require many clinical trials and post-trial surveillance to validate its safety and efficacy in earlier lines of treatment.

⁶ Allogeneic delivery of a therapeutic product refers to a donor-derived or off-the-shelf source of biological products as opposed to a patient-derived source
⁷ CAR-T market-sizing in this paper does not include advances and market potential of CAR natural killer (CAR-NK) cells.



In the US, 2017 marked a historic year for gene therapy, as the FDA approved two CAR-T immunotherapies targeting hematologic (blood) cancers. ARK estimates that the addressable market for immunotherapies in the US will approach over \$100 billion, as shown below, validating the burgeoning number of biotech companies entering the CAR-T space. Underlying this estimate is the assumption that CAR-T will address 70% of all liquid tumors but only 10% of solid tumors.

FIGURE 4
Annual US CAR-T TAM

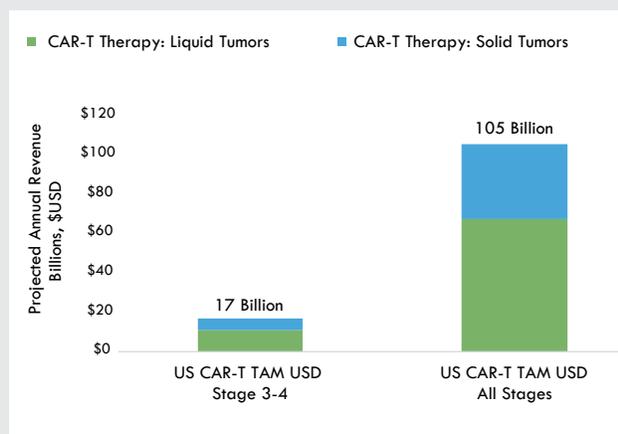
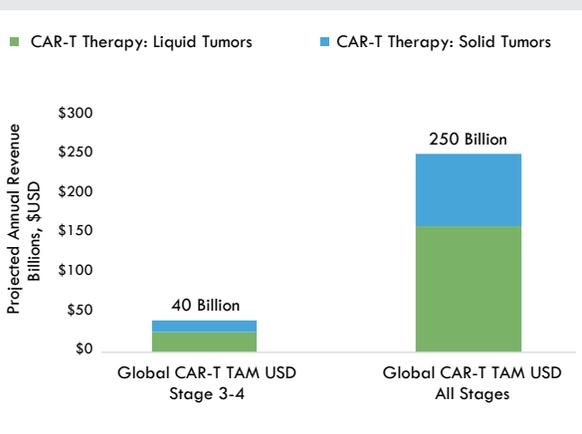


FIGURE 5
Global CAR-T TAM



Source: ARK Investment Management LLC, 2018 | TAM = Total Addressable Market

CARs are potential targets to which molecular geneticists can add epitopes to the receptor region of T cells and gain significant control over the human body’s immune system. Unlike traditional chemotherapy, CAR proteins force T cells to recognize and kill cancerous cells and arm the immune system’s “memory” cells to recognize any future invasions of malignant cells in the event of cancer recurrence, allowing complete cancer remissions in up to 90% of patients.⁸ While CAR-T treatments can cause serious side effects, such as cytokine release syndrome (CRS) and neurotoxicity, after failing multiple lines of therapy, metastatic cancer patients often have no other therapeutic option.

CAR-T is a “living drug”. In other words, no two CAR products are the same. Its response rates vary by indication, target, composition, manufacturing processes and other variables.

Unlike early CAR-T therapies, the next-generation will leverage CRISPR to enhance both therapeutic and manufacturing efficiencies. CRISPR can add precision to the delivery of CAR genes, unlike viral vectors which insert CAR genes randomly into T-cell DNA. Additionally, Researchers at Memorial Sloan Kettering Cancer Center (MSKCC) have shown that T-cells created using CRISPR are highly potent, outperforming traditional CAR-T cells.⁹

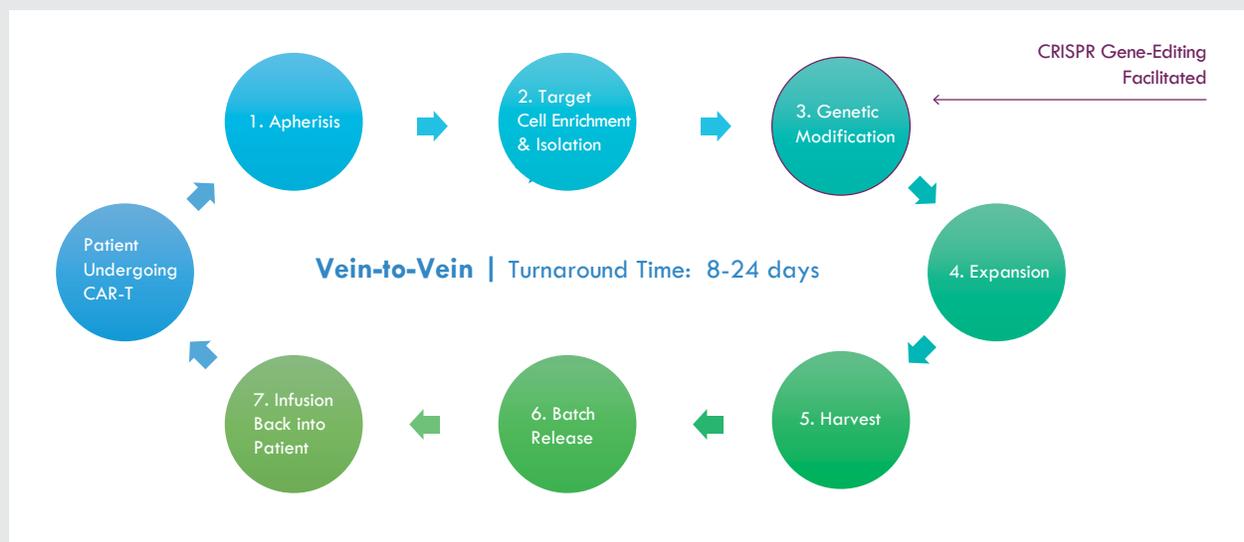
8 “The Promise of Chimeric Antigen Receptor T-Cell Therapy.” Cancer Network, 15 Oct. 2016, www.cancernetwork.com/oncology-journal/promise-chimeric-antigen-receptor-t-cell-therapy.

9 Eyquem, Justin, et al. “Targeting a CAR to the TRAC Locus with CRISPR/Cas9 Enhances Tumour Rejection.” Nature News, Nature Publishing Group, 22 Feb. 2017, www.nature.com/articles/nature21405.



Further, CRISPR-editing enhances anti-tumor activity by deleting genes that inhibit a T cell's ability to recognize tumors. Immune checkpoint protein PD-1 is a T-cell surface receptor that tumors often exploit to dampen a T-cell's activity to fight cancerous cells. In a trial at the University of Pennsylvania, researchers used CRISPR to disrupt the gene coding for PD-1 protein thereby creating PD-1 deficient CAR-T cells that could eradicate tumor cells.¹⁰ Because CAR-T cells are engineered outside of the body and tested for efficacy before being transfused into patients, cells edited by CRISPR are considered safe.

