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Developing a Conceptual Framework for a De Novo Cost-effectiveness Model in Sanfilippo Syndrome (MPS IIIA)

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BACKGROUND

- Sanfilippo syndrome type A, or Mucopolysaccharidosis type IIIA (MPS IIIA), is a severe, progressive, genetic disorder that leads to degeneration of the central nervous system. It results in cognitive decline, delayed speech and language development, behavioral and sleep disturbance, and loss of motor function usually leading to death in the second decade (Figure 1).
- Cognitive decline typically begins between ages 2 and 4, following a period of normal development[1,2]. Initially, children may exhibit mild developmental delays, but as the condition progresses, they experience significant intellectual impairment, leading to severe learning difficulties and loss of previously acquired skills. Behavioral and sleep issues often accompany cognitive decline, with many children displaying hyperactivity, aggression, and social withdrawal. As the disease advances, these challenges can intensify, resulting in increased frustration and behavioral problems, which further complicate interactions with caregivers and peers. Ultimately, the combination of cognitive decline and behavioral issues profoundly impacts the child's ability to engage in everyday activities and social relationships.
- The loss of motor function typically begins between ages 6 and 8, following a period of normal early development[3]. As the disease progresses, children may experience a decline in both fine and gross motor skills, leading to clumsiness, coordination difficulties, and an abnormal gait. Joint stiffness and muscle weakness further contribute to mobility challenges, resulting in increased dependence on caregivers for daily activities.
- Many individuals with MPS IIIA do not survive past their teenage years or early adulthood. The average life expectancy is often reported to be in the range of 15 to 20 years.
- Treatment primarily focuses on managing symptoms and enhancing quality of life. Key interventions include physical therapy to maintain mobility, occupational therapy to improve daily living skills, and speech therapy to address communication difficulties. Behavioral issues may be managed through behavioral therapy and psychological support. Nutritional support ensures adequate dietary intake, while medications may be prescribed to alleviate specific symptoms such as anxiety or sleep disturbances. Overall, a multidisciplinary approach is essential for providing comprehensive care to affected individuals and their families.
- Currently, there are no treatments approved for MPS IIIA, but there are several potential enzyme replacement and gene therapies in development headed for health technology assessment.

OBJECTIVE

- The primary objective of this research is to develop and validate a conceptual cost-effectiveness model that captures the progressive nature of MPS IIIA and the potential efficacy of future treatments.

METHODS

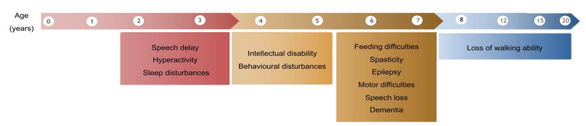
- To inform the model conceptualization, functionality, assumptions and data sources, a targeted literature review was conducted. The review considered epidemiology, clinical trials, new therapies, quality of life, costs, economics, and disease burden in MPS IIIA.
- A de-novo model structure had to be developed because the targeted literature review did not identify any existing model frameworks in MPS IIIA. Therefore, we reviewed economic studies in Duchenne muscular dystrophy, metachromatic leukodystrophy, and sickle cell disease, which share disease attributes with MPS IIIA (e.g., progressive, multi-comorbidities/complications, motor/neuron/cognitive decline, sleep disturbance, and loss of communication).
- Health-state unit costs, resource use, adverse event costs, and health-related quality of life data were identified from a targeted literature review. Publications on the natural history of patients with MPS III were used from various studies to estimate the disease progression over time. In addition, literature on analogue diseases was used to inform the model structure, as well as cost and utility inputs for the model.

RESULTS

PRIOR MODELS

- The targeted literature review did not identify any existing model frameworks in any type of MPS. Therefore, models were reviewed across disease analogues with shared disease attributes, (e.g., progressive, multi comorbidities/complications, motor/neuron/cognitive decline, sleep-disturbance, and loss of communication) that were represented in health states. A brief description of the structure for archetype models for these diseases are provided below.
- The cost-effectiveness model for **Metachromatic Leukodystrophy (MLD)** was developed using an eight-state partitioned survival framework and a Markov structure to simulate disease progression[4].
  - The model is based on the Gross Motor Function Classification scale for MLD, which ranges from normal motor function to complete loss of gross motor function.
  - Cognitive substates were included for one cohort to reflect variability in cognitive and motor decline.
  - Patient treatment responses were categorized into three groups: full responders, partial stable responders, and unstable partial responders.
  - A monthly model cycle was chosen to capture changes in motor function and cognitive decline, especially during rapid deterioration in patients receiving Best Supportive Care (BSC).
- A recent cost-effectiveness model for two gene therapies in **Sickle Cell Disease** includes four health states, eighteen events for acute and chronic complications such as vaso-occlusive crises, acute pain crises, organ damage, stroke, and pulmonary hypertension, and mortality[6].
  - The model considers the frequency and duration of hospitalizations due to these complications and the overall impact on patients' quality of life, including daily activities and mental health.
  - Despite uncertainties regarding long-term outcomes, both gene therapies are estimated to produce substantial gains in length and quality of life.
  - The model uses real-world evidence and links pain crises and hemoglobin levels to acute and chronic conditions, as well as mortality.
  - It incorporates societal effects, such as impacts on productivity and education, informed by patient and caregiver surveys.
- The cost-effectiveness model for **Duchenne Muscular Dystrophy (DMD)** uses a five-state partitioned survival model, consisting of early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory, and death states[7].
  - The model includes direct medical expenses such as drug costs, hospitalizations, outpatient visits, and supportive care, as well as non-medical costs like lost productivity and caregiver burden.
  - Health state utilities for DMD patients were taken from survey data in a prior study, using Health Utility Index values derived from primary caregivers.
  - The model also included caregiver utilities, and we fixed estimates for disutilities associated with adverse events.

