The Promise of a Cure: Measuring the Welfare Gain to Hemophilia a Patients From Gene Therapy

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The Promise of a Cure: Measuring the Welfare Gain to Hemophilia A Patients from Gene Therapy

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Abstract

As pharmaceutical expenditures in the United States continue to rise, many policymakers are calling for ways to curb healthcare spending. An often-overlooked possibility for better value from pharmaceuticals is the development and promotion of gene therapy. By correcting the genetic basis of disease, gene therapy can eliminate recurring prescription drug spending through a single, potentially curative, intervention. Hemophilia A, an inherited blood clotting disorder, has been a target disease for gene therapy proponents for decades due to its genetic cause, high cost of treatment ($500K+ per year) and long-term toll on patients. In this project, I fit a discrete choice demand system to hemophilia A drug consumption data and find demand to be sensitive to drug price, dosing frequency, and efficacy in reducing bleeds. I then use the fit model to simulate gene therapy’s market entry into the therapeutic space. I project that gene therapy will become the most popular treatment for hemophilia A, capturing 34% of the market and increasing total consumer surplus by $436M per annum or 25% of current spending. The substantial size of these welfare gains suggests a role for gene therapy in producing better treatment outcomes for patients and long-term cost savings for society.
Acknowledgments

First and foremost, I’d like to thank Ariel Pakes for providing consistent guidance and advice in the course of writing this thesis. Before the senior thesis process, Ariel had indicated he typically does not advise senior theses but was willing to give me a chance. I’m extremely grateful I was afforded the opportunity to work with him; at key bottlenecks, Ariel’s expertise on demand estimation and connections within the field to ensure that this project continued to progress. I can say with assurance that the ultimate conclusions of this thesis would be but a fraction of their current state without his input and recommendations.

I also extend my gratitude to my thesis seminar instructor, Judd Cramer, for ensuring that steady progress was made towards completion of this thesis over the past seven months. Judd’s experience in economics writing and the process of writing senior theses led to suggestions which were crucial towards the ultimate success of this project. Without Judd’s recommendations, this paper would not read nearly as smoothly nor the ultimate research question be framed in a manner so relevant to the major challenges faced by our society today.

I’d also like to give special thanks to Dr. Stacy Croteau of Boston Children’s Hospital. Dr. Croteau provided key input on both the medical qualities of Hemophilia A and structure of the Hemophilia A drug market and sponsored this project’s dataset proposal to the Centers for Disease Control (CDC). Gratitude is also due to the Executive Board of the American Thrombosis and Hematosis Network (ATHN), which also assisted in advancing this project’s dataset proposal to the CDC. At the CDC, I’d like to thank Meredith Oakley and Brandi DuPree for working with me to ensure the CDC’s dataset met the project’s needs.
Last but not least I’d like to acknowledge the contributions of Erica Moszkowski and Jeff Gortmaker for providing input on the model I employed and helping me design an estimation procedure to estimate such a model. Jeff Gortmaker and Chris Conlon played a crucial role in ensuring model convergence and estimation by authoring the pyblp script, which I used to fit my model of demand. Throughout the process of using the pyblp script for estimation, Jeff answered any questions I had with impressively short turnarounds and provided critical one-on-one time to help me debug and optimize my code.
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I. Introduction

Growing prescription drug spending is a core driver of rising healthcare costs in the US. In 2018, total prescription drug spending reached $476 billion, accounting for 2.3% of GDP, and representing a 5.5% year-over-year increase (more than doubling the rate of GDP growth). Given that prescription drugs now make up nearly 20% of total healthcare spending, calls for price controls have become increasingly intense from the US Congress. As of 2020, both the US Senate and House are discussing legislation aimed at reigning in rising prescription drug costs. Although these measures appear to have popular support, their benefit to patients remains unclear.

From a social planner’s perspective, the effect on social surplus of an increase in prescription drug spending is ambiguous. On one hand, an increase in prescription drug prices holding quality constant would result in a decrease in value delivered to patients.

Figure 1. US Prescription Drug Spending as Proportion of Total Healthcare Spending.


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patients, sacrificing patient welfare for higher producer profits. On the other hand, high spending may be resulting from improved quality of treatments that provides welfare gains to patients despite higher price tags. In addition, spending on prescription drugs may also act as a substitute for the remaining 80% of healthcare spending, including hospital visits, surgery and routine physician visits. Therefore, even with rising drug spending, it’s possible that patient welfare improves and total healthcare spending decreases due to gains from innovation. In particular, the development of “curative” therapies, which rectify the underlying cause of a disease after a single treatment regimen, may eliminate the need for conventional treatment (daily prescription drug use, regular physician / hospital visits, etc.) and provide sizable welfare gains to patients.

One promising area for healthcare cost savings and welfare gains is gene therapy. A gene therapy is a therapeutic regimen which alters the genetic content of a patient’s cells, thereby providing a long-lasting or permanent solution to otherwise chronic diseases. A number of intriguing clinical candidates are being developed to treat hemophilia A, including Biomarin’s Valrox which is projected to enter the market in Q4 of 2020. Hemophilia A is currently one of the most expensive diseases for payers and providers to treat; severe patients average roughly $700,000 in annual cost of care with some patients incurring upwards of $1M in cost of care annually. Introduction of a gene therapy to cure a fraction of the hemophilia patient population would eliminate many of these recurring costs and provide therapeutic intervention that lasts years.

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5 “Therapeutic Categories Outlook,” Equity Research (Cowen, September 2019).
This study provides the first rigorous estimates of the consumer welfare gain from the potential market entry of a gene therapy targeting hemophilia A. Expanding on previous work on anti-depressants and anti-cholesterol drugs, I provide the first application of a characteristic space model of discrete choice to the hemophilia A therapeutic market. Multinomial logit and Berry-Levinsohn-Pakes demand systems are used to fit empirically observed demand and provide estimates for patient valuation of key drug characteristics such as efficacy in reducing bleeds and dosing frequency. A novel gene therapy with a set of assumed product characteristics is then introduced to the demand system and demand is predicted based on the coefficients obtained from the original model estimates. The difference in patient welfare in the gene therapy and no gene therapy demand system is then computed.

I find demand in the hemophilia A therapeutic market to be quite price sensitive, leading to the market share of gene therapy rapidly dropping off as its price increases from $2M to $3M per dose. When priced at $2.5M per dose, gene therapy reaches an equilibrium market share of 34%, becoming the most popular treatment for severe cases of hemophilia A. At this price, the mean consumer surplus gain to the patients who chooses gene therapy is $236K/year, leading to a total consumer surplus of $436M/year. As current prescription drug spending for severe hemophilia A patients is approximately $1.7B/year, consumer welfare will increase by 25% of current spending following gene therapy market entry, although total spending also increases. Overall, I conclude that gene therapy priced in the

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$2 – 2.5M range will provide substantial welfare gains to hemophilia patients, profits to firms, and reductions in long-term spending on hemophilia treatments.

The paper is structured as follows: Section II gives a brief literature review of work on discrete choice. Section III discusses the market structure including the overall US pharmaceutical market, the medical characteristics of hemophilia, the market for hemophilia medications, and gene therapy. Section IV outlines the discrete choice models of patient demand (Multinomial Logit and BLP models). Section V discusses the data sources used to estimate demand and Section VI documents the estimation protocol used to fit the data to the model. Section VII presents the key results of demand estimation and predicted welfare effects from gene therapy. Section VIII concludes the paper by summarizing key findings.
II. Literature Review

A. Characteristic Models of Consumer Choice

Economists have long been interested in how consumers select one product from a set of differentiated products. To explain a consumer’s behavior, a series of discrete choice models have been proposed, grounded in the assumption from utility theory that each individual chooses the product which maximizes his or her utility. The industrial organization subfield applies these models of consumer theory to explain empirically observed consumption patterns within discrete choice markets. This paper takes advantage of the lengthy history of the discrete choice literature by modeling a patient/doctor’s joint decision to take/prescribe a given prescription drug as a problem of discrete choice.

There are two principal approaches to discrete choice commonly employed within the industrial organization subfield: the product space approach and the characteristic space approach. The product space approach views goods as indivisible entities that a consumer compares in their totality to other complete goods (e.g. compare a BMW 5 series to a Mercedes S-class). Conversely, the characteristic space approach breaks down products into their characteristics which include price, measures of quality, durability, etc. (e.g. a 500-hp V6 engine, leather interior, 40 mpg, etc.). At the heart of the disagreement in these two approaches is the question of whether consumers have preferences over whole products (e.g. a BMW 5-series), or they have preferences over characteristics of those products.

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products (i.e. horsepower, engine cylinders, fuel efficiency, etc.). As this difference is theoretical and may vary across individuals, both models provide stylized if imperfect takes on the discrete choice problem.

The product space and characteristic space differ in the type of markets they describe well. The product space approach tends to have the upper hand in describing consumer behavior in markets where product characteristics are difficult to measure such as food, beverages, and designer clothing. For example Hausman, Leonard, and Zona (1994) use the product space to estimate demand in the US beer market. Beer is a particularly suitable good for the product space as the characteristic space would require breaking products such as Bud Light and Coors Light into their demand-affecting characteristics, many of which are unobserved (e.g. malt taste). However, the product space struggles when there are a large number of products in the market; the number of parameters in the product space increases quadratically with the number of products, whereas the number of parameters in simpler characteristic space models increases linearly in the number of characteristics. Thus, in markets with a large number of differentiated products with measurable characteristics, the characteristic space approach is often more tractable, while in markets with a smaller number of products or characteristics that are more difficult to measure, the product space approach has a computational advantage.

Most important for this study is the characteristic space’s ability to forecast the effect of the market entry of a new product. As consumer preferences are measured solely over product characteristics, if one can accurately predict the characteristics of the entrant

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(for this study, drug efficacy, half-life, etc.), then the novel product can be introduced to the fitted demand system and market shares re-computed to account for it. By assuming a functional form for an individual’s utility, a prediction of consumer welfare can then be made following product entry and compared to consumer welfare in the original market. Such an estimate provides a lower bound on the welfare gain from product entry as this welfare estimate does not account for increased competition from product entry which would drive down the prices of other products, thereby further increasing consumer welfare. Ergo, this study’s focus on approximating the patient welfare gain from the entry of a novel gene therapy for hemophilia A makes the characteristic space an intuitive choice.

This study expands on previous literature documenting how a characteristic space demand system relying on core product characteristics (such as price and quality) and heterogeneous consumer tastes can be used to estimate demand in a discrete choice setting. The characteristic model was originally proposed by Lancaster (1966) and applied to a logit demand system by McFadden (1973). McFadden proposed a set of assumptions about a consumer’s utility to arrive at a conditional logit demand model that related the empirical market shares of each product to the underlying utility that a consumer experienced from consuming said product. Therefore, McFadden’s model provided a straightforward means of computing total consumer welfare from a fitted system of market demand.\(^\text{13}\)

However, early characteristic space models struggled to explain complex substitution patterns across the set of products. The conditional logit model produces predicted cross-price elasticities that are proportional to the conditional market share of the

competing product for some individual rather than the similarity between the two products. *Ceteris paribus*, one would expect that a price increase in a luxury BMW 5-series would have a greater effect on the more similar luxury Mercedes S-class demand than on the less-similar economy Toyota Corolla demand. Alas, the standard logit model produced cross-price elasticities in which a BMW price increase increases Toyota demand more than Mercedes demand due to Toyota’s larger market share.

Such a counter-intuitive result led to the proposal of the nested logit model in which consumers solve a two-step discrete choice problem: first they choose between product categories (luxury, economy, etc.) based on product characteristics and a price index of each category and second they select a product within their category of choice. The two-level nature of the nested logit model allows for the possibility that substitution probabilities are higher between products in the same category (e.g. Mercedes S-class and BMW 5-series in the luxury segment) which produces more reasonable substitution patterns. However, the nested logit model also requires the market be segmented into discrete product categories. As cross-price elasticities depend on how the market is segmented, its conclusions are most relevant in markets with clear segmentation rather than ones of horizontal differentiation. Overall, while the early logit and nested logit models could fit cross-sectional snapshots of a market well, they were limited in their effectiveness at drawing conclusions about the dynamic changes faced by markets (e.g. following price changes).

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To better estimate cross-price elasticities, Domencich and McFadden (1975) updated the conditional logit model of demand to allow for random coefficients on each product characteristic. This relaxation meant that individuals’ tastes for a product characteristic (e.g. dosing frequency in the drug market) can differ due to unobserved individual characteristics, so two individuals with the same observed characteristics may experience different choice probabilities. By providing this additional layer of complexity, the Random Coefficients Logit (RCL) model produced substitution patterns that came closer to those observed empirically. However, the RCL model also complexified the econometrician’s demand estimation problem; the number of parameters to estimate increases quadratically with the RCL compared to the standard conditional logit. While the standard conditional logit involves the estimation of \((K + 1) \times (D + 1)\) parameters, where \(K\) is the number of product characteristics and \(D\) is the number of individual characteristics in the model, the RCL requires estimation of \((K+1) \times (D + 1) + (K + 1)^2\) parameters to allow for random coefficients on each product characteristic. While distributional assumptions on these parameters can be made to ease the computational difficulty of parameter estimation, such assumptions also jeopardize the internal and external validity of the model used to estimate demand.

A tractable methodological approach to fitting a RCL characteristic space demand system using market-level product consumption data and consumer characteristics was pioneered by Berry, Levinsohn, and Pakes (1995). The BLP model provided an upgrade over previous models due to two key features. First, as discussed above, using random coefficients for individual’s preferences on characteristics allowed the model to better explain product substitution patterns. Second, the model captured the effect of unobserved
product characteristics through inclusion of a product-level unobservable demand shock vector. While this vector introduces the issue of price endogeneity (one would expect the shock to be correlated with price), BLP propose a series of exogeneous cost shifters as instruments for price to correct this problem. Taken as a whole, the model’s stylizing of consumer heterogeneity and price endogeneity distinguished it as the dominant framework used in demand estimation. Berry, Levinsohn, and Pakes (2004) followed this result with a paper that showed how micro-level data on individuals and the product choices they make can be utilized to improve the BLP’s parameter estimates. The richer model further improved the authors’ ability to replicate empirical substitution patterns and increased the precision of estimates of a given individual’s taste over product characteristics.

**B. Relevant Healthcare Literature**

Cleanthous (2002) applied the BLP demand estimation to the anti-depressant market to measure the welfare gains from innovation in the market from 1981-2001. Cleanthous estimates the annual per-patient welfare for the most valuable drug in the market, Prozac, to be approximately $55,000 for insured patients and $9,000 for uninsured patients (who pay out-of-pocket for the drug).\(^{15}\) Even the lesser uninsured patient surplus represents a substantial welfare gain over the cost of the drug; according to Cleanthous’s estimates, patient surplus is nearly 30 times the actual annual price of Prozac.\(^{16}\) Cleanthous’s numbers

\(^{15}\) The disparity in estimation is likely driven by insured patients who do not fully internalize the price of pharmaceuticals due to their insurer sharing the cost. This results in positively biased own-price elasticities and positively biased welfare gains for insured patients.

\(^{16}\) The high proportion of social surplus experienced by patients compared to producers for Prozac can be partially attributed to Prozac losing patent protection in 2001.
provide a benchmark for the welfare benefits from drug entry that this study investigates in a different market.

Dunn (2012) conducted similar work on the anti-cholesterol drug market, taking advantage of a richer dataset including patient-level health information and drug choice. From 1996-2007, Dunn found annual per patient welfare in the insured population increased from $277 to $321. While these figures are one to two orders less than Cleanthous’s estimates, Dunn’s estimates are on the order of the annual price for the average prescription anti-cholesterol drug (approximately $700).\textsuperscript{17} Dunn further shows that despite rising prices over time, the quality-adjusted price index of anti-cholesterol prescription drugs actually decreased a modest 9% over the period from 1996 to 2005.\textsuperscript{18}

\begin{flushleft}
\textsuperscript{17} Anti-cholesterol drugs tend to have smaller margins due to the abundance of generic options that convey similar benefits. For this reason, producer profits may fall short of consumer surplus when accounting for small margins on revenues.
\textsuperscript{18} Dunn, “Drug Innovations and Welfare Measures Computed from Market Demand: The Case of Anti-Cholesterol Drugs.”
\end{flushleft}
III. Market Overview

In this section I discuss the core characteristics of the market for pharmaceuticals. First, I identify general characteristics of the pharmaceutical markets in the United States and provide a brief disease profile for hemophilia. Subsequently I review more specific characteristics of the market for hemophilia drugs and gene therapies.

