The impact of varying the target population on the outcome of a cost-effectiveness analysis: Hemophilia B as an exemplary disease

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BACKGROUND

AAV-mediated gene therapy is a promising new treatment for hemophilia B patients. In contrast with the standard treatments that rely on replacing the missing clotting factor, either on-demand or by regular prophylactic infusions, gene therapy provides endogenous factor production long-term after a single infusion. Patients who have factor inhibitors or neutralizing AAV-antibodies are mostly not eligible to receive gene therapy and are thus often excluded from cost-effectiveness analyses.

OBJECTIVES

Our study examined the cost-effectiveness of gene therapy compared to alternative treatments in two target populations, the Gene Therapy-eligible cohort versus the total hemophilia B population.

METHODS

We constructed a microsimulation Markov model with the following characteristics:

- **Time horizon:** Lifetime horizon.
- **Perspective:** Societal perspective in the United States.
- **Intervention and comparator:** Six treatment approaches were compared: three different strategies – on-demand treatment, prophylaxis, and gene therapy - first two were administered with either standard (SHL) or extended half-life (EHL) factor replacement. For gene therapy, each factor replacement regimen was used prophylactically before gene therapy infusion and after the gene therapy effect waned. Gene Therapy–SHL was selected as reference approach for comparison with all other alternatives.
- **Patient population:** Our population-based analysis was conducted using two cohorts: a Gene Therapy-eligible cohort and all patients, inclusive of gene therapy ineligible patients.
- **Gene therapy ineligible population:** Factor IX inhibitors: 4.9%, AAV8 antibodies: 50%
- **Gene therapy price:** $2,000,000/patient
- **Gene therapy effectiveness:** 34 IU/dL post-infusion with 1 IU/dL decrement per year, switching back to prophylaxis at 3 IU/dL. Meaning, no bleeding episodes 0-9 years after infusion, incremental bleeding episodes 9-30 years, and switch back to prophylaxis at 31 years post-infusion.
- **Age at infusing gene therapy:** 18 years of age.
- **Discounting:** An annual discounting rate of 3% was applied.
- **Model input parameters:** Utilities and transition probabilities were obtained from the literature, micro-costing exercise was conducted to estimate the costs associated with each arm.
- **Cost effectiveness threshold:** $150,000/Quality adjusted life year (QALY).

RESULTS

In all scenarios, the reference intervention (Gene therapy preceded and followed by SHL prophylaxis) was either dominant or cost-effective compared to the five alternative treatment approaches. However, when the whole hemophilia population was included in the analysis, rather than the gene therapy eligible group only, the reference treatment intervention switched from being dominant to cost-effective with incremental cost-effectiveness ratio (ICER) of $40,000 and $90,000 when compared to on-demand treatment with SHL and EHL, respectively.

Population	Outcomes	On-demand		Prophylaxis		Gene Therapy	
		SHL	EHL	SHL	EHL	SHL	EHL
Gene therapy eligible group only	Costs	$8,110,000	$7,440,000	$10,060,000	$16,690,000	$6,390,000	$9,730,000
	QALYs	13.80	14.26	23.35	24.14	24.38	24.94
	Gene ICER						
All hemophilia B patients	Costs	$8,200,000	$7,690,000	$11,190,000	$18,500,000	$8,580,000	$14,020,000
	QALYs	13.80	14.26	23.07	23.56	23.81	24.04
	Gene ICER						

QALYs: Quality adjusted life years,
ICER: Incremental cost-effectiveness ratio .

	Reference intervention compared to all other alternatives.
	Dominant, reference is cheaper and more effective.
	Cost-effective, reference is more expensive yet more effective.
	Cost-effective, reference is less effective yet much cheaper.

CONCLUSIONS

By taking a population-based approach and including both eligible and ineligible GT patients, we identified additional aspects for policy makers to consider. There is added value in exploring the impact of different inclusion and exclusion criteria when choosing the target population in a cost-effectiveness analysis.