FIGURE 6
CAR-T therapy development and infusion process



Source: ARK Investment Management LLC, 2018

CAR-T requires the proliferation of tens to hundreds of millions of T-cells which can take two to three weeks. For that reason, sourcing T-cells from sick patients, or the autologous CAR-T process, can fail if the starting amount is too low.

Metastatic cancer patients do not have the luxury of time necessary to generate their own T-cells. Consequently, cultivating colonies of cancer-fighting T-cells “off the shelf”, also known as allogeneic CAR-T, often is more productive, cutting time and costs significantly. Of course, introducing somebody else’s T-cells into a patient’s body poses its own risks. If the body interprets those T-cells as foreign invaders it will fight them and accelerate the patient’s decline. In organ transplants doctors seek to avoid this sort of reaction, known as Graft versus Host Disease, by seeking genetically compatible donors, a process that is time-consuming, expensive and sometimes futile.

Obviating the need for a compatible donor, CRISPR can introduce genes that encode CARs into immune system cells in a non-major histocompatibility complex (MHC). Cellectis (CLLS) is one

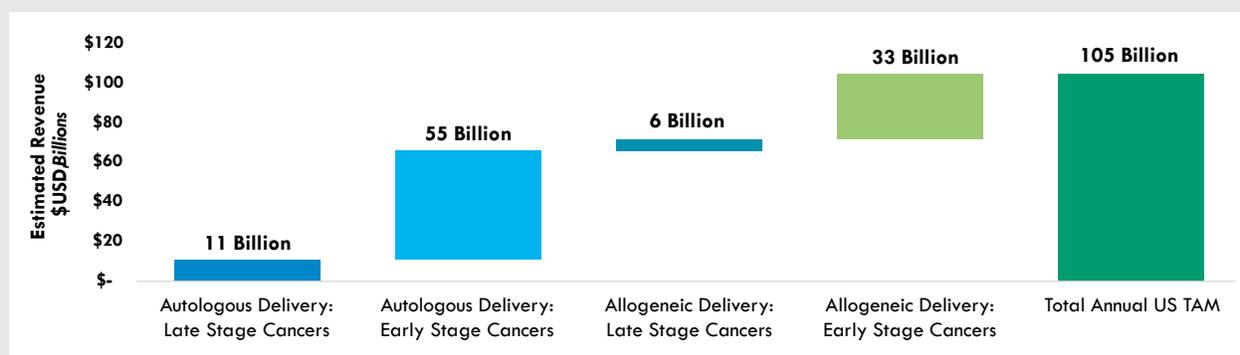
10 Rupp, Levi J., et al. “CRISPR/Cas9-Mediated PD-1 Disruption Enhances Anti-Tumor Efficacy of Human Chimeric Antigen Receptor T Cells.” *Nature News*, Nature Publishing Group, 7 Apr. 2017, www.nature.com/articles/s41598-017-00462-8.



of the companies focused on the allogeneic approach, albeit with TALEN gene-editing technology. Kite, now owned by Gilead, is developing allogeneic CAR-T therapies combining genome-editing and stem cells. Allogene, a private company founded by ex-Kite executives, has announced that it will collaborate with Cellectis on the development of allogeneic CAR-T therapies.

While ARK estimates that approximately 60% of cancers will submit to allogeneic administration, some indications will be too complex and, as with bone marrow transplants, will be limited to the autologous sourcing of T-cells. More costly to deliver but more effective in complex cancer cases, autologous CAR-T therapy could account for more than 60% of the total CAR-T addressable market, as depicted below. In other words, while allogeneic therapies might dominate the number of cancer treatments, autologous therapies probably will garner a disproportionate share of the revenues, as shown below.

FIGURE 7
US: CAR-T TAM projections by delivery mechanism and line of therapy



Source: ARK Investment Management LLC, 2018

While gene therapies are beginning to cure cancer, they are causing sticker shock in these early days. Novartis priced the first approved CAR-T therapy, Kymriah, at \$475,000, payable only if the patient responded within the first month, and Kite priced its CAR-T therapy, Yescarta, at \$373,000.¹¹

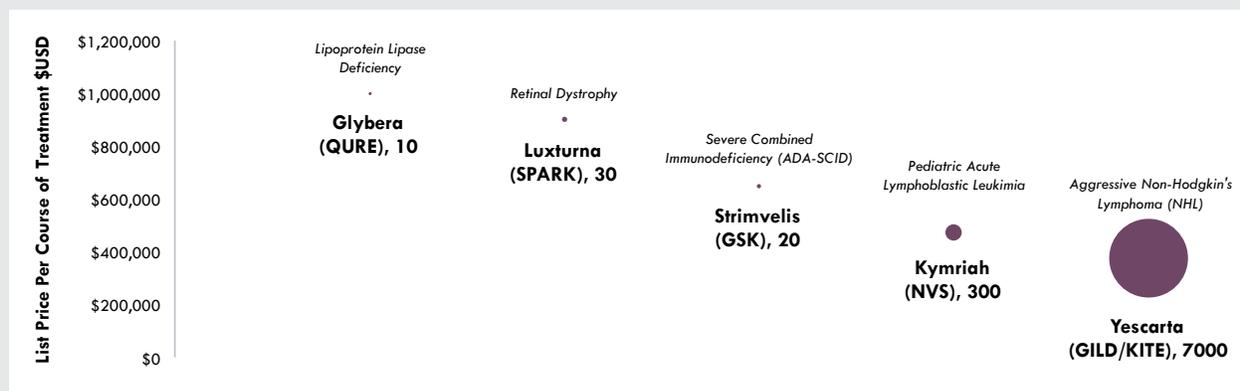
That said, compared to traditional therapies that suppress cancer, the costs relative to the benefits of gene therapy are in a different orbit. Moreover, as with most new technologies, the costs should decline as the market scales and, as shown in Figure 8, the price elasticity of demand associated with gene therapies is enormous.

Currently, more than 40 companies are developing increasingly advanced and safe CAR-T therapies for various cancer indications. Juno Therapeutics (JUNO), Poseida Therapeutics, Cellectis (CLLS), and Bellicum Pharmaceuticals (BLCM) are creating “kill switches” for CAR-T therapies to enhance its safety. Upon detection of negative side effects, physicians will be able to turn off CAR activity with a neutralizing agent. Now owned by Celgene, JUNO also is creating a protocol to administer CAR-T therapy on an outpatient basis, an indication of the rapid progress of this technology.

