Impact of Genomics on Biopharmaceutical Industry: Rare Diseases as Disruptive Innovation

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Abstract

The multinational biopharmaceutical industry grapples with intense financial pressures due to an increasingly cost-constrained and highly regulated health care environment, finite patent expiries on blockbuster drugs, generic competition, decreases in effective market exclusivity from new innovations, and a proliferation of smaller markets due to the escalating molecular segmentation patients populations (i.e., personalized medicine). Specifically, due to dramatic cost reductions in DNA sequencing following the development of "next-generation" sequence platforms in 2008, molecular diagnostics are increasingly being considered to be cost effective enough to be used as a standard medical test, both prospectively for risk assessment and confirmation of diseases---and increasingly, therapeutics. Although the progress in genomics is heralded as a solution to overcome certain rare diseases, some of the ethics and privacy questions to genomic research, such as how whole-person genomic information is collected and stored, and what constitutes informed consent are being vigorously debated. In the midst of these developments, pharmaceutical companies are obliged to reevaluate their drug development strategies and select among alternative future business models in order to stay relevant. Using a dynamic capabilities lens, this paper studied the impact of genomics generally and gene therapy specifically on the rare disease sector of the biopharmaceutical industry. This study found that increasing rates of cumulative returns depends on accumulating knowledge-based employees and expanding product portfolios of disruptive genomics-based technologies for treating rare diseases. Further, this study highlights the importance of building the capability and capacity to absorb expertise and accumulate knowledge for new product innovations and sustainable competitive advantage.

Keywords: Genomics, Rare Diseases, Disruptive Innovation, Dynamic Capabilities, Biopharmaceutical Industry

Introduction

In contrast to the current multinational pharmaceutical model which has dominated the market over the last generation (e.g., Merck, Pfizer, and Glaxo), where there was reluctance to invest in rare diseases because of small addressable patient populations and limited markets, pharmaceutical companies are gaining increased investment interest in rare disease treatment. Currently, there are 30 million Americans suffering from about 7,000 rare diseases (Only 5 percent of these conditions have approved treatments) [1, 2]. Among the technological advancements, one that has undoubtedly had a great influence on this economic shift is DNA sequencing which is mapping of the human genome. During the last 25 years, the cost of sequencing a human-sized genome has fallen dramatically from $100 million to $1000 [3]. Figure 1: Cost per genome evolution compared to hypothetical data reflecting Moore's law since 2008, which reflects the transition from Sanger-based sequencing to next-generation genome sequencing technologies [4]. Some of the other reasons behind the increasing interest in rare diseases from pharma companies are the significantly less time needed in terms of patient testing, increased government financial incentives, pediatric review voucher, and higher approval rates from US Food and Drug Administration (FDA) [5].As such, the genomics revolution is poised to significantly disrupt traditional multinational pharmaceutical industry structure reliant on large, blockbusters of chronic medications aimed at large patient populations. *These disruptive innovations such as gene therapy which delivers single treatment cures, will shift biopharmaceutical industry structure and requires companies to revise their strategies to stay competitive and relevant in such* ***high-velocity*** *markets.* Using the lens of dynamic capabilities, **this study aims to** study the effects of different financial, organizational, and product-related assets on the enterprise value of rare disease focused biopharmaceutical companies which are using genomics or gene therapy in their drug developments. In order to identify the impact of decreased cost and increased interest in genomics generally and gene therapies specifically (delivery of single treatment cure using corrective genes for fatal rare diseases) on biopharma companies, the industry background and the influence of genomics in rare diseases are studied. Furthermore this study emphasizes on the significance of building the capability and capacity to attract expertise and accumulate knowledge for new product innovations and sustainable competitive advantage for 24 rare disease focused biopharma companies amid current dynamic and high-velocity market environment in the United States.

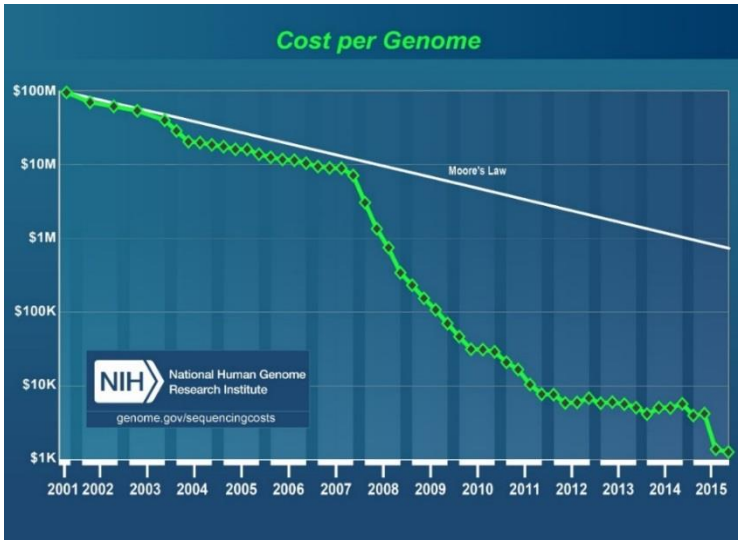

Figure 1: Cost per genome evolution compared to hypothetical data reflecting Moore's law [3]

