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By

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**The Lifetime Economic Burden of Monogenic Diseases And
The Social Motivations For Their Treatment With Genetic Therapy**

*A thesis submitted to the Public
Policy Program at
Rochester Institute of Technology*

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Abstract

The purpose of this thesis is to investigate the social cost motivations associated with paying for genetic therapies at the beginning of life for monogenic diseases from various perspectives including the social perspective and the perspective of an average member of the US population. The findings were generated by collecting direct medical cost data (in current USD) relevant to nine common monogenic diseases (Cystic Fibrosis, Sickle Cell Disease, Duchenne Muscular Dystrophy, Hemophilia A, Huntington's Disease, Polycystic Kidney Disease, Gaucher Disease, Hereditary Angioedema, and Pompe Disease) to conduct a Monte Carlo and Net Present Value analysis to generate robust lifetime cost distributions for each disease. One major finding of this research is that if an individual is known to have one of theses monogenic diseases then the direct social costs - the total cost of treatment when discounted down to a single value at year zero of life - based on direct medical costs using a 5% discount rate for a gene therapy which would bring about the removal of lifetime direct medical costs could be as high as $3,568,077 (SD $599,461) for Hemophilia A or as low as $30,467 (SD $21,164) for Huntington's syndrome. Other discount rates are also included in the models. Another major finding is that the direct social cost at year zero of life from the social perspective using a 5% discount rate for a gene therapy which would remove any risk of developing symptoms of, and therefore remove the direct medical costs for, all the diseases analyzed should be $496. Direct social cost should only increase as an individual's life continues, as explained within the thesis, so these cost figures represent very conservative estimates. It is shown that the direct social cost at the beginning of life for gene therapy, for individuals who are known to have monogenic disease, can be in the millions of dollars. It is also shown that direct social cost at the beginning of life for the removal of risk of monogenic disease in a member of the general US population should only be a few hundred dollars. These conclusions can be interpreted to show that there

should be a high direct social benefit for such therapies when applied to the population of

individuals who are at high risk of manifesting one of these monogenic diseases, but there

should be relatively low direct social benefit for the removal of the risks of manifesting one of

these diseases among the general US population.

A Note on Ethics

The advancements in efficiency and precision of gene editing brought about by the CRISPR system have allowed us to consider some previously theoretical implications of gene editing in a new and very real light. The issues with the implications of these advancements came to a head in 2015 when a team of Chinese scientists used the CRISPR system to remove an abnormal gene from a non-viable human embryo. It's very important to note that this embryo was non-viable and could never have resulted in a live birth. However, this early experiment acted as a solid proof of concept in the scientific community and spurred vigorous discussion and debate. This attracted the attention of the National Academy of Sciences, Engineering, and Medicine along with the scientific agencies of several other countries including the United Kingdom's Royal Society and the Chinese Academy of Sciences. These agencies held the first International Summit on Human Gene Editing in December 2015. Experts from many fields and from all over the world were invited to join the discussion about how we might move forward with this technology. The sentiments held at that summit were distilled into a document called "Human Genome Editing: Science, Ethics, and Governance".[47] This document contains comprehensive advice and policy strategies on how human genome editing might be implemented in an ethical and fair manner. I would advise anyone with interest in the subject of human gene editing or the policy issues and ethics thereof to read this document as it represents the distilled sentiments of the scientists and policymakers that know the technology best. It's important to mention that there are two main considerations that must be taken into account when talking about human gene editing. First, could the edits be inherited by offspring or not? Second, is the gene editing enhancing or therapeutic? The question of inheritable editing is important because any changes that are made can be passed down to future offspring

of edited individuals. When gene edits are made that can not be passed down it is called somatic editing. The question of enhancing versus therapeutic gene editing is also important with clear extremes, however, the middle ground between the two is still undefined.

The topics of this thesis seem to sit nicely within the realm of what is considered acceptable use of gene editing technology by the International Summit on Human Gene Editing. These topics and methods being the alleviation of chronic disease with no alternative cure, assuming that the methods alluded to in this work do not affect the germline and the risks of gene therapy are limited to the individual. The treatment of disease on the level of the individual while at the same time accepting the risks and side effects of the treatment at the level of the individual has come to be almost the sole perspective from which we view medical treatment (with perhaps the exception of vaccines). Where these new technologies require a deviation from the normal perspective is when the medical decisions of an individual can begin to affect more than just one person. If germline editing is made real then the medical decisions of individuals can now be allowed to echo down the halls of time in the voices of our children. Most would agree to the sentiment that gene editing should be used for the alleviation of suffering and that if the technology is used at all for enhancement then it must be done uniformly and fairly within the population.[47] While these sentiments are well intentioned they require us to ask questions which do not have, and may never have, clear answers. What is suffering? What is enhancement? What is normal?

Diseases and abnormalities which cause alienation and discomfort also bring together community and understanding. For example, dwarfism, which a member of the general population may consider to be undesirable is actually selected for by members of the short stature community. It will be impossible to move forward equitably until we can reach a consensus as a society as to what the best course of action is. The concerns and implication

regarding this technology are valid and deserve the attention of the public and the policymakers that represent them. These concerns, while being important, are not directly addressed in this thesis. It was never the goal of this thesis to directly address these concerns, however, it is my hope that the findings in this work will help add to the conversation concerning these groundbreaking advancements in gene editing.

Introduction

Several new technologies have been developed in the last 20 years that could lead to the possibility of genetically engineered humans within our lifetime. The most promising of these technologies is known as CRISPR, which stands for "Clustered Regularly Interspaced Short Palindromic Repeats". This breakthrough technology was discovered in 2013 and allows scientists to go into any part of an organism's DNA and edit it in almost any way. Traditional DNA editing methods are not as accurate and often take many tries before they are successful. CRISPR, in combination with other technologies, could be used in the near future to modify the DNA of humans and human embryos with more precision than ever before.[1] CRISPR is also developing into an extremely cost effective technique compared to traditional genetic engineering methods.[2] Most CRISPR product kits currently sell for under $1,000, which is close to 5x less than traditional gene editing technologies.[3] The mechanisms of CRISPR are also relatively easy to work within the lab compared to previous gene editing methods. These aspects in other technologies almost always lead to ubiquitous adoption and commercial competition which drives prices down. The main question that this thesis will be trying to support is:

How much should an individual be willing to pay to offset the direct social costs for the prenatal removal of a genetic disease?

The focus of this thesis will be an analysis of the direct social costs - the total cost of treatment when discounted down to a single value at year zero of life - to treat certain genetic diseases in order to establish a conservative baseline for willingness to pay for the removal of

those diseases' symptoms. New genetic engineering breakthroughs like CRISPR allow us to consider such questions. While the costs of treating many genetic diseases are relatively well known, the potential costs of prenatal genetic engineering (PGE), or any form of genetic engineering/therapy, are very much unknown. It is worth noting that while this thesis will use a purely economic analysis, there are many non-economic factors that affect the practice of human genetic engineering. While these non-economic factors, especially factors concerning ethics and social justice, must be addressed before the technology can be allowed to move forward they will not be addressed specifically in this thesis.

New gene editing technologies are coming faster than we might think. Some new gene based therapies are already being developed. In the fall of 2017, a man named Brian Madeux received a gene therapy which is aimed at functionally curing his Hunter Syndrome. Hunter Syndrome is a genetic disease which causes limited movement and degenerative heart and lung conditions. The gene therapy that Brian received changed the genome in some of his body cells and, if proven effective, will allow him to live a life free of the symptoms of Hunter Syndrome. Another notable gene therapy for a rare form of blindness was undergoing development in the US as recently as the winter of 2018. This therapy is said to cost around $450,000 per eye. [41] There are also other gene therapies on the market, and most of them are for very rare diseases. A European gene therapy called Strimvelis is aimed at curing a severe form of immunodeficiency and costs about $665,000.[42] One of the earlier gene therapies of this kind was called Glybera, it was priced at over $1.4 million for an individual dose and was supposed to cure a rare inherited disorder which causes severe pancreatitis.[46] Glybera was pulled from the market due to low demand. The $1.4 million price tag was meant to cover not only the cost of developing the treatment but also to develop it in such a way that it could be used as a toolkit to treat many different genetic diseases. These gene therapies are proving to

be extremely expensive compared to traditional drugs. When being compared to traditional drugs these gene therapies have one large advantage. Traditional drugs usually only treat or manage symptoms but if a gene therapy works correctly it can completely cure a genetic disease.

The idea of gene therapy which can be made affordable represents an admirable goal for the future of gene editing technology. Though there is the opposing and apparently more likely case that these therapies will become prohibitively expensive for most of the public. This case of extreme expense seems as though it will embody the early market for gene therapy. Given that several companies have already put gene based therapies on the market, and given that they all cost hundreds of thousands of dollars, we must ask ourselves if the costs of these therapies are worth the benefit.

Literature Review

Literature Review Method

The initial search for data regarding willingness to pay for genetic therapies was completed using Google Scholar, linked with the RIT Wallace Library database. The original search set out to find literature on the economics for the use of genetic therapies in humans. However, after several iterations of this search, less than three pieces of literature were found. The reasons for this extreme lack of literature are explored in the Results and Analysis section of this review. In order to continue exploring this topic, a new search was created. For reasons also explored in the Results and Analysis section, the new search aimed to find current literature on the economic costs of treatments and direct medical costs for genetic diseases in the US. The inclusion criteria for this search only allowed for articles published in the last 10 years which included the words "Cost/Economics of Rare Disease/Orphan Drugs" in the title. The optional terms included were "orphan drug", "rare disease", "genetic disease", "cost", "economics", "treat", "direct medical", "US", and "United States". A total of eight articles fully met these criteria. Search matches were excluded if they were news articles, social or indirect cost pieces, pieces entirely on the ethics and morals surrounding genetic disease and their treatments or cures, and textbook entries.

Table 1 **Literature Review Matrix**. Includes six articles on the most current analysis of the direct medical costs associated with the most common genetic diseases.

#	Author / Editor	Year	Type	Data Origin			Drug Cost	Avg Annual cost	Direct Medical	Social Cost	Single Disease	>1 Diseases	Title
				Survey	if yes, size?	Database							
1	Aitken, M	2017	Industry Report	X	N/A	X	X		X			X	Orphan Drugs in the United States
2	Boice N	2013	Industry Report	X	144				X	X		X	Shire Rare Disease Impact Report
3	Hadjivasiliou A	2017	Sponsored Report			X	X		X	X		X	2017 Orphan Drug Report
4	Field MJ	2010	Academic Research			X		X	X	X		X	Rare Diseases and Orphan Products
5	Zhou Y	2009	Academic Research			X	X		X	X		X	Rare disease research stimulator or commercial opportunity?
6	Angelis A	2015	Academic Review	X	1000+	X	X	X	X	X		X	Socio-economic burden of rare diseases: A systematic review of cost of illness evidence
7	Lopez JB	2010	Academic Research			X		X	X	X		X	Cost of Illness and Economic Evaluation in Rare Diseases
8	Urquhart L	2016	Sponsored Report			X	X	X	X	X		X	Report of Orphan Drugs 2016
9	MorganDeWitt E	2012	Academic Research	X	352			X	X	X	X		Resource Use, Costs, and Utility Estimates for Patients with Cystic Fibrosis with Mild Impairment in Lung Function: Analysis of Data Collected Alongside a 48-Week Multicenter Clinical Trial
10	Divino V	2013	Academic Research	X	1272			X	X		X		The direct medical costs of Huntington's disease by stage. A retrospective commercial and Medicaid claims data analysis.
11	Xheng-Yi	2015	Healthcare Research	X	222		X	X	X		X		Burden of illness: direct and indirect costs among persons with hemophilia A in the United States
12	Landfeldt E	2014	Healthcare Research	X	770			X	X	X	X		The burden of Duchenne muscular dystrophy
13	Kauf T	2009	Academic Research	X	4294		X	X	X		X		The cost of health care for children and adults with sickle cell disease
14	Beutler E	2007	Healthcare Research			X	X	X	X	X	X		Lysosomal storage diseases: Natural history and ethical and economic aspects

Literature Review Results

The subject of human genetic engineering is still novel in our society, Because of this, there is very little research that directly studies the economics of human genetic engineering and genetic therapies. Analysis of the costs of technologies and methods that have preceded human genetic engineering, i.e. genetic testing and genetic disease treatment, are used in this literature review to help shed light on the subject. These topics, i.e. enzyme replacement therapy for genetic disease, have been the subject of considerable scientific and economic study. The data and research that currently exists relative to these topics mainly consists of economic studies of the drugs and therapies used to treat genetic diseases and evaluations of the effectiveness of genetic tests. This data is mostly found in industry sponsored reviews and economic reports from rare disease advocacy groups. Eight of the pieces of included literature got their data from querying national databases. Additionally, only one multi-disease study got its data from a survey of patients rather than a database. A majority of the single disease studies also used patient survey data. This suggests that broad surveying of the genetically diseased population can be difficult. However, the single disease studies show that it can be relatively easy to gather data when one works with a specific disease. A single disease may be easier to gather data on because oftentimes disease advocacy groups have easy access to participants willing to take part in research. Also, research and treatment centers related to specific genetic diseases often gather data from the entire affected population as there tend to be only one or two of each in the US which makes them easier to query. The research pieces in this literature review were found through NCBI and the journals of Nature, and Science.

