Development of an Investigator Global Assessment of Severity in Propionic Acidemia

CO67

Nicola Longo,[1] Vanja Sikirica,[2] Stephanie Grunewald,[3] Olga Moshkovich,[4] Carlo Dionisi-Vici,[5] Jerry Vockley,[6] M. Alex Bellenger,[4] Javier de las Heras,[7] Geetanjoli Banerjee,[2] Ethan J. Schwartz[4]*

[1]University of Utah, Salt Lake City, UT, USA; [2]Moderna, Inc., Cambridge, MA, USA; [3]Metabolic Department, Great Ormond Street Hospital NHS Foundation Trust and Institute of Child Health, NIHR Biomedical Research Center, University College London, UK; [4]ICON Insights, Evidence and Value, Raleigh, NC, USA; [5]Division of Metabolic Diseases, Bambino Gesù Children's Hospital IRCCS, Rome, Italy; [6]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [7]Hospital Universitario Cruces, Biobizkaia Health Research Institute and University of the Basque Country, Bilbao, Spain
*Presenting author

Background

- Propionic acidemia (PA) is an ultra-rare pediatric disorder impacting multiple organ systems[1–4]
  - The burden of PA is not fully captured by existing endpoints or clinical outcome assessment instruments
- Delphi survey methodology involves consensus-building by disseminating surveys in several rounds,[5,6] and is a helpful tool in healthcare and life sciences research,[7] especially for identifying important concepts and achieving consensus among experts[8]

Objective

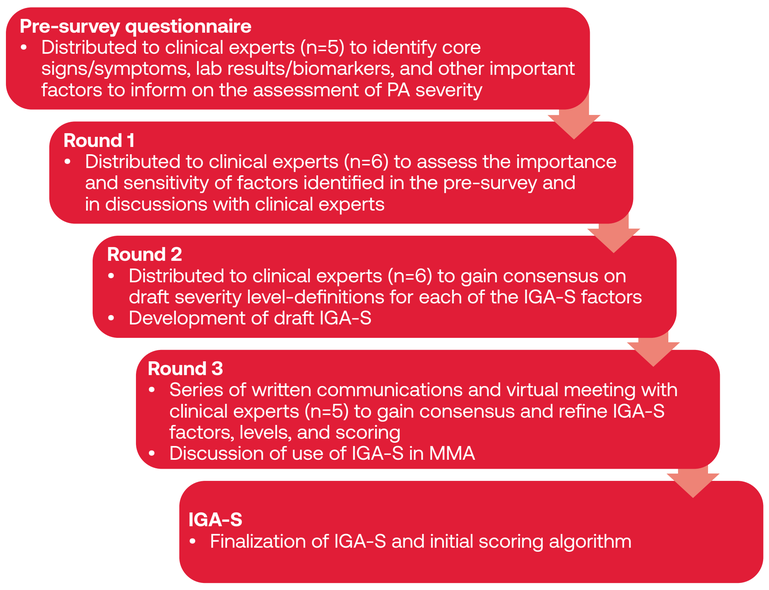
- To develop an Investigator Global Assessment of Severity (IGA-S) to standardize the assessment of disease severity objectively and consistently in patients with PA

Methods

Study design

- See **Figure 1** for an overview of the Delphi survey study design

Figure 1. Overview of the Delphi survey study design



IGA-S, Investigator Global Assessment of Severity; MMA, methylmalonic acidemia; PA, propionic acidemia

- The Delphi survey was designed to gain clinical expert consensus of the most important factors for assessing PA disease severity from a clinical perspective (without factoring in potential confounders, such as healthcare systems), as well as appropriate level-definitions for each factor
- The first two rounds were programmed into an online format using the Qualtrics online survey platform (Qualtrics, Provo, UT, USA). Individualized survey links were sent to the clinical experts
- Following the Round 2 online survey, the IGA-S was drafted and reviewed with the clinical experts in a series of group discussions
  - During these discussions, the items, response options, and scoring were further refined
  - Clinical experts were also asked to review each item and confirm its appropriateness for use in assessing methylmalonic acidemia (MMA) severity, another inborn error of metabolism with similar symptomology to PA[1,2,4,9]

Table 1. Clinical expert background

Characteristic	US1	US2	UK1	UK2	IT1	SP1
Country of practice	US	US	UK	UK	Italy	Spain
Primary medical specialty	Medical genetics	Medical genetics	Pediatric metabolic medicine	Pediatric metabolic medicine	Pediatrics	Pediatrics
Current role in treating patients with PA or MMA	Treating physician	Does limited clinical service, sees mostly research patients	Treating physician, PI for investigational trials, co-author of international guidelines	Responsible for overall medical management in collaboration with three colleagues	Head of a referring pediatric center for metabolic diseases	Referral coordinator for Hereditary Metabolic Disease Unit
Years practicing medicine	40	38	31	21	41	20
Years treating patients with PA or MMA	30	No information	25	13 years for both PA and MMA	36	13
Overall number of patients with PA treated	12	20–30	28	16	>30	11
Number of patients with PA treated in the last year	5	Does limited clinical service, sees mostly research patients	14	9	15	6
Overall number of patients with MMA treated	20	20–30	57	7 (limited to methylmalonyl CoA mutase patients only)	>30	12
Number of patients with MMA treated in the last year	6	Does limited clinical service, sees mostly research patients	21	2	15	5

IT, Italy; MMA, methylmalonic acidemia; PA, propionic acidemia; PI, principal investigator; SP, Spain; UK, United Kingdom; US, United States

