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A prescription for healthcare investing

Leveraging data and technology to modernize healthcare investing

MKTGH0723E/S-3026673-1/15

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Summary

- Biomedicine is at an inflection point. Rapid advances in technology are transforming patient care, easing the burden of disease, and generating potentially compelling new opportunities for investors.
- However, risks in therapeutic development — high cost, long duration and high failure rates — translate to challenges in healthcare investing. We believe a data-driven approach is ideally suited to address those challenges.
- The binary nature and low probabilities of clinical trial success suggest that investment selection in healthcare is paramount, and diversification is even more critical in healthcare investing than in other sectors.
- We propose enhancing a traditional approach to healthcare investing by leveraging data science to integrate insights from domain-specific experts into a scalable process. Our approach seeks to identify investment opportunities, construct portfolios and manage risks — helping to finance the next generation of healthcare innovation while striving to deliver positive outcomes for both patients and investors.

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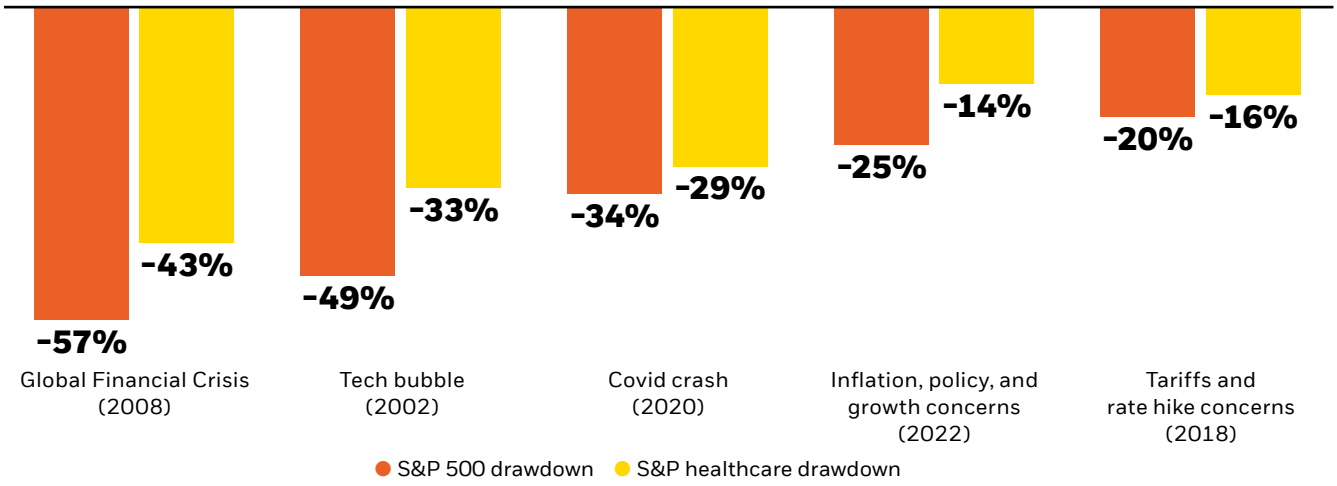
Biomedicine is at an inflection point

When discussing cancer treatments, oncologists rarely use the word "cure." Cancers often mutate and adapt, and patients that are initially treated successfully can relapse months or years later. But today's oncologists — and researchers in many other diseases — are now using the word "cure" more often, thanks to advances in computation, genomics, immunology, and precision medical technologies. In fact, experts observe that we're experiencing an inflection point in biomedicine — a truly exceptional period in history where breakthroughs in biology, medicine, and technology are converging to save lives and ease the burden of disease. Perhaps the most obvious illustration is the rapid development and deployment of effective COVID-19 vaccines and treatments in the face of one of the deadliest pandemics in human history. The tailwinds of the global pandemic which drove innovations in life science ecosystems are expected to continue to drive future growth and create compelling new investment opportunities.

A consequence of this convergence is that healthcare has become one of the most important and fastest growing sectors of the global economy. Global healthcare spending has more than doubled in real terms over the past 20 years, reaching US$8.5 trillion in 2019, the equivalent of 9.8% of global GDP.[1] This growth reflects the tremendous economic opportunities created by biomedical innovation. In 2021, there were more IPOs in the life sciences space than technology, and private equity markets saw record healthcare deal volume along with a record number of healthcare-focused funds raised.[2] Additionally, healthcare investing is also a direct example of "doing well by doing good," offering a potentially compelling option for investors who seek positive financial outcomes while also benefitting society.

One attractive feature of healthcare investing is the breadth of subsectors: the healthcare sector comprises payers and distributors (e.g., insurance companies), facilities and services (e.g., hospitals), life sciences tools and services, diagnostics, medical devices, pharmaceuticals and biotechnology. The diversity of business models and fundamentals, coupled with healthcare's relatively inelastic demand, characterize a sector that tends to be less correlated with broader economic cycles and less sensitive to macroeconomic factors. Healthcare is among the most "recession-proof" sectors because patients need to be treated regardless of whether business conditions are good or bad. As shown in Figure 1, the healthcare sector has historically been among the most resilient sectors in both late cycle and recessionary periods, providing a potentially compelling source of diversification in the context of a broader portfolio.

Figure 1: Comparing the drawdowns in healthcare vs. broader market



Source: Bloomberg. Drawdown periods reflect the five worst drawdowns in the S&P 500 Index over the 30-year period between January 1, 1993 and December 31, 2022, and the corresponding performance over the same time period of the S&P Healthcare Index. Index performance does not reflect any management fees, transaction costs or expenses. Indexes are unmanaged and one cannot invest directly in an index. Past performance does not guarantee future results.