¹¹ Lydia Ramsey, “A cutting-edge new cancer treatment has two different price tags, and it could be the future of how we pay for drugs”, May 7, 2018, <https://www.businessinsider.com/indication-based-pricing-for-novartis-car-t-cell-therapy-kymriah-2018-5>



FIGURE 8
Gene therapy prices by eligible patients per year (USD)



Source: ARK Investment Management LLC, 2018

Three publicly traded companies are enhancing various CAR-T products with CRISPR, while another is working with TALENs technology. As shown in the table below, Intellia Therapeutics (NTLA), Editas Medicine (EDIT), and Bluebird Bio (BLUE) have partnered with leading CAR-T companies, while CRISPR Therapeutics (CRSP) has opted to develop its own program

By partnering with established companies focused on CAR-T therapies, gene therapy companies should benefit from manufacturing and distribution scale while milestone- and royalty-based revenue continue to fund other CRISPR- or TALENS-based therapeutic initiatives. Bluebird Bio, for example, is collaborating with Celgene on the first CAR-T program to capitalize on its proprietary MegaTALENS gene-editing platform. The below chart summarizes these CAR-T/gene-editing collaborations.

GENE-EDITING COMPANIES	CAR-T COMPANIES	COLLABORATION ECONOMICS
Intellia Therapeutics	Novartis*	<ul style="list-style-type: none"> - Up to \$230M in milestone payments per product - Up to \$50M in committed collaboration funding - \$18M equity investment - Mid-single digit to low-teen royalties
Editas Medicine	Juno	<ul style="list-style-type: none"> - \$25M upfront plus \$22M in potential research support - \$230M in milestones per program - Low-double digit royalties
CRISPR Therapeutics	N/A	- no collaborations as of publication
Bluebird Bio	Celgene	<ul style="list-style-type: none"> - Undisclosed upfront payment - Up to \$225M per product in potential option fees and clinical and regulatory milestones - 50/50 co-development and profit share in the US

Source: ARK Investment Management LLC

*As of Dec. 12, 2017, NVS reduced its equity stake in NTLA by 3.61% down to 9.76% due to internal pipeline re-focusing efforts with a competing drug



Monogenic Disorders

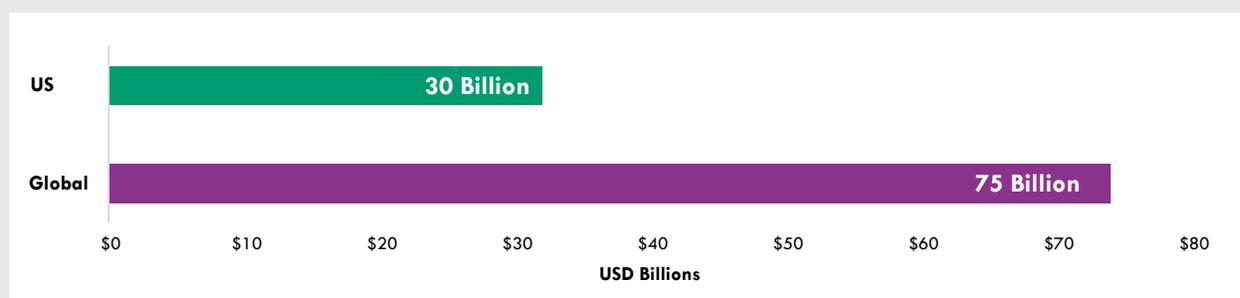
- | Addressing all monogenic diseases, CRISPR could generate up to \$75 billion in annual revenue based on the incidence of disease, and up to ~\$2 trillion based on the prevalence of disease.
- | Monogenic diseases account for only 2% of all genetic diseases, pointing to significant upside for CRISPR and other gene-editing technologies as they mature.

CRISPR's potential to correct genetic mutations and cure disease is profound. To date, scientists have identified approximately 10,000 human monogenic diseases, conditions caused by errors in a single gene.¹² While each is rare, the incidence of all 10,000 monogenic diseases is exceptionally high: 1 in 100 children is born with some sort of monogenic disease. Huntington's disease and hemophilia are two of the better-known examples. If CRISPR technology were to address all 10,000 of these monogenic diseases, the participating companies could generate \$75 billion in revenue globally per year.

While historically therapeutics have focused on symptoms of disease, gene therapy aims to address the underlying causes of disease by correcting the mutations in gene sequences encoded by DNA. In principle, correcting faulty genes should restore normal gene and protein function, reversing disease. While various gene therapy and genome-editing technologies have evolved in the last few decades CRISPR should be the most disruptive to traditional therapies.

FIGURE 9

Addressing all monogenic diseases could yield approx. \$75 billion in global annual treatment revenue on an incidence basis



Source: ARK Investment Management LLC, 2018

While each monogenic disease is rare, CRISPR should be able to address them all, potentially generating annual revenues of \$30 billion in the US and \$75 billion globally, as shown above. Today, therapies that treat the symptoms of rare disease can cost more than \$100,000 per year.¹³ Logically, a therapeutic cure

12 "Genes and Human Disease." World Health Organization, World Health Organization, 7 Dec. 2010, www.who.int/genomics/public/geneticdiseases/en/index2.html.

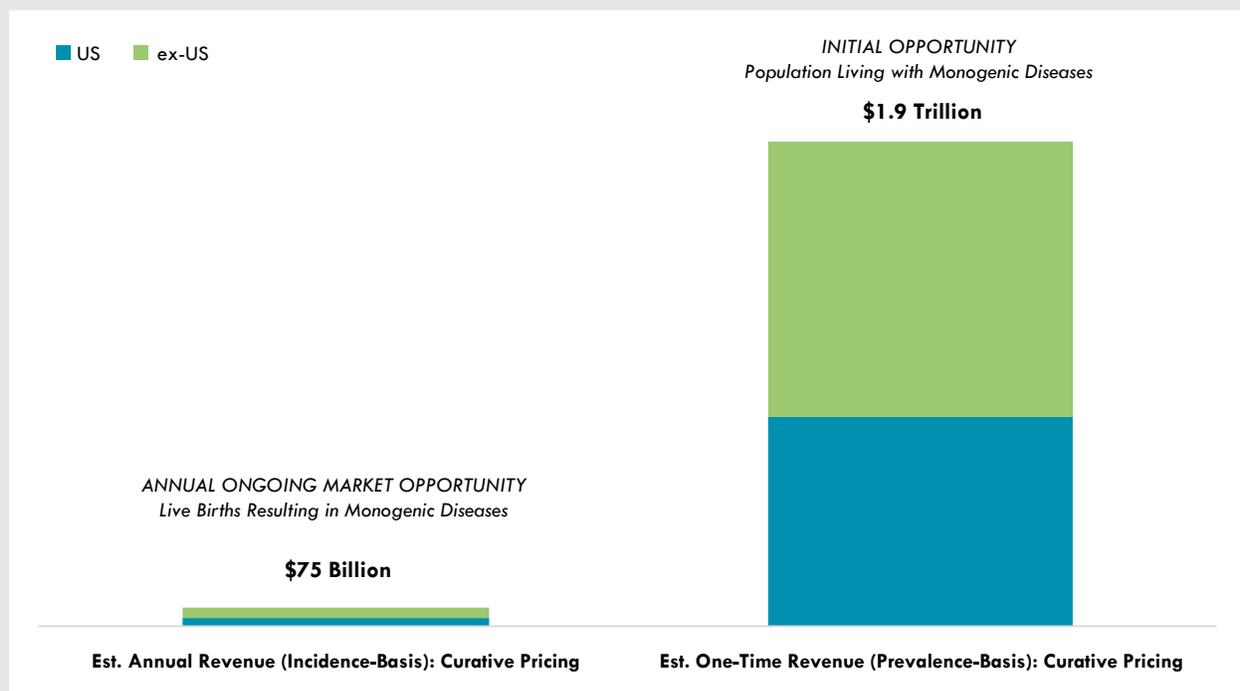
13 Smith, A. Gordon. "The Cost of Drugs for Rare Diseases Is Threatening the U.S. Health Care System." Harvard Business Review, 7 Apr. 2017, hbr.org/2017/04/the-cost-of-drugs-for-rare-diseases-is-threatening-the-u-s-health-care-system.



should command a substantial premium. While the average cost probably will be \$500,000 per cure, we estimate that \$2 million would be neutral compared to the current cost of treating chronic conditions. Based on ARK's research, higher upfront spending should eliminate future healthcare expenditures.