Biopharmaceutical Industry Background

The biopharmaceutical industry is a combination of traditional multinational drug manufacturers, biotechnology companies, and distribution companies mainly concentrated on medicinal and veterinary chemical and biological combinations. A pharmaceutical company can be characterized as a firm that performs commercial research and development, marketing, and distribution of drugs [6]. Biotechnology refers to techniques for changing micro-organisms, and a biotechnology firm is a company that maneuvers on influencing living cells (plants or animals) using biological expertise and knowledge [7]. In highly dynamic industries with intense global competition and entrepreneurial high tech organizations such as pharmaceuticals and biotechnology, new product development is one of the most significant factors of success [8]. Thus, drug development companies have been shifting their strategies from manipulating natural compounds to use of new biologic understanding and tools in order to research and develop new drugs [9, 10]. New insights and tools such as genomics, theranostics, and RNAi are the main drivers of the shift in the industry from active disease confirmation to treatment decision making, and avoidance [11]. As one of the largest employers of scientists and one of the highest levels of R&D among industries (increasing R&D expenditure from $2.0 billion in 1980 to $51.4 billion in 2014 in US), the pharmaceuticals industry addresses large global markets [10, 12]. The United States possesses 86% of global biotech financing, it can be seen as the health indicator of the whole industry [13]. Some of the other characteristics of this industry are long drug development times (10-12 years), low levels

of drug transformation from clinical trials to approved drugs (less than 12%), high drug development costs (from $179 million in 1970s to $2.6 billion in 2000s-early 2010s), and high R&D expenditure as sales fractions (23.4% and 17.9% for domestic and total sales respectively) [14, 15]. According to Ernest and Young (2016), 78 biotech companies went public and raised $5.2 billion in their IPOs, of which 45 were from US [13]. Based on Ahn et al (2010), multinational pharma and biotech companies are merging their technology collection strategies and emphasize the importance of alliances compared to proximity to partners when considering revenue, profitability, and market valuation growth [10].

One of the more disruptive sub-sectors of the biopharma industries is genomics which affects different sectors of the industry such as companies which focus on single treatments for rare diseases. Thus, many companies are significantly increasing R&D investment in genomics to tap the market for rare diseases and leverage the new opportunities to treat heretofore unmet medical needs.

Genomics and Rare Diseases

Genomics, which is defined as the scientific discipline of sequencing, mapping, and characterization of human genes, has significantly influenced drug discovery and development in the pharmaceutical industry [16, 17]. Following the first cloning of human genes in 1976 molecular genetics reached human genetics and two decades after that database searching gained a big role in genomic research, the advances in this area have made it as potentially auspicious tool in terms of assessing risk, early detection, and targeting therapies in diseases such as cancer [18]. The information that genomics provides can bolster our understanding of disease biology, personalized therapies and consequently better health decisions through their combination with new technologies [19, 20]. In the last two decades, the cost of sequencing a human-sized genome has fallen dramatically from $100 million to $1,000 and sequencing industry leader Illumina is aiming for a $100 genome. The sudden change of speed and per genome cost reduction since 2008 reflects the transition from Sanger-based sequencing to next-generation genome sequencing technologies [4]. The emergence of next-generation sequencing technologies in the marketplace has enabled the production of an enormous volume of data inexpensively (up to 1 billion short reads per instrument run) [21]. Some of the other reasons behind the raised interest in rare diseases from pharma companies is the significantly less time needed in terms of patient testing, government financial incentives, and higher approval rates

from US Food and Drug Administration (FDA). As a result, the genomics revolution seems poised to significantly disrupt traditional multinational pharmaceutical industry structure. However, according to Kahn (2011), there are still technological barriers such as information access, data security and privacy to enable genomics to reach its full research and commercial potential [22]. Khoury et al. (2011) emphasizes the existence of a significant gap between the promise and reality of genomics in terms of cancer and prevention. Reis-Filho (2009) argues that the most significant risks and potential problems associated with genomics technology are unknown and will emerge when high throughput parallel processing is applied [23].

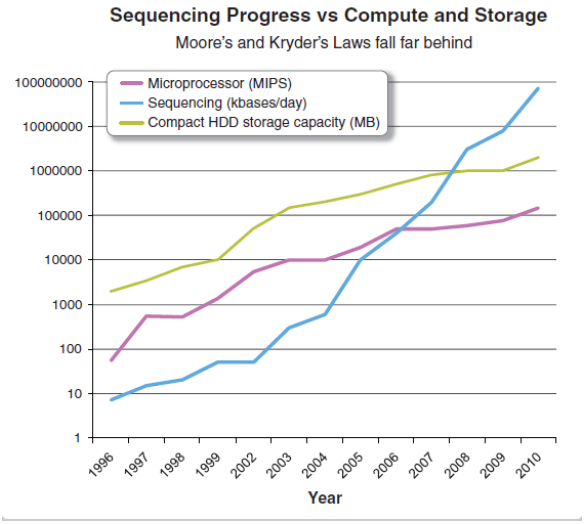

Figure 2: Sequencing Progress vs Computing and Storage [22]

