nature biotechnology

PERSPECTIVE

Just how good an investment is the biopharmaceutical sector?

Richard T Thakor[1], Nicholas Anaya[2], Yuwei Zhang[2], Christian Vilanilam[2], Kien Wei Siah[2,3], Chi Heem Wong[2,4] & Andrew W Lo[2–5]

Uncertainty surrounding the risk and reward of investments in biopharmaceutical companies poses a challenge to those interested in funding such enterprises. Using data on publicly traded stocks, we track the performance of 1,066 biopharmaceutical companies from 1930 to 2015—the most comprehensive financial analysis of this sector to date. Our systematic exploration of methods for distinguishing biotech and pharmaceutical companies yields a dynamic, more accurate classification method. We find that the performance of the biotech sector is highly sensitive to the presence of a few outlier companies, and confirm that nearly all biotech companies are loss-making enterprises, exhibiting high stock volatility. In contrast, since 2000, pharmaceutical companies have become increasingly profitable, with risk-adjusted returns consistently outperforming the market. The performance of all biopharmaceutical companies is subject not only to factors arising from their drug pipelines (idiosyncratic risk), but also from general economic conditions (systematic risk). The risk associated with returns has profound implications both for patterns of investment and for funding innovation in biomedical R&D.

The industrialization of biomedical sciences has become an important component of the global economy. In the United States, the biopharmaceutical sector accounts for 854,000 jobs, $150 billion in total wages and benefits, and 3.8% of total US output in 2014 (ref. 1). However, investment capital in this industry has waxed and waned over time in response to many factors, including preclinical scientific breakthroughs[2], clinical trial data[2], changes in regulatory oversight[3], healthcare policy reforms, pricing and healthcare technology assessment issues, and other seismic shifts in the economic environment for drug discovery and development. The most direct driver of capital flows into and out of this industry is, of course, the historical performance of biopharmaceutical investments—attractive returns draw additional investors into the industry and disappointing returns drive them away. It has been estimated that the cost of capital—a measure of the minimum return required by investors to compensate them for the risk of their investments—for biotech companies is 20% or higher[4]. Many biotech venture capital funds have not met this threshold since the early 2000s, which is likely a major factor in the substantial challenges to funding biomedical R&D, including the so-called 'valley of death', for early-stage translational medicine.

A contrasting view is that the biopharmaceutical industry is exceptionally profitable and has outpaced the aggregate stock market since the 1980s. Moreover, for big pharma, this success is alleged to have come with very little risk to an investor. "In a nutshell, the risk that large drug companies would have *diverse* fortunes, so evident in the 1970s, disappeared completely after 1980. They *all* do well. […] Investing at the drug company level is a good, solid, and basically riskless proposition"[5]. More recently, it has been argued that realized returns in healthcare venture capital outperformed all other venture sectors over the past decade, and that healthcare services, followed by biopharmaceutical companies, were the two best sub-sectors in venture capital investing, with an upward trend in both the number of biotech companies raising financing and the total financing raised[6]. A factor often cited for this extremely strong performance is a large rise in drug prices set by biopharmaceutical companies over the past decade[7].

We resolve these two contradictory views by disaggregating the financial performance—over time and across the pharmaceutical and biotech subsectors—of the biopharmaceutical industry. Using an algorithmic data-driven classification method that incorporates 21 different aspects of financial and product information to categorize companies into either the pharmaceutical or biotech sector, we performed an extensive statistical analysis of the financial risks and returns of all publicly traded US biopharmaceutical companies using historical daily and monthly data from January 1930 to December 2015 (**Box 1**). In a comprehensive sample of 1,066 current and defunct companies spanning eight decades, we document substantial heterogeneity and time variation in the financial performance of biotech and pharmaceutical sector investments.

Returns of the pharmaceutical and biotech sectors

During the period from 1930 to 1979, which pre-dates the biotech sector, the pharma sector outperformed the aggregate stock market by 3% per year with a similar level of risk, and only underperformed the stock market in three out of ten 5-year subperiods during this

[1]Carlson School of Management, University of Minnesota, Minneapolis, Minnesota, USA. [2]MIT Sloan School of Management and Laboratory for Financial Engineering, Cambridge, Massachusetts, USA. [3]MIT Department of Electrical Engineering and Computer Science, Cambridge, Massachusetts, USA. [4]MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, Massachusetts, USA. [5]AlphaSimplex Group, LLC, Cambridge, Massachusetts, USA. Correspondence should be addressed to A.W.L. (alo-admin@mit.edu).

Received 31 May 2016; accepted 31 October 2017; published online 8 December 2017; doi:10.1038/nbt.4023

time (**Fig. 1**). From 1980 to 2015, the pharma sector's performance was similar, with average annual returns that exceeded those of the stock market, again by 3%.

The pharma portfolio substantially outperformed the market portfolio (**Fig. 1a**). In particular, $1 invested in pharma companies at the beginning of 1980 would be worth roughly $114 at the end of 2015, whereas $1 invested in the market in 1980 would be worth about $44 at the end of 2015. The performance of pharma is very similar to that of the technology sector over most of the sample period; pharma began to outperform tech starting around 2000, which corresponds to when the tech (genomics) bubble burst.

In contrast to the performance of pharma, the biotech portfolio substantially underperformed compared with all of the other portfolios (**Fig. 1a**). $1 invested in biotech companies at the beginning of 1980 would be worth only about $8 at the end of 2015. This underperformance is especially pronounced in the late 1980s to early 1990s and in the years after 2001 (after the private equity (tech/genomics) bubble burst). The returns of the biotech sector are much less consistent over time and much riskier than those of either pharma or the stock market. Moreover, because of the outsized success of just a handful of companies, the cumulative returns of the biotech sector depend critically on whether these outliers are classified as biotech or pharma companies (**Box 2**).

