Evaluating the Economic Burden: Lifetime Direct and Indirect Costs of Managing Alpha-1 Antitrypsin Deficiency for Patients with the Pi*ZZ Genotype Receiving Augmentation Therapy in the United States

John J. Ko[1], Ryan A. Babakhani[1], Charlie Strange[2], Marc Miravitlles[3], Mark L. Brantly[4], Darrin Benjumea[5], Quan V. Doan[5], Frank Cinfio[5]

[1]Beam Therapeutics, Cambridge, MA, United States; [2]Medical University of South Carolina, Charleston, SC, United States; [3]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]University of Florida Health Science Center, Gainesville, FL, United States; [5]Genesis Research Group, Hoboken, NJ, United States

Background

- Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that predisposes patients to severe lung diseases, including emphysema and bronchiectasis.[1]
- The Pi*ZZ genotype is the most common cause of severe AATD, often requiring long-term alpha-1 protease inhibitor (A1PI) therapy (augmentation therapy) and, in advanced stages, lung transplantation.[2]
- This study quantified the lifetime direct costs of managing AATD in the U.S. from a commercial payer perspective and provided an optional estimate of indirect costs from a societal perspective.

Objective

- To develop an economic model to estimate the lifetime cost of AATD patients (Pi*ZZ genotype) in the United States (U.S.).

Methods

- A cohort-level Markov model simulated healthcare resource utilization and costs from diagnosis (age 55) until death in the base case scenario.
- The model used a one-year cycle length, a lifetime horizon from diagnosis to death, a U.S. commercial payer perspective, and applied a 3% annual discount rate to account for the time value of money.
- The three health states modeled were: 1) Alive on augmentation therapy: patients receiving augmentation therapy. 2) Post-lung transplant: patients transitioned to post-transplant care with no augmentation therapy. 3) Death: absorbing state; no further costs accrued.
- Direct costs included hospitalizations, outpatient visits, and medications, while indirect costs accounted for productivity losses, activity impairment, and early retirement (8.9 years earlier than the general population).
- Sensitivity analyses were conducted around key clinical and demographic features, including age at diagnosis (45 or 55 years), number of Prolastin-C vials per week (5 or 6), and mortality relative risk (MRR) (1.91 or 3.20), to assess their impact on lifetime costs.

Figure 1. Model Diagram

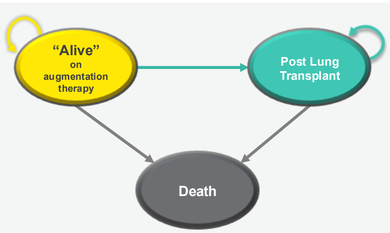


Table 1. Model Inputs

Key Parameters	Input Details
Hospitalization Costs	The costs associated with hospitalization (categorized by age groups: 18-44, 45-59, 60+) were obtained from Aggarwal et al.[3] The mean # of hospitalizations/year was applied to the age-specific hospitalization cost.[4]
Cost Inflation	All costs in the model were inflated to reflect current-day (2024) values: Consumer Price Index (CPI).[5]
Physician and Emergency Room Visit Costs	The costs per visit were retrieved from the CMS Physician Fee Schedule 2024 using CPT codes.[6] An adjustment factor (143%) was applied to the Medicare cost to convert to a commercial payer perspective.[7]
Augmentation Therapy Cost	It was assumed that all Pi*ZZ patients received augmentation therapy (Prolastin-C used since it has highest market share). The Wholesale Acquisition Cost (WAC) was $590 per 1,000 mg vial.[8] Prolastin-C is administered at a dosage of 60 mg/kg once weekly.[9] Average body weight for a patient was set to 85.4 kg.[10]
Other Therapy Costs	Other prescription drug costs incorporated overall expenses of non-augmentation drugs (inhalers, antibiotics, O2, etc.) annually.[11]
Testing Costs	Testing costs (labs) and monitoring costs (physician fee costs) were retrieved from the CMS Physician Fee Schedule 2024 using CPT codes (applied 143% adjustment for commercial payer perspective). The monitoring tests—liver function test, pulmonary function test, liver ultrasound, international normalized ratio (INR), and CT scan were referenced from Sandhaus et al.[12] Based on KOL recommendations, utilization for the kidney function test, complete blood count (CBC), Fibroscan, diffusion capacity test, and the 6-minute walk test were assumed in the model.
Lung Transplantation & Post-Transplant	The total cost of a lung transplant ($705,924) is distributed among the proportion of patients undergoing transplants in each cycle.[13,14] During the post-transplant year, patients accrued 7.2% of the total cost ($50,826), followed by an accumulation of 2.7% ($19,060) until death.[15]
Indirect Costs	The model incorporates indirect costs, including early retirement (8.9 yrs)[16], work productivity loss, and unpaid labor loss. Work impairment determines work productivity loss and activity impairment determines the unpaid labor loss.[17]

