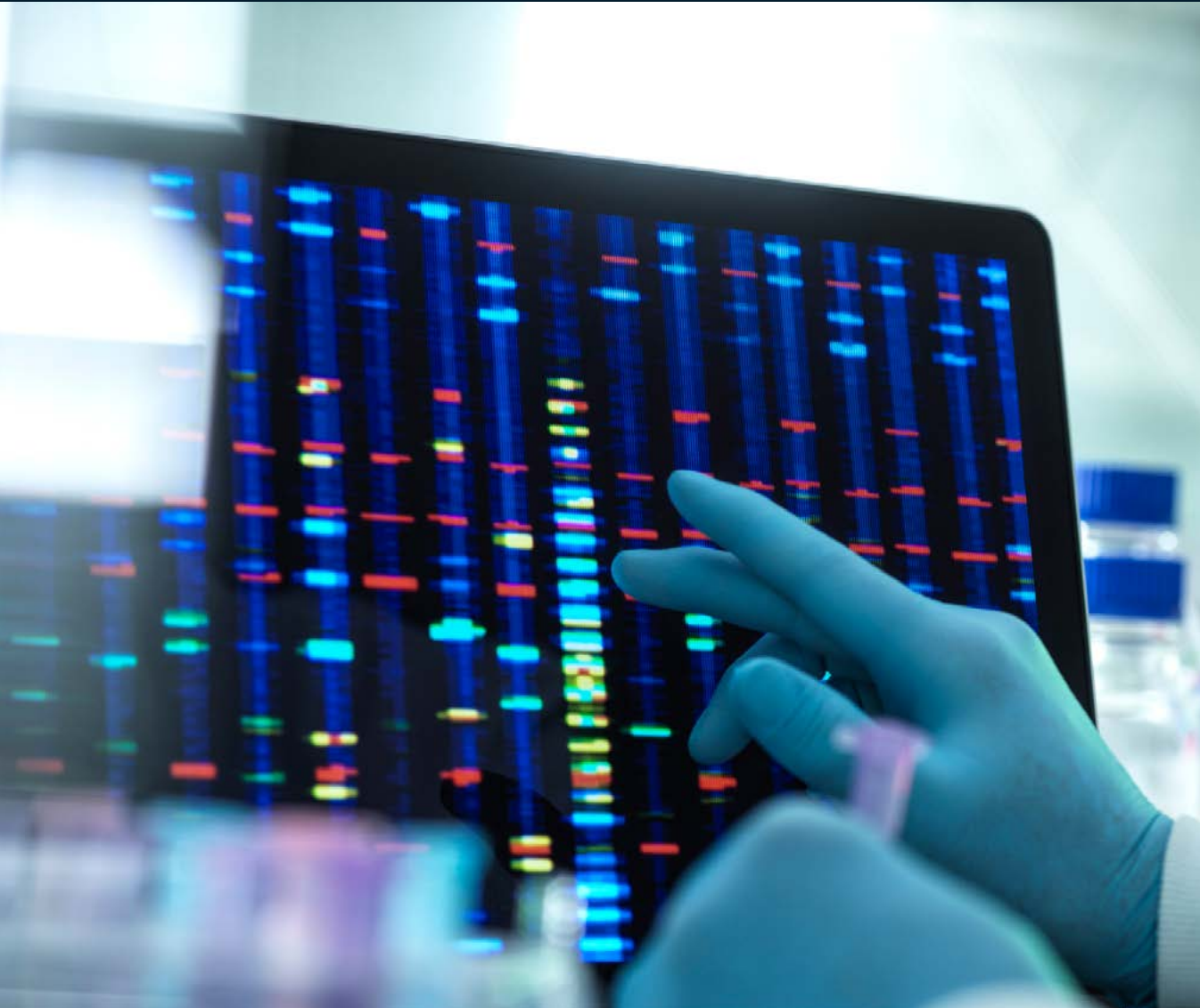




THEMATIC INSIGHTS

The information age of medicine

Genomics-driven innovation
as a catalyst for growth



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The “genomic age” of medicine