A. The Pharmaceutical Industry in the United States

The core business of pharmaceutical firms in the United States is the research, development and commercial promotion of prescription drugs. Compared to other R&D-intensive industries, the pharmaceutical industry on aggregate is relatively fragmented; Richman et al. (2016) estimates the Hirschman Herfindahl Index for the US to be around 500, suggesting the industry is not concentrated. However, these aggregate measures may misrepresent the industry’s degree of market competitiveness. Pharmaceutical products only obtain FDA approval for narrowly-defined “indications” which consist of a disease, line of care, and patient population (e.g. first-line therapy for hemophilia A pediatric patients). Given that each indication represents a mutually exclusive market, the individual market concentrations for these indications may be substantially higher, sometimes bordering on pure monopoly (the FTC measured the HHI for the Alzheimer’s market to be 9801 in 2000). Coupled with the patent protection and market exclusivity firms can obtain for their products (discussed in depth below), this narrower definition of pharmaceutical

markets implies that the industry is composed of monopolists or differentiated oligopolists competing across multiple very narrowly-defined markets.

A drug’s life cycle can be segmented into three phases, research, development, and commercial promotion, which are described below:

A drug’s life cycle typically begins with a patent being filed by a pharmaceutical firm or research university upon discovery of a novel chemical compound. These patents are often filed before rigorous lab testing and sometimes even before a clear application is identified by which the new molecule may treat disease. While most of these patents are of little or no value, they have a sizable positive expected value due to the small probability of the patented molecule becoming a blockbuster drug which could have billions of dollars in revenue.

In the US, the patent process differs for New Chemical Entities (NCE) and biologics. The majority of new drug approvals are NCE, which are small molecules with a clearly-defined chemical structure that typically can be mass-produced relatively cheaply and easily. NCE are protected by “composition of matter” patents which expire after 20 years, although this period can be lengthened by up to 5 years to account for time spent in clinical trials. Once the patent is up, generic molecules tend to rapidly enter the market. Biologics are macro-molecules that attempt to copy or modify proteins (including antibodies) or

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nucleic acids that are found naturally in biology. They can be orders larger (and more complex) than NCE and have been responsible for an increasing proportion of new drug approvals recently.\textsuperscript{23} Biologics can only be protected by “composition of matter” patents if they are comprised of a molecule different from that observed in nature. Otherwise, biologics manufacturers file for the weaker patent protection of the process by which they produce the biologic (often this is a unique cell line), or an application of the biologic to a particular disease area. Regardless of the type of patent protection, when biologics go off patent, they are not as easily replicated by generic manufacturers as NCE; “generic” biologics, called biosimilars require some upfront research & development cost as well as bear higher marginal costs than traditional generics. For this reason, biologic products tend to continue to collect substantial profits for their original developers long after going off patent.\textsuperscript{24} Once a patent is secured, firms research the mechanism by which their most promising candidates affect disease and proceed to drug development.

In the US, the drug development process is tightly regulated by the Food and Drug Administration (FDA). Development begins with preclinical testing, or research of drug candidates in animal or \textit{in vitro} models of disease. Firms then file an Investigational New Drug application (IND) with the FDA which decides whether to approve the start of clinical testing. The clinical trial process is broken into three pre-approval phases and one post-approval phase: Phase I typically tests the safety of the drug candidate in a small sample of healthy subjects, Phase II provides a more robust test of drug safety and a preliminary

\textsuperscript{23} De la torre and Albericio, “The Pharmaceutical Industry in 2016. An Analysis of FDA Drug Approvals from a Perspective of the Molecule Type.”

look at efficacy in the target population and Phase III provides an in-depth examination of drug efficacy in the target population. Should the clinical candidate achieve Phase III readouts which meet or exceed the efficacy of existing FDA-approved drugs (sometimes referred to as the standard of care) a pharmaceutical firm then submits a New Drug Application (NDA) to the FDA. The FDA reviews the NDA within the next 3 – 12 months and issues its decision whether to approve the drug as a treatment for a given indication. Finally Phase IV clinical trials continue to evaluate drug efficacy following FDA approval.25

The research & development process for the pharmaceutical industry is both long and expensive. On average, the three phrases of clinical trial testing last an average of 9.7 years and cost pharmaceutical firms $1.46 billion per approved drug.26 When research cost and pre-launch costs are accounted for, the cost incurred rises to $2.56 billion per new drug approval.27 However, returns to R&D spending vary widely across firms and over time. A Forbes analysis estimates total R&D cost per new drug approval for the largest pharmaceutical companies to be over $6 billion, with the least innovative pharmaceutical firms sinking upwards of $10 billion per new drug approval.28 Lack of well-defined industry standards (How should firms account for the cost of developing failed candidates? How should firms allocate fixed costs shared across drug candidates?) contribute to the firms themselves having trouble pinpointing their exact fixed cost of developing a new...
drug. Nonetheless, firms typically operate under the following two assumptions: 1) their cost function is dominated by the “sunk costs” from the R&D process and 2) the marginal cost of producing an additional unit of drug is negligible (often a few orders less) compared to payers’ willingness to pay and sunk costs. For these reasons, the profit-maximizing drug price is often exclusively determined by the demand for the drug.

Once a drug’s development is complete, firms transition towards commercial promotion, beginning with the highly confidential and complex process of drug pricing. US patent law and the FDA’s granting of market exclusivity gives firms substantial market power within a given indication, allowing each firm to price as a differentiated oligopolist. A successful FDA clinical trial can result in up to a 5-year extension for the drug’s patent and a 5 to 12-year period of market exclusivity depending on the type of molecule and the drug’s application. Typical NCE receive just 5 years of market exclusivity (although often their copy is protected longer than that by their patent), while biologics get a 12-year window of market exclusivity. Drugs approved for rare diseases (orphan drugs) get an additional two-years of market exclusivity and drugs approved for pediatric diseases get an additional 6 months.29 Collectively, these measures give substantial market power for a fixed period of time to innovative firms that successfully develop new treatments.30 Thus, a drug’s asset value to firms is the discounted value of oligopoly profits over a fixed time period. However, given that the therapeutic market is highly sensitive to market entry from

30 Lakdawalla, “Economics of the Pharmaceutical Industry.”
novel, innovative treatments, some drugs will become obsolete or be out-competed before their patent / exclusivity expiry.

Regulators, including the US FDA, Department of Justice (DOJ) and Federal Trade Commission (FTC) as well as a number of watchdog groups closely monitor the behavior of pharmaceutical firms and insurers in an effort to steadily increase patient welfare. The DOJ and FTC closely monitor the pharmaceutical industry to prevent flagrant exertion of market power by one firm in any given indication. One area of concern for the FTC/DOJ is collusion between firms. Many pharmaceutical firms repeatedly compete with each other across similar disease areas (e.g. Merck and Bristol Myers Squibb both have highly competitive oncology programs with contact in multiple different indications). Such widespread multi-market contact may facilitate collusion and as such is closely monitored by the FTC. 31

Pharmaceutical firms’ market power is counteracted by substantial market power for “payers,” the organizations which actually purchase the drugs. Payers in the market are the insurance providers; they can be either government health services (such as Medicaid or the British National Health Service) or private insurers (such as United Health or Aetna). Payers are the “gatekeepers” to prescription drugs because they can reject the price for a drug proposed by a pharmaceutical company if they deem it excessive. Such a credible threat denies the drug access to either an entire health insurance patient pool (e.g. patients with Aetna or Medicaid in the US) or an entire national health system (e.g. the UK). As these insurance providers are themselves monopolists or oligopolists, market power exists

on both sides of the market for pharmaceuticals, which provides some degree of downward pressure on pharmaceutical prices.\textsuperscript{32}

Still, price-cost margins in the pharmaceutical industry are notoriously high, averaging around 40\%, although the distribution of margins is bimodal due to two distinct segments of pharmaceutical competition.\textsuperscript{33} Competition among manufacturers of branded drugs follows an oligopolistic differentiated Bertrand model of competition.\textsuperscript{34} Therefore, price-cost margins for the best drugs can be extremely high (>95\%), while margins for older, less effective drugs will be lower. Conversely, competition among manufacturers of generic drugs follows an undifferentiated Bertrand model of competition so generic drugs are priced at or close to marginal cost (margin < 5\%). Therefore, once a drug goes off-patent and becomes available as a generic, price falls to marginal cost, giving patients sizable welfare gains. Most markets are a mix of “branded” and “generic” drugs and as such, the entry/availability of a high-quality generic at marginal cost can boost patient welfare and bring down the prices of branded drugs.

After payers and pharmaceutical manufacturers conclude negotiation on drug reimbursement, the drug is added to the insurer’s formulary, which is a list of drugs and the reimbursement amount that the insurer will pay for them. Patients and physicians then make the joint decision of which (if any) drug to be prescribed from the set of reimbursable


drugs in the insurer’s formulary.\textsuperscript{35} Physicians have the final say on which drug to prescribe. Therefore, many argue that physicians are the principal drivers of drug demand, citing work that shows physicians internalize their personal financial benefit when prescribing anti-cholesterol drugs in Japan.\textsuperscript{36} Others argue that patients drive prescription drug selection due to their credible threat to switch physicians should their physicians not prescribe their drug of choice. The sizable market of direct-to-consumer pharmaceutical advertisements as well as these ads’ causal potential to boost sales round out the argument that consumers play a pivotal role in the drug selection process.\textsuperscript{37}

One important caveat within this market is that insured patients may not internalize the full cost of the drug that their insurer pays. Cost-sharing programs such as deductibles, out-of-pocket copayments, and coinsurance rates for prescription drugs will distort how a patient internalizes the true cost of the drug. Further, the negotiated prices between insurers and pharmaceutical firms may end up being a fraction of the drug’s “list price,” further distorting individual’s price sensitivity if this final negotiated price is not observed (which is generally the case given the confidential nature of insurer price negotiations). Thus, as patients and physicians only partially internalize the list price of a prescription drug, observed price elasticities tend to be inelastic \textsuperscript{38}.

\textbf{B. Disease Profile of Hemophilia}

\textsuperscript{35} Lakdawalla, “Economics of the Pharmaceutical Industry.”
Hemophilia is a hereditary disease in which blood fails to properly clot due to an inability to produce enough of a specific blood clotting factor. It comes in two principal types: hemophilia A and hemophilia B, which result from a deficiency in blood clotting Factor VIII or Factor IX, respectively. Both types of hemophilia are caused by mutations of the F8 and F9 genes located on the X chromosome, making hemophilia a sex-linked disease.³⁹

The localization of the mutation in Factor VIII/IX to the X chromosome proves a critical determinant of who suffers from hemophilia. Females have two X chromosomes so development of severe forms of hemophilia is uncommon in females. Females with one healthy copy and one defective copy will be carriers of hemophilia and may or may not have deficiency of the coagulation proteins leading to a diagnosis of hemophilia. Females have a 50% chance of passing the “hemophilia gene” to their off-spring; males will only pass the hemophilia gene on to their daughters. Due to this sex-linked inheritance pattern of hemophilia, the great majority (93%) of hemophilia cases occur in males.⁴⁰

If left untreated, hemophilia can lead to severe, life-threatening internal or external bleeding which leads to a shortened life-expectancy. Hemophiliacs’ propensity to suffer from uncontrolled internal bleeding often leads to severe pain and swelling which negatively impacts quality of life. The most common sites of these prolonged bleeds are joints and muscles, which are especially susceptible to chronic damage and pain.⁴¹ Chronic

⁴⁰ Hoyer.
joint damage impairs hemophiliacs from engaging in exercise/physical activity or from conducting regular occupational tasks that require some motility. This chronic damage causes many adult hemophilia patients to qualify for Medicaid through their disability.\textsuperscript{42} Other symptoms of severe cases of hemophilia include brain hemorrhage and deep internal bleeding, which can lead to death.\textsuperscript{43}

This study focuses on the US hemophilia A population due to the uniqueness of the US private insurance markets and high-quality data available on the US hemophilia patient population collected by the Centers for Disease Control. Hemophilia A affects about 1 in every 5,000 live male births leading to roughly 400 babies being diagnosed in the US every year. Due to easily-detectable symptoms and a straightforward diagnostic exam of Factor VIII concentration, infants with severe hemophilia A tend to be diagnosed shortly after birth; median time to diagnosis from birth is one month for severe patients, 8 months for moderate patients, and 36 months for mild patients.\textsuperscript{44} For these reasons, there exists a very well-defined hemophilia A patient population in many high-income countries, such as the United States, many member-states of the European Union, Canada, Australia, New Zealand, and Japan. These large, well-funded markets with high willingness to pay for therapies make hemophilia an attractive therapeutic target for pharmaceutical companies.

The hemophilia patient population is growing at a moderate pace. Baker et al. (2013) estimates that the hemophilia A patient population reached 13,276 patients in 2010.


\textsuperscript{43} Darby et al., “Mortality Rates, Life Expectancy, and Causes of Death in People with Hemophilia A or B in the United Kingdom Who Were Not Infected with HIV.”

although some experts postulate that figure has risen to nearly 18,000 by 2019.\textsuperscript{45} This represents growth of 35\% in the patient population from 1990-2010, outpacing US population growth over the same period (24\%). Some of this growth can be attributed to high death rates for hemophiliacs in decades past, as many hemophiliacs contracted HIV or Hepatitis C from contaminated blood in the 1980s, causing the hemophilia population to plummet. Of hemophilia A’s 13,000 patients, approximately 93\% are male. Ethnically/racially, the distribution of patients is insignificantly different from overall US demographics, suggesting that hemophilia A is not more or less common in any particular ethnic groups. Additionally, the hemophilia patient population is overwhelmingly young compared to the US population as a whole; as of 2010, 46\% of hemophiliacs were under the age of 18 compared to just 24\% of the US population as a whole.\textsuperscript{46}

Prescribed treatment regimens for hemophiliacs tend to differ based on a patient’s disease severity. Hemophilia is commonly diagnosed as “severe”, “moderate,” or “mild” based on clotting factor concentration in the blood; roughly 50\% of hemophilia A cases qualify as “severe,” 20\% as “moderate,” and 30\% as “mild.”\textsuperscript{47} As of 2010, 77\% of severe patients used self-delivered intravenous prophylaxis (also referred to as self-infusion), as well as 51\% of moderate patients, and 21\% of mild patients.\textsuperscript{48} In addition to the three grades of disease severity, 25-30\% of severe hemophilia A patients develop neutralizing antibodies, or “inhibitors,” against factor replacement therapy. These inhibitors render conventional factor replacement therapy ineffectual and require advanced alternative

\textsuperscript{45} “Therapeutic Categories Outlook.”
\textsuperscript{47} Baker et al.
\textsuperscript{48} Baker et al.
therapies (bypassing agents) to treat bleed events and intensive factor VIII replacement (daily or twice daily) to try to tolerize the immune system to factor VIII. Overall, a patient’s disease severity and inhibitor status are highly predictive of whether the patient is prescribed the routine prophylaxis medications that this study focuses on.

Medical therapy for hemophiliacs is expensive. In the US, mean annual cost of factor replacement therapy has been estimated to be as high as $700K for severe hemophilia A patients.\textsuperscript{49} This mean is inflated by a fraction of hemophiliacs that experience extremely high costs which drives up mean cost of care. These patients are typically severe hemophiliacs who develop inhibitors and require immune tolerance induction; one study found the average cost of care for hemophiliacs with inhibitors is nearly $1.2M.\textsuperscript{50} Overall, the relatively high median cost and the small probability of patients with inhibitors racking up $1,000,000+ in annual costs to payers, makes hemophilia an especially burdensome disease is insurer’s risk pools.\textsuperscript{51}

\textit{C. History of Hemophilia}

While the prevalence of severe bleeding disorders in males was identified in ancient times, hemophilia first gained international notoriety due to its prevalence in the gene pools...
of many European royal families around the turn of the 19th century.\textsuperscript{52} Given the royal stature of many hemophilia B carriers (British Queen Victoria) and patients (Russian Prince Alexei), hemophilia is sometime referred to as “the royal disease.”\textsuperscript{53} The high profile and substantial resources of European royalty proved unable to control symptoms and risks for these royal hemophiliacs; British Prince Leopold (1853-1884), Spanish prince Alfonso (1907-1938), Russian prince Alexei (1904-1918)\textsuperscript{54} all perished within their first 31 years of life.\textsuperscript{55}

The molecular cause of hemophilia was first identified in 1947, by Alfredo Pavlovsky, an Argentine researcher who discovered his patients had mutations in genes encoding “anti-hemophilic globulins” which were later named Factor VIII and Factor IX.\textsuperscript{56} Despite the medical community learning the cause of hemophilia, therapy options remained limited for the next two decades, as the only viable therapy was blood or plasma transfusion upon the start of a severe bleeding episode. Such a treatment regimen was largely ineffective due to the low Factor VIII/IX concentration in normal plasma.\textsuperscript{57} However, by the 1960s Pool, Hershgold, and Pappenhagen (1964) discovered that plasma cryoprecipitate contains higher concentrations of Factor VIII, leading to cryoprecipitate replacing normal fresh frozen plasma as the therapy of choice.

