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ESTIMATING THE FINANCIAL IMPACT OF GENE THERAPY IN THE U.S.

Chi Heem Wong
Dexin Li
Nina Wang
Jonathan Gruber
Rena M. Conti
Andrew W. Lo

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ABSTRACT

We empirically assess the potential financial impact of future gene therapies on the US economy. After identifying 109 late-stage gene therapy clinical trials currently underway, we estimate the number of new and existing patients with corresponding diseases to be treated by these gene therapies, developing and applying novel mathematical models to estimate the increase in quality-adjusted life years for each approved gene therapy. We then simulate the launch prices and the expected spending for these therapies over a 15-year time horizon. Under conservative assumptions, the results of our simulation suggest that an expected total of 1.09 million patients will be treated by gene therapy from January 2020 to December 2034. The expected peak annual spending on these therapies is $25.3 billion, and the expected total spending from January 2020 to December 2034 is $306 billion. Assuming a linear pace of future gene therapy development fitted to past experience, our spending estimate increases by only 15.7% under conservative assumptions. As a proxy for the impact of expected spending on different public and private payers, we decompose the estimated annual spending by treated age group. Since experience suggests that insurers with annual budget constraints may restrict access to therapies with expected benefit to the patient, we consider various methods of payment to ensure access to these therapies even among those insured by the most budget-constrained payers.

Chi Heem Wong
MIT Laboratory for Financial Engineering
100 Main Street, E62-611
Cambridge, MA 02142
chiheem@mit.edu

Dexin Li
MIT Laboratory for Financial Engineering
100 Main Street, E62-611
Cambridge, MA 02142
dexinli@mit.edu

Nina Wang
MIT Laboratory for Financial Engineering
100 Main Street, E62-611
Cambridge, MA 02142
ninawang@mit.edu

Jonathan Gruber
Department of Economics, E52-434
MIT
77 Massachusetts Avenue
Cambridge, MA 02139
and NBER
gruberj@mit.edu

Rena M. Conti
Boston University
Questrom School of Business
Department of Markets, Public Policy and Law
595 Commonwealth Avenue
Boston, MA 02215
rconti@bu.edu

Andrew W. Lo
MIT Sloan School of Management
100 Main Street, E62-618
Cambridge, MA 02142
and NBER
alo-admin@mit.edu

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1 Introduction

Gene therapy is a new class of medical treatment that alters part of a patient's genome through the replacement, deletion, or insertion of genetic material to treat a disease. While still in its infancy, gene therapy has demonstrated immense potential to treat and even cure previously intractable diseases. The introduction of voretigene neparvovec (marketed as Luxturna®) for inherited retinal disease and onasemnogene abeparvovec-xioi (marketed as Zolgensma®) for spinal muscular atrophy (SMA) in the U.S. have improved the lives of treated patients [110, 112]. Nevertheless, the price per treatment of $425,000 per eye for Luxturna, and $2.1 million per patient for Zolgensma, have raised concerns regarding affordability among budget-constrained payers and patients alike.

Stakeholders have expressed concern that gene therapy will be too expensive for individual patients to afford, especially if it continues to be priced at more than 30 times the median household income of $61,937 [97], (or equivalently, at several multiples of the average U.S. home mortgage of $354,400 [125]). In addition, insurance coverage for gene therapy varies by type. Insurance policies may impose restrictive access policies to limit the number of patients who might be treated with these new therapies despite their potential benefits [75, 155]. Widespread uninsurance [115] and underinsurance [77], where payers require substantial out-of-pocket costs in the form of deductibles and coinsurance payments, may place gene therapy out of reach for patients in the U.S. who might benefit from treatment. Many health plans, especially those facing fixed annual budgets, have already warned they may not be able or willing to absorb the additional spending should a greater number of people become eligible for an expensive gene therapy once it reaches the market [158]. It is unknown how much spending on novel gene therapies would be paid for by Medicare, the relatively generous taxpayer-supported health insurance for Americans over the age of 65, or by more cash-constrained types of insurance .

In this paper, we estimate the potential fiscal impact of gene therapy on the U.S. market. To do so, we create a new model to estimate the future number of gene therapy approvals, the size of their potential patient populations, and the prices of these future treatments. We begin by surveying the clinical trial databases for late-stage gene therapy trials, defined here as phase 2/3 or phase 3, and compile the prevalence and incidence of the diseases targeted in these trials from a meta-analysis of published sources. We develop a novel method to estimate the price of each gene therapy under consideration by calculating the expected quality-adjusted life years gained for each therapy in the relevant patient population. Combining these results and previously published probabilities of technical success by therapeutic area, we simulate the probability that a disease will have an approved gene therapy over the

next fifteen years, the expected number of treated patients, and the expected spending from January 2020 to December 2034. Throughout this paper, the expected number of treated patients refers to the pool of eligible patients that remains after accounting for market penetration and the treatment schedule.

Our results, under conservative assumptions, suggest that an estimated total of 1.09 million patients will be treated with gene therapy by the end of December 2034. The number of patients receiving gene therapies annually will peak at 94,696 patients in 2025 before declining to 65,612 at the end of our time period. The annual spending across all expected products and patients is expected to reach $25.3 billion in 2026. The cumulative spending for treating these patients in the 15-year period is estimated to be $306 billion, or $241 billion when discounted by 3% per annum to 2020 dollars. This cumulative spending does not account for future inflation.

This estimate is conservative along a number of dimensions. As mentioned, it does not account for inflation. It only applies to drugs already in the development pipeline at the time of writing. If we assume that new drug development in this space follows the roughly linear trend of the recent past, our estimated expected spending over the next fifteen years increases by 15.7% to $354B. Given development lags and uncertainties, new developments are unlikely to have a major impact on costs over our fifteen-year window, although the longer run effects could be much larger.

We additionally decompose the expected spending by patient age group as a proxy for insurance type. We find that the estimated annual spending for the age group ineligible for Medicare or Medicaid is predicted to reach $12.2 billion. For those therapies that are not covered by these programs, we consider several alternate ways of financing, including outcome-based payments and a specialized national or international reinsurance vehicle, to meet this demand.

2 Methods and Data

A critical element in our simulation analysis is the number of gene therapies that will receive regulatory approval over the next few years. A brief summary of the drug development process is provided in Section A1 in the Supplementary Information (S.I.). To estimate the financial impact of gene therapies on the U.S. healthcare system, we first identify all existing late-stage clinical trials of gene therapies, then simulate their successes or failures from phase 2/3 or 3 to approval, then estimate the spending on the successful ones by summing the product of their expected prices and number of patients, as outlined in Figure 1. By using simulation analysis rather than purely deterministic methods, we are able to capture

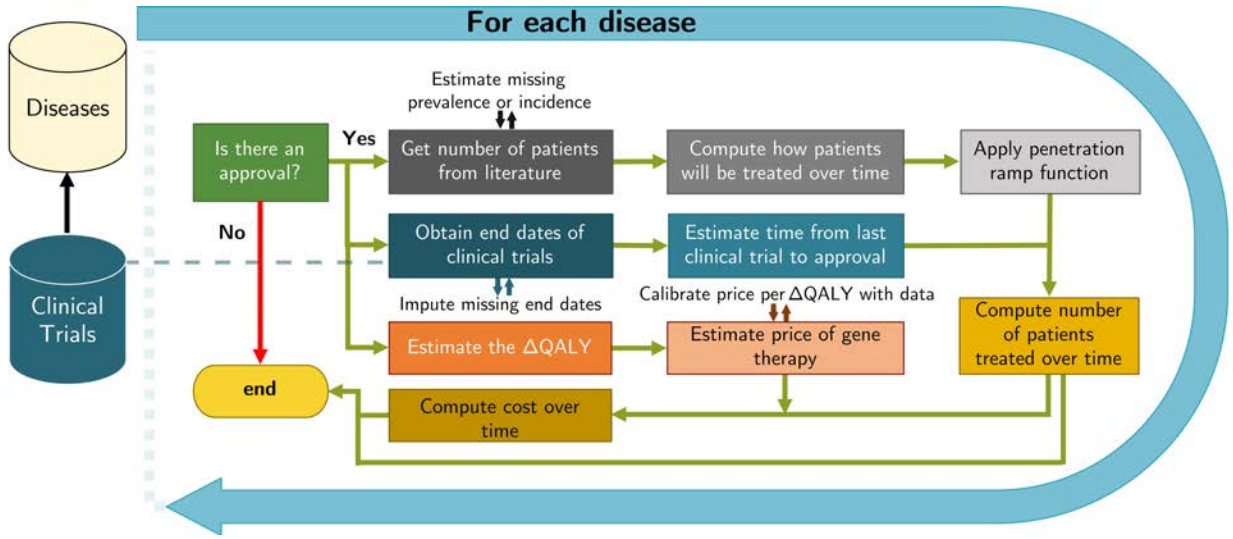


Figure 1: A flowchart showing the performance of the simulation. After extracting the information on each disease from the clinical trial databases, we simulate whether the disease will obtain an approval. If it fails to do so, the simulation will end for this disease in this iteration. Otherwise, we will estimate the expected number of patients to be treated, compute the corresponding cost of treatment, and store the results. At each step of the computation, we source data from literature and impute missing information.

the inherent uncertainty in costs, revenues, and other parameters of this new therapeutic class.

We organize the simulation into the following five distinct modules, and describe each of these in some detail: (1) identifying the number of gene therapies currently in clinical trials; (2) estimating the probabilities of success of these trials; (3) estimating the time to approval; (4) simulating the expected number of patients treated by these therapies if approved; and (5) estimating the expected market prices of the approved therapies. We describe the first four modules in Sections 2.1–2.4. Given the importance and potential controversies surrounding the pricing of gene therapies, we devote a standalone section to this issue in Section 3.

Throughout the article, we define a 'child' to be a patient below the age of 18 and an 'elderly' patient to be one who is older than 62 years old. The remainder of the patients are labeled as 'adults'. When breaking down the spending by funding source, we assume that all elderly people are covered by Medicare. We also assume that two in five children and one in seven adults in the U.S. are covered by Medicaid, as estimated by the Kaiser Family Foundation [118]. The remainder of the spending is expected to come from private sources, such as employer-provided or private insurance.

All the equations presented in the article are discretized from their continuous form in our calculations. When solving integrals using the trapezoidal rule to obtain the ΔQALY

(see., we use strip widths of 1 year for an age range from 0 to 110 years old, the resolution offered by the life tables. When simulating the number of patients and the cost over time, we use time intervals of 1 month. Our code is implemented on Python 3.6 backed by Numpy, and executed on a single 2.2GHz CPU core. Pseudo-code and further details of computation can be found in Section A2 in the Supplementary Materials.

We perform 1,000,000 iterations of the simulation to compute the mean number of patients and the total spending. At this number of iterations, one can expect the computed mean to be within 1.89% of the true mean 95% of the time (see Section A3 in the Supplementary Materials). We also report the 5th and 95th percentiles of the computed values as our upper and lower bounds respectively.

2.1 Clinical Trial Data

We use clinical trial metadata from the Citeline TrialTrove database and the U.S. National Library of Medicine's ClinicalTrials.gov database to determine the number of gene therapies currently under development and their potential number of patients.

We download data from the Citeline database, isolating trials tagged with 'gene therapy' under the 'therapeutic class' field. We supplement this information by searching for trials on the *clinicaltrials.gov* main page using the key words 'gene therapy', then reading the trial description to determine if the trial is in fact related to a gene therapy. All database queries were made before May 31, 2019. Clinical trials from both sources are merged before filtering for clinical trials that are in either phase 2/3 or phase 3 of the development process and are not known to be compassionate uses of the treatment.[1] The outcomes of compassionate use are rarely used as data points in the clinical development process. Even though adverse events from compassionate use are reported to the FDA, and in rare cases may be used to characterize the risk and benefits of a therapy, the FDA is cognizant that these uses often occur outside of clinical trial settings, and has almost never given an unfavorable decision to a product labeling because of an adverse outcome of compassionate use [86, 114]. We include clinical trials without U.S. trial site in our dataset because it is currently possible for the FDA, as empowered by Federal administrative law 21 CFR Part 312.120, to grant marketing approval using evidence from foreign clinical trials [65].

Our filtering criteria are intended to remove trial entries unrelated to the clinical development process, and to isolate gene therapies that are most likely to seek regulatory approval in the U.S. in the near future.

[1]Compassionate use, also known as 'expanded access', refers to the administration of investigational treatments outside of the clinical trial to treat patients with serious or immediately life-threatening diseases, or conditions when there are no comparable or satisfactory alternative treatment options.

We remove repeated entries, and identify the diseases and therapeutic areas targeted by each gene therapy. Each clinical trial entry in our dataset contains a brief title of the trial, its clinical phase, the disease being targeted, the start and end dates of the clinical trial, the therapy name, and the companies involved in the clinical trial.

This process yields 109 trials investigating 57 distinct diseases, listed in Table A1 in Supplementary Materials. We classify the diseases into three categories: cancer (oncology),[2] rare disease, and general disease. The distribution of disease and the clinical trials by category and therapeutic area are shown in Table 1 and Table 2. The majority of trials and diseases are in the area of oncology, followed by rare diseases. These two therapeutic areas are notoriously risky. Only 3.1% and 6.2% of the drug development programs in oncology and rare diseases go from phase 1 to approval, respectively, compared to the baseline of 13.8% across all drugs and indications [166].

Table 1: Count of number of clinical trials by category and therapeutic area.

Therapeutic Area	Cancer	General	Rare Disease	Subtotal
Autoimmune/Inflammation		3	2	5
Cardiovascular	-	15	1	16
CNS	-	3	7	10
Metabolic/Endocrinology	-	3	15	18
Oncology	52	-	1	53
Ophthalmology	-	-	7	7
Subtotal	52	24	33	109

Table 2: Count of number of diseases by category and therapeutic area.

Therapeutic Area	Cancer	General	Rare Disease	Subtotal
Autoimmune/Inflammation	-	2	1	3
Cardiovascular	-	6	1	7
CNS	-	1	4	5
Metabolic/Endocrinology	-	3	6	9
Oncology	28	-	1	29
Ophthalmology	-	-	4	4
Subtotal	28	12	17	57

[2]We classify Ewing's Sarcoma—a rare form of cancer—as a rare disease instead of cancer.

Table 3: The probability of success of drug development programs from phase 3 to approval (PoS_{3A}), categorized by therapeutic area. We assume that the probability of success for gene therapy follows a similar pattern.

Therapeutic Area	PoS_{3A} (%)
Autoimmune/Inflammation	48.5
Cardiovascular	50.1
Central Nervous System (CNS)	37.0
Metabolic/Endocrinology	45.7
Oncology	28.5
Ophthalmology	45.9

2.2 Probability of Success Estimates

We define a gene therapy development program as the set of clinical trials conducted by a sponsor testing a therapeutic for a disease. We consider whether a gene therapy will be developed for a disease by simulating correlated 'coin flips' for each gene therapy program, and observing if there is at least one approval.

Our computational method assumes that clinical trials are always perfectly correlated within the same development program.

It can be argued that different gene therapy treatments for a disease are highly correlated, since they operate on similar platforms (e.g. CAR-T or in-vivo gene delivery using adeno-associated virus vectors), even though different gene sequences may be targeted. To reflect this, we consider a correlation of 90% between development programs in our simulations. Our sensitivity analysis, however, demonstrates that these computations are insensitive to this parameter (see Section 4.3).

The phase 3 to approval probability of success (PoS_{3A}) for each disease is informed by prior studies on the probabilities of success of drug development programs by therapeutic area from the MIT Laboratory of Financial Engineering's Project ALPHA website [132]. These estimates for the probabilities of success are derived from over 55,000 drug development programs between January 2000 and January 2020, and computed using the path-by-path methods as introduced in Wong et al. [166]. The PoS_{3A} values used in our simulations are given in Table 3 and the mapping of diseases to therapeutic areas is shown in Table A2.

2.3 Time to Approval

We also require an estimate of the time to approval for gene therapy treatments in order to assess the patient impact and cost over time. Typically, companies submit their Biologics

License Application (BLA) to the FDA some time after the end of the clinical trial period. We assume that the time between the end of the last clinical trial for the disease and the submission of the BLA is a variable drawn from a triangular distribution between 0 and 365 days, with a median of 182.5 days. This is informed by the practical knowledge that it takes an average of 6 months to prepare the documents for the BLA submission [166].

In addition, there will be a lag time between the submission of the BLA and the decision of the FDA. The FDA has 60 days to decide if it will follow up on a BLA filing [89], and it can take another 10 months to deliver its decision [88]. This implies the maximum possible time between BLA submission and FDA approval will be 12 months. We thus assume that the time between the BLA submission and the FDA decision is drawn from a triangular distribution between 0 and 365 days, with a median of 182.5 days. Our assumptions are also valid for therapies that use the priority review pathways.

We also assume that the BLA will be filed only after the last clinical trial for a disease has ended. Trials with missing declared end dates will have their end dates imputed by adding random durations to the trial start date, drawn from a gamma distribution fitted to clinical trials with complete date information in our data (see Figure 2).

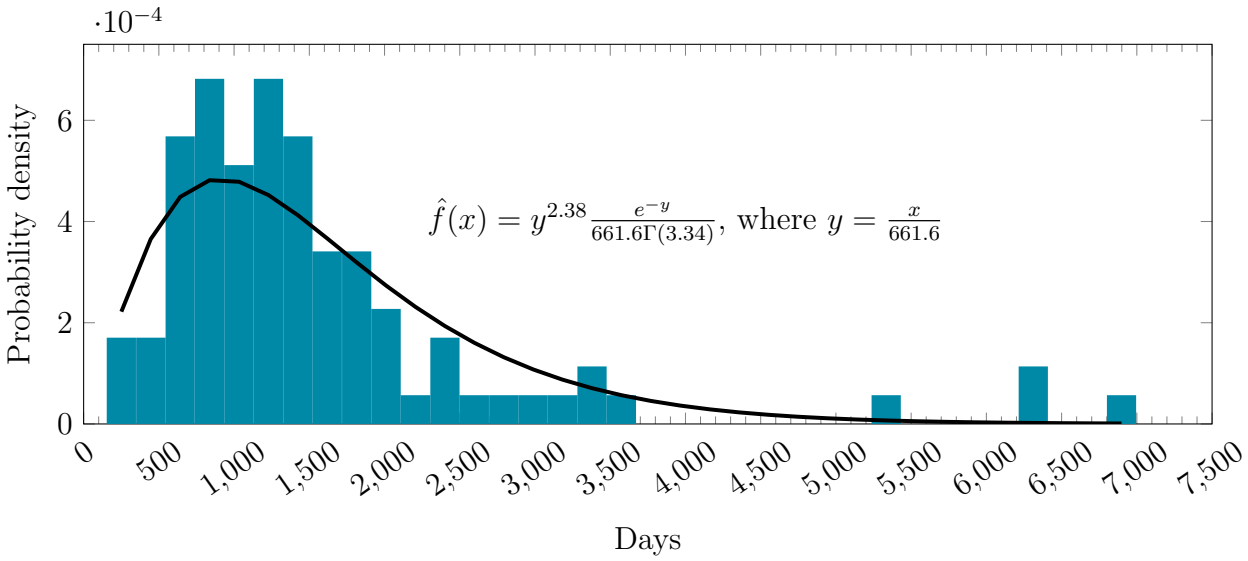


Figure 2: The empirical distribution of duration against our fitted gamma distribution.

Diseases with a prior approved therapy will automatically be considered to be approved as of January 1st, 2020. Diseases whose last clinical trial ended before January 2017 will be treated as though they have failed.

2.4 Number of Patients

The second module simulates the number of new and existing patients that will be treated over time, conditioned on the disease receiving an approved gene therapy.

We consider only the superset of the patient segments listed in the clinical trials for each disease. For example, if there are two clinical trials, one targeting 'patients above the age of 40' and the other targeting 'patients above the age of 18', we only consider the latter when estimating the patient population for the disease. If insufficient information about the sub-population is given, we assume that all the patients with that disease are eligible. The proportion of patients who are eligible for treatment and are willing to do so will be taken into account later in the analysis, as we explain in Section 2.4.

Incidence and Prevalence

For the number of currently affected patients and the number of new patients per year for each indication, we source medical journals and online data repositories, such as the Surveillance, Epidemiology, and End Results (SEER) website and *cancer.net*. If we are able to find an estimated patient population, we cite it directly. Otherwise, we multiply the prevalence and incidence rates by the population of the U.S., which we take to be 327.7 million [160]. When necessary, we also make the assumption that the female to male ratio is 1:1.

In cases in which we are able to find estimates for the disease incidence but not the prevalence, we combine the incidence of the disease (i.e., i new patients a year) and the disease survival rate (i.e., p% of the people with a disease will be alive after k years) to obtain the steady-state estimate of the prevalence (j) using Equation Equation 1. The incidence can also be estimate from the prevalence by rearranging Equation Equation 1 to yield Equation 2.

$$\text{Prevalence } (j) = \frac{ki}{1-p} \tag{1}$$

$$\text{Incidence } (i) = \frac{j(1-p)}{k} \tag{2}$$

The equations can be derived by assuming that the number of patients will be constant through the years at a level j. Since ki new patients are added over k years and $j(1-p)$ patients that will die over the same period, $ki = j(1-p)$ for the number of patients to be constant over time. Rearranging this equation will yield Equation 1 and Equation 2. The number of patients for each disease are presented in Table A3 in the appendix. We adjust

these estimates to avoid double-counting in cases of overlapping patient populations, e.g., the number of patients for 'Spinal Muscular Atrophy' is the difference between 'Spinal Muscular Atrophy' and 'Spinal Muscular Atrophy I' (a sub-category of the former).

Treatment of Patients over Time

In our simulation, we assume that newly diagnosed patients are treated immediately upon diagnosis. We further assume that the proportion of existing patients who seek treatment do so in such a way that the existing stock of patient declines exponentially, with a half-life of λ. Mathematically, the proportion of existing patients that seek treatment between time t and $t+\delta$ after approval is given by $E(t,\delta,\lambda)$, where:

$$E(t,\delta,\lambda) = e^{-\frac{t\ln 2}{\lambda}} - e^{-\frac{(t+\delta)\ln 2}{\lambda}}, t \geq 0 \tag{3}$$

In the face of limited information, we assume that 25% of the existing stock of patients will seek treatment in the first year of our simulation. This requires that the half-life be set to 28.91 months, which in turn implies that 95% of all patients who are diagnosed prior to the approval of the gene therapy want treatments within 10.5 years. We perform a sensitivity analysis to determine this assumption's impact on our results in Section 4.3.