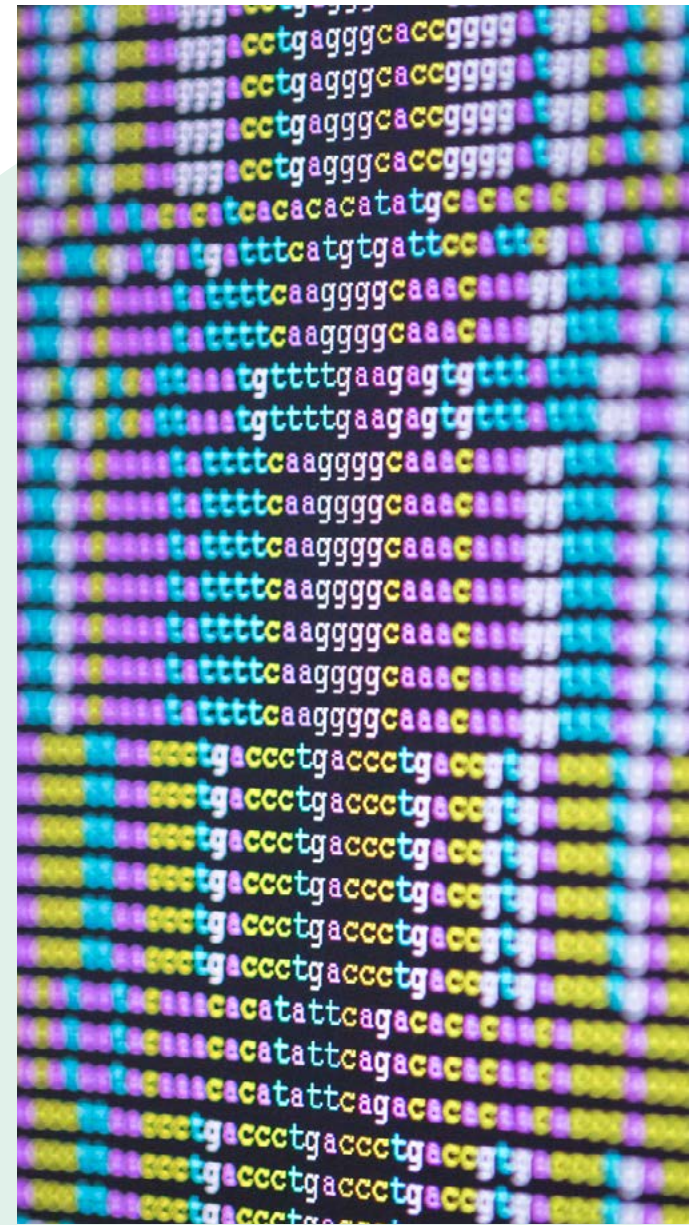
Over the past half-decade, we have passed key inflection points in the ability to access, manipulate, and understand the human body’s fundamental molecular building blocks:

- » The cost to sequence a genome, once a nine-figure nation-state-worthy endeavor, has fallen into the hundreds of dollars.¹
- » It is now possible to edit DNA and deploy that editing ability² against pervasive, chronic disease.
- » For the first time, living therapies³ can be delivered into the body; a one-time dose that potentially may serve as a long-term cure.
- » Bioinformatics⁴ is tying DNA sequence information and therapeutic initiatives to patient outcomes, providing scientists, corporations, and clinicians with an unprecedented understanding of how the body can break down and how it might be mended.

This “genomic age” of medicine carries deep implications for human health and for the companies that might accelerate it becoming reality:

- » Tool providers that enable basic and product research, sharpen diagnostic precision and help guide personalized medicine could see positive inflections in demand.
- » Data that accrues onto diagnostic platforms and informs transformations in how to treat disease may prove durable and valuable.
- » Companies deploying such tools and data to create next-generation treatments and cures could reverse a multi-decade decay in returns on therapeutic research and development.

ARK Invest estimates that, by 2025, hundreds of billion in new revenue will be realized and trillions in new market capitalization may accrue across therapeutic pipelines and enabling tool providers as a result of the transition to this genomic age.⁵



1 <https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost>
 2 <https://en.wikipedia.org/wiki/CRISPR>
 3 <https://www.asgct.org/education/more-resources/gene-and-cell-therapy-faqs>
 4 <https://www.nature.com/articles/527S14a>
 5 <https://ark-invest.com/big-ideas-2020/>

What are the technological platforms catalyzing the genomic age?