Overshadowing the economic research is a great deal of research into the ethical and social implications of these and future technologies. If one was to search "genetic engineering in humans" on Google Scholar, you would find that at least half of the first page contains material on the ethics and morality of the subject. It is clear that most of our society views human genetic engineering as a slippery slope and as a technology with a great deal of power. Many people in the scientific community, including the researchers developing the technology, believe that robust policies need to be in place before human genetic engineering technology is made available to the public.[1] The social implications of human genetic engineering are clearly important, however, these implications are out of the scope of this review.

There is not a significant amount of research on the costs associated specifically with genetic disease. However there is a substantial amount of information regarding rare diseases in the US and according the the US Institute of Medicine in their review of rare diseases and orphan drugs in the US: "experts on rare diseases generally agree that the great majority of rare diseases—perhaps 80 percent or more—are genetic in origin",[4] the review goes on to say that the remaining 20% of rare diseases are most likely caused by a combination of genetic and environmental factors. Given the lack of research on genetic diseases specifically, research on the impacts and costs of rare diseases will have to suffice. The term "rare disease" covers even the most common monogenic disease in the US, Cystic Fibrosis,[5] so the term should be suitable for use in further analysis. The Rare Diseases Act of 2002 defines a rare disease as "any disease or condition that affects less than 200,000 persons in the United States".[6] The National Organization for Rare Disorders (NORD), which was instrumental in establishing the Rare Disease Act, currently estimates 30 million Americans suffer from over 7,000 rare diseases. The most common monogenic disease, Cystic Fibrosis, affects about 30,000 people in the US, putting it safely within the category of a rare disease.[7] With this information we can start to use

cost data to determine the annual cost to treat the average genetic disease. Knowing what is already spent to treat rare diseases, and by proxy, genetic diseases, it can be determined what one might be willing to pay to cure a monogenic disease altogether.

Orphan drugs are the primary drug products used to treat rare diseases. As stated in the 2017 Orphan Drug Report published by the EvaluatePharma Group: "an orphan drug is a pharmaceutical product aimed at rare diseases or disorders".[8] The orphan drug report also estimates that the average cost per patient per year in 2016 was $140,450 compared to the average $27,750 for normal (non-orphan) prescription drugs. Since orphan drug prices are inversely correlated with the number of patients receiving the drug.[9] The average calculated cost per patient can be very high while the median costs can be significantly lower. The EvaluatePharma report states that the median annual cost per patient is approximately $83,000. This suggests a lognormal distribution of cost data instead of a normal distribution. A lognormal distribution is a distribution that by definition cannot have values below zero and is hallmarked by a long and right-skewed tail, an example of this can be seen in Figure 1. This trend of the average cost being significantly higher than the median can be seen in most of the reviewed literature. This information will do well to inform the disease cost models that have been created for this thesis.

Figure 1

Log Normal distribution and Normal distribution
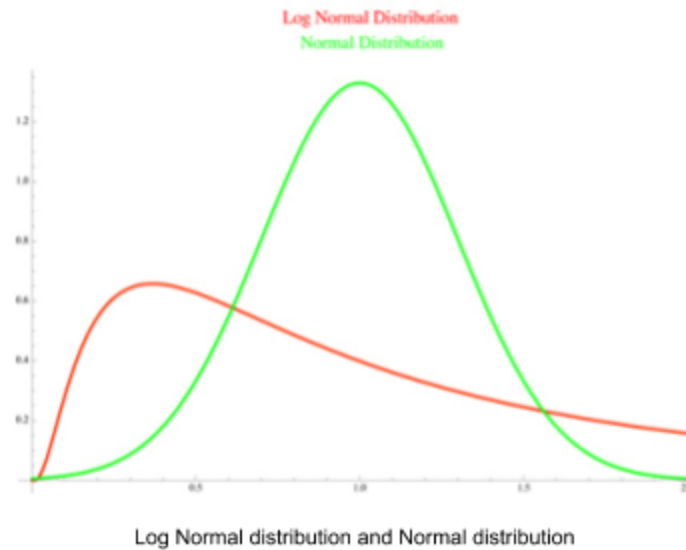
Another industry report seems to confirm these findings. The October 2017 "Orphan Drugs in the United States" report published by the Quintiles Institute in New Jersey shows that median annual cost per patient per year to also be around $80,000.[10] This report used the FDA orphan drug database to generate a list of all orphan drugs currently being offered in the US, they then used the IMS Health database (a database that provides physician prescribing data) to assign prescription rates and prices to each drug. This report did not take into account anything other than direct medical costs. While direct spending can often make up the majority of an individual's costs for treatment, it rarely makes up the total spending. Rare disease patients can end up spending a significant amount on specialist visits, tests, transportation, and home care. Other than individual cost, the report by the Quintiles Institute mainly focuses on the growth of spending on rare diseases and orphan drugs in the US. The report goes on to say that of the $450 billion of drug sales in the US, $36 Billion is spent on rare diseases, which is about 8%.[10] These types of findings in the report suggest that the reports are mainly tailored to investors in the pharmaceutical industry.

A separate industry impact report took a survey of over 100 rare disease patients and their caregivers in the US.[11] The report was sponsored by the rare disease therapy company known as Shire Human Genetic Therapies and was conducted through the RARE Project (a NJ based genetic disease advocacy group). This report mainly goes into the social, emotional, and health care impacts of rare disease. The report goes on to say that individuals with rare diseases experience a quality of life that is 60% worse than the average healthy person. They found that 53% of individuals in the US with rare diseases had to borrow money to pay their bills and that 55% of that same population incurred direct medical costs that were not covered by their insurance. Offering a more social perspective, the Impact Report continues to say that a large amount of costs due to rare disease are indirect and that 61% of patients are diagnosed with untreatable depression linked to their condition.

The information from these sources seems to show that most individuals are willing to pay, or at least have to pay, very high prices for healthcare related to their disease. This information also suggests that genetic diseases have high costs both socially and economically. This means that as a society, or as individuals, we should be willing to pay equally high prices to eliminate genetic disease altogether.

In mentioning limitations, most articles mention that direct medical costs do not represent the total of costs associated with a genetic disease. Direct medical costs, indirect medical costs, and social costs (if quantifiable) would make up the sum total of cost for a genetic disease patient and are respectfully harder to calculate. Three of the eight articles mention that indirect medical costs most likely exceed direct medical costs per patient. This means that in most cases direct medical costs may represent less than half of total costs incurred by genetic diseases. Most articles do not directly mention this as a limitation. These same papers also look at genetic disease as a whole. While most articles use figures for the "average genetic disease",

no genetic disease case is average. When looking into data on individual diseases it can be seen that annual costs can vary between diseases by a factor of 100x.[12] Genetic diseases are highly varied and should be looked at with fine granularity in order to understand the full picture. Another limitation of the studies comes from those that conducted surveys. Of the three articles that included survey data, none of them actually conducted the survey themselves and were citing data that was collected by other institutions; one of them directly mentioned this as a limitation.

Finally, most articles aimed to analyze both the social and the economic costs associated with genetic diseases. It should be made very clear that all costs associated with genetic disease are worth considering and that the social and moral burden of genetic diseases and their possible cures hold considerable value. However, this review aims only to determine the extent of research into direct medical costs to genetic disease patients. Social, moral, and ethical implications of these topics are out of scope for this analysis.

Literature Review Discussion

Precisely editing the DNA of an organism, human or otherwise, has been considered both extremely difficult, inaccurate, and exceptionally costly up until the last decade. In 2013, scientists from MIT and UC Berkeley published research showing that they had discovered a set of enzymes called "C.R.I.S.P.R". This set of enzymes, when utilized correctly, gave researchers the ability to edit the DNA of any organism with extreme accuracy.[13] Since then, there has been substantial speculation in the scientific community about the uses for this technology. The idea of cheap and accurate gene editing is certainly enough to lead anyone to think about the many

implications of such technology, and with CRISPR these implications are now more possible than ever.

Now that gene therapies are becoming safer, cheaper, and more precise, the effects of this technology on our lives must be considered. Individuals with genetic diseases are an obvious first target for genetic modification. A given genetic disease can cost an individual considerable funds to treat, cause substantial suffering, and could feasibly be fixed using gene editing technology. These individuals also represent a target for the biotech companies that manufacture relief therapies that are non-genetic in nature. There are many individuals in the US suffering from genetic diseases. The National Organization for Rare Disorders estimates that approximately 25 million Americans or about 8% suffer from some type of rare disease.[7]

Looking at the literature as a whole, there seems to be agreement that the median annual direct medical cost per patient across all genetic diseases is around $80,000 per year. This figure includes the many extremely rare diseases with US patient counts below 1,000 persons.[10] It is commonly accepted in the world of genetic diseases that the rarer a disease is the more costly it is to treat. This follows with the basic supply and demand principle of economics. The median annual direct medical costs per patient for some of the more common genetic diseases is closer to $30,000 per year.[8] Even when looking at only the most common and therefore least costly genetic diseases one finds that annual direct medical costs are in the tens of thousands of dollars.

Several articles analyze orphan drugs and rare disease as areas of financial growth and investment. The orphan drug act offers companies the potential to form monopolies in treating particular genetic diseases.[10] Rare diseases and their treatments represent a $36 billion industry. It makes sense that financially minded institutions would give attention to how this market has grown and how this market is predicted to grow in the future. It could be said that

this activity shows a large desire to profit from the genetic disease market and a possible lack of incentivization to decrease prices of treatments for genetic diseases. This could mean that theoretical cures to genetic disease may face pushback from large investment institutions, the pharmaceutical industry, and other large healthcare stakeholders.

We must move forward carefully and respectfully as we advance this technology. The information from these sources seems to show that most individuals are willing to pay, or at least have to pay, very high prices ($80k avg) for healthcare related directly to genetic disease. This information also suggests that genetic disease has high costs socially as well as economically. As a society or as individuals we should be willing to pay equally high prices to eliminate genetic disease altogether.

Methods

The analysis of net present costs of various monogenic diseases to determine the direct social benefits - the inverse of total cost of treatment when discounted down to a single value at year zero of life - of gene therapy was performed from the societal perspective as well as the perspective of an individual who wishes to remove a genetic disease from a human who has yet to be born or has very recently been born and has a known risk or a family history of genetic disease. The beginning of viable life has been chosen as the point of analysis for two reasons. The first is because genome editing is much easier and effective when working with earlier embryos and the concept of editing embryos has already been proven.[1] The second reason is that when the total lifetime costs are calculated with net present value analysis, using the beginning of life as one's starting point results in the lowest and most conservative lifetime cost estimates because all of your potential costs are as far away as they could possibly be in one's lifetime. Costs will be calculated from the social perspective (i.e the sum total direct costs to both the insurance provider and the individual).[14] Indirect medical costs (i.e reduced productivity, work loss, lost taxable income, travel to specialist, expenses, etc) [14] will not be within the scope of this study. The social, emotional, and ethical benefits of a life free from genetic diseases are abundant but undefined and are out of the scope of this thesis. The economic benefits also remain largely unexplored and will be the sole focus of this thesis. It would be an obvious desire of any caretaker to remove a genetic disease from their future offspring. Given that the answer to the question "Should I pay for gene therapy?" is most likely an emphatic "yes" from most caretakers faced with the possibility of genetic disease in their offspring, the main goal of this thesis is to help aid individuals in determining if gene therapy is economically justified. In order to accomplish this, the economic benefit of removing the direct medical costs associated with a

lifetime of a given genetic disease at different discount rates will be used as a stand-in to determine direct social cost. For use within this thesis, this direct social cost stand-in will be acceptable, however it should be noted that it is not without its complications, which are detailed throughout this thesis.