The annual stock return distributions of individual pharma and biotech companies over time are shown in **Figure 1b**,**c**, respectively. Both industries exhibit substantial variation, and the median com-

Box 1 Data sources and analyses

Our primary data for returns come from the Wharton Research Data Services (WRDS) CRSP/Compustat database. We extracted stock return data for all publicly traded pharma and biotech companies from 1930 to 2015. Our main results use monthly stock return data, but we also make use of daily stock return data to calculate various risk characteristics that are more accurately measured with higher frequency data. We focus on firms that do business related to biomedicine, and exclude firms that do business in unrelated fields but are still classified as either pharma or biotech firms. This gives us a total of 1,066 unique firms in our sample, for a total of 125,277 firm-month observations (2,585,900 firm-day observations). We take the market portfolio return data from CRSP, and risk-free interest rate data from Kenneth French's website: http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html. The **Supplementary Data** and **Supplementary Table 1** contain more details regarding the construction of our data sample. We construct two value-weighted portfolios: one for pharma firms, and one for biotech firms (the details of this portfolio construction are presented in the **Supplementary Methods**). We use these value-weighted portfolios to reflect the way investors typically invest in the biopharmaceutical sector as a whole. To classify whether a company is a pharma or a biotech company, we use a '*k*-means' algorithm, which places companies into categories based on how similar they are to each other on a host of characteristics. The *k*-means algorithm starts with prototypical 'seed' companies in the pharma and biotech categories, and then places each additional company into either category by calculating a distance between that company and the seed companies based upon each company's characteristics. We run the *k*-means classification algorithm dynamically, meaning that we identify seed companies each year, and classify a company as either pharma or biotech based on its characteristics in that year. This allows a company to change its classification over time—for example, a company that grows and evolves from a biotech to a pharma company. We use a data-driven method to identify the seed companies each year for the algorithm by using a set of eight characteristics from the CRSP/Compustat database: total assets, dividends, number of employees, assets-in place (property, plant, and equipment), advertising expenses, intangible assets, and age (years since a company's initial public offering). We start running the *k*-means algorithm in 1980 to make a distinction between pharma and biotech companies, because this is the first year in which there are consistently enough biotech seed companies to run the algorithm. We therefore consider companies in the years before 1980 in our sample to be pharma companies. Further details of this classification method are included in **Supplementary Methods**.

The *k*-means classification algorithm has several advantages over other industry classification systems traditionally used in the Finance and Economics literature (such as the Standard Industrial Classification, or SIC, system). First, the *k*-means algorithm uses detailed information from a wide variety of financial and company characteristics to finely classify firms. In contrast, other industry classification systems only use a handful of broad common characteristics, such as products or services. Second, using more traditional classification methods makes it challenging to identify newer industries—for example, SIC codes were established in 1937, and many emerging industries have not cleanly fit into the existing classifications. Thus, existing classifications may not be ideal for distinguishing between pharma and biotech firms, given that biotech firms tend to be newer and produce observationally similar products and services to pharma firms in many cases but use methods different from traditional small-molecule discovery and development. Finally, most other industry classification systems are static in the sense that they are based on when a company is first incorporated, and the classification does not change after that. The *k*-means algorithm is dynamic, and thus allows us to capture when a company may change industries between pharma and biotech. As a result, although others have also pointed out some of these shortcomings of existing classifications, we argue that our classification method is an improvement over what has previously been done[25].

However, these shortcomings notwithstanding, to explore how the classification method may affect our results, we also re-ran our analysis using seven alternative methods for classifying whether a company belongs to the pharma or biotech industry: collaborative filtering (a machine-learning method for matching similar items in order to provide recommendations); Global Industry Classification Standard (GICS), a classification scheme published by MSCI (Morgan Stanley Capital International); the North American Industry Classification System (NAICS), a standard classification scheme used by federal statistical agencies; the Standard Industrial Classification (SIC) system, an older classification system established in 1937; 'Unanimity', a classification scheme limiting the biotech and pharma sample set to only those companies shared by all of the above five classification methods; 'Majority rule', a classification scheme limiting the biotech and pharma sample set to those companies appearing in the majority (3/5) of the above five classification methods; and 'Hoberg-Phillips', a recent text-based industry classification system based on company 10-K reports (**Supplementary Notes**, **Supplementary Fig. 1**, **Supplementary Tables 2–4** and **Box 2**)[26,27].

pany return in both industries is positive in some years and negative in other years, suggesting that the majority of firms in each industry do not deliver consistently positive stock return performance—there appears to be substantial risk across companies. However, there are some important differences.

The median pharma return curve (**Fig. 1b**) exhibits smaller fluctuations and spends more time above 0% than the median biotech return (**Fig. 1c**). Both observations are consistent with the common perception that pharma is less financially risky than biotech. In contrast, the biotech sector's cross-sectional distribution of returns (**Fig. 1c**) exhibits a strong but surprisingly consistent cyclical pattern of widening and narrowing. This confirms the boom/bust cycle of biotech venture capital funding, investing, and initial public offering exits (IPO windows) that have frustrated investors and entrepreneurs since the advent of the biotech industry.

Profits in the pharmaceutical and biotech sectors

We calculated the profitability of the pharmaceutical and biotech sectors, scaled by total assets so as to adjust for size differences across companies (**Fig. 2**). The profitability of the median pharmaceutical company (**Fig. 2a**) was consistently positive until the early 1990s, indicating that over half of pharmaceutical companies posted positive profits from 1950 to 1990. However, after 1990, the median pharma company's profitability declined and, after 2000, turned consistently negative. Indeed, after the early 1980s, the various percentiles all exhibit a general pattern of decline. This decline was accompanied by a striking increase in cross-sectional dispersion. Although many pharmaceutical companies did well over the sample period, a substantial number also experienced negative profitability, and thus outcomes were varied between companies. This evolving pattern of profitability can be partly attributed to the influx of non-profitable smaller pharma companies over time. In particular, while the median big pharma company has maintained relatively stable positive profits over the last 30 years, smaller pharma companies experienced consistently declining and, since the early 1980s, negative median profitability. Moreover, the dispersion of profitability for smaller pharma companies is much more striking than for big pharma companies.

An even starker pattern emerges for biotech firms (**Fig. 2b**). The profitability of firms in all of the percentiles has also been dropping over time, but even firms in the 75th percentile have had consistently negative profitability over time. This reflects the fact that biotech companies typically do not generate revenues but are repositories for intellectual property (IP) that is monetized when companies are acquired or their IP is in-licensed by big pharma. Moreover, biotech firms seem to incur much larger losses than their counterparts in the pharma industry, consistent with the fact that many biotech companies focus on R&D and do not have lines of commercialized drugs that they actively manufacture and sell. However, the 95th percentile was consistently profitable over the entire sample period, suggesting that it is possible for biotech companies to become sustainable business entities in their own right, even if this is the exception rather than the rule. These trends of declining profitability for pharma and biotech are more pronounced than the documented trends in other sectors (**Fig. 2c**)[8]. The decline in median pharma profitability was similar in size to that of tech and all other sectors (excluding pharma and biotech), but was more pronounced after the mid-1990s. The decline in median biotech profitability was much starker than pharma's or the other sectors'. This suggests that the profitability trends for pharma and biotech are not simply part of a more general trend affecting all publicly listed companies.

