



Genomics Innovation: A Catalyst For Growth

Health Care In The Genomic Age

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About the Author



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Brett joined ARK in February 2014 and has worked alongside Cathie for almost 15 years since their time at AllianceBernstein. As Director of Research, Brett guides and manages the proprietary research of ARK’s investment team. The team recognizes that disruptive innovation demands a dynamic and universal approach. By researching across sectors, industries and markets, ARK’s investment team seeks to gain a deeper understanding of the convergence and market potential of disruptive innovations, and thus size investment opportunities more appropriately.

Prior to ARK, Brett served as a Vice President and Senior Analyst on the Research on Strategic Change team at AllianceBernstein. In that role, Brett conducted thematic research, served on the thematic portfolios strategy committee under Cathie Wood’s stewardship, and advised portfolio managers across asset classes. His research topics included Global Energy in the Face of Carbon Dioxide Regulation; Social Media and the Rise of Facebook; the Reformation of the Financial Services Landscape; and the Emergence of Electric Vehicles. He also is the Founder and Principal at iamB Consulting, providing strategy consulting to early stage startups. Prior to 2007, Brett worked in business development in the Radio-Frequency Identification industry after serving as a founding teacher at a charter high school in Los Angeles. Brett earned his Bachelor of Science in Mechanical Engineering at the Massachusetts Institute of Technology (MIT).



GENOMICS INNOVATION: A CATALYST FOR GROWTH

Health Care In The Genomic Age

The “Genomic Age”

Over the last five years, we have passed key inflection points in the ability to access, manipulate, and understand the molecular building blocks of the human body:

- The cost to sequence a genome, once a nine-figure nation-state-worthy project, has dropped into the hundreds of dollars.¹
- Editing DNA² is becoming an antidote to pervasive, chronic disease.
- For the first time, living therapies³ are likely to cure certain diseases with just one dose.
- Bioinformatics⁴ is tying DNA sequencing data and therapeutic initiatives to patient outcomes, providing scientists, corporations, and clinicians with an unprecedented understanding of how the human genome can break down and how it might be mended.

The “genomic age” of medicine promises profound ramifications for human health and for the companies involved, among them:

- Tool providers that enable basic research, sharpen the precision of diagnostics, and guide personalized medicine.
- Diagnostic platforms deploying data that informs the treatment of disease.
- Other companies deploying technology and data to create next-generation treatments and cures, increasing returns on therapeutic research and development for the first time in 20 years.

ARK Invest estimates that by 2024 therapeutic pipelines and tool providers should generate hundreds of billions of dollars in new revenue and trillions in new market capitalizations as they transition to the genomic age.⁵

1 “The Human Genome Project.” *Genome.gov*, www.genome.gov/human-genome-project.

2 “CRISPR.” *Wikipedia*, Wikimedia Foundation, 30 June 2020, en.wikipedia.org/wiki/CRISPR.

3 “Gene; Cell Therapy FAQs: ASGCT - American Society of Gene and Cell Therapy.” *American Society of Gene and Cell Therapy*, www.asgct.org/education/more-resources/gene-and-cell-therapy-faqs.

4 Delude, Cathryn M. “Deep Phenotyping: The Details of Disease.” *Nature News*, Nature Publishing Group, 4 Nov. 2015, www.nature.com/articles/527514a.

5 “Big Ideas 2020.” *ARK Invest*, 29 Apr. 2020, ark-invest.com/big-ideas-2020/.



