Fiera Apex: Our approach to biotech investing

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Healthcare remains one of the largest and fastest-growing sectors in the U.S. economy. We see the sector's prolific innovation, resilient demand, and support from long-term demographic trends and fundamentals as providing long-term drivers for continued growth.

National health expenditures are projected to continue outpacing average Gross Domestic Product (GDP) growth, accounting for 17.3% of the economy in 2022 and expected to reach 19.6% of GDP in 2031.[1] Driven by accelerating scientific discovery and innovation, combined with macro tailwinds, healthcare – and biopharma (i.e., biotechnology and pharmaceuticals) in particular – has emerged as one of the decade's most attractive and successful investment areas. Since 2015, the proportion by market cap of biopharma names in the Russell 2500 Growth Index[2] has grown from 8% to almost 12% in 2024, making it one of the largest Industry groupings within the index. The increasing presence and outstanding returns makes ignoring biopharma increasingly difficult, particularly for active strategies benchmarked against the index. However, the prevalence of binary outcomes in this industry provokes a need for a thoughtful approach to identifying investments and minimizing risk. The Fiera Apex team's investment process is attuned to navigate exactly this scenario, identifying the top-down secular trends providing tailwinds to growth in combination with bottom-up fundamental research to qualify buy candidates.

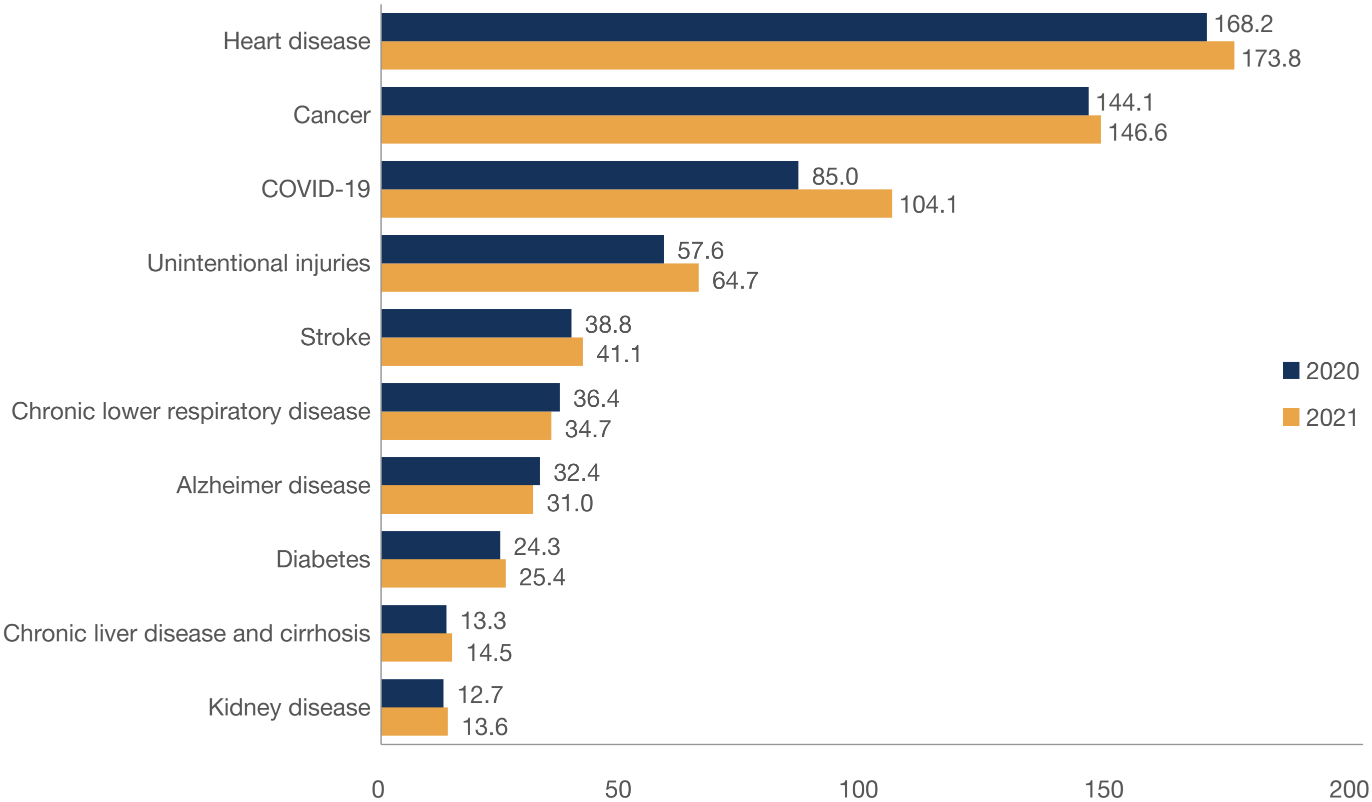
As of March 30, 2024 unless otherwise stated.