1 World Health Organization. "Global Expenditure on Health: Public Spending on the Rise?," December 15, 2021. https://www.who.int/publications/i/item/9789240041219.
2 Source: BlackRock and CB Insights as of October 31, 2022.

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Despite favorable fundamentals and a rich opportunity set, healthcare investing has traditionally been the domain of a relatively small community of sector-specific specialists. Three factors — high cost, long duration, and high failure rates — make therapeutic development challenging, limiting the amount of capital available to this sector, depriving non-specialist investors of attractive opportunities for return and diversification, and slowing the development of new life-saving treatments for patients. Most healthcare investors rely on a traditional fundamental approach, leveraging key opinion leaders and their own scientific assessment to determine a company's attractiveness.[3] This manual process can mean that the coverage area is narrow, scale is harder to achieve, reaction times are slower, and insights can be subject to human bias.

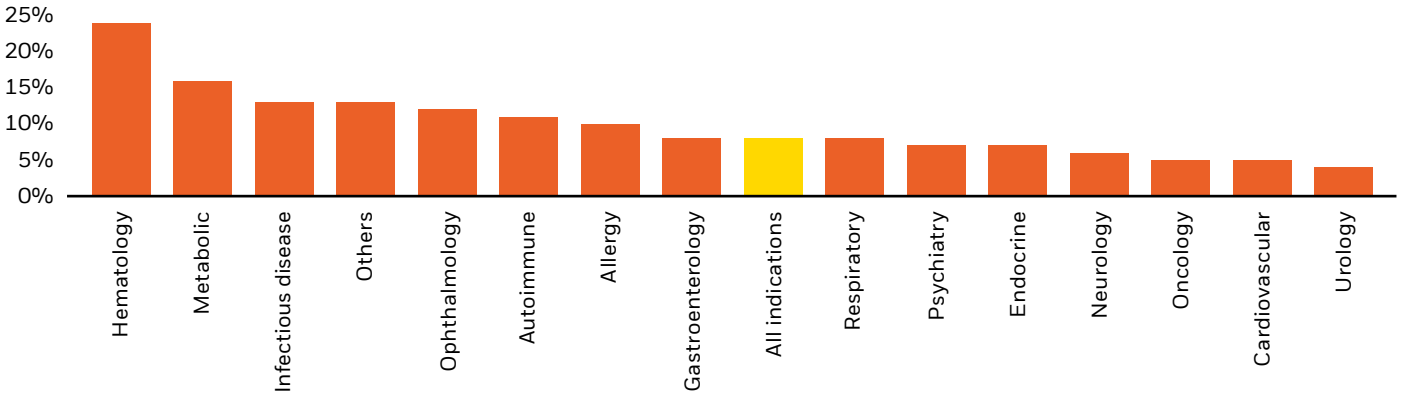
We believe that leveraging data science can transform healthcare investing by codifying the insights of domain-specific experts into a modern, scalable investment process. In this article, we introduce a data-driven investment framework that combines expert scientific insights with robust portfolio construction techniques that seek to better select the most promising treatments and provide greater diversification potential. Thanks to recent advances in artificial intelligence, data science, and computing power, tasks that were previously best accomplished manually — such as estimating probabilities of clinical success, conducting scientific literature reviews, and performing discounted cash flow analyses — can now be automated to a significant degree and systematically applied to thousands of drugs, clinical trials, and therapeutic areas. We believe these advances are poised to provide an unprecedented level of access and transparency to a wider spectrum of investors, attract greater amounts of capital to this important sector, and lead to even more breakthroughs for patients in need — all while delivering potentially compelling returns to investors.

A specific set of risks

Although healthcare presents a potentially compelling set of opportunities for investors, it is not without risk. There are challenges and attributes specific to this sector, some of which are directly related to the life-saving nature of biomedical innovation.

By its very nature, healthcare investments tend to have binary outcomes: either a drug is safe and effective or it's not; there is rarely any middle ground. Given the rigorous safety standards to which therapeutics are held, the likelihood of success for a new therapeutic has historically been quite low across the industry, with fewer than 10% of therapies ultimately receiving approval.[4] Certain sectors have even lower approval rates: the historical success rate of a cancer drug from early clinical trials through final approval is only 5.3%.[4] Exacerbating the investment challenge is the often-unappreciated correlation between these clinical trials: outcomes are not necessarily independent, and without proper risk management, the innate correlations can compound the high level of risk already present when investing in clinical-stage biotech companies.[5]

Figure 2: Overall likelihood of approval from phase 1 by disease area



Source: Clinical Development Success Rates and Contributing Factors 2011-2020. Authors: Biotechnology Innovation Organization (BIO), PharmaIntelligence, QLS Advisors. Data covers individual drug program phase transitions from January 1, 2011 to November 30, 2020.

3 Source: BlackRock, QLS, as of March 2023. **4** BIO, Informa Pharma Intelligence, QLS Advisors. "Clinical Development Success Rates and Contributing Factors 2011-2020," Feb. 2021. Available at https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_ga=2.47898913.722379450.1679511745-574711257.1679511744. **5** Risk management seeks to mitigate, but cannot eliminate, risk nor does it imply low risk.