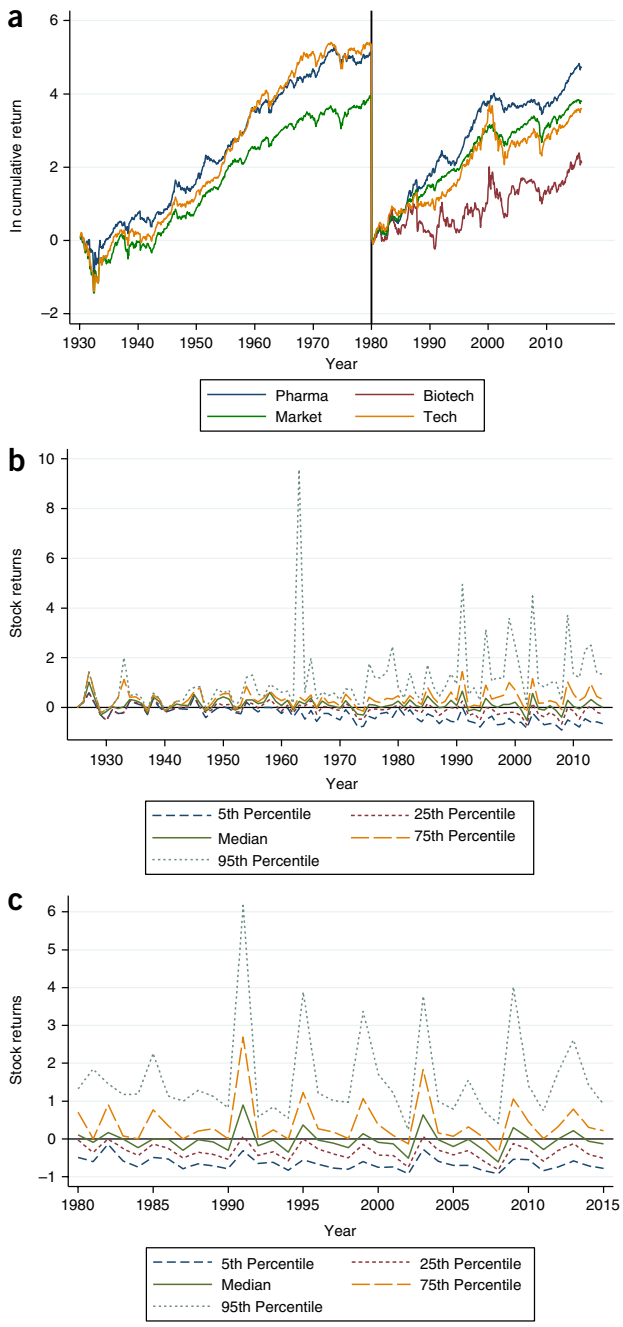

Figure 1 Returns for the biopharmaceutical sector. Returns are plotted over several time periods and compared to the returns of the overall market and the technology sector, both taken from CRSP. (**a**) Cumulative returns are plotted (on a logarithmic scale) comparing the pharma, tech, and biotech sectors (classified according to the *k*-means algorithm) to the market in two distinct time periods—from 1930 to 1980 (pre-biotech) and from 1980 to 2015 (post-biotech). The sample is segmented in this way because 1980 is the first year in which the data permit a distinction between pharma and biotech firms, thus yielding reasonable benefits from the averaging process and facilitating a fairer comparison between the groups for the pre- and post-biotech periods. (**b**) Individual annual returns for pharma companies at various percentiles. (**c**) Individual annual returns for biotech companies at various percentiles.

Overall, these profitability results show that, although a number of firms in the pharmaceutical sector have been profitable, especially since 2000, over half of these firms have been unprofitable and posted financial

Box 2 The importance of classification accuracy and outlier companies

During the course of our analysis, we noted a wide variation in cumulative returns for the biotech sector depending on the classification method used for determining whether a given company is a pharmaceutical company or a biotech company (**Supplementary Methods**). In contrast, the different classification methods yield very similar results in terms of the performance of the pharmaceutical sector compared with the market.

We ran analyses using eight different classification systems: *k*-means (used in the main paper), collaborative filtering, GICS, NAICS, SIC, Unanimity, Majority rule, and Hoberg-Phillips (for more details, see **Box 1**). The *k*-means, collaborative filtering, and Unanimity classification schemes produced similar results for the biotech sector, showing companies to consistently underperform in terms of returns compared with the market in nearly every subperiod. In contrast, another set of classification schemes (GICS, NAICS, SIC, and Majority rule) shows the biotech sector fares worse than the pharmaceutical sector before 1990, but subsequently performs better (except for the 2000s). Hoberg-Phillips shows biotech matching the performance of pharma during the entire period from 1980–2015 (**Supplementary Notes**, **Supplementary Fig. 1**, and **Supplementary Table 2**).

The conclusion is that the relative performance of the biotech sector is strikingly different depending on the classification method used. In particular, three of the classification methods show biotech underperforming the market. In contrast, while Hoberg-Phillips has biotech consistently outperforming the market, four of the remaining methods have biotech outperforming the market starting in the 2000s, and subsequently even catching up to pharma. The differences between the classification methods underscore an important point when considering the performance of the biotech sector—its performance is heavily dependent on how one classifies companies as pharma companies or biotech companies.

For example, the *k*-means classification method that we use initially considers Amgen and Gilead to be biotech companies, but subsequently, they are classified as pharma companies due to their size and scale, whereas the GICS/NAICS/SIC methods classify these companies as biotech companies. Both of these companies achieved very high returns over the sample period, and whether they are included in the biotech portfolio substantially affects the portfolio's returns. Indeed, in terms of cumulative returns, most of the material differences between the classification methods can be attributed to whether the following companies are classified as biotech companies: Amgen, Gilead, Genzyme, Genentech, and Sepracor. Removing these outlier companies from the biotech portfolio for these alternative classification methods yields returns that match those of the *k*-means method, indicating that our main results are robust barring these outliers. One reason that a small number of companies can greatly affect the biotech portfolio's returns is that most biotech companies are smaller, with a relatively low market capitalization, and thus including a larger company with higher returns will have a substantial impact on the biotech portfolio as a whole. The impact of including or excluding these companies on the pharma portfolio is smaller because the pharma portfolio contains a number of large companies that all of the classification methods would consider to be pharma companies. Further details and discussion of these differences can be found in **Supplementary Notes**, **Supplementary Methods**, and **Supplementary Results**.

losses. Conversely in the biotech sector, the vast majority of firms have been consistently and profoundly unprofitable, and trends of declining profitability and increased disparity of profits among companies in the sector have become more pronounced. The results generally indicate an increase in the variability of fortunes and confirm that the financial risks at the individual company level have been increasing over time.