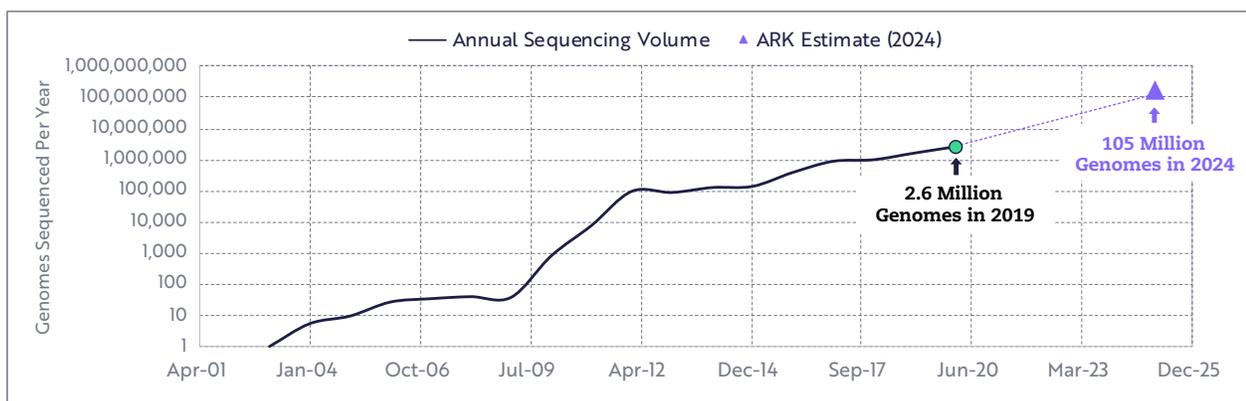
Technological Platforms Catalyzing the Genomic Age

Next-Generation DNA Sequencing

The human genome is the blueprint of human life. The genome’s three billion letters determine how homo sapiens grow, live, and thrive. Bones, eyes, and all matter and manner of human beings—the similarities and differences—are encoded compactly in a microscopic, spaghetti-string molecule. One DNA strand from every human who ever lived⁶ would weigh less than ten drops of water. Yet, while central to human life, the structure and hereditary mechanism of DNA⁷ were unknown until the early 1950s. Their discovery unleashed intense biological inquiry that has taken decades to translate into clinical practice.

Completed in 2003, the Human Genome Project⁸ was the first systematic attempt at decoding the whole human genome. The Project cost roughly \$2.7 billion and took over a decade. Fewer than two decades later, the cost to sequence a human genome has dropped to less than \$600⁹ and, according to ARK Invest’s research, should drop to less than \$100 in the next five years. These lower price points have been and will be critical in driving the adoption of genomic sequencing. Despite its rapid decline, the high cost of sequencing has prevented its use in fundamental research until recently. Below \$1,000, the case for clinical adoption becomes more compelling. Powered by sequencing, diagnostic tests are becoming cheaper and more comprehensive than legacy tests. ARK Invest forecasts that clinical adoption of next generation DNA sequencing (NGS) will drive volumes from ~2.6 million in 2019 to more than 100 million in 2024, as shown below.

Figure 1: The Growth of Genomic Sequencing (Log Scale)



Source: ARK Investment Management LLC, 2020 | Sequence volume is measured in whole human genome data equivalents, which is defined as 96 giga-bases of genomic data (3.2 GB genome at an average coverage of 30X).

6 "How Many People Have Ever Lived on Earth?" Population Reference Bureau, 24 Aug. 2018, www.prb.org/howmanypeoplehaveeverlivedonearth/.
 7 Nature News, Nature Publishing Group, www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397/.
 8 "The Human Genome Project." Genome.gov, www.genome.gov/human-genome-project.
 9 Illumina Q2 Source Book. Illumina, July 2019, www.illumina.com/content/dam/illumina-marketing/documents/company/investor-relations/ILMN-Q219-Source-Book.pdf.



NGS is the foundation for precision medicine: by sequencing inherited - germline - mutations, clinicians can understand an individual’s predisposition to conditions such as coronary artery disease and cancer. NGS also can diagnose rare inherited disorders in infants, a process that took years previously. Specific germline mutations also can inform therapeutic options for cancer patients, such as PARP inhibitors¹⁰ for pancreatic cancer patients.