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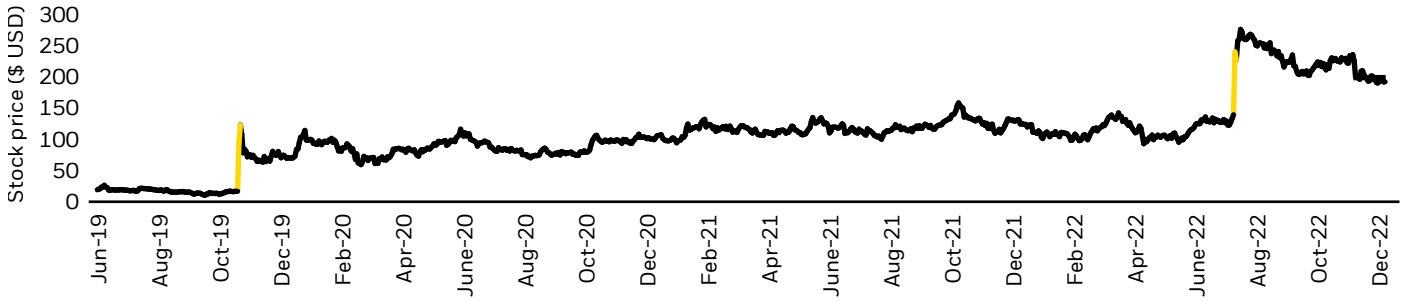
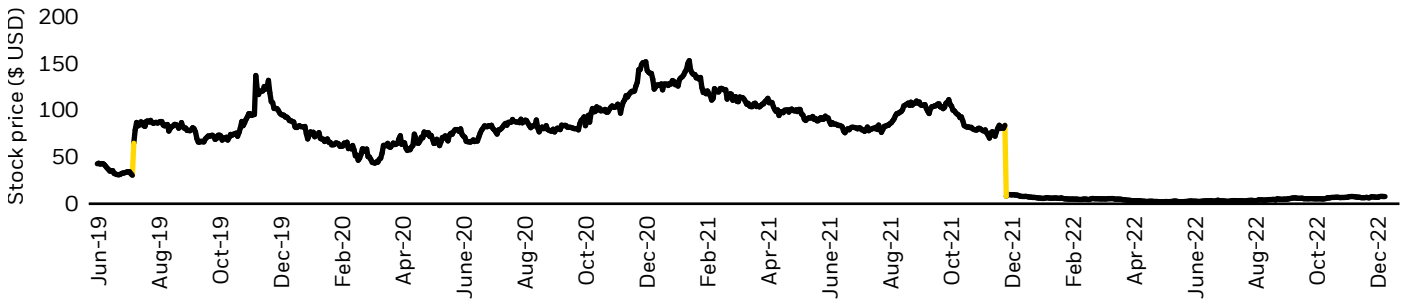
As a result, the financial risks associated with an investment in a clinical trial tend to be binary as well — a trial either succeeds or fails, and stock prices tend to experience significant moves in response to such news. Therefore, a clinical-stage biopharma company faces significant event risk on a regular basis. Figure 3 provides two recent examples: Karuna Therapeutics and Allakos.[6] Since going public in June 2019, Karuna Therapeutics has experienced two significant one-day stock price jumps in response to positive clinical trial results: first, a +443% jump on November 18, 2019 in response to encouraging results from the phase 2 clinical trial of its lead investigational therapy, KarXT, in patients with schizophrenia,[7] followed by a +72% jump on August 8, 2022 in response to positive topline results from its phase 3 EMERGENT-2 trial on the same therapy.[8] Allakos has similarly experienced two significant 1-day moves, first a +111% jump on August 5, 2019 after the announcement of positive results from its phase 2 trial of lirentelimab (AK002),[9] followed by a 1-day decline of 90% on December 22, 2021 after the announcement that the phase 3 and phase 2/3 clinical trials on the same drug failed to meet certain endpoints.[10]

Figure 3a: Historical stock price of Karuna Therapeutics



Source: Bloomberg, as of December 31, 2022. The 1-day jumps in stock price on November 18, 2019 and August 8, 2022 were each in response to positive clinical trial data. Karuna Therapeutics was selected from the ICE Biotech Index universe to show the magnitude of possible stock price moves that can occur in response to clinical trial data releases: it is the company with the largest 1-day relative price appreciation as of December 31, 2022. Past performance does not guarantee future results. Reference to the names of each company mentioned in this communication is for illustrative purposes only to explain the market environment and should not be construed as investment advice or an investment recommendation of those companies.

Figure 3b: Historical stock price of Allakos, Inc.



Source: Bloomberg, as of December 31, 2022. The 1-day jumps in stock price on August 5, 2019 and December 22, 2021 were in response to positive and negative clinical trial results, respectively. Allakos was selected from the ICE Biotech Index universe to show the magnitude of possible stock price moves that can occur in response to clinical trial data releases: it is the company with the largest 1-day relative price depreciation as of December 31, 2022. Past performance does not guarantee future results. Reference to the names of each company mentioned in this communication is for illustrative purposes only to explain the market environment and should not be construed as investment advice or an investment recommendation of those companies.

6 Reference of the company names mentioned in this paper is for illustrative purposes only and should not be construed as investment advice or investment recommendation of the company. **7** Karuna Therapeutics. "Karuna Therapeutics Announces KarXT Met Primary Endpoint in Phase 2 Clinical Trial of Acute Psychosis in Patients with Schizophrenia | Karuna Therapeutics," n.d. https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-announces-karxt-met-primary-endpoint-phase-2. **8** Karuna Therapeutics. "Karuna Therapeutics Announces Positive Results from Phase 3 EMERGENT-2 Trial of KarXT in Schizophrenia | Karuna Therapeutics," n.d. https://investors.karunatx.com/node/8656/pdf. **9** Allakos. "Allakos Announces AK002 Met All Prespecified Primary and Secondary Endpoints in Phase 2 Randomized, Double-Blind, Placebo-Controlled Study in Patients with Eosinophilic Gastritis (EG) and/or Eosinophilic Gastroenteritis (EGE) | Allakos," n.d. https://investor.allakos.com/news-releases/news-release-details/allakos-announces-ak002-met-all-prespecified-primary-and. **10** Allakos. "Allakos Announces Topline Phase 3 Data from the ENIGMA 2 Study and Phase 2/3 Data from the KRYPTOS Study in Patients with Eosinophilic Gastrointestinal Diseases | Allakos," n.d. https://investor.allakos.com/news-releases/news-release-details/allakos-announces-topline-phase-3-data-enigma-2-study-and-phase.