Risk in the pharmaceutical and biotech sectors

Although the above data on returns provide a view of the long-term performance trends of the pharmaceutical and biotech sectors, they also reveal some interesting variation during certain subperiods. To delve further into the nature of this performance variation over time, we examined the risk of the returns. As investors expect a higher rate of return in exchange for higher risk, the returns of pharmaceutical and biotech industries may or may not be high after adjusting for the financial risk that each industry bears.

We provide the annualized mean returns of each industry for five-year subperiods, as well as the annualized volatilities of each industry's returns as a measure of financial risk (**Table 1**). To examine whether returns were high compared with the amount of risk taken by firms in a given industry, we also calculated the Sharpe ratio, a commonly used measure of an investment's return per unit of total risk (**Supplementary Methods**).

These results underscore the finding that the pharmaceutical sector has generally outperformed the market over previous decades and outperformed the tech sector since 2000. From 1980 to 2015, the annualized mean return of the pharmaceutical sector was higher than that of the market (14% compared with 11%) and either closely matched (was within 1% of) or was higher than the market's in every subperiod. Although the risk of the pharma sector was slightly higher on average than the market's during this period, the Sharpe ratio of the pharma sector was higher than that of the market overall, indicating that the risk-adjusted returns of the pharma sector were better than the market.

The impressive performance historically of the pharmaceutical sector contrasts sharply with that of the biotech sector. In particular, the biotech sector posted lower mean returns than pharma in every subperiod, except for the period from 2000 to 2004. The risk of the biotech sector was also higher than that of pharma overall and in every subperiod. As a result, biotech's Sharpe ratios are substantially worse than pharma's over the entire sample period, and in every subperiod barring the early 2000s.

We next examined the total return volatility over time of each portfolio—which was calculated by taking the s.d. of daily returns for each portfolio for the past year—and then consider the channels through which these risks are created.

Figure 3a shows the time-series behavior of the total return volatility for the pharmaceutical and biotech industries. Both had volatility that was generally higher than that of the overall market. Starting in the 1970s, there were larger spikes in volatility for both industries and a slight upward trend, providing evidence that the risk in these industries has been increasing over time. The volatility of the biotech portfolio was also substantially higher than that of both the pharmaceutical portfolio and the market, which indicates that biotech firms have substantial risk overall. There also appears to be substantial co-movement of the volatilities of the market and the pharma/biotech

portfolios, suggesting that there is a large systematic component to the risks.

To further illuminate the nature of the above risks, we decomposed the risk of the pharma and biotech portfolios into its systematic and idiosyncratic components (**Supplementary Methods**). Systematic risk is risk that is related to common aggregate factors affecting all companies in the economy and cannot be diversified away (i.e., the general market environment), and should command a higher average return by investors. Idiosyncratic risk, in contrast, is risk that is not related to factors in the overall economy but is unique to the individual company (e.g., whether a drug successfully completes a phase trial) and can thus be diversified away by investors.

When we examined the time-series risk estimates, the majority of the total risk in most years for the pharmaceutical portfolio is systematic risk (**Fig. 3b**). In contrast, the biotech portfolio has both systematic and idiosyncratic risk, with a much higher idiosyncratic risk than in the pharma portfolio (**Fig. 3c**). This is consistent with the higher perceived risk of biotech firms, related to the fact that their businesses are focused more on new R&D than pharma firms' and less on existing product lines. However, the biotech portfolio also has high systematic risk, with the systematic component comprising a substantial portion of the total risk. Moreover, this systematic risk is roughly as large as that of the pharma portfolio in most periods and substantially larger than that of the pharma portfolio in some periods.

To explore the magnitude of this risk, we next looked at the 'betas' of the pharmaceutical and biotech portfolios. Betas are a more direct indicator of the relative extent of systematic exposure in the returns of the portfolios; they represent a portfolio's co-movement with the market, a higher beta indicating more systematic risk.

Figure 3d displays the time-series estimates of the market betas of the pharma and biotech portfolios estimated via the Capital Asset Pricing Model (CAPM) using the previous two years of daily data for each portfolio. The pharmaceutical portfolio experienced a general decline in its betas from 1990 to 2010, although this was reversed over the subsequent years. This decline may be consistent with the evidence of a shift in investment focus from assets in place to R&D by companies in response to competition[9]. The market beta for the pharma portfolio drops steeply around 2001, which coincides with the bursting of the private equity bubble (also known as the 'genomics bubble'). It is also notable that biotech companies had similar betas to pharma companies when they first appeared in the 1980s, but since that time they have had consistently higher betas, and thus their returns are more related to the market than those of pharma companies. These results for volatility and betas are qualitatively robust across the alternative classification methods, as well as using a model other than the CAPM (**Supplementary Results** and **Supplementary Figs. 2** and **3**).

Risk-adjusted excess returns

As a final step in our analysis, we asked whether the returns of these sectors are high relative to the risk that they have taken on. In other words, given the risks of each sector, have their returns exceeded what would be predicted by financial asset-pricing models? This is of critical importance for evaluating the investment prospect of the pharma and biotech sectors, as investors withdraw their capital from sectors that offer lower returns than are commensurate with their risks.

To examine this, we computed the CAPM alphas, which measure investment return that is in excess of the return predicted by the market risk factor of the CAPM (which assumes investors expect a higher rate of return in exchange for higher systematic (market) risk). In other words, CAPM alphas measure abnormally high returns—returns above and beyond what investors expect when accounting for the systematic risk of each asset.