Nonetheless, the treatment of rare disease has been one of the biggest and most disruptive windows of opportunity opened by the progress in genomics. Rare diseases provides researchers with smaller population of patients, and opportunity to cost effectively develop drugs spanning across highly non-homogeneous spectrum of diseases within a specific genetic disorder *[24]*. A rare disease is defined by the Rare Disease Act of 2002 as "any disease or condition that affects fewer than 200,000 people in the United States" *[25]*. Genomics is helping researchers to better understand the nature, severity, rate of progression, and clinical presentation of these diseases, many of which affect pediatric populations. As an example, Avexis is developing AVXS-101 (gene therapy) working on treating Spinal Muscular Atrophy (SMA) which has four (with 60% type 1) different types, is uniformly fatal by 2 years of age, 50% by 7 month and 90% by 12 months in infants *[26]*. This disease is caused by a single genetic defect and Avexis has the goal of mitigating or treating this disorder completely using

a single treatment gene therapy. Initial results presented in 2017 demonstrated that 15 of 15 (100%) patients were event-free at 13.6 months (versus an expected event-free survival rate based on the natural history of the disease of 25%). Many companies such as Avexis, Biomarin, Bluebird, Aboena, Dimension, and Spark are targeting different debilitating rare diseases.

As another example, in their quest for utilizing genomics driven therapies, Biomarin has developed the only enzyme replacement therapy to treat Morquioi A which is approved in United States, EU, Canada, Japan, Australia, Mexico, and Brazil (Vimizim). Biomarin also has five other products aimed at rare diseases approved by FDA and in the market while having four other drugs in the clinical testing stages. This company is one of the good examples of the attraction of great leadership and research team in order to better accumulate knowledge and turn it into new innovative therapies, robust portfolio and eventually financial success. This strategies has led Biomarin to go over $1 billion in revenues in 2016 (26% increase over 2015) driven by two of their products including Vimizim and Kuvan [27].

Many of these biotech firms are also forming partnerships in developing treatments. Some of the examples are Bluebird bio's partnership with Celgene; or Spark Therapeutics partnership with Pfizer in the development of SPK-9001 drug for the treatment of Hemophilia B *[28]*. Another important aspect of these rare disease focused biotech companies is they are located in biotech clusters such as Massachusetts (also east-coast states such as Virginia, Maryland, and New Jersey) and California (With one company in Seattle WA) which account for 17 of the 24 studied companies. Biotech clusters enhance access to academic research centers, qualified employees, experienced vendors and suppliers, informed life science venture investors, and shared resource arrangements *[29] [30]*.

In sum, biopharma companies need to acquire dynamic capabilities to recognize, understand, transform, and exploit [31] their tangible and intangible assets (tacit knowledge, R&D know-how, new product development, partnerships and acquisitions, and skilled workforce attraction) in order to accelerate innovation [32]. Markets such as biopharma are finely tuned to recognize and evaluate value, manage risks and reward companies who innovate in targeted therapies [30].

Dynamic Capabilities

In the world of new product development, faster information flow, and easier access to markets, managing intangible assets and the way companies orchestrate them are keys to building unique values and competitive advantage [33]. Teece et al. (1997) suggest that competitive advantage is built and protected not in product markets but in markets for know-how and other intangibles which they refer to as the dynamic capabilities. There are multiple definitions of dynamic capabilities in the literature. Pisano and Teece (1994) define it as organizational and strategic routines which allows managers to change, jettison, integrate, and re-connect resources in order to create new value-generating blueprints [34, 35]. Dynamic capabilities are tools for generating, evolving, and morphing of resources to attain sustainable competitive advantage [36, 37]. By merging these definitions, Eisenhardt et al. defines dynamic capabilities as the company's organizational and strategic actions to use, integrate, recombine, acquire and dispose of resources to equal or generate market change as a response to emergence, evolution, division, and demise of markets [38]. Some of these actions can be alliances, acquisitions, new product development, and strategic decision making. Eisenhardt et al. posited several commonalities amongst dynamic capabilities across high-tech organizations. Although dynamic capabilities differ across various firms, technology-based firms possess some common traits such as being "equifinal" (reaching dynamic capabilities from different roads and being path dependent); "compatible" (effectiveness of some capabilities across different industries); and "dependent on market animation and learning methods" [38, 39]. Furthermore, for a fast-changing pharmaceutical and biotech markets, dynamic capabilities are dependent on the generation of new knowledge for increasingly specific patient populations. Eisenhardt defines these types of adaptive knowledge creating activities as real time information, prototyping, multi-criteria decision-making, and experimenting in an iterative and cognitive way which leads to unpredictable outcomes [38].

