PCR129

Development of a Conceptual Model & COA Measurement Strategy in Propionic Acidemia / Methylmalonic Acidemia

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BACKGROUND

- Propionic acidemia (PA) and methylmalonic acidemia (MMA) are both ultra-rare, multi-systemic, and primarily pediatric disorders with shared clinical signs and symptoms, which confer a significant morbidity and mortality, and impact numerous organ systems in a heterogeneous manner (Baumgartner et al, 2014; Haijes et al, 2019; Schelechkov et al, 2012; Zhou et al, 2018; Forny et al, 2021).
- For both PA and MMA, the symptomatology is complex and the burden of the disease is not captured fully by existing endpoints or validated clinical outcome assessment (COA) instruments.

OBJECTIVES

- To develop a conceptual model in PA and MMA.
- To evaluate potential COA measures as fit-for-purpose (FFP) for PA/MMA clinical trials.

METHODS

- Concept elicitation interviews were conducted following a semi-structured interview guide with patients with PA/MMA and their caregivers. Interviews were conducted in-person as well as via telephone.
- Interviews were audio-recorded and transcribed for analysis. Thematic analysis identified important concepts, including signs/symptoms and health-related quality-of-life (HRQoL) impacts, for patients/caregivers (Joffe & Yardley, 2004; Clarke & Braun, 2013).
- Disease experts provided input into study material development and eligibility criteria. They also helped to contextualize the interview findings, determine the disease-defining aspects of MMA and PA, and offered recommendations for the assessment of specific concepts.
- Potential COAs were assessed for measuring relevant concepts to PA/MMA, by mapping items to the conceptual model.
  - Concepts in the PA/MMA conceptual model were mapped to the MetabQoL 1.0 (Zeltner et al, 2017), PedsQL™ Generic Core Scales (GCS) [covering ages 13 months to 18 years], and Family Impact Module, on a per-item basis. The Cogstate computerized battery, NIH Toolbox Motor Battery, Bayley Scales of Infant and Toddler Development (Bayley™-4) were also assessed for their overall relevance and appropriateness.
  - An FFP assessment was conducted to examine the evidence of content validity, psychometric properties, and other instrument details in the intended context-of-use, as compared to the 2009 FDA Guidance on PRO Labeling Claims (FDA, 2009).

RESULTS

Sample Characteristics

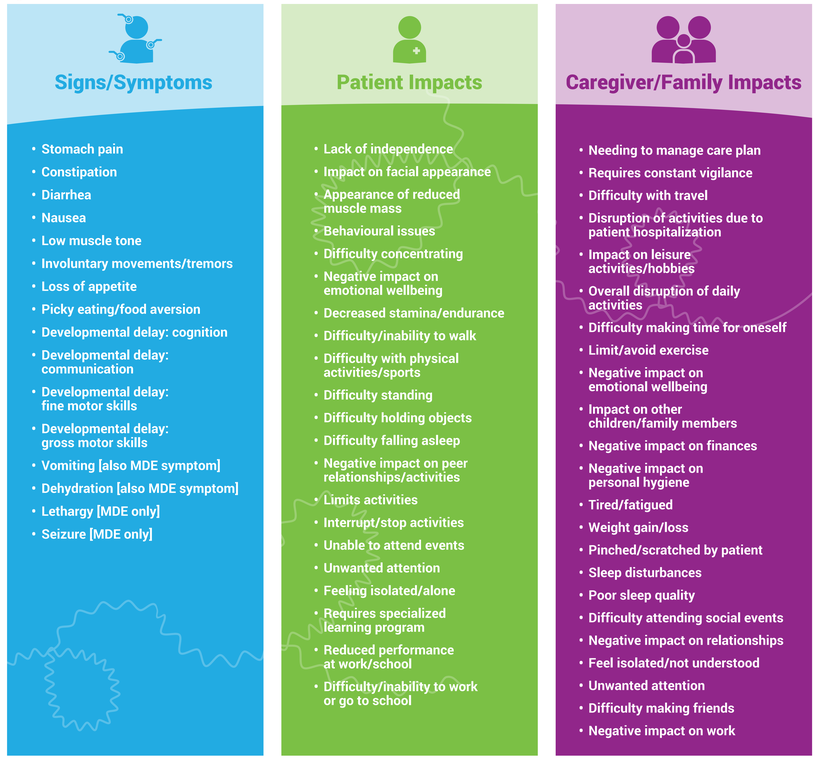
- Twenty-six interviews were conducted in total (caregivers: n=14 PA, n=7 MMA; patients: n=3 PA, n=2 MMA), representing 17 patients ages 0.5-34 years (median 9 years). Eleven (64.7%) of the patients were male.
- A majority of caregivers interviewed were female (n=15, 71.4%), a majority were working full time (n=13, 61.8%) at the time of the interview, and their ages ranged from 25 to 67 years (median 45 years). Approximately half of the caregiver sample had a bachelor's degree or higher (52.4%).
- The four disease experts were clinicians who are metabolic specialists (n=3) treating PA and MMA and a patient advocate (n=1), who is also a mother of a child with PA.