The direct medical costs of each disease are the primary data input for the analysis of lifetime costs. Direct medical costs are those that apply directly to medications, medical care, hospital visits, and physician fees. These costs are easily documented and are made up of elements that are commonly covered by both private and public healthcare providers. Direct medical costs were chosen as the main base of analysis in the interest of creating concrete and conservative estimates that will have relevance to policy making in the domains of health insurance and government. It should be mentioned that total medical costs for rare disease, which are made up of the sum of direct and indirect medical costs, have been shown to be mainly comprised of indirect medical costs.[15] Indirect medical costs (costs comprising of work loss, lost taxable income, travel to specialists, expenses, etc) are harder to calculate than direct costs and also vary widely among individuals. Given that indirect medical costs can make up the majority of costs to an individual with a rare disease it should be considered that, while the estimates in this thesis are purposefully conservative, an estimate for total costs associated with a disease could be over double the amount of direct medical costs.

The main goal of these methods will be to produce a lifetime direct medical cost distribution for a given genetic disease. Then to take these cost distributions and equate them to a single lump cost at the beginning of life using net present value calculations. That lump sum cost will be used as a conservative limit for estimating a direct social benefit for prenatal genetic therapy. Diseases to be analyzed will be the most common monogenic (single gene) diseases. Monogenic diseases represent a feasible target for upcoming human gene therapies because

erroneous genetic material is limited to a single location in the genome are often as simple as a single incorrect or missing letter in the DNA sequence. The data is collected from research papers with the intent of investigating the direct medical costs of a given monogenic disease. Direct medical cost figures are collected before the costs are split between the health insurance provider and the patient. The existence and prevalence of direct medical cost data will help to compensate for the intricate nature of the US health insurance system. The cost data utilized will come from the most recent research papers published within the last 10 years in the US that have statistically significant sample sizes. Other inclusion criteria is outlined are the Data section of this thesis.

In order to accurately quantify a lifetime of payments into a single lump sum of money, a "net present value" of the payments must be calculated. A Net Present Value (NPV) is a term used in economics to describe the worth of a present sum of money as compared to a future sum or sums of money with respect to a discount rate. The concept of NPV is based on the principle that money is worth more right now and worth less the further into the future you go. Discount rates are expressed as a percent and roughly correlates to how much return on investment an individual or institution needs in order to find an investment acceptable. Privately acting individuals might operate with a discount rate between 3% and 7%, larger corporations and institutions like health insurance and pharmaceutical companies might operate with discount rates between 10% and 30%.[16]

Monte Carlo analysis techniques will be used to account for the high variability in yearly costs of genetic diseases, as well as variability in diagnosis age and expected lifetimes. Monte Carlo analysis works by simulating hundreds, or in this case thousands, of different possible scenarios to determine a probabilistic breakdown of possible outcomes. This will work well to give most likely cost figures and distributions for each disease. All of the considered diseases

have different stages, average onset ages, mortality ages, and severities, each with different

costs associated with them. These cost factors will all be considered in the model. For example,

a lifetime direct medical cost breakdown for Huntington's disease may look like Figure 2 below.

It can be seen that the disease starts incurring costs later in life with the price increasing in three

stages over time. Once a distribution of the lifetime annual direct medical costs for each disease

is generated the costs will then be calculated into a single lump sum at one year before birth.

Figure 2
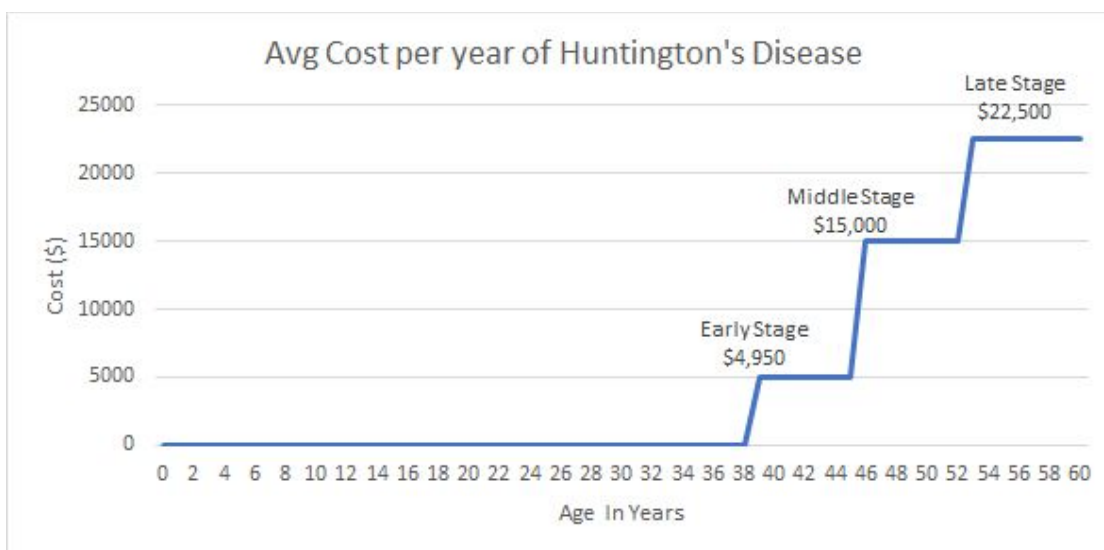
Figure 2 shows an example of a lifetime direct medical
cost breakdown for Huntington's disease

Each lifetime disease cost estimate is produced by simulating thousands of theoretical

individuals, each with different variables associated with their disease and costs and defined by

statistically significant input data. The net present value of each individual's lifetime direct

medical spending is then calculated and added to the pool of all theoretical individuals with the

given disease to determine the final cost distribution. Once the cost distributions are generated

in the Monte Carlo model for each disease they can be adjusted for sensitivity analysis. Such

analysis would include different discount rates for the NPV calculations, the possibility of an

individual having a child with the same disease, and different onset ages for each stage. Using

the example of Huntington's disease, the cost data and onset ages of the different stages and

their variabilities would be added to the model to reflect the stepped increase of costs over time

in an individual's life.

Data

In order to accurately and robustly answer the question posed by this thesis a representative number of genetic diseases must be considered. Several methods of disease selection have been considered for this process. The method that is currently the most reasonable is to include a selection of the most common monogenic disorders. Monogenic diseases make up the some of the most common genetic disorders and have the highest likelihood of benefitting from CRISPR based genetic therapy. Monogenic diseases are a subset of genetic diseases where there is only a single gene mutated or missing. Collecting data on the annual treatment costs of these diseases is key. Most genetic diseases have advocacy groups associated with them. These advocacy groups tend to collect data regarding the costs associated with their genetic disease. Input data comes primarily from these groups and various other institutions carrying out surveys for the collection of cost data.

The criteria for data inclusion began by searching for monogenic (single gene) diseases as they are most likely to be treated by upcoming gene editing technology. From that list only the monogenic diseases which were most prevalent in the US population according to the US Center for Disease Control's resources were selected. The search for cost data began with the most prevalent and moved to the least prevalent as time allowed. In total, nine diseases were included in this thesis. For each disease only research that included data specifically regarding direct medical costs or direct medical resource utilization was included. Data from Medicare and Medicaid was prioritized where available in order to produce more conservative cost estimates. Data from surveys within the last 10 years and data with the largest sample sizes were also prioritized.

Table 2: Disease Cost Data

	Avg Annual Direct Medical Costs	Cost Data Year Published	Cost Data Population Sample Size	Medicad or Medicare Data Specifically Used?	Life Expectancy in Years	Onset/Diagnosis Age	Multiple Stages?
Cystic Fibrosis [1,2]	$38,493 ($26,275)	2012	352	Partial	47.7 (1.95)	<1	
Duchenne Muscular Dystrophy [3,4]	$54,270 ($48,740)	2014	284	No	35 (4)	5 (0.5)	Partial
Gaucher Disease [5,6,7]	$185,000 ($21,000)	2017	N/A	No	68 (8)	20 (10)	
Hemophilia A [8,9]	$185,257 ($190,620)	2015	222	Yes	68 (4)	<1	
Hereditary Angioedema Type 1 [10,11]	$25,884 (- -)	2010	457	No	54 (23)	5(1)	
Huntington's [12,13]	$17,694 ($16,586)	2013	520	Yes	Onset age + 20 (2)	40 (12)	Yes
Polycystic Kidney Disease [14,15]	$25,857 ($44,357)	2015	4,234	No	60 (5)	43.3 (13)	Yes
Pompe Disease [16,17]	$200,000 ($20,000)	2017	N/A	No	30 (10)	<1	
Sickle Cell Disease [18,19]	$16,600 ($29,500)	2009	4,294	Yes	43 (3)	<1	

All numbers shown as : **Number (SD)**, if the standard deviation is available

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Table 3: Monogenic Disease Data Ranked by Prevailance [1]	Prevailance: 1 in ...	Approx % Cases with little/no family history	Dominance Type
Polycystic Kidney Disease[2]	2450 (clinically<1000)	5%	Dominant
Cystic Fibrosis	2,500	100%	Recessive
Sickle Cell Disease	3,200	100%	Recessive
Hemophilia A [3]	10,000	15%	X Linked
Duchenne Muscular Dystrophy [4]	10,000	10%	X linked
Huntington's [5]	14,200	0.10%	Dominant
Gaucher Disease	40,000	100%	Recessive
Hereditary Angioedema Type 1	58,800	20%	Dominant
Pompe Disease	100,000	100%	Recessive

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Data on nine different diseases has been collected. A summary of that data can be seen in the tables 2 and 3 above. Additional cost data which relates to the different stages of each disease are not included in the summary table but are included in the model. These additional data are mentioned in the Disease section. In the data most of the diseases show median costs which are lower than the average costs and some standard deviations which were higher than the mean. This reinforces that most individual diseases also closely follow lognormal distributions of cost. Medicare and Medicaid costs are both utilized in the models. They are both government run health insurance programs that help cover elderly and low income individuals respectively. Prices for various healthcare products (i.e. prescription drugs, hospital stays, surgeries, etc) are negotiated by the government with these two systems and tend to be lower than prices set by private health insurance entities. This is a simplification of the Medicare and Medicaid systems, however, the result is that using prices set for the Medicare and Medicaid systems allows for accurately conservative cost estimates in general.

Table 3 shows that Polycystic Kidney Disease has a different clinical prevalence than that which has been reflected by surveys estimating the current number of individuals suffering from the disease in the US population. This is because Polycystic Kidney Disease usually only presents in late middle age and some individuals can be asymptomatic for the entirety of their lives. It is not uncommon for an individual with Polycystic Kidney Disease to die (either of kidney related causes or other causes) and to have their disease revealed and diagnosed via autopsy or postmortem blood work.[17] It can also be seen in table 3 that recessive diseases are shown to have 100% of their cases occur with little or no family history. This is a simplification. It is certainly possible for individuals to be born with these recessive genetic diseases and also have family history, although these cases a much rarer. This simplification has been made in order to

streamline some of the analysis performed in this thesis, particularly the White Pill thought experiment which can be found in the Results section.

All genetic diseases are worthy of consideration, the diseases in this thesis have been chosen for their readily available and recently published data along with their theoretical ease of treatment with gene editing technologies. There are several monogenic diseases, including Familial Hypercholesterolemia, Hereditary Spherocytosis, β-Thalassemia, and Neurofibromatosis, that are more common in the US and World populations than several of the diseases chosen for analysis in this thesis. These diseases were not included due to their highly complex nature and high variance between individuals which makes basic economic tracking difficult. The omission of these diseases is not a deliberate rejection but a recognition that there is still much to be understood about the economics of genetic diseases.

β-Thalassemia is a prime example of one of these diseases. It happens to be one of the most prevalent genetic diseases in the world and is as common as 1 in 10,000 in certain countries.[18] However, β-Thalassemia mostly affects demographics that are not extremely common in the United States (namely Italian, Greek, Middle Eastern, and South Asian). β-Thalassemia also presents a wide range of symptoms from dizziness to enlarged spleen.[18] This combination of factors in a disease makes it hard to accurately track costs in US dollars even though it is a relatively common genetic disease and is prevalent worldwide.