Next-Generation DNA Sequencing

The human genome is the human blueprint. The genome's three billion letters determine how homo sapiens grow, live, and thrive. A person's bones, their eyes—the similarities to and differences from every other human—all are compactly encoded in a microscopic, spaghetti-spring molecule. One DNA strand from every human that has ever lived⁶ would weigh less than ten drops of water. Despite its centrality to life, the structure of DNA⁷ and its mechanisms for heredity were unknown until the early 1950s. This discovery launched an intense era of biological inquiry, but it has taken decades for the knowledge of human genetics to translate into clinical practice.

Completed in 2003, the Human Genome Project⁸ was the first systematic attempt at decoding the entire human genome. This global endeavor took over a decade to complete and cost roughly USD 2.7 billion. Today, less than two decades later, a human genome can be sequenced for less than USD 600⁹. ARK Invest has forecast that by 2024, that same sequence might cost less than USD 100.

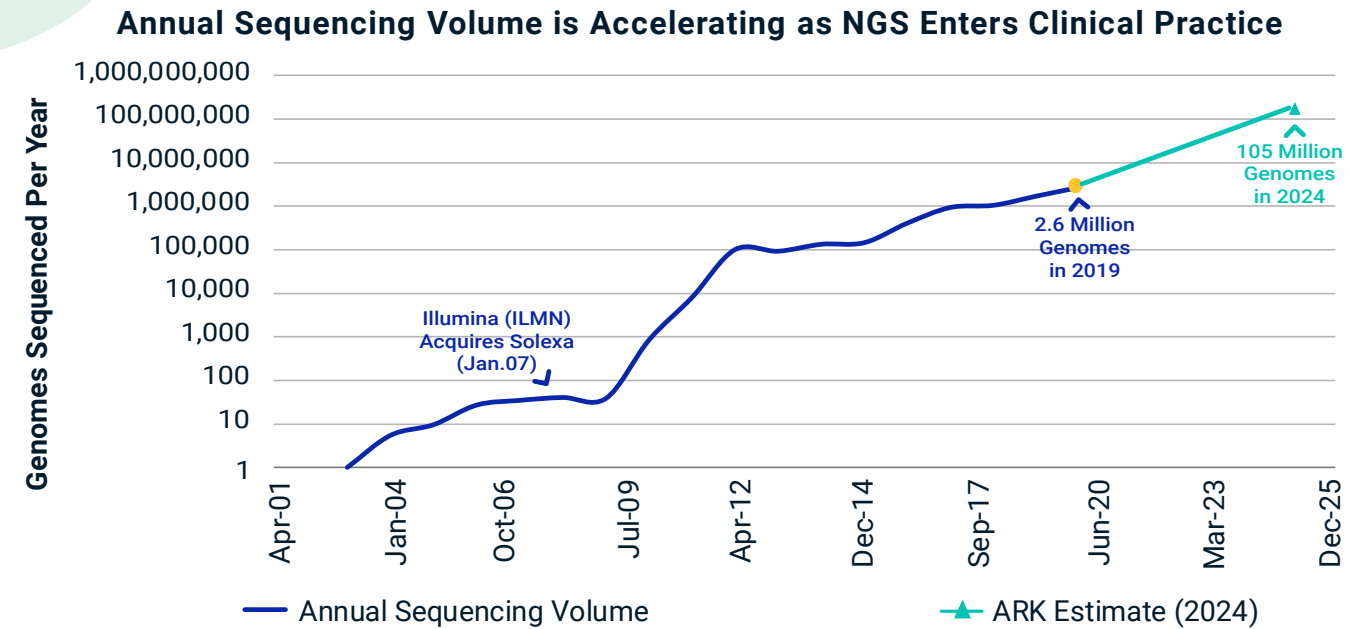
Why are these price levels important? Despite their rapid decline, the high costs of sequencing constrained its use to serving fundamental research. However, below USD 1,000, the unit economic case for the clinical adoption of sequencing becomes arguable. Sequencing-powered diagnostic tests, based on this fundamental research,

are now becoming cheaper and more comprehensive than some competing legacy tests. ARK Invest forecasts that clinical adoption of next generation DNA sequencing (NGS) will drive annual sequencing volumes from ~2.6 million in 2019 to over 100 million in 2024.