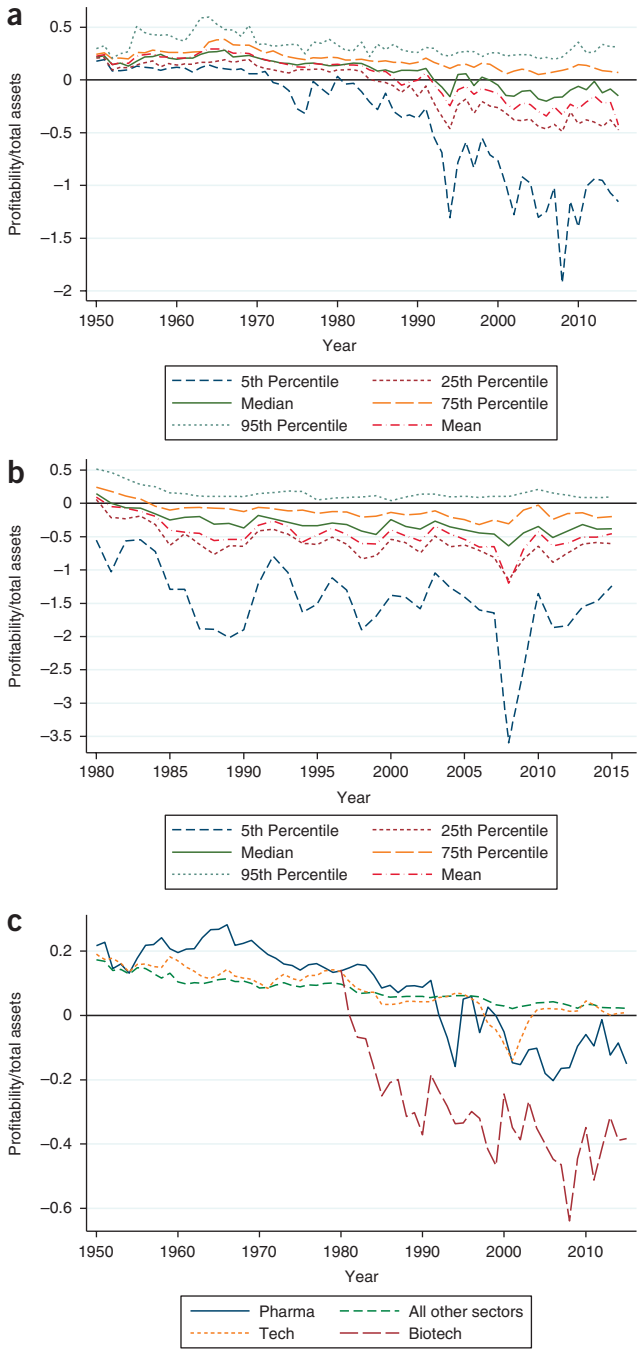

Figure 2 Profitability in the biopharmaceutical sector. (**a**) Profitability of pharmaceutical companies. (**b**) Profitability of biotech companies. (**c**) Median profitability of the pharmaceutical and biotech sectors compared to the tech sector and all other sectors apart from pharma/biotech. Profitability is defined as earnings (revenues minus costs) before interest and taxes, scaled by total assets. Each line represents either mean profitability or profitability at the indicated percentile.

Table 2 provides CAPM alpha estimates for each five-year subperiod from 1930 to 2015 and also indicates whether the alphas are statistically significant. Consistent with previous findings, the pharmaceutical sector alphas posted a positive and statistically significant alpha from 1930 to 2015 (ref. 10). This was also true when we

Table 1 Returns, volatilities, and Sharpe ratios for market, tech, pharma, and biotech over five-year subperiods

Time period	Annualized mean returns				Annualized volatilities				Sharpe ratios			
	Market	Tech	Pharma	Biotech	Market	Tech	Pharma	Biotech	Market	Tech	Pharma	Biotech
1930–1934	–10%	–5%	2%	–	0.33	0.36	0.34	–	–0.05	0.06	0.23	–
1935–1939	10%	11%	15%	–	0.21	0.18	0.14	–	0.51	0.55	0.86	–
1940–1944	9%	10%	2%	–	0.12	0.11	0.12	–	0.58	0.64	0.17	–
1945–1949	11%	15%	17%	–	0.13	0.14	0.15	–	0.71	0.90	0.88	–
1950–1954	22%	23%	17%	–	0.09	0.11	0.12	–	1.70	1.45	0.89	–
1955–1959	15%	30%	26%	–	0.11	0.14	0.15	–	1.10	1.52	1.43	–
1960–1964	10%	9%	11%	–	0.10	0.17	0.14	–	0.61	0.41	0.52	–
1965–1969	6%	22%	12%	–	0.09	0.16	0.11	–	0.18	1.00	0.53	–
1970–1974	–4%	–8%	4%	–	0.15	0.26	0.18	–	–0.48	–0.62	0.02	–
1975–1979	18%	14%	6%	–	0.11	0.34	0.14	–	0.73	0.46	0.04	–
1980–1984	14%	29%	13%	4%	0.14	0.43	0.15	0.21	0.26	0.71	0.19	–0.12
1985–1989	18%	5%	28%	0%	0.16	0.21	0.21	0.25	0.69	0.02	0.99	–0.03
1990–1994	9%	15%	9%	0%	0.11	0.17	0.18	0.23	0.36	0.58	0.33	0.05
1995–1999	27%	46%	34%	27%	0.15	0.46	0.21	0.23	1.39	1.42	1.45	0.74
2000–2004	–1%	–14%	–1%	0%	0.20	0.49	0.23	0.39	–0.15	–0.21	–0.16	0.15
2005–2009	2%	4%	1%	–1%	0.24	0.25	0.19	0.26	0.02	0.15	–0.02	–0.07
2010–2015	11%	13%	18%	14%	0.16	0.18	0.16	0.26	0.87	0.82	1.38	0.66
1980–2015	11%	13%	14%	6%	0.17	0.34	0.19	0.27	0.47	0.42	0.61	0.20
1930–1979	8%	11%	11%	–	0.17	0.22	0.17	–	0.36	0.49	0.47	–
1930–2015	9%	12%	12%	–	0.17	0.27	0.18	–	0.40	0.45	0.51	–

Firms are classified as either pharma or biotech using the *k*-means algorithm. The annualized mean returns and Sharpe ratios are calculated using monthly stock return data, whereas the volatilities are calculated using daily return data. Calculation details can be found in **Supplementary Methods**.

examined the post-biotech period from 1980 to 2015. Our findings indicate that, over longer horizons and over many specific subperiods, the pharmaceutical sector's average return exceeded the average return required by investors, according to the CAPM.

In comparison, the tech sector has not posted a statistically significant alpha since 1990, and the risk-adjusted performance of the pharma sector was generally higher than that of the tech sector (results that are similar when considering other classifications and factors apart from the market factor; see **Supplementary Results**, and **Supplementary Tables 5** and **6**).

In contrast, the alphas for the biotech sector were negative over the entire biotech sample from 1980 to 2015, although they were statistically insignificant. Indeed, the alphas for the biotech sector were not statistically significant in any of the subperiods except for 1985–1989, where they were negative and statistically significant. This suggests that the biotech sector has not delivered returns that exceed what is expected by investors, whereas the pharma sector has.

The data and software used to conduct this analysis are shown in **Box 3**.