Patient Penetration

It is unlikely that all the patients under consideration will receive gene therapy treatments. This may be due to ineligibility, lack of awareness of the treatment, among many other reasons. We term the percentage of the patients that receive gene therapy treatments the 'patient penetration rate', and model it using a ramp function, $\rho(t,\Theta_{max},T_{max})$:

$$\rho(t,\Theta_{max},T_{max}) = \begin{cases} \dfrac{t\cdot\Theta_{max}}{T_{max}}, 0 \leq t \leq T_{max} \\ \Theta_{max}, \text{ otherwise} \end{cases} \tag{4}$$

An illustration of the ramp function is given in Figure 3.

Θ_{max} and T_{max} are assumed to follow Gaussian distributions $N(\mu_\theta,\sigma_\theta^2)$ and $N(\mu_T,\sigma_T^2)$, respectively. The parameter settings are listed in Tables 4 and 5. When setting μ_θ and μ_T, we need to take into the account the nature of the diseases. At one extreme, we have rare diseases, which are often life-threatening, and affect a relatively small number of people. Faced with these prospects of survival, more patients are willing to enroll in new treatments quickly after they are approved. In addition, since the number of patients is relatively small,

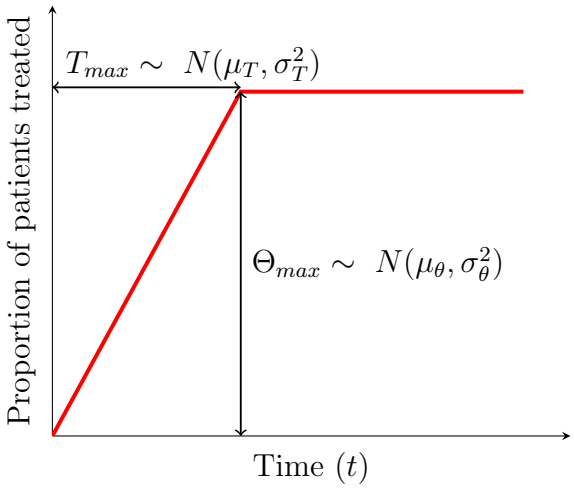


Figure 3: An illustration of the ramp function used to model the patient penetration rate over time.

manufacturers are more able to cope with a larger proportion of patients. Given these, we assign a high value of 40% for μ_θ, and a low value of 6 months for μ_T.

On the other hand, patients of general diseases often have access to an acceptable standard of care and may be less inclined to use new treatments due to fear of the unfamiliar. We thus assume that the maximum penetration rate will be 1%, and the ramp-up period, 5 years.

As an intermediate case, cancers have characteristics that fall between these two extremes, but in general, they are more similar to rare diseases. We therefore assign values of 10% and 12 months to the maximum penetration rate and ramp-up period, respectively. All variances are set to 10% of the means to model moderate uncertainty in our numbers. They do not affect our mean estimates of the number of impacted patients or spending on gene therapy.

Classification	μ_θ	σ_θ^2
General	0.01	0.002
Rare Diseases	0.4	0.08
Cancer	0.1	0.02

Table 4: Parameter settings for $\Theta_{max} \sim N(\mu_\theta, \sigma_\theta^2)$.

The net number of patients to be treated for the disease at time t after the approval of a gene therapy is given by:

$$\texttt{Patients}_t = \rho(t, \theta_{max}, T_{max}) \cdot [\texttt{New patients}_t + E(t, \delta, \lambda) \cdot \texttt{Existing patients}_t] \quad (5)$$

We do not consider the effect of market competition among different therapies for the

Classification	μ_T	σ_T^2
General	60	6
Rare Diseases	6	0.6
Cancer	12	0.12

Table 5: Parameter settings for $T_{max} \sim N(\mu_T, \sigma_T^2)$. We consider the severity of the disease and the number of patients when making the assumptions.

same disease and patient groups on the number of treated patients. In our model, there is only one approval per disease, and a fraction of the eligible patients will receive that treatment.

3 Pricing

The cost to the healthcare system of providing the gene therapy for a disease for all patients being treated at time t after approval is given by $C(t)$, where

$$C(t) = \texttt{Patients}_t \times \texttt{Price of gene therapy} \tag{6}$$

The price of each treatment is crucial to computing the expected total spending, and a source of considerable controversy because of the high price of gene therapies relative to many conventional therapeutics. The Institute for Clinical and Economic Review (ICER)—an independent nonprofit organization that aims to evaluate the clinical and economic value of healthcare innovation—has advocated pricing drugs and gene therapies by the relative risk and benefit to the patient. This is typically done by comparing the quality-adjusted life years (QALY) with and without the treatment, then multiplying the change in QALY (ΔQALY) by a constant, typically set between \$50,000 and \$150,000 per ΔQALY [135].

$$\texttt{Price of gene therapy} = \frac{\texttt{Price}}{\Delta\text{QALY}} \times \Delta\text{QALY} \tag{7}$$

ICER has published reports containing its estimates of QALY gained by patients with vision loss associated with biallelic RPE65-mediated retinal disease following treatment with Luxturna® [110], and with SMA Type I following treatment with Zolgensma® [111]. These reports compute ΔQALY using the results of clinical trials to make informed estimates about the potential improvements in the quality of life and life expectancy of the patients.

While ICER's methods are considered by some stakeholders to be the gold standard for this type of calculation, replicating its methods for all the clinical trials under consideration is not feasible in this paper, given the fact pricing decisions are made when the trials conclude.

As an alternative, we develop a mathematical model to estimate the expected increase in QALY for each disease in our sample.

3.1 Estimating ΔQALY

We consider a representative patient who is expected to live to the age of x with a probability of $l(x)$. The function $l(x)$ is also known as the survival curve of the population. The patient enjoys a quality of life, $f(s,x)$, that is dependent on his age, x, and his state of health, s. The expected QALY of a typical person in the baseline state of s_0 (the 'healthy' state) can be computed by integrating $l(x)f(s_0,x)$ over x.

$$\text{Expected QALY (healthy)} = \int_0^\infty l(x)f(s_0,x)dx \tag{8}$$

Suppose that the patient is afflicted with a disease at time a, which changes his survival curve after time a from $l(x)$ to $\widetilde{l}(x)$. Likewise, his quality of life after diagnosis changes from $f(s_0,x)$ to $f(s_d,x)$. This patient will then have an expected QALY of:

$$\text{Expected QALY (unhealthy)} = \int_0^a l(x)f(s_0,x)dx + \int_a^\infty \widetilde{l}(x)f(s_d,x)dx \tag{9}$$

The change in the expected QALY due to the disease can then be expressed as:

$$\begin{aligned}
\Delta\text{QALY} &= \text{Expected QALY (unhealthy)} - \text{Expected QALY (healthy)} && (10)\\
&= \int_0^a l(x)f(s_0,x)dx + \int_a^\infty \widetilde{l}(x)f(s_d,x)dx - \int_0^\infty l(x)f(s_0,x)dx && (11)\\
&= \int_a^\infty \widetilde{l}(x)f(s_d,x) - l(x)f(s_0,x)dx && (12)\\
&\leq 0 && (13)
\end{aligned}$$

It is customary in the literature to incorporate time preferences into the model. This is done by multiplying the integrand by the discount factor, $r(x-a)$. There is a normalization term $l(a)$ to reflect conditional survival to age x.

$$\Delta\text{QALY} = \int_a^\infty \frac{r(x-a)}{l(a)}\left[\widetilde{l}(x)f(s_d,x) - l(x)f(s_0,x)\right]dx \tag{14}$$

If the distribution of age when the patient population contracts the disease is given by $A(a)$, then the expected decrease in QALY over the patient population is given by:

$$\text{E}(\Delta\text{QALY}) = \int_0^\infty A(a)\int_a^\infty \frac{r(x-a)}{l(a)}\left[\widetilde{l}(x)f(s_d,x) - l(x)f(s_0,x)\right]dxda \tag{15}$$

Equation 15 is a general formula that accounts for the expected value of the changes in QALY between two states of health using only three variables: the time of disease onset, and the utility of the two health states. By making the relevant substitutions, we can also apply this formula to compute the expected changes in QALY given a gene therapy (gt) and an alternative treatment (alt).

$$\mathrm{E}(\Delta\mathrm{QALY}) = \int_0^\infty A(a) \int_a^\infty \frac{r(x-a)}{l(a)} \left[\widetilde{l}_{gt}(x) f(s_{gt}, x) - \widetilde{l}_{alt}(x) f(s_{alt}, x)\right] dxda \tag{16}$$

While death and patient statistics can be collected to determine $l(x)$ and $A(a)$ empirically, determining $f(s, x)$ and $\widetilde{l}(x)$ is challenging. Therefore, we use simple functions to modify these variables. In particular, we assume that being afflicted with a severe disease will modify the survival curve by a multiplicative factor, $D(t)$. That is, the survival curve of a patient after he is diagnosed at age a is given by:

$$\widetilde{l}(x) = l(x) \cdot D(x-a) \tag{17}$$

This functional form assumes that the disease is age-agnostic, and affects the survival curve only through the time elapsed since the patient has been diagnosed. For example, if the disease does not affect mortality (e.g. blindness), then $D(x-a) = 1$ for all $x - a > 0$. On the other hand, if the condition causes death immediately, then $D(x-a) = 0$ for all $x - a > 0$.

For the utility function, $f(s, x)$, we assume that it can be decomposed into two multiplicative factors, one dependent only on age, $f_a(x)$, and the other dependent only on the state of health, $f_h(s)$:

$$f(s, x) = f_a(x) \cdot f_h(s) \tag{18}$$

Assuming that Equations 17 and 18 hold, Equation 16 can be simplified to:

$$\mathrm{E}(\Delta\mathrm{QALY}) = \int_0^\infty A(a) \int_a^\infty \frac{l(x)}{l(a)} f_a(x) r(x-a) K(x, a) dxda \tag{19}$$

where $K(x, a)$ is the change in the quality-adjusted life years:

$$K(x, a) = D_{gt}(x-a) f_h(s_{gt}) - D_{s_{alt}}(x-a) f_h(s_{alt}) \tag{20}$$

3.2 Calibration of ΔQALY

For each of these variables, we attempt to obtain empirical values from the literature as much as possible. When necessary, we interpolate values, briefly explaining our assumptions

and the data collection methods for the inputs to the model.

For the age-dependent QoL, $f_a(x)$, we extract the general population utility values from Institute for Clinical and Economic Review [112] and fit a linear model across the data. The QoL values and the fitted model are shown in Figure 4.

Age Group	Mean
18–29	0.922
30–39	0.901
40–49	0.871
50–59	0.842
60–69	0.823
70–79	0.790
≥80	0.736

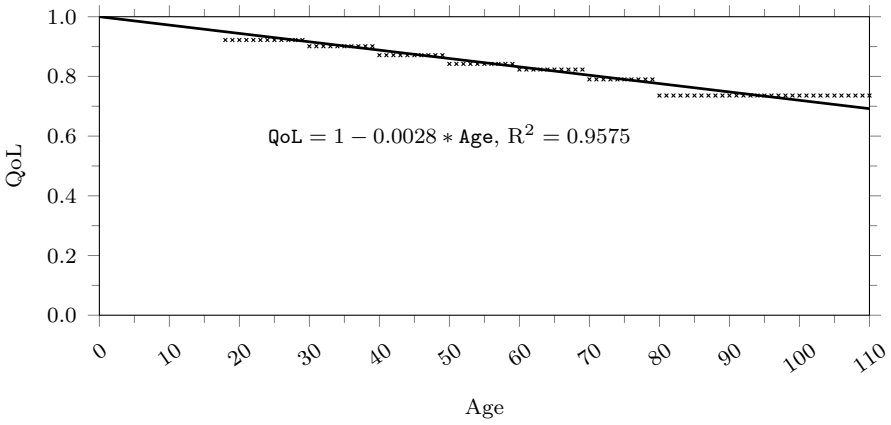


Figure 4: Age-dependent QoL, $f_a(x)$. The values extracted from ICER's SMA final report [112] are replicated in the table on the left and are presented as crosses in the figure on the right. A linear function, with its intercept set to 1, is fitted to the data points.

Since we are unable to know the patient outcomes for these potential gene therapies ahead of their approval, we assume that the gene therapy treatments will restore a person's survivability to that of a normal individual. This implies that $D_{gt}(x-a) = 1$. To estimate the impact of a disease on patient survivability, we model its survival curve, $D_{alt}(x-a)$, using the exponential survival curve shown in Equation 21. In the equation, λ is the force of mortality, and μ is the normalization factor. We estimate λ and μ by matching the function to T-year survival rates, which are the proportions of the patients (k) who will be alive after T years, from data. The parameter values and their sources are listed in Table A4 in the Supplementary Material.

$$D_{alt}(x-a) = D_{alt}(t) = \lambda e^{-\lambda(t-\mu)}, \text{ where } \mu = \frac{1}{\lambda}\ln\frac{1}{\lambda} \;\&\; \lambda = -\frac{\ln k}{T} \;\&\; t = x-a \tag{21}$$

The health-related quality of life variables, $f_h(s_{gt})$ & $f_h(s_{alt})$, are treated separately, depending on the disease classification. For cancer indications, we assume that the quality of life of the patients is not affected by the disease, which implies an upper bound for the computed ΔQALY. For non-cancer indications, we source the medical literature for the available quality of life (QoL) estimates. We use the QoL for the typical disease condition to approximate the 'before treatment' QoL, $f_h(s_{alt})$, and use the best possible outcome for each condition as the 'post-treatment' QoL, $f_h(s_{gt})$. We interpolate the missing values using

linear regressions of the sourced QoLs against disease severity. To do this, we first give scores, ζ, ranging from one to five for each disease, based on our perception of disease severity. We then fit a line of $f_h(s_{alt})$ against ζ in order to estimate the missing 'before treatment' QoL values, $f_h(s_{alt})$ (see Figure 5). We define $\Delta\text{QoL} = f_h(s_{gt}) - f_h(s_{alt})$. Separately, we regress ΔQoL against ζ to interpolate the change in QoL (see Figure 6). Given ΔQoL and $f_h(s_{alt})$, we can then estimate the missing values of $f_h(s_{gt})$. Our estimated values are reported in Table A5 in the Supplementary Material.

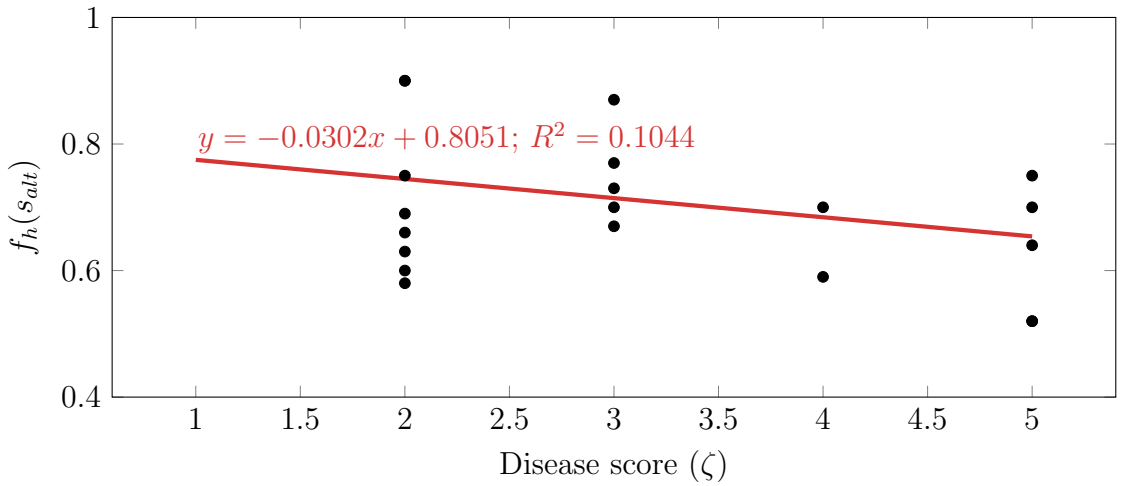


Figure 5: Scatter plot of $f_h(s_{alt})$ against disease score (ζ)

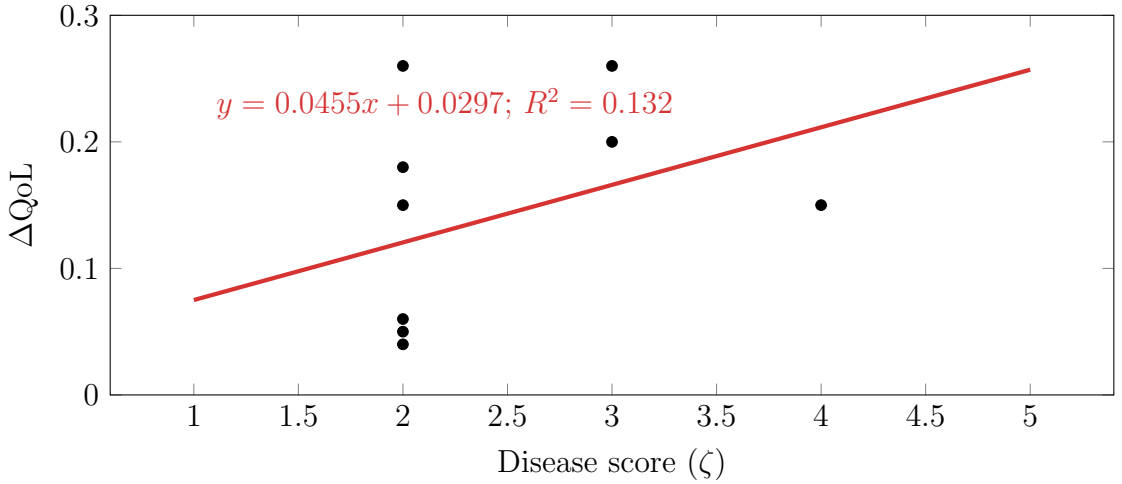


Figure 6: Scatter plot of ΔQoL against disease score (ζ)

We are able to extract the distribution of the age of cancer onset from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program website.

However, empirical age distributions are practically nonexistent for non-cancer diseases. To overcome this, we search the literature for the average age of diagnosis of each disease, and fit a triangle distribution for each disease using the optimization program shown in Figure 7.

$$\underset{x_{min},\, x_{max},\, c,\, z}{\text{maximize}} \quad x_{max} - x_{min} \tag{22}$$

$$\text{subject to} \quad x_{min} \leq c \leq x_{max}, \tag{23}$$

$$\frac{1}{2} z (x_{max} - x_{min}) = 1, \tag{24}$$

$$\int_{x_{min}}^{x_{max}} x f(x) dx = \mu_{age} \tag{25}$$

$$\text{where} \quad f(x) = \begin{cases} z \dfrac{x - x_{min}}{c - x_{min}} \text{ if } x \leq c \\ z(1 - \dfrac{x - c}{x_{max} - c}) \text{ otherwise} \end{cases} \tag{26}$$

Figure 7: An optimization program to obtain the triangle distribution given the average age of diagnosis, μ_{age}. x_{min} and x_{max} are coordinates of the base of the triangle. c and z are the mode and height of triangle.

This program maximizes the domain's interval (Equation 22) while imposing the requirement that the distribution's mode, c, has to be in the domain (Equation 23). In addition, the area under the curve has to be equal to 1 (Equation 24), and the mean of the distribution has to be equal to the average age (Equation 25).

We have experimented with an impulse function and an uniform distribution to model the age distribution, but these functions created unrealistic scenarios. Modeling the age distribution with the impulse function, while simple, will force Equation 15 to collapse into a single point, and lose any nuance in the QALY gained by patients of different ages. On the other hand, estimating a uniform distribution from the average age creates distributions with narrow support. The distributions from our optimization program have a wider base of support and avoid sharp changes in density. We illustrate this with some examples in Figure A2 in the Supplementary Materials.

We assume a 3% per annum discount rate, as suggested by ICER for high-impact single or short-term therapy (SST) [113].

3.3 Price per ΔQALY

To estimate a realistic market price of gene therapy, we calibrate our assumed price per ΔQALY with the 4 data points currently available: Zolgensma, priced at $2.1 million per

patient [131], Luxturna, priced at $0.425 million per eye treated [156], Kymriah, priced at $0.475 million for a one-time dose [64], and Yescarta, priced at $0.373 million for a one-time dose [64]. Separately, Zynteglo, sold at a cost of 1.6 million Euros (approximately $1.8 million), has been approved in the European Union. The data points are listed in Table 6.

Table 6: Diseases under consideration, approved gene therapy treatments used as proxy, prices of approved treatments, countries/areas in which treatments have been approved, and computed expected change in QALY.

Disease	Approved treatment	Country approved	List price	E(ΔQALY)
Beta-Thalassemia	Zynteglo	E.U.	1.8M	4.58
Diffuse Large B Cell Lymphoma (DLBCL)	Yescarta	U.S.	0.373M	6.19
Leber Congenital Amaurosis due to RPE65 Mutations	Luxturna	U.S.	0.425M	4.63
Leukemia (Acute Lymphoblastic)	Kymriah	U.S.	0.475M	13.02
Spinal Muscular Atrophy Type 1	Zolgensma	U.S.	2.125M	20.56

We calibrate the price per ΔQALY by minimizing the mean-squared error (MSE) between the estimated price given the expected change in QALY and the actual price. We report the mean absolute percentage error (MAPE) between the estimated price and the actual price in addition to the MSE. We note that Zolgensma, Zynteglo, and Luxturna are gene replacement therapies for rare diseases, while Kymriah and Yescarta are chimeric antigen receptor T-cell (CAR-T) therapies indicated for cancers. As such, we perform two separate calibrations, one for rare diseases and the other for cancer indications. We assume that the price per ΔQALY for general diseases is identical to that for cancer.

Considering only the therapies approved in the United States, we estimate a price per E(ΔQALY) of $101,663 (MSE: 2.18×10^9, MAPE: 11.2%) for rare diseases and $40,797 (MSE: 1.77×10^10, MAPE: 44.2%) for other diseases. Using all the data points, the price per E(ΔQALY) for rare diseases increases to $114,781 (MSE: 1.70×10^{12}, MAPE: 108%). In this paper, we use the former for our calculations since it has a smaller mean-squared error and better reflects prices in the U.S., our focus. This value will give us estimates of $2.09M per patient for Zolgensma and $0.470M per eye for Luxturna.