Biotech and pharmaceutical companies have to deal with fast changing markets and rapid learning processes. This environment can stress the importance of learning from experience as a way to generate dynamic capabilities [40]. Studies demonstrate that the learning mechanism, rather than detailed *a priori* plans, plays an important part of the evolution of dynamic capabilities for firms. Repeated practices (in activities such as acquisitions, integration, and resource jettison) which lead to specific and tacit knowledge gain can be crucial for firms [41,

42, 43]. What is more important about learned knowledge is company's ability to systemize, articulate, share, and embed them into procedures and know-how which leads to the expedition of learning mechanisms [38, 42, 44]. Moreover, managers must acquire information from mistakes. Kim (1998) and Eisenhardt et al. (2000) emphasize the importance of mistakes and crises (real time and/or simulated scenarios) in the evolution of dynamic capabilities with examples of Hyundai and Yahoo respectively [45, 46]. Moderate experience speed can also bolster the creation of dynamic capabilities since rapid incoming experience can overpower managers' decision making ability and slow incoming experience deprives managers from keeping their knowledge updated [38, 42]. Another important factor that should be accounted for in fast-changing markets is the importance of the experience selection and jettison based on distinctive market changes [40, 47]. Lastly, Eisenhardt et al. (2001) and Brown et al. (1997) discuss the importance of "sequenced steps" in the generating dynamic capabilities [38, 43]. By assuming that dynamic capabilities are modular and composed of smaller components (ingredients), the order of composition and implementation of smaller modules into a dynamic capability (recipe) is crucial for firms.

In sum, in high tech environments such as biopharmaceuticals with a high rate of change, competitive advantage can be fleeting and erratic. Hence, constant management of intangible assets and resources (sensing, seizing, and transforming) in order to form and orchestrate dynamic capabilities is crucial to firms' success.

Hypotheses and Data Collection

Next, we consider the disruptive biopharma sub-sector of rare disease being driven by advances in genomics to consider elements of dynamic capabilities in building, creating and capturing value. Data from 24 biotech companies, 18 of which focus exclusively on gene therapy, with focus on rare disease therapy were chosen. The data collected are for the second quarter of 2017. Data were collected for each company in 11 categories (revenue, enterprise value, net income, retained earnings/ total financing, cash, number of employees, CEO tenure, number of board of director members, year of foundation, year of IPO, clinical/commercial products, and number of total products). The definition for each of these criterion is shown in Figure 3. The enterprise value (EV) has been defined as follows:

$$\boldsymbol{Enterprise\ Value\ (EV)} = \boldsymbol{market\ value\ of\ common\ stock + market\ value\ of\ preferred\ equity + market\ value\ of\ debt + minority\ interest - cash\ and\ investments}$$

Where market capitalization is the total value of a company's balance sheet and total cash is the sum of all the cash that a firm has in its books [48]. The complete table of collected data for the 24 companies is shown in Appendix A/Table 6: Collected Data. In order to determine the status of each company in terms of new product development, data from their drug pipeline were collected in order to see how many products each company has in different production stages (discovery, preclinical, Phase 1-3, and commercialization). The feasibility, iterative testing, and safety-related information is collected during preclinical development. The first phase of clinical trials refers to testing new drug products or treatments on small number of people to evaluate its effectiveness and safety. Phase 2 is further evaluation of drug or treatment's safety and effectiveness on a larger group of people. Phase 3 however, refers to the evaluation of drug's effectiveness, side effects, and safety on a large groups of people. In the commercialization and marketing phase, data still needs to be collected on drugs effectiveness and safety on bigger and diverse groups of people. Biotech and pharmaceutical company's pipeline catalogue can be seen as investment potentials and because of that different companies have different drugs in different areas in different stages of their pipeline. As mentioned before pharmaceuticals industry is characterized by its long development times (7.5 to 19 years [49]). U.S Food and Drug Administration (FDA) however, has some expedited programs for approving rare disease drugs which some companies can see as opportunity to shift their strategy towards gene therapy and rare diseases. The studied companies are concentrated in biotech clusters located in Eastern and Western States like Massachusetts, and California. The map of companies can be seen in Figure 3: Geographical Locations of Studied Companies.

Figure 3: Geographical Locations of Studied Companies

Table 1: Variable Definitions

	Definition
Enterprise Value	The market capitalization of a company is simply its share price multiplied by the number of shares a company has outstanding. Enterprise value is calculated as the market capitalization plus debt, minority interest and preferred shares, minus total cash and cash equivalents.
Market Capitalization	The value of a company that is traded on the stock market, calculated by multiplying the total number of shares by the present share price.
Revenue	Income, especially when of a company or organization and of a substantial nature.
Net Income	Net income (NI) is a company's total earnings (or profit); net income is calculated by taking revenues and subtracting the costs of doing business such as depreciation, interest, taxes and other expenses.
Retained Earnings	Retained earnings refer to the percentage of net earnings not paid out as dividends, but retained by the company to be reinvested in its core business, or to pay debt. It is recorded under shareholders' equity on the balance sheet.
No of Employees	# of Employees
CEO Tenure	# of years since the last CEO change
No of Board Members	# of people in the board of directors
Year Founded	Company establishment year
IPO	An initial public offering (IPO) is the first time that the stock of a private company is offered to the public. IPOs are often issued by smaller, younger companies seeking capital to expand, but they can also be done by large privately owned companies looking to become publicly traded.
# of Clinical and Marketed Products	Total number of products in phase 1,2,3 and commercial
Total # of Products	Total number of products in program area, discovery, preclinical, phase 1-3, Commercial levels

In the studied categories, finance-related assets of the firms include revenue, net income, cash and retained earnings. Moreover, organizational-related assets include the employees, CEO tenure, and number of the board of directors' members, year of foundation, and year of IPO. Finally, product-related assets include the number of products in various stages of development.