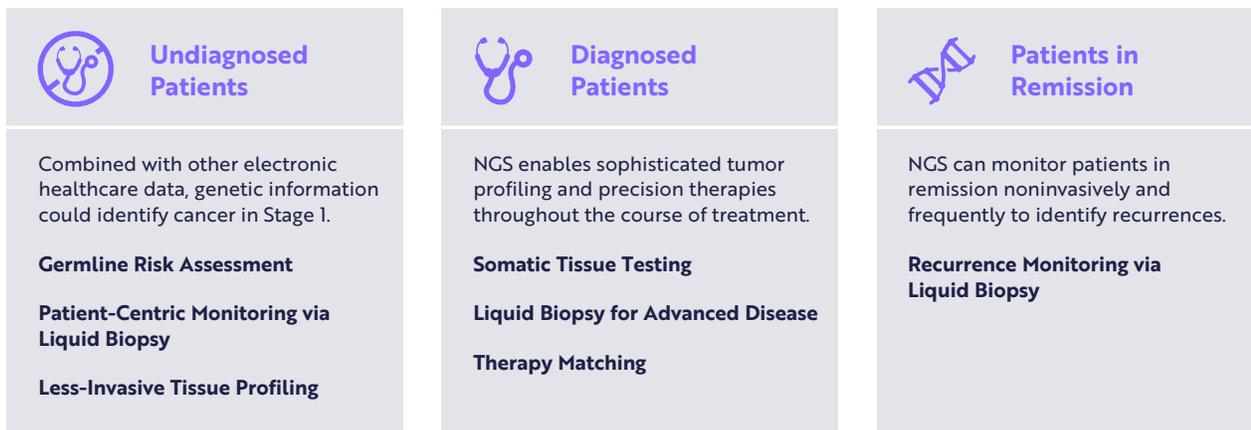
NGS is likely to transform oncology profoundly. Unlike predispositions to germline mutations, patients can contract somatic mutations that spontaneously lead to cancer. With machine learning, clinicians now can profile a patient’s tumor for somatic mutations, surfacing the best therapy to treat it.

In recent years, scientists have discovered that tumors shed fragments of mutated DNA into the bloodstream that can be identified by liquid biopsies. Today, these non-invasive blood tests can guide therapy and monitor patients in remission and, soon, should detect cancer at an early stage, as shown in Figure 2 below.

Indeed, given recent research advances, an early stage pan-cancer detection test could become commercially available within the next few years, with profound impacts on human health: if every Stage 4 cancer were detected instead in Stages 1, 2 or 3, the US cancer mortality rates could decline by as much as 25%.¹¹

Figure 2: Potential Clinical Applications Of Genomic Sequencing

NGS enables clinicians to gauge an individual’s risk of cancer, treat diagnosed patients, and monitor disease recurrence more precisely.



¹⁰ Kahl, Kristie L. FDA Approves First PARP Inhibitor as Frontline Maintenance in Pancreatic Cancer. 30 Dec. 2019, www.cancernetwork.com/news/fda-approves-first-parp-inhibitor-frontline-maintenance-pancreatic-cancer.

¹¹ “How liquid biopsies will become a standard in recurrence monitoring” S. Barnett, ARK Invest White Paper, May 2019; “Liquid biopsies to detect cancer could boost annual sequencing volume by 40-fold” S. Barnett, ARK Invest White Paper, March 2019; Sensitive and Specific Multi-Cancer Detection and Localization Using Methylation Signatures in Cell-Free DNA. *Annals of Oncology*, 30 Mar. 2020, [www.annalsofoncology.org/article/S0923-7534\(20\)36058-0/fulltext#%20](http://www.annalsofoncology.org/article/S0923-7534(20)36058-0/fulltext#%20); Clarke, Christina A., et al. “Projected Reductions in Absolute Cancer-Related Deaths from Diagnosing Cancers Before Metastasis, 2006–2015.” *Cancer Epidemiology, Biomarkers & Prevention, American Association for Cancer Research*, 30 Mar. 2020, cebp.aacrjournals.org/content/early/2020/02/25/1055-9965.EPI-19-1366.



CRISPR Gene-Editing

Clustered Regularly Interspaced Short Palindromic Repeats (“CRISPR”) gene-editing technology has accelerated the pace of modern biotechnological research dramatically. Thanks to its accessible cost and ease-of-use, CRISPR has democratized the use of genome editing. Many companies are deploying the CRISPR platform to commercialize novel therapies and to increase research and development productivity not only in drug discovery, but also in agriculture, diagnostics, chemicals, and material sciences.¹²

While gene-editing debuted during the biotechnology boom in the 1980s, studies of viral invaders and bacterial immune defense systems led to the discovery of CRISPR in 2012. The first targeted edit was in a yeast cell during the 1980s,¹³ as shown below, but the major gene-editing breakthroughs have taken place in the last ten years. Gene-editing technology could become the major breakthrough for medicine in this century.