- 6 <https://www.prb.org/howmanypeoplehaveeverlivedonearth/>
- 7 <https://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397/>
- 8 <https://www.genome.gov/human-genome-project>
- 9 <https://www.illumina.com/content/dam/illumina-marketing/documents/company/investor-relations/ILMN-Q219-Source-Book.pdf>



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



Source: ARX Invest

*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).

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 be used to diagnose rare inherited disorders in infants, a process that previously might have taken years. Specific germline mutations also can inform new therapeutic options for patients with cancer, such as PARP inhibitors¹⁰ for pancreatic cancer patients.

Oncology is one area currently being profoundly transformed by NGS. Unlike germline mutations, somatic mutations are acquired spontaneously and may

lead to cancer. Clinicians now are able to profile a patient's tumor for the somatic drivers of disease. Once determined and parsed by a machine-learning classifier, the clinically best targeted therapy for a patient can be outlined.

In recent years, scientists have discovered that tumors shed small fragments of mutated DNA into the bloodstream. This facilitates a key advance in cancer care: a liquid biopsy. Such non-invasive blood tests can guide therapy for patients with advanced cancer, monitor patients in remission, and may, it is hoped, be able to detect cancer at an early stage for improved treatment.

Exhibit 2:
Potential clinical applications of genomic sequencing

Undiagnosed patients	Diagnosed patients	Patients in remission
Combined with other electronic healthcare data, genetic information could identify cancer in Stage 1.	NGS enables sophisticated tumor profiling and precision therapies throughout the course of treatment.	NGS can monitor patients in remission noninvasively and frequently to identify recurrences.
Germline Risk Assessment	Somatic Tissue Testing	Recurrence Monitoring via Liquid Biopsy
Patient-Centric Monitoring via Liquid Biopsy	Liquid Biopsy for Advanced Disease	
Less-Invasive Tissue Profiling	Therapy Matching	

It has been forecast, given recent research advances¹¹, a pan-cancer early stage detection test could become commercially available within the next few years. The human-health impact could be profound: if every stage 4 cancer were instead detected in Stages 1, 2 and 3 then US cancer mortality rates might decline by as much as 25%¹¹.

CRISPR Gene Editing

Clustered Regularly Interspaced Short Palindromic Repeats ("CRISPR") genome-editing technology has dramatically accelerated the pace of modern biological and biotechnological research. Thanks to its accessible cost and ease-of-use, CRISPR techniques have democratized the use of genome editing. Many companies now 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.¹²

¹⁰ <https://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, ARX Invest White Paper, May 2019; "Liquid biopsies to detect cancer could boost annual sequencing volume by 40-fold" S. Barnett, ARX Invest White Paper, March 2019 [https://www.annalsofoncology.org/article/S0923-7534\(20\)36058-0/fulltext](https://www.annalsofoncology.org/article/S0923-7534(20)36058-0/fulltext) <https://cebp.aacrjournals.org/content/early/2020/02/25/1055-9965.EPI-19-1366>

¹² "Understanding DNA, the human genome, and the rise of CRISPR" M. Samy, ARX Invest White Paper, August 2018

Gene-editing debuted during the biotechnology boom in the 1980s while CRISPR was discovered through studies of viral invaders and bacterial immune defense systems. As shown in Exhibit 3, the first targeted edit was in a yeast cell during the 1980s.¹³ The major therapeutic breakthroughs associated with gene-editing, however, have only taken place in the past decade. Genome-editing remains a rapidly developing field for 21st century medicine.

Exhibit 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 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 Invest

CRISPR has a wide range of applications, is an accessible technology, and fast to use. While associated primarily with gene-editing today, CRISPR may ultimately be used to control gene processes and protein expression. CRISPR is evolving into a novel platform in the bioengineering space, accelerating innovation in basic research, drug discovery, animal models, drug development, therapeutics, agriculture, diagnostics, data storage, material sciences and others. In medicine, CRISPR's addressable market in the monogenic disease space has been estimated at more than USD 75 billion annually with nearly USD 2 trillion in latent demand from unaddressed populations¹⁴ while monogenic diseases only account for perhaps 2% of all genetic diseases.

¹³ <https://onlinelibrary.wiley.com/doi/full/10.1002/yea.3300>

¹⁴ "CRISPR genome-editing: market opportunity and key players" M. Samy, ARK Invest White Paper, August 2018



Living Drugs

Oncologic therapies have evolved from radical surgery and cauterization to cytotoxic chemotherapy and now towards personalized medicine by way of targeted and living therapies. Biologic therapies are treatments that use material made from living organisms to treat disease. “Living drugs” harness the body’s biological production processes to propagate and sustain a therapy. Though they have become known for their success against cancer, these treatment strategies likely will be deployed against a panoply of serious disorders.