Diseases

The following section provides overviews of each disease and relevant information regarding medical resource utilization for the generation of lifetime cost models. Information regarding disease symptoms comes primarily from the CDC's index of diseases and conditions [19] unless otherwise cited.

Cystic Fibrosis (CF)

Cystic Fibrosis is a disease where the secretions of the body are unusually thick. The disease is most prevalent in the lungs as they can build up with mucus. The liver, pancreas, kidneys and intestine can also be affected. Cystic Fibrosis is usually diagnosed within the first year of life and is associated with a diminished life expectancy of approximately 47 years.[20] Antibiotics and other medications are often prescribed to ward off lung infections and increase quality of life. In some cases as lung condition worsens mechanical breathing and even lung transplantation may be necessary.

Sickle Cell Disease (SCD)

Sickle Cell Disease is a blood disorder caused by an abnormality in the gene for hemoglobin and is also commonly known as Sickle Cell Anemia. The most prominent feature of this disease is that the defective hemoglobin causes some blood cells to deform into crescent or sickle shapes. These abnormally shaped blood cells can get caught in capillaries and cause various kinds of damage throughout the body. Symptoms include pain crisis, acute chest syndrome, aplastic crisis, fatigue, and many others. Diagnosis is often within the first year of life and can be done with a simple blood test. SCD is associated with a lifespan shortened to

around 45 years.[44] Treatment for SCD includes daily administration of penicillin for individuals under six years old, pain medication, blood transfusions, prescription Hydroxyurea, and others. The data collected utilizes Medicaid dollars.[43]

Duchenne Muscular Dystrophy (DMD)

Duchenne Muscular Dystrophy is a severe form of muscular dystrophy which is hallmarked by muscle weakness in the legs which eventually develops into widespread muscle weakness. DMD is an X linked disease so it disproportionately affects males. Treatments include prescription of corticosteroids, use of orthopedic appliances such as leg braces and wheelchairs, and a volume ventilator/respirator for sleep hours which may eventually be needed for all hours. Other treatments may also be used. Symptoms for DMD usually begin around age five.[21] No significant data could be found resolving the distribution of onset age further, so an average onset age of five years with a standard deviation of one year was used in the model to add as much accuracy as possible. The available cost data is calculated in "international dollars" which is based on the buying power of the US dollar in the US, so it is functionally equivalent to a US dollar. The main study from which the cost data was taken did not explicitly state whether or not it used Medicare or Medicaid data,[22] in the case that it did not, this may explain why the estimates seem higher than what might be intuitively concluded. In a separate cost analysis of DMD it is suggested the costs usually double around age 14,[23] however the cost figures of that study did not meet inclusion criteria for this thesis. The second cost analysis study suggests that total loss of mobility is correlated with an increase in medical costs and is known to happen about halfway through the course of the disease. This is still accounted for in the model by having the costs set to 65% of the known lifetime mean for the first half of life and

135% of the known lifetime mean for the second half of life. Life expectancy with DMD is approximated at 35 years.[23]

Hemophilia A (HA)

Hemophilia A is a disorder in the blood's clotting mechanisms which impairs the body's ability to form clots which can lead to excessive bleeding along with joint swelling and other symptoms. Diagnosis is typical within the first year of life.[24] Treatment can include the use of prescribed clotting factors based on severity, also prescribed pain medications, steroids, and physical therapy can be used to decrease pain. No research on life expectancy that meets inclusion requirements for this thesis could be found. Most life expectancy research is either from over two decades ago or includes a sample population which is not statistically significant. The World Hemophilia Organization does include in their annual report that most hemophilia patients live to be over 45 years old and that "Without adequate treatment, many people with hemophilia die before they reach adulthood".[25] However, with proper treatment "life expectancy for people with hemophilia is about 10 years less than that of males without hemophilia".[26] With this, it will be assumed that hemophilia morality is about 10 years earlier than that of the average US life expectancy which is 68 compared to the US average of 78.[26] The data used in the model utilizes Medicare and Medicaid data. [25]

Huntington's Disease (HD)

Huntington's Disease or HD is a genetic disease associated with the slow death of brain cells beginning in middle age. Early stages of the disease are associated with affected mood, mental ability, and coordination. Later stages are associated with dementia, and total loss of motor control. Symptoms of early stages can be treated with various pharmaceuticals, however

as the disease progresses and psychomotor function declines individuals with HD will require

full time care. The Huntington's model was made using stage based costs from a 2013 study of

direct medical costs.[27] The distributions for age of onset were taken from a separate piece of

research which specifically studied onset ages and length of disease stages.[28] Based on this

data, the model assumes an average age of onset of 40 (SD 12) and an average duration until

end of life of 20 years (SD 2). Extreme cases of Huntington's onset in very early or very late life

(before the age of 30 or after the age of 60) have been known to correlate with shortened

subsequent stage durations and lifespans, however, these represent fringe cases and will not

be incorporated into the model. [28 29] The progression of the disease has three stages. Early

stage, middle stage and late stage are associated with annual costs of $3,257 (SD $5,670),

$12,330 (SD $16,986), and $34,495 ($27,111) respectively.[27] It is assumed that each stage

lasts about one third of the total time between onset and end of life which is based on a

probabilistically generated onset age. HD represents an interesting genetic disease for this

economic analysis because symptoms and treatment do not start until around 40 years of age.[29]

This puts all the costs associated with HD at the end of life and therefore results in a low net

present value when compared to diseases with similar treatments. This low relative net present

value makes HD an exemplary case for the lower bound of the lifetime cost of any genetic

disease.

Polycystic Kidney Disease (PKD)

Also known as Autosomal Dominant Polycystic Kidney Disease or ADPKD, it is one of

the most common genetic diseases in the US. PKD is hallmarked by the slow accumulation of

numerous fluid filled cysts that grow on the kidneys and cause degenerative kidney failure. PKD

takes several decades to develop symptoms that can be noticed clinically, this is why many

patients are not diagnosed until symptoms onset in middle age. Seven separate stages are identified with the progression of PKD. These stages and their rounded associated mean annual costs are stage 1: $10,500 (SD $25,000), stage 2: $8,600 (SD $28,000), stage 3: $10,700 (SD $31,000), stage 4: $15,600 (SD $30,000), stage 5 $45,500 (SD $65,300), dialysis: $57,900 (SD $79,000), and post-transplantation: $32,200 (SD 52,000).[29] Stages 1-5 are associated with measured decline in kidney function until failure. After the five stages an individual must undergo dialysis until a transplant can be found. It is assumed that each stage lasts 2 years, dialysis lasts 3.5 years [30], and the post transplantation stage lasts until end of life. An estimate based on data published in the New England Journal of Medicine has PKD affecting approximately 1 in 2500 Americans.[31] This makes PKD the most common chronic genetic disease in the US. Approximately 10% of all renal replacement therapy in the US and a significant number of US kidney transplants are utilized by PKD patients.[32] Steadily removing the burden of PKD from the US transplant and renal replacement systems could mean a lot for those who remain in those systems.

Gaucher Disease (GD)

Gaucher Disease is what's known as a lysosomal storage disorder. The body cells in individuals with this disease lack an enzyme that allows for the removal of wastes known as sphingolipids. These wastes then build up in the liver, kidneys, lungs, brain, and other organs. The buildup of wastes is slow, so it may take years for an individual to begin showing symptoms and be properly diagnosed.[33] The drugs used to treat GD, known as enzyme replacement therapies or ERT, make for an interesting case because they alleviate the symptoms of the disease almost totally. An individual who has been receiving ERT for GD would, almost miraculously, show almost no symptoms of the disease. This means that an individual with GD

has very few direct medical costs associated with their disease other than those associated with their ERT.[34] The average annual cost data for GD was calculated by averaging the annual cost for the drugs used to treat the disease, and the standard deviation required for the model was taken from the standard deviation of the different drug prices.

Hereditary Angioedema, Type 1 (HAE)

Hereditary Angioedema type 1 is the most common form of HAE and is primarily caused by a deficiency in blood proteins that suppress the body's inflammatory system. Overstimulation of the inflammatory system can cause severe swelling in the arms, legs, face, and intestinal tract. In some cases, swelling can occur in the airways of patients which, without immediate medical attention, can lead to asphyxiation. Various prescription drugs can be taken to decrease the frequency and severity of swelling episodes. Some patients may be prescribed an enzyme replacement therapy to help restore their deficient blood proteins. No standard deviation data was available with the HAE annual cost data used in this paper. Any HAE research that did include standard deviations with the annual cost data did not meet the inclusion criteria for this paper. Knowing that HAE is a dynamic disease with many varied symptoms, a standard deviation needed to be approximated for the annual per patient cost data in the model. This standard deviation was made by averaging the ratios of the standard deviations of each disease to their direct medical costs. Most of the monogenic diseases represented in this thesis have direct medical costs with standard deviations that come close to or exceed the mean. The standard deviation produced by this method was 91%. While this method may not be entirely accurate It has provided a standard deviation which approximates a common monogenic disease.

Pompe Disease (PD)

Pompe Disease (PD) is also known as glycogen storage disease type II, Pompe Disease is another lysosomal storage disease similar to Gaucher's Disease which primarily affects juveniles. PD is associated with the buildup of complex sugars in certain tissues and organs, especially the muscles.[35] Poor muscle tone, enlarged liver, heart defects, and developmental disorders are hallmarks of this disease. PD is also associated with an extremely attenuated lifespan.[36] PD is another disease which can be treated with enzyme replacement therapy. Cost is variable by an individual's weight. The annual cost for an infant/juvenile being approximately $100,000. [37] Approximate cost for adults is around $300,000 annually given their increase in size and switch to a slightly different adult version of the drug.[38] These drugs have had fairly consistent prices since their inception, because of this a fairly low standard deviation relative to the mean (10%) was used in the model [8] and is based on the drug's fluctuation in prices since approved. The lifesaving enzyme replacement therapy which makes up the primary component of the cost of Pompe Disease was recently approved by the FDA in 2006 and had clinical trials of the therapy in the years leading up to it.[38] Due to the therapy's recent approval, only now are some of the individuals who participated in early clinical trials beginning to live into their 20s.[39]

Results

Cystic Fibrosis (CF)

Figure 3
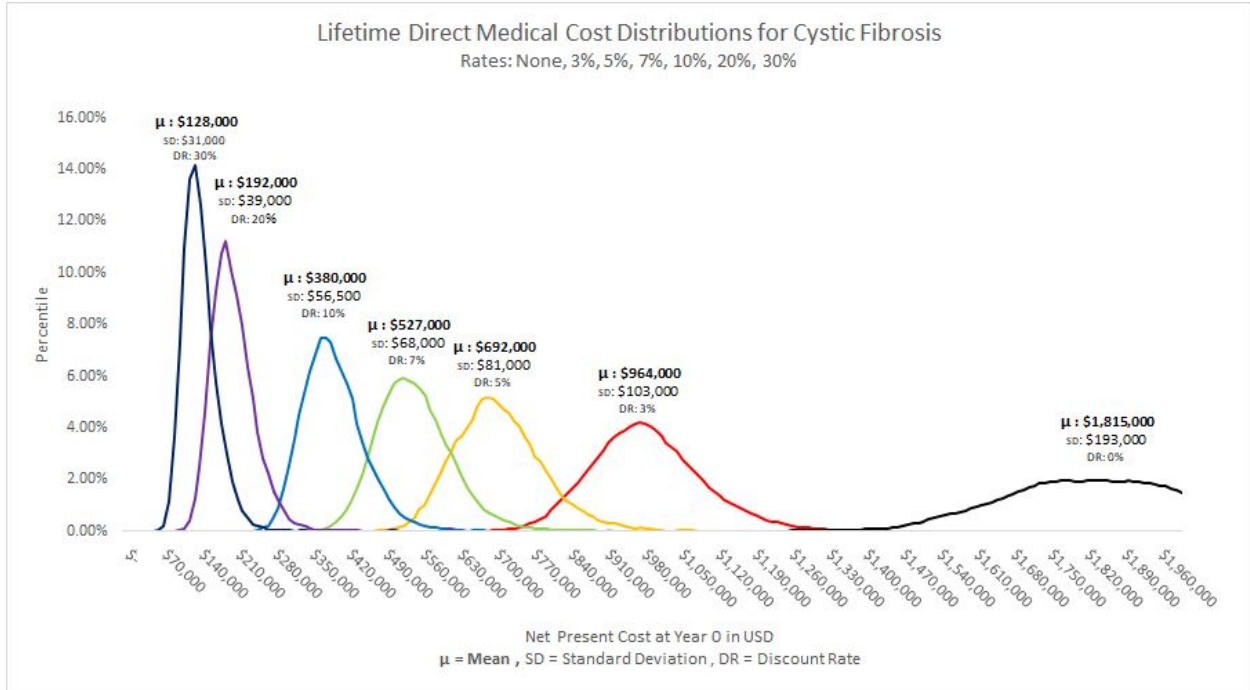
Lifetime Direct Medical Cost Distributions for Cystic Fibrosis
Rates: None, 3%, 5%, 7%, 10%, 20%, 30%