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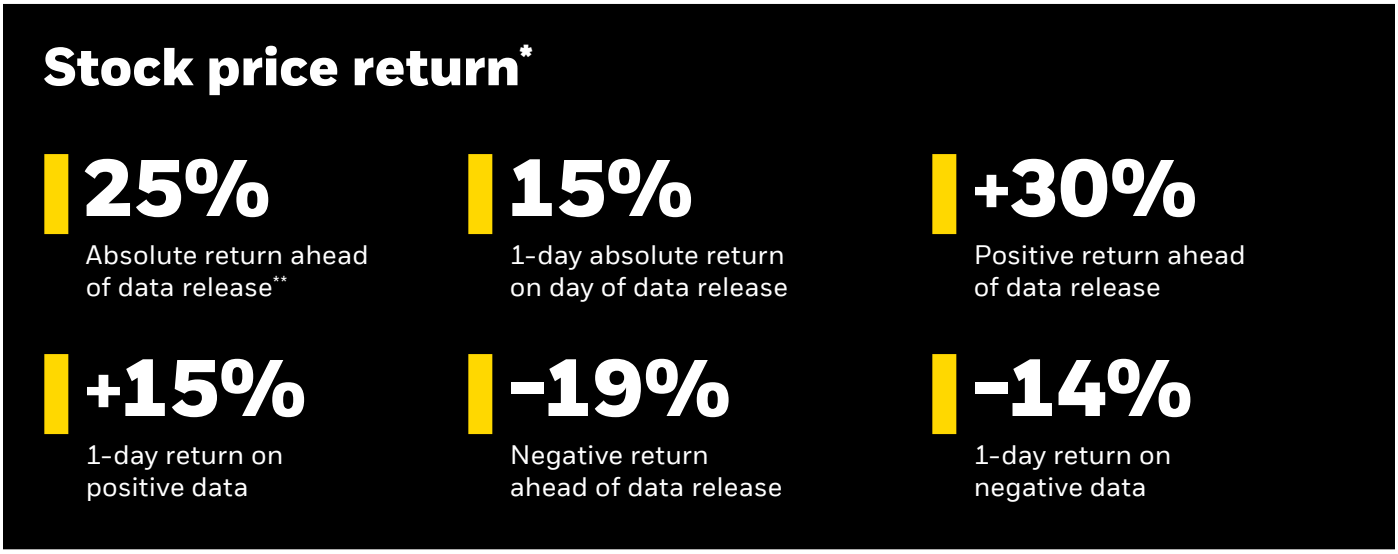
While most publicly traded equities may experience such dramatic volatility on occasion, for clinical-stage therapeutics companies this is the norm rather than the exception (see Figure 4).

Figure 4: Average stock price return in anticipation and response to clinical trial outcomes



Source: QLS. * Stock price return of all public healthcare companies which had phase 2 and 3 clinical trial events between January 1, 2012 – April 30, 2022. ** Average holding period of 131 calendar days (starting the first day of the quarter before the readout quarter). Past performance is not a reliable indicator of future results and should not be the sole factor of consideration when selecting a product or strategy.

The binary nature of healthcare risk implies that even a well-diversified portfolio of such companies will exhibit higher levels of risk than less-binary investments, risk that is temporally concentrated near and on clinical trial readouts. This underscores the importance of robust portfolio construction and thoughtful risk management.[11]

The thorough process by which a novel therapeutic candidate is tested gives rise to two other challenges: long duration and high cost. Candidates typically undergo four stages of development: preclinical studies, followed by phase 1, phase 2 and phase 3 clinical trials, after which the sponsor can file for regulatory approval. Drugs are tested first in the laboratory and then in multiple phases of clinical trials involving human volunteers to evaluate the safety and efficacy of the therapy on the target patient population. Each phase typically takes one to three years to complete and requires significant financial resources.[12] The entire process from preclinical testing to regulatory approval filing can easily span more than a decade and cost tens to hundreds of millions of dollars. In fact, the latest estimate of the average cost of developing an approved drug — which includes the cost of failed attempts along the way — is $2.8 billion in 2018 dollars.[13]

The milestones along this methodical process are often referred to by industry insiders as "de-risking" events because the achievement of each milestone reduces the risk of the therapeutic candidate and brings it one step closer to regulatory approval. In private markets and early-stage public investments, the de-risking process may also be useful to investors. By breaking up the therapeutic development process into multiple stages, investors can impose contingencies on their capital commitments which can reduce their overall financial risk. For example, instead of investing in the entire sequence of clinical trials, an investor can fund a phase 1 trial first and decide whether to fund phase 2 only after seeing the phase 1 outcome. Phase 3 can then be funded contingent on the outcome of phase 2, and so on.

Measuring and managing the specific types of risk of the healthcare sector requires a new set of tools to supplement those used in standard asset management contexts. We discuss some of these tools in the following sections.

11 Risk management seeks to mitigate, but cannot eliminate, risk nor does it imply low risk. **12** Lo, Andrew W., and Shomesh E. Chaudhuri. *Healthcare Finance: Modern Financial Analysis for Accelerating Biomedical Innovation.* Princeton University Press, 2023. **13** DiMasi, J. 2020. "Research and development costs of new drugs." Journal of the American Medical Association 324:517. doi:10.1001/jama.2020.8648.