Results

- The lifetime direct costs for individuals with the Pi*ZZ genotype (base case: diagnosed at 55 years old):
  - Undiscounted direct cost = $4,108,085
  - Discounted direct cost = $2,979,108
- The lifetime indirect costs for these patients were:
  - Undiscounted indirect cost = $1,296,517
  - Discounted indirect cost = $1,023,897
- Total lifetime costs (direct + indirect) equaled:
  - Undiscounted total cost = $5,404,602
  - Discounted total cost = $4,003,005
- Augmentation therapy for Pi*ZZ genotype patients constitutes the largest portion of these costs, contributing approximately 73.63% to the total.
- Factors such as the average weight of patients, 85.4 kg, and the number of vials required for therapy administration, 5 vials, are considered when calculating costs. Hospitalizations, accounting for about 19.29% of the total, show another significant aspect of the financial burden associated with managing this condition.

Table 2. Cumulative Lifetime Cost Results by Category

Lifetime Costs	Undiscounted	Discounted
Alive - AATD	$4,084,327	$2,960,293
Lung transplantation*	$17,881	$14,875
Post lung transplant	$5,877	$3,940
Total direct cost	**$4,108,085**	**$2,979,108**
Cost of early retirement	$648,645	$571,986
Work productivity loss	$2,375	$2,375
Unpaid labor hours	$645,497	$449,536
Total indirect (societal) cost	**$1,296,517**	**$1,023,897**
Total lifetime cost (direct + indirect costs)	**$5,404,602**	**$4,003,005**

*Lung transplantation is a high-cost procedure; however, the average lifetime cost reflects its low probability in the cohort-based model in which only 0.2% of subjects receive this procedure.[14] The value represents an expected per-patient cost averaged across the full modeled Pi*ZZ population.

Table 3. Annual Costs and Healthcare Resource Utilization (HCRU)

Cost Category	Annual HCRU	Unit Cost	Annual Cost	% of Total
Cost of hospitalization (age: 45-59)	0.6	$67,213	$40,328	19.29%
Primary physician visit	3.1	$80	$247	0.12%
Specialist visit	2.9	$254	$736	0.35%
Emergency department visit	1.6	$243	$390	0.19%
Augmentation therapy* (drug)	261	$590	$153,927	73.63%
Augmentation therapy (infusion)	52.2	$89	$4,669	2.23%
Other drugs	1	$7,320	$7,320	3.50%
Oxygen therapy	6.3	$147	$921	0.44%
Pulmonary function test	1	$118	$118	0.06%
Liver function test	1	$12	$12	0.01%
Liver ultrasound	1	$152	$152	0.07%
International normalized ratio	1	$16	$16	0.01%
CT scan (post-baseline scan)	0	$283	$0	0.00%
Kidney function test	1	$12	$12	0.01%
Complete blood count	1	$9	$9	0.00%
Fibroscan	0.5	$147	$73	0.04%
Diffusion capacity test	1	$80	$80	0.04%
6-minute walk test	1	$48	$48	0.02%
Alive - AATD (Annual Total Cost)			**$209,057**	**100.00%**
Alive - AATD (Annual Total Cost w/o Hospitalization or Augmentation Therapy)			**$10,133**	**4.85%**

*Prolastin-C 1,000 mg vial; the wholesale acquisition cost (WAC) was updated on 1/1/2025. $570 per 1,000 mg vial to $590 per 1,000 mg vial

Figure 2. Cumulative Total Lifetime Costs (Direct + Indirect)