Important to note, the addressable populations include not just individuals born with disease – the incidence rate of disease any given year - but also those who were diagnosed in prior years - or the prevalence of disease. The latter group typically has been treated with expensive and inadequate therapies. If CRISPR were to target monogenic diseases by prevalence as opposed to incidence, its one time global addressable market would expand by an additional \$1.9 trillion.

FIGURE 10
2021 Global monogenic market treatment opportunity



Source: ARK Investment Management LLC, 2018

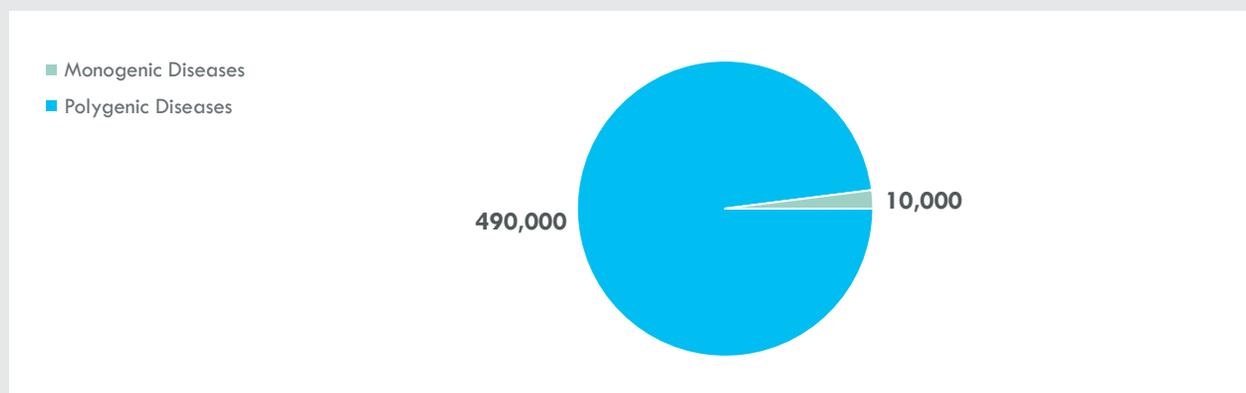
Of course, every disease indication will require its own R&D effort and submit to different delivery vectors and RNA guides. Consequently, a number of CRISPR-based companies will become beneficiaries of the technology. Currently, only three stocks traded on US exchanges are focused on CRISPR human therapeutics: Intellia, Editas, and CRISPR Therapeutics. The sheer size of the market opportunity suggests that many companies could be large beneficiaries.



Complex Polygenic Diseases

Caused by just one gene in the human genome, monogenic diseases have become the primary focus of the first generation of CRISPR therapeutics. CRISPR is still a relatively new genome-editing technology, so scientists are proceeding cautiously. Monogenic diseases comprise only 2% of all diseases known to have a genetic basis.¹⁴ The majority of other diseases is caused by mutations in multiple genes. Nearly all non-infectious and infectious diseases are genetic in nature, the genes at fault being in human cells in the former and in bacteria or viruses in the latter.

FIGURE 11
Monogenic diseases comprise 2% off all known genetic diseases



Source: Krimsky, Sheldon, and Jeremy Gruber. Genetic Explanations: Sense and Nonsense. Harvard University Press, 2013.

While many lab groups have corrected mutations in animal models in the US, human trials have just begun. Regulatory approval will be lengthy, as scientists establish safety and efficacy guidelines. Currently, the three US listed CRISPR companies - CRISPR Therapeutics, Intellia, and Editas - are focused on optimizing vector delivery systems and targeting monogenic diseases safely. Still in pre-clinical studies, Editas and CRISPR Therapeutics expect to file investigational new drug applications (INDs) for human trials in 2018, and Intellia in 2019, suggesting commercialization in the next five to seven years if traditional therapeutic development timelines apply. We would not be surprised to see an accelerated approval process if CRISPR-based therapeutics result in outright cures.

14 Krimsky, Sheldon, and Jeremy Gruber. Genetic Explanations: Sense and Nonsense. Harvard University Press, 2013.

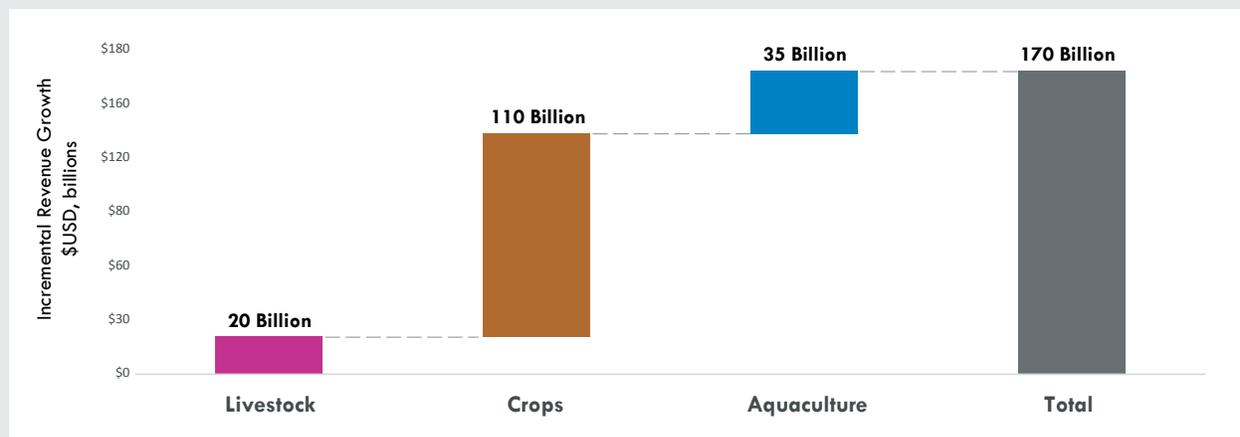


3 CRISPR MARKET OPPORTUNITY: AGRICULTURE

According to ARK’s research and as shown below, CRISPR technology will expand the global agriculture industry—crops, livestock, and aquaculture— by \$170 billion between now and 2025. CRISPR can increase crop yields, create climate-resistant traits, make meat “meatier” and taste “tastier”, add nutritional value to food products, and increase production efficiency in other ways while mitigating environmental risks.