Our calibrated price per E(ΔQALY) for cancer indications is just slightly below ICER's $50,000 to $100,000 range for 'intermediate care value'. The higher price per E(ΔQALY) for rare diseases also reaffirms the general belief that developers of treatments for rare diseases should be compensated more for their elevated R&D risk and the low financial prospects of serving a small population of patients. It is assumed that the clinical cost of delivering the gene therapy is a negligible fraction of the overall cost of development (though they are considerably higher than the delivery cost of conventional therapeutics). It is also highly likely that the outside option cost will be similar.

The expected increases in QALY computed by our model are close to those provided by

the ICER reports for the treatments [110, 112]. For example, we estimate that treatments for Spinal Muscular Atrophy Type 1 and Leber Congenital Amaurosis due to RPE65 Mutations provide 20.56 and 4.63 incremental QALYs, whereas ICER estimates Zolgensma and Luxturna to provide 12.23 to 26.58 and 1.3 to 2.7 incremental QALYs[3], respectively. We have deliberately applied the same methods and assumptions used for the all other diseases to estimate the expected changes in QALY for Spinal Muscular Atrophy Type 1 and Leber Congenital Amaurosis due to RPE65 Mutations even though we could have obtained these numbers directly from ICER reports. By doing so, our price per ΔQALY calibration will correct for potential biases in our data, and our price estimates will be more realistic.

Our estimated change in QALY, the price per unit change in QALY, and the estimated price of therapy for each disease are shown in Table A6 in the Supplementary Materials.

4 Results

4.1 Expected Number of Approvals and Patients

Our simulations, based on the conservative assumptions detailed in the previous section, indicate that the expected number of gene therapies approved between January 2020 and January 2034 is 18.3, with a 90% confidence interval of $[14.0, 23.0]$ (see Figure 8).

Table 7 shows the annual number of treated patients over time by age groups. Our simulations expect the number of patients treated to grow from 16,244 in 2020 to 94,696 in 2025 before declining to 65,612 in 2034. The decline can be attributed to the declining stock of existing patients as they are treated, and the fact that we do not consider new development programs launched in the future. The proportions of patients who are children, adults and elderly are 17.9%, 35.4%, and 46.7% respectively.

We show the number of patients treated by month in Figure 9a. We can see that our simulations expect the number of patients treated to peak at around 7911 (CI: [3978, 12477]) per month in Jul 2025 before declining to 5424 (CI: [2778, 8350]) by December 2034. The monthly number of existing patients treated exceeds the monthly number of newly-diagnosed patients treated until Sep 2024, when this trend is expected to reverse (see Figure 9b). Only 7% of all patients treated in December 2034 are preexisting patients. Cancer patients are expected to form the biggest group of patients receiving gene therapy treatments, simply due to the number of cancer indications being targeted. We expect the relative proportions of cancer, general disease, and rare disease patients to be 48.0%, 30.0%, and 22.0%, respectively,

[3]ICER provides a range of ΔQALY estimates corresponding to different age groups. We have considered the distribution of ages to produce a weighted average estimate.

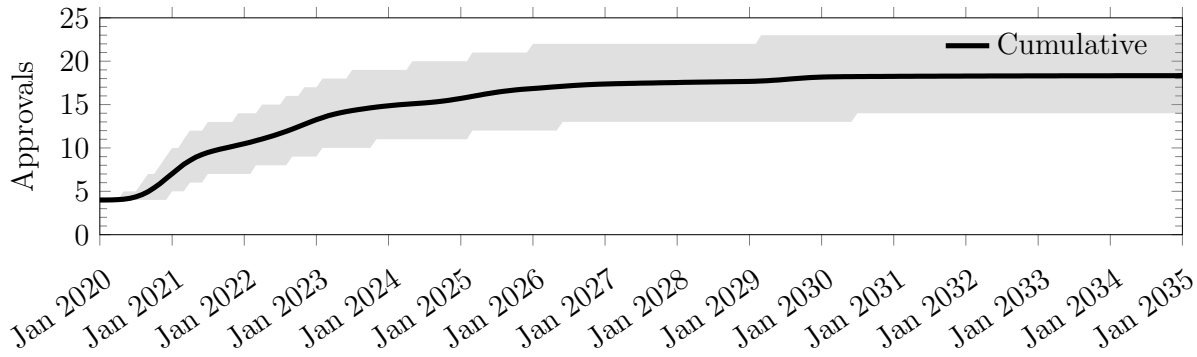


Figure 8: Cumulative number of approvals between January 2020 and December 2034, obtained from 1,000,000 simulation runs.

in December 2034. The cumulative number of patients to be treated is expected to be 1.09 million (CI: [0.595M, 1.66M]) by the end of December 2034 (see Figure 9c).

4.2 Expected Spending

We expect an increase in spending up to $2.11 billion per month (CI: [1.01B, 3.88B]) in Apr 2026, before decreasing slowly to a steady-state rate of $1.62 billion (CI: [0.624B, 2.9B]) per month (see Figure 10a). We emphasize that the total spending eventually declines because our simulations analyze a fixed stock of innovations, and do not account for new development programs that may be launched in the future. Treating existing cancer patients initially consumes over 45.6% of the total monthly expenditure, but declines to only 0.99% by December 2034. In contrast, the proportion of spending on new patients in the 'general disease' and 'rare disease' groups will increase from 0.0% and 4.26%, respectively, in Feb 2020 to 21.2% and 46.2% by December 2034. The monthly spending on treating existing patients is expected to exceed the monthly spending on treating newly diagnosed patients in Nov 2023. The cumulative discounted spending on treating patients with approved gene therapy products is expected to reach $241 billion (CI: [123B, 402B]) by December 2034, 15 years after the start of our simulation.

In terms of annual spending on approved gene therapies, we expect that $5.15 billion will be spent in 2020, increasing to $25.3B in 2026 before declining to $21.0B in 2034 (see Table 8). Children, adults and the elderly will consume 43.2%, 26.0%, and 30.9%, respectively, of the total spending.

The expected annual spending by Medicare, Medicaid [4] and private sources respectively may reach $8.1, $5.44, and $12.2 billion (see Table 9). We discuss the implications of these

[4]The spending estimates for Medicaid do not take into account the 23.1% drug rebate that it is expected to receive [74].

estimates in Section 5.

The total expected increase in QALY over these 15 years is 5.59 million (see Figure 11), which translates to an average increase of 5.12 years of QALY per patient. This comes at an average 2020 present value cost of $43,110 per unit change in QALY.

Table 7: Expected annual number of patients treated by gene therapy between 2020 and 2035, conditioned on the age group and patient type. 'Children', 'adult' and 'elderly' are defined to be 'below the age of 18', 'between the ages of 18 and 62', and 'greater than 62 years old', respectively.

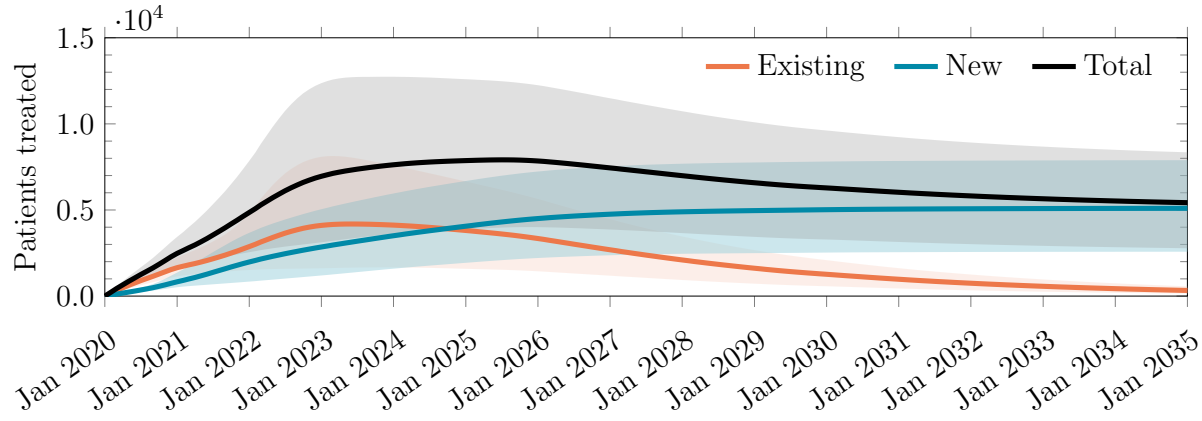
Year	**Children**			**Adult**			**Elderly**			**Total**
	Existing	New	Subtotal	Existing	New	Subtotal	Existing	New	Subtotal	
2020	1,630	417	2,047	3,682	1,657	5,339	6,006	2,853	8,859	16,244
	(1,283, 1,995)	(322, 522)	(1,614, 2,500)	(2,557, 4,943)	(1,080, 2,454)	(3,670, 7,237)	(3,928, 8,282)	(1,813, 4,142)	(5,785, 12,250)	(11,349, 21,685)
2021	2,833	1,294	4,127	9,921	6,399	16,320	14,278	9,540	23,818	44,265
	(2,001, 4,357)	(681, 1,950)	(2,770, 6,326)	(5,857, 14,948)	(2,970, 11,725)	(9,380, 24,834)	(8,578, 21,422)	(4,783, 17,438)	(14,050, 36,234)	(26,876, 65,911)
2022	3,832	3,235	7,067	16,809	11,041	27,849	23,112	15,513	38,625	73,543
	(2,000, 8,352)	(947, 14,178)	(3,224, 22,601)	(6,965, 31,751)	(4,364, 19,680)	(12,843, 47,995)	(9,343, 46,360)	(6,561, 28,346)	(17,258, 69,494)	(35,001, 126,974)
2023	4,722	5,612	10,334	19,364	13,890	33,254	25,862	19,031	44,893	88,482
	(2,001, 11,596)	(1,243, 25,879)	(3,614, 37,353)	(7,340, 36,474)	(5,999, 23,487)	(15,161, 56,955)	(9,222, 52,202)	(8,407, 32,988)	(19,347, 80,954)	(41,055, 151,872)
2024	4,922	7,734	12,656	18,580	16,230	34,810	24,122	21,781	45,902	93,371
	(1,832, 11,745)	(1,490, 29,056)	(3,681, 40,322)	(7,284, 32,906)	(7,683, 26,300)	(16,794, 56,353)	(8,817, 45,862)	(10,261, 36,233)	(21,011, 77,784)	(45,504, 151,799)
2025	5,235	9,621	14,856	16,570	18,159	34,728	21,115	23,994	45,110	94,696
	(1,865, 11,736)	(1,741, 30,664)	(3,996, 41,541)	(6,585, 28,364)	(9,026, 28,683)	(17,320, 54,531)	(7,795, 38,698)	(11,748, 38,878)	(21,451, 73,552)	(47,833, 148,985)
2026	4,998	11,086	16,085	13,653	19,350	33,003	17,220	25,370	42,592	91,682
	(1,667, 11,079)	(1,918, 31,601)	(3,996, 41,494)	(5,511, 23,012)	(9,839, 30,163)	(16,868, 50,992)	(6,444, 30,948)	(12,692, 40,529)	(20,887, 67,946)	(47,432, 141,917)
2027	4,246	12,120	16,366	10,687	19,915	30,604	13,402	26,032	39,433	86,401
	(1,323, 9,859)	(2,004, 32,129)	(3,676, 40,559)	(4,403, 17,871)	(10,254, 30,847)	(15,948, 46,843)	(5,129, 23,798)	(13,206, 41,300)	(19,847, 62,104)	(45,218, 132,708)
2028	3,522	12,842	16,364	8,203	20,129	28,332	10,215	26,242	36,457	81,153
	(1,024, 8,638)	(2,052, 32,455)	(3,369, 39,508)	(3,402, 13,700)	(10,409, 31,105)	(14,899, 43,197)	(3,945, 18,068)	(13,367, 41,550)	(18,583, 57,103)	(42,510, 124,357)
2029	2,978	13,373	16,351	6,259	20,219	26,478	7,744	26,315	34,059	76,888
	(851, 7,552)	(2,114, 32,684)	(3,217, 38,620)	(2,594, 10,485)	(10,480, 31,214)	(13,969, 40,339)	(3,002, 13,682)	(13,432, 41,632)	(17,475, 53,231)	(40,221, 117,723)
2030	2,656	13,807	16,463	4,764	20,276	25,040	5,863	26,361	32,224	73,726
	(712, 6,628)	(2,222, 32,909)	(3,228, 38,011)	(1,969, 8,027)	(10,526, 31,277)	(13,223, 38,155)	(2,275, 10,366)	(13,473, 41,682)	(16,597, 50,343)	(38,538, 112,779)
2031	2,116	14,039	16,154	3,620	20,313	23,933	4,434	26,391	30,826	70,914
	(540, 5,433)	(2,241, 32,998)	(3,032, 37,097)	(1,490, 6,146)	(10,558, 31,324)	(12,635, 36,496)	(1,720, 7,852)	(13,501, 41,715)	(15,896, 48,190)	(36,887, 108,603)
2032	1,654	14,185	15,840	2,746	20,338	23,084	3,349	26,411	29,759	68,684
	(408, 4,332)	(2,251, 33,049)	(2,861, 36,273)	(1,125, 4,698)	(10,577, 31,355)	(12,174, 35,255)	(1,298, 5,938)	(13,518, 41,736)	(15,350, 46,585)	(35,539, 105,370)
2033	1,286	14,282	15,567	2,079	20,354	22,434	2,528	26,424	28,953	66,952
	(308, 3,400)	(2,257, 33,084)	(2,726, 35,611)	(847, 3,575)	(10,591, 31,374)	(11,813, 34,313)	(978, 4,482)	(13,529, 41,751)	(14,926, 45,369)	(34,479, 102,883)
2034	993	14,344	15,337	1,572	20,364	21,937	1,906	26,432	28,338	65,612
	(232, 2,644)	(2,262, 33,106)	(2,619, 35,063)	(638, 2,713)	(10,601, 31,387)	(11,533, 33,602)	(735, 3,379)	(13,536, 41,761)	(14,597, 44,479)	(33,666, 100,944)

Table 8: Expected annual spending on gene therapy between 2020 and 2035, conditioned on the age group and patient type. 'Children', 'adult' and 'elderly' are defined to be 'below the age of 18', 'between the ages of 18 and 62', and 'greater than 62 years old' respectively. Numbers in billions.

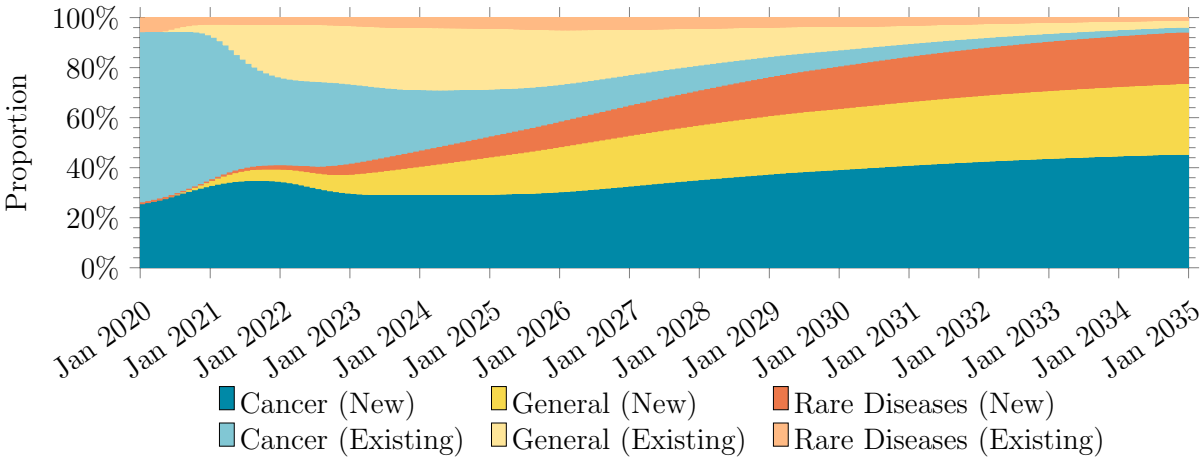
Year	**Children**			**Adult**			**Elderly**			**Total**
	Existing	New	Subtotal	Existing	New	Subtotal	Existing	New	Subtotal	
2020	1.77	0.32	2.10	0.91	0.37	1.29	1.20	0.57	1.77	5.15
	(1.31, 2.25)	(0.25, 0.40)	(1.55, 2.65)	(0.67, 1.18)	(0.26, 0.53)	(0.93, 1.69)	(0.79, 1.65)	(0.36, 0.80)	(1.15, 2.45)	(4.00, 6.39)
2021	2.23	0.72	2.94	2.19	1.31	3.51	2.76	1.80	4.56	11.01
	(1.60, 3.19)	(0.42, 0.86)	(2.03, 4.06)	(1.43, 3.16)	(0.68, 2.33)	(2.17, 5.31)	(1.73, 3.98)	(0.96, 3.42)	(2.77, 7.20)	(7.47, 15.85)
2022	2.37	1.79	4.16	2.91	2.09	5.01	3.52	2.70	6.22	15.38
	(1.39, 5.76)	(0.50, 9.98)	(1.97, 15.78)	(1.63, 4.41)	(0.94, 3.70)	(2.72, 7.76)	(1.92, 5.30)	(1.31, 5.03)	(3.39, 9.99)	(8.76, 27.15)
2023	2.91	3.33	6.25	3.37	2.67	6.04	3.79	3.34	7.13	19.41
	(1.26, 8.02)	(0.60, 18.48)	(1.97, 26.43)	(1.80, 5.12)	(1.30, 4.42)	(3.34, 9.10)	(1.97, 5.77)	(1.71, 5.81)	(3.88, 11.05)	(10.30, 39.86)
2024	3.06	4.79	7.85	3.46	3.26	6.72	3.84	4.02	7.86	22.43
	(1.06, 8.12)	(0.67, 20.70)	(1.84, 28.46)	(1.80, 5.27)	(1.66, 5.17)	(3.75, 9.99)	(1.94, 5.89)	(2.11, 6.65)	(4.31, 11.92)	(11.27, 44.10)
2025	3.50	6.11	9.61	3.18	3.76	6.94	3.51	4.59	8.10	24.65
	(0.98, 8.37)	(0.77, 21.79)	(1.95, 29.48)	(1.62, 4.88)	(1.96, 5.81)	(3.85, 10.27)	(1.74, 5.43)	(2.42, 7.36)	(4.44, 12.19)	(12.04, 46.08)
2026	3.49	7.15	10.64	2.67	4.08	6.75	2.94	4.96	7.89	25.28
	(0.88, 8.08)	(0.85, 22.43)	(1.94, 29.57)	(1.35, 4.12)	(2.14, 6.25)	(3.74, 10.00)	(1.46, 4.53)	(2.62, 7.84)	(4.33, 11.85)	(11.98, 45.94)
2027	2.97	7.89	10.86	2.14	4.27	6.40	2.34	5.17	7.51	24.77
	(0.70, 7.18)	(0.88, 22.79)	(1.77, 28.88)	(1.08, 3.32)	(2.24, 6.51)	(3.53, 9.49)	(1.17, 3.59)	(2.74, 8.11)	(4.13, 11.27)	(11.28, 44.52)
2028	2.47	8.42	10.89	1.66	4.34	6.00	1.80	5.24	7.04	23.92
	(0.54, 6.30)	(0.89, 23.01)	(1.62, 28.11)	(0.83, 2.63)	(2.28, 6.61)	(3.29, 8.93)	(0.90, 2.75)	(2.78, 8.20)	(3.87, 10.61)	(10.48, 42.84)
2029	2.25	8.86	11.10	1.28	4.36	5.64	1.37	5.26	6.63	23.37
	(0.48, 5.71)	(0.95, 23.22)	(1.62, 27.70)	(0.64, 2.07)	(2.30, 6.64)	(3.08, 8.42)	(0.69, 2.10)	(2.79, 8.22)	(3.64, 10.04)	(10.03, 41.59)
2030	2.37	9.31	11.68	0.98	4.38	5.36	1.04	5.27	6.31	23.35
	(0.39, 5.52)	(1.02, 23.53)	(1.58, 27.89)	(0.48, 1.62)	(2.31, 6.66)	(2.91, 8.02)	(0.52, 1.60)	(2.80, 8.24)	(3.45, 9.60)	(9.98, 41.08)
2031	1.90	9.49	11.39	0.75	4.39	5.14	0.79	5.28	6.07	22.59
	(0.30, 4.51)	(1.03, 23.61)	(1.47, 27.11)	(0.36, 1.26)	(2.32, 6.67)	(2.78, 7.71)	(0.39, 1.22)	(2.81, 8.25)	(3.31, 9.28)	(9.47, 39.80)
2032	1.47	9.60	11.07	0.57	4.40	4.97	0.60	5.28	5.88	21.92
	(0.22, 3.57)	(1.03, 23.64)	(1.38, 26.37)	(0.28, 0.97)	(2.32, 6.68)	(2.68, 7.47)	(0.30, 0.93)	(2.82, 8.25)	(3.20, 9.03)	(9.02, 38.69)
2033	1.14	9.67	10.81	0.43	4.40	4.84	0.45	5.29	5.74	21.38
	(0.17, 2.78)	(1.04, 23.67)	(1.30, 25.78)	(0.21, 0.74)	(2.33, 6.69)	(2.60, 7.29)	(0.22, 0.70)	(2.82, 8.25)	(3.11, 8.84)	(8.67, 37.83)
2034	0.87	9.72	10.59	0.33	4.41	4.73	0.34	5.29	5.63	20.95
	(0.13, 2.15)	(1.04, 23.68)	(1.24, 25.31)	(0.16, 0.57)	(2.33, 6.69)	(2.53, 7.15)	(0.17, 0.53)	(2.82, 8.26)	(3.04, 8.70)	(8.40, 37.13)

Table 9: Expected annual spending on gene therapy between 2020 and 2035 by funding source. Numbers in billions.