To date only six such living drugs have been approved for clinical use,¹⁵ but there are hundreds in research and development pipelines.¹⁶ The human health impact of these treatments could prove profound.

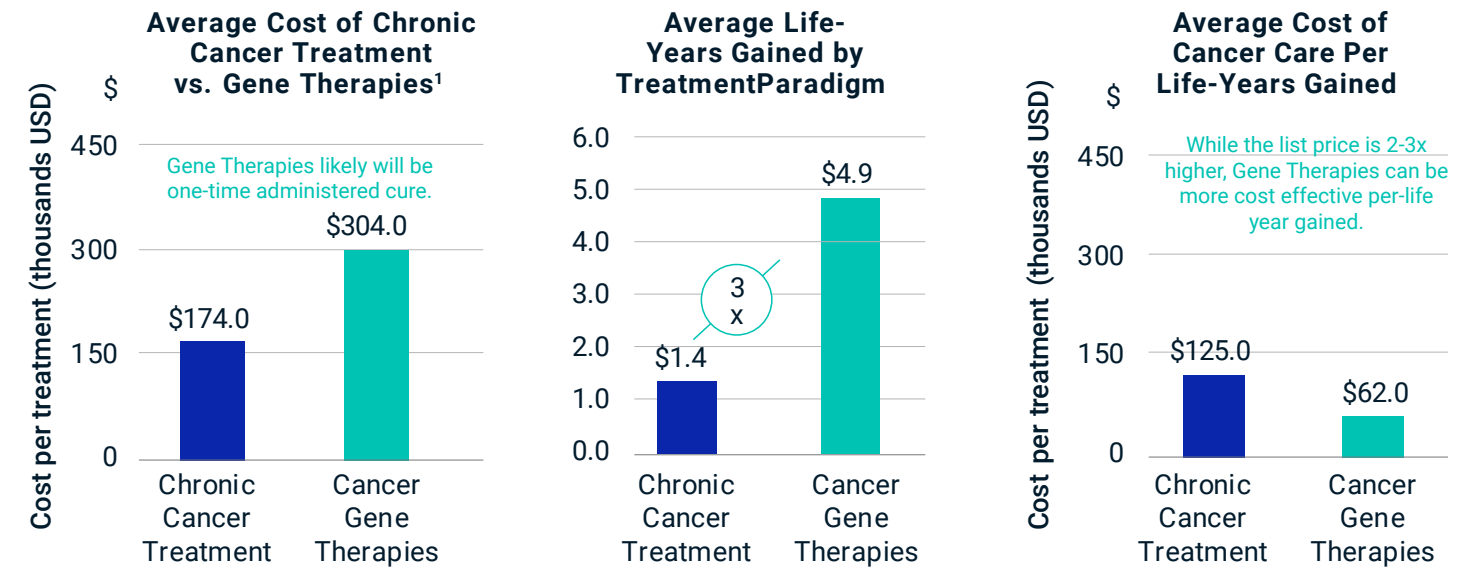
As might be expected for therapies that seem to serve as effective cures, living drugs such as CAR-T cell therapies

currently command premium pricing. Compared to other recently approved cancer treatments, these gene therapies carry sticker prices almost 2x higher. Accounting for the life-extension that the therapies provide, however, can be used to justify even the expense of initial pricing. As measured on a dollars-spent-per-life-year-saved basis Kymriah, a living drug targeting blood cancer, was one of the cheapest cancer therapies released in the US over the past two decades despite carrying a price tag exceeding USD 400,000.¹⁷

The addressable market for living drugs within oncology has been forecasted to exceed USD 200 billion annually¹⁸ as the safety profiles of these therapies become more refined, and they are used at an earlier stage and across a broader range of cancer types. The applications of this type of therapy, enabled by gene editing technology, are not limited to oncology and hence could have a material impact on longevity curves.