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A better measure

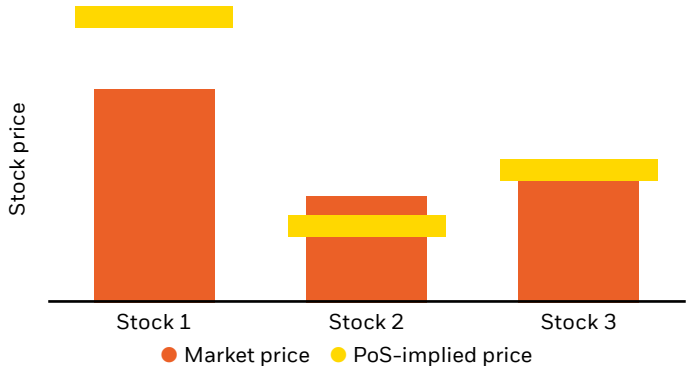
To better understand the nature of risk and reward, one natural starting point is the "Fundamental Law of Healthcare Finance."[14] This is a stylized expression of the economic value of a therapeutic program, written as a function of just four terms:

E [NPV]= PV [Cash Flows] × PoS – Costs

The expected net present value (NPV) of a therapeutic candidate is equal to the product of the present value (PV) of all future cash flows from sales of the therapy if approved times the probability of success (PoS), less the cost of developing, manufacturing and delivering the therapy to patients ("Costs").

In practice, the Fundamental Law of Healthcare Finance can be applied many times over, asset by asset through the well-known discounted cash flow calculations that lie at the core of fundamental equity analysis. Information and assumptions about revenues, costs, and PoS are combined to yield an estimated price per share which can then be compared to the current market price to determine whether the company is attractively valued. We illustrate this concept through a hypothetical example in Figure 5: our PoS-implied price estimate for Stock 1 leads to a higher assessment of fair value, suggesting the market is currently undervaluing the stock and it might therefore be an attractive position to hold. Conversely, our PoS-implied estimate for Stock 2 suggests the market is overvaluing the stock, while we think current pricing is reasonably fair for Stock 3.

Figure 5: Market vs. PoS-implied pricing



Source: BlackRock, as of December 31, 2022. Graphic is shown for illustrative purposes only and does not depict actual data. Orange bars are meant to represent a hypothetical market price for each hypothetical stock; the yellow bars represent the hypothetical price calculated using a hypothetical PoS estimate. None of the stocks represent an actual stock, holding, nor position; all data points are selected to illustrate the concept.

More accurate predictions with machine learning

Given that clinical trial outcomes tend to have a significant impact on stock returns, accurately estimating the PoS for any given clinical trial is paramount to successful healthcare investing. Sophisticated analytical techniques can improve the accuracy of PoS estimations by leveraging data to achieve scale, update estimates in real time, and mitigate human bias.

The potential benefits of incorporating a data-driven systematic approach can be illustrated by comparing it with more traditional, fundamental approaches to healthcare investing. Fundamental analysts construct, evaluate, and maintain an updated profile for each company under their coverage, and are attentive to any imminent clinical or regulatory events sponsored by those companies. Their forward sales models and clinical risk estimates reflect potential implications of new data, changes in company or competitor messaging, investor expectations and regulatory or commercial dynamics for each drug development program. They also keep a close watch on other elements of overall company health and the latest news from competing programs and products. Consequently, successful fundamental life sciences investing today relies on vigilant awareness, manual curation, and qualitative assimilation of multiple streams of real-time information. In practice, fundamental analysts typically cover between 20 and 40 companies to maintain the depth of coverage needed to manage the binary risk innate to the sector.

A systematic approach to healthcare investing is based on similar insights and analytics but uses data-driven tools to add value at scale by augmenting the effective throughput of the conventional healthcare analyst and exploiting empirical regularities that are not apparent or tractable through fundamental analysis. Unlike a traditional approach, a data-driven approach to PoS may help mitigate human bias while allowing for the consideration of many more data points, in real time, across more therapies. Advanced technologies such as machine learning and artificial intelligence afford the opportunity to leverage data from hundreds of thousands of clinical trial events across an array of therapeutics. Using many features of a company's therapeutic candidate — including the target disease, the biological and chemical nature of

14 Lo, A. and S. Chaudhuri. 2023. *Healthcare Finance Modern Financial Analysis for Accelerating Biomedical Innovation.*

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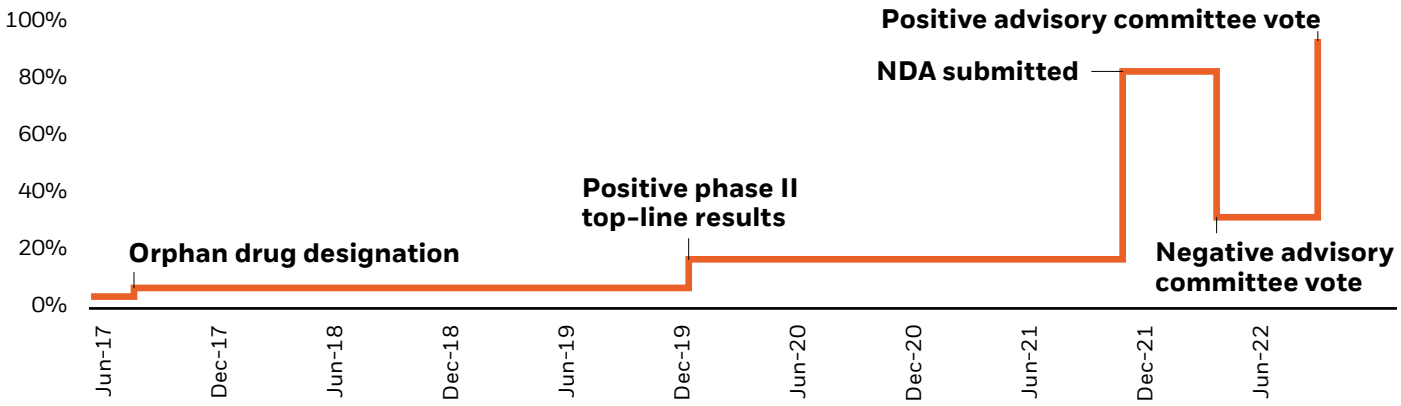
the candidate, the design aspects of the clinical trial, and the researchers' and companies' track records, among others — can allow us to form a more accurate PoS.