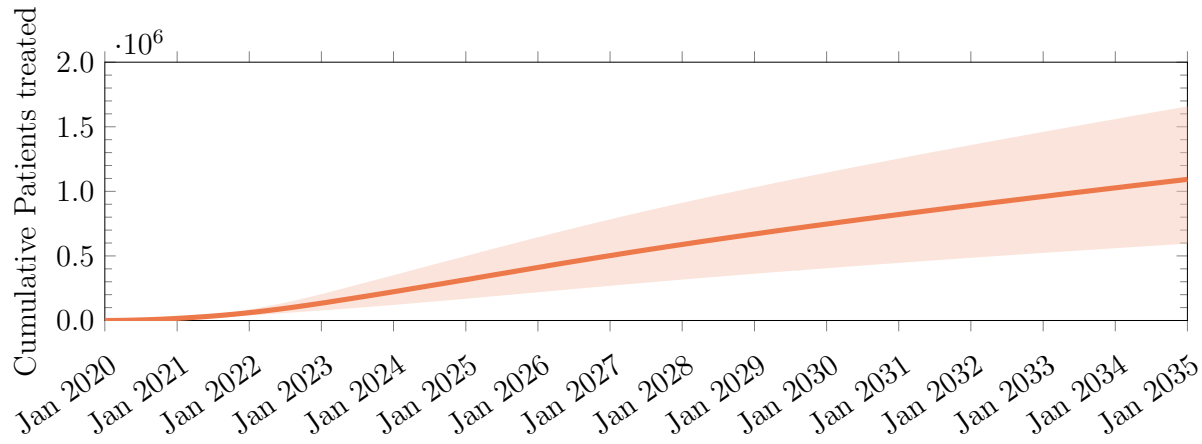
	Medicare	Medicaid	Private
2020	1.77 (1.15, 2.45)	1.02 (0.79, 1.26)	2.36 (1.87, 2.87)
2021	4.56 (2.77, 7.20)	1.68 (1.20, 2.28)	4.77 (3.29, 6.78)
2022	6.22 (3.39, 9.99)	2.38 (1.27, 7.02)	6.79 (3.79, 13.75)
2023	7.13 (3.88, 11.05)	3.36 (1.40, 11.44)	8.92 (4.46, 21.11)
2024	7.86 (4.31, 11.92)	4.10 (1.43, 12.37)	10.47 (4.84, 23.19)
2025	8.10 (4.44, 12.19)	4.83 (1.55, 12.82)	11.71 (5.22, 24.14)
2026	7.89 (4.33, 11.85)	5.22 (1.55, 12.83)	12.17 (5.20, 24.08)
2027	7.51 (4.13, 11.27)	5.26 (1.43, 12.50)	12.01 (4.86, 23.37)
2028	7.04 (3.87, 10.61)	5.21 (1.32, 12.14)	11.68 (4.50, 22.55)
2029	6.63 (3.64, 10.04)	5.25 (1.28, 11.92)	11.50 (4.32, 21.97)
2030	6.31 (3.45, 9.60)	5.44 (1.26, 11.96)	11.60 (4.33, 21.81)
2031	6.07 (3.31, 9.28)	5.29 (1.19, 11.61)	11.24 (4.09, 21.13)
2032	5.88 (3.20, 9.03)	5.14 (1.13, 11.29)	10.90 (3.89, 20.54)
2033	5.74 (3.11, 8.84)	5.01 (1.08, 11.03)	10.63 (3.73, 20.06)
2034	5.63 (3.04, 8.70)	4.91 (1.04, 10.83)	10.41 (3.60, 19.69)



(a) Monthly number of patients treated with gene therapy across all diseases. The line represents the mean and the shaded region represents the 5th and 95th percentiles of our simulation.

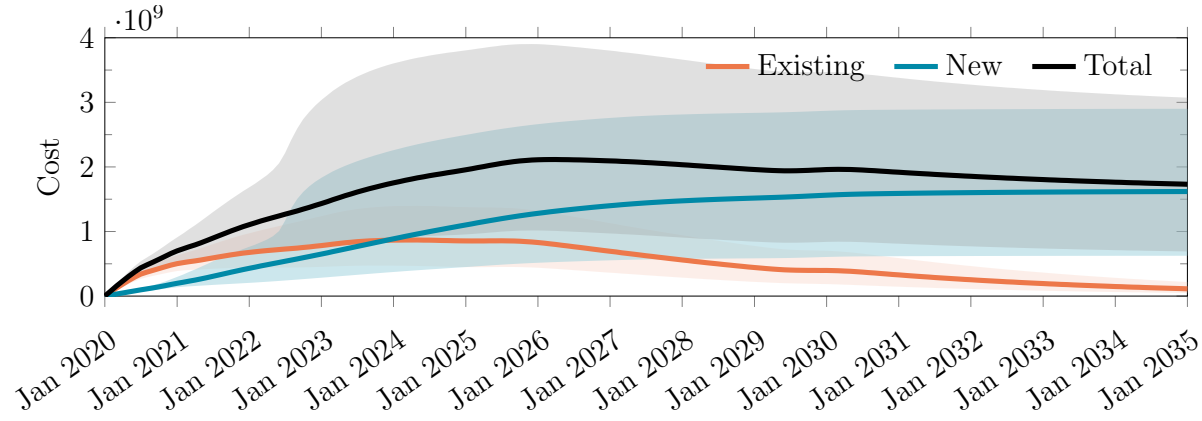


(b) Stacked chart depicting the proportion of existing and new patients treated in that month, by disease category.

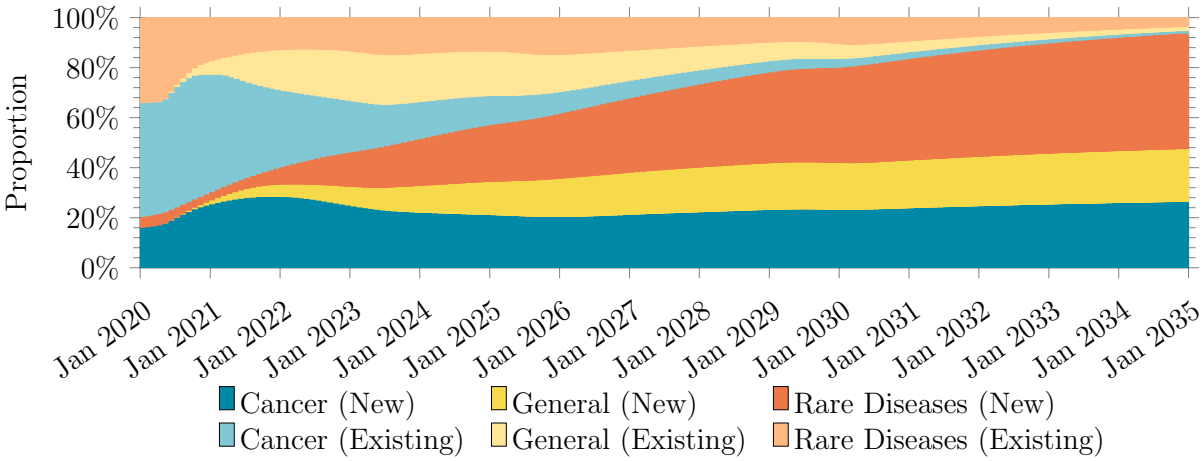


(c) Cumulative number of patients treated. The line represents the mean and the shaded region represents the 5th and 95th percentiles of our simulation.

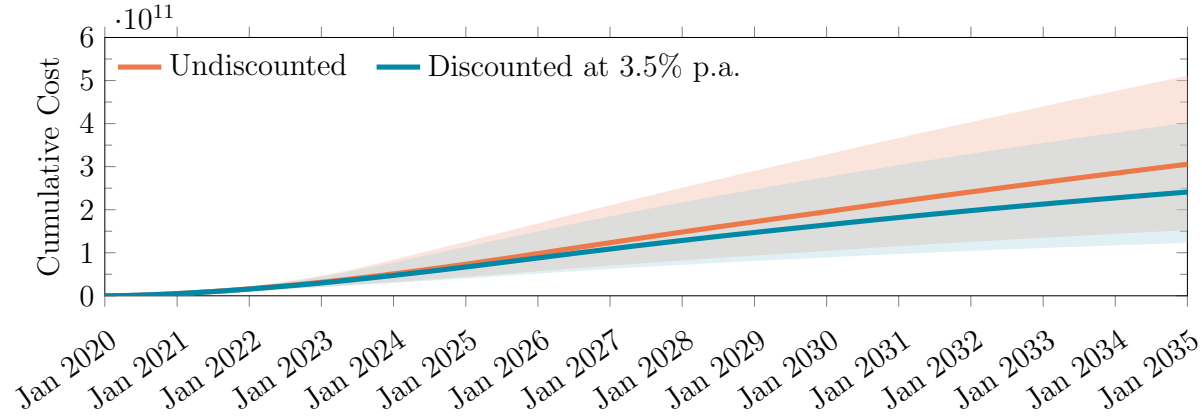
Figure 9: Number of patients treated between January 2020 and December 2034, obtained from 1,000,000 simulation runs.



(a) Monthly spending on treating existing and new patients with gene therapy. The line represents the mean and the shaded region represents the 5th and 95th percentiles from our simulation.

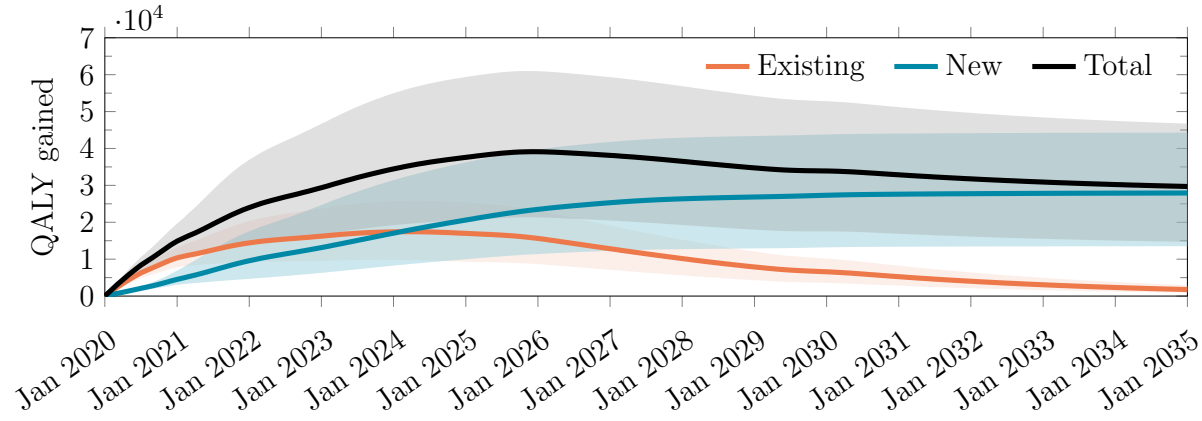


(b) Stacked chart depicting the proportion of spending on treating existing and new patients in that month, by disease category.

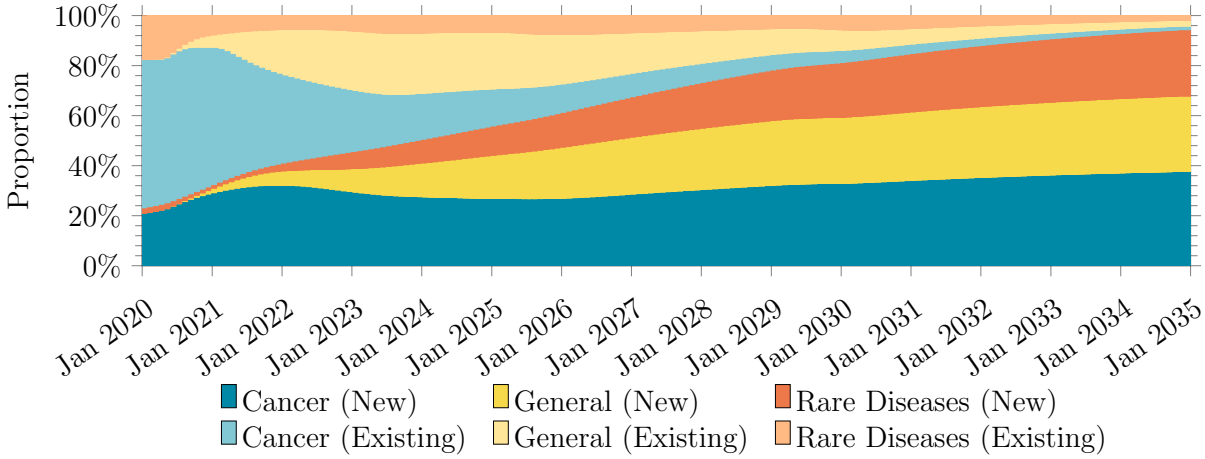


(c) Cumulative spending on treating patients with gene therapy. The line represents the mean and the shaded region represents the 5th and 95th percentiles of our simulation.

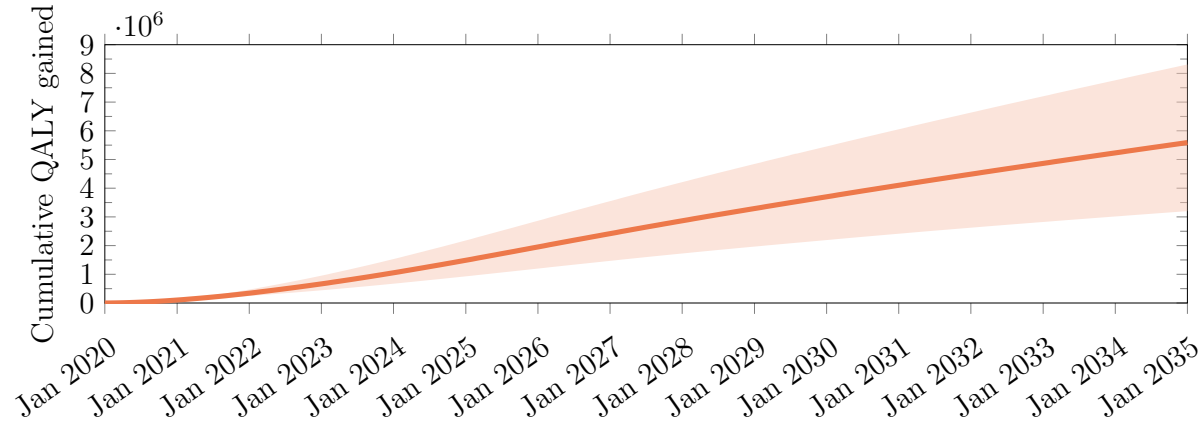
Figure 10: Spending on gene therapy between January 2020 and December 2034, obtained from 1,000,000 simulation runs.



(a) QALY gained by treating existing and new patients with gene therapy. The line represents the mean and the shaded region represents the 5th and 95th percentiles from our simulation.



(b) Stacked chart depicting the QALY gained by treating existing and new patients in that month, by disease category.



(c) Cumulative QALY gained by treating patients with gene therapy. The line represents the mean and the shaded region represents the 5th and 95th percentiles of our simulation.

Figure 11: Expected ΔQALY made possible by gene therapy treatments between January 2020 and December 2034, obtained from 1,000,000 simulation runs.

4.3 Sensitivity Analysis

To test the sensitivity of our results to initial conditions, we simulate ±20% changes in the following variables, analyzing their impact on our results.

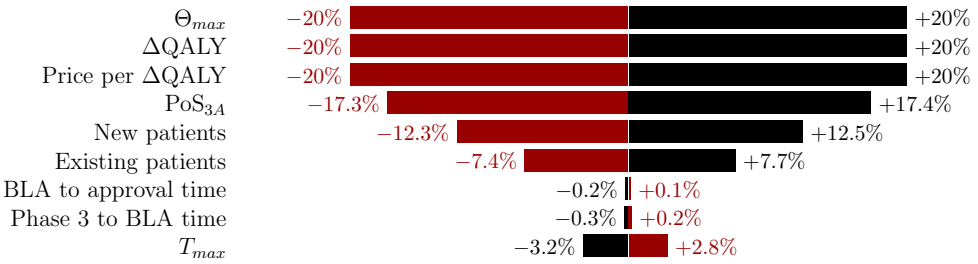
1. The maximum penetration rate in the ramp function, Θ_{max}
2. The time to maximum penetration rate in the ramp function, T_{max}
3. The amount of QALY gained in each disease
4. The price per ΔQALY
5. The phase-3-to-approval probability of success (PoS_{3A})
6. The number of new patients of each disease
7. The number of existing patients of each disease
8. The time from phase 3 to BLA
9. The time from BLA to approval

For each of these factors, we consider its impact on the the peak monthly spending and the cumulative spending from January 2020 to December 2034 of patient treatment. We also look at how the variables change the timing of the peak monthly spending.

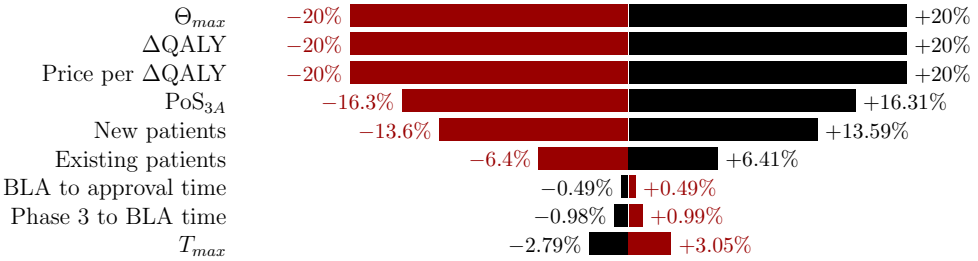
As can be seen from Figure 12, the percentage change in the discounted cumulative spending and the maximum monthly spending on treating all patients with gene therapy scale linearly with the percentage change in several variables: the maximum penetration rate (Θ_{max}), the QALY gained (ΔQALY), and the price per ΔQALY. Increasing or decreasing the transition probability from phase 3 to approval, or the number of new or existing patients only leads to sublinear increases or decreases in the discounted cumulative spending and the maximum monthly spending. However, changing the time variables, such as the number of days from phase 3 to BLA, from BLA to approval, or the ramp-up period (T_{max}), induce a small change in the opposite direction.

Introducing perturbations of 20% in the probability of success, the number of new patients, the number of days from Phase 3 to BLA or from BLA to approval, or the time to maximum penetration rate in the ramp function (T_{max}) will change the date of the peak monthly spending in the same direction as the perturbation, by up to 10 months. Increasing or decreasing the number of existing patients, on the other hand, will cause a shift of up to 4 months in the date of peak spending in the opposite direction. Perturbing the maximum penetration rate (Θ_{max}), the QALY gained (ΔQALY), and the price per ΔQALY will not change the date of peak spending.

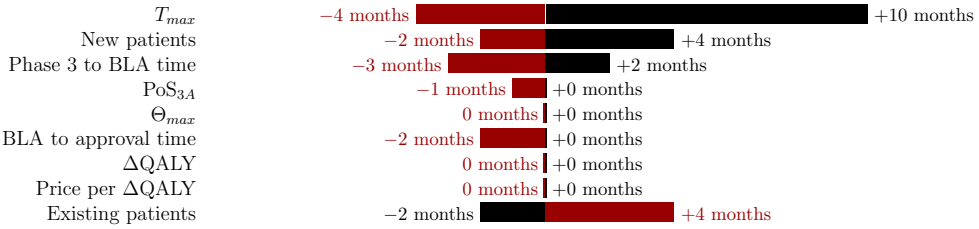
We also study the effect of changing the correlation between development programs. Changing the correlation from our assumed value of 0.9 to 0 (i.e., perfectly uncorrelated)



(a) Tornado chart of the impact of the variables on the peak value.



(b) Tornado chart of the impact of the variables on the cumulative spending (both nominal and discounted).



(c) Tornado chart of the impact of the variables on the date of peak value. Since we compute by calendar month, a small machine precision error may change the results by 1 month.

Figure 12: Tornado charts showing the sensitivity of the variables on the different metrics. The black bars represent the effect of increasing the variable by 20% and the red bars represent the effect of decreasing the variable by 20%.

increases the mean discounted cumulative spending by 3.4%, from $241 billion to $245 billion. Increasing the correlation to 1.0 instead will decrease the mean discounted cumulative spending by 0.4% to $236 billion.

In addition, we vary the proportion of existing patients seeking treatment in the first year—which determines the λ parameter in Equation 3—and observe that mean discounted cumulative spending changes by between -32% and +0.08% (see Figure 13). We can expect the results to differ by less than 5% from the baseline if the proportion of existing patients seeking treatments in the first year is between 8% and 45%.

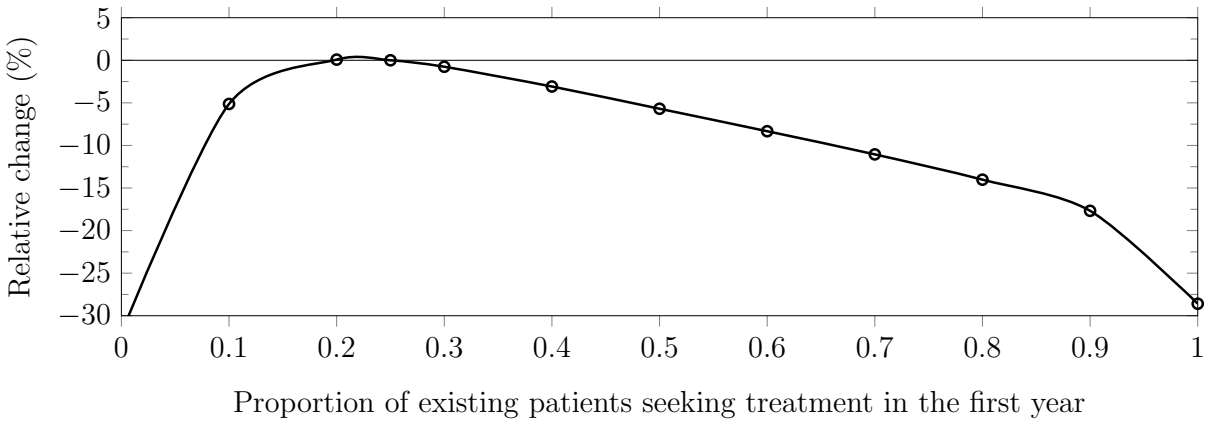


Figure 13: Percentage change in the discounted cumulative spending compared to the baseline when the proportion of existing patients seeking treatment in the first year changes.

4.4 Effect of additional gene therapy programs

In order to prevent boundary conditions from affecting our results, we simulate additional gene therapy programs that may enter the pipeline in the future, and compare the results against our baseline.

In order to do so, we fit a linear function of the number of gene therapy programs initiated in a given year against the date (see Figure 14). We extrapolate the fitted line to obtain the expected number of new gene therapy programs entering the pipeline between 2020 and 2035.