\textsuperscript{53} Franchini and Mannucci.
\textsuperscript{54} Alexei’s was murdered in 1918 during the Bolshevik revolution.
\textsuperscript{57} Hoyer, “Hemophilia A.”
Hemophilia treatment experienced a major breakthrough in the 1970s due to the ability to fractionate and concentrate FVIII or FIX from plasma and to lyophilize (freeze-dry) if for later reconstitution when needed. At the start of the decade, most hemophiliacs were still being treated “on-demand,” meaning they’d only be transfused with the cryoprecipitate following the start of a bleeding episode. The effect of these improved factor concentrates was multiplied by the impact of primary prophylaxis, the preemptive infusion of coagulation factors into the blood to prevent prolonged bleeding episodes, that a team of Swedish researchers pioneered and popularized in the 1960s. Over the next four decades, prophylaxis would not only displace the need for on-demand care, but availability of lyophilized factor concentrate enabled hemophiliacs to self-infuse themselves at home, removing costly visits to their doctors. When coupled with further innovations enabling the purification of Factor VIII/IX concentrate from blood plasma, primary prophylaxis represented a promising path towards normalization of life for hemophilia patients.

In the US, such advances were also buttressed by the public sector. Recognizing the potential to improve the lives of hemophiliacs, the U.S. government passed The Public Health Service Act establishing the hemophilia diagnostic and treatment center program in 1975, which leveraged government resources and the existing healthcare system to improve ease of receiving care for hemophiliacs. The measure set up a system of Hemophilia Treatment Centers (HTC) around the country where insured hemophiliacs could seek prophylaxis and/or on-demand care. However, despite expanded options for

58 Hoyer.
care, the high cost of prophylaxis, coupled with low insurance spending caps made continuous prophylaxis unaffordable for the first few decades of national HTCs. Once a patient hit his insurer’s spending cap (1 – 3 years typically), he would often have to switch his employer to qualify for a new insurance plan. Thus, while the 1970s contained a number of key medical advances for hemophilia patients, it would take over 30 years before American hemophiliacs gained expanded access to continuous prophylaxis.

If the 1970s marked a leap forward for hemophilia, the 1980s signified a step back. Infusion of Factor VIII/IX concentrates harbored a key risk: as each dose of these coagulant factor concentrates sourced coagulant from hundreds if not thousands of different blood donors, hemophiliacs were broadly exposed to risk of contracting blood-borne diseases. Ergo, come the early 1980s, contamination of coagulant concentrates led to roughly 50% of hemophiliacs contracting Human Immunodeficiency Virus (HIV) and comparable fraction contracting Hepatitis C Virus (HCV) from contaminated portions of the blood stock.61 Thus, despite medical progress being made in controlling bleeding in hemophiliacs, the majority of the hemophilic population succumbed to AIDS or Hepatitis C-related complications by the end of the decade.62

The tide turned again for hemophilia during the late 1980s and 1990s as FVIII/FIX concentrates became and cheaper to produce due to breakthroughs in producing recombinant FVIII/FIX. Recombinant clotting factors are produced in animal cell lines rather than purified from plasma, effectively eliminating the risk of contamination and enabling the inexpensive production of large amounts of clotting factors. Two of these

62 White.
recombinant clotting factors: Baxter’s Recombinate (1992) and Bayer’s Kogenate (1993), became blockbuster drugs that dominated the hemophilia market for over a decade.\(^\text{63}\) Interestingly enough however, despite the lower production costs associated with these recombinant factor concentrates, their list price to insurers began to steadily rise over time, leading to the high cost of continuous prophylaxis today.

![Evolution of Hemophilia Treatment](https://genetherapy.isth.org/images/2019/06/30/mod2-post.jpg)

**Figure 2.** Evolution of Hemophilia Treatment.  
Source: International Society on Thrombosis and Haematosis  
https://genetherapy.isth.org/images/2019/06/30/mod2-post.jpg

### D. Market for Hemophilia A Drugs Today

Currently, there are 28 FDA-approved drugs to treat hemophilia A, although not all of them are regularly-prescribed. The oldest hemophilia A drugs still on the market (Hemofil M & Koate-DVI) are Factor VIII concentrates purified from human plasma donors that date back to the 1960s and 1970s. These plasma-derived Factor VIII concentrates are

\(^{63}\) White.
typically used to control bleeding upon visiting a hospital or HTC rather than for prophylaxis. The most numerous products in the market are recombinant Factor VIII concentrates, the first of which entered the market in 1992 (Recombinate). The first-generation recombinant Factor VIII concentrates are very similar to plasma-derived Factor VIII concentrates except they are produced by \textit{in vitro} cell lines rather than obtained from other humans, which limits the potential for contamination. From the 1990s to the present, a series of next-generation recombinant Factor VIII concentrates (e.g. Eloctate, Jivi, and Adynovate) were developed with the potential for an extended half-life (EHL) compared to their predecessors. Finally, Roche’s Hemlibra – an antibody rather than a factor replacement therapy – gained FDA approval in 2017 and quickly became the drug of choice for patients with severe hemophilia and inhibitors and increasingly used for hemophilia A patients on prophylaxis without inhibitors.

Product differentiation in the hemophilia A market occurs primarily along two relevant dimensions; efficacy and duration of effect. Efficacy is measured by quantifying how much a given therapy reduces bleeding and can vary greatly across individual patients. Most clinical studies report the mean and median of the annualized bleeding rate (ABR), defined as the number of uncontrolled bleeds per year. As patients may have differing thresholds for what constitutes a bleed event, this metric is a noisy proxy for efficacy. Studies also report the percentage of patients without a bleeding episode over the course of a year. Although subject to the same noisiness as ABR, percent without a bleeding episode has the advantage of suggesting the percentage of patients for which such a therapy appears optimal (given that no bleeds are the best-case scenario for patients).
Duration of effect is often measured in half-life, measured in hours. Plasma-derived and early recombinant Factor VIII concentrates have a half-life of about 12 hours, while later-generation Factor VIII concentrates have an “extended half-life” of up to 24 hours. Roche’s Hemlibra, an antibody rather than a Factor VIII concentrate, has a half-life of roughly 4 weeks and is therefore highly-differentiated from its Factor VIII concentrate competitors. An alternative metric to measure the durability of a drug’s effect employed in this study is the number of doses recommended per year, which scales inversely with half-life.

The hemophilia prescription drug market is also segmented between factor replacement therapies and non-factor replacement therapies. Factor replacement therapies tend to be the medication of choice for moderate patients and severe patients without inhibitors. Non-factor replacement therapies headlined by Hemlibra are used for prophylaxis in hemophilia patients with or without inhibitors; however, factor replacement therapy is still required peri-operatively or for bleed treatment. Recently, non-factor replacement therapies such as Hemlibra have been shown to be effective in patients without inhibitors as well and have been rapidly absorbing market share among all severe hemophilia patients.

The hemophilia prescription drug market possesses a set of core features which make it an attractive market for pharmaceutical firms. First, hemophilia is a rare disease, affecting just 0.005% of the US population. Conventional economic theory suggests such a small market size would deter firms from attempting to enter the market due to difficulty in recouping R&D costs. To counteract this implication, the US Orphan Drug Act of 1983

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incentivizes firms to target rare indications by offering extended market exclusivity, substantial R & D subsidization, and the potential of smaller, less expensive clinical trials. As such, the net cost of developing a new drug in a rare disease such as hemophilia can be a fraction of the cost to develop a new drug in a larger indication such as a common type of cancer. Further, extended market exclusivity for “orphan drugs” provides firms with a lengthier revenue stream of huge margins for drugs targeting rare diseases.65

Second, the hemophilia patient pool is very young; approximately 50% of hemophilia patients are under 21 years of age and greater than 30% of patients are less than 12 years of age. The young patient population has fueled steady mid-single-digit growth in the hemophilia therapeutic market over the past five years. Cowen projects that campaigns to keep adolescents and young adults on the factor replacement therapies they started as children and improved quality (longer-lasting) factor replacement therapies will keep the hemophilia therapeutic market growing at a CAGR of 5-6% over the next 5 years.66 Further, given the high proportion of children who suffer from the disease, hemophilia qualifies as a pediatric indication. FDA-approved drugs in pediatric indications are eligible for an additional 6 months of market exclusivity to incentivize pharmaceutical firms to develop innovative therapies in pediatric disease.67

A third key characteristic of the market is that all FDA-approved drugs to treat hemophilia A are biologics. No firm has successfully developed a “generic” biosimilar to treat hemophilia. The lack of generics to treat hemophilia has inflated hemophilia drug

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66 “Therapeutic Categories Outlook.”
67 “Therapeutic Categories Outlook.”
prices compared to drug prices in indications with popular and effective generics (e.g. anti-
cholesterol and anti-depressants).

The hemophilia prescription drug market is also an attractive market for study by economists. First, due to the aforementioned Public Health Service Act establishing the hemophilia diagnostic and treatment center program of 1975, nearly all hemophiliacs exclusively seek treatment at a hospital or clinic that is a registered Hemophilia Treatment Center (HTC). This provides HTCs with the unique capability of collecting high-quality datasets on a large sample of the hemophilia patient population. Second, existence of inexpensive and effective hemophilia A diagnostics produces a well-defined patient population. Third, as emphasized earlier, hemophilia is extremely costly to treat; as severe patients average annual cost of care of $350,000 – $700,000 per patient, innovation has the potential to realize cost savings on the order of tens if not hundreds of millions of dollars per year. If realized, these cost savings will reduce the burden on payers that expensive factor replacement and non-factor replacement therapies have placed. Fourth, current treatments for hemophilia are chronic in nature (cannot be ended). Given the seemingly endless cost streams to payers from these therapies, the hemophilia A therapeutic market is a framework where one imagines a cure would be extremely beneficial. Fifth, and perhaps most germane, there exist three gene therapies in Phase III clinical trials, which are projected to be up for FDA approval beginning with Q3 of 2020. These therapies are the agents of change which may disrupt the hemophilia A market to the benefit of patients.

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**E. The Promise of Gene Therapy**

A gene therapy is a treatment which attempts to remedy a genetic disease by introducing to the genetic material (DNA) needed to instruct the body how to make specific proteins. As many diseases such a hemophilia A have a single-gene genetic basis, gene therapy attempts to take advantage of this by proposing a fix that by introducing a normal copy of the gene so that the body can begin to produce FVIII itself rather than relying on exogenous replacement with FVIII concentrate. Gene therapies follow one of three main therapeutic approaches: 1) replace a non-functioning mutated gene with a properly functioning gene, 2) inactivate a mutated gene that is driving disease, 3) introduce a novel gene to fight disease.69


*Figure 3. The Principle of Gene Therapy.*

As of December, 2019, two-FDA approved gene therapies have gained FDA approval. Spark Therapeutics’ Luxturna, which cures a rare form of blindness, was the first gene therapy to gain FDA approval in 2017. Luxturna is a one-time treatment priced at $850,000.

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Spark Therapeutics is effectively a monopolist as Luxturna is the only FDA-approved drug for this rare type of blindness.\textsuperscript{70} Novartis’s Zolgensma, a cure for Spinal Muscular Atrophy (SMA), followed Luxturna in 2019 to become the second FDA-approved gene therapy. Zolgensma carries an even higher price tag of $2.125 million, making it the most expensive drug on the market.\textsuperscript{71} As it must be administered to infants less than two years of age, Novartis likely took advantage of the high willingness-to-pay amongst parents of SMA patients, as the disease would prove fatal otherwise. Contrary to Luxturna, Zolgensma competes with Biogen’s Spinraza (which is not curative) in the SMA therapeutic market. Spinraza has a hefty price tag itself of $750,000 for year one, and $375,000 thereafter. As SMA patients must take Spinraza for their full length of life (estimated to be 18 years), 5 years on Spinraza carries an equivalent price to Zolgensma.\textsuperscript{72} For patients who live longer than 5 years, Zolgensma offers millions in cost-savings, even at its high price.

Both Luxturna and Zolgensma work similarly, delivering a functioning copy of a gene that is mutated in the target disease. To do so, they use a type of delivery system called an Adeno-associated virus (AAV) vector, which is modeled after a type of virus which commonly infects human cells but does not cause disease in humans. These vectors have been shown to possess the ability to preferentially infect specific cell types and introduce new genes that can be stably expressed in the targeted cells.\textsuperscript{73} However, these target cells

have a limited life-span themselves; scientists have combatted this by directing gene therapies at stem-cell populations or long-lived cell types so the gene therapy maintains its efficacy over the long-term. Given that progress towards successful gene therapy is a recent phenomenon (although attempts have been made for over thirty years), few clinical trials have extended beyond 10 years, so whether gene therapies last a lifetime, a decade, or less, is still hotly-contested within the scientific community. Readers seeking a more comprehensive discussion of the science behind gene therapy should reference Dunbar et al. (2018).\textsuperscript{74}

For hemophilia A, there are six gene therapies in clinical development as of March 2020 (Table 1). All six of these gene therapy candidates use the same mechanistic approach: an AAV viral vector is used to deliver a functioning copy of the Factor VIII gene to hemophilia A patients’ hematopoietic (blood cell-producing) stem cells.\textsuperscript{75} Biomarin’s Valrox, the most-advanced of the clinical candidates, is wrapping up a Phase III clinical trial following strong Phase II readouts. In December of 2019, Biomarin submitted a Biologic License Application (BLA) to the FDA, grounded in interim results from its Phase III trial of Valrox; the FDA has pledged to review this BLA and make a final regulatory decision on Valrox by August of 2020.\textsuperscript{76} Gene therapy candidates being developed by Spark, Bayer, and Sangamo will likely be beat to market by Valrox but project to challenge Valrox within the next five years. Therefore, hemophilia A may be the first indication

\textsuperscript{74} Dunbar et al.
\textsuperscript{76} “Therapeutic Categories Outlook.”
where multiple curative gene therapies exist.\textsuperscript{77} Market entry of a second line of gene therapies will likely prove beneficial for patients as firm competition may drive down prices, increasing the proportion of social surplus that patients and payers are able to capture.\textsuperscript{78}

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Table 1. Gene Therapy Candidates in Hemophilia A (Source: clinicaltrials.gov)

Hemophilia’s unique medical characteristics distinguish it from previous diseases which have been successfully treated with gene therapy. One important caveat is that hemophiliacs with a history of inhibitors are not eligible for gene therapy. As prevalence of any history of inhibitors is about 30% of severe hemophiliacs, a large fraction of patients will be unable to benefit from the frontline gene therapies.\textsuperscript{79} Second, hemophilia differs from indications such as SMA in that a large class of successful therapies already exists to

\textsuperscript{77} If not Hemophilia A, Hemophilia B is another plausible candidate for having multiple FDA-approved gene therapies


treat hemophilia. Should the final readouts from the Phase III gene therapy trials be inconclusive, physicians may be hesitant to prescribe gene therapies to patients who have their disease under control with factor replacement therapy. Third, as hemophilia occurs in varying degrees of severity, it is unclear whether payers plan to cover gene therapies for mild or even moderate hemophiliacs. The degree of coverage likely will depend on the price at which a gene therapy is launched, the payer’s ability to negotiate discounts for its patient pool, and the benefits to patient that gene therapy provides over conventional prophylaxis.

Beyond the scientific uncertainties surrounding gene therapies, many questions exist surrounding how to pay for these therapies. Take the SMA therapeutic market as an example. Roughly 10,000 children in the US have SMA. Assuming the population stays constant over 10 years, treating all children with Spinraza would cost an average of approximately $4 billion USD annually or $40 billion over the 10-year period. Conversely, curing all 10,000 patients up front would cost over $20 billion in year 1 and $0 for each of the remaining 9 years. While the gene therapy would realize $20 billion in savings over the 10-year period, national health systems and private insurers rarely have $20 billion lying around upfront in order to realize this future cost savings. However, even if these health systems and insurers could afford curing everybody up front, it’s not clear that they should as it’s possible that the gene therapy will stop working after a few years, leaving payers with a massive bill but few results to show for it.

Financing strategies have been proposed to make gene therapies (or curative therapies in general) affordable for payers. One straightforward proposal is to finance the cost of gene therapy over a long-term timeframe, perhaps over 10 years. Instead of paying $2
million up front for gene therapy, payers would pay $200,000 annually for a period of 10 years. First, these financing plans have the potential to make gene therapies cheaper on an annual-basis than their non-curative competitors by spreading out cost savings over an extended period. However, this financing model presents the additional question of “who bears the cost of the financing in the short term?” A resource-rich institution must put up the money up front to finance the purchase of the gene therapy from the pharmaceutical firms. Financial institutions, governments, or pharmaceutical firms themselves have been proposed as potential financers of these payment plans, although no consensus has been reached to date.  