For the sake of evaluating the correlations between the enterprises value of the studied firms with these financial, organizational, and product assets in order to see if the disruptive biopharma sub-sector of rare disease is being driven by advances in genomics, ten hypotheses will be tested in this study:

H_1: Revenue of rare-disease focused biotech companies is positively correlated with their enterprise value.

H_2: The net income of rare-disease focused biotech companies is positively correlated with their enterprise value.

H_3: Retained earnings of rare-disease focused biotech companies is positively correlated with their enterprise value.

H_4: Number of employees in rare-disease focused biotech companies is positively correlated with their enterprise value.

H_5: Length of CEO tenure in rare-disease focused biotech companies is positively correlated with their enterprise value.

H_6: Number of board members in rare-disease focused biotech companies is positively correlated with their enterprise value.

H_7: The establishment year of rare-disease focused biotech companies is positively correlated with their enterprise value.

H_8: Years since the initial public offering of rare-disease focused biotech companies is positively correlated with their enterprise value.

H_9: Number of products in clinical or commercial stages in rare-disease focused biotech companies is positively correlated with their enterprise value.

H_{10}: Number of total products (From discovery to commercial stages) in rare-disease focused biotech companies is positively correlated with their enterprise value.

Methodology

In order to test these hypotheses, linear regression is used in this study. The dependent variable is "Enterprise Value" is tested against independent variables corresponding to each hypothesis. Some of the important results that are going to be summarized in the next section are Correlation, P-value, and R-square. Correlation is the degree which two metric variables are related in a linear manner (0-(-) 0.3 is considered as weak correlation/ (-) 0.3-(-) 0.5 is considered medium correlation/ (-) 0.5-(-) 1.0 is considered as strong correlation). Negative correlations mean that increase or decrease in the independent variable would result in the decrease or increase in the dependent value respectively.

In addition, the p-value shows the significance ($p < 0.05$) of the hypothesis. This means that if the p-value for each of the tests is >0.05 we reject the hypothesis. However, if the p-value is <0.05, we accept the hypothesis and consider the underlying assertion valid.

R-square refers to the percentage of the enterprise value that can be explained by different independent variables. In other words, R-square is determines the proportion of the variance in enterprise value that can be predated using the tested independent variable.

Finally, the non-standardized coefficient shows the amount of unit changes in the "Enterprise Value" with a one unit change in each independent variable.

The scatterplots for some of the independent variables are also shown to better illustrate the changes in the magnitude and direction of enterprise value (dependent variable) with respect to increases or decreases in the independent variables. In these plots, the independent variable is represented as Y-axis while the independent variables are delineated by the X-axis. The results of regression tests and scatterplots are discussed next.

Results & Discussion

Linear regression analysis was used to test if each of the independent variables can significantly predict the studied companies' enterprise value. Among the tested independent variables, the effect of "Net Income", "CEO Tenure", and "Year Founded" on "Enterprise Value" are insignificant based on the results of linear regression analysis with p-values >0.05 (in addition to having weak correlation values). On the other hand "Revenue", "Retained Earnings", "Number of Employees", "Number of Board Members", "IPO", "Clinical/Marketed Products", and "Total Number of Items in the Pipeline" had significant prediction power of enterprise value for the studied companies. In terms of correlation, the number of employees and revenue are most correlated with the enterprise value with 0.96 and 0.91 correlations respectively followed by number of products in clinical/market phase with 0.73 correlation. A -0.50 correlation between IPO and enterprise value means that the older the IPO date can result in higher enterprise value in a less strong correlation value. Based on the regression coefficient obtained from the test, a new drug added to the company's clinical/marketed portfolio can lead to about 1.3 billion units increase in their enterprise value; while having an extra employee can lead to $8.4 million in enterprise value. Finally the R-squared values for number of employees, and revenue, are 93% and 82% of the enterprise value can be explained by the mentioned variables respectively. These results mean that we reject H_2, H_5, and H_7 (colored columns), while we fail to reject the other hypotheses as those independent values have significant power in predicting enterprise value. While we fail to reject 7 out of 10 hypotheses, only four of them

are strongly correlated with the enterprise value with correlation values closer to 1.0 (two with correlation of higher than 0.9). All the mentioned information from the regression analysis is shown in Table 2: Regression Results for All Companies.

Table 2: Regression Results for All Companies (Enterprise Value as Dependent Value)

	Revenue	Net Income	Retained Earnings	No of Employees	CEO Tenure	Board Members	Year Founded	IPO	Clinical-Marketing	Total Pipeline
Correlations	0.91	0.18	0.732	0.967	0.026	0.56	-0.206	-0.506	0735	0.555
R Square	0.82	0.032	0.538	0.934	0.001	0.314	0.042	0.256	0.536	0.308
Coefficient	8.432	6.330	8.441	8.405	39.587	2354.9	-116.348	-444.64	1300.7	628.122
P-value	.000	.401	.000	.000	.906	0.004	.335	.014	0.000	0.005

In order to better understand if these variables have effects on companies based on their market capitalization size, large/medium and small companies were studied separately as well (according to Biocentury conference, 2017). Companies with less than $1 billion market capitalization are considered to be small in terms of market value. Large cap have market capitalization of more than $10 billion while medium cap companies have $1-$10 billion. Since only two of the twenty four studied companies fall under large cap category, large and medium cap companies are merged. Based on the data in Table 3: Regression Results for Big-Medium Companies, we can see that although revenue and number of employees are still highly correlated with enterprise value, retained earnings are more highly correlated compared to the previous table. Based on the second linear regression analysis, IPO, clinical/marketed products,

and number of board members are more correlated with enterprise value as well. However, H_{10} is added to the rejected hypotheses compare to the test with all the companies. Finally it can be seen that, based on R-Square, significant amount of enterprise value can be explained by number of employees, retained earnings, and revenue.

