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Estimating health state utilities (HSUs) for aromatic L-amino acid decarboxylase deficiency (AADCd) in the United States

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Background & Objective:

- Aromatic L-amino acid decarboxylase deficiency (AADCd) is an ultra-rare neurometabolic disorder with infantile onset.[1]
- Patients have motor dysfunction and severe developmental delays that substantially impact their ability to be independent, with the most severe patients potentially being bedridden and having a higher risk of mortality.[2,3]
- Determination of health state utilities (HSUs), which indicate an individual's preferences for different health states, is needed for assessing the value of new treatments for AADCd.
- Estimation of HSUs in pediatric rare disease populations such as AADCd is challenging, given:
  1. The impossibility of directly and reliably asking patients with AADCd, who may be very young and severely impacted, to complete health surveys to evaluate their quality of life.
  2. The difficulty of capturing sufficient health-related quality of life (HRQoL) data for individuals in all states of the disease due to its rarity.
- Time-trade-off (TTO) vignettes (a methodology recommended by the National Institute for Health and Care Excellence[4]) may be used to elicit HSUs in AADCd given these limitations.

This study aimed to estimate AADCd HSUs in the United States (US).

Methods:

Defining health states

- For the TTO valuation method, the following approach was taken:
  - Vignettes for five AADCd health states (**Table 1**) previously developed by Hanbury et al.[5] were revised based on: 1) published literature;[5-7] and 2) in-depth interviews with health care providers (HCPs) and caregivers. The revision aimed to better describe the impact of AADCd on quality of life and ensure face and content validity of the vignette.
  - Key revisions to the health state vignettes included (refer to **Supplementary Materials** for full list of revisions):
    - Addition of four domains (daily activities, leisure activities, social interactions, pain and discomfort) to the health state vignettes
    - Shifting the framing of the health state valuation from a parent/carer perspective to a child perspective.
  - To capture the disutility of a feeding tube, an additional health state was created (Health State 6: Full head control without feeding tube) by removing language around feeding tube from Health State 2 (Full head control).
    - This Health State served as the base/reference health state for estimation of disutility of feeding tube in Health State 2.
  - Qualitative interviews were conducted with 5 HCPs with experience managing patients with AADCd and 4 caregivers for patients with AADCd for further feedback.

Table 1. Health states definitions

Health state	Health state label	Definition based on motor functioning
1	Bedridden	No motor function
2	Full head control	Patient can sit supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds.
3	Able to sit unaided	Patient is required to sit without support and maintain balance while in sitting position for 30 to 59 seconds.
4	Standing with support	Patient is able to take 2 to 3 alternating steps, either in place or in forward motion, with support around the trunk.
5	Walking with assistance	Patient can walk at 4 to 7 feet with alternating steps, with minimal support.

Increasing level of disease severity

Target population & recruitment

- 120 members of the US general public were recruited through a specialist recruitment agency. Recruitment quotas were set to ensure that the sample was representative of US population demographics based on age, sex, and ethnicity.
- Eligibility criteria:
  - Aged ≥18 years, living in the US as of the study conduct, able to participate in an online video interview using a teleconference software, willing and able to give consent to take part in a 60-minute interview.
  - Those with an acute illness or cognitive impairment that may affect study requirements were not eligible.

Methods continued:

TTO interviews

- Following participants' completion of an online screening survey, informed consent, and background questionnaire, TTO interviews were conducted 1:1 over Zoom.
- The interview procedure involved the following steps:
  1. On a visual analog scale (VAS) of 0-100, with 100 representing full health, participants ranked health states in order of preference.
  2. Participants were then presented with health state vignettes to elicit utilities using TTO. Participants also rated a vignette described as 'dead'.
     - For each health state, participants were asked to choose if they preferred a child being in that health state for 10 years followed by death, or a child being in full health for (10-X) years. Time in full health was varied iteratively according to a standard TTO script until participants considered the choices to be the same (the point of indifference).
     - If participants preferred the state 'dead' instead of living 10 years in a particular health state, they were considered to rate the health state as worse than dead. In such cases, participants were asked to compare between living (10-X) years in full health and then die or living 10 years in full health, followed by 10 years in the valued health state and then die (i.e. lead-time TTO). X was again varied iteratively until the point of indifference was reached.