Annualizing payment for gene therapy is often mentioned in tandem with a second proposed pricing innovation: value-based pricing. Value-based pricing is an initiative undertaken by pharmaceutical firms to charge payers differing prices proportional to the welfare gains the patients receive and the cost savings the patient pool experiences. As such, it is a type of price discrimination in which patients whose treatment is unsuccessful pay less. For example, if a patient’s gene therapy stopped working within the payment period (e.g. after 6 years), the remaining cost of the therapy would be written off to the pharmaceutical firm (so the total payment for a $2 million drug pro-rated over 10 years would be $1.2 million). These pricing plans have been implemented by a number of

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81 Hampson et al.
pharmaceutical companies including Alnylam Therapeutics which uses value-based pricing metrics for its amyloidosis therapy Onpattro.\(^2\)

Third, a number of healthcare advocates have proposed switching over to a “Netflix Model” of paying for drugs. If a novel gene therapy realizes long-term cost savings over competitors, it is optimal in the long-run for society to cure most patients as quickly as possible to eliminate the cost of chronic drugs (such as the aforementioned Spinraza). This puts a huge burden on payers in the short run. The Netflix model proposes to solve this issue by promoting pharmaceutical firms to license use of the novel therapy to payers for a fixed time period, perhaps of 10 years. Payers would pay a fixed annual fee over the period but the patients in their pool can be prescribed the drug by physicians without incurring the insurer any additional cost. Note how incentives are inverted by this payment model, as the drug developer no longer wishes to advertise or promote its drug as its revenue is fixed at the annual licensing fee and costs mildly increasing in the number of patients treated. Conversely, the payer desires to get all individuals in its patient pool cured before the license runs out, as patient welfare is increasing in the number of patients treated. Further, patients can be cured right at the beginning of the licensing period without the payer incurring additional fee-for-service. Currently, the Netflix model is being used to pay for Gilead Sciences’ expensive Hepatitis C therapy Harvoni in the state of Louisiana.

The Louisiana experiment will inform future attempts to optimize and implement this model of drug pricing.\textsuperscript{83}

In the hemophilia market, Biomarin has been rumored to be considering pricing Valrox somewhere between $1 – 3 million per dose. Any price above Zolgensma’s price ($2.125M) would make Valrox the most expensive drug on the market. Biomarin cites the long-term potential for cost savings as justification of the high price, although critics point out that Valrox’s Phase I/II data showed treated patient’s Factor VIII concentration decreased over time, suggesting Valrox may not be curative and may need to be re-administered after a few years for maximum effectiveness but presently mechanisms for being able to re-dose do not exist.\textsuperscript{84}


IV. The Model

I build off of the relevant literature on discrete choice (see section II) to model hemophilia A patient demand for pharmaceutical products. To do so, I employ a characteristic space approach in which patient demand for a given hemophilia A drug is determined by demand for the drug’s characteristics. The richer models I use allow patient heterogeneity in taste for each characteristic as well. I begin by defining a utility specification common to all models being used and proceed to individually explain the two models I estimate, the multinomial logit and the Berry Levinsohn Pakes model, before providing the theory behind computing patient welfare.

A. Utility Specification

Assume that there are \( N \) patients in the hemophilia A market and any given patient, \( i \), attempts to maximize his utility by choosing to consume one or none of the drugs in the choice set currently offered to him. Let \( J = 0, 1, ..., n_j \) be the choice set of drugs each hemophilia A patient faces, where \( j \) refers to the \( j \)-th drug in the set. I denote patient \( i \)'s drug choice from choice set \( J \) as \( \phi_i(J) \), where \( \phi_{ij}(J) = 1 \) if patient \( i \) chooses drug \( j \) and \( \phi_{ij}(J) = 0 \) otherwise. Let patient \( i \)'s utility from drug \( j \) be denoted as \( U_{ij} \).

**Assumption 1** Each patient chooses the drug in his choice set which maximizes his utility and consumes one unit of this drug. Mathematically this implies:

\[
\phi_i(J) = \arg\max_{j \in J} \left[ U_{ij} \right] = \{ j | U_{ij} > U_{ik}, \forall k \neq j \}
\]

This assumption forms the basis of the micro-founded utility-maximization model and is made commonly in the discrete choice literature.8586

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I next decompose patient \( i \)’s utility into an average utility component and two patient-specific utility components:

\[
U_{ij} = \delta_j + \mu_{ij} + \epsilon_{ij}
\]  

(1)

where \( \delta_j \) is the average utility from drug \( j \) in the population, \( \mu_{ij} \) captures patient heterogeneity in taste dependent on drug \( j \)’s observed characteristics and \( \epsilon_{ij} \) is patient \( i \)’s residual taste shock for drug \( j \). As a patient’s average utility from drug \( j \) is dependent on the drug’s characteristics, I break down \( \delta_j \) into:

\[
\delta_j = x_j' \bar{\beta} + \xi_j
\]  

(2)

where \( x_j \) is a \( K \times 1 \) vector of characteristics of drug \( j \) (including price), \( \bar{\beta} \) is a \( K \times 1 \) vector of coefficients to estimate, and \( \xi_j \) is a product-specific demand shock vector capturing the effect of any unobserved drug characteristics on demand for product \( j \). Note that each entry \( \bar{\beta}_k \) captures the average patient’s marginal utility/disutility from of one unit of characteristic \( k \). Further, as the first entry in \( x_j \) is \( p_j \), or product \( j \)’s price for one unit (normalized to the annual average cost of taking drug \( j \)), the first entry in \( \bar{\beta} \) is \( \bar{\alpha} \), which represents the average price sensitivity in the patient population.

I next further decompose \( \mu_{ij} \) into:

\[
\mu_{ij} = \left( x_j' \ 1 \right) \left( \Pi z_i + \Lambda \nu_i \right) + \epsilon_{ij}
\]  

(3)

where \( z_i \) is a \( R \times 1 \) vector of patient \( i \)’s observed demographic characteristics and \( \nu_i \) is a \( (K + 1) \times 1 \) vector of patient \( i \)’s unobserved characteristics. The matrix \( \Pi \) is a \( (K + 1) \times R \) matrix of interaction coefficients, where \( \Pi_{kr} = \beta_{kr}^p \) is the coefficient of the interaction between the \( k \)-th product characteristic (or a constant) and the \( r \)-th observed demographic characteristic. The matrix \( \Lambda \) is a \( (K + 1) \times (K + 1) \) matrix of interaction coefficients, where \( \Lambda_{kl} = \beta_{kl}^u \) is the coefficient of the interaction between the \( k \)-th product characteristic
(or a constant) and the \( l \)-th unobserved and therefore randomly-determined demographic characteristic. Typically the dimensionality of \( \Lambda \) matches the dimensionality of the number of product characteristics (plus a constant) so that each entry in \( \Lambda \) corresponds to a random coefficient on taste for each product characteristic. I assume \( \Lambda \) to be diagonal to ease in the estimation of the model as well.

The \( \epsilon_{ij} \) are difficult to interpret in this model and typically only included for the tractability of the model. In general however, it is assumed that the patient knows the value of this taste shock for assumption 1 to be satisfied.\(^{87}\) To take advantage of the desirable properties of the multinomial logit model, I assume the distribution of \( \epsilon_{ij} \).

**Assumption 2** Individual taste shocks, \( \epsilon_{ij} \), are identically and independently distributed as Type I Extreme value random variables.

See the Appendix for the distributional definition of the Type I Extreme distribution. Assumption 2 allows a patient’s choice probability to take on a closed-form. Thus, I write patient \( i \)'s probability of choosing drug \( j \) as:

\[
\Pr(\phi_{ij}(J) = 1) = \frac{\exp\{\delta_j + \mu_{ij}\}}{1 + \sum_{k=1}^{nJ} \exp\{\delta_k + \mu_{ik}\}} = \hat{s}_{ij}
\]

\( \hat{s}_{ij} \) represents patient \( i \)'s probability of picking drug \( j \) as determined by the model and its fitted parameters. This choice probability is convenient to work with because of its closed form and because it allows me to compute \( \delta_j \) and \( \mu_{ij} \) based on observed patient preferences. From individual choice probabilities, I compute aggregate market shares by integrating over the distribution of patient characteristics. If \( z_i \sim f_z(\cdot) \) and \( \nu_i \sim f_\nu(\cdot) \), where \( f_z(\cdot) \) is an empirically determined distribution and \( f_\nu(\cdot) \) is an assumed distribution, aggregate market shares are written as:

\[
\hat{s}_j = \int_\nu \int_z (\hat{s}_{ij}|z_i, \nu_i) f_z(\cdot) f_\nu(\cdot)
\]

\(^{87}\) Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium”
This expression for market share can then be inverted by log-transforming individual market shares \( s_{ij} \) and choice probabilities as pioneered by Berry, Levinsohn, and Pakes. In the logit model, inverting the market shares allows them to be written as a linear function of patient \( i \)'s utility from drug \( j \), while in the BLP model, a contraction mapping is required to obtain consistent estimates of the parameters of interest (explained below). Regardless, taking the natural logarithm of equation (4) yields:

\[
\ln(\hat{s}_{ij}) = \delta_j + \mu_{ij} - \ln(1 + \sum_{k=1}^{n_j} \exp\{\delta_k + \mu_{ik}\})
\]  

(6)

The last term in this expression is difficult to compute but can be dealt with by the following assumption:

**Assumption 3** There exists an outside option the hemophilia A drug market \( j = 0 \) equivalent to not taking any prophylaxis. In the market for hemophilia A prophylaxis drugs, the outside option represents electing to treat hemophilia with on-demand factor replacement therapy. The utility from this option is normalized to 0 such that \( \delta_0 = 0 \) and \( \mu_{i0} = 0 \) \( \forall i \).

As this last term is constant across all \( j \), I can subtract the log market share of the outside option from it to obtain log market share of drug \( j \) as a function of drug \( j \)'s characteristics and its product-specific demand shock, \( \xi_j \), producing the following equation:

\[
\ln(\hat{s}_{ij}) - \ln(\hat{s}_{i0}) = \delta_j + \mu_{ij} = x'_j \bar{\beta} + \xi_j + \left( x'_j \begin{pmatrix} 1 \\ \mu_{ij} \end{pmatrix} \right) (\Pi z_i + \Lambda \nu_i)
\]  

(7)

**B. Standard Multinomial Logit Model of Demand with homogeneous patients**

Starting from the assumptions and notation in the above utility specification, to arrive at the most basic model I use, the multinomial logit with homogeneous patients, I make the following two simplifying assumptions.

---

88. Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium”
Assumption 4  There exists no data connecting individual patients demographics to a patient’s drug choice.

Assumption 5  Patients are homogeneous in their preferences for all drug characteristics. Therefore,  \( \mu_{ij} = 0 \forall (i,j) \) and demand for some drug  \( j \) is determined entirely by  \( \delta_j \) and patients’ individual logit taste shocks,  \( \epsilon_{ij} \).

Mathematically, this implies I can write patient  \( i \)’s utility from drug  \( j \) as:

\[
U_{ij} = \delta_j + \epsilon_{ij} \tag{8}
\]

\( \delta_j \) is defined by equation 2 above. Note that as the mean utility from drug  \( j \),  \( \delta_j \) does not depend on  \( i \) and is therefore the same for each patient, all heterogeneity in patient tastes comes from the individual taste shock,  \( \epsilon_{ij} \).

This simplified utility function allows for a modified form of equation 4 to be written in which the choice probability of patient  \( i \) choosing drug  \( j \) as:

\[
\hat{s}_{ij} = \frac{\exp\{\delta_j\}}{1 + \sum_{k=0}^{n_j} \exp\{\delta_k\}} \tag{9}
\]

Thus, each patient faces the same choice probability of choosing a given drug so predicted market share no longer needs to be patient-specific. Therefore the patient-specific \( \hat{s}_{ij} \) can be written as the patient-generic,  \( \hat{s}_j \), and easily fit to observed aggregate market shares.

Following the market share inversion outlined above, equation 7 simplifies to:

\[
\ln(s_j) - \ln(s_0) = x'_j \bar{\beta} + \xi_j \tag{10}
\]

which lends itself to a GMM estimation procedure using an instrument for price (see Estimation).
C. Berry-Levinsohn-Pakes Model of Demand

The BLP model provides a more flexible model of demand. It provides this flexibility by allowing for both a patient’s observed and unobserved characteristics to alter a patient’s taste for each drug characteristic $j$. It accomplishes this by including random coefficients on an individual’s preference for each product characteristic.\(^{89}\)

I start from the base utility specification and relax assumptions 4 and 5 from the above sections. Therefore, patient $i$’s utility from drug $j$ is described exactly by equation 3 in the original utility specification. I re-write this utility function in terms of nested sums as:

$$U_{ij} = \sum_k x_{jk} \beta_{ik} + \xi_j + \epsilon_{ij} = \sum_k x_{jk} \beta_k + \xi_j + \sum_k \sum_r x_{jk} z_{ir} \beta_{rk} + \sum_k x_{jk} \nu_{ik} \beta_k + \epsilon_{ij}$$

(11)

where $z_{ir}$ is patient $i$’s $r$-th observed demographic characteristic, $\beta_{rk}$ is the coefficient on the interaction between product characteristic $k$ and observed characteristic $r$, $\nu_{ik}$ is patient $i$’s $k$-th unobserved characteristic, and $\beta_k$ is the coefficient on the interaction between product characteristic $k$ and unobserved characteristic $k$.

I interpret the first nested sum in $\mu_{ij}$ as allowing an individual’s preference for some product characteristic, $k$ to vary with his observed demographic characteristics. The second nested sum then allows for a patient’s unobserved characteristics to influence his choice probabilities as the $\nu_i$ distribution is determined at random.\(^{90}\) Therefore, patients with the same demographic characteristics may have differing choice probabilities. For tractability, I must assume a distribution for $\nu_i$:

**Assumption 6** $\nu_i$ are independently and identically distributed as multi-variate normal

---


90. Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium”
random variables of dimension $K + 1$, such that:

$$
\nu_i \sim \mathcal{N} \left( \mu_{\nu}, \sum_{K+1 \times K+1} \right) \quad \Sigma_{mn} = \begin{cases} 
\sigma_m & m = n \\
0 & m \neq n 
\end{cases}
$$

This assumption requires that none of the unobserved demographic characteristics are correlated with one another. I argue that $\mu_{\nu}$ is absorbed into $\delta_j$ and can be assumed to be 0. Further, $\sigma_m$ is not identifiable on its own, but can be assumed to be 1 without loss of generality, so any effect is absorbed into $\beta^u$.\footnote{Berry, Levinsohn, and Pakes, “Differentiated Products Demand Systems from a Combination of Micro and Macro Data: The New Car Market”} For the model to be tractable one final assumption is required:

**Assumption 7** The distributions of $z_i$ and $\nu_i$ are independent of one another.

This assures I can integrate over the joint distribution of $z_i$ and $\nu_i$ by multiplying the empirically observed marginal distribution of $z_i$ and the assumed distribution of $\nu_i$. This will then produce aggregate market shares which can be log-transformed.

The $\beta^o$ and $\beta^u$ in the BLP model are interpreted as variance terms that scale with any observed or unobserved deviation from the mean vector, $\bar{\beta}$.\footnote{ibid.} As these variances are non-linear I cannot apply linear techniques to estimate the model, so non-linear optimization techniques, (discussed below) are required.

The BLP model offers the greatest external validity and richness in modeling demand of the models employed in this paper. First, allowing for unobserved product and patient characteristics captures a much more accurate snapshot of market demand. The most straightforward way of envisioning the better fit is through substitution patterns/elasticities. Assume patient $i$ is currently on a drug with an extended half-life (indicating the patient only has to take the drug relatively infrequently, perhaps twice a week). If the patient’s observed demographic characteristics (insurance, age, etc.) otherwise suggest that the agent
would be likely to choose a cheaper drug rather than the more expensive extended half-life
drug, it is likely there is some other patient characteristic which is omitted from the model
but is causing patient $i$ to value that drug’s extended half-life. For example, the patient may
have to travel extensively for work and prefers to only self-infuse with factor replacement
therapy when at home rather than on the road. This omitted characteristic can be captured
by the $\nu_i$ vector, by a large coefficient for patient $i$ on the interaction term between half-
life (say characteristic $k$) and $\nu_{ik}$. Therefore the patient’s $\nu_{ik}$ value allows me to assume
that this patient gets additional welfare from this drug’s extended half-life and would be
more likely to switch to other extended half-life drugs than switching to a standard half life
drug.\footnote{Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium”}

\section*{D. Counterfactual Simulation of Product Entry}

Once the above models are fit, a counterfactual scenario in which a new product is
introduced to the market is simulated. This counterfactual scenario requires a number of
assumptions to be made which I outline here.