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 3 shows the estimated lifetime direct medical costs for Cystic Fibrosis as probabilistic distributions of lifetime direct medical cost at seven different discount rates. The distributions for Cystic Fibrosis are mostly normal bell shaped curves.
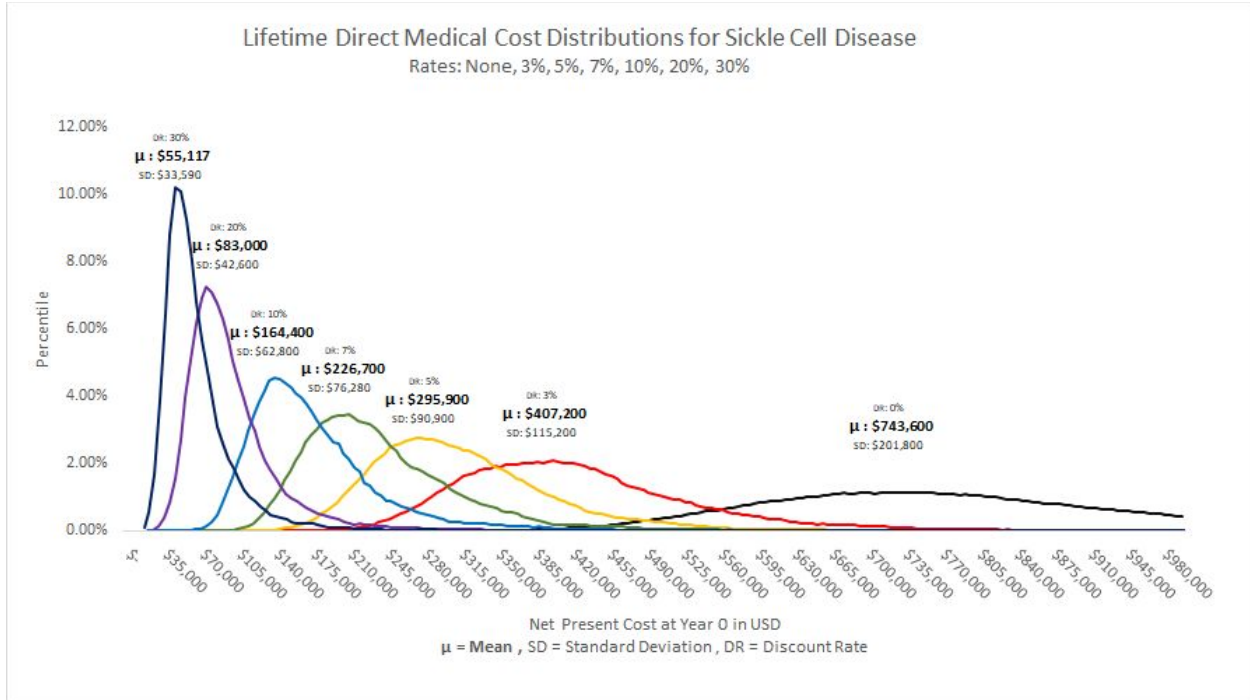
Sickle Cell Disease (SCD)

Figure 4

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 4 shows the estimated lifetime direct medical costs for Sickle Cell Disease as probabilistic distributions of lifetime direct medical cost at seven different discount rates. The distributions for SCD follow normal bell shaped curves.

Duchenne Muscular Dystrophy (DMD)

Figure 5

Lifetime Direct Medical Cost Distributions for Duchenne Muscular Dystrophy
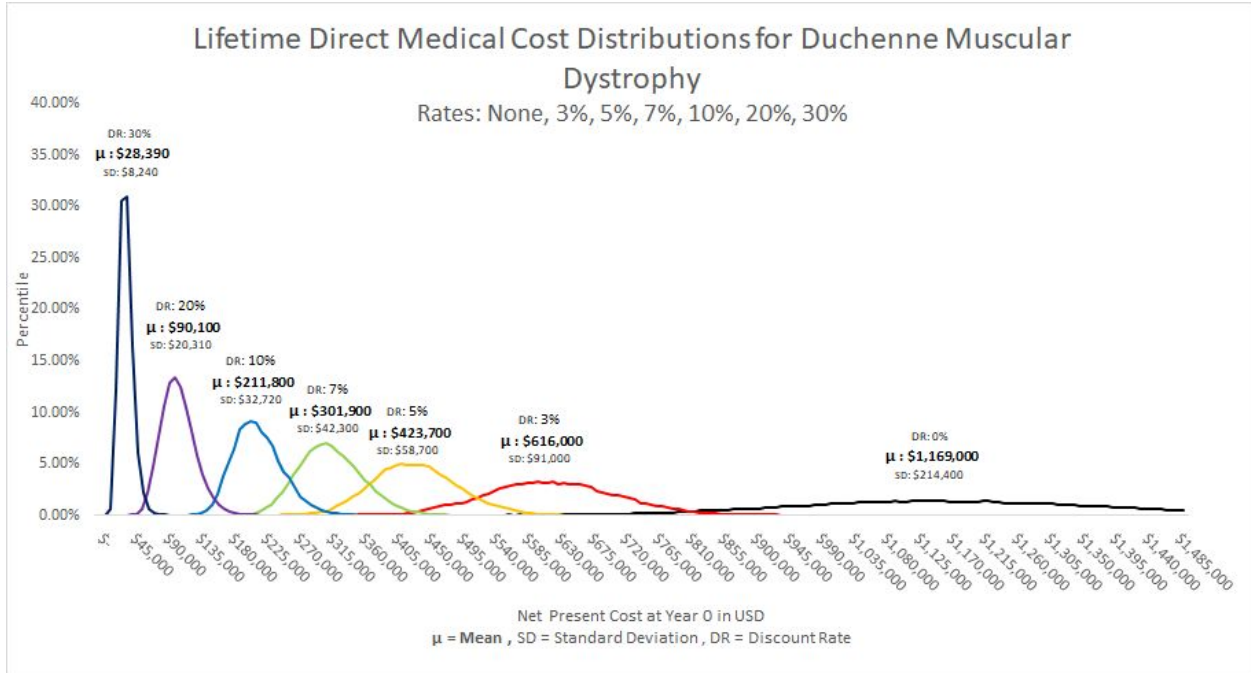Rates: None, 3%, 5%, 7%, 10%, 20%, 30%

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 5 shows the estimated lifetime direct medical costs for Duchenne Muscular Dystrophy as probabilistic distributions of lifetime direct medical cost at seven different discount rates. The distributions for DMD follow normal bell shaped curves.
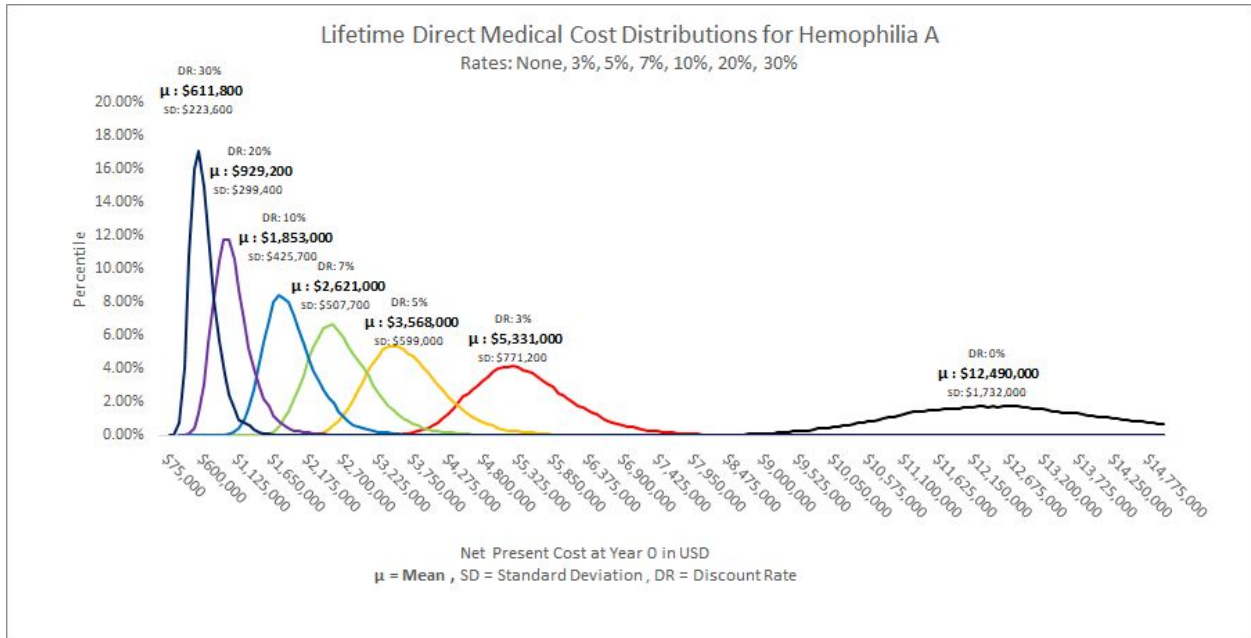
Hemophilia A (HA)

Figure 6

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 6 shows the estimated lifetime direct medical costs for Hemophilia A as probabilistic distributions of lifetime direct medical cost at seven different discount rates. The distributions for HA follow normal bell shaped curves.
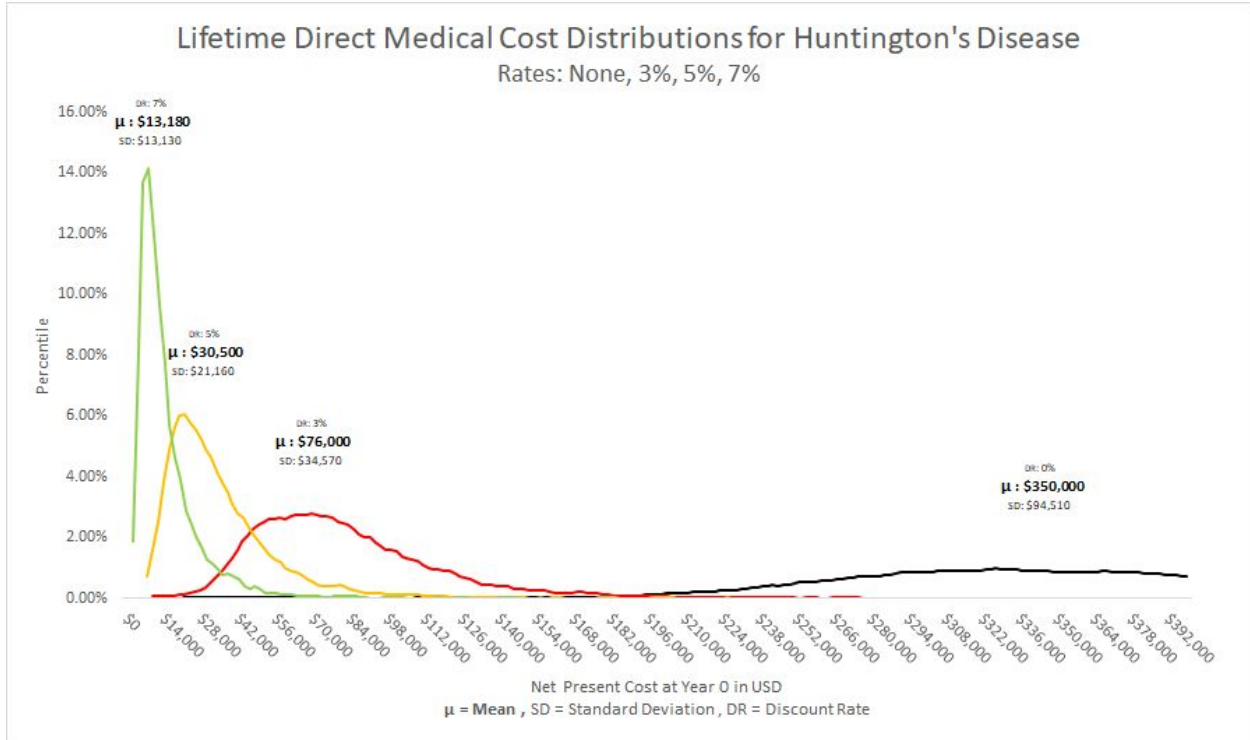
Huntington's Disease (HD)

Figure 7

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Huntington's disease has the lowest calculated NPV of any monogenic disease covered in this thesis. Due to the low relative NPV and the onset of the disease later in life, the higher discount rates produce distributions that are highly clustered close to $0 in Figure 6. To increase overall comprehension of Figure 6, all discount rate distributions of 10% and above have been removed from the chart. The mean and SD of those higher discount rates for Huntington's can be found in Table 4.