While the agricultural industry has made tremendous progress in the past century, thanks to evolving animal and plant domestication techniques, the current model is unsustainable. The demand for higher yields and more nutritious agricultural products is increasing rapidly, not only because of population growth but also because of evolving dietary needs and preferences, changing climate conditions, and increasing demand for biofuels. According to the United Nations, the global population will expand from more than 7 billion people today to approximately 9.6 billion, pushing food demand up 70%, by 2050.¹⁵

FIGURE 12
CRISPR may expand the global agriculture market to \$170 billion by 2025



Source: ARK Investment Management LLC, 2018 | Note: Values Rounded to the Nearest 5 billion

Not only will existing technologies be unable to meet these food production goals but inefficiencies in supply chain management will exacerbate the problem, preventing what food is produced from reaching hungry consumers. Pollution caused by the anthropogenic use of land and sea for the breeding and rearing of livestock and aquaculture also could impede progress. Not only should CRISPR technology be able to satisfy the future demand for agriculture but it also could overcome many of these distribution and environmental challenges.

15 “High-Level Expert Forum: How to Feed the World 2050.” Rome, Italy, Oct. 2009.
http://www.fao.org/fileadmin/templates/wsfs/docs/Issues_papers/HLEF2050_Global_Agriculture.pdf



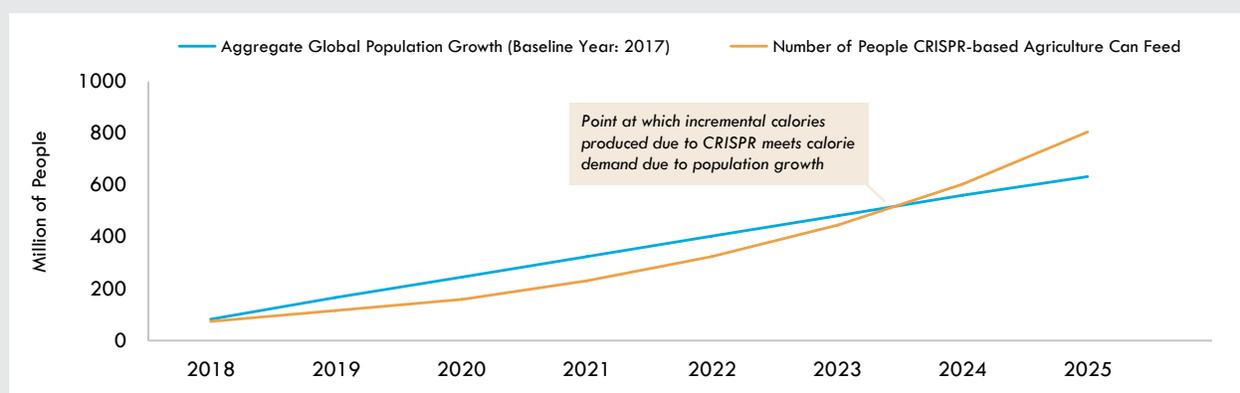
Because farmed fishing has not been a beneficiary of much innovation, CRISPR will impact aquaculture growth more dramatically than that of any other agricultural sub-industry, as shown below. In dollar terms, however, it should impact aquaculture the least, while the largest of the sub-industries, crops, will benefit the most. Because of unknown secondary effects, livestock producers are likely to adopt CRISPR technology slowly, awaiting evidence of stronger farm animals with longer lifespans.

Agriculture Sub-Industries	2017 Global Industry Value	Expected Growth in the Next 8 Years
Crops	\$1.3 Trillion Industry	25%
Livestock	\$560 Billion Industry	10%
Aquaculture	\$160 Billion Industry	35%

Source: ARK Investment Management LLC

CRISPR technology should help generate enough calories to accommodate global population growth during the next five to ten years. Currently, the global population is growing at a rate of 1.12%, or 78-83 million people per year,¹⁶ pointing to an increase of 630 million people who will require roughly 460 trillion calories to satisfy the FDA’s guideline of 2,000 calories per day, between 2017 and 2025.¹⁷ According to our calculations, CRISPR will be able to boost overall calories available for global consumption by 6%, exceeding the number necessary for 630 million people by 27%. Indeed, as illustrated below, CRISPR should boost agricultural productivity at a rate faster than population growth over time.

FIGURE 13
CRISPR improvement to agricultural productivity will outpace population growth



Source: ARK Investment Management LLC, 2018

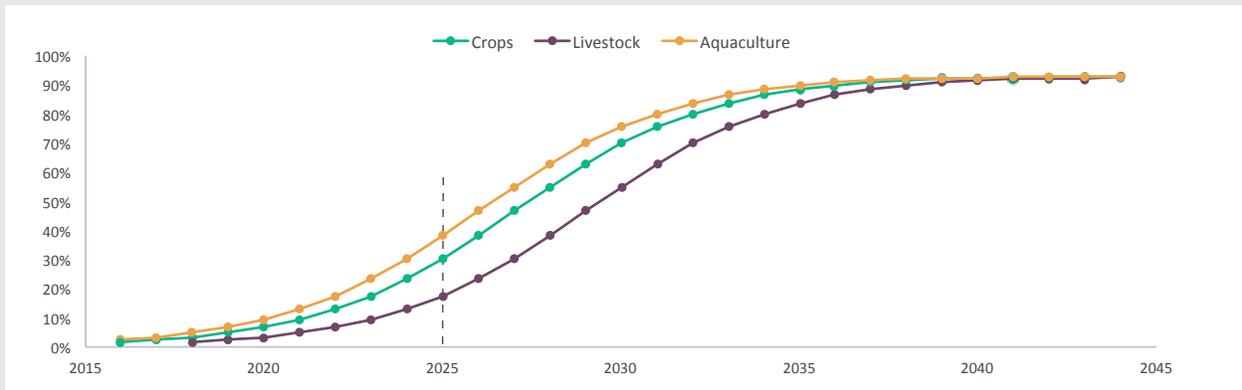
16 "Current World Population." Worlds Population (2018) - Worldometers, www.worldometers.info/world-population/.

17 "Efficient" production refers to net calories produced and not lost to crops used for purposes other than consumption



Of course, this forecast relies on an efficient farm-to-table ecosystem, not only in terms of calorie allocation but also supply chain management. Surprisingly, 40% of the US food supply, roughly \$180 billion,¹⁸ is lost to waste. While it might be able to address as much as 27% of the damage today, CRISPR ultimately could solve the problem completely, all else equal, as shown in the graph below.

FIGURE 14
Timeline: CRISPR penetration into agriculture



Source: ARK Investment Management LLC, 2018

In the chart below are examples of CRISPR’s potential impact on agricultural sub-industries.

FIGURE 15
Examples of how CRISPR can help agricultural sub-industries.