Concept Elicitation

- Signs/symptoms reported most frequently by caregivers included vomiting (n=19, 90.5%), dehydration (n=19, 90.5%), stomach pain (n=16, 76.2%), loss of appetite (n=15, 71.4%), cognitive development delay (n=15, 71.4%), communication development delay (n=15, 71.4%), constipation (n=15, 71.4%), diarrhea (n=13, 61.9%), picky eating/food aversion (n=13, 61.9%), breathing issues (n=12, 57.1%), nausea (n=11, 52.4%), fine motor development delay (n=11, 52.4%), low muscle tone (n=11, 52.4%), and involuntary movements/tremors (n=11, 52.4%).
- In discussing metabolic crises, all caregivers reported hospitalizations (n=21, 100.0%), and many reported increased susceptibility to infections (n=15, 71.4%), seizures (n=13, 61.9%), and coma (n=13, 61.9%). Other signs/symptoms associated with metabolic crises included prolonged vomiting (n=11, 52.4%), weight loss (n=11, 52.4%), and lethargy (n=10, 47.6%).
- HRQoL impacts included requiring specialized learning programs at school (n=19, 90.5%), impacts on peer relationships (n=18, 85.7%), negative emotional impacts (n=16, 76.2%), decreased stamina/endurance (n=15, 71.4%), limits on activities/sports (n=13, 61.9%), and sleep disturbances (n=11, 52.4%).
- Impacts on caregivers/family included needing to manage the care plan for their child (n=21, 100%), negative impact on emotional well-being (n=19, 90.5%), and difficulty attending social events (n=14, 66.7%).
- With additional input from the four disease experts, a conceptual model was developed for PA and MMA (**Figure 1**).

RESULTS (*cont'd*)

Figure 1: PA and MMA Conceptual Model



Gap Analysis

- The Cogstate, NIH Toolbox Motor Battery, and Bayley™-4 were determined to be FFP for measuring cognitive and/or motor function (depending on age of patient) [**Table 1**].
  - However, it should be noted that ages 3.5-4 years are not covered by these measures. Also, PA- or MMA-specific measures of these concepts were not identified.
- The MetabQoL 1.0, which was developed for patients with intoxication-type inborn errors of metabolism, captures nausea and items associated with loss of appetite, but does not include other key symptoms as reported by patients, caregivers, and/or clinical experts in the qualitative study. Other limitations include:
  - It was developed for ages 8 and older, so concepts relevant to patients < 8 years old may not be captured.
  - The proxy-report version asks caregivers to assess the extent to which the different items bother their child, a concept which is not always directly observable.
  - The recall period of "usual health" or over the past year would likely be challenged by a regulatory agency as too vague or too long, respectively.
  - The psychometric validation results are limited (in both scope and methodology) and are missing an assessment of key properties required for full validation and interpretation of the instrument's measurement properties including meaningful change.
- As such, there were no FFP COA measures identified which could be used within clinical trials or which would meet regulatory guidelines to measure other core signs/symptoms of PA and MMA.
- The PedsQL™ GCS, specifically, the physical functioning, emotional functioning, social functioning, and school functioning domains mapped closely to HRQoL impacts in the PA/MMA conceptual model (**Table 2**).
  - Additional physical symptom and cognitive functioning items in the infant version did not map to the PA/MMA conceptual model.
- The PedsQL™ Family Impact module also showed good overlap with the PA/MMA conceptual model (**Table 3**).

Table 1: Concept Mapping: Signs/Symptoms

Signs/Symptoms	Bayley™-4 16 days-42 months	NIH Toolbox Motor Battery 4+ years	Cogstate 4+ years	MetabQoL 1.0 Ages 8-18
Developmental delay: cognition	X		X	X
Developmental delay: communication	X		X	
Developmental delay: fine motor skills	X	X		
Developmental delay: gross motor skills	X	X		
Vomiting				
Dehydration				
Stomach pain				
Constipation				
Diarrhea				
Nausea				X
Low muscle tone				
Involuntary movements/tremors				
Loss of appetite				X
Picky eating/food aversion				
Restricted mobility				