Polycystic Kidney Disease (PKD)

Figure 8

Lifetime Direct Medical Cost Distributions for Polycystic Kidney Disease
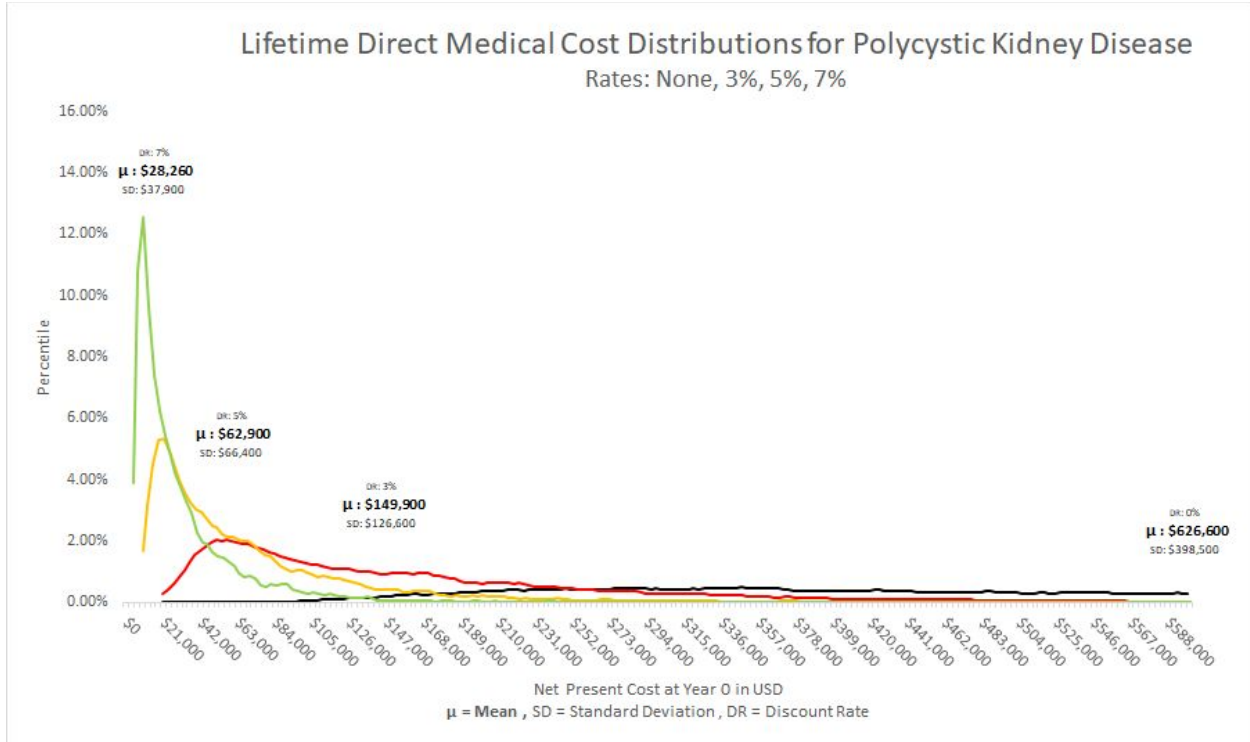Rates: None, 3%, 5%, 7%

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

There are relatively few people with severe forms of Polycystic Kidney Disease, however the direct medical costs increase dramatically with severity. This leads to distributions with left skewed peaks and long rightward tails as can be seen in Figure 8. To increase overall comprehension of Figure 8, all discount rate distributions of 10% and above have been removed from the chart. The mean and SD of those higher discount rates for PKD can be found in the Ranking Direct Social Cost table below.
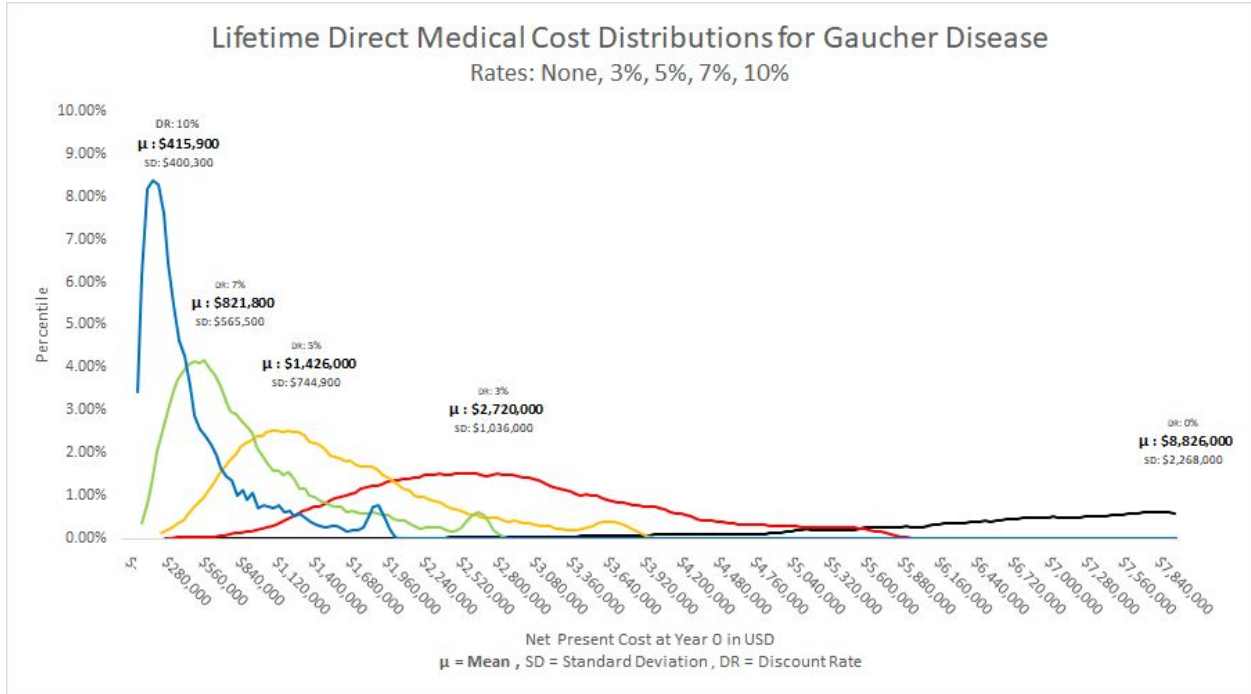
Gaucher Disease (GD)

Figure 9

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Small spikes in the tails of the distributions for Gaucher Disease in Figure 9. These small spikes most likely represent cases which are diagnosed and begin treatment within the first year of life. This causes a high cost in the NPV calculation because costs in year zero are not subject to discounting in the direct medical cost distribution model.

Hereditary Angioedema Type 1 (HAE)
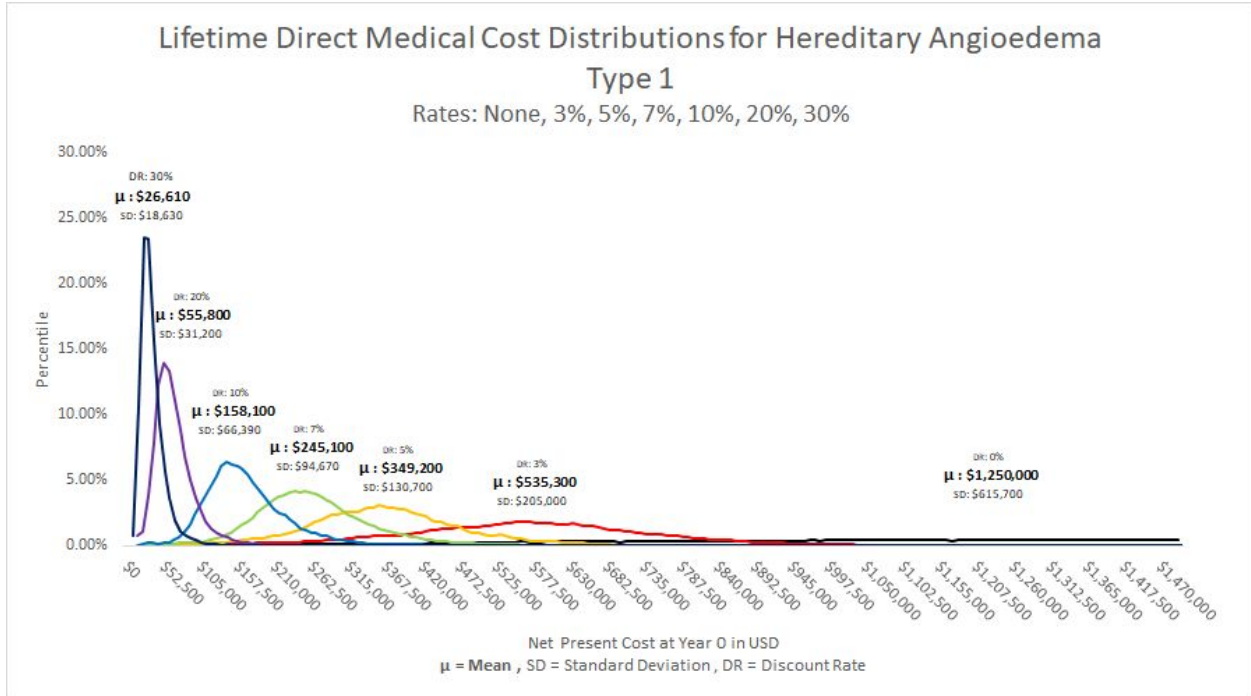
Figure 10

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 10 shows the estimated lifetime direct medical costs for Hereditary Angioedema Type 1 as probabilistic distributions of lifetime direct medical cost at seven different discount rates. The distributions for HAE follow normal bell shaped curves.

Pompe Disease (PD)

Figure 11

Lifetime Direct Medical Cost Distributions for Pompe Disease
Rates: None, 3%, 5%, 7%, 10%, 20%, 30%

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

Figure 11 shows shows the estimated lifetime direct medical costs for Pompe Disease at seven different discount rates..There is some irregularity in the distributions which might be explained by a diagnosis of the disease close to birth and high direct medical costs thereafter.