Table 3: Regression Results for Big-Medium Companies (Enterprise Value as Dependent Value)

	Revenue	Net Income	Retained Earnings	No of Employees	CEO Tenure	Board Members	Year Founded	IPO	Clinical-Marketing	Total Pipeline
Correlations	0.9	0.448	0.909	0.962	-0.147	0.682	-0.324	-0.675	0.747	0.493
R Square	0.823	0.201	0.827	0.925	0.022	0.465	0.105	0.456	0.558	0.243
Coefficient	8.075	15.616	9.680	8.568	-303.4	3798.318	-254.8	-726.0	1699.34	576.59
P-value	.000[b]	0.167	.000	.000	0.666	0.021	0.331	0.023	0.008	0.123

Finally, the analysis for the small cap companies' linear regression shows that, surprisingly, the only correlation we fail to reject is the net income with having -0.77 correlation with the enterprise value (due to the fact that most of the studied companies have negative net incomes). This shows that it is harder to impute different variables to enterprise value when companies have smaller capitalization values as shown in Table 4: Regression Results for Small Companies.

Table 4: Regression Results for Small Companies (Enterprise Value as Dependent Value)

	Revenue	Net Income	Retained Earnings	No of Employees	CEO Tenure	Board Members	Year Founded	IPO	Clinical-Marketing	Total Pipeline
Correlations	-0.28	-0.777	-0.453	-0.214	-0.099	-0.332	0.116	-0.356	0.118	0.413
R Square	0.078	0.604	0.206	0.046	0.01	0.11	0.013	0.127	0.014	0.170
Coefficient	-0.775	-4.939	-0.676	-0.949	-6.579	-66.98	2.683	-13.50	16.16	44.06
P-value	0.379	0.002	0.12	0.483	0.76	0.267	0.706	0.256	0.700	0.161

The summary of the results of hypotheses in each scenario is shown in Table 5: Results of Hypotheses in Different Scenarios.

Table 5: Results of Hypotheses in Different Scenarios

Type of Company	Hypotheses Which Are Not Rejected
All	H_1, H_3, H_4, H_6, H_8, H_9, H_{10}
Only large and medium	H_1, H_3, H_4, H_6, H_8, H_9
Only small	H_2