¹⁵ <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>
¹⁶ <https://clinicaltrials.gov/ct2/results?cond=cellular+and+gene+therapies&term=&cntry=&state=&city=&dist=>
¹⁷ For example <https://jamanetwork.com/journals/jamapediatrics/article-abstract/2704489>
¹⁸ “CRISPR genome-editing: market opportunity and key players” M. Samy, ARK Invest White Paper, August 2018

Exhibit 4:
Cost-effectiveness analysis for gene therapies – an example



¹ Chronic cancer treatments include treatments approved 2014 to 2019. 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,Alizera,et.al>.
 “Development and Clinical Translation of Approved Gene Therapy Products for Gene Disorders.” Frontiers, Frontiers, Aug 2019, <https://arkinv.st/39MZ0xg>

Bioinformatics

These new biological technologies rely upon the ability to aggregate and make sense of disparate healthcare data. Longitudinal information about patient health following treatment can now be collected via personal connected devices, and specialized medical devices are increasingly designed to transmit data back to clinicians to allow for more nuanced monitoring of patient well-being. These data, when mined for insights using machine learning, can enhance R&D efficiency throughout therapy development, helping to better monitor clinical studies, more precisely determine the efficacy of trial treatments, and better establish treatment best-practices for treatments already in the field. When combined with the quantity of genomic data likely to enter the healthcare ecosystem, these real-time monitors could more closely tie the underlying biology to the health outcome experienced. Against this backdrop, the medical internet of things is expected to approach USD 200 billion in spend by 2024¹⁹.

¹⁹ <https://www.prnewswire.com/news-releases/global-200-billion-internet-of-things-iot-in-healthcare-markets-to-2024-300944152.html>

How might these advances relate to listed equity markets?

ARK forecasts that these “genomic age” technologies could lead to USD trillions in market capitalization accrual by 2024, with advanced genetic diagnostic tests likely to command tens of billions of annual revenues,²⁰ hundreds of billions likely to be spent on connected medical devices,²¹ and within oncology alone living drugs potentially generating in excess of USD 200 billion in annual revenue.²² The greatest impact of genomic age technologies, however, will likely be realized within drug development pipelines.

Historically for every commercialized drug, 24 other candidates fail along the way.²³ If genetically targeted therapies prove more likely to succeed than their historical analogues then the economics of drug development can dramatically transform. A 10% reduction in the odds of a failure at each stage of the drug development process would lead to a doubling on the return on drug research and development spend²⁴.