Key secular trends

A long runway for medical and technological innovation provides opportunities for durable, secular growth. The latest version of the International Statistical Classification of Diseases and Related Health Problems has about 85,000 listings.[3] However, current the Food and Drug Administration (FDA) approved therapies address only a fraction of these conditions, reflecting a vast field of unmet medical needs. Looking ahead, we believe progress in drug discovery, diagnostics, devices, IT, and services will help improve prevention, identification, and treatment, while also resulting in lower costs wider access to care. Some themes we view as particularly key to strong secular growth include:

Solving unmet medical needs. Molecular and protein therapeutics have provided solutions that have reined in epidemics, such as HIV and COVID-19, and transformed the course of chronic diseases, such as cystic fibrosis and rheumatoid arthritis, drastically improving and extending patients' lives. Recently, newer modalities, such as cell and gene therapy, have cleared roads to novel medicines with curative potential. Supported by the integration of genomic data and bioinformatics, we believe progress will continue to accelerate, with a strong likelihood of near-term breakthroughs of blockbuster potential across the spectrum of human health, from the leading causes of death (Chart 1), to the rarest orphan indications (Chart 2).

Chart 1: Leading causes of death per 100,000 U.S. standard population



Source: NCHS, National Vital Statistics System, Mortality (December 2022). For more information please see the disclosures on the last page.

A demographic tailwind: healthcare demands will grow as the population skews older. As the Baby Boomer generation ages into retirement, the proportion of people in the United States aged 65 and older is projected to increase from 17% in 2022 to about 22% in 2035.[4] Meanwhile, Medicare spending is also expected to continue accelerating, reaching an average of 7.8% growth per year between 2025 and 2031, the fastest rate among the major payers.[5]

- Payer spending for polychronics (having >2 chronic conditions) is 5 times greater than those with no chronic conditions; 70% of people over the age of 65 are polychronic.[6]

Advances in health technology will support system efficiency, rein in costs, and increase access to care.

- With the cracking of the human genetic code, combined with evolving high-density data processing systems for testing and analysis, the surge in scientific progress has been – and should continue to be – exponential, propelling significant improvements across healthcare subsectors. Drug development has become faster and more precise, and the newer class of gene-based therapies have just begun to introduce some of the first potential cures for previously intractable conditions.

Chart 2: Orphan diseases

Over **7000** rare diseases identified

Rare disease affects more than **350 million people** worldwide

Approximately **30%** of children with these dibilitating diseases will not live to see their 5th birthday

Approximately **80**% of rare diseases are genetic

Only **5%** of rare diseases have an FDA approved drug

50% of people affected by rare disease are children

Source: FDA, October 2017.