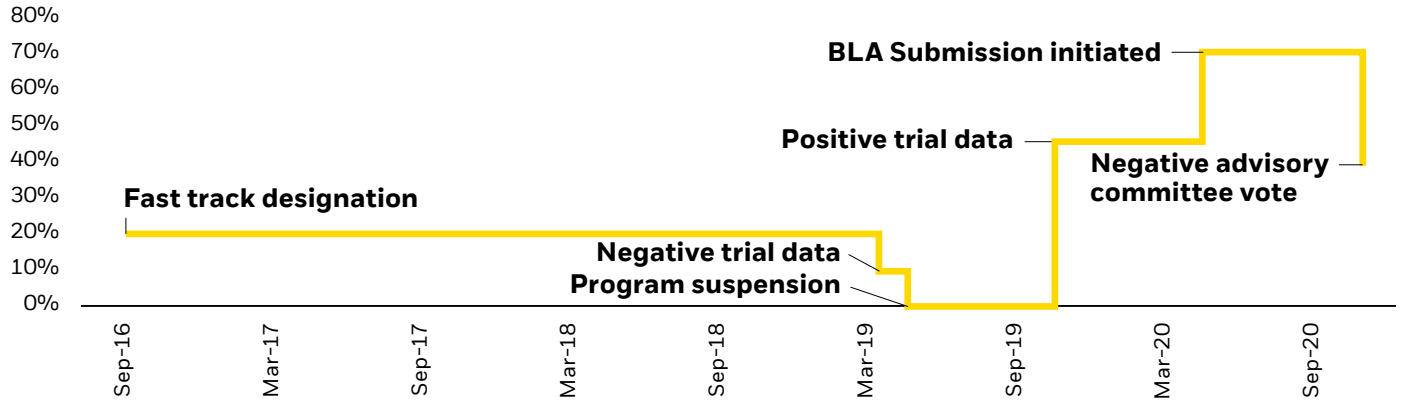
We have developed a machine-learned PoS predictor that is updated nightly, allowing our models to incorporate, quantify, and reflect relevant updates in the underlying features, or information about milestone catalyst events, in real time. Two examples of how the PoS estimates evolve in response to these events are shown in Figure 6.[15] Figure 6a reflects the point-in-time estimates for AMX0035, a drug created by Amylyx Pharmaceuticals to treat Amyotrophic Lateral Sclerosis, better known as ALS. Figure 6b shows the point-in-time estimates for aducanumab, a drug jointly developed by Biogen and Eisai to treat Alzheimer's Disease.

Figure 6a: Point in time PoS estimates for AMX0035



Source: QLS. Figure 6a lists the milestone catalyst events of the AMX0035 clinical development program through September 9, 2022 and illustrate how the point-in-time PoS estimates change in response to each event. This case study is shown for illustrative purposes only and was selected to demonstrate capabilities with respect to estimating probability of success. There is no guarantee than an actual strategy will be executed or executed as shown above, or that if executed, will be profitable. This investment was selected as it represents a systematic approach to analyzing large quantities of clinical data and generating a probability of success estimate at a given point in time. This case study does not predict future results, even if a similar approach is used. Reference of the company names mentioned in this communication is for illustrative purposes only and should not be construed as investment advice or investment recommendation of the company.

Figure 6b: Point in time PoS estimates for aducanumab



Source: QLS. Figure 6b lists the milestone catalyst events of the aducanumab clinical development program through June 6, 2021 and illustrate how the point-in-time PoS estimates change in response to each event. This case study is shown for illustrative purposes only and was selected to demonstrate capabilities with respect to estimating probability of success. There is no guarantee than an actual strategy will be executed or executed as shown above, or that if executed, will be profitable. This investment was selected as it represents a systematic approach to analyzing large quantities of clinical data and generating a probability of success estimate at a given point in time. This case study does not predict future results, even if a similar approach is used. Reference of the company names mentioned in this communication is for illustrative purposes only and should not be construed as investment advice or investment recommendation of the company.

15 Reference of the company names mentioned in this communication is for illustrative purposes only and should not be construed as investment advice or investment recommendation of the company.