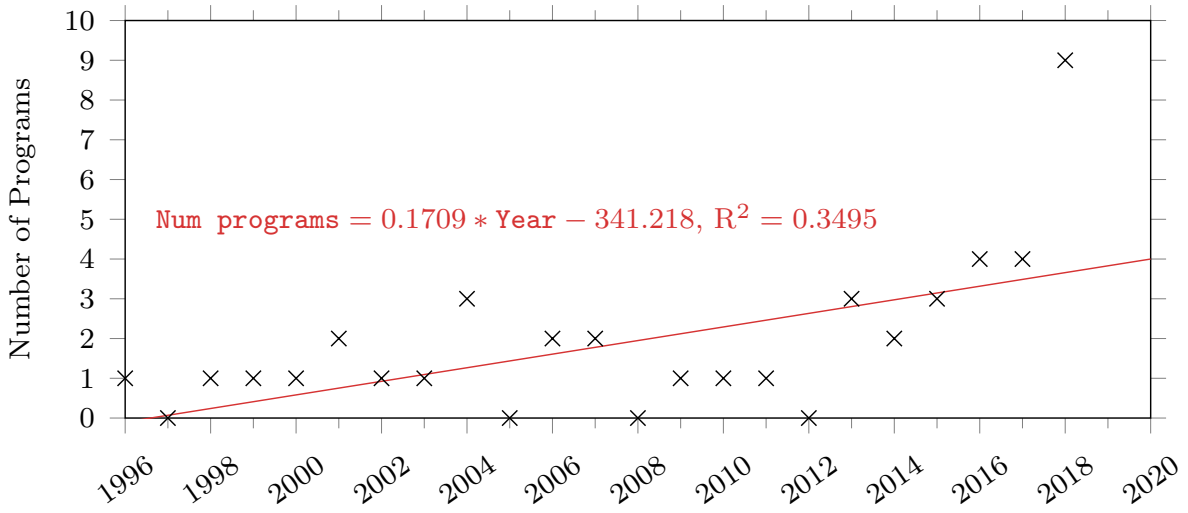


Figure 14: A plot of the number of programs initiated over time in our dataset.

We model the occurrence of new gene therapy programs with a Poisson process, with the

time between occurrences following an exponential distribution. More precisely, if κ programs are expected in a year, the time between consecutive events ($t > 0$) has a probability density of $\kappa e^{-\kappa t}$. For every event, we randomly assign its disease classification before simulating the success of the program, and if successful, its time of approval, the number of patients treated, and spending on the therapy over time. The means of the variables for each disease classification used in our simulations are summarized in Table 10.

Table 10: A summary of the variables used in the simulation of new gene therapy programs entering the pipeline between 2020 and 2035.

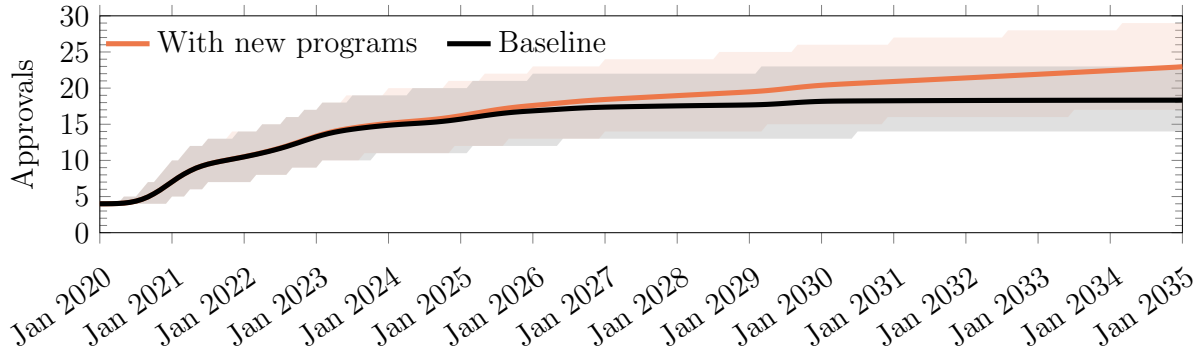
	General Disease	Rare Disease	Cancer
Probability of occurrence	21.4%	35.7%	42.9%
PoS_{3A}	47.3%	42.5%	28.5%
New patients per year	426,100	4,901	46,240
Existing patients	7,455,134	17,710	269,711
Cost	$254,638	$1,133,568	$287,068

As can be seen from Figure 15, while introducing new gene therapies into the pipeline increases the cumulative number of approvals by 25.1% from 18.3 to 23.0, the cumulative number of patients increases by only 15.3% from 1.09M to 1.26M. Similarly, the cumulative spending increases by 15.7% from $306B to $354B.

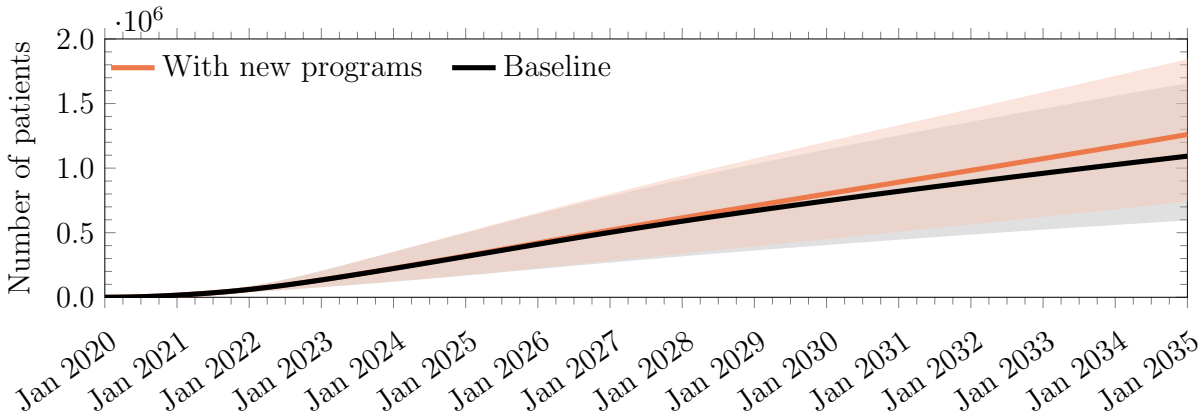
4.5 Comparison to prior work

Our study is independent of the results by Quinn et al. [141], who estimated that 341,775 patients will have been treated with gene therapy by December 2030, increasing by approximately 50,000 per year in the steady state. In contrast, our simulation expects that about 820,425 patients will be treated by the end of December 2030, with a steady-state increase of around 61,170 per year in the long run.

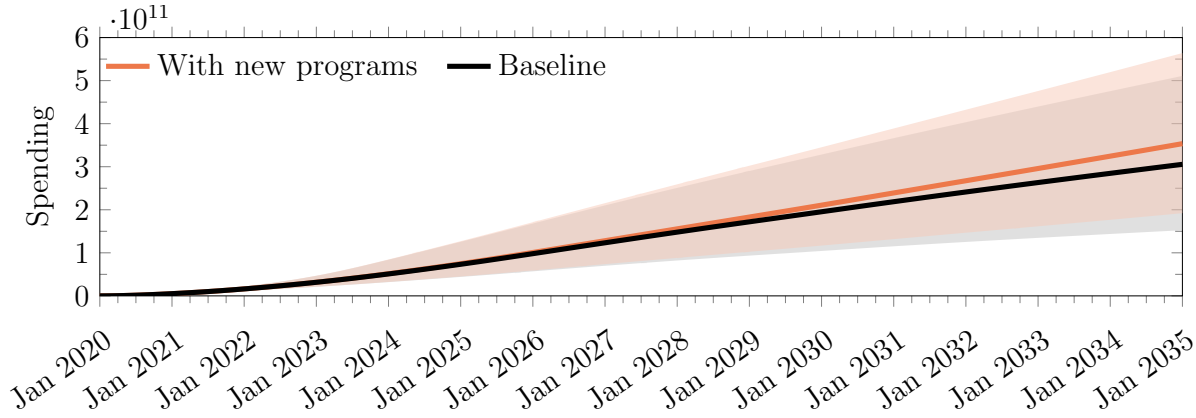
The differences between our estimates and this other report are due to differences in sample inclusion criteria and the use of different data for patient prevalence and incidence of disease. For example, Quinn et al. [141] considers "durable" gene therapies under all phases of clinical investigation whereas we consider any therapy with late-stage clinical trial(s). Furthermore, they assume that the 'potentially treatable pool in oncology is entirely incident—there is no prevalence'. Another difference arises from our decision to start with the broadest range of patients, and then deflate these numbers through the penetration rate, rather than attempting to estimate the prevalence and incidence for each patient segment. If we removed existing oncology patients from our simulation, the cumulative number of patients treated



(a) Cumulative number of approvals.



(b) Cumulative number of patients treated.



(c) Cumulative spending on gene therapy.

Figure 15: Comparison between the results with and without assuming additional gene therapy programs entering the pipeline. The line represents the mean and the shaded region represents the 5th and 95th percentiles of our simulation.

by December 2030 becomes 666,895, approximately 1.95 times the estimate in Quinn et al. [141]. We can obtain similar patient estimates to Quinn et al. [141] simply by reducing our

penetration rates by 48.8%, which will lower our estimated cumulative spending on gene therapy between January 2020 and December 2034 to $149 billion.

5 Discussion

We estimate that 1.09 million patients will be treated with gene therapy by the end of December 2034, spending up to $25.3B annually. These estimates are likely to be lower bounds, since our simulation employs conservative assumptions about the speed and volume of gene therapy development. Specifically, we consider only late-stage gene therapy development programs, defined as those already in phase 2/3 or phase 3, and do not account for the possibility that a program in phase 1 or phase 2 may be fast-tracked or granted accelerated approval. As shown in Section 4.4, extrapolating past trends in the number of new development programs affects our mean estimated cost and number of patients by less than 16%, although the long-run effects could be much larger.

A potential criticism of our approach is that estimating the cost of gene therapies solely based on the change in QALY will overestimate the aggregate spending in the U.S. For example, we do not take into account the potential cost savings to gene therapies due to avoiding multiple costly therapeutic sessions over time based on the current standard of care, or to the recovery of the opportunity cost of caregivers. While there are cases where gene therapy is predicted to provide net cost-savings in treatment after accounting for the direct medical cost (e.g., valoctocogene roxaparvovec for the management of hemophilia A [79]), there is not yet evidence to show that gene therapy will result in net long-term cost savings. In addition, research has shown that new medical technologies generally raise health costs, and that cost-increasing changes in treatments outweigh cost-saving changes the majority of the time [95]. We also do not consider any markup that happens under the prevalent 'buy-and-bill' process in the U.S. For these reasons, our estimates are likely to be lower bounds for realized costs over the next 15 years. Nonetheless, we have taken care to calibrate our price per ΔQALY using actual prices for approved therapeutics and estimating QALYs for those diseases, thereby allowing us to produce price estimates that closely track past data.

Another potential criticism is that we fail to consider the possibility that having multiple gene therapies for the same disease may lower the prices of the therapies. However, there is no analogous evidence that the presence of multiple brand-name drugs in the same class lowers the list prices of the drugs [148].

Based on our assumptions, the annual spending on gene therapy will average $20.4 billion, and may reach $25.3 billion in 2026. The cumulative spending on all future gene therapies from from January 2020 to January 2034 will be approximately $306 billion, or $241 billion

when discounted at a cost of capital of 3% per annum over the next 15 years. We estimate the cost of gene therapy to average $43,110 per unit QALY, several times the average annual expenditure of $16,346 for American cancer patients between 2010 and 2014 [137].

However, when viewed from the broader perspective of aggregate U.S. spending, these figures seem less daunting. In 2018, the U.S. tax revenue was $3.33 trillion, of which individual income tax and payroll tax revenues were $1.68 and $1.17 trillion, respectively [78]. Fully funding the average spending of $20.4 billion through income and payroll taxes will require an increase of 0.612%.

Since all elderly patients are covered by Medicare, we estimate that the program would need to increase its annual budget by up to $7.89 billion, or 1.1% of its 2018 spending of $750.2 billion [73]. Funding this increase would require either an increase in payroll taxes or a reduction in other expenditures.

We estimate that annual gene therapy spending by Medicaid may reach $5.44 billion. This is approximately 0.9% of its 2018 spending of $597.4 billion [73]. Since Medicaid must be provided to all eligible Americans without any preset cap, managing this increase will require either raising funds from state and federal governments to pay for these additional costs, or cutting benefits.

Annual spending by children and adults who are ineligible for Medicare or Medicaid—and therefore must rely on private insurers—is predicted to reach $12.2 billion. This spending poses a significant challenge for insurers and companies, who face annual budgets and competing priorities. In order to manage spending, many insurance policies might choose not to cover spending on gene therapy, or impose restrictive policies to limit the number of potential patients who might be treated [155]. Many private insurers are already warning they may not be able or willing to absorb the additional spending should a greater number of people become eligible for expensive gene therapy treatments once new ones reach the market [158].

Many novel methods to finance gene therapy treatments through the existing healthcare infrastructure have been proposed, such as outcome-based payments, whereby the manufacturers would be paid only if the patients achieve predefined outcomes after treatment [68]. We note that both Zolgensma and Luxturna have offered outcome-based payment methods to payers. There have also been proposals to allow mortgage-like payments, and performance-based annuity payments, as ways to finance gene therapy treatments [133]. In September 2019, Cigna, one of the largest U.S. health insurance companies, announced a program called Embarc Benefit Protection in which employers, health plans, and unions pay a monthly per-member premium that provides members with access to the two FDA-approved gene therapies, Luxturna and Zolgensma, with no out-of-pocket costs if their physicians authorize treatment. At the time of writing, however, Luxturna is not provided under Embarc

Benefit Protection, and it is unclear if the program is still in effect. Cigna hopes to keep the monthly cost of the program to below $1 per member [164], but if our simulations are accurate, this will be financially infeasible.

A more ambitious proposal involves creating a national and possibly international gene therapy reinsurance company that performs a similar function to Embarc, but which serves a large number of primary health insurance providers. By allowing multiple primary insurers to cede the specific risk of gene therapy patients to the reinsurer, these risks could be diversified over a much larger pool members, lowering the cost of capital. The capital required for such a reinsurer could be raised through securitization techniques as described in [133], who simulated such a structure, and concluded that the returns to investors would be quite attractive under a broad range of assumptions. However, their simulations were not specifically calibrated for gene therapy, hence our framework may provide a useful complement to their analysis.

Also, it may be more cost-effective for the reinsurer to assume the responsibility of delivering the gene therapies it reinsures through nationally distributed Centers of Excellence (CoEs). This may seem too far afield for a reinsurance company, but the ability to have direct control over the quality of delivery, and to be able to collect data on the performance of these therapies over time, are two compelling reasons for the reinsurer to take this on. The data collected from these centers will be critical, not only for assessing the actuarial risk of reinsurance, but also for implementing performance-related contractual agreements, e.g., if a gene therapy ceases to be effective, then any remaining payments for the therapy will be cancelled.

An additional benefit of a single reinsurer to manage the risk and responsibility of delivering gene therapy is the ability of that reinsurer to avoid the adverse selection problem that often plagues individual insurers [67]. This problem arises when some insurers are willing to pay for gene therapy treatments while others are not, leading patients who require gene therapies to enroll en masse with those insurers providing coverage. Since these policies will likely have higher premiums to cover the high cost of gene therapy, patients have an incentive to leave the policy after receiving the treatment, leaving the insurers to pay the remaining cost without being able to recover the expenses. If a single reinsurer can aggregate this risk across a large pool of gene therapy patients and coordinate payouts across all the insurers, this adverse selection problem can be greatly mitigated, or altogether avoided. The viability of such a reinsurance vehicle would depend critically on the various parameters of the modules in our simulation, as well as the ability to engage with the largest health insurer of all, the U.S. government.

In this paper, we make multiple assumptions to the best of our knowledge in order to

simplify data collection and make the computations required by our simulation framework tractable. We emphasize that our model requires many different inputs, some of which are based on scarce or extrapolated data. We also acknowledge that some of the development programs that we considered to be 'in-progress' at the time of analysis have subsequently failed. However, we believe that our simulation framework can accept new data and incorporate new assumptions as the amount of available information improves.

6 Conclusion

In this paper, we estimate the number of patients who will be treated by gene therapy between January 2020 and December 2034 using various data sources. We also develop a mathematical model to estimate the cost of these gene therapies, and calibrated the model to yield realistic cost estimates. It is our hope that this study, and our estimates of the potential financial impact of gene therapy in the U.S., will clarify some of the unknowns surrounding the impact of this new class of treatment, and allow policymakers, healthcare providers, insurance companies and patients alike to make more informed financial decisions about the future of this important therapeutic class.

Conflicts of Interest Disclosure

C.W., D.L., and N.W. report no conflicts.

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A.L. reports personal investments in private biotech companies, biotech venture capital funds, and mutual funds. A.L. is a co-founder and partner of QLS Advisors, a healthcare analytics and consulting company; an advisor to BrightEdge Ventures; a director of BridgeBio Pharma, Roivant Sciences, and Annual Reviews; chairman emeritus and senior advisor to AlphaSimplex Group; and a member of the Board of Overseers at Beth Israel Deaconess Medical Center and the NIH's National Center for Advancing Translational Sciences Advisory Council and Cures Acceleration Network Review Board. During the most recent six-year period, A.L. has received speaking/consulting fees, honoraria, or other forms of compensation from: AIG, AlphaSimplex Group, BIS, BridgeBio Pharma, Citigroup, Chicago Mercantile Exchange, Financial Times, FONDS Professionell, Harvard University, IMF, National Bank of Belgium, Q Group, Roivant Sciences, Scotia Bank, State Street Bank, University of Chicago, and Yale University.

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Supplementary Materials

A1 The Drug Development Process

Since the passing of the Food, Drug, and Cosmetic Act in 1938, pharmaceuticals developed by companies have to be reviewed by the Food and Drug Administration (FDA) for safety and efficacy before they can be marketed in the U.S. The application for marketing approval differs slightly by the type of therapy: New Drug Applications (NDAs) are for small molecules, and Biologics License Applications (BLAs) are for biologics. Gene therapy is considered a biologic product, hence the BLA designation applies.

Clinical investigations in human subjects typically take place in three phases—phases 1, 2 and 3—before marketing approvals are sought. Phase 1 trials are designed to investigate the dosage and safety of the treatment, while phase 2 trials attempt to detect early signs of efficacy and possible side effects in a relatively small sample of patients. Phase 3 trials are intended to demonstrate a statistically significant treatment effect when compared to the best standard of care in a broader population of patients. Some clinical trials combine multiple phases into a single design, with the phase numbers separated by a slash. For example, a phase 2/3 trial combines elements of phase 2 and phase 3 investigations into a single trial design in order to reduce the overall development time and cost, and maximize the participation of subjects with orphan disease willing to participate in trials. The clinical development of therapeutics is a tedious and costly process that may span decades and cost billions of dollars, with the bulk of the cost and time spent conducting phase 3 clinical trials [60, 82]. The process is also very risky, with only 13.8% of therapeutic development programs entering phase 1 reaching approval [166].

A2 Pseudo-Code and Implementation Details

Pseudo-code

We perform a Monte Carlo simulation to determine the total number of patients undergoing gene therapy and the cost of these gene therapies at specific points in time. The sequence of computations for each iteration of the simulation is detailed in Algorithm 1.

Input : $\mathbb{D}$: A list of diseases
Output: Arrays of $[1 \times T]$, where T is the number of time steps.
$\mathbb{P}$: Number of patients over time
$\mathbb{C}$: Total cost over time
$\mathbb{P} \leftarrow$ `1 × T array of zeros`
$\mathbb{C} \leftarrow$ `1 × T array of zeros`
for *d* in $\mathbb{D}$ **do**
  p $\leftarrow$ getPoS(d) `// Get probability of success`
  if `random.uniform`(0,1) $\leq p$ **then**
    `// If the disease gets an approval...`
    `existing` $\leftarrow$ `getExistingPatients(d)` ; `// Get existing patients (1 × T)`
    `new` $\leftarrow$ `getNewPatients(d) // Get new patients (1 × T)`
    $\rho \leftarrow$ `getRampFunction(d) // Get penetration ramp (1 × T)`
    `price` $\leftarrow$ `getPrice(d) // Get price of GT (scalar)`
    $\mathbb{P}+ =$ (`existing` + `new`)$\otimes\rho$ `// Store number of patients`
    $\mathbb{C}+ = \mathbb{P}\times$ `price // Store cost of treatment`
  end
end
return $\mathbb{P}$, $\mathbb{C}$

Algorithm 1: Pseudocode for one iteration of the simulation.

Implementation

All the equations are discretized for computation from their continuous forms. When solving the integrals using the trapezoidal rule to obtain ΔQALY, we use strip widths of 1 year across a range from 0 to 110 years old, the resolution offered by the life tables. When simulating the number of patients and the cost over time, we use steps of 1 month.

Our codes are implemented on Python 3.6 backed by Numpy. Our vectorized implementation averages 6.120ms per iteration over 1,000,000 runs on a single thread of an Intel Xeon Gold 5120, clocked at 2.20GHz with 20GB of RAM. We attempted to use PyTorch to speed up the computations using a GPU, but it ran more slowly than a single-threaded CPU. We determined this took place for two reasons. First, generating random numbers must be sequential, since PyTorch delegates it solely to the CPU, which limits the amount of parallelization that can be achieved, as dictated by Amdahl's law. Second, because our computations require a large amount of data from different sources, they must be batched

due to the GPU's limited RAM. The constant movement of data through the PCIe bridge, however, turns out to be a massive bottleneck to the overall speed.

A3 Simulation Convergence Criteria

Let X_k be the results of the k-th simulation. X_k has a true mean of μ and variance σ^2. Let the mean of the Monte Carlo simulations over n runs be $\hat{\mu}_n = \frac{1}{n}\sum_k^n X_k$. Then, by Lindeberg–Lévy's Central Limit Theorem, $\hat{\mu}_n$ converges in distribution to a normal distribution with mean μ and variance of $n\sigma^2$. The 95 percent confidence interval for μ is given by:

$$\hat{\mu}_n \pm \frac{1.96 s_n}{\sqrt{n}} \tag{27}$$

where s_n is the sample variance of $\{X_1, \cdots, X_n\}$.

Since we are using 1-by-T vectors, we investigated the error in our simulation by dividing the half-range of the confidence interval in each time-step by $\hat{\mu}_n$ before taking the maximum across the time series. As can be seen from Figure A1, we should expect the simulated mean to be within 1.89% of the true mean 95% of the time with 1,000,000 iterations.