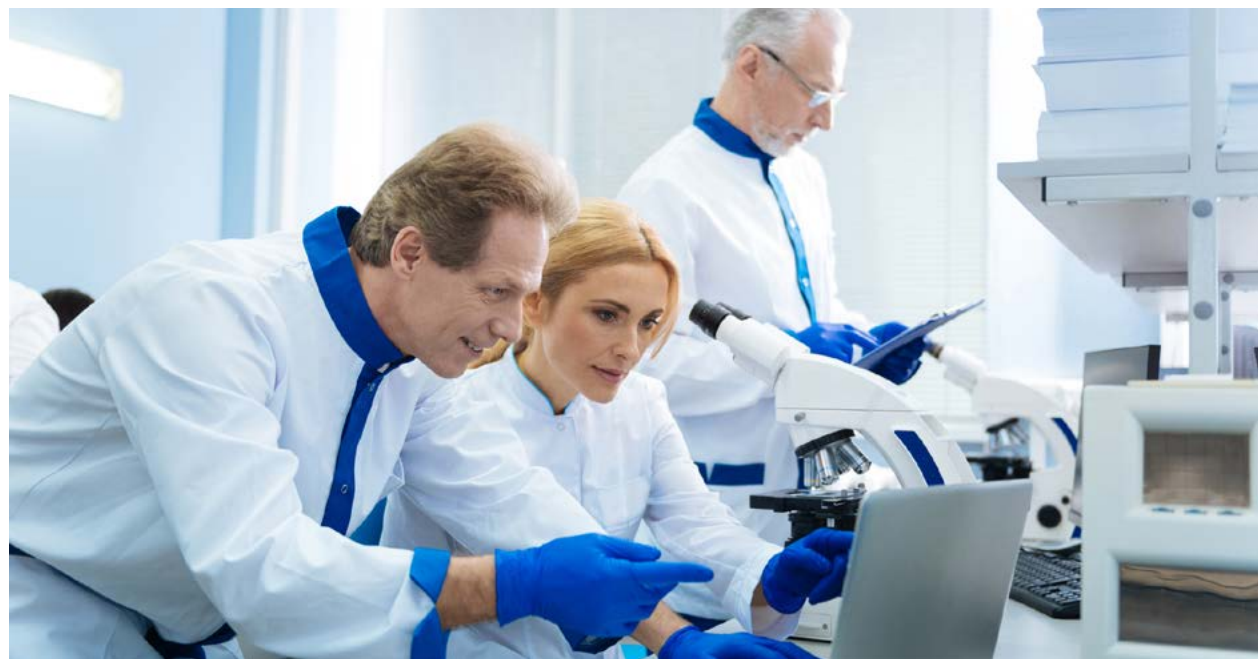
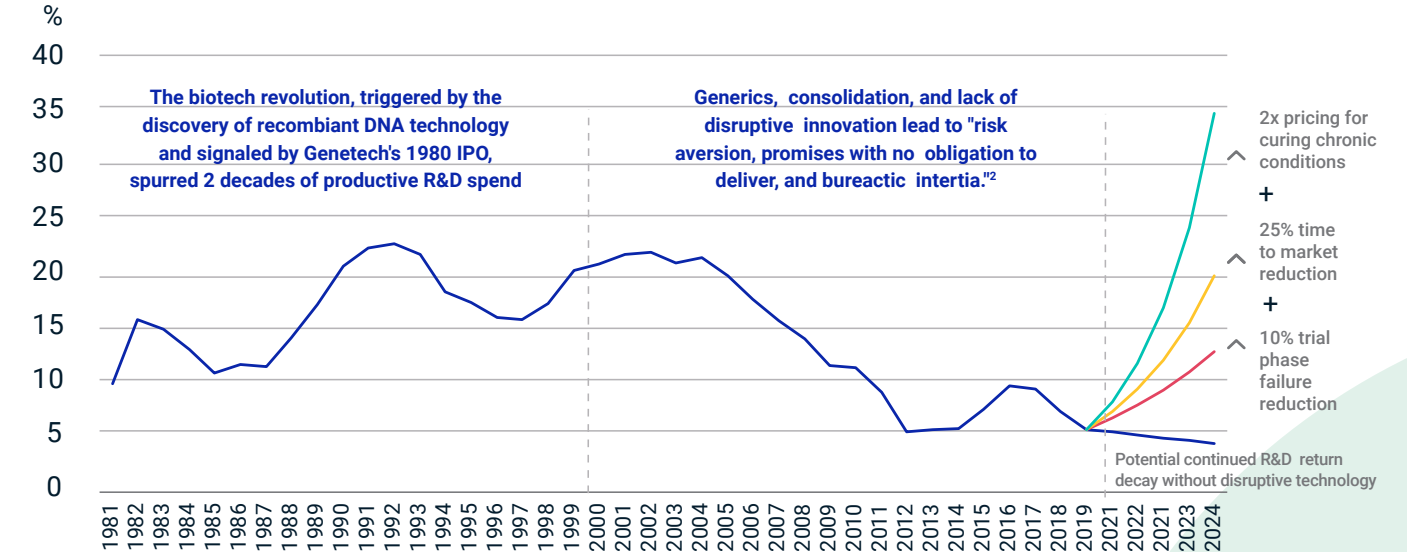


Exhibit 5: Returns on drug research and development

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 earning 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://arkinv.st/37JCLp>

If the use of connected devices combined with machine learning allows a drug to move 25% more quickly through the clinical trial process, returns could roughly triple.

The result could be more efficacious treatments, longer lives, avoided surgeries and the displacement of legacy therapies as well as dramatic value creation. In 2019, annual research and development spend by publicly listed drug development companies exceeded USD 100 billion and has almost doubled over the past 5 years²⁵. A marginal change in the return on those tens of billions being invested annually could yield USD trillions in enterprise value creation.

As should be clear, the commercial implications are profound and the human health implications perhaps more so. Genomics is the motive force behind the era of

precision medicine. The convergence of NGS, AI, and gene editing is critical in order that for the first time, diseases will be cured, not merely managed.

20 <https://www.gminsights.com/pressrelease/genetic-testing-market>
 21 <https://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 <https://www.nature.com/articles/nrd3078>
 24 Inclusive of 3 pre-clinical stages and 3 clinical stages.
 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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