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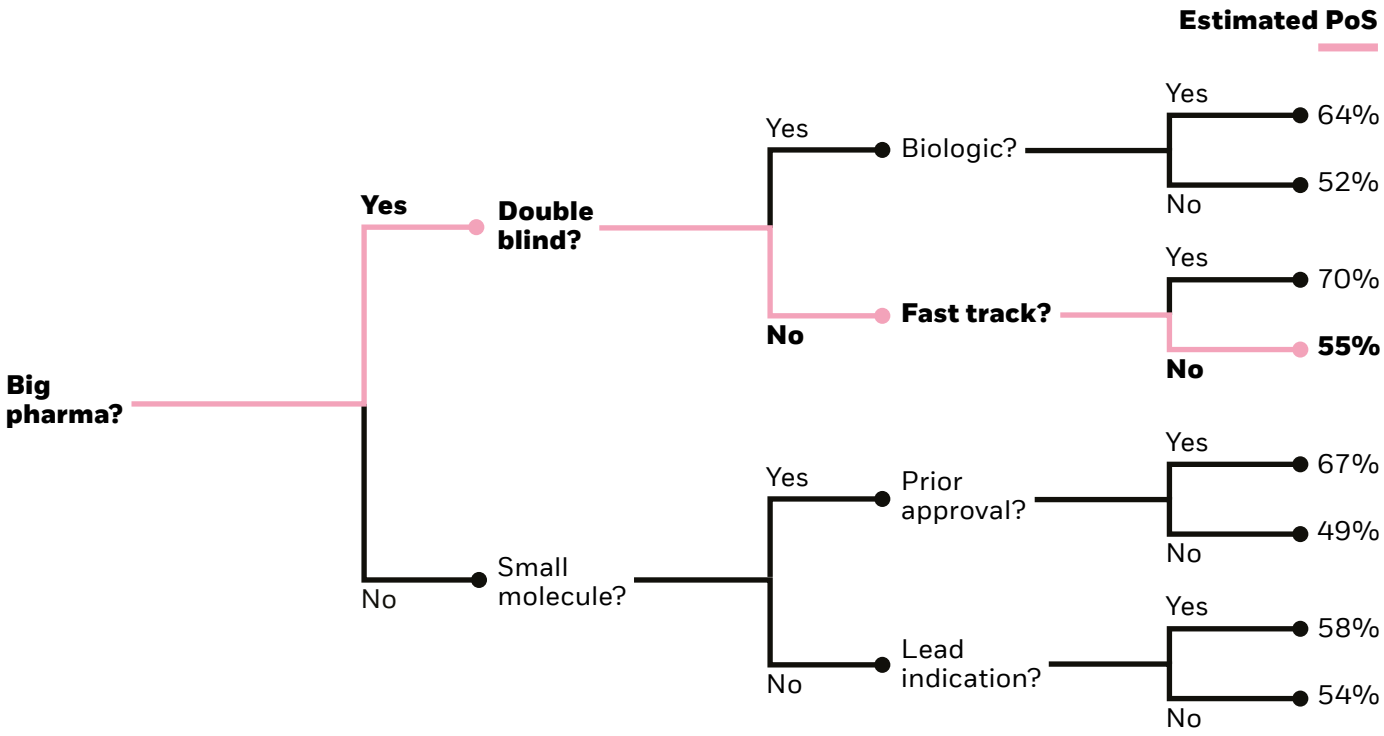
Given the magnitudes of the cash flows involved in approved drugs, small differences in PoS estimates can lead to very large differences in valuations and, therefore, investment decisions. Moreover, this systematic approach to estimating PoS may be easily automated and scaled to encompass the broader universe of potential therapeutic investments, allowing large portfolios to be monitored and managed efficiently and transparently.

Why use machine learning?

Recent advances in machine learning and artificial intelligence can identify non-linear predictive patterns with many different sources of data. For example, when training a decision tree, one task is to learn the most informative questions to ask at each branch point of the tree. The algorithm might ask, "Is the sponsor a big pharma company?" If the answer is "yes," then the algorithm would move to the "yes" branch of the decision tree and then ask, "Is the trial double-blind?" On the other hand, if the answer is "no," then the algorithm would move to the "no" branch of the decision tree, and ask, "Is the drug a small molecule?" and so on, until enough information has been collected about the drug-program to make a prediction about its success or failure.

The motivation for a random forest (a commonly used machine learning algorithm) is then to aggregate the predictions of many different decision trees, each of which is trained over a randomized subset of variables. As in the "wisdom of crowds" phenomenon, while each individual tree may be a weak predictor, their collective average yields a much stronger predictor. By identifying subtle patterns in a sufficiently large database of historical drug transitions, machine learning algorithms can potentially improve the accuracy of predictions.

Figure 7: Illustrative example of machine learning decision tree to analyze clinical trial data



Source: BlackRock and QLS as of December 2022. The machine-learned probability of success rate is being provided for illustrative purposes only as a hypothetical example of what the process seeks to potentially achieve. The information is not a prediction of future performance of any investments selected by the process and does not represent any actual success rates of the process. Note that the above process information is hypothetical and illustrative based on the current market environment; it does not reflect actual positions proposed. Strategies and targets depend upon a variety of factors, including prevailing market conditions and investment availability. There is no guarantee that they will be achieved or that any particular investment will meet the target criteria.