Figure 3: A Timeline Of The Development Of Gene-Editing Technologies

1980's	First targeted gene-editing, performed on yeast cells in several laboratories
1987	First report of clustered repeats in bacteria genes, the key discovery required for CRISPR development
1991	First insights into how zinc finger proteins recognize specific DNA sequences
1994	Discovery that DNA breaks induced by a nuclease can be repaired efficiently by homologous recombination, a foundation of current gene editing technology
2002	First targeted gene edit made in an organism
2002	Clustered repeats discovered in 1987 renamed to 'Clustered Regularly Interspaced Short Palindromic Repeats' or CRISPR
2009	Discovery of a simple code explaining how transcription activator-like effectors (TALEs) can recognize specific DNA sequences
2012	First reports of engineered CRISPR-Cas9 systems that can cut specific DNA sequences
2013	First reports of engineered CRISPR-Cas9 systems to modify genes in human cells
2014	New England Journal of Medicine report on the first human clinical trial using Zinc Finger Nucleases (ZFN) to target and destroy the CCR5 gene in T-cells of 12 people with HIV
2016	First AIDS patient treated with ZFN-treated stem cells
2016	First cancer patient treated with CRISPR-edited immune cells in China
2017	First FDA approval of CRISPR-based clinical trial
2019	First human dosing of CRISPR and first patient data released

Source: ARK Investment Management LLC, 2020

¹² "Understanding DNA, the Human Genome, and the Rise of CRISPR" M. Samy, ARK Invest White Paper, August 2018.

¹³ Alexander, William G. "A History of Genome Editing in *Saccharomyces Cerevisiae*." Wiley Online Library, John Wiley ; Sons, Ltd, 29 Jan. 2018, onlinelibrary.wiley.com/doi/full/10.1002/yea.3300.



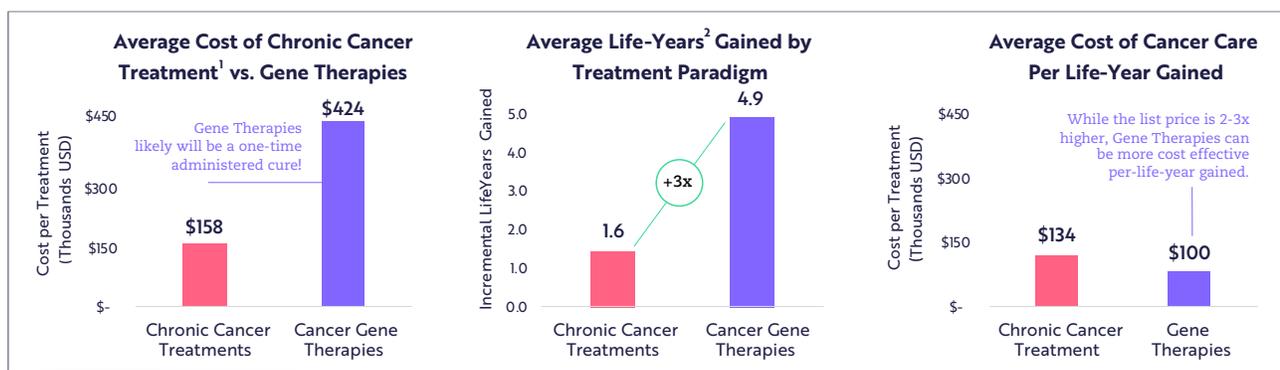
CRISPR is an application that not only is wide-ranging but also is accessible in real time. While associated primarily with gene-editing today, CRISPR ultimately could control gene processes and protein expression. CRISPR is a novel platform in the bioengineering space that is accelerating innovation in basic research, drug discovery, animal models, drug development, therapeutics, agriculture, diagnostics, data storage, and material sciences, to name a few. According to our research, CRISPR’s addressable market in the monogenic disease space could scale to \$75 billion annually with nearly \$2 trillion in latent demand from unaddressed populations,¹⁴ as monogenic diseases account for only 2% of all genetic diseases.