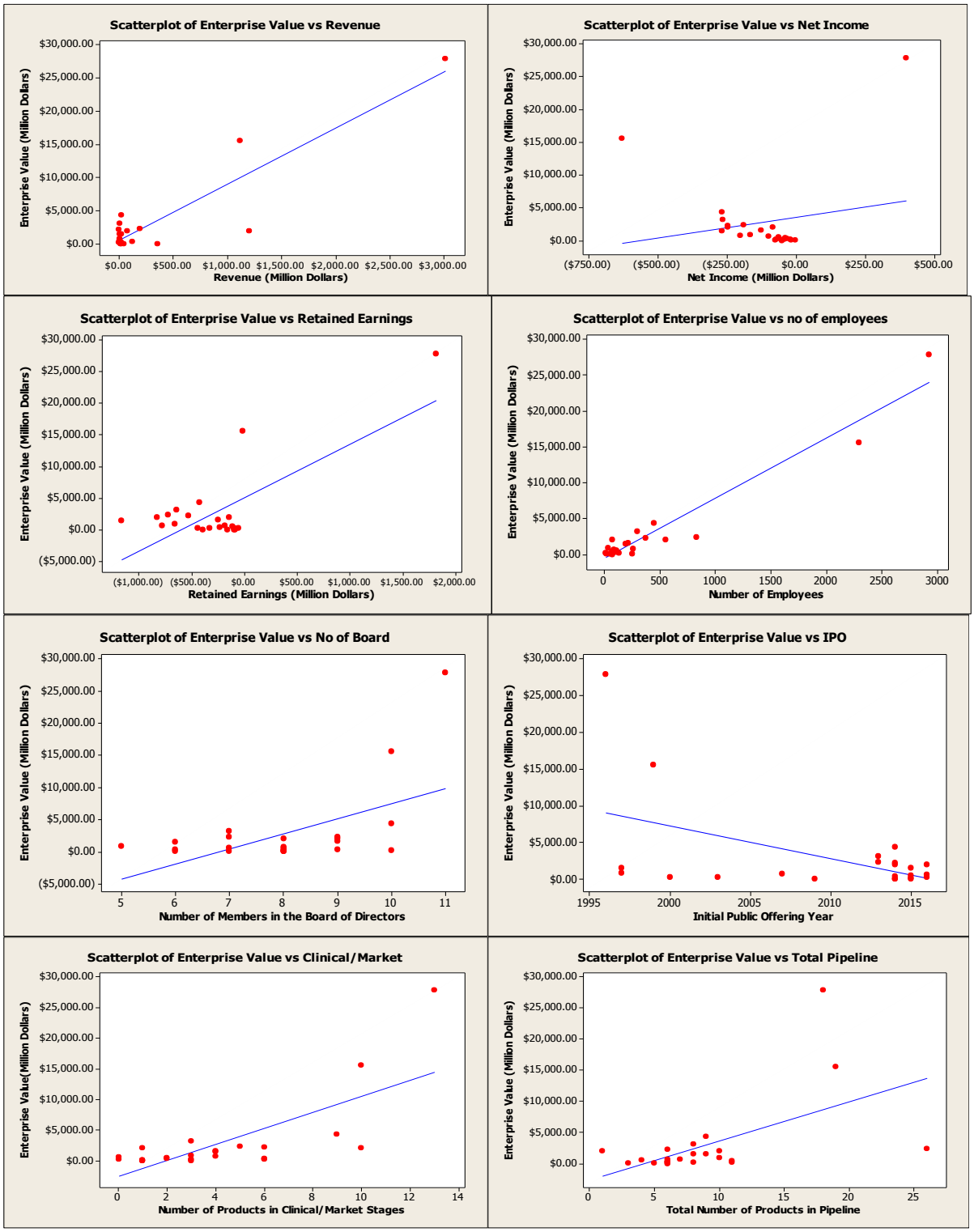

Figure 4: Enterprise Value Curve Estimations for Different Variable

Conclusion

Biopharma companies have to constantly deal with intense financial, competitive, regulative, technological, and market fluctuation pressures. Due to these high change rates, competitive advantage can be fleeting and short-lived. Hence, constant morphing and management of intangible assets and resources (sensing, seizing, and transformation) can be crucial to biopharma companies' success and survival. Several firm commonalities in terms of dynamic capabilities such as equifinality, substitutability, and that the fact that the competitive advantages are fleeting in high-tech markets were identified and evaluated in the context of dynamic capabilities. Examples of dynamic capabilities can be found in technology-based firm literature highlighting the need to respond to market price changes, acquisition in order to reconfigure resources, product innovation for organizational renewal, organizational structure reconfiguration, and resource divestment [50, 51, 52, 53, 54]. In order to attain these capabilities and build value, it is important for high-tech to attract expertise (employees in different levels of the organization such as researchers and board of director members) in order to steer company towards competitive advantage and commercial success. The skilled and innovative employees can lead the development of new product innovation and guide it towards a more versatile and efficient product pipeline. The know-how and experience that the workforce can bring (especially in bigger companies) can be seen as a bolstering factor in leveraging dynamic capabilities which can be recognized, understood , and transformed in order to align with company goals and lead to commercial success (revenue). In other words, technology managers' job is not only to manage the financial aspects of the technology, but also to manage activities such as management of people and making sure that their expertise is used efficiently towards faster and better innovation. Strong dynamic capabilities can be formed with the accumulation of experience, articulation and codification of knowledge and companies need to have to ability to change the way they solve problems as the environment changes [55]. In the case of Biopharma industries, more efficient, prolific, and versatile staff can lead to better new product development and a more efficient research and development pipeline.

The disruptive genomics revolution can provide rare disease-based biopharma companies the opportunity to create significant value and upend the entire global industry from mass market to personalized medicine. Leveraging genomics and new technologies can guide biopharma

firms to a better product innovation and bolster their chances of attracting employee expertise, insightful boards of directors, and management teams. Biopharma managers should be alert in sensing the opportunities, threats, and resources followed by seizing them and reconfiguring them to fit their organization in order to gain and sustain series of fleeting competitive advantages.

In this study, 24 rare disease focused biopharma companies were studied and several variables were tested against enterprise value. The companies have been analyzed in three groups "general", "large/medium capitalization", and "small capitalization" separately.

Through the hypotheses in this study, we found that variables such as "number of employees", "revenue", "number of products in clinical/market stages" ,and "retained earnings", are strongly correlated (in that order) with the enterprise value in rare disease focused biopharma companies . These correlations seem to be less true as company capitalization size decreases making the process of connecting the causes of companies' enterprise value increase an even more daunting task.

Using a dynamic capabilities lens, this paper studied the impact of genomics generally and gene therapy specifically on the rare disease sector of the biopharmaceutical industry. This study found that increasing rates of cumulative returns depends on accumulating knowledge-based employees and expanding product portfolios of disruptive genomics-based technologies for treating rare diseases. Further, this study highlights the importance of building the capability and capacity to absorb expertise and accumulate knowledge for new product innovations and sustainable competitive advantage.