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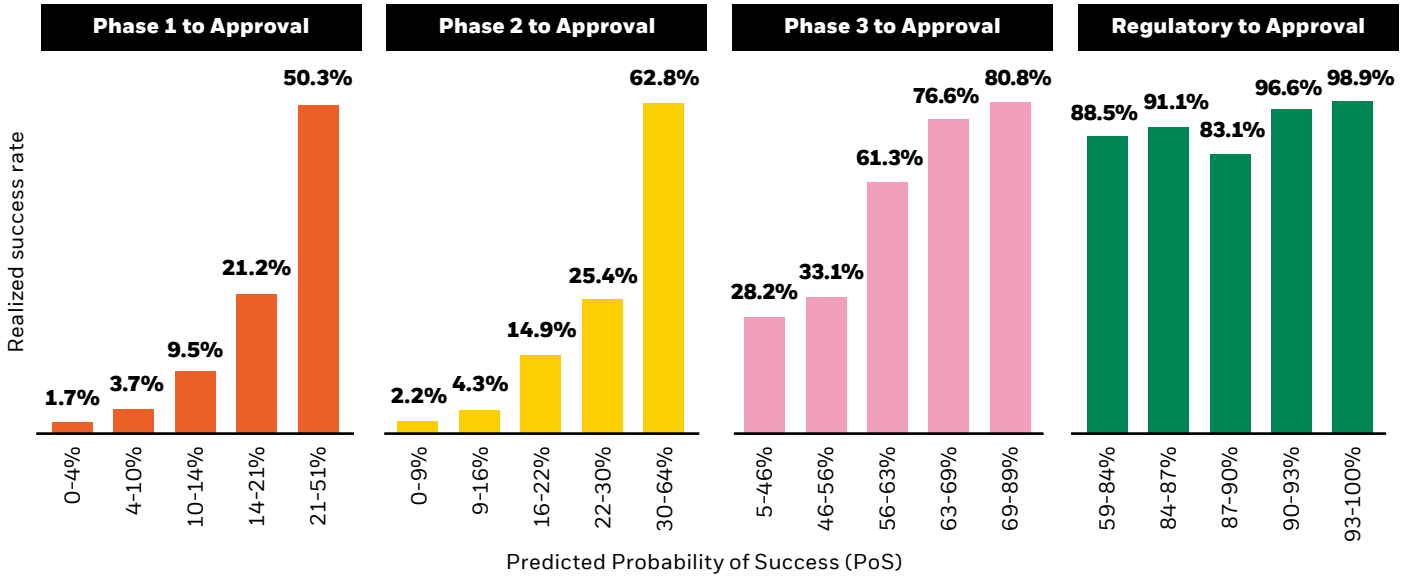
Predicting clinical success

Figure 8 compares our models' point-in-time predicted PoS for over 4,000 clinical trials versus the realized outcome of each trial. The positive relationships capture the predictive power of our models. We look at clinical trials across four stages, each represented by one of the four histograms below: phase 1 to approval, phase 2 to approval, phase 3 to approval, and regulatory filing to approval. The x-axis of each histogram groups our PoS predictions into quintiles.

The heights of each bar represent the quintile's realized frequency of success in the 2020 – 2021 out-of-sample period. The upward sloping linear relationship in each histogram demonstrates a direct relation between the predictions and subsequent performance: for each stage, the clinical trials with lower forecasted PoS have lower realized success rates relative to the trials with higher forecasted PoS. Although the out-of-sample realized success rates aren't precisely equal to the forecasted rates, the similarity is suggestive of significant forecast power in these machine learning estimates.

Figure 8: Estimates of clinical success are positively correlated with realized clinical success



Source: BlackRock using data from QLS as of December 31, 2021. The graph plots the model's predicted probability of clinical trial success (trials grouped into ranges) vs. the realized clinical success rates for the same groups of trials. Predictions are shown for programs which were discontinued or received approval in 2019 or later; the predictions are based on a model trained on data from the years 2000 to 2019 (no overlap). The results show the model's forecast power on out-of-sample outcomes: trials with higher probability estimates were more likely to be approved, and vice versa.

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Accounting for correlations

In addition to transforming a sea of raw data into useful investment insights, a systematic investment approach can mitigate downside risk by building a more robust portfolio that accounts for the correlations between clinical trial outcomes and, therefore, companies. Diversification in biotech is predicated on the ability to measure the correlation between healthcare companies and between pipeline assets within a company.[16] The same systematic techniques that may potentially better predict the PoS for a given treatment can also be used to estimate the correlations between any pair of treatments. Intuitively, two therapeutic programs targeting the same disease mechanism using the same or similar biological agents are more highly correlated — a failure of the first program doesn't bode well for the prospects of the second. On the other hand, two programs focused on completely different diseases and involving different drug compounds may be much less correlated. We can use this information to help construct a portfolio of diversified assets and more robustly manage the risk of the portfolio.

Complementary insights

While clinical trial outcomes are an important driver of the financial success of therapeutic companies, there are several other factors that impact valuations and stock price. Creating a robust view about the company's prospects — whether a public company or private company — requires assessing the company's fundamentals, sentiment from market participants, the competitive landscape, and industry trends alongside healthcare-specific insights. Alternative data can be a rich and granular source of information. Applying advanced technologies to big data allows us to uncover insights amidst market complexity, discovering information that might not otherwise be obvious to investors. For example, demographic data coupled with historical health insurance claims can help identify growing unmet medical needs. We also leverage data which gives us insight into a company's broader financial picture, such as employee sentiment, balance sheet strength, or broker attention. In aggregate, these diverse and complementary insights provide a robust profile to evaluate a given company.

16 Diversification does not assure a profit and may not protect against loss of principal. Diversification among investment options and asset classes may help to reduce overall volatility.

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Creating value for investors and society

As the healthcare sector grows in importance, relevance and size against a backdrop of an aging global population and rapid scientific innovation, so too does the potential opportunity for investors. Therapeutic development programs have the potential to deliver attractive investment returns, but as biomedicine has grown more complex, so have the challenges in identifying and assessing risks for investors.

By leveraging the wealth of available data, applying a systematic approach to healthcare investing can offer the distinct advantages of a scalable, transparent, and risk-managed investment process to invest in the healthcare sector. Systematic tools can help scale the breadth and depth of analysis, enhancing more traditional approaches, while remaining anchored in fundamental science. A machine-learned approach — which can analyze hundreds of thousands of clinical trial data points in real time — can account for unapparent linkages to estimate probabilities of clinical success more comprehensively, while the application of sophisticated technologies to alternative data sets can help glean useful information about complementary drivers of valuations, such as fundamentals, sentiment, and trends. This novel approach has the potential to generate better outcomes for investors, increase the availability of capital to fund underinvested but high-need areas of healthcare innovation and research, and improve our society's future wellbeing.

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