DISCUSSION

Our empirical results show that investments in the pharmaceutical industry have outperformed the broader stock market over a long period of time, whereas investments in the biotech industry have underperformed the market. However, the relative performance between the two industries and the market depends on the time period under examination, and also critically depends on whether certain companies are classified into either the pharma or biotech industry. After adjusting for risk, pharma still performs well compared with the market, but does not consistently outperform the market in every subperiod. However, biotech consistently posts disappointing results compared with both pharma and the market. In addition, the returns and profitability across individual companies of the biotech and pharma sectors vary widely, with many firms posting negative returns and profitability.

This striking difference in performance between pharma and biotech may result from several factors. First, unlike pharma companies, biotech companies are not necessarily focused solely on generating earnings, but often deploy large amounts of cash to reach key milestones such as phase 1 and phase 2 endpoints, which can then be monetized through licensing, joint development deals, and mergers with big pharma. Second, because biotech companies are generally involved in earlier-stage drug discovery and development, they face greater scientific risks, which translate into lower risk-adjusted returns in aggregate, other things being equal. Third, as our understanding of the biology of human diseases grows, the number of

Box 3 Data and software

The data analyzed in this study came from the following sources:

Center for Research in Security Prices (CRSP) stock database and the Compustat Capital IQ database from Standard & Poor's. Both available through Wharton Research Data Services (WRDS): https://wrds-www.wharton.upenn.edu/pages/about/

Kenneth R. French Data Library: http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html

The analysis was carried out using the following software:

STATA version 14.2: https://www.stata.com

Python v2.7, pandas v0.19, and numpy v1.12, available through the Anaconda distribution: https://www.anaconda.com/download/

Matlab R2015a from MathWorks: https://www.mathworks.com/products/matlab.html

Conjugate gradient optimizer script for Matlab: https://www.mathworks.com/matlabcentral/fileexchange/42770-logistic-regression-with-regularization-used-to-classify-hand-written-digits?focused=3791937&tab=function

Microsoft Excel 2016: https://products.office.com/en-us/excel

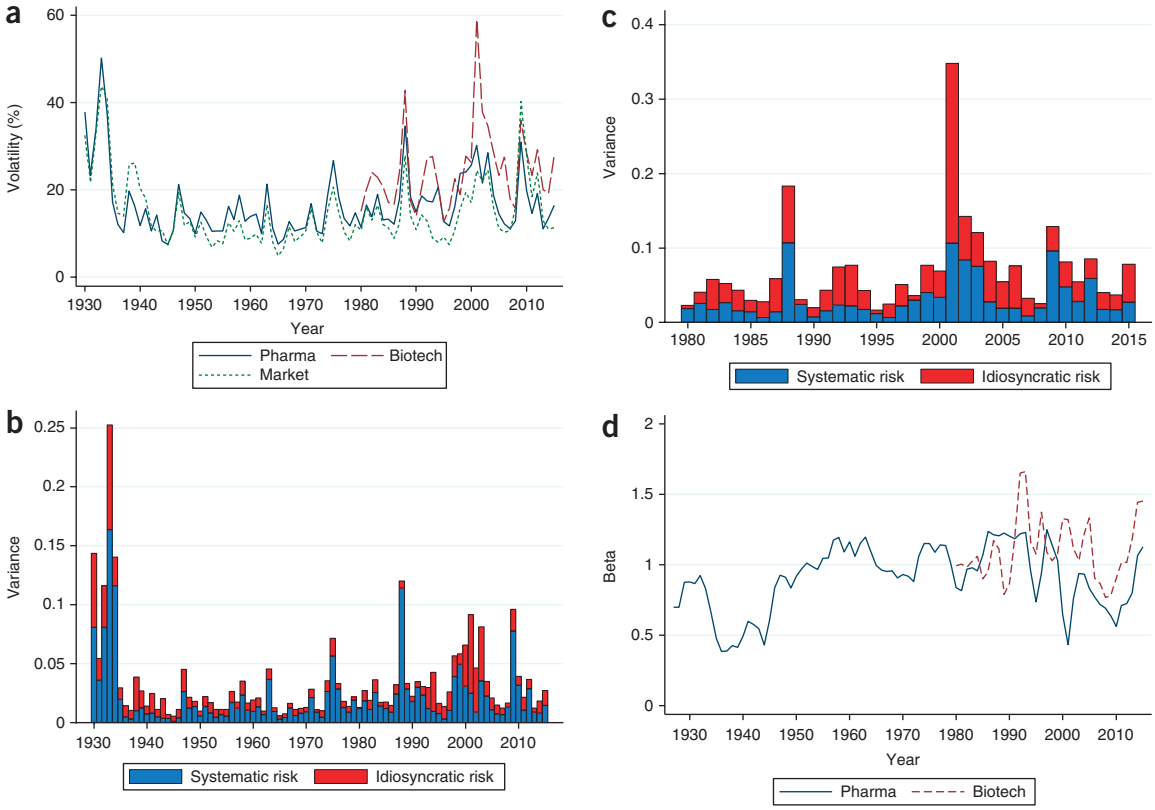

Figure 3 Risk in the biopharmaceutical sector. (**a**) Annualized total stock return volatility over time of the pharmaceutical (blue), biotech (red), and market (green) portfolios. Volatilities are calculated by taking the s.d. of the daily returns of each portfolio for each year, and are annualized. (**b**) The total variance of the pharma value-weighted portfolios, decomposed into systematic and idiosyncratic risk. (**c**) The total variance of the biotech value-weighted portfolio decomposed into systematic and idiosyncratic risk. Variances are calculated using daily returns within each year, as well as beta estimates for each portfolio. (**d**) Capital Asset Pricing Model (CAPM) market beta estimates of the pharma (blue) and biotech (red) portfolios. Betas are calculated by estimating the CAPM each month, using the past two years of daily returns.

potential pathways and mechanisms for developing therapeutics multiplies, further increasing the financial risks of drug discovery and development.

Finally, biotech companies face substantial financing risk in the form of business- and credit-cycle downturns, which may deprive them of capital even when they achieve their milestones. Such fundraising challenges can lead to disruptive interruptions in scientific programs and the departure of key personnel, destroying considerable value in the process. Gauging the relative importance of these and other factors contributing to performance differences between pharma and biotech requires more detailed analysis and should be explored in future research.

The above results are also contrary to the view that biopharmaceutical firms fare exceptionally well financially on a consistent basis. In fact, investments in these industries are accompanied by substantial risks, and these risks have generally been increasing over time[5]. Surprisingly, the risk of pharma and biotech firms has a notable systematic component, which is higher in biotech firms than in pharma firms. This higher level of systematic risk explains the origin of the high cost of capital of biotech firms, based on financial models of risk-adjusted returns, such as the CAPM or the Fama-French three-factor model.