	<ul style="list-style-type: none"> • TB-Resistant Cattle; confer disease resistant traits • Faster & precise breeding practices unlike traditional selective breeding techniques • Pigs with lower fat content • Increase milk-production yield 	<p>Companies utilizing CRISPR for agricultural progress:</p> <ul style="list-style-type: none"> • Caribou* • ERS Genomics* • Dow DuPont • Casebia** • Genus • Recombinetics • Yield10 • Horizon Discovery <p><small>*Primary CRISPR Patent Holder</small> <small>**Joint Venture between Bayer and CRISPR Therapeutics</small></p>
	<ul style="list-style-type: none"> • Higher yield, pesticide-free weather/bug resistant crops • Enhance taste and nutritional value • Quickly determine new seed variants for hard to modify staples such as wheat and rice 	
	<ul style="list-style-type: none"> • Reduce gestation period in half • Increase feed conversion ratio • Sterilize farmed fish to protect wildlife • Disease resistant aquaculture to avoid food poisoning 	

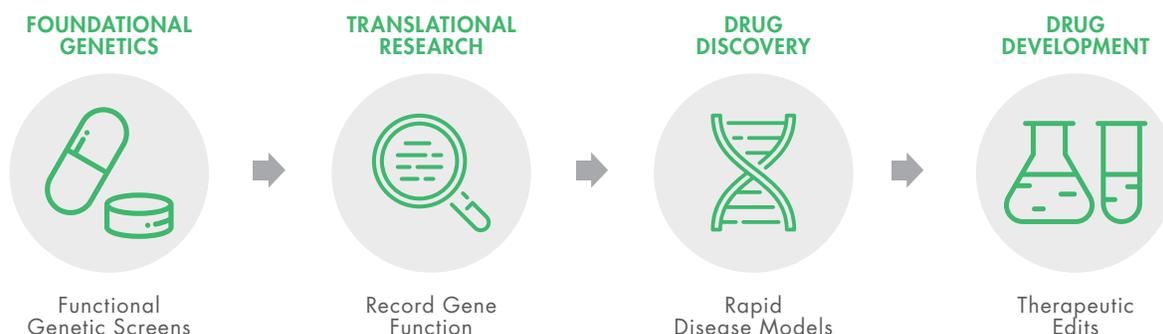
Source: ARK Investment Management LLC, 2018

18 “OCE | U.S. Food Waste Challenge | FAQ’s.” USDA, www.usda.gov/oce/foodwaste/faqs.htm.



4 CRISPR MARKET OPPORTUNITY: DIAGNOSTICS, ANIMAL DISEASE MODELS, ANTI-MICROBIAL RESISTANCE, AND DNA STORAGE

CRISPR is enabling scientists to delve into human biology, from basic research through drug development. Now they can engineer biological circuits and understand cellular systems aimed at reversing disease states. CRISPR offers improvements throughout every step of the drug development process:



Thanks to CRISPR technology, scientists have accomplished the following:

- Removed HIV from three living organisms¹⁸
- Reversed Huntington's disease in mice¹⁹
- Engineered algae to produce twice as much biofuel compared to unmodified algae²⁰
- Encoded and played back a video of a galloping horse in living E. coli bacteria cells²¹
- Edited genetic disease out of human embryonic cells²²
- Delivered nanoparticle of CRISPR constructs to the liver with a single prick and 80% efficiency²³
- Hacked bacterial genomes to create a pharmaceutical manufacturing factory²⁴
- Mapped DNA mutations using new CRISPR-based Imaging²⁵
- Altered disease phenotypes without epigenetically cutting DNA²⁶



19 "Gene Editing Strategy Eliminates HIV-1 Infection in Live Animals." ScienceDaily, ScienceDaily, 1 May 2017, www.sciencedaily.com

20 "Gene Editing Reverses Huntington's in Mouse Model." Emory News Center, 20 June 2017, news.emory.edu/stories/2017/06/li_hd_jci-CRISPR/index.html.

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22 Shipman, Seth L., et al. "CRISPR-Cas Encoding of a Digital Movie into the Genomes of a Population of Living Bacteria." Nature News, Nature Publishing Group, 12 July 2017, www.nature.com/articles/nature23017.

23 Connor, Steve. "First Human Embryos Edited in U.S., Using CRISPR." MIT Technology Review, MIT Technology Review, 29 Dec. 2017, www.technologyreview.com/s/608350/first-human-embryos-edited-in-us/

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27 "Researchers Use CRISPR to Epigenetically Alter Disease Phenotypes in Mice." GenomeWeb, 7 Dec. 2017, www.genomeweb.com/gene-silencing-gene-editing/researchers-use-crispr-epigenetically-alter-disease-phenotypes-mice?utm_source=Sailthru&utm_medium=email&utm_campaign=GWDN-Thurs PM 2017-12-07&utm_term=GW Daily News Bulletin#.W2DPHi2ZPy8.



CRISPR's applications extend well beyond therapeutics and agriculture. A “molecular Swiss army knife”, CRISPR is flexible, easy to use, and cost effective, so much so that researchers have re-purposed it to address other unmet needs. Among the CRISPR applications that have evolved since its discovery in 2012 are the following:

1. DIAGNOSTICS

CRISPR can detect viruses that are infinitesimally small, enabling robust, cost-effective and rapid point-of-care (POC) diagnostic tools. It can detect viruses at a molecular concentration of 10^{-18} , the atto level of precision that researchers rarely observe. Yet, Feng Zhang, one of the intellectual property holders for SHERLOCK (see below), estimates that a CRISPR-powered diagnostic test might cost as little as \$0.61.²⁸

Scientists at both UC Berkeley and the Broad Institute have evolved competing diagnostic platforms. UC Berkeley is developing its platform on CRISPR-Cas12a, while the Broad Institute is developing on CRISPR-Cas13. Unlike Cas9, when Cas12a targets DNA it unleashes an enzyme that indiscriminately cuts all single stranded DNA. Cas13 targets RNA instead of DNA and devours it. Both teams have leveraged the devouring functionality to release a fluorescent protein in the presence of a particular virus.

Both UC Berkeley and the Broad Institute hopes their platforms, DETECTR (Endonuclease Targeted CRISPR Trans Report) and SHERLOCK (Specific High-sensitivity Enzymatic Reporter unLOCKing), respectively, will be able to respond to viral and bacterial outbreaks, monitor antimicrobial resistance, detect cancer in blood samples at Stage 1, and monitor cancer mutations over time. Their impact on public health, particularly in emerging markets without access to adequate health care, could be profound.

2. ANIMAL DISEASE MODELS

Before entering human tests, an investigational drug must pass rigorous safety and toxicity tests in animals. Before CRISPR, creating a mouse model with a single mutation took years, with costs mounting to \$20,000 per mutation²⁹ not counting animal breeding chambers and infrastructure.

CRISPR allows researchers to create complex animal disease models in as little as three months.³⁰ Transgenic animal models no longer need to be backcrossed, a process that typically requires 10 to 11 generations of breeding.³¹ Instead researchers edit animal genomes directly, generating a strain of their choosing. Operating at the germline level, scientists can create entirely new animal lineages with customized complex mutations.