\textbf{Assumption 8} All characteristics of the existing drugs in the market, $x_j$, including $p_j$
stay fixed following market entry of any novel therapy. Further, no firm chooses to withdraw its
product from the market following novel therapy entry.

This assumption allows me to define the new set of drugs available in the market as:

$$J' = J \cup j^*$$

(12)

where $j^*$ is the entrant drug. In the simulated counterfactuals, that means that $j^*$ either
represents the novel gene therapy which enters the market, $j = GT$, which is modeled
after Biomarin’s Valrox in expected characteristics or an inexpensive biosimilar version of
Takeda’s Advate, $j = GEN$ priced at 30\% of Advate’s current average sales price.
I also must make an assumption on the $\xi_j$ vector for the entrant products. In previous literature, economists use the average demand shock for the firm which launches the new product as an estimate for the new products demand shock.\textsuperscript{94} However, this technique cannot be applied to my project as the novel entrant is being launched by a firm which is not already in the hemophilia therapeutic space (Biomarin). Therefore I make the following assumption:

**Assumption 9** The novel entrant drug, $j^*$ has a product-level demand shock, $\xi_{j^*} = 0$.

While my best estimate for $\xi_{j^*}$ may be 0, I also include robustness checks to ensure that the welfare results upon gene therapy entry are robust to $\xi_{GT}$ taking on a large positive or negative value. To test for robustness, I take set of observed $\hat{\xi}_j$ from the fitting of each model and compute the range of the 95% confidence interval for the mean of $\hat{\xi}_j$. I then allow $\xi_{GT}$ to vary the range of the 95% confidence interval for the mean of $\hat{\xi}_j$. I then report the lower and upper bounds of predicted market share and patient welfare dependent on this range of $\xi_{GT}$.

**E. Computing Patient Welfare**

Patients’ preferences, as revealed through their drug choices, allow for consumer surplus to be computed. If I assume all parameters in the model are properly estimated, consumer surplus can be easily computed using the fit model. As all three of the above models are based on the multinomial logit model, there exists a closed form representation of consumer surplus in the market. I first write out the equation for individual $i$’s consumer surplus:

$$CS_i = \ln \left( 1 + \sum_{j=1}^{n_j} \exp\{U_{ij}\} \right) * \frac{\partial U_{ij}}{\partial p_j} = \frac{1}{\alpha_i} * \ln \left( 1 + \sum_{j=1}^{n_j} \exp\{U_{ij}\} \right)$$

(13)

Mean individual consumer surplus can then be summed over individuals:

\[
\overline{CS} = \frac{1}{N} \sum_i CS_i
\]  

(14)

I then use (13) to define an individual’s change in consumer surplus following product entry as:

\[
\Delta CS_i(J') = \frac{1}{\alpha_i} \left[ \ln \left( 1 + \exp \{ U_{ij^*} \} \right) + \sum_{j=1}^{n_j} \exp \{ U_{ij} \} \right] - \ln \left( 1 + \sum_{j=1}^{n_j} \exp \{ U_{ij} \} \right)
\]  

(15)

recalling that \( J' = J \cup j^* \) where \( j^* \) is a novel market entrant such as a gene therapy \( j_{GT} \) or generic \( j_{GEN} \).

By analyzing this expression for the change in welfare I draw a few \textit{ex ante} conclusions from this model of demand estimation / product entry. First off, as \( J' \supset J \), total welfare following the introduction of a new product must be weakly greater than before the product’s introduction (as any patient can keep his therapy if it still maximizes his utility). Second, individual \( i \)'s change in consumer surplus is decreasing in the original market’s consumer surplus. Therefore, a patient who had a large consumer surplus before product entry, would have to get an extremely high utility from the entrant to increase his consumer surplus by a significant amount.

I also note that I make the stylistic decision to keep this model static in nature; I assume prices stay constant after new product entry. In reality, product entry is likely to put downward pressure on the prices of incumbents, especially if the new product is predicted to capture a large portion of the market. Therefore, the computed change in welfare represents a lower bound on the welfare effects of product entry as competing products are likely to slash prices, further increasing welfare gains to patients.\(^95\)

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\(^95\). Cleanthous, “Patient welfare implications of innovation in the US antidepressant market”
V. Data

I use three data sources to derive the market shares, $s_j^{obs}$, prices $p_j$, drug characteristics, $x_j$, and individual characteristics, $z_i$, which are inputs to the model.

A. FDA Package Inserts

For all FDA-approved drugs, the FDA issues a drug package insert that contains extensive information on the drug including clinical trial information, side effects, dosing information, year of approval, etc. I manually tabulated data from the most recent version of the FDA drug labels corresponding to the 13 drugs which are FDA-approved and currently still prescribed for continuous prophylaxis to treat hemophilia A. However, this data source presents challenges to obtaining consistent and reliable high-quality data. First, each firm has a decent amount flexibility in the design of the clinical trial which evaluates effectiveness of its drug. Over time, the metrics most commonly reported in each clinical trial (such as median or mean ABR on prophylaxis in the market of interest) change. This poses a challenge to data quality as the package inserts of some of the older factor replacement therapies (Alphanate, Recombinate), do not include information on mean/median ABR for hemophilia A patients on continuous prophylaxis. Therefore, additional studies including other clinical trial / descriptive studies and peer metrics were used to obtain the variables eff1, eff2, and eff3 for these drugs. Second, even if the same metric is reported across different clinical trials, the study population, bleed definitions, dosages, etc. may vary substantially across these trials. As this is an especially difficult set of variables to control for, I choose to omit them and simply employ median ABR ($eff1$), mean ABR ($eff2$), and % of patients without a bleed in a one-year period ($eff3$) as the proxies for product efficacy, disregarding the underlying trial specifics.

Taking these considerations into account, the FDA package inserts are used to construct the $x_j$ vector for each drug $j$, which consists of the following variables:
Table 2: Variables from FDA Drug Labels

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ann-dos</td>
<td>mean number of annual doses for a patient on the drug’s least frequent dosing schedule</td>
</tr>
<tr>
<td>half-life</td>
<td>mean pharmacokinetic half-life of drug in adults</td>
</tr>
<tr>
<td>eff1</td>
<td>median ABR in most recent clinical trial</td>
</tr>
<tr>
<td>eff2</td>
<td>mean ABR in most recent clinical trial</td>
</tr>
<tr>
<td>eff3</td>
<td>% of patients without a bleeding event in most recent clinical trial</td>
</tr>
<tr>
<td>year-app</td>
<td>year in which drug was approved by FDA</td>
</tr>
</tbody>
</table>

From the FDA drug label, I also obtain a variable that will be pivotal in my instrumental variable approach to control for price endogeneity. This variable which I term $pax$, is the number of patients (including both adults and children) enrolled in the Phase III clinical trial which evaluated the effectiveness of continuous prophylaxis for each of the drugs that are FDA-approved.

B. Centers for Disease Control (CDC) Community Counts Dataset

The Community Counts dataset provides a large sample of hemophilia A, B, and Von Willebrand Disease patients who seek treatment at any of the 141 registered Hemophilia Treatment Centers (HTC) in the US. The dataset contains demographic, treatment, insurance, and other health information on individual hemophilia patients. Each entry is on the de-identified patient level. There are roughly 9000 patients with hemophilia A (approximately 60% of the total hemophilia A patients in the US) reported in the Community Counts dataset, which makes the dataset an extremely large sample of the total US hemophilia A population.

The portion of the dataset used for this study is limited to males, diagnosed with hemophilia A (according to international standards) without comorbidities (diagnosis of another chronic bleeding disease) and without a history of inhibitors. Female patients in the hemophilia A patient population are excluded due to the small size of the female sample and different factor replacement needs amongst female hemophiliacs due to menstrual bleeding. Patients with comorbidities and inhibitors are left out as these patients have been excluded from most gene therapy clinical trials to date and are unlikely to be included in
Table 3: Variables from Community Counts Dataset

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>patient age at time of most recent visit</td>
</tr>
<tr>
<td>race</td>
<td>patient racial background</td>
</tr>
<tr>
<td>state</td>
<td>patient state of residence</td>
</tr>
<tr>
<td>ins</td>
<td>primary type of health insurance</td>
</tr>
<tr>
<td>empl</td>
<td>patient employment status</td>
</tr>
<tr>
<td>treat</td>
<td>treatment regimen currently practiced by patient</td>
</tr>
<tr>
<td>drug</td>
<td>product used for continuous prophylaxis</td>
</tr>
</tbody>
</table>

a gene therapy’s indication following FDA approval. Therefore the excluded patients are unlikely to benefit from the first generation of hemophilia A gene therapies.

The `treat` and `drug` variables are used to construct the $s^{obs}$ vector. $s^{obs}_0$ is defined as the share of patients in the population who are on "on-demand prophylaxis" rather than continuous prophylaxis and $s^{obs}_j$ is defined as the proportion of patients who are on continuous prophylaxis ($treat = "continuous prophylaxis") and are specifically on factor replacement therapy $j$ ($drug = j$). `race`, `state`, `ins`, `empl`, `treat`, and `drug` are categorical variables.

Special thanks to Dr. Stacy Croteau of Boston Children’s Hospital and the ATHN (American Thrombosis and Hematosis Network) executive board for sponsoring my proposal for the Community Counts dataset to the CDC’s Project Review Committee.

C. Price Information

Pricing of pharmaceuticals is generally difficult to observe as patients, insurers, pharmacies, and wholesalers face different prices for the same drug and a drug’s pricing can be impacted by arcane rebate rules which drop actual prices below list prices. Without claims data, I’m unable to observe heterogeneity in the prices faced by patients for the same drug. Therefore, I assume that the unit price of each drug is determined by the drug’s Average Sales Price (ASP), or the average price per unit which the US Center for Medicare Medicaid Services (CMS) computes and publishes online.\footnote{“2020 ASP Drug Pricing Files — CMS,” accessed March 29, 2020, \url{https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files}} For patients on Medicare or Medicaid, the CMS will typically reimburse up to 106% of these average sales prices. For
patients with commercial insurance, I’m unable to observe the true cost of the products of interest to neither patient nor insurer, and assume that the ASP is a good proxy for actual price paid per unit.

In reality, prices will likely differ substantially from the ASP. The markups added by wholesalers and pharmacies may increase price over ASP. Conversely, manufacturer rebates or rebates issued by pharmacy benefit managers (PBM, an intermediary between pharmacies and insurers) to insurers may decrease prices from those listed by manufacturers. While the magnitude of the two effects are difficult to measure, I assume that in general ASP is probably less than the prices faced by patients with private insurance but more than that faced by patients with public (Medicaid, Medicare, etc.) insurance.

Pricing also depends on the units of a drug which a patient consumes. To get to the price variable from ASP, I multiply ASP (measured in USD/IU) by the mean annual prescribed dosage per kilogram (IU/kg) and average patient mass (assumed to be 70 kg).\(^97\) I obtain mean annual prescribed dosages per kilo from an Italian study of the cost of continuous prophylaxis in Europe.\(^98\) I use these estimates because I assume dosing should be similar across the patient population in Europe and the United States and no comprehensive American studies of factor usage exist documenting product-specific usage statistics. Thus, as the price of taking a given continuous prophylaxis product is normalized to the average annual price of that drug and the decision to take a drug is binary, a patient selecting a given drug is modeled as a patient taking it over the course of a full year.

\(^97\) as 70 kg is the mean mass of an adult male, it will likely cause the mean price computed to be greater than the price faced by most pediatric patients. However, pediatric patients do tend to take higher dosages which may counteract the effect of weighing less.

\(^98\) Ash Bullement et al., “Cost-Effectiveness Analysis of Recombinant Factor VIII Fc-Fusion Protein (rFVIIIFc) for the Treatment of Severe Hemophilia A in Italy Incorporating Real-World Dosing and Joint Health Data,” *PharmacoEconomics - Open* 4, no. 1 (March 1, 2020): 133–142, ISSN: 2509-4254
VI. Estimation

A. Estimation Procedure for the Multinomial Logit

Fitting the logit demand model requires estimates to be obtained for the parameters \( \theta = (\delta_1, \ldots, \delta_J, \alpha, \beta) \). The first step in estimation is to log-transform the vector of observed market shares, \( s_{\text{obs}} = \begin{pmatrix} s_{0,\text{obs}} \\ \vdots \\ s_{J,\text{obs}} \end{pmatrix} \) to obtain log market shares, which are then to be written as a linear function of product characteristics.\(^99\) Log observed market shares are then regressed on a vector of drug characteristics as implied by equation 10 above. As all drug characteristics except price (half-life, approval year, efficacy, etc.) are determined from product inception and cannot be altered by firms, I argue that all variables in \( x_j \) besides \( p_j \) are exogeneous and need not be instrumented. However, a firm sets price, \( p_j \) only after observing all other drug characteristics as well as the product-dependent demand shock (\( \xi_j \)) which means that \( p_j \) is likely correlated with this demand shock (\( E[p_j \xi_j] \neq 0 \)). Therefore, to correct for the endogeneity of \( p_j \), an instrumental variable approach is required.

I desire an instrumental variable, \( Z \), that is correlated with price but uncorrelated with the demand shock residual. Therefore any instrument must meet both the following two restrictions:

1. Exclusion Restriction: \( E[Z_j \xi_j] = 0 \)

2. Relevancy Restriction: \( E[Z_j p_j] \neq 0 \)

I propose that the number of patients enrolled in the Phase III clinical trial of each product as an instrument for price. As marginal cost is very low compared to sales price for most of the drugs in the market, the up front sunk costs of developing a drug make up the majority of a firm’s cost. Much of this cost is tied up in running lengthy and expensive clinical trials. Throughout a patient’s participation in a clinical trial, the pharmaceutical

\(^{99}\) Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium”
firm coordinating the trial must pay for the full cost of treatment. Therefore running a multi-year clinical trial can easily add millions to a firm’s cost base, and a positive shift in costs will raise the equilibrium price which a firm chooses for its drug.\textsuperscript{100} From this line of reasoning, number of trial patients has a clear effect on price, and should be positively correlated. The catch with using this instrument is that it may also be mildly correlated with the demand shock vector, $\xi_j$, making the exclusion restriction a strong assumption. Consider that a product tested in larger clinical trials may appeal to doctors and patients as their confidence in the product is bolstered by the additional data on the product from the additional patients. However, I argue that in the hemophilia market, this effect is minimal if present. First off, due to the rarity of hemophilia in the US, clinical trial size is often bound by the number of patients available for recruitment. Further, few hemophilia clinical studies are "powered" to identify statistically significant improvements for one product over another, which is the typical standard which the medical field uses to evaluate comparative efficacy.\textsuperscript{101} As neither a clinical study with 100 nor 200 patients will likely meet this statistically significant threshold, physicians lack conclusive statistical evidence of one product being superior to another. Overall, given the limited ability for the econometrician to observe price or cost-shifting variables in the pharmaceutical market, I argue that use of $pax$, or number of patients in the product’s clinical trial is a relatively strong instrument for price endogeneity.

Using $pax$ as an instrument for price, I construct a matrix of instruments consisting of $pax$ substituted for price and the remaining exogenous variables ($X_{2j}, X_{3j}, \ldots, X_{Kj}$) to get the matrix $Z$. I then take the General Methods of Moments Estimate (GMM) for the parameters of the model defined above, $\theta$. GMM in this context is consistent, asymptotically

\textsuperscript{100} Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, “Innovation in the pharmaceutical industry: New estimates of R&D costs,” \textit{Journal of Health Economics} 47 (May 1, 2016): 20–33, ISSN: 0167-6296

\textsuperscript{101} SARA FISHER ELLISON and CHRISTOPHER M. SNYDER, “COUNTERVAILING POWER IN WHOLESALE PHARMACEUTICALS*,” \textit{The Journal of Industrial Economics} 58, no. 1 (March 1, 2010): 32–53, ISSN: 0022-1821
efficient, and minimizes the objective function:

$$\min_{\theta} q(\theta) = \tilde{g}(\theta)'W\tilde{g}(\theta)$$

where $\tilde{g} = \frac{1}{N}\sum_j Z_j'\xi_j$. The GMM program used to estimate the logit comes from pyblp and reports robust standard errors. Further, the pyblp package allows for calculation of the optimal instruments as defined by Chamberlain (1987).\footnote{Gary Chamberlain, “Asymptotic efficiency in estimation with conditional moment restrictions,” *Journal of Econometrics* 34, no. 3 (March 1, 1987): 305–334, ISSN: 0304-4076} After fitting the model with my instrumental variable above, I then re-estimate the model with an approximation of Chamberlain’s optimal instruments. All results reported are based on these optimal instrument results. Once estimates for these parameters are obtained, total welfare can be computed using equations (13) and (14).