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Appendix A/Table 6: Collected Data

Company #	Company Name	Classification $MM (Small, Mid Large Cap)	Rare Disease	Gene Therapy	Market Cap (Million)	Revenues(Million)	Enterprise Value (Million)	Net Income(Million)	Retained Earnings	Cash (Million)	# of Employees	CEO Tenure (Years)	# Board members	Year of Founding	Year of IPO	Number of Products	In pipeline products	Discovery/preclinical products
1	ALEXION PHARMA	Large	Y		$29,230.00	$3,011	$27,770	$399	$1,818	$1,460	2,924	1	11	1992	1996	**4**	**9**	**5**
2	BIOMARIN	Large	Y		$16,330.00	$1,116	$15,540	($630)	($15)	$789	2,293	12	10	1997	1999	**6**	**4**	**9**
3	KITE PHARMA	Med	Y	Y	$4,740.00	$22	$4,325	($267)	($427)	$414	447	3	10	2009	2014	0	9	0
4	BLUEBIRD BIO	Med	Y	Y	$3,820.00	$6	$3,116	($264)	($646)	$704	300	7	7	1992	2013	0	3	5
5	INTREXON	Med	Y		$2,530.00	$190	$2,285	($186)	($729)	$244	832	8	9	1998	2013	0	5	21
6	ULTRAGENYX PHARMA	Med	Y		$2,590.00	$0	$2,208	($245)	($531)	$381	376	8	7	2010	2014	0	6	0
7	AVEXIS INC	Med	Y	Y	$2,230.00	$1,200	$1,989	($83)	($141)	$240	70	2	8	2010	2016	0	1	0
8	JUNO THERAPEUTICS	Med	Y	Y	$2,720.00	$79	$1,987	($245)	($831)	$732	553	4	9	2013	2014	0	10	0
9	SPARK THERAPEUTICS	Med	Y	Y	$1,830.00	$20	$1,533	($123)	($252)	$296	213	6.5	9	2013	2015	0	4	4
10	SAREPTA THERAPEUTICS	Med	Y		$1,840.00	$5	$1,448	($267)	($1,166)	$391	197	0.5	6	1980	1997	1	3	5
11	ZIOPHARM ONCOLOGY	Small	Y	Y	$930.60	$6	$849	($165)	($658)	$81	36	2	5	1998	1997	0	3	7
12	AMICUS THERAPEUTICS	Med	Y		$1,010.00	$5	$679	($200)	($780)	$330	263	12	8	2002	2007	1	3	2
13	EDITAS MEDICINE	Small	Y	Y	$784.30	$6	$599	($97)	($186)	$185	89	3	7	2013	2016	0	0	7
14	REGENXBIO	Small	Y	Y	$569.90	$4	$480	($63)	($115)	$89	107	8	8	2008	2015	0	2	2
15	BELLICUM PHARMACEUTL	Small	Y	Y	$436.00	$123	$332	($39)	($231)	$103	72	0.5	8	2004	2014	0	6	5
16	AUDENTES THERAPEUTIC	Small	Y	Y	$391.30	$0	$285	($59)	($100)	$105	97	5	9	2012	2016	0	2	4
17	INTELLIA THERAPEUTIC	Small	Y	Y	$488.90	$16	$215	($31)	($54)	$273	119	3	6	2014	2016	0	0	6
18	SANGAMO THERAPEUTICS	Small	Y	Y	$330.20	$19	$187	($71)	($441)	$142	131	1	8	1995	2000	0	6	5
19	ABEONA THERAPEUTICS	Small	Y	Y	$227.40	$1	$184	($19)	($332)	$42	15	2.5	10	1974	2003	0	3	5
20	VOYAGER THERAPEUTICS	Small	Y	Y	$251.90	$14	$77	($40)	($90)	$174	77	3	8	2013	2015	0	1	5
21	FIBROCELL SCIENCE	Small	Y	Y	$28.30	$355	$10	($15)	($163)	$17	23	0.5	7	1992	2009	0	1	2
22	APPLIED GENETIC TECH	Small	Y	Y	$103.10	$47	$4	($1)	($90)	$98	53	15	8	1999	2014	0	3	3
23	UNIQURE	Small	Y	Y	$129.40	$25	($28)	($73)	($396)	$157	251	1	6	1998	2014	0	1	4
24	DIMENSION THERAPEUTI	Small	Y	Y	$33.80	$11	($45)	($49)	($100)	$79	74	2.9	8	2013	2015	0	1	5

Appendix B/ Table 7: Descriptive Statistics for the Studied Companies

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Enterprise Value (Million)	24	$27,816	-$46	$27,770	$2,751.68	$6,199.315
Revenue (Million)	24	$3,011	$0	$3,011	$273.40	$681.683
Net Income (Million)	24	$1,029	-$630	$399	-$118.39	$175.985
Retained Earnings(Million)	24	$2,984	-$1,166	$1,818	-$277.46	$538.745
Number of Employees	24	2909.00	15.00	2924.00	400.5000	712.92520
CEO Tenure	24	14.50	.50	15.00	4.7130	4.15477
Number of Board	24	6.00	5.00	11.00	8.0000	1.47442
Year Founded	24	40.00	1974.00	2014.00	2002.0417	10.96429
IPO Year	24	20.00	1996.00	2016.00	2010.0833	7.13788
Clinical and Marketed	24	13.00	.00	13.00	4.0833	3.48807
Total Pipeline	24	25.00	1.00	26.00	8.7083	5.47309