28 “SHERLOCK Team Advances Its CRISPR-Based Diagnostic Tool.” Broad Institute, 30 May 2018, www.broadinstitute.org/news/sherlock-team-advances-its-crispr-based-diagnostic-tool.

29 “CRISPR: Gene Editing Is Just the Beginning.” Nature News, Nature Publishing Group, www.nature.com/news/crispr-gene-editing-is-just-the-beginning-1.19510#/hacking.

30 Breakthrough CRISPR/Cas9 Rat Model Technology.” PR Newswire: News Distribution, Targeting and Monitoring, PRNewswire, www.prnewswire.com/news-releases/breakthrough-crisprcas9-rat-model-technology-300537725.html.

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3. MICROBIOME RESEARCH AND DRUG RESISTANCE

CRISPR technology should be able to combat drug resistance and add new dimensions to microbiome research. Increasingly, research studies are showing that the composition of the gut microbiome is complicit in both disease and health.

During the third quarter of 2017, Eligo Biosciences sealed a \$20 million Series A venture funding³² after reporting in vivo proof-of-concept data demonstrating the power of targeting gut bacteria selectively. Co-founded by Luciano Marraffini, also a founding member of Intellia Therapeutics, the private French company harnesses the power of CRISPR-Cas3 technology to target and kill “bad” bacteria while preserving “good” bacteria in the human microbiome. Once CRISPR finds the target sequence associated with bad bacteria, Cas3 devours it, disabling its ability to replicate.

Eligo’s platform has wide-ranging ramifications for health care, particularly because it can address drug-resistant bacteria such as MRSA and *C. diff*. As it discovers causal relationships among the 10 trillion bacteria in the human microbiome, Eligo’s addressable opportunity could grow significantly. Current antibiotic treatments kill not only bad bacteria but also the bacteria necessary for human health. Moreover, antibiotics can cause both bacterial-resistance and superbugs. Indeed, according to some estimates, by 2050 antibiotic microbial resistance (AMR) will cause mortality rates even greater than the number of lives lost to cancer. By 2050, 10 million lives per year could be lost to antimicrobial resistance compared to 8.2 million lives lost to cancer.³³ Consequently, CRISPR-mediated bacterial targeting could change the course of human health.

4. DNA STORAGE

Lights. Camera, Action! For the first time in history, scientists stored and played back data in living cells. Led by a team including George Church from the Harvard Wyss Institute, scientists successfully hacked a natural bacterial immune system and used it as a repository for digital data.

DNA is not only the most stable structure in nature but also one of the most durable at high levels of heat. Each human cell contains 3.2 billion base pairs of genetic code, 6 feet of information if placed end to end, effectively a powerful storage device. No wonder scientists have been working towards storing digital data in human cells for years.

In addition to storing DNA, one day CRISPR could create a way to record events that cells undergo during development, otherwise known as “synthetically created memory hotspots”.³⁴ Scientists from the Broad Institute have been studying the CRISPR Cas1 and Cas2 proteins, re-engineering their functions to create

32 “Eligo Bioscience Secures \$20 Million Series A from Khosla Ventures and Seventure to Bring Precision Medicine to the Microbiome.” PR Newswire: News Distribution, Targeting and Monitoring, PRNewswire, www.prnewswire.com/news-releases/eligo-bioscience-secures-20-million-series-a-from-khosla-ventures-and-seventure-to-bring-precision-medicine-to-the-microbiome-300525473.html?_hsenc=p2ANqtz-_5yH3nUoMdegfsv6SN-qJkQOZpNx7WNND91vNf3icjpf03bTrRk7sxTP9pa9TNIawdmqaAyMYb9HZOOm19Ebf4l-xrVuVUTT1hOLcHBG5scQbvBl&_hsmi=56887319.

33 Abrams, Lindsay. “Deadlier than Cancer: Antibiotic-Resistant Superbugs Could Be One of the World’s Top Killers by...” Salon, Salon.com, 11 Dec. 2014, www.salon.com/2014/12/11/deadlier_than_cancer_antibiotic_resistant_superbugs_could_be_one_of_the_worlds_top_killers_by_2050/

34 Boettner, Benjamin. “Taking Cells out to the Movies with New CRISPR Technology.” Harvard Gazette, Harvard Gazette, 25 Apr. 2018, news.harvard.edu/gazette/story/2017/07/taking-cells-out-to-the-movies-with-new-crispr-technology/.



a “molecular memory” bank, instead of focusing on the “molecular scissors” function.

Derived from a bacterial adaptive immune system which fends off viral invaders, CRISPR depends on immunological memory. It records molecular events in living cells, such as past viral infections, by integrating short bits of viral DNA into a genomic array. Recently, scientists have discovered the role that Cas1-Cas2 enzymes play in bacterial immunity. The viral sequences, known as “protospacers”, depend on the Cas1-Cas2 complex for integration into the host genome, at which point the memory sequence becomes the “spacer”. New spacers occupy distinct moments so that, over time, the genomic array evolves from a long history of spacers, all in chronological order.

Thus far, scientists at the Broad Institute have recorded specific and arbitrary DNA sequences in living bacterial cells over a number of days. In the future, they hope to establish molecular guidelines for recording key moments in cell formation, including neural development and fate decisions from early stem cells to a highly specialized cell types.

5. CRISPRi/CRISPRa: DIMMER, EPIGENETIC REGULATOR, & TRACKER

While scientists are harnessing CRISPR technology to edit DNA and cure genetic diseases, they also are grappling with the risk of off-target effects that can alter the genome deleteriously and permanently. To overcome safety issues, they have begun to edit RNA instead of DNA with CRISPR technology, controlling protein production at the post-transcription level. Targeting protein production at the RNA level obviates the need to make permanent changes at the DNA level. Therapeutics based on RNA-targeting are reversible.

CRISPRi and CRISPRa, or CRISPR activation, act like dimmer switches, changing a gene’s ability to code proteins without altering its structure. Scientists have been using CRISPR with a deactivated form of Cas9, dCas9, to track the movement of proteins and identify the presence of genes given environmental, or epigenetic, changes. With a fluorescent protein attached to a deactivated Cas9, CRISPR can track biological processes, including cell and drug metabolism.

NUCLEASE	CHARACTERISTICS DIFFERENTIATOR	BEST SUITED FOR...
Cas9	Cuts double stranded DNA	Gene Knock-down Research
Cpf1	Offsets double-stranded cut	Gene Knock-in potentially easier to deliver due to smaller size
Cas13a	Targets RNA	Diagnostics purposes with low expression levels
Cas3	Demolishes DNA completely	Elimination of bacteria

Source: ARK Investment Management LLC



REGULATORY HURDLES AND ETHICS

The US regulatory system is robust, pro-patient and pro-innovation. It serves as a model for other countries seeking best practices in the research on and development of genome-editing. With decades of experience reviewing gene therapy-related research, the FDA has the authority in the US to regulate products derived from human cells and gene therapy as biologics or drugs which cannot be marketed or commercialized before they demonstrate safety and efficacy. That said, in 2017 the FDA approved two gene therapies, Kymriah for pediatric acute lymphoblastic leukemia (ALL) and Yescarta for aggressive Non-Hodgkin's Lymphoma (NHL), highlighting one of FDA Commissioner Scott Gottlieb's primary goals, to work with biotech companies to expedite breakthrough therapies that will transform patient lives.