**B. Estimation Procedure for the Berry-Levinsohn-Pakes Model of Demand**

I seek to estimate the parameters $\theta = (\delta_1, \ldots, \delta_j, \tilde{\beta}, \beta^o, \beta^u)$. This estimation is more difficult than in the standard logit model due to the randomly-determined unobserved individual characteristics that are taken into account. Inclusion of these unobserved patient characteristics, makes the coefficients $\beta^o$ and $\beta^u$ non-linear, so standard GMM cannot be employed. To do so, a multi-step estimation procedure is employed using the nested-fixed point algorithm, first discussed by BLP (1995) and implemented in the library pyBLP.\footnote{Berry, Levinsohn, and Pakes, “Automobile Prices in Market Equilibrium"} \footnote{Christopher Conlon and Jeff Gortmaker, “Best practices for differentiated products demand estimation with pyblp,” *Unpublished Manuscript*, 2019.} I draw on the lecture notes of Pakes and Moszcowski to summarize the key components of the algorithm here:

1. Simulate draws from $\nu_i$ according to the multi-variate normal distribution defined in the model.

2. Guess a value of $(\beta^o, \beta^u)$
3. Obtain the unique contraction mapping of $\delta_j(\beta^o, \beta^u)$ using the following iterative scheme until convergence:

$$\delta_j^{(t+1)} = \delta_j^{(t)} + \log(s_{obs}^j) - \log(s_j(\beta^o, \beta^u, \delta^{(t)}))$$

4. Use GMM to solve for $\hat{\beta}$ and compute $\hat{\xi}_j = \hat{\delta}_j - x'_j \hat{\beta}$

5. Minimize GMM objective function, $g(\hat{\xi}, \beta)$ by computing its value and repeating steps 2-4, searching over $(\beta^o, \beta^u)$ until objective function reaches a minimum and parameter solution converges.\(^{105}\)

Note that the public domain python script pyblp.py is used to implement this estimation technique. For more detailed characterization of the algorithm an non-linear optimization programs used in pyblp please reference Conlon and Gortmaker, 2020.\(^{106}\)

To deal with price endogeneity, I use the same instrument, $pax$, as explained in the previous subsection. However, additional instrumental variables are required to pinpoint the standard deviation of the random coefficients, $\beta^o, \beta^u$ on each product characteristic. Therefore, I use "differentiation instruments" as proposed by Gandhi and Houde to provide the additional instruments to identify the random coefficients in the model.\(^{107}\) Differentiation instruments work similarly to classic "BLP" instruments, quantifying how close a given product’s characteristics are to the other products in the product space, which should affect the product’s equilibrium markup and therefore its price. I construct the quadratic versions of these differentiation instruments, complete with interactions using the functionality provided by pyblp. Lastly, as mentioned above, I re-compute all my results for the BLP model using Chamberlain’s optimal instruments to produce the results reported below.

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\(^{105}\) When using observed demographic characteristics, I use micro data on patient choices to compute the covariance between a patient’s observed demographic characteristic and the observed product characteristics of the patient’s first choice drug. I add these empirical covariances as moments to the GMM objective function to help pin down the values of the interaction coefficients in $\Pi$

\(^{106}\) Conlon and Gortmaker, “Best practices for differentiated products demand estimation with pyblp”

\(^{107}\) Gandhi and Houde, *Measuring substitution patterns in differentiated products industries*
VII. Results

A. Drug Characteristics

13 hemophilia A treatments in the dataset have > 0.1% national market shares and therefore qualified to be included in the dataset. These treatments are produced by nine different firms, with one firm, Takeda (through its acquisitions of Shire which had previously acquired former-industry leader Baxter) producing 3 products. I separate out Roche’s Hemlibra, a non-factor replacement therapy, from the summary of the set of factor replacement therapies due to its unique properties and exceptionally long half-life. For the factor replacement therapies, half-life is approximately normally distributed around mean 14.7, with a standard deviation of 2.7. The mean number of doses per year according to the least frequent dosing frequency recommended on a drug’s FDA drug label (ann-dos) is 135, with a standard deviation of 43. Half-life is negatively correlated with ann-dos and both signal how long a product lasts so I only include one of the two in each demand estimation model below. Proxies for efficacy, eff1 (median ABR) and eff2 (mean ABR) both exhibit large variance likely due to the sampling error from the reporting and collecting bleed data. Lastly, products vary substantially in their date of FDA approval; the oldest product in the sample, Grifol’s Alphanate, gained FDA approval in 1978 while the newest entrant in the sample, Bayer’s Jivi, gained FDA-approval in 2018.

Table 4: Summary Statistics of Drug Characteristics

<table>
<thead>
<tr>
<th>Metric</th>
<th>half-life</th>
<th>ann-dos</th>
<th>eff1</th>
<th>eff2</th>
<th>eff3</th>
<th>year-app</th>
<th>ASP</th>
<th>prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>14.41</td>
<td>141.0</td>
<td>1.122</td>
<td>2.834</td>
<td>46.66</td>
<td>2005.7</td>
<td>1.395</td>
<td>457100</td>
</tr>
<tr>
<td>std dev</td>
<td>2.69</td>
<td>40.51</td>
<td>0.9196</td>
<td>0.9891</td>
<td>4.522</td>
<td>12.79</td>
<td>0.2869</td>
<td>66660</td>
</tr>
<tr>
<td>min</td>
<td>10.8</td>
<td>73</td>
<td>0</td>
<td>1.6</td>
<td>38</td>
<td>1978</td>
<td>1.071</td>
<td>364900</td>
</tr>
<tr>
<td>median</td>
<td>14.3</td>
<td>156.4</td>
<td>1</td>
<td>2.633</td>
<td>45.71</td>
<td>20013</td>
<td>1.26</td>
<td>427900</td>
</tr>
<tr>
<td>max</td>
<td>19.0</td>
<td>182.5</td>
<td>2.9</td>
<td>4.4</td>
<td>52</td>
<td>2016</td>
<td>2.08</td>
<td>554000</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

hemlibra 646 26.07 0 1.3 60 2017 47.348* 517000

* ASP unit pricing for hemlibra is per 0.5 mg rather than per IU
The characteristics of the novel drugs used in counterfactual product entry simulations are provided in Table 5. Valrox’s half-life of nearly 19000 hours (approximately 26 months) is extremely long compared to standard factor replacement therapies (approximately 1000 times longer). This implies that the log transformation of half-life may be necessary to ensure that patient utility gains from drug durability are linear in nature. I draw this conclusion because it seems much more likely that a gene therapy’s long lifespan makes hemophiliacs 3 times better off (the ratio of log half-life) than 1000 times better off (ratio of half-life).

I assume Valrox’s average number of annual doses to be 0.33 doses per year as Biomarin and the FDA have yet to propose a dosing schedule for the gene therapy. I make this assumption from my half-life computation above and Valrox’s phase II trial data, which suggests that the gene therapy is roughly half as effective at 3 years out from dosing as it was shortly after the original dosing. This decline in effectiveness suggests that Valrox (as well as other first generation gene therapies in hemophilia A) will likely not continue to be effective the course of a patient’s lifetime and instead may have to be re-administered years after the first dosing. Thus, I make the conservative estimate that gene therapy will have to be re-administered every three years to be a reliable substitute for continuous prophylaxis.

Other differentiation points of Valrox include its low bleeding rates in clinical trials (eff1 - eff3), which represent improvements over the most desirable product characteristic of the products already on the market.

108. I computed half-life from Phase II clinical trial data by taking a linear regression of log factor VIII concentration on time to get the rate constant of reduction in the drug’s effect, $k_e$. I then use the formula: $t_{1/2} = \frac{\log(2)}{k_e}$ to compute the drug’s half-life.

109. The rationale to use a log-transformation can also be deduced by comparing the ratio of drug durability (half-life, log(half-life)) with the ratio of drug prices. The ratio of prices of gene therapy to standard therapies is likely to be close to 3 and therefore if I assume utility scales linearly with price, a log scale for drug half-life seems much more reasonable than a linear scale.


111. ibid.
As Valrox has yet to be FDA-approved nor commercially launched, I also must make an assumption on its price. Biomarin has been rumored to be pricing Valrox in the range of $1 - 3 M per dose.\textsuperscript{112} As one gene therapy dose will likely last longer than one year (my implicit assumption by assuming that \textit{annodos} = 0.33 is that a dose lasts 3 years), I assume that patients internalize the price of gene therapy to be total cost of gene therapy amortized over three years when making their drug decision. Therefore, if I plug in a gene therapy price of $3M to the model, patients would choose between one year of a standard drug at its average annual price and one year of gene therapy at $1M. I argue that patients internalize amortized gene therapy price for the following two reasons: first, the aforementioned clinical trial data is convincing enough to suggest that gene therapy is a suitable substitute for continuous prophylaxis for the three years which the study spanned.\textsuperscript{113} While the study left opened the possibility that gene therapy lasts longer than three years - in which case I might wish to amortize price over this longer period - a three year period for gene therapy’s duration of effectiveness is a conservative assumption that I can make with assurance. Second, given gene therapy’s high price, there is already talk of creating financial payment plans which effectively amortize the cost of gene therapy over the length of the gene therapy’s effectiveness. These payment plans would offer a concrete mechanism by which patients/insurers would spread the cost of gene therapy over multiple years.\textsuperscript{114} Together, these stipulations imply that the fairest comparison of gene therapy to conventional prophylaxis therapy is when the cost of gene therapy is spread over its lifespan.

For the entrant product attempting to simulate a generic / biosimilar product entering the market, I assume that the product will have similar physical characteristics to Advate, a SHL factor replacement therapy that is widely used, but has characteristics (half-life, bleeding rates) that are just average in the drug space. However, I differentiate the generic


\textsuperscript{113} Perrin, Herzog, and Markusic, “Update on clinical gene therapy for hemophilia”

A biosimilar entrant from Advate in two key respects. First, I assume that the biosimilar will come at 30% of the cost of the branded Advate drug, an estimate that I obtain from work comparing generic prices to their branded counterparts. Second, I assume that the product-specific demand shock for the generic is 0 in all markets. This assumption ensures that the branded effects of Advate aren’t also gained by its generic counterpart (as these branded effects can be quite large and are rarely shared by generics).

Table 5: Characteristics of market entrants

<table>
<thead>
<tr>
<th>Drug</th>
<th>half-life (h)</th>
<th>ann-dos (doses)</th>
<th>eff1</th>
<th>eff2</th>
<th>eff3</th>
<th>year-app</th>
<th>ASP ($/IU)</th>
<th>prices ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>valrox</td>
<td>18912</td>
<td>0.1</td>
<td>0</td>
<td>0.7</td>
<td>86</td>
<td>2020</td>
<td>n/a</td>
<td>2.4M*</td>
</tr>
<tr>
<td>generic*</td>
<td>12</td>
<td>121.7</td>
<td>1</td>
<td>1.75</td>
<td>42</td>
<td>2020</td>
<td>0.375</td>
<td>127800</td>
</tr>
</tbody>
</table>

* I allow Valrox’s price to vary between $1 - 3.5 M per dosage.
** The simulated generic is assumed to be Advate at \( \frac{1}{3} \) of its average cost

A full table of drug characteristics can be found in the Appendix.

B. Market Shares

Aggregate national market shares for the full sample (Table 6) indicate that the most popular treatment option is on-demand prophylaxis, representing the choice of 44.8% of hemophilia A patients in the sample. Of patients on continuous prophylaxis treatments, Takeda’s Advate, a standard half-life (SHL) factor replacement therapy holds the top position in the market, capturing 16.3% of patients. Sanofi’s Eloctate (10.2% market share), an extended half-life (EHL) factor replacement therapy, and Roche’s Hemlibra (8.3% market share), a non-factor replacement therapy also used for prophylaxis, finish a distant second and third to Advate, respectively. Bayer’s Kogenate (5.7% market share) is a SHL competitor to Advate, with similar product characteristics, while Takeda’s Adynovate (5.1% market share) is an EHL competitor to Eloctate. A number of relatively new products, including CSL Behring’s Afstyla, Bayer’s Jivi and Kovaltry, and Octapharma’s Nuwiq give patients

116. Cleanthous, “Patient welfare implications of innovation in the US antidepressant market”
and doctors a large choice set in the extended half-life product segment, although none of them has eclipsed a 1% market share in the sample to date.

Given different therapeutic needs for different patients, I next attempt to segment the market by grouping patients based on their disease severity. The International Society on Thrombosis and Hematosis (ISTH) classifies each case of hemophilia A into one of three severity grades, severe, moderate, and mild.\textsuperscript{117} \textsuperscript{118} I use these classifications to compute product market for each severity class, also reported in table 6.

Mild patients rarely opt for a continuous prophylaxis regimen, with 95% choosing to control their disease via on-demand therapy. Similarly, the majority of moderate cases (63%) are managed via on-demand therapy. These patients who currently use on-demand treatment are unlikely to be early candidates for gene therapy. Such patients pose less of a cost burden to insurers and typically suffer from less severe cases of hemophilia than those patients on continuous prophylaxis. Most actuarial studies of the cost of hemophilia focus on the severe patient population because its average cost per patient far surpasses that for moderate and mild patients. In fact, half of hemophilia A patients in the US have average claims costs to insurers of less than $100K per year, with the bulk of these ”low-cost” patients suffering from only mild or moderate hemophilia A and being treated with on-demand therapy.\textsuperscript{119} Therefore, a gene therapy priced over $1 M would take 10+ years to provide any cost savings to insurers over on-demand treatment. Further, current evidence on gene therapies such as Valrox indicates that they may not last a full ten years, so purchase of gene therapy every 3-years, even at $1 M per-dose would more than double insurers costs for moderate to mild hemophiliacs. This financial uncertainty is also exacerbated by

\textsuperscript{117} “Severe” cases of hemophilia A are defined by plasma concentrations of less than 0.01 IU/mL of Factor VIII, or < 1% of normal Factor VIII activity. “Moderate” cases of are defined by plasma concentrations of 0.01 – 0.05 IU/mL or 1% – 5% of normal activity. “Mild” cases are defined as 0.05 – 0.40 IU/mL of Factor VIII, or 5% – 40% of normal activity.

\textsuperscript{118} Gilbert C White et al., “Scientific and Standardization Committee Communication Definitions in Hemophilia”:2

frequent switching of insurers for many American hemophiliacs which opens the loophole that a patient could potentially get a $1M+ gene therapy paid for by their insurer, only to switch insurers shortly after. For these reasons, insurers are unlikely to offer reimbursement for gene therapy in moderate or mild hemophiliacs.

Table 6: Drug market shares for each grade of hemophilia severity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>advate</td>
<td>0.2492</td>
<td>0.1200</td>
<td>0.0153</td>
<td>0.1628</td>
</tr>
<tr>
<td>adynovate</td>
<td>0.0812</td>
<td>0.0307</td>
<td>0.0033</td>
<td>0.0510</td>
</tr>
<tr>
<td>afstyla</td>
<td>0.0058</td>
<td>0.0028</td>
<td>0</td>
<td>0.0037</td>
</tr>
<tr>
<td>alphanate</td>
<td>0.0222</td>
<td>0.0098</td>
<td>0.0014</td>
<td>0.0144</td>
</tr>
<tr>
<td>eloctate</td>
<td>0.1562</td>
<td>0.0726</td>
<td>0.0096</td>
<td>0.1015</td>
</tr>
<tr>
<td>hemlibra</td>
<td>0.1303</td>
<td>0.0579</td>
<td>0.0048</td>
<td>0.0833</td>
</tr>
<tr>
<td>jivi</td>
<td>0.0087</td>
<td>0.0028</td>
<td>0.000</td>
<td>0.0053</td>
</tr>
<tr>
<td>kogenate</td>
<td>0.0954</td>
<td>0.0230</td>
<td>0.0019</td>
<td>0.0571</td>
</tr>
<tr>
<td>kovaltry</td>
<td>0.0140</td>
<td>0.0070</td>
<td>0.0014</td>
<td>0.094</td>
</tr>
<tr>
<td>novoeight</td>
<td>0.0133</td>
<td>0.0028</td>
<td>0.0014</td>
<td>0.0082</td>
</tr>
<tr>
<td>nuwiq</td>
<td>0.0152</td>
<td>0.0056</td>
<td>0.000</td>
<td>0.0094</td>
</tr>
<tr>
<td>recombinante</td>
<td>0.0372</td>
<td>0.0147</td>
<td>0.0019</td>
<td>0.0236</td>
</tr>
<tr>
<td>xyntha</td>
<td>0.0348</td>
<td>0.0126</td>
<td>0.0029</td>
<td>0.0222</td>
</tr>
<tr>
<td>none</td>
<td>0.1363</td>
<td>0.6378</td>
<td>0.9560</td>
<td>0.4482</td>
</tr>
<tr>
<td>N</td>
<td>4276</td>
<td>1433</td>
<td>2091</td>
<td>7800</td>
</tr>
</tbody>
</table>

The aggregate market shares amongst severe patients suggest the importance of continuous prophylaxis in managing hemophilia in its most severe cases. Only 13.6% of patients with severe hemophilia manage their disease through on-demand treatment, meaning the great majority of these patients are on continuous prophylaxis regimens. 24.9% currently manage their hemophilia with Advate, while another 15.6% use Eloctate, and 13.0% use Hemlibra for prophylaxis. Overall, the sizable difference in the proportion of patients on on-demand treatment for severe hemophilia compared to the equivalent proportion for moderate or mild hemophilia (over 50 percentage points) warrants consideration of the severe hemophilia A patient population as its own distinct market. This market also happens to be the likely launch market for the first gene therapies.120 Thus, due to the key differences

120. Bell, “BioMarin inches closer to a gene therapy first”
in demand for continuous prophylaxis between severe, moderate, and mild hemophilia patients, I choose to narrow the market to be estimated to severe hemophilia A patients of which there are \( N = 4276 \) in the sample.