Table 2: Concept Mapping: Patient Impacts

Impacts	PedsQL GCS 13-24 months	2-4 years	5-7 years	8-12 years	13-18 years	MetabQoL 1.0 Ages 8-18
Lack of independence	X (1)	X (1)	X (1)	X (1)	X (1)	
Difficulty concentrating	X (1)	X (1)	X (1)	X (1)	X (1)	X (1)
Negative impact on emotional wellbeing	X (9)	X (4)	X (4)	X (4)	X (4)	X (8)
Decreased stamina/endurance	X (4)	X (1)	X (1)	X (1)	X (1)	X (1)
Difficulty/inability to walk	X (1)	X (1)	X (1)	X (1)	X (1)	X (1)
Difficulty with physical activities/sports	X (1)	X (3)	X (3)	X (3)	X (3)	X (1)
Difficulty falling asleep	X (3)	X (1)	X (1)	X (1)	X (1)	
Peer relationships/activities	X (5)	X (3)	X (3)	X (3)	X (3)	X (2)
Limits activities		X (2)	X (2)	X (2)	X (2)	
Requires specialized learning program		X (1)				X (1)
Miss work/school		X (2)	X (3)	X (3)	X (3)	X (1)
Difficulty/inability to work or go to school						X (1)
Difficulty standing						
Difficulty holding objects						
Interrupt/stop activities						X (1)
Unable to attend events						
Unwanted attention						X (3)
Isolated/alone						X (1)
Reduced performance						X (1)
Behavioral issues						
Impact on facial appearance						
Appearance of reduced muscle mass						
Other	*X (19)*	*X (3)*	*X (3)*	*X (3)*	*X (3)*	*X (5)*

Table 3: Concept Mapping: Caregiver/Family Impacts

Impacts	PedsQL Family Impact Module
Manage care plan	X (2)
Impact on leisure activities/hobbies	X (1)
Overall disruption of daily activities	X (1)
Negative impact on emotional wellbeing	X (10)
Impact on other children/family members	X (5)
Tired/fatigued	X (4)
Difficulty attending social events	X (2)
Feel isolated/not understood	X (2)
Negative impact on work	X (2)
Constant vigilance	
Difficulty with travel	
Disruption of activities due to patient hospitalization	
Difficulty making time for oneself	
Limit/avoid exercise	
Negative impact on finances	
Negative impact on personal hygiene	
Weight gain/loss	
Pinched/scratched by patient	
Sleep disturbances	
Poor sleep quality	
Negative impact on relationships	
Unwanted attention	
Difficulty making friends	
Other	*X (11)*

CONCLUSIONS

- This is the first conceptual model for PA/MMA identifying core concepts of patient/caregiver importance.
- The Cogstate, NIH Toolbox Motor Battery, and Bayley™-4 appropriately measure cognitive and/or motor function impacts in PA/MMA.
- Impacts were broad-ranging and the PedsQL™ GCS and Family Impact modules map appropriately to assess HRQoL in the PA/MMA patients and caregivers, respectively.
- There is a gap in FFP COAs to measure other core signs/symptoms of PA and MMA for use in clinical trials which meet regulatory development guidelines.
- Future research is working to develop and validate a measure of core signs/symptoms in PA/MMA.

ABSTRACT PLAIN LANGUAGE SUMMARY

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REFERENCES

1. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014 Sep 2;9:130. doi: 10.1186/s13023-014-0130-8. PMID: 25205257; PMCID: PMC4180313.
2. Haijes HA, van Hasselt PM, Jans JJM, Verhoeven-Duif NM, 'Pathophysiology of propionic and methylmalonic acidemias. Part 2: Treatment strategies'. J Inherit Metab Dis. 2019;42(5):745–761. doi: 10.1002/jimd.12128. Epub 2019 Jul 9. PMID: 31119742.
3. Shchelochkov OA, Carrillo N, Venditti C. Propionic Acidemia. 2012 May 17 [Updated 2016 Oct 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92946/
4. Zhou X, Cui Y, Han J. Methylmalonic acidemia: Current status and research priorities. Intractable Rare Dis Res. 2018;7(2):73-78. doi:10.5582/irdr.2018.01026.
5. Forny P, Hörster F, Ballhausen D, Chakrapani A, Chapman KA, Dionisi-Vici C, et al. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. J Inherit Metab Dis. 2021 May;44(3):566-592. doi: 10.1002/jimd.12370. Epub 2021 Mar 9. Erratum in: J Inherit Metab Dis. 2022 Jul;45(4):862. PMID: 33595124; PMCID: PMC8252715.
6. Joffe H, Yardley L. Content and Thematic Analysis. In: Marks D, Yardley L, editors. Research Methods for Clinical and Health Psychology. London: Sage Publications; 2004. p. 39-55.
7. Clarke V, Braun V. Teaching thematic analysis: Overcoming challenges and developing strategies for effective learning. The Psychologist. 2013;26(2):39-55.
8. Zeltner NA, Baumgartner MR, Bondarenko A, Ensenauer R, Karall D, Kölker S, et al. Development and Psychometric Evaluation of the MetabQoL 1.0: A Quality of Life Questionnaire for Paediatric Patients with Intoxication-Type Inborn Errors of Metabolism. JIMD Rep. 2017;37:27-35. doi: 10.1007/8904_2017_11. Epub 2017 Mar 1. PMID: 28247338; PMCID: PMC5740049.
9. US Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Federal Register. 2009;74(235):65132-65133.

DISCLOSURES

This study was funded by ModernaTX, Inc. ES and OM are employees of ICON plc, who were paid consultants to ModernaTX, Inc., in connection with this study. VS is an employee of and holds stock/stock options in ModernaTX, Inc.

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