Detailed Distributions of all Included Diseases:

Figure 12

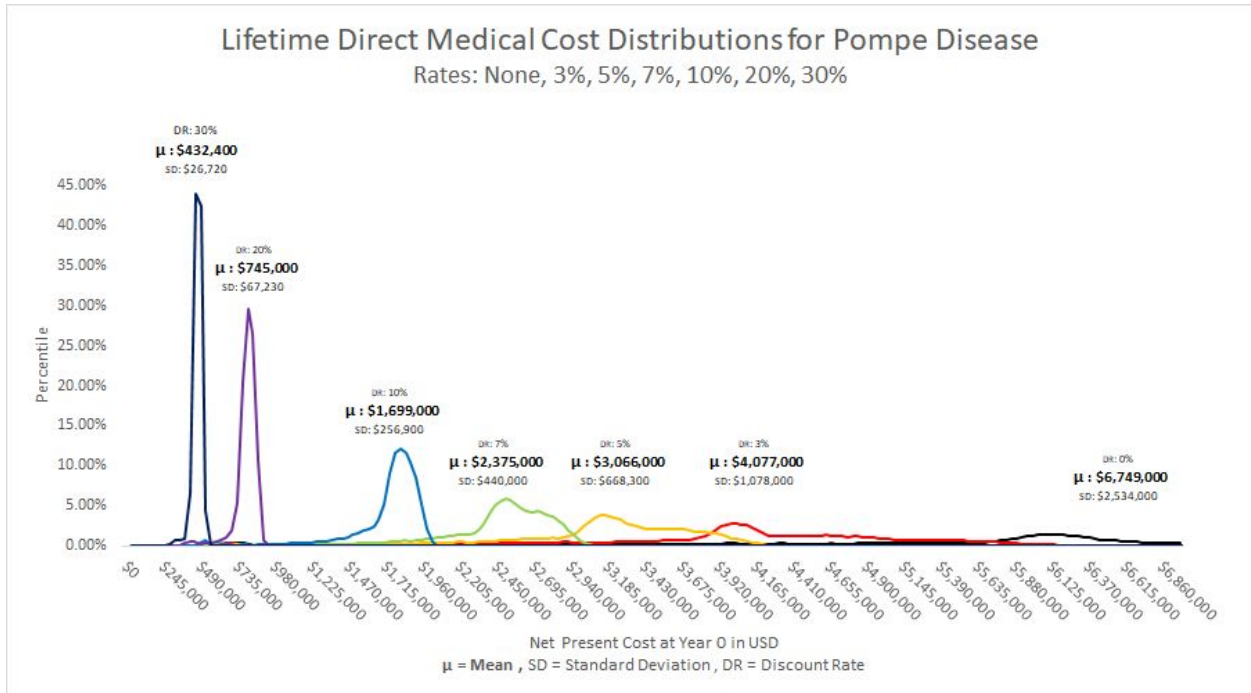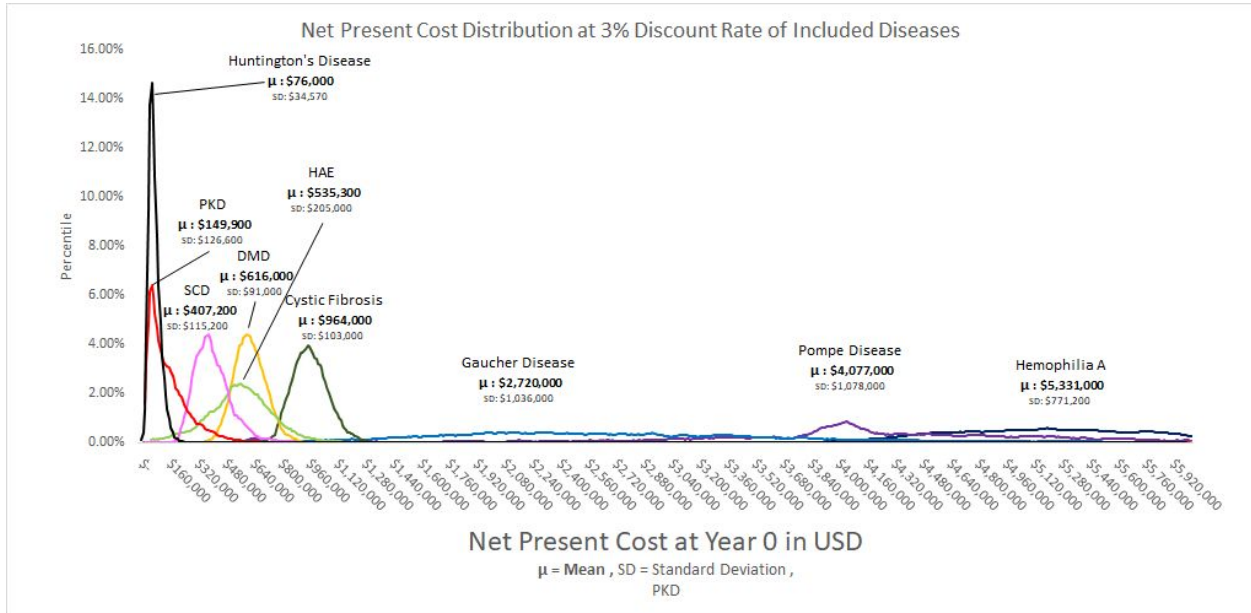Net Present Cost Distribution at 3% Discount Rate of Included Diseases

This figure of lifetime direct medical costs shows the probabilistic distributions of lifetime direct medical costs at different discount rates. The higher a distribution for one of these discount rates, the more predictable the mean lifetime costs are according to this model. The further to the right a disease's distribution is, the higher the average lifetime cost. Mean, standard deviation (SD), and discount rate (DR) are all labeled for each distribution.

It can be seen in Figure 12 that the nine chosen diseases represent a wide range of lifetime cost distributions. The higher a spike is for one of these diseases the more predictable the lifetime costs are according to this model. The further to the right a disease's distribution is the higher the average lifetime cost. While having all the different cost distributions placed on a single graph may be somewhat disorienting, it is important to visualize the stark differences between them. Some diseases, like PKD and Huntington's Disease, occur later in life and have lower and more predictable costs which lead to tighter distributions and a lower average net present value. Other diseases, like Pompe Disease and Gaucher Disease, have very unpredictable associated lifespans along with higher costs incurred earlier in life which lead to very spread out distributions with very high net present costs. Hemophilia A, which can be seen at the far right of

Figure 12, has both the highest costs and one of the largest associated variability. This is most likely because Hemophilia A can range greatly in severity between individuals. Individuals with Hemophilia A also tend to live life spans of about average length and have high annual costs throughout their lives. Another interesting note is that the Hemophilia model used Medicare and Medicaid data as its inputs. These sources are known to produce more conservative cost estimates. Despite this, Hemophilia still has the highest lifetime cost of any disease in this thesis.

All inputs into this net present value model were chosen in order to generate a conservative cost estimate per disease which would in turn give a conservative maximum direct social benefit per removal of disease associated medical costs. Direct medical cost estimates from Medicare and Medicaid were used whenever available, the usefulness of this is explained in the Data section of this thesis. The cost analysis also begins at year zero of an individual's life. This is for two reasons; the first is to provide a cost estimate over an entire lifetime of an individual, the second reason is to provide a conservative net present value analysis. The costs of each disease in this thesis continue all the way until the end of life, therefore, performing the net present value analysis at year zero results in the lowest and most conservative total cost estimate.

Ranked Direct Social Cost Table

Table 4:

Disease Names	Ranked Lifetime Direct Social Cost (NPV of direct medical costs) per Disease by Discount Rate						
	Discount Rates						
	0%	3%	5%	7%	10%	20%	30%
Hemophilia A	$12,490,000 ($1,732,000)	$5,331,000 ($771,200)	$3,568,000 ($599,000)	$2,621,000 ($507,700)	$1,853,000 ($425,700)	$929,200 ($299,400)	$611,800 ($223,600)
Pompe Disease	$6,749,000 ($2,534,000)	$4,077,000 ($1,078,000)	$3,066,000 ($668,300)	$2,375,000 ($440,300)	$1,699,000 ($256,900)	$745,000 ($67,230)	$432,400 ($26,720)
Gaucher Disease	$8,826,000 ($2,268,000)	$2,720,000 ($1,036,000)	$1,426,000 ($744,900)	$821,800 ($565,500)	$415,900 ($400,300)	$95,960 ($183,800)	$42,120 ($114,700)
Cystic Fibrosis	$1,813,000 ($192,500)	$964,000 ($103,000)	$692,200 ($80,870)	$527,000 ($68,450)	$380,600 ($57,220)	$192,600 ($39,880)	$128,500 ($31,890)
Duchenne Muscular Dystrophy	$1,169,000 ($214,400)	$616,000 ($91,000)	$423,700 ($58,700)	$301,900 ($42,300)	$211,800 ($32,720)	$90,100 ($20,310)	$28,390 ($8,240)
Hereditary Angioedema	$1,250,000 ($615,700)	$535,300 ($205,000)	$349,200 ($130,700)	$245,100 ($94,670)	$158,100 ($66,390)	$55,800 ($31,200)	$26,610 ($18,630)
Sickle Cell Disease	$743,600 ($201,800)	$407,200 ($115,200)	$295,900 ($90,900)	$226,700 ($76,280)	$164,400 ($62,800)	$83,000 ($42,600)	$55,117 ($33,590)
Polycystic Kidney Disease	$626,600 ($398,500)	$149,900 ($126,600)	$62,900 ($66,400)	$28,260 ($37,900)	$9,670 ($18,880)	$743 ($4,350)	$173 ($1,940)
Huntington's	$350,000 ($94,510)	$76,000 ($34,570)	$30,500 ($21,160)	$13,180 ($13,130)	$4,200 ($6,850)	$282 ($1,560)	$58 ($690)

All numbers shown as : **Mean (SD)**

The numbers in this table represent a conservative estimate for the maximum direct social benefit for a theoretical gene therapy which would remove the symptoms of, and therefore the direct medical costs of, a given genetic disease over a lifetime. These estimates were generated using the methods described in this thesis. The diseases in this table are positioned based on their value at the 5% discount rate.

The numbers in Table 4 represent a conservative estimate for the maximum direct social benefit for a theoretical gene therapy which would remove the symptoms of, and therefore the direct medical costs of, a given genetic disease over a lifetime. The diseases are arranged in the table according to the value of each at the 5% discount rate with the highest value at the top of Table 4. An economically rational entity operating from the social perspective should be

willing to pay no more than the costs shown above to offset a lifetime's worth of direct medical costs associated with a given genetic disease.

"White Pill" - Gene Therapy Analysis

The following analysis takes the results of this thesis a step further and applies the costs to the US population in general. It happens very often in the healthcare system that individuals are faced with the decision to spend resources in order to avoid risk. This analysis attempts to establish a baseline willingness to pay for the removal of the cost risk associated with being born with, and incurring costs related to, a genetic disease. It has been demonstrated in this thesis that the costs of a lifetime with a common monogenic disease can be very high, however, the chance that an individual being born with one of these diseases given no known family history is very low. This analysis will hopefully add perspective to both the huge costs associated with common monogenic diseases and the low probability of being born with one of these diseases.

This analysis assumes the following theoretical situation adapted from Ronald Howard's famous Black Pill / White Pill thought experiment [40] : an individual acting for the maximization of social benefit is offered the chance to distribute a theoretical therapy to prenatal patients that will surely repair any genes associated with a given genetic disease and therefore remove all direct medical costs associated with a lifetime of that disease. If a given patient does not receive a pill then they are subject to the normal (very low) probabilities associated with living their entire life with a monogenic disease. Therefore, how much should that individual be willing to pay per pill?

Table 5:

| Disease Names | "White Pill" Table | | | | | | |
| | Discount Rates | | | | | | |
	0%	3%	5%	7%	10%	20%	30%
Cystic Fibrosis	$725.00	$385.00	$276.00	$210.00	$152.00	$77.00	$51.00
Sickle Cell Disease	$232.00	$127.00	$92.00	$70.00	$51.40	$26.00	$17.00
Hemophilia A	$187.00	$79.90	$53.50	$39.00	$27.80	$14.00	$9.20
Gaucher Disease	$220.00	$68.00	$35.00	$20.50	$10.40	$2.40	$1.05
Pompe Disease	$67.50	$40.00	$30.00	$23.00	$17.00	$7.40	$4.30
Duchenne Muscular Dystrophy	$11.60	$6.20	$4.20	$3.00	$2.12	$0.90	$0.28
Polycystic Kidney Disease	$12.00	$3.00	$1.30	$0.58	$0.20	$0.02	$0
Hereditary Angioedema	$4.25	$1.80	$1.20	$0.83	$0.54	$0.19	$0.09
Huntington's	$0.02	$0.01	$0	$0	$0	$0	$0
Total	$1,461	$712	$495	$369	$261	$127	$83

The figures in this table were generated by multiplying the chance of an individual within the US population being born with a given genetic disease and having no family history of the given genetic disease, by an estimated US population of 330 million people, by the average direct medical costs per disease per discount rate which can be found in Table 4.
(Probability of birth with genetic disease)*(Average cost per disease)*(US population) = (Risk avoidance payment)
The diseases in this table are positioned based on their value at the 5% discount rate.