Aggregate market shares also shed light on the degree of concentration within the hemophilia A therapeutic market. The degree of market concentration has been found to impact equilibrium markups in both theoretical and empirical economic work and therefore is of interest to the public health official and regulator.\(^\text{121,122}\) To evaluate market concentration, I compute the Herfindahl-Hirschman Index (HHI), of the hemophilia A therapeutic market as a proxy for market concentration and competitiveness. The HHI is defined as:

\[
HHI = 10000 \sum_{f \in F} \left( \sum_{j \in P_f} s_j \right)^2
\]

where \( F \) is the set of firms and \( P_f \) is the set of products produced by firm \( f \). Therefore HHI is the sum of the squared market shares of each firm in a given market. As prices and choice sets are fixed across states, I argue that the US pharmaceutical market is essentially one large market and compute the HHI of the national market. As is the case with many questions of market concentration, the degree to which the market appears to be concentrated is highly-dependent on the market definition. If the hemophilia A therapeutic market is designated as all males meeting ISTH standards for any hemophilia A diagnosis, then the market appears to be unconcentrated. Only roughly 1 in 2 of these patients choose any continuous prophylaxis treatment.\(^\text{123}\) Ergo, the HHI of this national market is measured to be just 796, suggesting a market that is highly fragmented. The top 4 firms in the market capture just 49% of the total market share which is low considering the small number of firms in the market.

\(^{121}\) Alexandre Corhay, Howard Kung, and Lukas Schmid, “Competition, markups and predictable returns,” Available at SSRN 2550981, 2017.


\(^{123}\) This bounds the HHI by a maximum possible value of roughly 2500 (should all those who do choose continuous prophylaxis choose the same drug).
Conversely, if the market is defined as just consisting of hemophilia A patients with a severe diagnosis, a much more concentrated picture of the market is painted. Given only 14% of these patients choose the outside option and the leading drug captures approximately 25% of the market, the HHI of the national market is 1926, suggesting a market with a moderately-high level of concentration. Further the top 4 firms capture 77% of the market, suggesting these firms both dominate the market and possess substantial market power within it.

Overall, this high concentration reduces incentive to undercut competitors by dropping prices and may facilitate collusion should the same firms interact with each other over a series of separate pharmaceutical markets.\textsuperscript{124} While equilibrium markups are not observed nor estimated in this paper, the high-degree of market concentration provides a framework in which a social planner would wish to reduce barriers to promote market entry to increase competitiveness. Therefore, the high market concentration suggests that the FDA may desire to be somewhat lenient in approving a hemophilia A gene therapy if it believes that it will decrease HHI and increase market competitiveness. Conversely, if the regulator expects gene therapy to rapidly dominate the market, gaining substantial market power itself, the FDA may wish to enact tighter standards on potentially disruptive drugs such as gene therapies. FDA guidance of late has taken a middle ground, encouraging the market entry of gene therapies while also attempting to facilitate secondary gene therapy entrants to markets where one gene therapy is dominant.\textsuperscript{125}

\textbf{C. Patient Characteristics}

The full dataset includes $N = 9297$ unique males who had have been diagnosed with hemophilia A without related co-morbidities (e.g. hemophilia B).\textsuperscript{126} While the dataset included multiple treatment regimen options, I narrowed down the observations to only pa-

\textsuperscript{125} Bell, “BioMarin inches closer to a gene therapy first”
\textsuperscript{126} If patients had multiple observations I only used their most recent visit.
patients who were either on "continuous prophylaxis" or "on-demand prophylaxis", as these patients represent the market of interest, and the outside option, respectively.

Figure 4: Distribution of hemophilia A patients across US States

The sample is geographically-distributed as roughly one would expect, with a large number of cases in populous states such as CA, TX, and NY, and just a handful of cases in sparsely populated states. Figure 4 maps the distribution of hemophilia A patients across states. As the map shows, hemophilia A does not appear to be more or less prevalent in any particular geographic region or state other than the deviations expected from state population.

Summary statistics of demographic characteristics in the severe patient population and the empirical distribution of categorical variables are reported in Tables 7 and 8. The variables ins-ind, emp-ind and rac-ind in Table 7 are indicators that indicate whether a patient
is commercially insured, employed at least part-time and white, respectively.\textsuperscript{127} Mean age in the hemophilia A patient population is just over 23 years, coinciding with other population surveys suggesting the average hemophilia A patient is quite young.\textsuperscript{128} About half of patients have commercial insurance and most of those who don’t qualify for Medicaid, Medicare or other forms of public healthcare assistance. About one-half of patients are children or full-time students and one-third of patients have a full or part time job, leaving a bit over 15\% of the population as disabled, unemployed, or retired. The majority of the population (62\%) is white, while a minority identify as people of color. The racial distribution of hemophilia A approximately matches the US’s racial distribution at-large.\textsuperscript{129}

\begin{table}[h]
\centering
\begin{tabular}{lrrrr}
\hline
name  & age (y) & ins-ind & emp-ind & rac-ind \\
\hline
mean  & 23.36   & 0.5056  & 0.3337  & 0.6356  \\
std dev & 15.85   & 0.5000  & 0.4716  & 0.4838  \\
min   & 0       & 0       & 0       & 0       \\
median & 20      & 1       & 0       & 1       \\
max   & 86      & 1       & 1       & 1       \\
\hline
\end{tabular}
\caption{Summary Statistics of Patient Characteristics for Severe Patients}
\end{table}

\textbf{D. Demand Estimation}

I report parameter estimates for the multinomial logit model and BLP model in (Table 9). Logit forms 1 - 3 differ in how patients value how long a drug lasts (drug durability).\textsuperscript{130} In logit specifications 1 and 2, patients get linear disutility from the log number of annual doses, whereas in specification 3 patients get linear disutility from the linear number of doses, whereas in specification 3 patients get linear disutility from the linear number of doses.

\textsuperscript{127} Only ins-ind is used in the fitting of the model, as when the other demographics were included, the estimation routine failed to converge.


\textsuperscript{129} Bell, “BioMarin inches closer to a gene therapy first”

\textsuperscript{130} I also fit logit models with half-life or log(half-life) as an alternative measure of drug durability to annual doses. Use of the half-life variable caused border solutions to be reached once gene therapy was introduced, causing gene therapy to absorb the whole market (if half-life was included in the product formulation), or none of the market (if log(half-life) was included in the formulation).
Table 8: Distribution of categorical Patient Characteristics

<table>
<thead>
<tr>
<th>ins</th>
<th>emp</th>
<th>rac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Insurance</td>
<td>Child or Student</td>
<td>White</td>
</tr>
<tr>
<td>0.5056</td>
<td>0.5108</td>
<td>0.6265</td>
</tr>
<tr>
<td>Medicaid</td>
<td>Employed Full-time</td>
<td>Hispanic</td>
</tr>
<tr>
<td>0.2865</td>
<td>0.2633</td>
<td>0.1637</td>
</tr>
<tr>
<td>Medicare</td>
<td>Disabled</td>
<td>Black</td>
</tr>
<tr>
<td>0.0793</td>
<td>0.0842</td>
<td>0.1363</td>
</tr>
<tr>
<td>Public*</td>
<td>Employed part-time</td>
<td>Asian</td>
</tr>
<tr>
<td>0.0636</td>
<td>0.0704</td>
<td>0.0461</td>
</tr>
<tr>
<td>Other</td>
<td>Unemployed</td>
<td>Multi-racial</td>
</tr>
<tr>
<td>0.0472</td>
<td>0.0503</td>
<td>0.0117</td>
</tr>
<tr>
<td>Uninsured</td>
<td>Retired</td>
<td>Native-American</td>
</tr>
<tr>
<td>0.0178</td>
<td>0.0129</td>
<td>0.0110</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0082</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

doses. Specifications 1 and 2 differ by specification 2 also including a measure of drug efficacy, eff2 (mean ABR) in the linear product formulation. In all 3 of these logit specifications, the coefficient on price is negative as expected and is significant at the 5% level in Logit 1 and Logit 3. The coefficient on price is insignificant in Logit 2 and substantially smaller than the equivalent coefficient in Logit 1. As the only difference between these specifications is eff2 factoring into the product formulation in Logit 2, the shrinking of the coefficient on price is likely driven from eff2 being partially colinear with the instrument for price. The coefficients on ann-dos or its log-transformation are also negative and significant at the 1% level, suggesting patients are to be made worse off for each additional dose they must take. the coefficient on eff2 in Logit 2 is negative and significant at the 1% level, indicating a higher average number of bleeds gives a patient disutility.

BLP 1 and BLP 2 are adapted formulations of Logit 1 and Logit 2 that incorporate random coefficients on the constant term and price. In BLP 1 and BLP 2 the Π matrix

---

131 The rationale for adapting these BLP models from logit specifications 1 2 is twofold; first, by using log(ann-dos) to stylize how patients value a drug’s duration of effect, these formulations ensure that patient’s
Table 9: Logit Formulation Demand Coefficients

<table>
<thead>
<tr>
<th>Specification Variable</th>
<th>Logit Form 1</th>
<th>Logit Form 2</th>
<th>Logit Form 3</th>
<th>BLP 1</th>
<th>BLP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( \beta )</td>
<td>( \beta )</td>
<td>( \Lambda )</td>
<td>( \Lambda )</td>
</tr>
<tr>
<td>prices</td>
<td>-2.226E-5**</td>
<td>-5.438E-6</td>
<td>-3.899E-5**</td>
<td>-5.64E-5***</td>
<td>6.137E-6</td>
</tr>
<tr>
<td></td>
<td>(5.927E-6)</td>
<td>(4.147E-6)</td>
<td>(1.244E-5)</td>
<td>(7.073E-6)</td>
<td>(1.064E-5)</td>
</tr>
<tr>
<td>log(anndos)</td>
<td>-1.893***</td>
<td>-0.5476**</td>
<td>-3.875***</td>
<td>-1.4538***</td>
<td>2.774 E-9</td>
</tr>
<tr>
<td></td>
<td>(0.3458)</td>
<td>(0.2812)</td>
<td>(0.4984)</td>
<td>(0.5654)</td>
<td>(0.2334)</td>
</tr>
<tr>
<td>eff2</td>
<td>-0.4270***</td>
<td>-0.08849</td>
<td>2.399</td>
<td>13.51***</td>
<td></td>
</tr>
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<td>12.70***</td>
<td>0.01122</td>
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<tr>
<td></td>
<td>(0.9938)</td>
<td>(0.0080911)</td>
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\(* p < 0.1, ** p < 0.05, *** p < 0.01\)
of coefficients on interactions between observed product characteristics and demographic characteristics is fixed to 0. BLP 3 is an adaptation of BLP 2 that includes an interaction term between a patient’s insurance type (commercial or public) and his preferences for each drug characteristic. In each model, the coefficients on price and the constant take on a random distribution, with mean $\bar{\beta}$ and standard deviation $\Lambda$.

In each BLP model, the mean of each beta coefficient ($\bar{\beta}_k$) takes on the same sign as the corresponding coefficient in the the logit model, suggesting robustness across the models. All the $\bar{\beta}$, or linear coefficients in BLP 1-3 are significant at the 1% level except the coefficient on eff2 in BLP 2. While the coefficient on eff2 takes on a negative sign as expected in BLP 2, it is likely insignificant due to the variation in patient preferences for various drugs being explained by differences in price (as well as heterogeneous tastes for price) and dosing frequency.

The random coefficient on the constant in these models allows for patients to vary in their preferences for taking a continuous prophylaxis treatment compared to using an on-demand treatment regimen (e.g. the base utility from choosing any drug in the choice set is pulled from a normal distribution). Its mean varies substantially among the specifications with BLP 2 having the highest mean which suggests higher mean utility levels from continuous prophylaxis in this model. Interestingly, the standard deviation of this random coefficient is relatively consistent across BLP 1 and BLP 2 but is nearly an order smaller in BLP 3. BLP 3’s smaller standard deviation is likely due to the inclusion of insurance type explaining some of the variance in patient preferences.

The random coefficient on price allows for patients to vary in their price sensitivity. The mean of the random coefficient is five fold greater in BLP 1 than in BLP 2 & 3 but is very consistent across BLP 2 & 3. In all three specifications, the price sensitivity’s valuation of a long-lasting drug only grows at a log rate so the model is unlikely to produce an uninformative boundary solution. Second, the proportion of patients that adopt gene therapy in these specifications is along the sensitive portion of the demand curve. This sensitive portion of the demand curve happens to be inline with market forecasts as well, so the conclusions to be drawn are potentially more informative given their $ex post$ validity.

132. For patients with commercial insurance, ins-ind = 1 and for patients with public insurance, ins-ind = 0.
standard deviation is small compared to its mean (smaller by roughly one order in BLP 1 & 3 and four orders in BLP 2). The fact that so much less heterogeneity in price sensitivity is seen in BLP 2 is surprising, as including eff2 should not impact heterogeneity in taste that severely. One possible explanation is that because optimal instruments were used to compute the reported solution, these instruments were different for each of the original solutions and therefore affected the parameter estimate for the Λ on price. Regardless, the fact that the standard deviation of the coefficient on price is at least an order less than its mean should preclude patients from having positive price sensitivities in my counterfactual simulations.

BLP 3’s estimate for Π measures the difference in β for the population of commercially insured patients versus the β for the population of publicly-insured patients (patients with medicaid, medicare, etc.). The coefficient on the interaction between price and insurance type is negative and statistically significant at the 5% level. I interpret the coefficient as the average commercially-insured patient being 39% more sensitive to price than a publicly-insured patient. This makes intuitive sense as a commercially-insured patient likely has to share a greater proportion of the cost of his treatment than a patient on public assistance. While the coefficient on the interaction between a constant and insurance type is also negative, it is insignificant small in magnitude compared to the mean of the constant so I conclude that being commercially insured does not affect whether a patient is more likely to be on continuous prophylaxis.

E. Gene Therapy Entry

The β, Λ, and Π coefficients contain important information about average preferences in the population of patients for various drug characteristics and how these preferences vary across patients. Thus, I use these parameter estimates to characterize patient demand

---

133. To account for this I 1) fit an adaptation of BLP 2 only allowing a linear coefficient on price but this model converged to a positive price sensitivity and 2) ran the non-linear optimization program for BLP 2 using the parameter estimates in BLP 1 and vice versa and confirmed that these converged solutions are in fact global and not local solutions.
for hemophilia A therapies and run counterfactual scenarios such as novel product entry. I focus on the welfare effects of gene therapy entry for hemophilia A including the change in consumer surplus following market entry of a gene therapy or generic product, and the predicted market share of the entrant product.

I first compute the demand curve for gene therapy with price ranging from $1M to $3.5M in Figure 5. Demand is downward-sloping and the formulations which include eff2 (Logit 2, BLP 2, and BLP 3) have much flatter slopes than the formulations which exclude it (Logit 1 and BLP 1). Logit 1 and BLP 1 predict that gene therapy will capture nearly the whole market at a price of $2M but would capture only a sliver of the market at a price of $3M, while Logit 2, BLP 2 & 3 predict that gene therapy will capture the majority of the market at a price of $2M (~67%) and a sizable minority of the market at a price of $3M (~20%). Thus, demand for gene therapy appears to be especially sensitive to changes in price in the $2M to $3M range, which coincides with the upper half of the rumored price range being considered for Valrox.

The demand curve also provides insight into the profit-maximizing price Biomarin should charge for Valrox. To compute the optimal price for Valrox, I must make an assumption on its marginal cost of production, which I assume to be negligible (MC = 0). I work from this assumption to create Figure 6 which plots the profit-maximizing price for each model specification. Optimal price ranges from $1.7M to $2.1M with my preferred specification, BLP 2, suggesting an optimal price of $1.9M for Valrox. To ensure that this range is robust to non-zero marginal price, I then re-optimize for marginal costs as high as $50,000 (likely much greater than Valrox’s actual marginal cost) and find that the price reported in Figure 6 stays optimal at non-zero marginal costs. This result makes intuitive sense as marginal cost (likely on the order of $10K) is far less than patient’s willingness to pay (on the order of $2M).