Data analysis

- Participants' socio-demographic characteristics were summarized descriptively.
- VAS ratings for each vignette were rescaled such that the value for the dead state was fixed at zero and all other values varied between 100 and the worst health state.
- Mean (standard deviation [SD]) TTO utilities were calculated for each health state, and regression models were used to explore potential utility predictors.
- Generalized estimating equation regression models were used to explore potential utility predictors, such as participant's age, sex, parental status and carer experience, as well as to estimate disutility associated with use of feeding tube.

Results:

Finalization of health states vignettes

- Based on feedback from in-depth interviews with HCPs and caregivers, further changes were made to finalize the health state vignettes (**Supplementary Materials**).

Sample population

- Key demographics of the 120 participants who completed the TTO task were:
  - Mean age: 47 years
  - Sex: 50.0% female
  - Race/Ethnicity: 70.0% White, 20.0% Hispanic or Latino
  - Employed full-time: 47.5%
  - College or university qualifications: 81.7%
  - Parent, caregiver, or legal guardian of a child <18 years: 37.5%
- Overall, the study sample was not significantly different compared to US population norms in terms of sex, race, and ethnicity (**Table 2**).
- Six (5.0%) participants who appeared to misunderstand the exercise were excluded. These participants rated the worst health state (i.e., 'Bedridden') as better than or equal to the best health state (i.e., 'Walking with assistance'), and/or rated the best health state as equal to or worse than dead.

HSU estimation

- Each vignette was presented to participants as "*Imagine a 10-year-old child with a severe medical condition*" followed by a description of the characteristics of a child in that particular health state.
- VAS ratings for the health states vignettes ranged from mean (SD) 7.4 (13.1) for the 'Bedridden' health state (i.e., preferred least), to 48.1 (18.2) for the 'Walking with assistance' health state (i.e., preferred most, **Table 3**).
- Overall, TTO utilities were aligned with the ranking of the health states on the VAS scales.
  - Participants preferred health states with less severe symptoms and better motor ability.
- Mean (SD) TTO utilities ranged from -0.258 (0.534) for the 'Bedridden' state to 0.796 (0.235) for 'Walking with assistance' (**Table 3**, **Figure 1**).
- Participants valued the two most severe health states ('Bedridden' and 'Full head control') as worse than dead (i.e., values were below zero). They did not significantly differentiate between these two most severe health states (p=0.158 for TTO utility difference).
- The need for a feeding tube was associated with a disutility of 0.07.

Results continued:

- When potential utility predictors were assessed, male participants were found to assign a higher utility for the most severe health state compared to female participants, and lower utilities for the less severe health states.
  - No other participant characteristics influenced health state valuations.

Table 2. Sample characteristics and US population norms

Characteristic	Study sample (N = 120)	US population
Age, mean (SD; range)	47.0 (15.9; 21.0, 78.0)	
Female sex, n (%)	60 (50.0%)	
Race, n (%)		
White	84 (70.0%)	75.5%[a]
Black or African American	15 (12.5%)	13.6%[a]
Asian or Asian American	7 (5.8%)	6.3%[a]
Mixed Race	7 (5.8%)	3%[a]
Native American and Alaska Native	1 (0.8%)	1.3%[a]
Native Hawaiians and Other Pacific Islander	0 (0%)	0.3%[a]
Other	6.0 (5.0%)	
Employment status		
Employed or self-employed, full-time	57 (47.5%)	
Employed or self-employed, part-time	23 (19.2%)	
Homemaker or full-time carer	11 (9.2%)	
Retired	15 (12.5%)	
Other (including long-term sick leave, seeking work, student)	14 (11.7%)	
Education level		
No formal qualifications	0 (0%)	
High school qualification	14 (11.7%)	
College or university qualifications	98 (81.7%)	
Other (including vocational qualifications or other trade certificates)	8 (6.7%)	
Parent, caregiver, or legal guardian of a child aged under 18 years, n (%)	45 (37.5%)	
Presence of long-term condition, n (%)	65 (54.2%)	
Been a carer for a close friend or relative with a long-term illness or condition, n (%)	69 (57.5%)	
Caregiver for:		
Your partner	12 (10.0%)	
Your child	11 (9.2%)	
Your parent or sibling	44 (36.7%)	
Other	7 (5.8%)	
EQ-5D, mean (SD)	0.809 (0.199)	0.867[b]

Abbreviations: SD, standard deviation; US, United States
[a]Figures based on 2020 data from United States Census Bureau https://www.census.gov/
[b]Based on US population norms in A. Szende et al. (eds.), Self-Reported Population Health: An International Perspective based on EQ-5D, 2014.