Table 5 shows an evaluation of the willingness to pay from the social perspective to avoid the risk of a lifetime of costs associated with a genetic disease as outlined by the thought experiment above. The figures in Table 5 were generated by multiplying the chance of an individual within the US population being born with a given genetic disease and having no family history of the given genetic disease, by an estimated US population of 330 million people, by the average direct medical costs per disease per discount rate which can be found in table 4.

$$(Probability\ of\ birth\ with\ genetic\ disease) \times (Average\ cost\ per\ disease) \times (US\ population) = (Risk\ avoidance\ payment)$$

To give an example using this data, if the individual in the thought experiment above were operating with a discount rate of 5% then they should be willing to pay no more than about $276 for a therapy to remove Cystic Fibrosis. Alternatively if this individual were acting to remove Huntington's Disease then the therapy should be worth no more than a few cents regardless of discount rate. This Huntington's example produces such low values because

being born with the disease without family history is so improbable and the costs associated

with the disease all occur in late middle age. Cystic Fibrosis, alternatively, is far more common

without family history and is generally more expensive over a lifetime.

"Magic Wand" Analysis

Table 6:

"Magic Wand" Table:
Speculative direct medical cost savings of removal within US populaiton (x Million $)

Disease Names	0%	3%	5%	7%	10%	20%	30%
			Discount Rates				
Hemophilia A	412,288	170,610	114,178	83,883	59,285	29,734	19,580
Cystic Fibrosis	232,116	123,350	88,598	67,462	48,724	24,655	16,446
Sickle Cell Disease	74,364	40,724	29,586	22,674	16,442	8,302	5,511
Duchenne Muscular Dystrophy	38,305	19,717	13,560	9,661	6,778	2,883	908
Gaucher Disease	70,607	21,761	11,406	6,574	3,327	767	337
Pompe Disease	21,595	13,045	9,811	7,600	5,438	2,383	1,383
Polycystic Kidney Disease	81,839	19,588	8,217	3,691	1,263	97	22.5
Hereditary Angioedema	6,797	2,912	1,900	1,333	860	303	144
Huntington's Disease	7,888	1,714	686	297	96	6.3	1.3
Total	945,804	413,426	277,947	203,179	142,218	69,134	44,336

The figures in this table were generated by multiplying the prevalence in the US of each disease (form Table 3), by an assumed US population of 330 million, by the net present value of the lifetime direct medical costs per disease (from Table 4).
The diseases in this table are positioned based on their value at the 5% discount rate.

Table 6 represents a speculative analysis of what the cost savings might be from the

social perspective if each disease was completely removed from the US population using gene

therapy. The term "magic wand" is meant to hint at the improbability of this scenario. Table 6

was generated by multiplying the prevalence in the US of each disease, by the US population, by the net present value of the lifetime direct medical costs per disease as seen in Table 4. This analysis is by no means perfectly accurate but I believe that it strongly hints at the large scale of spending related to genetic disease in the US. Recognize that these figures are based only on direct medical costs and do not take into account indirect medical costs associated with each disease. Also, these figures do not account for the fact that the diseased populations within the US are comprised of different age groups and are all born at different times. Another factor not accounted for is that it would take some number of years to distribute gene therapies among the population and that gene therapy may not be effective on all individuals. Even though this piece of analysis has its flaws the implications are worth considering. Even the most heavily discounted total figures imply a social cost savings of at least 40 billion dollars. As a rough example, it is estimated by the Rare Disease Research Institute that CF costs about one billion dollars per year in hospital visits alone.[7] Multiplied by an average life expectancy of 48 years [17] and you get a very rough approximation of 48 billion dollars of cost for all the cystic fibrosis patients in the US over their lifetimes. Total annual medical costs for SCD are also estimated to cost 1.1 billion dollars per year.[43] Multiplying this by the average SCD life expectancy of 43 years [44] you get 47.3 billion dollars. To lend some perspective, the annual budget of NASA is 18.8 billion dollars.[45]

Discussion

This thesis shows the extremely high prices that individuals should be willing to pay from the social perspective for gene therapies which would remove all the direct medical costs associated with a lifetime of monogenic disease. The idea of paying tens of thousands of dollars for a single medical treatment may sound ridiculous at first, but when the alternative is paying totals of hundreds of thousands of dollars then the idea becomes a little more reasonable.

Treating the symptoms of genetic diseases in the traditional ways can incur tremendous costs over a lifetime. Removing the symptoms of these diseases from the lives of at risk individuals has much more value than simply relieving the direct medical costs as was analyzed in this thesis. It can be intuited that the treatment for the chronic conditions and symptoms associated with genetic diseases would incur high direct medical costs. Therefore, it should come as no surprise that an individual should be willing to pay an equally high price to remove those costs and symptoms from a lifetime.

It is conceivable that insurance institutions with more long term agendas, such as Medicare and Medicaid, would be well incentivized to pay for gene therapies which would remove the direct medical costs of a disease, e.g. by functionally curing the disease. It can be shown that other institutions and individuals would also be willing to pay for gene therapies with curative and cost removing effects. An individual would have to be operating with an absurdly high discount rate, over 30% in most cases, in order for the money they spent toward gene therapy to not be worth it. It is clear that almost all sufferers of genetic disease and their caretakers would be willing to pay for gene therapy with curative properties. Parents expecting children would also be well incentivized to pay for these types of therapies too, especially if there is associated family history of a given genetic disease.

It is possible that the introduction of gene therapies which have costs that are within the direct social cost estimates outlined by this thesis would face considerable pushback from pharmaceutical and biotech companies, particularly those companies which produce enzyme replacement therapies and drugs used to treat some of the diseases brought up in this paper. In the case of enzyme replacement therapies for Pompe and Gaucher Disease, the average direct social cost estimate represents about 10 years worth of treatment using currently manufactured enzyme replacement therapy drugs.[51] The possible loss to the drug companies represents a lifetime's worth of payments from their patients. These pharmaceutical and biotech companies stand to lose millions of dollars in potential revenue per patient if gene therapies are to be implemented within their patient populations. Another threat to these companies is that their patient populations in the US are very small, only a few thousand in some cases (NGF 2018). This means that gene therapies have the potential to wipe out their patient populations entirely if made affordable and accessible enough.

A lifetime with one of the monogenic diseases evaluated in this thesis costs a considerable amount of money. Many of these diseases incur lifetime costs that exceed the average US lifetime gained wealth of approximately 1 million dollars.[52] It is more than likely that individuals with these diseases will either need to have very good insurance or at least need to borrow money in order to pay for their treatments.[11] The therapeutic removal of these diseases could result in a great deal of social benefit.

Given that a lifetime with one of these diseases can cost so much, most individuals faced with the choice of either paying for corrective gene therapy or facing the direct medical costs associated with the disease treatment would most likely be willing to choose the gene therapy. It's almost impossible to say what gene therapies in the future will cost, however given the high relative cost of a lifetime with a genetic disease, there is a large opportunity for the

companies providing these gene therapies to take advantage of vulnerable individuals by charging unnecessarily high prices for life changing gene therapies. In the scenario that gene therapies become relatively cheap to produce, it would be extremely unethical to upcharge vulnerable individuals and create a situation where even a single individual was denied life changing gene therapy due to inflated profit margins.

One policy implication that may result from prohibitively expensive gene therapy regards health insurance companies. It is unclear how well incentivized they will be to cover gene therapies if they cost several hundreds of thousands of dollars. Health insurance companies would want to cover the cost of gene therapy so that they might avoid the future costs to treat the symptoms of the genetic disease. However, if the upfront cost of gene therapy is prohibitively expensive even for a health insurance company then that company might have a valid reason to be concerned that the individual receiving the gene therapy would leave the payer pool and take all the cost benefits of their gene therapy to another insurer. It may be worth considering having individuals sign contracts with their health insurance companies so that they might stay in the payer pool long enough to make the health insurance company's investment worthwhile.

To add analysis on something we stand to lose if the world moves forward with human gene therapies: Sickle Cell Disease represents an interesting case for two reasons first that it is unevenly distributed within the American population. Sickle cell affects approximately 1 in 3,000 Americans and about 1 in 700 African Americans according to the CDC's webpage on Sickle Cell Disease.[19] Second is that it is autosomal recessive and requires an individual to have two copies of the defective gene in order to cause any problems. If an individual only has one copy of the gene and is a carrier, however, they will have high resistance to a deadly form of malaria known as *Plasmodium Falciparum* [53]. While purely speculative, genetic repair of the Sickle Cell

gene could remove some potential benefits of Malaria resistance in current and future

generations. While the probability of contracting Malaria in the United States is functionally zero

and several effective antimalarial drugs are available to individuals wishing to travel to areas where

contracting the disease may be a problem. Curing Sickle Cell Disease could mean the removal of

Malaria resistance in many individuals. This would be considered a loss, even if a minor one.

Discussion up to this point has been concerned with individuals who have genetic

diseases, and with what the social benefit might be if their diseases were cured with gene

therapy. What is more difficult to consider is what these gene therapies might cost. The social

benefit associated with the removal of some of the more expensive monogenic diseases

covered in this thesis from a member of the general US population using a reasonable personal

discount rate of 3% or 5% is still several hundred dollars and can be seen in the "White Pill"

table. Current CRISPR gene editing kits cost about $1,000 [3]. The Yale Genome Editing Center

already does custom genome editing work with mouse embryos. They currently charge around

$20,000 to produce a viable mouse embryo with a "knock in" gene of your choice.[49] Pricing for

enzyme replacement therapies (ERTs) could be another benchmark for what gene therapies

might cost in the future. ERTs are produced using some of the same methods that a future gene

therapy might be and they are administered in a similar fashion. ERTs are produced in large

bioreactors and require a large amount of research to determine how the ERT might effectively

treat (but not cure) a genetic disease. VPRIV is an ERT used to treat Gaucher Disease and is

one of the more common ERTs, so it will be used as an example. VPRIV costs about $1,400 for

a vial with 400 units and requires 38 units per kilogram of bodyweight for a single course of

treatment.[48] To treat a person with a bodyweight of 70kg it costs about $9,300. Currently prices

for new gene therapies are in the hundreds of thousands of dollars. [41][42][46] It is hard to estimate

where the prices for these new technologies will be in a few years, but it is worth considering.

Given adequate market pressures, a gene therapy could exist within the next decade or so that could be within the direct social benefit thresholds for many of the diseases outlined above. However, seeing that most diseases at most discount rates would need to be relatively cheap for an individual to be willing to pay for them, it can be said that this theoretical therapy may not be worth the investment for the average American yet.

Conclusions

This thesis demonstrates the high direct social costs for treatments which would remove a lifetime's worth of costs associated with monogenic disease in individuals with know risk or with family history. It is shown that the NPV of direct medical costs associated with several common monogenic diseases can be very high. In the Direct Social Cost table it can be seen that Huntington's Disease represents the monogenic disease with the lowest average NPV of lifetime direct medical costs at approximately $30,500 given a 5% discount rate as can be seen in table 4. The monogenic disease with the highest average NPV in this thesis is Hemophilia A with an average approximate NPV of $3,560,000 at the 5% discount rate. An approximate estimate of willingness to pay for gene therapy within the general US population is also calculated in this thesis. For example, based on a 5% discount rate the willingness to pay from the social perspective for an individual in the US population for the removal of the suite of monogenic diseases evaluated in this thesis would be approximately $490 per individual treated given no family history of the disease as seen in Table 5. The disease in this thesis with the highest estimated individual willingness to pay within the general US population using a 5% discount rate is Cystic Fibrosis at approximately $275 per individual treated given no family history of the disease. The disease with the lowest estimated willingness to pay within the US population is Huntington's disease with an approximate willingness to pay of less than $0.01 per individual treated given no previous family history of the disease. Lastly, an evaluation of the direct social cost savings in the US for the removal of the suite of monogenic diseases in this thesis also shows that if all these diseases could "magically" be removed from the population then the approximate overall savings would be 277 billion dollars given a discount rate of 5% as seen in the Magic Wand Table.

Ultimately this thesis comes to four main conclusions. First, that there are extremely high lifetime direct medical costs associated with one of the monogenic diseases evaluated in this thesis. The second main conclusion of this thesis is the existence of high theoretical direct social benefit associated with the removal of the lifetime direct medical costs of these diseases. Third, the relatively low willingness to pay for gene therapy for a member of the general US population. The final main conclusion is that there is a potential social cost savings of billions of dollars in the US if the diseases evaluated in this theses could be "magically" removed from the population.

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