I report the welfare effects of gene therapy and generic entry based on logit specifications 1-2 and BLP specifications 1-3 in Table 10. To characterize these welfare effects, I
Figure 5: Demand Curve for Hemophilia A Gene Therapy

Figure 6: Biomarin’s Profit-maximizing Price to Charge for Valrox
report the simulated market share of the entrant gene therapy or generic, average change in consumer surplus conditional on choice of gene therapy and total market welfare gain from gene therapy entry. Below each estimate I provide a robustness interval accounting for potential variation in the product-specific demand shock for gene therapy, $\xi_{GT}$. The interval is constructed by constructing a 95% confidence interval for $\hat{\xi}$ based on the fit model and re-running each counter-factual simulation by allowing $\xi_{GT}$ to vary from the minimum to the maximum of the confidence interval. In all estimates I assume the price of gene therapy is $2.5M, which will be amortized by patients to $833K/year. A price of $2.5M is towards the upper end of Valrox’s rumored price range and would make the entrant gene therapy the most expensive FDA-approved drug ever.

Table 10: Welfare Effects and Market Shares Following Novel Product Entry

<table>
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<tr>
<th>Variable</th>
<th>Logit 1</th>
<th>Logit 2</th>
<th>BLP 1</th>
<th>BLP 2</th>
<th>BLP 3</th>
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<tr>
<td>market share of GT</td>
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<td>0.32</td>
<td>0.43</td>
<td>0.43</td>
<td>0.24</td>
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<tr>
<td>(0.06, 0.96)</td>
<td>(0.12, 0.62)</td>
<td>(0.10, 0.82)</td>
<td>(0.27, 0.63)</td>
<td>(0.08, 0.52)</td>
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<td>$\Delta CS$ GT patient ($K$)</td>
<td>69</td>
<td>231</td>
<td>89</td>
<td>236</td>
<td>151</td>
</tr>
<tr>
<td>(47, 153)</td>
<td>(199, 303)</td>
<td>(64, 149)</td>
<td>(221, 270)</td>
<td>(130, 188)</td>
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<tr>
<td>Total $\Delta CS$ post-GT ($M$)</td>
<td>161</td>
<td>319</td>
<td>162</td>
<td>436</td>
<td>158</td>
</tr>
<tr>
<td>(13, 625)</td>
<td>(103, 800)</td>
<td>(28, 522)</td>
<td>(252, 719)</td>
<td>(44, 424)</td>
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<tr>
<td>market share of GEN</td>
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<td>0.36</td>
<td>0.99</td>
<td>0.71</td>
<td>0.84</td>
</tr>
<tr>
<td>$\Delta CS$ GEN patient ($K$)</td>
<td>215</td>
<td>237</td>
<td>115</td>
<td>237</td>
<td>202</td>
</tr>
<tr>
<td>(13, 625)</td>
<td>(103, 800)</td>
<td>(28, 522)</td>
<td>(252, 719)</td>
<td>(44, 424)</td>
<td></td>
</tr>
<tr>
<td>Total $\Delta CS$ post-GEN ($M$)</td>
<td>913</td>
<td>361</td>
<td>484</td>
<td>719</td>
<td>727</td>
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</table>

GT = gene therapy (assumed to be Valrox); GEN = generic factor replacement therapy. $\Delta CS$ values reported are means

At a price of $2.5M, gene therapy is consistently projected to achieve the top position in the market, capturing between 24% and 55% of the severe hemophilia A market. The most reliable estimates, coming from the full BLP formulations 2 and 3 predict gene therapy to achieve a market share of 43% or 24%. The estimate from BLP 2 is very close to the 40% of patients which a survey of hematologists estimated would be on gene therapy within three years of its commercial launch.\textsuperscript{134}

The change in consumer surplus for the patients who choose to take gene therapy is estimated to be $236K in my preferred specification, BLP 2. Given the proportion of

\textsuperscript{134} Bell, “BioMarin inches closer to a gene therapy first”
patients projected to switch to gene therapy, this causes a total patient welfare gain of $436M per annum. These welfare effects are comparable to the welfare increase from generic entry, as mean change in consumer surplus is essentially the same under gene therapy entry or generic entry while the total welfare gain is somewhat larger under generic entry by about $280M. The gene therapy result for BLP 2 is also somewhat robust to variance in $\xi_{GT}$, as the interval of possible market shares spans just 36 percentage points (27% to 63%) and $\Delta CS$ per gene therapy patient spans just $49K ($221K to $270K). However, total $\Delta CS$ spans a range $467M due to the multiplicative effects of the changes in market share and consumer surplus.

To put these figures in context, Biomarin’s year 1 revenue from Valrox (assuming an amortized payment plan) would be $1.5B, which is enormous considering that total annual revenues in the market pre-gene therapy entry are just $1.7B. Therefore, the predicted welfare gain to patients ($436M) is roughly 30% of the revenue being paid out to Biomarin or 25% of the total revenue in the market pre-gene therapy entry. Thus, my model essentially predicts that the effect of gene therapy for patients is equivalent to collecting $\frac{1}{4}$ of current drug spending on hemophilia A and redistributing these revenues to the 40% of the patients who choose to take gene therapy! Albeit, a large increase in total spending is required to achieve this outcome, so while there is no free lunch in the market for pharmaceuticals, this result suggests innovation from gene therapy will make a profound impact on many hemophiliacs if their insurers invest the necessary funds to provide them with gene therapy.

To better understand the distributive welfare effects for patients compared to pharmaceutical firms, I perform a few back-of-the-envelope calculations to approximate the share of social surplus which patients will receive from gene therapy. First off, I consider the change in social surplus over a three-year period, my assumed lifespan for gene therapy. If I multiply the above welfare and revenue estimates over this lifespan, Biomarin collects $4.6B in revenue, while patients collect $1.3B in additional consumer surplus.

To determine Biomarin’s profits from this revenue, I must make assumptions on its
costs. I reassert the previously-made assumption that Biomarin’s marginal cost of production for Valrox can be approximated to 0. However, Biomarin’s sunk cost in developing Valrox is difficult to approximate; thus, I use a ballpark estimate of total development cost of $5B which was suggested in the literature. Normally one would amortize this cost over a drug’s pre-obsolescence lifespan, which is averages about 10 years. However, with gene therapy the problem arises that revenues for Valrox may decrease year-over-year due to gene therapy shrinking the market size as patients need no further medication to control their illness. Therefore, to account for potentially decreasing revenues over time, I assume that Biomarin amortizes half of Valrox’s development cost over the first three years on the market, as it’s likely (at least) half of its revenue from the drug will be earned over this period. This gives a sunk cost charge over Valrox’s first three years of $2.5B.

From this cost basis, I compute that Biomarin earns $4.6B - $2.5B = $2.1B in profits, while patients collect $1.3B in consumer surplus for a total increase in social surplus from gene therapy of $3.4B over three years or about $1.1B/year. This implies the welfare gain to patients makes up 38% of the total increase in social surplus. Interestingly, this proportion of social surplus gained by patients is only half the equivalent proportions estimated in Sweden and the UK in the high cholesterol drug market, although this is likely due to differing structural market characteristics. Still, that hemophilia A patients capture more than \( \frac{1}{3} \) of social surplus from gene therapy - even at the high price point of $2.5M - suggests that this technology is so beneficial to patients that record-setting drug prices will still leave them with a substantial cut of the increase in social surplus.

136. Note that this computation does not factor in profit stealing from other firms, so actual total profits in the market may increase by less than the total of Biomarin’s profits, further increasing patient’s cut of social surplus.
VIII. Conclusion

In this study, I use a characteristic space discrete choice model to characterize demand for hemophilia A therapeutics. By focusing on the drug preferences of the severe patient population and fitting both a multinomial logit demand system and more detailed Berry-Levinsohn-Pakes demand system, I estimate patients’ price sensitivity, demand for drug durability and demand for drug efficacy as either fixed parameters or random coefficients, to obtain realistic descriptions of demand. I find that the patient population of interest is relatively sensitive to price when choosing drugs, but prefers drugs that require less frequent dosing and do a better job at reducing bleeding frequency on average.

Using these parameter estimates I then simulate the effect that entry of a novel gene therapy or generic product would have on the market, keeping all other products fixed. My simulations stand apart from previous attempts to evaluate the welfare effects of gene therapy as I calibrate my welfare estimates using the information elicited from patient’s current drug choices rather than survey-based Quality Adjusted Life Years (QALY), a common if abstract metric used in healthcare economics. In my counterfactual simulation, I find that gene therapy captures an impressive 43% of the hemophilia A therapeutic market when priced at $2.5M per dose. This estimate is close to the 40% of severe hemophilia patients that hematologists expect to be prescribed gene therapy within three years of approval according to a Citi Research report. Thus, following FDA-approval, my model predicts gene therapy to become the most popular hemophilia A therapy on the market.

The main goal of this project was not only to estimate how popular gene therapy will become, but also how much it will make patients better off. On this note, I find that gene therapy will provide substantial consumer surplus gains to the patients who choose to take it; mean welfare gain to a patient on gene therapy in the model is $236K. In total this means that the whole hemophilia A patient population will experience growth in consumer surplus

140. Bell, “BioMarin inches closer to a gene therapy first”
on the order of $436M/year. Given that current total annual revenue for severe hemophilia A treatments is about $1.7B, consumer surplus gains amount to roughly 25% of current spending. I also make a back-of-the-envelope estimate of firm profits and the distribution of social surplus and conclude that given a price point of $2.5M, patients capture 38% of the total social surplus gain from gene therapy. Thus, I find that even for a high priced therapy, there are Should gene therapy be priced less than this amount, patients will benefit from an even greater share of social surplus.

However, there is no free lunch in the healthcare industry; market entry of gene therapy also projects to greatly increase spending on hemophilia A therapeutics over the short term, to the benefit of pharmaceutical firms but detriment of payers. My model predicts Valrox to hit $4.6B in revenues over its first three years on the market. While much of this revenue will be reallocated from spending on other expensive drugs, my model predicts total annual spending to swell by $400M to $2.1B following Valrox’s launch. Funding of this interim spending increase is imperative to realize long-term savings on the order of Valrox’s revenue ($1.5B/year). A number of financing options have been proposed and discussed in this paper including amortizing payment for gene therapy - perhaps implemented in tandem with value-based pricing - and the ”Netflix Model” of license-based drug pricing. However payers and pharmaceutical firms are unlikely to agree to these more complex pricing systems before Valrox’s target FDA approval in August 2020. Only time will tell which of insurers, patients, governments, financial markets, and pharmaceutical firms will provide the interim liquidity to deliver gene therapies to the patients who need them most.

I also emphasize that these predicted market shares are predicated on the assumption that competing drugs’ prices will stay constant following gene therapy entry. Economic models of competition suggest this assumption is unlikely to hold as competitors (Advate, Eloctate, Hemlibra, etc.) may look to slash prices to steal market share away from the entrant gene therapy.\footnote{Richard E. Caves et al., “Patent expiration, entry, and competition in the US pharmaceutical industry,” ISBN: 1057-8641 Publisher: JSTOR, \textit{Brookings papers on economic activity. Microeconomics} 1991 (1991): 141.} If competing firms do choose to slash drug prices, gene therapy’s
market share will likely be lower than that predicted by the model. Nonetheless, patient welfare, as measured in the change in consumer surplus post product entry can only weakly increase following drug price cuts as patients will only choose the newly-discounted drug if it provides greater utility than gene therapy would. Thus, when patients face a full choice set of incumbent prophylaxis therapies as well as gene therapy, the findings of this study represent the lower bound in the gain in patient welfare from gene therapy market entry.

Besides pricing, regulators should also watch other firm behaviors that may reduce the consumer surplus gains to patients. One mechanism of concern is an insurer’s strategic design of formularies. In many drug markets, an insurer won’t provide a full set of drugs on its formulary but instead will negotiate with pharmaceutical firms to only list certain products (often at discounted prices to the insurer). However, this practice has the potential to deny an insurer’s patients access to drugs which do not make the formulary and therefore cannot be reimbursed. Insurers also supplement their formularies with reimbursement rules that stipulate only patients diagnosed with very specific indications/diagnoses (e.g. severe hemophilia A with inhibitors) are eligible for reimbursement. Insurers are keenly aware that they could face the brunt of gene therapy’s enormous short-term cost burden and may try to limit reimbursements to curb costs. Therefore, regulators and watchdogs should anticipate especially strict formularies for gene therapy and advocate for patient access to these gene therapies when deemed necessary.

While I take a static approach to gene therapy entry in the study, analysis of the welfare effects of market entry would be incomplete without considering potential dynamic effects. I’ve already discussed the potential for gene therapy to drive down competitor prices, but a second or third gene therapy entering the market and driving down the price of the incumbent gene therapy from competition may ultimately have greater welfare effects in the long run. If I consider a gene therapy to be a type of durable good, patients face the canonical

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problem that if they believe that the price may drop in the near future, they may stay on their existing prophylaxis treatment in the interim and wait to take gene therapy until its price drops. The first entrant in the hemophilia A market - likely to be Biomarin - will therefore desire to enact a pricing system and marketing campaign to combat this behavior, as not only does waiting for a price drop cut into Biomarin’s short-term revenues but it also may cause Valrox to lose market share to a newer, better gene therapy with time. With drugs as expensive to research, develop, and purchase as gene therapies, even proportionally small diversions due to entrants will cause incumbent firms to lose massive streams of revenues - and profits - due to switchers. Ergo, as multiple gene therapies disrupt the hemophilia A therapeutic market over time, patients are likely to see even greater welfare gains due to falling gene therapy prices.

Moving forward, the work compiled in this paper can be expanded upon in a number of directions. For one, it would be particularly useful to compare the projections made in this paper to the changes observed in the hemophilia A therapeutic market following Valrox’s commercial launch. The counterfactual estimates of revenues and market shares made here can be compared to those realized following the actual market entry of gene therapy. This exercise would motivate model improvements and provide a valuable test case to compare the model predictions made by the discrete choice model used here to the markov chain models more popular in the public health field. An improved model could then be re-applied to a number of other exciting gene therapy indications ranging from genetically-inherited diseases such as Cystic Fibrosis to infectious diseases such as HIV-AIDS. Nonetheless, the findings of this study on the impact of gene therapy for hemophilia A leave little room for equivocation; gene therapy has the potential to transform the lives of those suffering from hemophilia A. Now it is up to pharmaceutical firms, payers, and policy-makers to ensure that our healthcare system is ready to deliver these patients the therapy to end all therapies: gene therapy.

IX. Appendix

A. Definition of Type I Extreme Value Distribution

The Type I Extreme Value Distribution is defined by the probability density function:

\[ f(\epsilon_i) = e^{-\epsilon_i}e^{-\epsilon_i} \]

for the cumulative distribution function:

\[ F(\epsilon_i) = e^{-\epsilon_i} \]

B. Table of Drug Characteristics
Table 11: Summary Statistics of Drug Characteristics

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<tr>
<th>Drug</th>
<th>half-life (h)</th>
<th>ann-dos (doses)</th>
<th>eff1 (ABR)</th>
<th>eff2 (ABR)</th>
<th>eff3 (%)</th>
<th>year-app</th>
<th>ASP ($/IU)</th>
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<td>182.5</td>
<td>0.9</td>
<td>2.28</td>
<td>50</td>
<td>2015</td>
<td>1.24</td>
<td>422.5</td>
</tr>
<tr>
<td>Recombinate</td>
<td>14.6</td>
<td>182.5</td>
<td>0</td>
<td>2</td>
<td>52</td>
<td>1992</td>
<td>1.528</td>
<td>520.6</td>
</tr>
<tr>
<td>Xyntha</td>
<td>11.2</td>
<td>182.5</td>
<td>1.9</td>
<td>3.9</td>
<td>45.7</td>
<td>2008</td>
<td>1.256</td>
<td>427.9</td>
</tr>
<tr>
<td>Valrox generic***</td>
<td>189/12</td>
<td>0.1</td>
<td>0</td>
<td>0.7</td>
<td>86</td>
<td>2020</td>
<td>n/a</td>
<td>2500*</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>121.7</td>
<td>1</td>
<td>1.75</td>
<td>42</td>
<td>2020</td>
<td>0.375</td>
<td>127.8</td>
</tr>
</tbody>
</table>

* ASP unit pricing for hemlibra is per 0.5 mg rather than per IU

** Valrox’s price is rumored to be between $1 - 3 M per dosage. Multiple prices were used to account for this

*** The simulated generic is assumed to have the same characteristics as Advate at 1 \( \frac{1}{3} \) of the cost
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