Our findings are consistent with the conclusions of previous studies[3,4,11,12]. However, while pharma firms have existing product lines that may contribute to systematic risk, many biotech firms engage in primarily R&D research. In light of the observation that much of the risk in (at least early-stage) R&D is idiosyncratic, the high systematic risk in biotech firms is surprising, and implies that the fortunes of such firms are strongly related to the overall economy. This is counter-intuitive—the scientific risks associated with enterprises carrying out early-stage biomedical R&D should be uncorrelated with stock market fluctuations—which explains the high cost of capital estimates of other studies[4].

We propose two explanations for the high degree of systematic risk for biotech and pharma firms. The first explanation is what we refer to as the 'financing channel'. The intuition is along the same lines as the 'financing risk' for innovation described by others[13–15]. The large investments needed for biomedical R&D are usually funded in one of three ways: external financing, a mergers and acquisitions (M&A) deal, or an alliance with another pharma or biotech firm. The likelihood of each of these types of deals is influenced by how well the stock market as a whole is doing. For example, it has been documented that there are equity financing cycles with biotech firms, where the amount of equity financing and alliances made by biotech firms are influenced by the overall stock market[16]. Moreover, venture capitalists and others who invest in biotech firms do so with an 'exit option' in mind, and this exit often occurs either through an initial public offering or when the biotech firm is acquired by another firm, typically a larger pharmaceutical firm. This means that the returns of investors in biotech firms will be affected by the probability of such exits, which clearly increase with the aggregate stock market. Thus, both external financing and exits are more likely during bull markets, implying that R&D financing risk is systematic.

Table 2 Annualized alpha estimates for the pharma, biotech, and tech sectors for five-year subperiods from 1930 to 2015[a]

Time period	Pharma	Significance	Biotech	Significance	Tech	Significance
1930–1934	0.104		–		0.077	
1935–1939	0.091	*	–		0.038	
1940–1944	–0.023		–		0.034	
1945–1949	0.069	*	–		0.053	
1950–1954	–0.034		–		0.051	
1955–1959	0.086	**	–		0.133	***
1960–1964	0.013		–		–0.022	
1965–1969	0.059	*	–		0.156	***
1970–1974	0.103	***	–		–0.087	
1975–1979	–0.123	***	–		–0.007	
1980–1984	–0.004		–0.064		0.312	*
1985–1989	0.061	*	–0.146	*	0.123	***
1990–1994	0.010		–0.063		0.054	
1995–1999	0.047		0.000		0.003	
2000–2004	0.001		0.069		–0.053	
2005–2009	–0.007		–0.017		0.022	
2010–2015	0.083	**	0.018		0.007	
1980–2015	0.042	**	–0.027		0.019	
1930–1979	0.038	**	–		0.038	*
1930–2015	0.040	***	–		0.031	

Statistical significance: *10% level; **5% level; ***1% level. [a]Alpha estimates are calculated via the CAPM using daily returns for the indicated periods.

The second explanation is the 'R&D leverage channel'. Because large fixed costs are associated with biopharmaceutical R&D, and financing a large investment is more difficult and/or costly when the economy is down than when it is up, maintaining this fixed commitment to R&D becomes risky, and the risk is therefore systematic. This fixed-cost element is referred to as 'R&D leverage'[11]. Financing risk and R&D leverage are not unrelated, however, as the financial constraint imposed by R&D leverage is likely to amplify the effect of the financing channel described above. Because biotech firms have higher R&D leverage (their R&D commitment is large relative to their size), this effect should be stronger for them, thus contributing to higher systematic risk for biotech firms.

Overall, this pattern of risk is important for investors for two reasons. First, some investors buy stocks in specific industries to avoid systematic risk—as a result, investors in the pharmaceutical and biotech industries may be exposed to greater systematic risk than they anticipate, which may run the risk of capital withdrawal if certain events occur in the economy. Second, the high level of systematic risk implies that drug development is dependent on how the economy is faring. This may mean that such development slows down during economic downturns. As the impact of diseases remains constant, a biopharmaceutical sector constrained by such economic factors is clearly unsatisfactory from a societal standpoint. This implies there may be potential benefits to insulating these activities from such risk through more efficient risk-sharing business models and public policies.

The risks in these industries have potentially far-reaching implications for investors, and, because of their documented reliance on capital market financing[16–19], the amount of funding available for biomedical R&D. Given the underperformance of biotech and the large amount of systematic and idiosyncratic risk in both industries, the typical response of investors and firms is to reduce the amount of capital allocated to underperforming investments. Such a response may be one underlying financial cause of the 'valley of death' in biomedicine. Moreover, the elevated levels of systematic risk in both industries imply that the amount of funding available to R&D is dependent on the fortunes of the broader economy. Economic downturns could, therefore, turn into periods of decelerating innovation in biomedicine.

Despite the financial underperformance of the biotech sector, there is no doubt that this important sector provides the pipeline of innovations on which the pharma sector has become increasingly dependent. Therefore, a pressing challenge is how to attenuate the biotech sector's performance cycles. One possibility is to change the business and financing structure of the biomedical industry. With respect to business structure, adopting a more dynamic project-oriented approach to biomedical innovation—along the lines of Hollywood film studios—can improve efficiency and reduce costs[20]. Film studios now produce movies by bringing in the necessary expertise on a project-by-project basis rather than maintaining a full-time roster of directors, actors, writers, and so on. By being more flexible, studios are able to attract the top talent for a given project while saving costs associated with employing a large staff that might be idle for extended periods of time between projects.

And with respect to financing structure, using megafund portfolios proposed by previous studies can substantially reduce the cost of capital and allow a larger number of projects to be financed while offering more attractive returns to investors[21,22]. When a large number of projects are funded by a single pooled financial vehicle, the aggregate risks are reduced as long as the financial returns of the individual projects are not perfectly correlated with each other. More sophisticated uses of derivative securities and securitization techniques can lower the risks even further, and this risk reduction naturally leads to lower required rates of return by investors, and increased funding for biopharmaceutical companies[23,24].

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

ACKNOWLEDGMENTS

We thank Jayna Cummings for editorial support. Funding support from the MIT Laboratory for Financial Engineering is gratefully acknowledged.