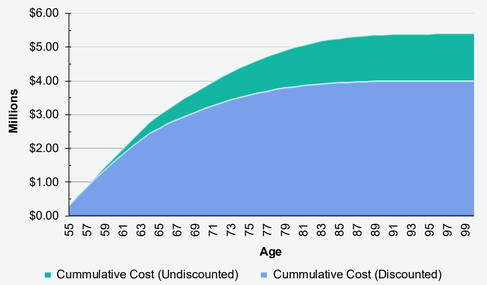


Figure 3. Health State Membership

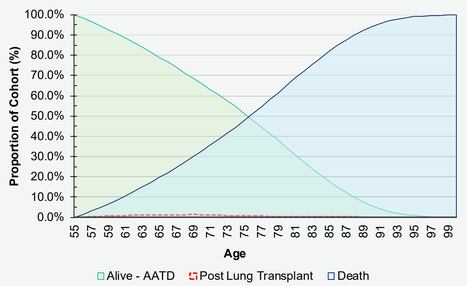
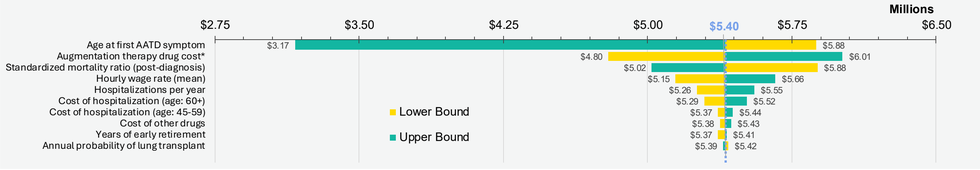


Figure 4. One-Way Sensitivity Analysis (± 20%) on Undiscounted Lifetime Cost



*Drug cost is a function of dose × weight × unit cost; only the overall drug cost for augmentation therapy is shown for simplicity.

Assumptions

- Patients remain on augmentation therapy (Prolastin-C) until they undergo a lung transplant or die. Augmentation therapy is discontinued after transplantation.
- The model primarily adopts a commercial payer perspective for direct costs but also includes indirect costs from a societal perspective.
- Annual rates of hospitalizations, outpatient visits, testing, and medication use (sourced from literature and physician feedback) remain constant over time.
- The annual probability of lung transplantation is based on fixed rates applied to eligible patients.
- Patients aged 70 or older are ineligible for lung transplants in the model.
- Mortality was modeled by applying a standardized mortality ratio (SMR) of 1.91 to age-specific mortality rates from US life tables. This SMR functions as a mortality relative risk (MRR) to reflect elevated mortality risk among patients with AATD.

Limitations

- Costs/health resource utilization data are based on the U.S. and may not reflect practices/costs in other regions.
- Variability in individual patient characteristics (e.g., disease severity, comorbidities) is not explicitly modeled.
- Augmentation therapy is assumed to stop after transplantation, but some patients may continue therapy post-transplant in real-world settings.
- The impact of comorbid conditions unrelated to AATD, such as cardiovascular disease, is excluded.
- Annual health resource utilization is assumed to remain constant over a patient's lifetime, which may not reflect disease progression or changes in treatment guidelines.
- Mortality risks are derived from generalized standardized mortality ratios, which may not fully capture variability in survival outcomes.

Table 4. Results of Base Case and Scenario Analysis

Scenario	# Vials of Prolastin-C/ Week	Age of Diagnosis	Mortality (MRR)	Undiscounted			Discounted*
				Direct Cost	Indirect Cost	Total	Total
Base case	5	55	1.91	$4,108,085	$1,296,517	**$5,404,602**	**$4,003,005**
Earlier age of diagnosis	5	**45**	1.91	$5,639,449	$1,679,341	**$7,318,790**	**$4,866,394**
6 Vials	**6**	55	1.91	$4,717,050	$1,296,517	**$6,013,567**	**$4,443,830**
Higher mortality relative risk	5	55	**3.20**	$3,235,162	$1,104,395	**$4,339,557**	**$3,383,248**
Earlier age of diagnosis, 6 vials	**6**	**45**	1.91	$6,470,786	$1,679,341	**$8,150,127**	**$5,414,097**

*: Discounted costs represent costs adjusted to account for the changing value of money over time. A 3% discount rate is applied to reflect how money available today is considered more valuable than in the future.
MRR = mortality relative risk (relative risk of death compared to the general population; MRR above 1 indicates a higher risk of death relative to the general population. MRR of 1.91 and 3.2 were sourced from Mostafavi et al 2019 and Tanash et al 2017, respectively)

Conclusions

- The economic and clinical burden of Pi*ZZ genotype is substantial with lifetime total costs reaching $5.4M (undiscounted) or $4.0M (discounted).
- Hospital stays often occur due to complications or exacerbations related to respiratory or liver issues commonly seen in individuals with AATD.
- Targeted therapies offer the potential to offset some of the direct and indirect costs associated with AATD.
- Comprehensive clinical and economic evaluations remain critical to inform healthcare decisions and policy interventions for individuals affected by AATD.

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