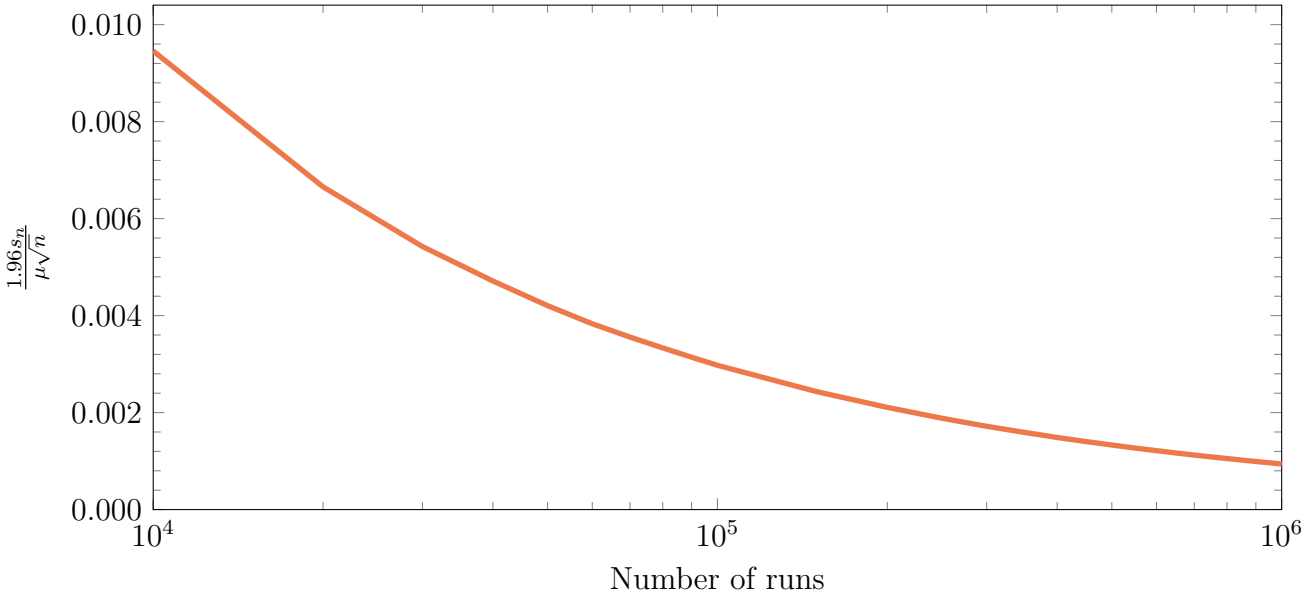

Figure A1: Plot of $\frac{1.96 s_n}{\mu\sqrt{n}}$ against the number of iterations of simulations of the cost.

A4 Current Gene Therapy Clinical Trials

As mentioned in the main paper, we list the clinical trials that are used in this study in the following table.

Table A1: List of clinical trials used in this study. 'TT' and 'CT' indicates 'TrialTrove' and '*clinicaltrials.gov*' respectively.

Trial Title	Disease	Sponsors	Source
Randomized, double-blind, placebo-controlled study of AMG0(HGF plasmid) for patients with arteriosclerosis obliterans	Arteriosclerosis Obliterans	AnGes	TT
Tisagenlecleucel Versus Standard of Care in Adult Patients With Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphoma: A Randomized, Open Label, Phase III Trial (BELINDA)	B-Cell Non-Hodgkin's Lymphoma	Novartis	TT
A Global Randomized Multicenter Phase III Trial of JCAR017 Compared to Standard of Care in Adult Subjects With High-risk, Second-line, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM).	B-Cell Non-Hodgkin's Lymphoma	Celgene	TT
A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN (rAd-IFN)/Syn3) Administered Intravesically to Patients With High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC)	BCG Unresponsive NMIBC	FKD Therapeutics	TT
A Phase III Study of BC-819 in Patients with Bladder Cancer who Failed Initial Treatment of BCG	BCG Unresponsive NMIBC	Anchiano Therapeutics	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects With Transfusion-dependent beta-Thalassemia, Who do Not Have a beta0/beta0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo With a Lentiviral betaA-T87Q-Globin Vector in Subjects < or = 50 Years of Age	Beta-Thalassemia	bluebird bio	TT
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects With Transfusion-dependent beta-Thalassemia, Who Have a beta0/beta0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo With a Lentiviral betaA-T87Q-Globin Vector in Subjects < or = 50 Years of Age	Beta-Thalassemia	bluebird bio	TT
An Integrated Phase II/III, Open Label, Randomized and Controlled Study of the Safety and Efficacy of CG0070 Adenovirus Vector Expressing GM-CSF in Patients With Non-Muscle Invasive Bladder Cancer With Carcinoma In Situ Disease Who Have Failed BCG Bladder Oncolytic virus for Non-muscle invasive bladder cancer Disease (BOND)	Bladder Cancer, in situ concurrent with Papillary Tumors	Cold Genesys	TT
A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced With Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD)	Cerebral Adrenoleukodystrophy (CALD)	bluebird bio	CT
Efficacy and Safety of AAV2-REP1 for the Treatment of Choroideremia	Choroideremia	Nightstar Therapeutics	CT

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Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AMG0 in Subjects With Critical Limb Ischemia Efficacy and Safety of AMG0 in Subjects With Critical Limb Ischemia (AGILITY)	Critical Limb Ischemia	AnGes	TT
Safety and Efficacy of Recombinant Adeno-Associated Virus Containing the CFTR Gene in the Treatment of Cystic Fibrosis	Cystic Fibrosis	Targeted Genetics Corporation/ Cystic Fibrosis Foundation Therapeutics	CT
A Placebo Controlled, Double-blind, Randomized, Parallel-group, Multi-center Phase III study to determine the Efficacy and Safety of TisssueGene-C in Patients with Degenerative Arthritis	Degenerative Arthritis	Kolon Life Science	TT
Safety and Efficacy Study of Pl-VEGF165 to Treat Diabetic Foot Syndrome	Diabetic Foot Syndrome	Human Stem Cells Institute	TT
A Phase III, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Asses the Safety and Efficacy of VM202 to Treat Chronic Nonhealing Foot Ulcers in Diabetic Patients With Concomitant Peripheral Arterial Disease (PAD)	Diabetic Foot Ulcers	Helixmith	TT
A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects With Painful Diabetic Peripheral Neuropathy	Diabetic Peripheral Neuropathy	Helixmith	TT
A Phase III, Randomized, Open-Label Study Evaluating Efficacy of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma	Diffuse Large B Cell Lymphoma (DLBCL)	Gilead Sciences/Kite Pharma	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Multi-center Phase III, Randomized, Open-Label Trial of Vigil (Bi-shRNAfurin and GMCSF Augmented Autologous Tumor Cell Immunotherapy) in Combination With Irinotecan and Temozolomide as a Second-Line Regimen for Ewing's Sarcoma	Ewing's Sarcoma	Gradalis	TT
A Phase III Study of INGN 241 in Combination with Radiation Therapy in Patients with Advanced Solid Tumors and Head and neck cancer.	Head and Neck Cancer	Introgen Therapeutics	TT
An Open-Label, Randomized, Multi-Center Phase III Clinical Trial Comparing E10A Plus Chemotherapy And Chemotherapy Alone For Treatment Of Head And Neck Cancer	Head and Neck Cancer	Marsala Biotech	TT
A Randomized, Open-label, Multi-center Phase III Study Designed to Evaluate the Safety and Efficacy of E10A in Patients With Recurrent/Unresectable Squamous Cell Carcinoma of the Head and Neck Region	Head and Neck Cancer	Guangzhou Double Bioproducts Co.	TT
A Phase III, Pivotal, Randomized, Placebo-controlled, Double-Blind, Multicenter Study to Evaluate RT-100 AC6 Gene Transfer in Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction;Heart Failure with Reduced Left Ventricular Ejection Fraction: One-time Gene Transfer Using RT-100 Intracoronary Administration of Adenovirus 5 encoding Human AC6 (FLOURISH)	Heart Failure	Renova Therapeutics	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients With Residual FVIII Levels = 1 IU/dL Receiving Prophylactic FVIII Infusions	Hemophilia A	BioMarin	TT
Phase 3 Study To Evaluate Efficacy/Safety of Valoctocogene Roxaparvovec an AAV Vector-Mediated Gene Transfer of hFVIII at a Dose of 4E13vg/kg in Hemophilia A Patients With Residual FVIII Levels < or = 1IU/dL Receiving Prophylactic FVIII Infusions	Hemophilia A	BioMarin	TT
A Phase III Run In trial to Evaluate SPK-8011 in Patients with Hemophilia A	Hemophilia A	Roche/Spark Therapeutics	TT
An open-label, single-dose, multi-center, multi-national, Phase III pivotal trial to investigate efficacy and safety of AMT-061 in severe or moderately severe hemophilia B; HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients; Phase III, Open-label, Single-dose, Multi-center, Multinational Trial Investigating a Serotype 5 Adeno-associated Viral Vector Containing the Padua Variant of a Codon-optimized Human Factor IX Gene (AAV5-hFIXco-Padua, AMT-061) Administered to Adult Subjects With Severe or Moderately Severe Hemophilia B	Hemophilia B	uniQure	TT

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Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Pivotal Phase III Study of PF-06838435 in Patients with Hemophilia B; Phase 3, Open Label, Single Arm Study To Evaluate Efficacy And Safety Of Fix Gene Transfer With Pf-06838435 (Raav-Spark100-Hfix-Padua) In Adult Male Participants With Moderately Severe To Severe Hemophilia B (Fix:C < or =2%)	Hemophilia B	Pfizer	TT
A Pivotal Phase III Study to Evalaute AMT-060 in Patients with Hemophilia B	Hemophilia B	uniQure	TT
Multicenter Randomized Controlled Trial of Adenovirus-mediated Adjuvant Gene Therapy Improving Outcome of Liver Transplantation in Patients With Advanced Hepatocellular Carcinoma	Hepatocellular Carcinoma	Wuhan Tiandakang Bio-Tech Engineering Co./ Shenzhen Tiandakang Gene Engineering Co.	TT
A Phase III Randomized, Open-Label Study Comparing Pexa Vec (Vaccinia GM CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy	Hepatocellular Carcinoma	Transgene/ Sillajen Biotherapeutics /Jennerex/ Lees Pharmaceutical	TT
Phase III Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma Multiforme	High-Grade Glioma	Novartis/Sandoz	TT

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Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Controlled, Randomised, Parallel Group Study Of The Efficacy And Safety Of Herpes Simplex Virus Thymidine Kinase Gene Therapy (Cerepro) with Subsequent Ganciclovir For The Treatment Of Patients With Operable High-Grade Glioma.	High-Grade Glioma	Trizell	TT
A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Phase 3 Study to Determine the Efficacy of TG-C in Subjects With Kellgren and Lawrence Grade (KLG) 2 or 3 Osteoarthritis of the Knee	Knee Osteoarthritis with Kellgren & Lawrence Grade 2 or 3	Kolon TissueGene	TT
A Multicenter, Randomized, Placebo Controlled, Double-blind, Parallel, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Invossa K Injection in Patients Diagnosed as Knee Osteoarthritis With Kellgren & Lawrence Grade 2	Knee Osteoarthritis with Kellgren & Lawrence Grade 2 or 3	Kolon Life Science	TT
Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis	Leber Congenital Amaurosis due to RPE65 Mutations	Spark Therapeutics	CT
Efficacy Study of GS010 for Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the ND4 Mutation	Leber Hereditary Optic Neuropathy	GenSight Biologics	CT
Efficacy Study of GS010 for the Treatment of Vision Loss up to 6 Months From Onset in LHON Due to the ND4 Mutation	Leber Hereditary Optic Neuropathy	GenSight Biologics	CT
Efficacy and Safety Study of Bilateral Intravitreal Injection of GS010 for the Treatment of Vision Loss up to 1 Year From Onset in LHON Due to the ND4 Mutation	Leber Hereditary Optic Neuropathy	GenSight Biologics	CT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
Tisagenlecleucel Versus Blinatumomab or Inotuzumab for Adult Patients With Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia: A Randomized Open Label, Multicenter, Phase III Trial	Leukemia (Acute Lymphoblastic)	Novartis	TT
Phase IIIb Study for Relapsed/Refractory Pediatric/Young Adult Acute Lymphoblastic Leukemia Patients to be Treated With CTL019	Leukemia (Acute Lymphoblastic)	Novartis	TT
A Phase II/III Prospective, Open Label Study to Evaluate Safety and Efficacy of Intravenous Autologous CD19 CAR-T Cells for Relapsed/ Refractory B-Acute Lymphoblastic Leukemia	Leukemia (Acute Lymphoblastic)	Gaia Science	TT
A Randomized Phase II/III Study of $\alpha\beta$ T Cell-Depleted, Related, Haploidentical Hematopoietic Stem Cell Transplant (Haplo-HSCT) Plus Rivogenlecleucel vs. Haplo-HSCT Plus Post-Transplant Cyclophosphamide (PTCy) in Patients With AML or MDS	Leukemia (Acute Myelogenous)	Bellicum Pharmaceuticals	TT
Randomized, Registrational, Controlled Study of BPX-501 with Allogeneic Hematopoietic Stem Cells (Allo-HSCT) in Patients with Acute Myelogenous Leukemia	Leukemia (Acute Myelogenous)	Bellicum Pharmaceuticals	TT
TK008: Randomized Phase III Trial of Haploidentical HCT With or Without an Add Back Strategy of HSV-Tk Donor Lymphocytes in Patients With High Risk Acute Leukemia	Leukemia (Acute Myelogenous)	Molmed	TT
A Phase IIb/III Study of AST-VAC1 in Patients with Acute Myelogenous Leukemia (AML)	Leukemia (Acute Myelogenous)	Asterias/Lineage Cell Therapeutics	TT
A Study of Glybera for the Treatment of Lipoprotein Lipase (LPL) Deficiency	Lipoprotein Lipase Deficiency (LPLD)	uniQure	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Study to Determine the Safety and Efficacy in Lipoprotein Lipase-Deficient Subjects After Intramuscular Administration of AMT-011, an Adeno-Associated Viral Vector Expressing Human Lipoprotein LipaseS447X.	Lipoprotein Lipase Deficiency (LPLD)	uniQure	TT
An Open-label Study to Assess the Efficacy and Safety of Alipogene Tiparvovec (AMT-011), Human LPL [S447X], Expressed by an Adeno-Associated Viral Vector After Intramuscular Administration in LPL-deficient Adult Subjects	Lipoprotein Lipase Deficiency (LPLD)	uniQure	TT
A Study of AMT-011 in Patients With LPL Deficiency	Lipoprotein Lipase Deficiency (LPLD)	uniQure	TT
A Phase III Trial of Glybera for Dyslipidemia	Lipoprotein Lipase Deficiency (LPLD)	uniQure	TT
Phase II/III study of Ad-IFNg in Cutaneous T-cell lymphoma	Lymphoma	Transgene	TT
A Safety and Efficacy Study of Cryopreserved GSK2696274 for Treatment of Metachromatic Leukodystrophy (MLD)	Metachromatic Leukodystrophy	GlaxoSmithKline	CT
PV-10 Intralesional Injection vs Systemic Chemotherapy or Oncolytic Viral Therapy for Treatment of Locally Advanced Cutaneous Melanoma	Melanoma (Locally Advanced Cutaneous)	Provectus Biopharmaceuticals	TT
A Phase Ib/III, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265/KEYNOTE-034)	Melanoma (Metastatic)	Amgen/ Merck & Co./Merck Sharp & Dohme (MSD)	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Phase III Clinical Trial to Evaluate the Safety and Efficacy of Treatment With 2 mg Intralesional Allovectin-7 Compared to Dacarbazine (DTIC) or Temozolomide (TMZ) in Subjects With Recurrent Metastatic Melanoma;Allovectin-7 Immunotherapeutic for Metastatic Melanoma (AIMM).	Melanoma (Metastatic)	Brickell Biotech, AnGes	TT
A Randomized Phase III Clinical Trial to Evaluate the Efficacy and Safety of Treatment With OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients With Unresectable Stage IIIb, IIIc and IV Disease	Melanoma (Metastatic)	Amgen	TT
An Extension Protocol to Evaluate the Efficacy and Safety of Extended Use Treatment With OncoVEXGM-CSF for Eligible Melanoma Patients Participating in Study 005/05	Melanoma (Metastatic)	Amgen	TT
A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine With and Without Allovectin-7 in Patients With Metastatic Melanoma.	Melanoma (Metastatic)	Brickell Biotech	TT
Open-label, Single-arm, Multi-center Study of Intracerebral Administration of Adeno-associated Viral (AAV) Serotype rh.10 Carrying Human N-sulfoglucosamine Sulfohydrolase (SGSH) cDNA for Treatment of Mucopolysaccharidosis Type IIIA	Mucopolysaccharidosis Type IIIa	LYSOGENE	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Phase III, Single Arm, Multi-Center Study to Assess the Efficacy and Safety of Clarithromycin(Biaxin)-Lenalidomide-Low-Dose-Dexamethasone (BiRd) Combined With B-cell Muturation Antigen (BCMA)-Directed Chimeric Antigen Receptor (CAR) T-cell Therapy in Patients With Newly Diagnosed Multiple Myeloma	Multiple Myeloma (Newly Diagnosed)	Shanghai Unicar-Therapy Bio-medicine	TT
Clinical Trial of Recombinant Adenovirus-p53 (Gendicine) Combined with Radiotherapy in Nasopharyngeal Carcinoma Patients.;	Nasopharyngeal Carcinoma	Shenzhen SiBiono GeneTech Co.	TT
A Phase II/III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intralesional Administration of RPR/INGN 201 in Combination with Taxotere and Carboplatin and Radiotherapy Versus Taxotere and Carboplatin and Radiotherapy Alone in Patients with Locally Advanced Unresectable Non-Small Cell Lung Cancer (NSCLC)	NSCLC	Introgen Therapeutics	TT
A Phase IIB/III Randomized, Double-blind, Placebo Controlled Study Comparing First Line Therapy With or Without TG4010 Immunotherapy Product in Patients With Stage IV Non-Small Cell Lung Cancer (NSCLC)	NSCLC	Transgene	TT
Phase III multi-center, open, randomized clinical trial of percutaneous intratumoral injection of genetically engineered adenovirus (injection of H101), IL-2, TB hyperthermia and systemic chemotherapy in the treatment of advanced non-small cell lung cancer	NSCLC	Shanghai Sunway Biotech	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
Phase III Study of Lucanix (Belagenpumatucel-L) in Advanced Non-small Cell Lung Cancer: An International Multicenter, Randomized, Double-blinded, Placebo-controlled Study of Lucanix Maintenance Therapy for Stages III/IV NSCLC Subjects Who Have Responded to or Have Stable Disease Following One Regimen of Front-line, Platinum-based Combination Chemotherapy; Survival, Tumor-free, Overall and Progression-free (STOP)	NSCLC Stage 3	Activate Immunotherapy	TT
rAd-p53 Combined Chemotherapy Via Selective Arterial Cannula in The Treatment of Advanced Oral Cancer, A Randomized Controlled Trial	Oral Cancer (Advanced)	Shenzhen SiBiono GeneTech Co.	TT
A Randomized, Controlled, Double-Arm, Open-Label, Multi-Center Study of Ofranergene Obadenovec (VB-111) Combined With Paclitaxel vs. Paclitaxel Monotherapy for the Treatment of Recurrent Platinum-Resistant Ovarian Cancer	Ovarian Cancer (Platinum-Resistant)	Gynecologic Oncology Group (GOG)/ VBL Therapeutics	TT
A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients With Greater Than or Equal to 0.5 cm and Less Than or Equal to 2 cm Residual Disease Following Surgery	Ovarian Cancer, Primary Peritoneal Cavity Cancer	Merck & Co./Merck Sharp & Dohme (MSD)	TT
A Randomized, Phase II/III, Study of TNFerade Biologic With 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer	Pancreatic Cancer (Locally Advanced)	Precigen	TT

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Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
Phase II/III Study of ProSavin for the Treatment of Parkinson's Disease	Parkinson's Disease	Oxford BioMedica	TT
Phase III Trial of CERE-120 for Parkinson's Disease	Parkinson's Disease	Sanofi/Sanofi Genzyme, Sangamo Therapeutics	TT
A Randomized, Placebo-controlled Phase IIIa Pivotal Confirmatory Study to Evaluate Safety and Efficacy of VY-AADC in Patients with Parkinson's Disease	Parkinson's Disease	Neurocrine Biosciences	TT
A Randomized Double-Blind Placebo-Controlled Parallel Group Study of the Efficacy and Safety of XRP0038/NV1FGF on Amputation or Any Death in Critical Limb Ischemia Patients With Skin Lesions	Peripheral Artery Disease	Sanofi	TT
Efficiency, Safety and Portability of Neovasculgen	Peripheral Artery Disease	Human Stem Cell Institute, Russia	CT
Gene Therapy using Intramuscular Administration of AMG0001 in Patients with Peripheral Arterial Disease;	Peripheral Artery Disease	AnGes	TT
Hepatocyte Growth Factor to Improve Functioning in Peripheral Artery Disease: The HI-PAD Study;	Peripheral Artery Disease	Helixmith	TT
A phase III study of HGF Plasmid in Peripheral Arterial Disease (PAD) in the US	Peripheral Artery Disease	AnGes	TT
Phase 3 Study of Efficiency, Safety and Portability of Gene Therapy Drug Neovasculgen (DNA Encoding the 165-amino-acid Isoform of Human Vascular Endothelial Growth Factor (pCMV - VEGF165) for Peripheral Arterial Disease Complex Treatment	Peripheral Artery Disease	Human Stem Cells Institute	TT
Provenge (Sipuleucel-T) Active Cellular Immunotherapy Treatment of Metastatic Prostate Cancer After Failing Hormone Therapy	Prostate Cancer	Dendreon	CT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Randomized, Controlled Trial of Replication-Competent Adenovirus-Mediated Suicide Gene Therapy in Combination With IMRT Versus IMRT Alone for the Treatment of Newly-Diagnosed Prostate Cancer With an Intermediate Risk Profile	Prostate Cancer (Localized)	Henry Ford Health System	TT
A Randomized Controlled Trial of ProstAtak as Adjuvant to Up-front Radiation Therapy For Localized Prostate Cancer	Prostate Cancer (Localized)	Candel Therapeutics	TT
A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Estramustine in Patients with Metastatic Hormone-Refractory Prostate Cancer Who are Chemotherapy-Naive.	Prostate Cancer (Metastatic Hormone-Refractory)	ANI Pharmaceuticals, Takeda	TT
A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients With Metastatic Hormone-Refractory Prostate Cancer Who Are Chemotherapy-Naive.	Prostate Cancer (Metastatic Hormone-Refractory)	ANI Pharmaceuticals, Takeda	TT
A Phase III Randomized, Open-Label Study of Docetaxel in Combination With CG1940 and CG8711 Versus Docetaxel and Prednisone in Taxane-Nave Patients With Metastatic Hormone-Refractory Prostate Cancer With Pain.	Prostate Cancer (Metastatic Hormone-Refractory)	ANI Pharmaceuticals, Takeda	TT
A Randomized Controlled Trial Of AdV-tk + Valacyclovir Administered During Active Surveillance For Newly Diagnosed Prostate Cancer	Prostate Cancer (Newly Diagnosed)	Candel Therapeutics	TT
An Open label,Randomized, Multi-Centered, Intra-Patient Controlled Phase III Study of FCX-007 in Patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB)	Recessive Dystrophic Epidermolysis Bullosa	Fibrocell Science	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
VITAL: A Pivotal Phase 3 Study of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) (GENE TRANSFER)	Recessive Dystrophic Epidermolysis Bullosa	Stanford University Medical Center/ Abeona Therapeutics	TT
A Phase III, Randomized, Controlled, Double-Arm, Open-Label, Multi-center Study of VB-111 Combined With Bevacizumab vs. Bevacizumab Monotherapy in Patients With Recurrent Glioblastoma	Recurrent Glioblastoma	VBL Therapeutics	TT
A Phase II/III Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC Versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma	Recurrent Glioblastoma	Tocagen	TT
A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter, Phase 3 Study to Evaluate the Safety and Efficacy of Ad5FGF-4 in Patients With Refractory Angina Due to Myocardial Ischemia;Ad5FGF-4 In Patients With Refractory Angina Due to Myocardial Ischemia (AFFIRM)	Refractory Angina due to Myocardial Ischemia (AFFIRM)	Gene Biotherapeutics/Angionetics	TT
A Phase III, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Triplet Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)	Relapsed and Refractory Multiple Myeloma (RRMM)	Celgene	TT
A Single Global Phase 3 trial of RST-001 in Patients With Retinitis Pigmentosa (RP)	Retinitis Pigmentosa	Abbvie/Allergan	TT
A Phase II/III Expansion Study to Evaluate Safety and Efficacy of NSR-RPGR in Patients with a Diagnosis of X - Linked Retinitis Pigmentosa due to RPGR mutations	Retinitis Pigmentosa	NightstaRx	TT