- Life science technologies are integrating Artificial Intelligence and Machine Learning capabilities to process immense amounts of molecular and genomic data, paving the way to a deeper understanding of biology, better treatment decisions, and a new wave of medicines.
- Digital health and data could also drive a greater emphasis on preventative strategies to support healthy aging, as well as reduce inefficiencies and associated wasted costs that accumulate throughout the continuum of care.
- Additional opportunities exist in solutions to organize administrative and operative processes, as well as bring care to more people through remote monitoring and medical services.

The goal is early, accurate, and rapid disease identification in inexpensive and minimally invasive ways, while also determining some of the most successful routes of care, avoiding extra costs associated with misdiagnoses and incorrect treatment decisions, and ultimately improving health.

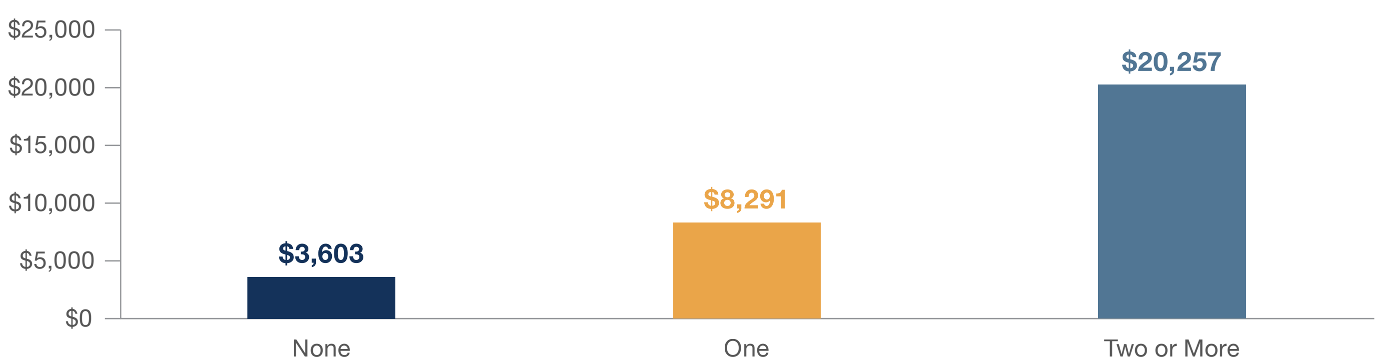
Outlook for biopharma

Biopharma's positive fundamentals, bolstered by a constructive backdrop of innovation, regulatory tailwinds, and expanding access, should continue to fuel sector performance. Driven by rapid and dynamic advances in medicine and technology, we continue to view healthcare as holding some of the greatest potential for outsized returns. Current understanding of biology is just scratching the surface, and regulatory agencies are catching up with the speed of innovation, approving new medicines and technologies with increasing efficiency. Meanwhile, the complex payor environment is slowly becoming less burdened, bringing access to more people. Scientific breakthroughs have changed lives and facilitated dozens of multi-billion-dollar franchises and acquisitions. We believe innovation at all levels will drive market returns and rotation into the sector for years to come.

We aim to build our strategy to participate in the growth of the industry while seeking to minimize downside risk. Biopharma is largely an emerging growth industry, driven by powerful and persistent fundamental trends. However, we recognize the potential for risk when investing in the space. Across healthcare, we take a diversified approach, balancing emerging growth names, such as early biopharma companies, with stable growth names, including more mature and defensive companies across life science tools, technology, and services. From a bottom-up perspective, we believe a deep understanding of the science behind each company is key to unlocking investment insights and finding resilience and growth. We seek companies with some of the strongest science and durable competitive advantages, with businesses that solve problems in healthcare, whether by reducing costs, enhancing efficiency, and/or improving patient outcomes. We evaluate investment opportunities with vigorous, comprehensive research, conducting analysis at the scientific, financial, and market levels, as well as speaking to management teams and independent experts in the sector. Incorporating top-down research, we also assess macro drivers such as landscape evolution, policy updates, regulatory changes, and the capital markets environment, to assess overall probabilities of success.