Editing Diseases in Human Embryos

As scientists have begun to research the gene editing of human embryonic stem cells, they have elicited both ethical and safety concerns. Genome editing in germline cells— cells involved in reproduction and responsible for passing down traits to offspring—could have unpredictable effects on future generations. Critics believe such research could be exploited for non-therapeutic modifications and trait selection, otherwise known as eugenics or the creation of “designer babies”, hindering research on the elimination of genetic disorders.

Although concerns about germline editing are valid, more than 40 countries discourage or ban such research.³⁵ That said, China is blazing a trail in embryonic research while the US, which does not prohibit germline modification, is making tepid advances.

During the second quarter of 2017 a team of researchers led by Shoukhrat Mitalipov in Portland, Oregon, edited the first human embryo in the United States.³⁶ As the news went viral, critics began railing against the prospect of “designer babies,” commenting that “the creation of gene-edited persons could be attempted at any moment, including at IVF [in vitro fertilization] clinics...in countries where there are no such legal restrictions.”

In February 2017, prior to the first edit of a human embryo, the U.S. National Academy of Science (NAS) summarized its views on genome-editing,³⁷ dividing it into three categories:

1. basic research on human genome editing,
2. the use of such editing to treat diseases in living people, and
3. its use to change the genomes of embryos that could be inherited in future generations

35 “Don’t Edit the Human Germ Line.” Nature News, Nature Publishing Group, www.nature.com/news/don-t-edit-the-human-germ-line-1.17111.

36 Connor, Steve. “First Human Embryos Edited in U.S.” MIT Technology Review, MIT Technology Review, 29 Dec. 2017, www.technologyreview.com/s/608350/first-human-embryos-edited-in-us/

37 “News - The National Academies of Sciences - Engineering - Medicine”. 14 Feb, 2017 <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24623>



While it suggested that the first two applications could have favorable benefits relative to risks, the NAS also concluded that embryonic editing will require extensive ethical discussion. In other words, editing the DNA of a human embryo to prevent a disease in a baby may be approved one day, perhaps in rare circumstances.

Thus far, regulators have not permitted edited human embryos to grow beyond an 8-cell blastula.³⁸ The odds of these fertilized eggs surviving if implanted are very low, given the low efficiency of embryonic editing. Philosophically or ethically justifiable applications for this technology will be moot until researchers achieve safe outcomes and attain reproducible data over multiple generations.

In the meantime, CRISPR editing should continue to transform the course of disease in cells that cannot be passed down to future generations.

Regulatory Controls on CRISPR in Agriculture

Beyond biomedical applications, CRISPR will expedite crop and livestock breeding. Unlike genetically modified organisms (GMOs), CRISPR-modification edits a plant's native genome without introducing foreign, or transgenic, DNA from other plants and animals. Accordingly, CRISPR-modified crops are more acceptable ethically, as they evolve much like they do in nature.

Consequently, in 2016 the US Department of Agriculture (USDA) decided not to regulate a strain of non-browning CRISPR-modified mushrooms, setting a precedent for future CRISPR-modified crops.³⁹ Its decision should accelerate innovation in the crops market now that they can be cultivated and commercialized without a lengthy and costly regulatory process.

In contrast to CRISPR crops, CRISPR-modified livestock will face more delays. In draft guidance released in early 2017, the FDA indicated that it will require "intentionally modified" animals to seek regulatory approval, much like traditional pharmaceuticals.⁴⁰ The ruling seems to be precautionary. In fact, the existence of guidance for gene-edited animals highlights the FDA's willingness to embrace CRISPR-modified organisms and is tacit acknowledgement that their adoption is imminent.

CONCLUSION

The potential uses for genome-editing, include treating and preventing human disease and ensuring a more robust and reliable food supply. Although early human studies and advances showcased in this paper hold great promise, medical research is a long, expensive and meticulous process. Every promising

38 Britannica, The Editors of Encyclopaedia. "Blastula." Encyclopædia Britannica, Encyclopædia Britannica, Inc., 3 Mar. 2011, www.britannica.com/science/blastula.

39 Emily Waltz, "Gene-edited CRISPR mushroom escapes US regulation", 14 April 2016, <https://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754>

40 Medicine, Center for Veterinary. "Animals with Intentionally Altered Genomic DNA." US Food and Drug Administration, Center for Biologics Evaluation and Research, www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/default.htm.



application for genome-editing, like all medical treatments, must undergo rigorous clinical trials following well established regulations to protect patient safety before it is available for routine use. Nonetheless, the FDA is forward-looking and is likely to approve the first CRISPR therapy in the next few years.

Beyond its potential to treat specific diseases, genome-editing is also giving researchers the unique capability to manipulate genes in their laboratories. This type of research, which scientists call “basic,” is anything but basic. It improves our scientific understanding of biological processes, further advancing the rate of innovation and enhancing human health while addressing issues caused by increasing rates of globalization.

Current breakthroughs in CRISPR technology are just the beginning, and we can expect the field to evolve rapidly. Until recently, sequencing DNA, has not been operationally significant. CRISPR enables researchers to engage with DNA sequencing data, interrogating gene function and modifying sequences. Prior to CRISPR, diagnostic tests had little value and justifying their reimbursement was painstaking. As therapeutic options expand for disease states, the value of diagnostic tests, including whole genome sequencing, should increase dramatically.

CRISPR is democratizing science and changing how we view disease and healthcare. Thus far, we have succeeded in reading DNA and editing DNA. In the next step of this trajectory, we can expect to “write” DNA through DNA synthesis. Just as editing capabilities have transformed the value of reading DNA, we can expect DNA synthesis technology to enhance the value of DNA editing. 2018 and 2019 should be big years for CRISPR, thanks to many clinical trials and an ever-increasing list of potential use cases.

What a time to be alive (and a time to live longer)!



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Prior to ARK, Manisha worked as a management consultant for Kepler Cannon. Before that, she gained experience as a business solutions analyst at Attensity America. Manisha has over eight years of experience in translational research. Her experience includes the Weissman Lab at Stanford’s Institute of Stem Cell Biology and Regenerative Medicine Department where she won the Jessica Lynn Fellowship Award in Research from the School of Medicine. She also worked in the Late Life and Neurodegenerative Disorders Lab and the Education Technology Department for the School of Medicine, authoring virtual patients for differential diagnosis. Manisha gained experience at Memorial Sloan Kettering Cancer Center in the Human Oncology & Pathogenesis Program before she worked as a health policy project manager at Research Triangle Institute. Manisha graduated from Stanford with a Bachelor of Science in Science, Technology, and Society: Life Sciences and Biotechnology.

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