Figure 1. Mean (95% CI) TTO utilities (N = 114) with frequency and density distribution

Abbreviations: CI, confidence interval; TTO, time-trade-off
Note: Orange markers indicate the mean TTO utilities, and the error bars indicate 95% CI. Grey bars indicate the frequency distribution, and the shaded area represents the density distribution with Gaussian smoothing function.

Results continued:

Table 3. VAS and TTO utilities for health state vignettes

Health states		VAS (N=113[a,b])	TTO (N=114[a])
HS1: Bedridden	**Mean (SD)**	**7.38 (13.1)**	**-0.258 (0.534)**
	95% CI	4.97, 9.79	-0.356, -0.160
HS2: Full head control	**Mean (SD)**	**11.5 (14.3)**	**-0.155 (0.569)**
	95% CI	8.91, 14.2	-0.259, -0.050
HS3: Able to sit unaided	**Mean (SD)**	**28.0 (18.2)**	**0.452 (0.523)**
	95% CI	24.7, 31.4	0.356, 0.548
HS4: Standing with support	**Mean (SD)**	**40.7 (17.2)**	**0.775 (0.242)**
	95% CI	37.0, 43.3	0.731, 0.819
HS5: Walking with assistance	**Mean (SD)**	**48.1 (18.2)**	**0.796 (0.235)**
	95% CI	44.7, 51.5	0.753, 0.839
HS6: Full head control + without feeding tube	**Mean (SD)**	**11.7 (14.1)**	**-0.081 (0.578)**
	95% CI	9.12, 14.3	-0.187, 0.025

Abbreviations: CI, confidence interval; SD, standard deviation; TTO, time-trade-off; VAS, visual analog scale
[a] Six participants were excluded as they did not understand the task
[b] Data from one participant was excluded as they rated dead as 100 on the VAS scale

Discussion:

- This study reviewed and updated existing vignettes of five health states for AADCd and subsequently implemented TTO methods to estimate utilities for the five health states from the perspective of the US general population.
- The process and findings highlight the importance of 1) developing robust health state vignettes through HCP and caregiver feedback to describe the impact on HRQoL, and 2) using the standard TTO method to elicit utility values that capture the range in burden associated with a disease, especially for diseases with very severe health and quality of life impacts, such as AADCd.
- There is no consensus regarding how best to contextualize child health states for valuation. Previous studies have noted issues with heterogeneity related to how vignettes are framed (e.g., imagine yourself vs imagine a 10-year-old child). This heterogeneity may introduce different sources of bias and potentially impact life-years traded in different ways.[8,9]
- These vignettes aimed to describe the symptoms and impact of AADCd whilst referring to age-specific functioning and ability, (e.g., such as crawling). While child-specific descriptions could be considered a strength of the study, it should be noted this could influence number of life-years traded.

Limitations:

- Vignettes were not able to capture the variability in individuals within a particular health state.
- Lengthy descriptions may make it challenging for participants to consider all aspects of the vignette in the TTO exercise.

Strengths:

- Development of initial health state vignettes was based on multiple sources of evidence and refined iteratively.[5] The content validity of the vignettes is crucial, because the content in large part determines the utility estimates.
- Use of lead-time TTO allowed the utilities of health states considered worse than dead to span between -1 to 0. This allows the perceived burden and severity of AADCd to be captured accurately from the perspective of the members of the general public.

Conclusions:

The utilities generated from this study accurately reflect disease burden and impact of AADCd in different health states. The range of the elicited utilities (-0.258 to 0.796) demonstrates the devastation of the disease when patients are in the most severe condition, and a significant impact on quality of life when their health state is improved. This also suggests that therapies that are able to help patients improve their AADCd will also substantially improve their quality of life.

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