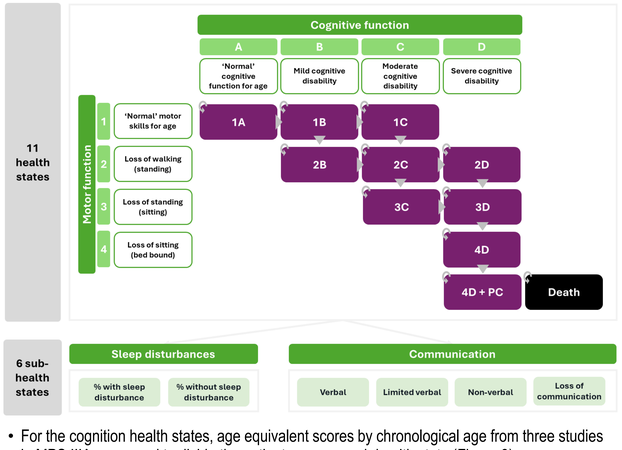
Figure 1: Progressive loss of functional ability in MPS IIIA



MPS IIIA MODEL STRUCTURE

- Based on the targeted literature review and feedback from the clinical/endpoint expert, a de-novo eleven-state Markov model framework encompassing the natural history of MPS IIIA was developed. The framework spanned two domains: **cognition and motor function**, each with four levels of severity (Figure 2). The health states were further defined by two **sleep-**related and four **communication-**related sub-health states. The levels of severity were informed by expert opinion and were linked to specific elements of the Bayley III test, a comprehensive assessment tool used to evaluate developmental progress in children aged 1 to 42 months[8].

Figure 2: Conceptual model framework for MPS IIIA



- For the cognition health states, age equivalent scores by chronological age from three studies in MPS IIIA were used to divide the patients across each health state (Figure 3).
  - Until the age of 24 months all patients have normal cognitive function, as cognitive decline is typically only observed after that age.
  - From 24 months onwards cognitive health states are defined by age equivalent scores (AES) by level. The threshold for each level in the model is based on the standard deviation from the mean (and corresponding development quotient; DQ) and the AES, as follows:
    - ≤-2 SD (DQ: 100-70) is normal cognition
    - 2-3 SD (DQ: 70-55) is mild cognitive impairment
    - 3 SD to 12 months AES is moderate cognitive impairment
    - <12 months AES is severe cognitive impairment
- For the motor function health states, natural history data from various studies was used and converted into Kaplan-Meier (KM) curves (Figure 4)[9, 10-11]. These data were extrapolated over a lifetime horizon through survival analysis and the best-fitting curve was selected. Empiric data from the KM curves was used for follow-up periods and best fitting survival curves were used for post-follow-up period projections. Motor function levels include normal motor skills for age, walking with support, sitting, and loss of sitting. The transition to the latter state is assumed to be the average between the transition to sitting and the transition to death for MPS IIIA.

Figure 3: Natural history of cognitive impairment in patients with MPS IIIA, and the division by health state

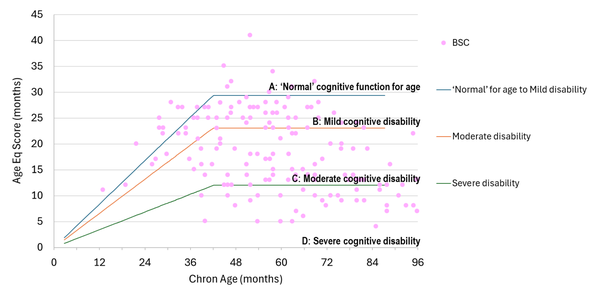
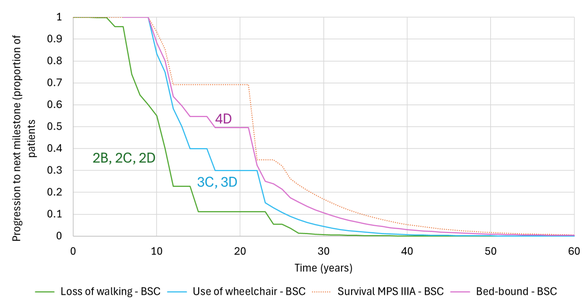


Figure 4: Natural history of motor milestone health states in patients with MPS IIIA