AUTHOR CONTRIBUTIONS

A.W.L. first conceived of the idea of analyzing the financial risks and return of the biotech and pharmaceutical industries, proposed the basic design of the empirical and statistical analysis, assembled key members of the project team, provided funding through the MIT Laboratory for Financial Engineering, and was responsible for overall project management, manuscript preparation, and journal submission. Initial data collection, data cleaning, and preliminary analysis of company-specific stock returns were performed by N.A., Y.Z., and C.V., and reviewed by A.W.L. and R.T.T. More comprehensive data collection, data cleaning,

financial modeling, and detailed analysis of stock returns and accounting data were performed by R.T.T., who was involved in every aspect of the design of the project and the data analysis, with input from A.W.L. All aspects of the financial modeling and data analysis were reviewed by A.W.L. A.W.L. conceived of using an algorithmic approach to perform industrial classification on a rolling-window basis, and K.W.S. and C.H.W. developed the algorithms for classifying companies into biotech and pharma industries with input from and review by R.T.T. and A.W.L. All authors participated in preparing the first draft of the main manuscript, and A.W.L. reviewed and edited this draft to produce the final version. K.W.S. and C.H.W. prepared the initial draft of **Supplementary Methods** with input from R.T.T. and A.W.L., and R.T.T. and A.W.L. edited this draft to produce the final version. R.T.T. prepared the initial draft of **Supplementary Notes** and **Supplementary Results** with input from A.W.L., and A.W.L. edited this draft to produce the final version.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

1. TEConomy Partners. *The Economic Impact of the US Biopharmaceutical Industry: National and State Estimates* http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceuticaul-industry-economic-impact.pdf (Washington, DC: Pharmaceutical Research and Manufacturers of America, 2016).
2. Cortright, J. & Mayer, H. *Signs of Life: the Growth of Biotechnology Centers in the US* https://www.brookings.edu/wp-content/uploads/2016/06/biotech.pdf (Center on Urban and Metropolitan Policy, The Brookings Institution, 2002).
3. Golec, J. & Vernon, J.A. Financial risk of the biotech industry versus the pharmaceutical industry. *Appl. Health Econ. Health Policy* **7**, 155–165 (2009).
4. Cockburn, I. & Lerner, J. The cost of capital for early stage biotechnology ventures. Congressional Briefing http://buchpedersen.com/wp-content/uploads/2016/02/The-Cost-of-Capital-for-Early-Stage-Biotechnology-Ventures_CockburnLerner.pdf (2009).
5. Finkelstein, S. & Temin, P. *Reasonable Rx: Solving the Drug Price Crisis*. (FT Press, 2008).
6. Booth, B. Debunking myths about biotech venture capital. *Forbes* **22**, http://www.forbes.com/sites/brucebooth/2013/05/22/debunking-myths-about-biotech-venture-capital/ (2013).
7. Howard, D.H., Bach, P.B., Berndt, E.R. & Conti, R.M. Pricing in the market for anticancer drugs. *J. Econ. Perspect.* **29**, 139–162 (2015).
8. Fama, E.F. & French, K.R. Disappearing dividends: changing firm characteristics or lower propensity to pay? *J. Financ. Econ.* **60**, 3–43 (2001).
9. Thakor, R.T. & Lo, A.W. Competition and R&D financing decisions: evidence from the biopharmaceutical industry. Working Paper, MIT Sloan School of Management, 2016.
10. Koijen, R.S.J., Philipson, T.J. & Uhlig, H. Financial health economics. *Econometrica* **84**, 195–242 (2016).
11. Myers, S.C. & Howe, C.D. A life-cycle financial model of pharmaceutical R&D http://www.worldcat.org/title/life-cycle-financial-model-of-pharmaceutical-r-d/oclc/42739394 Program on the Pharmaceutical Industry, Sloan School of Management, Massachusetts Institute of Technology, 1997.
12. Myers, S.C. & Shyam-Sunder, L. in *Competitive Strategies in the Pharmaceutical Industry*, (ed. Helms, R.B. 208–237) (American Enterprise Institute for Public Policy: Washington, DC, 1995).
13. Lyandres, E. & Palazzo, B. Cash holdings, competition, and innovation. *J. Financ. Quant. Anal.* **51**, 1823–1861 (2016).
14. Nanda, R. & Rhodes-Kropf, M. Investment cycles and startup innovation. *J. Financ. Econ.* **110**, 403–418 (2013).
15. Nanda, R. & Rhodes-Kropf, M. Financing risk and innovation. *Manage. Sci.* **63**, 901–918 (2016).
16. Lerner, J., Shane, H. & Tsai, A. Do equity financing cycles matter? Evidence from biotechnology alliances. *J. Financ. Econ.* **67**, 411–446 (2003).
17. Rajan, R.G. & Zingales, L. Financial dependence and growth. *Am. Econ. Rev.* **88**, 559–586 (1998).
18. Brown, J.R., Fazzari, S.M. & Petersen, B.C. Financing innovation and growth: Cash flow, external equity, and the 1990s R&D boom. *J. Finance* **64**, 151–185 (2009).
19. Kerr, W.R. & Nanda, R. Financing innovation. *Annu. Rev. Financ. Econ.* **7**, 445–462 (2015).
20. Lo, A.W. & Pisano, G. Lessons From Hollywood: a new approach to funding innovation. *Sloan Manage. Rev.* **57**, 47–57 (2015).
21. Fagnan, D.E., Fernandez, J.M., Lo, A.W. & Stein, R.M. Can financial engineering cure cancer? *Am. Econ. Rev.* **103**, 406–411 (2013).
22. Fernandez, J.-M., Stein, R.M. & Lo, A.W. Commercializing biomedical research through securitization techniques. *Nat. Biotechnol.* **30**, 964–975 (2012).
23. Jørring, A., Lo, A.W., Philipson, T.J., Singh, M. & Thakor, R.T. Sharing R&D risk in healthcare via FDA hedges. No. w23344 http://www.nber.org/papers/w23344 (National Bureau of Economic Research, 2017).
24. Philipson, T. Hedging pipeline risk in pharma: FDA swaps and annuities https://pdfs.semanticscholar.org/6b84/3c138131fd45f279e51ddd8b2a1c8bc008d3.pdf (Milken Institute, March 2015).
25. Carlson, R. Estimating the biotech sector's contribution to the US economy. *Nat. Biotechnol.* **34**, 247–255 (2016).
26. Hoberg, G. & Phillips, G. Text-based network industries and endogenous product differentiation. *J. Polit. Econ.* **124**, 1423–1465 (2016).
27. Hoberg, G. & Phillips, G. Product market synergies and competition in mergers and acquisitions: A text-based analysis. *Rev. Financ. Stud.* **23**, 3773–3811 (2010).