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Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
Phase 3 HGB-210 study of LentiGlobin in patients with SCD	Sickle Cell Anemia	bluebird bio	TT
Open-label, historical controlled study of AVXS-101 for treatment of spinal muscular atrophy	Spinal Muscular Atrophy	Novartis/AveXis	TT
A Multi-National Study of a One-Time Intrathecal Dose of AVXS-101 in Patients with Spinal Muscular Atrophy Types 1, 2, 3	Spinal Muscular Atrophy	Novartis/AveXis	TT
A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy With Multiple Copies of SMN2	Spinal Muscular Atrophy Type 1	Novartis/AveXis	TT
European, Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 With One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion	Spinal Muscular Atrophy Type 1	Novartis/AveXis	TT
Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 With One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion	Spinal Muscular Atrophy Type 1	Novartis/AveXis	TT
A Phase Ib/III Multicenter, Randomized, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	Squamous Cell Cancer of Head and Neck or Esophagus	Amgen/ Merck & Co./Merck Sharp & Dohme (MSD)	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
Phase III randomized clinical trial of intratumoral injection of E1B gene-deleted adenovirus (H101) combined with cisplatin-based chemotherapy in treating squamous cell cancer of head and neck or esophagus.	Squamous Cell Cancer of Head and Neck or Esophagus	Shanghai Sunway Biotech	TT
Phase III Randomized Study of Ad5CMV-p53 Gene Therapy (INGN 201) Versus Methotrexate in Patients With Refractory Squamous Cell Carcinoma of the Head and Neck (T301).	Squamous Cell Cancer of Head and Neck or Esophagus	Sanofi, Introgen Therapeutics	TT
A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN)	Squamous Cell Cancer of Head and Neck or Esophagus	Introgen Therapeutics	TT
A Randomized, Controlled, Parallel Group, Multicenter Phase 3 Study to Evaluate the Efficacy and Safety of Ad5FGF-4 Using SPECT Myocardial Perfusion Imaging in Patients With Stable Angina Pectoris	Stable Angina	Gene Biotherapeutics/ Angionetics/ Gene Biotherapeutics	TT
A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Female Patients With Stable Angina Pectoris Who Are Not Candidates for Revascularization;Angiogenesis in Women with Angina pectoris who are not candidates for Revascularization [AWARE]	Stable Angina	Gene Biotherapeutics/ Angionetics/ Gene Biotherapeutics	TT

Continued on next page

Table A1 – continued from previous page

Trial Title	Disease	Sponsors	Source
A Multinational Multicenter, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Patients With Stable Angina;(The Angiogenic Gene Therapy Trial - 4 [AGENT 4]).	Stable Angina	Bayer AG/Bayer HealthCare, Gene Biotherapeutics	TT
A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Patients With Stable Angina (The Angiogeneic Gene Therapy Trial - 3 [AGENT 3])	Stable Angina	Bayer AG/Bayer HealthCare, Gene Biotherapeutics	TT
Multicentre, Randomized,Double Blind, Placebo Controlled Trial of Myocardial Angiogenesis Using VEGF165, Intramyocardial Gene Delivery in Patients With Severe Angina Pectoris	Stable Angina	Johnson & Johnson	TT
A Pivotal Study of NY-ESO-1 in Patients with Synovial Sarcoma including Myxoid Round Cell Liposarcoma	Synovial Sarcoma	GlaxoSmithKline/ AdaptImmune	TT

A5 Disease-to-Therapeutic Area Mapping

As mentioned in the main paper, we show how the diseases are related to the therapeutic areas in the table below.

Table A2: Diseases with ongoing gene therapy trials and their associated therapeutic areas.

Disease	Therapeutic Area
– General Conditions –	
Arteriosclerosis Obliterans	Cardiovascular
Critical Limb Ischemia	Cardiovascular
Degenerative Arthritis	Autoimmune/Inflammation
Diabetic Foot Symptoms	Metabolic/Endocrinology
Diabetic Foot Ulcers	Metabolic/Endocrinology
Diabetic Peripheral Neuropathy	Metabolic/Endocrinology
Heart Failure	Cardiovascular
Knee Osteoarthritis with Kellgren & Lawrence Grade 3	Autoimmune/Inflammation
Parkinson's Disease	CNS
Peripheral Artery Disease	Cardiovascular
Refractory Angina due to Myocardial Ischemia (AFFIRM)	Cardiovascular
Stable Angina	Cardiovascular
– Rare Diseases –	
Beta-Thalassemia	Metabolic/Endocrinology
Cerebral Adrenoleukodystrophy (CALD)	CNS
Choroideremia	Ophthalmology
Cystic Fibrosis	Cardiovascular
Ewing's Sarcoma	Oncology
Hemophilia A	Metabolic/Endocrinology
Hemophilia B	Metabolic/Endocrinology
Leber Congenital Amaurosis due to RPE65 Mutations	Ophthalmology
Leber Hereditary Optic Neuropathy	Ophthalmology
Lipoprotein Lipase Deficiency (LPLD)	Metabolic/Endocrinology
Metachromatic Leukodystrophy	Metabolic/Endocrinology
Mucopolysaccharidosis Type IIIa	CNS
Recessive Dystrophic Epidermolysis Bullosa	Autoimmune/Inflammation
Retinitis Pigmentosa	Ophthalmology
Sickle Cell Anemia	Metabolic/Endocrinology
Spinal Muscular Atrophy	CNS
Spinal Muscular Atrophy Type 1	CNS
– Cancer –	
B-Cell Non-Hodgkin's Lymphoma	Oncology
BCG Unresponsive NMIBC	Oncology
Bladder Cancer, in situ concurrent with Papillary Tumors	Oncology

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Table A2 – continued from previous page

Disease	**Therapeutic Area**
Diffuse Large B Cell Lymphoma (DLBCL)	Oncology
Head and Neck Cancer	Oncology
Hepatocellular Carcinoma	Oncology
High-Grade Glioma	Oncology
Leukemia (Acute Lymphoblastic)	Oncology
Leukemia (Acute Myelogenous)	Oncology
Lymphoma	Oncology
Melanoma (Locally Advanced Cutaneous)	Oncology
Melanoma (Metastatic)	Oncology
Multiple Myeloma (Newly Diagnosed)	Oncology
Nasopharyngeal Carcinoma	Oncology
NSCLC	Oncology
NSCLC Stage 3	Oncology
Oral Cancer (Advanced)	Oncology
Ovarian Cancer (Platinum-Resistant)	Oncology
Ovarian Cancer, Primary Peritoneal Cavity Cancer	Oncology
Pancreatic Cancer (Locally Advanced)	Oncology
Prostate Cancer	Oncology
Prostate Cancer (Localized)	Oncology
Prostate Cancer (Metastatic Hormone-Refractory)	Oncology
Prostate Cancer (Newly Diagnosed)	Oncology
Recurrent Glioblastoma	Oncology
Relapsed and Refractory Multiple Myeloma (RRMM)	Oncology
Squamous Cell Cancer of Head and Neck or Esophagus	Oncology
Synovial Sarcoma	Oncology

A6 Patient Population Estimation

We source the patient prevalence and incidence of the diseases from different sources. When necessary, we compute the prevalence from the incidence using Equation 1, or vice versa, using Equation 2. Our results are shown in Table A3. These numbers do not reflect the adjustments we make to NSC lung cancer, prostrate cancer and spinal muscular atrophy in order to minimize overlapping patient groups.

Table A3: Number of current patients and annual new patients for each disease. An asterisk (∗) indicates that either the prevalence is computed from the incidence using Equation 1, or vice versa, using Equation 2.

Disease	Current patients	New patients per year
– General Conditions –		
Arteriosclerosis Obliterans	[91] 8500000	*192100
Critical Limb Ischemia	[83] 975000	[83] 300000
Degenerative Arthritis	[161] 27000000	*486000
Diabetic Foot Ulcers	[129] 2250000	[128] 112500
Diabetic Peripheral Neuropathy	[66,92,168] 9441480	[66,92,168] 467400
Heart Failure	[100] 5800000	[100] 812000
Knee Osteoarthritis with Kellgren & Lawrence Grade 2 or/and 3	*2929730	[161] 542000
Parkinson's Disease	[18] 500000	[18] 50000
Peripheral Artery Disease	[91] 8500000	*564400
Refractory Angina due to Myocardial Ischemia (AFFIRM)	[4] 8200000	[4,69] 565000
Stable Angina	[42] 10000000	[42] 500000
– Rare Diseases –		
Beta-Thalassemia	[10] 1000	[136] 3277
Cerebral Adrenoleukodystrophy (CALD)	[63] 411	[63] 37
Choroideremia	[126] 6554	[126] 77
Cystic Fibrosis	[62] 30000	[62] 1000
Ewing's Sarcoma	[12,13,58] 15003	[12,13,58] 200
Hemophilia A	[45] 16000	[45] 360
Hemophilia B	[45] 4000	[45] 90
Leber Congenital Amaurosis due to RPE65 Mutations	[76] 187	[76] 19
Leber Hereditary Optic Neuropathy	[25] 6540	[25] 654
Lipoprotein Lipase Deficiency (LPLD)	[70] 328	*33
Metachromatic Leukodystrophy	[46,138] 9333	[46,138] 771
Mucopolysaccharidosis Type IIIa	[28] 1638	[28] 39
Recessive Dystrophic Epidermolysis Bullosa	[107] 100	*10

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Table A3 – continued from previous page

Disease	Current patients	New patients per year
Retinitis Pigmentosa	[143]87387	[143]8739
Sickle Cell Anemia	[55]100000	[56]58745
Spinal Muscular Atrophy	[123]8526	[123]290
Spinal Muscular Atrophy Type 1	[40]17500	[111]500
– Cancer –		
B-Cell Non-Hodgkin's Lymphoma	[8,9]694704	[8,9]74200
BCG Unresponsive NMIBC	[11,101,117,119]371933	[11,101,117,119]42625
Bladder Cancer, in situ concurrent with Papillary Tumors	[11]356720	[11]41040
Diffuse Large B Cell Lymphoma (DLBCL)	[108]257	[108]18351
Head and Neck Cancer	[48,51,52,53]134337	[48,51,52,53]75275
Hepatocellular Carcinoma	[14,96,98]11287	[14,96,98]2032
High-Grade Glioma	[2,7,47,49,146]87540	[2,7,47,49,146]16334
Leukemia (Acute Lymphoblastic)	[5]95764	[5]5930
Leukemia (Acute Myelogenous)	[6]61048	[6]21450
Lymphoma	[15,32]905678	[15,32]82310
Melanoma (Locally Advanced Cutaneous)	[16]107605	[16]8683
Melanoma (Metastatic)	[16]47824	[16]3859
Multiple Myeloma (Newly Diagnosed)	0	[1]32270
Nasopharyngeal Carcinoma	[109]5390	[109]327
NSC Lung Cancer	[33,54]454469	[54] 191646
NSC Lung Cancer Stage 3	[33,54,140]151490	[54,140]63882
Oral Cancer (Advanced)	[3]250000	[3]53000
Ovarian Cancer (Platinum-Resistant)	[34,35,36]141150	[34,35,36]13956
Ovarian Cancer, Primary Peritoneal Cavity Cancer	[38]2290	[38]240
Pancreatic Cancer (Locally Advanced)	[37,147]22066	[37,147]17031
Prostate Cancer	[17]3110403	[17]174650
Prostate Cancer (Localized)	[17]2395010	[17]134481
Prostate Cancer (Metastatic Hormone-Refractory)	[17]186624	[17]10479
Prostate Cancer (Newly Diagnosed)	0	[17]174650
Recurrent Glioblastoma	[7,47,49,146]64127	[7,47,49,146]12120
Relapsed and Refractory Multiple Myeloma (RRMM)	[39,80]48840	[39,80]16280
Squamous Cell Cancer of Head and Neck or Esophagus	[48,51,52,53]120903	[48,51,52,53]67747
Synovial Sarcoma	[41,87]7282	[87]655

A7 Calibration of Survival Functions $D_{alt}(x-a)$

We source either the survival or mortality rate from literature and use them to compute λ, the time parameter in the exponential survival function. We show our result in the table below.

Table A4: List of survival rate or mortality rate and λ, for each disease. An asterisk $(*)$ under λ denotes that the disease does not affect mortality directly.

Disease	k years survival rate		k years mortality rate			λ
	$k=5$	$k=10$	$k=1$	$k=5$	$k=10$	
Arteriosclerosis Obliterans				[159]11.3		0.024
Critical Limb Ischemia				[84]50		0.139
Degenerative Arthritis		[163]82				0.020
Diabetic Foot Ulcers				[145]49		0.135
Diabetic Peripheral Neuropathy					[59]5	0.005
Heart Failure				[50]42.3		0.110
Knee Osteoarthritis with Kellgren & Lawrence Grade 2	[154]7.5					0.518
Knee Osteoarthritis with Kellgren & Lawrence Grade 3	[154]7.5					0.518
Parkinson's Disease	[165]40					0.174
Peripheral Artery Disease				[71]33.2		0.081
Refractory Angina due to Myocardial Ischemia (AFFIRM)			[103]3.9			0.040
Stable Angina	[104]90					0.021
Beta-Thalassemia		[169]98.3				0.002
Cerebral Adrenoleukodystrophy (CALD)	[142]55					0.120
Choroideremia						*
Cystic Fibrosis					[120]28	0.033
Ewing's Sarcoma	[130]70					0.071
Hemophilia A					[139]9.7	0.010
Hemophilia B					[139]9.7	0.010
Leber Congenital Amaurosis due to RPE65 Mutations						*

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Table A4 – continued from previous page

Disease	k years survival rate $k=5$	$k=10$	k years mortality rate $k=1$	$k=5$	$k=10$	λ
Leber Hereditary Optic Neuropathy						*
Lipoprotein Lipase Deficiency (LPLD)						*
Metachromatic Leukodystrophy	[127]52					0.131
Mucopolysaccharidosis Type III		[124]60				0.051
Recessive Dystrophic Epidermolysis Bullosa						*
Retinitis Pigmentosa						*
Sickle Cell Anemia		[94]96				0.004
Spinal Muscular Atrophy	[81]40					0.183
Spinal Muscular Atrophy Type 1	[170]10.13					0.458
B-Cell Non-Hodgkin's Lymphoma	[29]72					0.066
BCG Unresponsive Non-Muscle Invasive Bladder Cancer	[119]78					0.050
Bladder Cancer, Transitional Cell Carcinoma	[19]95.8					0.009
Diffuse Large B-Cell Lymphoma (DLBCL)	[24]63.2					0.092
Head and Neck Cancer	[20]64					0.089
Hepatocellular Carcinoma	[98]10					0.461
High-Grade Glioma	[106]9.87					0.463
Leukemia (Acute Lymphoblastic)	[5]68.8					0.075
Leukemia (Acute Myelogenous)	[6]28.7					0.250
Lymphoma	[27]72					0.066
Melanoma (Locally Advanced Cutaneous)	[26]64					0.089
Melanoma (Metastatic)	[26]23					0.294
Multiple Myeloma (Newly Diagnosed)	[57]52					0.131
Nasopharyngeal Carcinoma	[30]72					0.066
NSCLC	[43]23					0.294
NSCLC (Stage 3)	[43]33					0.222
Oral Cancer (Advanced)	[20]39.1					0.188

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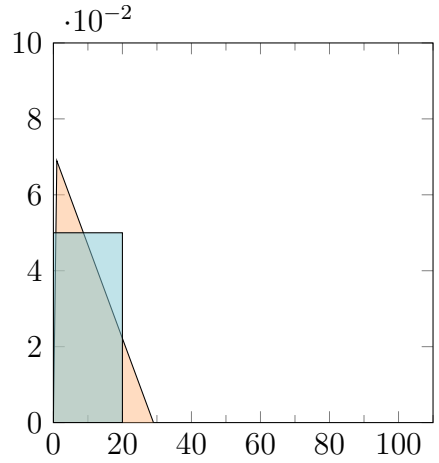
Table A4 – continued from previous page

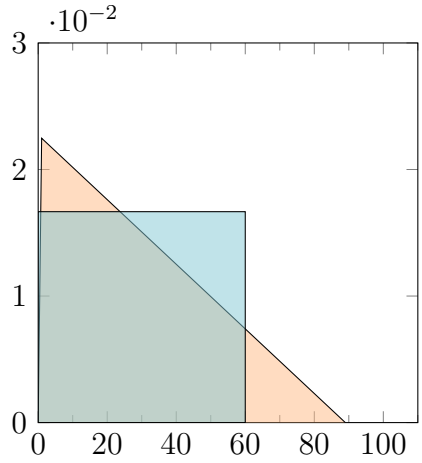
Disease	k years survival rate		k years mortality rate			λ
	$k = 5$	$k = 10$	$k = 1$	$k = 5$	$k = 10$	
Ovarian Cancer (Platinum-Resistant)	[162]1.9					0.793
Ovarian Cancer, Primary Peritoneal Cavity Cancer	[21]47.6					0.148
Pancreatic Cancer (Locally Advanced)	[22]12.4					0.417
Prostate Cancer	[23]98					0.004
Prostate Cancer (Localized)	[23]98					0.004
Prostate Cancer (Metastatic Hormone Refractory)	[23]30.5					0.237
Prostate Cancer (Newly Diagnosed)	[23]95.1					0.010
Recurrent Glioblastoma	[122]10					0.461
Relapsed and Refractory Multiple Myeloma (RRMM)	[44]9.92					0.462
Squamous Cell Cancer of Head and Neck or Esophagus	[20]64					0.089
Synovial Sarcoma	[31]55					0.120

A8 Calibration of Age Distribution $A(x)$

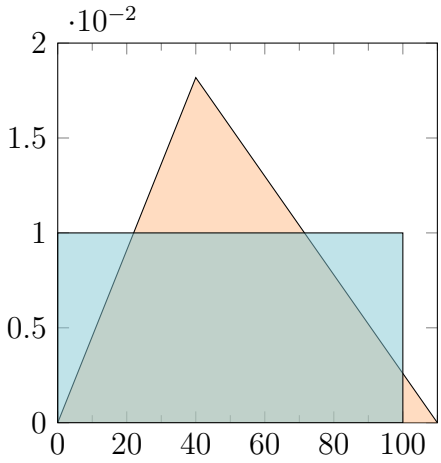
As mentioned in the main paper, our optimization program produces triangular age distributions that conforms to data, have wider support compared to fitting uniform distributions and, avoids sharp changes in the probability density. We illustrate some examples that compare triangle distributions with the uniform distributions with the same average age.



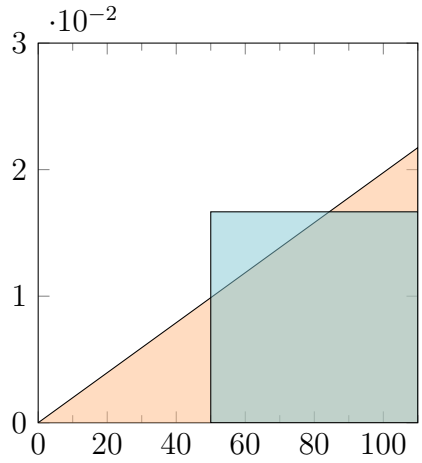
(a) Comparative probability distributions when $\mu_{age} = 10$



(b) Comparative probability distributions when $\mu_{age} = 30$



(c) Comparative probability distributions when $\mu_{age} = 50$



(d) Comparative probability distributions when $\mu_{age} = 80$

Figure A2: Age distributions given various mean ages, μ_{age}. The red triangles represent the solutions obtained by our optimization program, while the blue rectangles represent the solutions given by an uniform distribution. The distributions from the optimization program have a wider base of support and avoid sharp changes in density.

A9 Quality of Life Estimation

The results of our literature search and estimation for the change in QoL for each disease is shown in the table below.

Table A5: Table of disease scores (ζ), estimated quality of life values before treatment $\hat{f}_h(s_{alt})$, after treatment $\hat{f}_h(s_{gt})$, and the change in quality of life (ΔQoL). Asterisks ($*$) indicate that the values are interpolated. Cancers are not included, as we assume that the gains in survival dominate the gains in QoL.