Living Drugs

Cancer therapies have evolved from radical surgery and cytotoxic chemotherapy to personalized medicine with targeted and living therapies. Biologic therapies use materials from living organisms to treat disease. “Living drugs” harness the body’s biological processes, including its immune system, as therapies. Though known for their success against cancer, these treatments should be applicable to a panoply of serious disorders.

While only six living drugs have been approved by the FDA,¹⁵ hundreds are evolving in research and development pipelines,¹⁶ many of them potentially curing diseases. As potential cures, living drugs like CAR-T cell therapies command premium pricing. Compared with recently approved cancer treatments, the price points of these gene therapies are almost twice as high as traditional therapies. Because they extend life, we believe these therapies can justify these price points easily. As measured by dollars-spent-per-life-year-gained, for example, Novartis’ Kymriah - a living drug targeting blood cancer – has been one of the most cost-effective cancer therapies released during the last 20 years in the US despite a price tag at more than \$400,000.¹⁷

Figure 4: Cost-Effectiveness Analysis For Gene Therapies (Example)



[1] Chronic cancer treatments include treatments approved 2014 to 2019. | [2] Life-year: Year of survival while on therapy. Source: ARK Investment Management LLC, 2019; Biologics Evaluation and Research. “Approved Cellular and Gene Therapy Products.” U.S. Food and Drug Administration, FDA, <https://arkinv.st/37LrKQh>; Shahryari, Alireza, et al. “Development and Clinical Translation of Approved Gene Therapy Products for Genetic Disorders.” *Frontiers*, Frontiers, 20 Aug. 2019, <https://arkinv.st/39MZOXg>.

14 “CRISPR Genome-Editing: Market Opportunity and Key Players” M. Samy, ARK Invest White Paper, August 2018.
 15 Center for Biologics Evaluation and Research. “Approved Cellular and Gene Therapy Products.” U.S. Food and Drug Administration, FDA, www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.
 16 “Cellular and Gene Therapies.” *Clinical Trials*, U.S. National Library of Medicine, clinicaltrials.gov/ct2/results?cond=cellular%2Band%2Bgene%2Btherapies&term=&cntry=&state=&city=&dist=.
 17 For example: Melanie D. Whittington, PhD. “Long-Term Survival and Value of Tisagenlecleucel for Pediatric Patients With Relapsed or Refractory Leukemia.” *JAMA Pediatrics*, American Medical Association, 1 Dec. 2018, jamanetwork.com/journals/jamapediatrics/article-abstract/2704489.



The addressable market for living drugs in oncology could exceed \$200 billion annually¹⁸ as they impact more types of cancer at earlier stages than historically has been the case. Enabled by gene-editing, the applications could extend well beyond oncology, impacting the longevity of human life materially.

Bioinformatics

Health care data is powering these breakthrough biological technologies. With connected and specialized medical devices, patients can contribute longitudinal information on their responses to treatment. In turn, machine learning can enhance the efficiency of R&D, as companies monitor clinical studies, determine best-practices, and tie underlying biology to health outcomes. Against this backdrop, spending on the medical internet of things could approach \$200 billion by 2024.¹⁹

Potential impact on listed equity markets?

ARK believes that the “genomic age” could create trillions of dollars in equity market capitalization by 2024. Advanced molecular diagnostic tests could command tens of billions in annual revenues,²⁰ while connected medical devices generate hundreds of billions,²¹ and living drugs in oncology alone more than \$200 billion.²²

Genomic age technologies should impact drug development pipelines profoundly. Historically, for every drug candidate commercialized, 24 others have failed.²³ If genetically targeted therapies prove more successful than their historical analogues then the economics of drug development will transform dramatically. Just a 10% reduction in the failure rate at each stage of the drug development process, for example, would double the return on drug research and development,²⁴ and if connected devices combined with machine learning are able to move a drug 25% more quickly through the clinical trial process than otherwise would have been the case, returns could triple, as shown in Figure 5.

18 “CRISPR Genome-Editing: Market Opportunity and Key Players” M. Samy, ARK Invest White Paper, August 2018.

19 Markets, Research and. “Global \$200 Billion Internet of Things (IoT) in Healthcare Markets to 2024.” PR Newswire: News Distribution, Targeting and Monitoring, 23 Oct. 2019, www.prnewswire.com/news-releases/global-200-billion-internet-of-things-iot-in-healthcare-markets-to-2024-300944152.html.