Growth and good data are important. Following our thematic framework, we take a longer-term oriented investment approach, guided by catalyst-driven progress that aims to navigate short-term market volatility. Industry growth within the index, as well as the potential for strong performance, may present significant investment opportunities, with potential alpha coming from strategic fundamental research, sector allocation, and stock selection.

Spending per person by number of chronic conditions



Source: HCCI 2017 Health Care Cost and Utilization Report (February 2019).

Investment example – Karuna Therapeutics

To evaluate the investment opportunity for Karuna Therapeutics, we performed a deep assessment of the company's investigational assets and corresponding market potential. Based in Boston and founded in 2009, Karuna focused on developing therapies to treat neurological disorders of high unmet need.

Assessing the science. We take a comprehensive approach to evaluating a company's development platform, which we view as the foundation of a successful biopharma company. For any compound in development, we study the science behind it to determine how it works, what other effects it might have (e.g., potential interactions, off-target effects), and how successful it may be. Karuna's lead asset, KarXT, was a novel, investigational medicine for schizophrenia, a disease that remains difficult to treat. Current drugs are only effective in some patients and only ameliorate psychosis (i.e., positive symptoms, such as delusions and hallucinations), while also coming with serious side effects such as weight gain, sedation, and cardiometabolic dysfunction. For our research, we reviewed all available basic and clinical literature, including using chemical databases to study its molecular structure and scrutinizing publications in scientific journals and conference presentations. Based on KarXT's differentiated mechanism, we saw the potential for improved efficacy on positive symptoms, but also on negative symptoms (depression, apathy) and cognitive function (memory, attention), while maintaining a benign side effect profile. We spoke with independent experts to understand the unmet need and gain confidence on the commercial side. We concluded that KarXT was one of the highest quality, de-risked assets in the industry and was poised to become the key to unlocking indication and platform upside for the company.

Assessing the value. For smaller, pre- positive cash flow biopharma companies such as Karuna, we use an adjusted "Sum of the Parts" analysis to determine the fair value of the stock. Based on extensive research and a detailed analysis of the competitive landscape, we built a forward-looking predictive model incorporating our estimates of the potential market size and the probabilities of success for each product. Milestones that the company would be expected to hit were clearly defined and tracked in order to validate our assumptions and thesis on an on-going basis.

Endnotes

Sources accessed February 2020

1. CMS Office of the Actuary
2. The Russell 2500™ Growth Index measures the performance of the small to mid-cap growth segment of the U.S. equity universe.
3. World Health Organization
4. United States Census Bureau
5. Centers for Medicare
6. William Blair & Co.

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Strategy Risks: The following risks may be inherent in the funds and strategies mentioned on these pages.

Equity risk: the risk that the value of stock may decline rapidly for issuer- related or other reasons and can remain low indefinitely. **Market risk:** the risk that the market value of a security may move up or down, sometimes rapidly and unpredictably, based upon a change in market or economic conditions. **Liquidity risk:** the risk that the strategy may be unable to find a buyer for its investments when it seeks to sell them. **General risk:** any investment that has the possibility for profits also has the possibility of losses, including loss of principal. **ESG and Sustainability risk:** ESG and sustainability risk may result in a material negative impact on the value of an investment and performance of the portfolio. **Geographic concentration risk:** geographic concentration risk may result in performance being more strongly affected by any social, political, economic, environmental or market conditions affecting those countries or regions in which the portfolio’s assets are concentrated. **Investment portfolio risk:** investing in portfolios involves certain risks an investor would not face if investing in markets directly. **Operational risk:** operational risk may cause losses as a result of incidents caused by people, systems, and/or processes.

Chronic condition is a health condition or disease that is persistent or otherwise long-lasting in its effects or a disease that comes with time. The term chronic is often applied when the course of the disease lasts for more than three months.

Alpha is a term used in investing to describe an investment strategy’s ability to beat the market/benchmark.

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