- The communication sub-health states are further divided into verbal, limited verbal, non-verbal, and non-communicative.
- Having sleep disturbances or not, are considered sub-health states and were linked to the age of the patient when the disturbance started. Due to the lack of data, the proportion of patients in each sub-health state are based on assumptions and linked to the main health states.
- For the end-of-life there is a palliative health state and a death state. The transition to the death state is based on overall survival in the general population and in various cohorts of patients with MPS II (Figure 5)[12]. MPS II is considered a good proxy for MPS IIIA, in the absence of health-state specific survival data in the latter indication. Survival analyses have been used to extrapolate KM data from these studies and the best-fitting curves are applied to each health state. The palliative health state is assumed to start one year before death.
- The conceptual cost-effectiveness model framework considers two perspectives: the US healthcare payer for the base case and the US societal perspective for the scenario (Table 1). The targeted population includes patients with MPS IIIA. The model uses a lifetime horizon to capture long-term costs and benefits. The primary intervention considered is disease modifying therapy, compared with BSC.

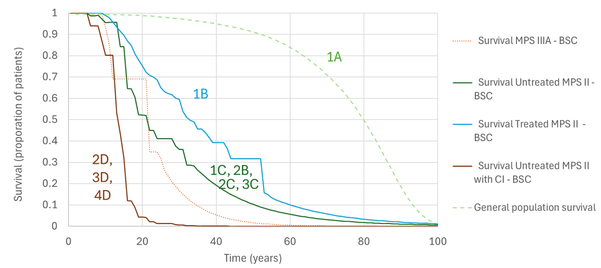
Table 1: Key model elements

Model Elements	Description
Perspective	• US healthcare payer (base case) • US societal (scenario)
Population	• MPS IIIA patients (Sanfilippo Syndrome Type A)
Time Horizon	• Lifetime
Intervention	• Disease modifying therapy
Comparators	• Best supportive care
Utility	• Utility weights by health states for patients and caregivers • Disutility for complications (e.g., sleep disturbances)

Economic and Health Resource Utilizations	• MPS IIIA natural history data
	  ◦ Development of cognitive impairment, speech loss, mobility/motor skills, sleep disturbances, and communication
	  ◦ (Clinical study) data on transition states and length of time in health states by comparator
	  ◦ Probability of survival by health state (and/or age)
	• Costs of treatment
	• Healthcare costs
	  ◦ Physician visits
	  ◦ Physical therapy visits
	  ◦ Speech therapy visits
	  ◦ Surgeries
	  ◦ Support services
	  ◦ Laboratory/monitoring
	  ◦ Cardiology
	  ◦ Imaging
	  ◦ Sleep-disturbance related costs
	  ◦ Seizure-associated costs
	  ◦ Pain-associated costs
	  ◦ Management of behavioral issues
	• Non-healthcare costs (mobility equipment, special education needs, productivity)
	• Discounting of costs and benefits

Outcomes	• Total costs over the time • Total life years and quality-adjusted life years • Incremental cost-effectiveness ration (ICER) • Probabilistic and deterministic sensitivity analysis • Scenario analyses

Figure 5: Overall survival in patients with MPS II and IIIA, linked to each health state



- Clinical data includes the natural history of MPS IIIA, development of cognitive impairment, speech loss, mobility/motor skills, sleep disturbances, and communication. It also includes clinical study data on transition states and length of time in health states for each comparator, and the probability of survival by health state and/or age.
- Utility weights[13,14,15] by health states for patients and caregivers are considered, along with a disutility for complications such as sleep disturbances. Healthcare resource utilization and costs include treatment costs, healthcare costs, physician visits, physical therapy visits, speech therapy visits, surgeries, support services, laboratory/monitoring, cardiology, imaging, sleep-disturbance related costs, seizure-associated costs, pain-associated costs, management of behavioral issues, and non-healthcare costs such as mobility equipment, special education needs, and lost productivity[16,17]. The model applies discounting to both costs and benefits. Outcomes measured include total costs over time, total life years and quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), probabilistic and deterministic sensitivity analysis, and scenario analyses.

CONCLUSIONS

- **In conclusion, MPS IIIA is a severe, progressive genetic disorder that leads to significant cognitive decline, delayed and declining speech/communication and language development, behavioral and sleep disturbances, and loss of motor function, generally resulting in death in the second decade of life.**
- **The development of a conceptual cost-effectiveness model framework for MPS IIIA is crucial for evaluating the potential value of future treatments.**
- **This de-novo framework was validated by experts and captures the progressive nature of the disease while considering various aspects such as clinical, economic, and quality of life data.**
- **By taking a comprehensive approach, this conceptual framework can be used to evaluate the cost-effectiveness of potential new treatments for MPS IIIA.**

ACKNOWLEDGMENTS

- This study was funded by Ultragenyx Pharmaceutical Inc.
- MS and DG are employees and stockholders of Ultragenyx Pharmaceutical Inc. JK, AJ, and IJ are employees of Precision AQ, which received funding from Ultragenyx.
- We thank Heather Lau and Melissa Wolf for their input and guidance.

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