20 “Genetic Testing Market Size Will Exceed \$28.5 Bn by 2026.” Global Market Insights, Inc., 26 Feb. 2020, www.gminsights.com/pressrelease/genetic-testing-market.

21 Markets, Research and. “Global \$200 Billion Internet of Things (IoT) in Healthcare Markets to 2024.” PR Newswire: News Distribution, Targeting and Monitoring, 23 Oct. 2019, www.prnewswire.com/news-releases/global-200-billion-internet-of-things-iot-in-healthcare-markets-to-2024-300944152.html.

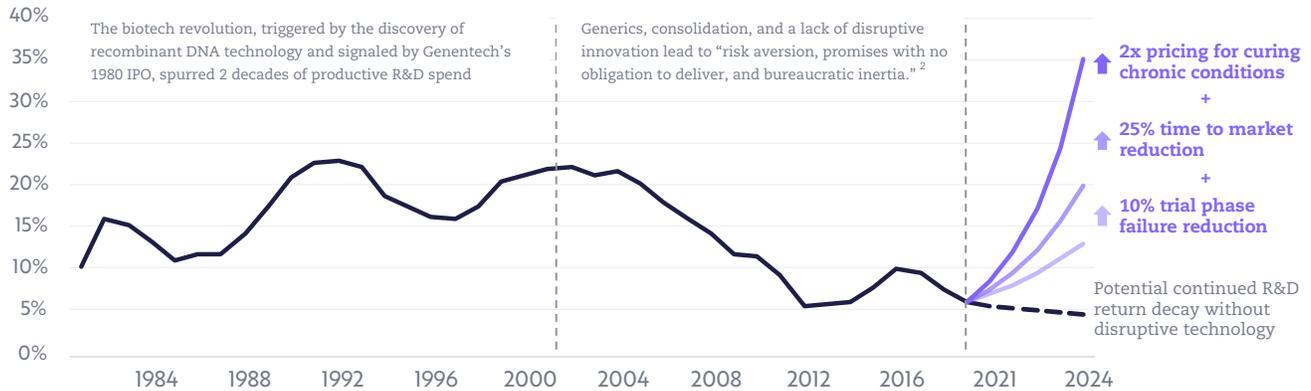
22 “CRISPR Genome-Editing: Market Opportunity and Key Players” M. Samy, ARK Invest White Paper, August 2018.

23 Paul, Steven M., et al. “How to Improve R;D Productivity: the Pharmaceutical Industry’s Grand Challenge.” Nature News, Nature Publishing Group, 19 Feb. 2010, www.nature.com/articles/nrd3078.

24 Inclusive of three pre-clinical stages and three clinical stages.



Figure 5: Pharma and Biotech: Returns on Drug R&D¹ and Potential Trajectories
(5 Year Moving Average)



[1] Returns on Drug R&D = The rate of return, less the risk-free rate, on the R&D dollars spent (inclusive of drug failures) in the years leading up to drug releases and associated present value of earnings in any given year. | [2] Garnier, J-P. 2008. *Rebuilding the R&D Engine in Big Pharma*. Harvard Business Review May 2008.

Source: ARK Investment Management LLC, 2019; Garnier, Jean-Pierre. "Rebuilding the R&D Engine in Big Pharma." Harvard Business Review, 1 Aug. 2014, <https://arkinvst/37JCLlp>. | Forecasts are inherently limited and cannot be relied upon.

The genomic revolution could lead to more effective and efficient health care, longer lives, fewer surgeries, and dramatic value creation. In 2019, publicly listed drug development companies spent \$100 billion on research and development, nearly double the amount spent five years earlier.²⁵ Marginal changes in the return on that investment could add trillions of dollars to the value of enterprises involved in drug development.

While the commercial ramifications of the genomic revolution are likely to be profound, the impact on human health will be even more so. Genomics might be the force behind precision medicine, but the convergence of NGS, AI, and gene-editing could cure disease.

²⁵ Tabulated from 850 publicly listed company reports, ARK Invest estimates that drug manufacturers will have invested \$110 billion in R&D in 2019 up from \$60 billion in 2014.



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