Non-Cancer Disease	ζ	$\hat{\mathbf{f}}_\mathbf{h}(\mathbf{s_{alt}})$	**ΔQoL**	$\hat{\mathbf{f}}_\mathbf{h}(\mathbf{s_{gt}})$
Arteriosclerosis Obliterans	1	*0.775	*0.075	*0.850
Beta-Thalassemia	3	[150]0.870	*0.166	*1.000
Cerebral Adrenoleukodystrophy (CALD)	5	*0.654	*0.257	*0.911
Choroideremia	3	*0.715	*0.166	*0.881
Critical Limb Ischemia	4	*0.684	*0.212	*0.896
Cystic Fibrosis	3	[61]0.671	*0.166	*0.837
Degenerative Arthritis	3	*0.715	*0.166	*0.881
Diabetic Foot Ulcers	3	[153]0.703	[153]0.258	[153]0.961
Diabetic Peripheral Neuropathy	2	[152]0.630	[152]0.180	[152]0.810
Ewing's Sarcoma	2	[144]0.690	*0.121	*0.811
Heart Failure	4	*0.684	*0.212	*0.896
Hemophilia A	5	[72]0.750	*0.257	*1.000
Hemophilia B	5	[72]0.700	*0.257	*0.957
Knee Osteoarthritis, Kellgren & Lawrence Grade 2	2	[134]0.900	[134]0.042	*0.942
Knee Osteoarthritis, Kellgren & Lawrence Grade 3	2	[134]0.900	[134]0.048	*0.948
Leber Congenital Amaurosis (RPE65 Mutations)	3	*0.715	*0.166	*0.881
Leber Hereditary Optic Neuropathy	3	*0.715	*0.166	*0.881
Lipoprotein Lipase Deficiency	4	*0.684	*0.212	*0.896
Lysosomal Storage Disease	5	[93]0.640	*0.257	*0.897
Mucopolysaccharidosis Type IIIa	2	[102]0.582	[102]0.264	[102]0.846
Osteoarthritis	2	[157]0.900	[157]0.040	*0.940
Parkinson's Disease	4	[85,151]0.700	[85]0.150	[85]0.850
Peripheral Artery Disease	2	[105]0.660	[105]0.060	[105]0.720
Recessive Dystrophic Epidermolysis Bullosa	4	[116]0.590	*0.212	*0.802
Refractory Angina due to Myocardial Ischemia	2	[99]0.600	*0.121	*0.721
Retinitis Pigmentosa	3	[149]0.770	*0.166	*0.936
Sickle Cell Anemia	3	[90]0.732	[90]0.198	[90]0.930
Spinal Muscular Atrophy[5]	5	0.520	*0.257	*0.777
Spinal Muscular Atrophy Type 1	5	[171]0.520	*0.257	*0.777
Stable Angina	2	[121,167]0.750	[167]0.150	[167]0.900

[5]We are unable to find QoL values for SMA only and assume that they are the same as SMA Type 1.

Table A6: Estimated ΔQALY, assumed price per ΔQALY and estimated price of gene therapies per disease. Prices are given to 3 significant figures for display in this table.

Disease	ΔQALY	$\frac{\text{Cost}}{\Delta\text{QALY}}$ ($)	Price ($)
General Diseases:			
Arteriosclerosis Obliterans	2.96	41K	121K
Critical Limb Ischemia	7.32	41K	299K
Degenerative Arthritis	3.53	41K	144K
Diabetic Foot Ulcers	7.92	41K	323K
Diabetic Peripheral Neuropathy	3.95	41K	161K
Heart Failure	6.92	41K	282K
Knee Osteoarthritis with Kellgren & Lawrence Grade 3	10.62	41K	433K
Parkinson's Disease	8.26	41K	337K
Peripheral Artery Disease	4.52	41K	184K
Refractory Angina due to Myocardial Ischemia (AFFIRM)	3.80	41K	155K
Stable Angina	3.85	41K	157K
Rare Diseases:			
Beta-Thalassemia	4.58	102K	466K
Cerebral Adrenoleukodystrophy (CALD)	20.33	102K	2.07M
Choroideremia	4.24	102K	431K
Cystic Fibrosis	13.20	102K	1.34M
Ewing's Sarcoma	14.04	102K	1.43M
Hemophilia A	11.18	102K	1.14M
Hemophilia B	10.63	102K	1.08M
Leber Congenital Amaurosis due to RPE65 Mutations	4.63	102K	470K
Leber Hereditary Optic Neuropathy	3.97	102K	404K
Lipoprotein Lipase Deficiency (LPLD)	5.74	102K	584K
Metachromatic Leukodystrophy	21.06	102K	2.14M
Mucopolysaccharidosis Type IIIa	16.27	102K	1.65M
Recessive Dystrophic Epidermolysis Bullosa	5.89	102K	599K
Retinitis Pigmentosa	3.28	102K	333K
Sickle Cell Anemia	7.36	102K	748K
Spinal Muscular Atrophy	19.23	102K	1.96M
Spinal Muscular Atrophy Type 1	20.56	102K	2.09M
Cancer:			
B-Cell Non-Hodgkin's Lymphoma	4.90	41K	200K
BCG Unresponsive NMIBC	2.86	41K	117K
Bladder Cancer, in situ concurrent with Papillary Tumors	0.66	41K	26.9K

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Table A6 – continued from previous page

Disease	**ΔQALY**	$\frac{\textbf{Cost}}{\textbf{ΔQALY}}$ **($)**	**Price ($)**
Diffuse Large B Cell Lymphoma (DLBCL)	6.19	41K	253K
Head and Neck Cancer	6.13	41K	250K
Hepatocellular Carcinoma	9.30	41K	380K
High-Grade Glioma	12.56	41K	512K
Leukemia (Acute Lymphoblastic)	13.04	41K	532K
Leukemia (Acute Myelogenous)	8.55	41K	349K
Lymphoma	4.90	41K	200K
Melanoma (Locally Advanced Cutaneous)	6.23	41K	254K
Melanoma (Metastatic)	9.22	41K	376K
Multiple Myeloma (Newly Diagnosed)	5.90	41K	241K
Nasopharyngeal Carcinoma	5.20	41K	212K
NSC Lung Cancer	7.04	41K	287K
NSC Lung Cancer Stage 3	6.52	41K	266K
Oral Cancer (Advanced)	8.21	41K	335K
Ovarian Cancer (Platinum-Resistant)	10.83	41K	442K
Ovarian Cancer, Primary Peritoneal Cavity Cancer	7.93	41K	324K
Pancreatic Cancer (Locally Advanced)	7.64	41K	312K
Prostate Cancer	0.42	41K	17.1K
Prostate Cancer (Localized)	0.42	41K	17.1K
Prostate Cancer (Metastatic Hormone-Refractory)	7.75	41K	316K
Prostate Cancer (Newly Diagnosed)	0.99	41K	40.4K
Recurrent Glioblastoma	12.55	41K	512K
Relapsed and Refractory Multiple Myeloma (RRMM)	8.33	41K	340K
Squamous Cell Cancer of Head and Neck or Esophagus	5.51	41K	225K
Synovial Sarcoma	8.65	41K	353K

A10 Visualization of the Cost over Time

In this section, we visualize how the monthly cost of treating patients with gene therapy will be affected by changes to the variables. The results are summarized in the tornado chart presented in the main paper.

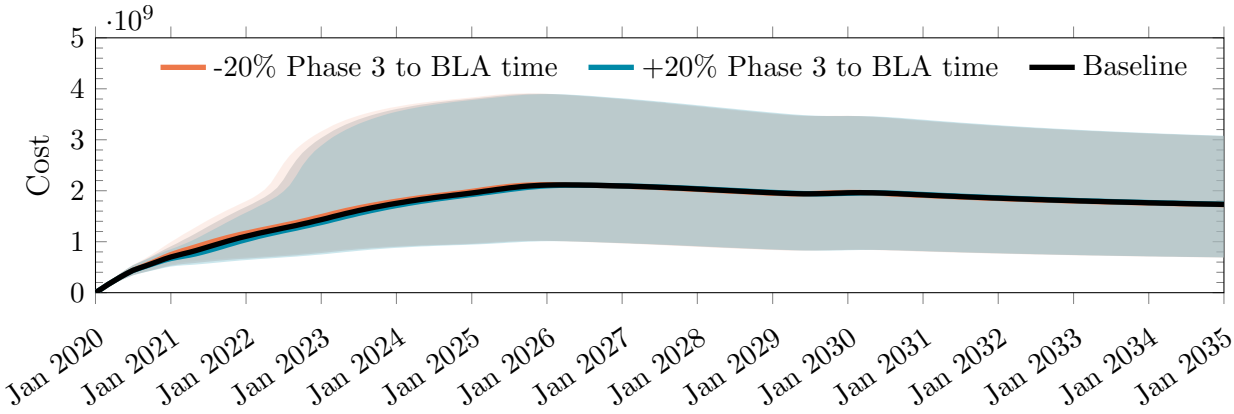

Figure A3: Impact on monthly cost of treating patients given a ±20% change in the time from phase 3 to BLA.

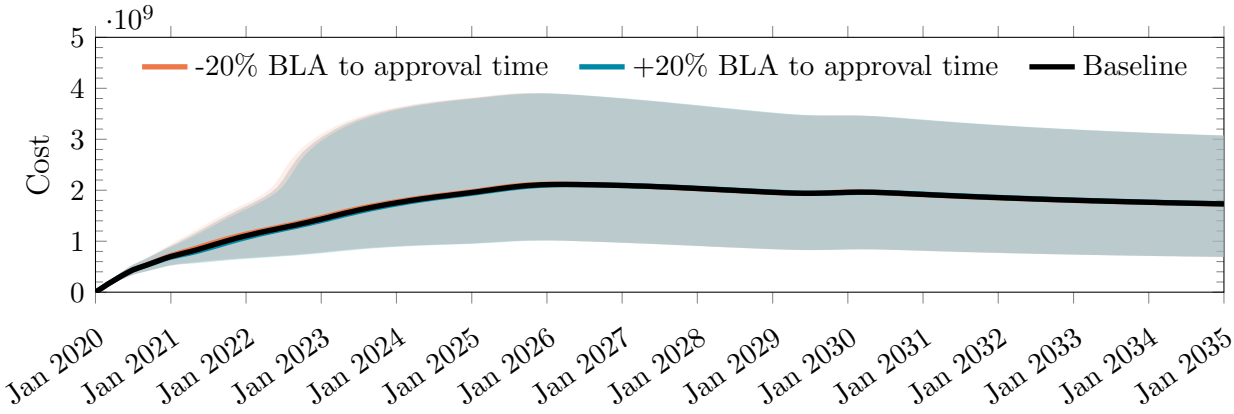

Figure A4: Impact on monthly cost of treating patients given a ±20% change in the time from BLA to approval.

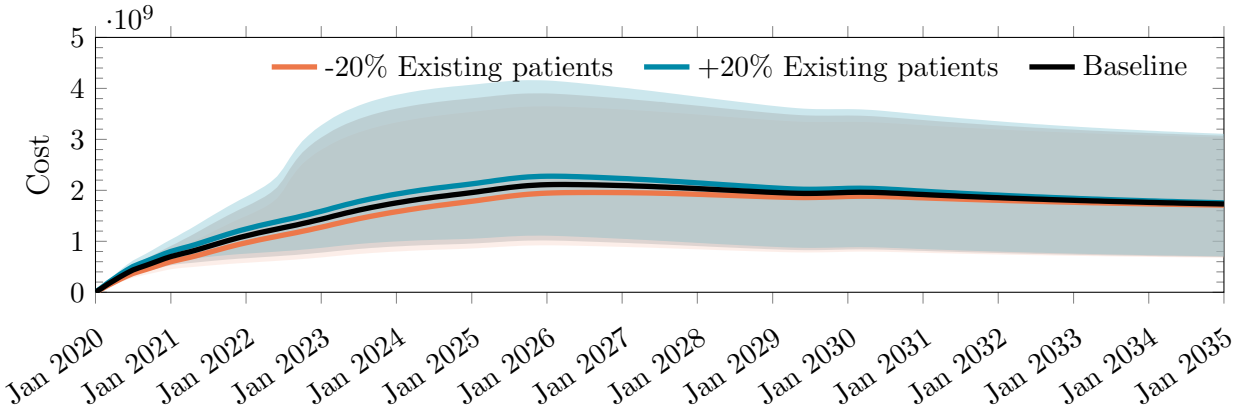

Figure A5: Impact on monthly cost of treating patients given a ±20% change in the number of existing patients.

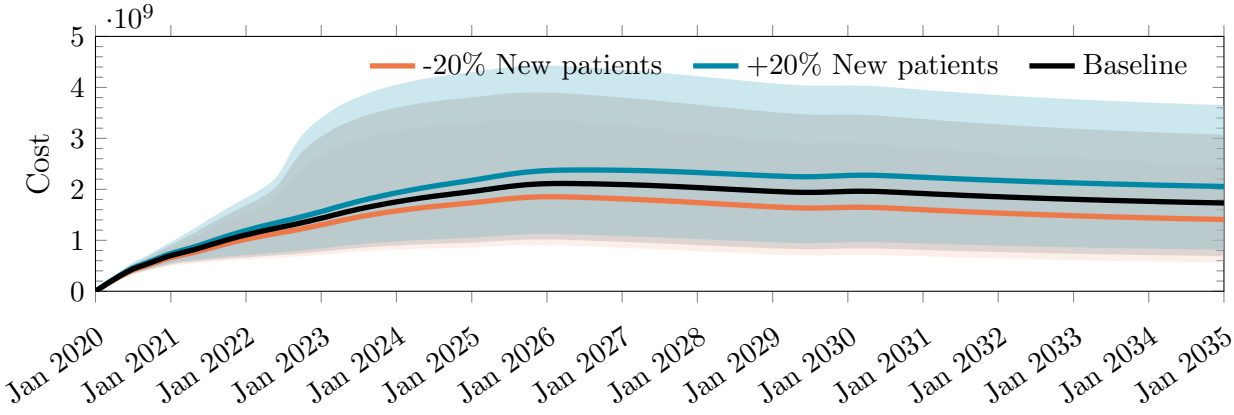

Figure A6: Impact on monthly cost of treating patients given a ±20% change in the number of new patients.

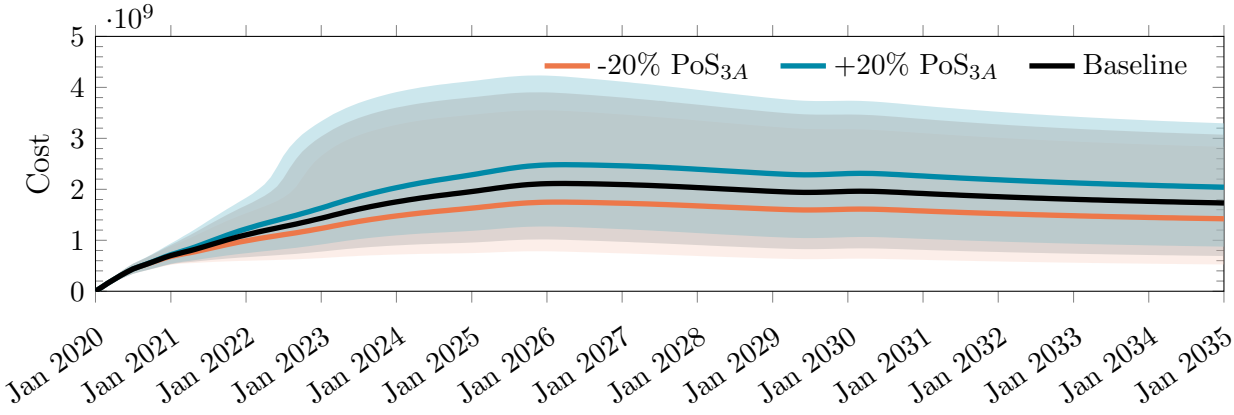

Figure A7: Impact on monthly cost of treating patients given a ±20% change in the PoS_{3A}.

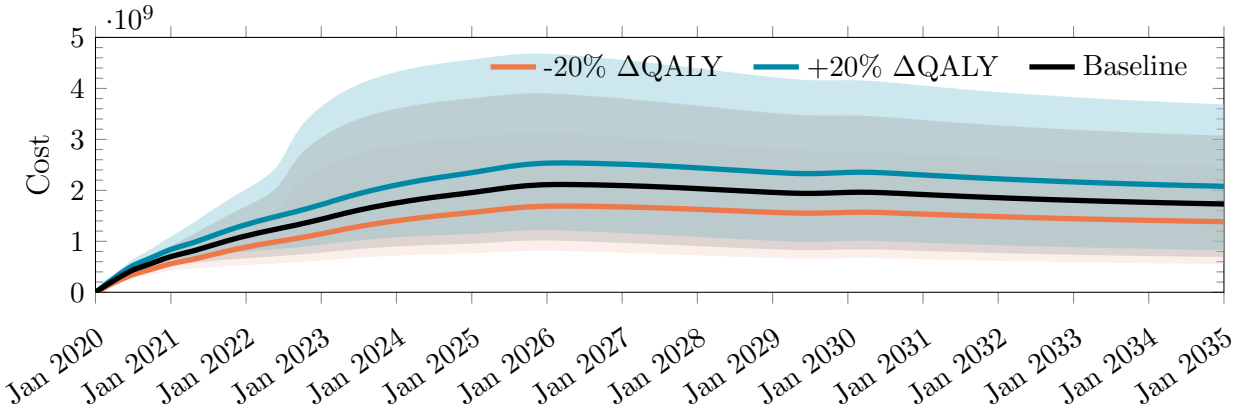

Figure A8: Impact on monthly cost of treating patients given a ±20% change in ΔQALY gained.

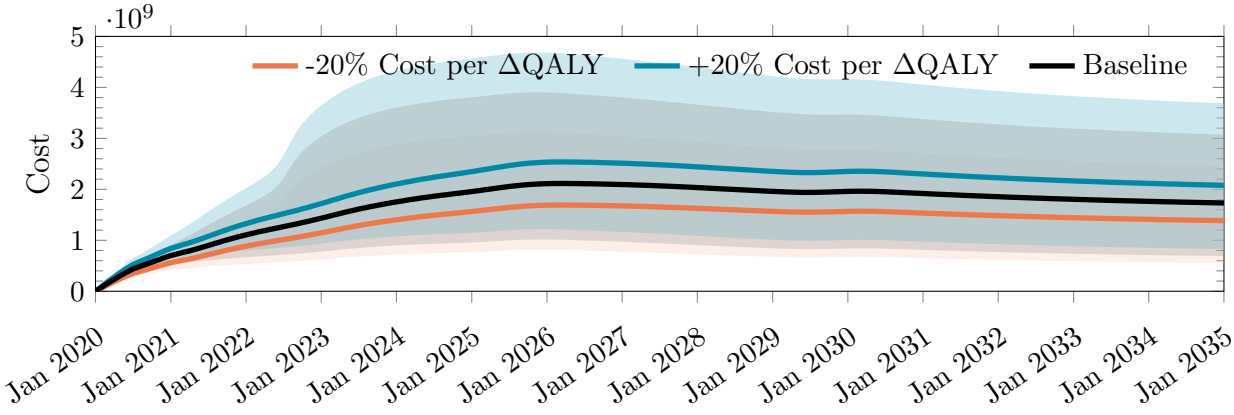

Figure A9: Impact on monthly cost of treating patients given a ±20% change in the cost per ΔQALY.

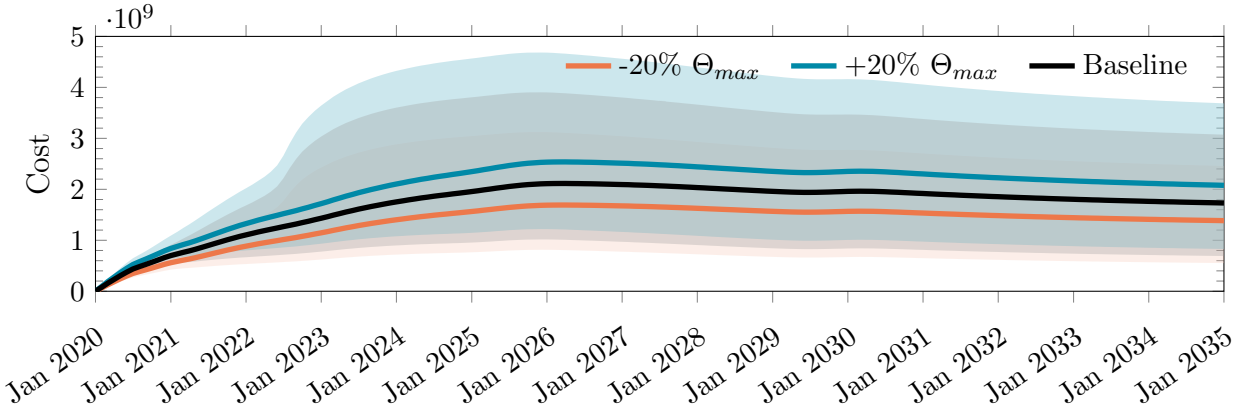

Figure A10: Impact on monthly cost of treating patients given a ±20% change in Θ_{max}.

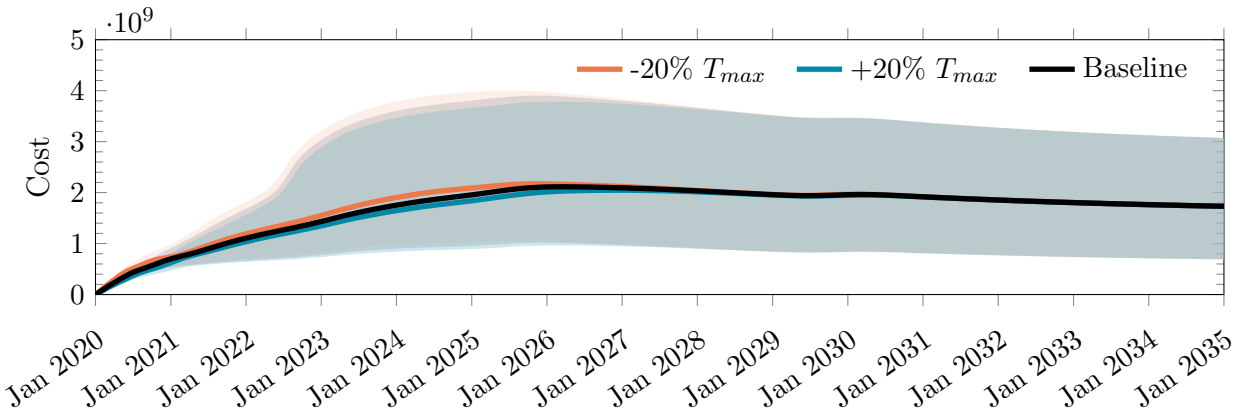

Figure A11: Impact on monthly cost of treating patients given a ±20% change in T_{max}.