Economic Modeling Considerations for Rare Neurodegenerative Diseases of Infancy and Early Childhood

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BACKGROUND

- Innovations in regenerative therapies in the past decade have provided much-needed treatment options for rare neurodegenerative diseases of infancy and early childhood that were once considered untreatable.
- Challenges in evaluating regenerative therapies and other treatments for rare, neurological diseases using cost-effectiveness analyses (CEAs) have been reported widely.[1-3]
- Establishing best practices for quantifying disease burden and long-term value of new therapies is critical to ensure access of potentially life-changing therapies among infants and young children affected by rare neurodegenerative diseases.

OBJECTIVES

1. Review model structures and methods utilized in selected CEAs of new treatment options in rare neurodegenerative diseases of infancy and early childhood
2. Summarize key considerations when selecting a model structure

METHODS

- A targeted search and review were conducted to summarize approaches used in CEAs for treatments for rare neurodegenerative diseases in infancy and early childhood.
- The search strategy was specified to identify published CEAs, cost-effectiveness models evaluated by the National Institute for Health and Care Excellence (NICE), and cost-effectiveness models published by the United States Institute for Clinical and Economic Review (ICER) in the past 5 years.

RESULTS

- 6 economic evaluations were selected across 5 rare neurodegenerative diseases of infancy and early childhood: spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), neuronal ceroid lipofuscinosis 2 (CLN2), metachromatic leukodystrophy (MLD), and Pompe disease.
- Table 1 summarizes the reviewed cost-effectiveness models.

Key Model Design Considerations

- All 6 evaluations utilized cohort-based models with a lifetime time horizon.
- Key outcomes incorporated include: patients' survival (6/6), ventilatory status (5/6), motor milestones (6/6), and additional developmental milestones such as cognitive functioning or language development (2/6).
- Model structure considerations were based on anticipated treatment efficacy.
  - Multistate Markov models were used commonly when efficacy was anticipated to delay or halt progression.[4-7]
  - Transition probabilities among patients treated with a novel therapy were estimated using hazard ratios relative to the untreated population[4,7] or following some type of stabilization assumptions.[5,6]
  - Alternative methods were most often used when treatment effects were expected to improve patients' motor/cognitive development and disease trajectory.[8,9]
- Flexibility to vary baseline patient severity based on the natural history of the disease may also be a consideration when selecting an appropriate model structure.[5]

Key Challenges and Data Gaps Reported in Reviewed Models

- A lack of long-term efficacy and survival data was identified as a key area of uncertainty ("treatment durability").
- Across all 6 models, data on costs and utility weights associated with health states were limited, with 3 studies relying on a vignette study to elicit utility values.
  - The majority of reviewed studies incorporated the impact on indirect costs to patients and/or caregivers (5/6) and caregiver disutility (3/6).

Table 1. Summary of Reviewed Cost-effectiveness Models

Study	Disease area	Model type	Health states	Motor functioning	Cognitive functioning	Language	Ventilatory status	Survival	Time horizon	Method of long-term extrapolation	Supported by expert opinion	Utility	Societal Considerations
Malone et al.,[8]	SMA	Markov multistate cure cohort model	Motor milestones, permanent ventilation, and death	X			X	X	Lifetime	Survival curves based on proxy disease	X	PedsQL mapped to EQ-5D-Y	
ICER[9]	SMA	2-stage (short-term and long-term extrapolation) cohort model	Motor milestones, permanent ventilation, and death	X			X	X	Lifetime	Conditional on health states at end of trial period (motor function milestones achieved at the end of follow-up were sustained until death)	X	Primarily EU-based cross sectional study of individuals with SMA parent-/proxy-assessed EQ-5D	Productivity loss considered for patients in a scenario
Landfelt et al.[4]	DMD	3 individual Markov cohort models (DMDSAT, ambulatory status, ventilation status)	Varies; all models include permanent ventilation and death	X			X	X	Lifetime	Hypothetical relative reduction in linear progression for SOC (25% reduction efficacy)	X	Patient: Proxy-assessed HUI Caregiver: EQ 5D-3L	Disutility and productivity loss considered for patients and caregivers in a scenario
NICE[5]	CLN2	Markov cohort Model	CLN2 clinical rating scale (6-0), vision loss, palliative care, and death	X		X	X	X	Lifetime	Assumption of no further decline (stabilization) after 96 weeks	X	Vignettes (completed by 8 clinical experts using EQ-5D-5L)	Caregiver and sibling disutility incorporated in base case; productivity loss for family caregivers considered in scenario
NICE[6]	MLD	7-state Markov model based on partitioned survival curves	Motor milestones based on GMFC-MLD stages and death	X	X			X	Lifetime	Long-term durability of efficacy of similar therapies shown in previous studies (remain event free)	X	Vignette and TTO utility study of the general public	Caregiver disutility incorporated in base case
Richardson et al.[7]	Pompe disease	State transition microsimulation model	No symptoms, mild, moderate, severe, died from Pompe disease, and died from other causes	X			X	X	Lifetime	Estimated treatment effectiveness relative to untreated population	X	TTO survey of nationally representative, community-based sample	Productivity loss for patients and caregivers included in scenario

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DMDSAT = Duchenne muscular dystrophy functional ability self-assessment tool; EU = European Union; GMFC = gross motor function classification; HUI = Health Utilities Index; PedsQL = Pediatric Quality of Life Inventory; SOC = standard of care; TTO = time tradeoff.

CONCLUSIONS

- This review identified challenges in modeling comprehensive, clinically important aspects of health outcomes in CEAs of treatments for rare pediatric neurodegenerative diseases.
- Outcomes beyond motor milestones were rarely modeled despite the fact that social, cognitive, and emotional domains are key domains in major developmental assessment tools.
- Further research should strive to establish methods for assessing the effects of improving multidimensional aspects of developmental outcomes.

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