Clinical expert selection

- Criteria for clinical expert participation included: being in practice for at least 20 years, actively treating patients with PA and MMA, and also conducting or participating in relevant research
  - A multi-national panel (USA: n=2; UK: n=2; Italy: n=1; Spain: n=1) was intentionally sought to address potential differences across regions
  - The clinical experts' background is shown in **Table 1**

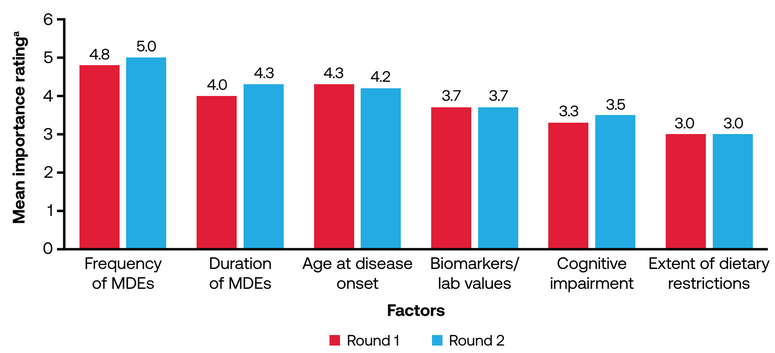
Analysis

- The data collected throughout the study were summarized using descriptive statistics (eg, n, percentage, mean, standard deviation [SD])
- Free-text data was analyzed via qualitative content analysis to identify key concepts, establish categories, and count frequencies of occurrence[10]

Results

- Following the Round 2 survey, the most important factors for evaluating PA severity were frequency of metabolic decompensation events (MDEs; mean [SD]: 5.0 [0.0]), duration of MDEs (4.3 [1.2]), age at onset (4.2 [0.4]), biomarkers/lab values (3.7 [0.5]), cognitive impairment (3.5 [0.5]), and dietary restrictions (3.0 [1.3])
  - See **Figure 2** for Round 2 compared with Round 1 regarding mean rating of the overall importance of individual factors

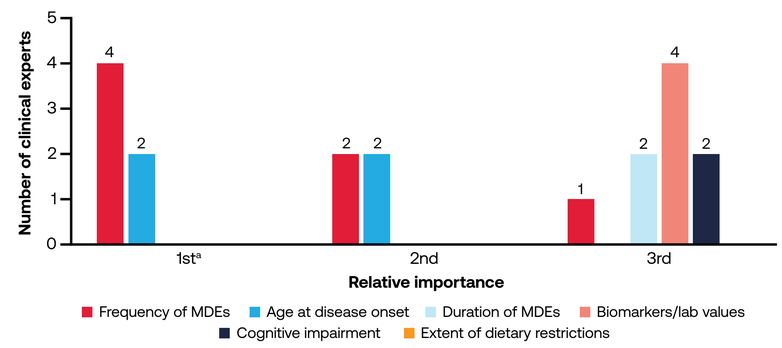
Figure 2. Overall importance of individual factors in evaluating PA severity, Round 2 vs Round 1 (N=6)



[a]Importance rated on a scale from 1 = "not at all important" to 5 = "extremely important"
MDE, metabolic decompensation event; PA, propionic acidemia

- During the Round 2 survey, clinicians selected frequency of MDEs (n=4, 67%) and age at onset (n=2, 33%) as the top two most important factors
  - See **Figure 3** for additional details on the relative importance of the factors

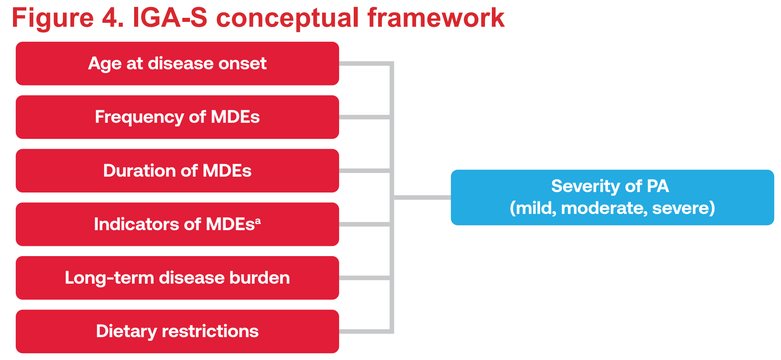
Figure 3. Rank order of the top three most important factors in evaluating PA severity, Round 2 (N=6)



[a]1st = most important
MDE, metabolic decompensation event; PA, propionic acidemia

- Following the Round 2 survey, a series of discussions led to further refinement and finalization of the IGA-S
  - These discussions focused on other long-term disease complications, clarification on routine vs non-routine biomarkers/lab values, use of "sick day diet" regimen, the possibility of initiating treatment prior to the initial presentation (if detected via newborn screening), an initial proposed scoring algorithm, and confirmation that the instrument is appropriate to use in MMA
  - The final conceptual framework of the IGA-S is shown in **Figure 4**

Figure 4. IGA-S conceptual framework



[a]Indicators of MDEs include biomarkers or relevant lab values
MDE, metabolic decompensation event; PA, propionic acidemia

Conclusions

- This study established consensus among clinical experts and standardized concepts to assess the severity of PA consistently in patients with PA, including age at disease onset, frequency of MDEs, duration of MDEs, indicators of MDEs, long-term disease burden, and dietary restrictions
  - The IGA-S is fit-for-purpose for use in clinical trials in patients with PA, and could also be used in general clinical practice
  - The IGA-S was also confirmed to be fit-for-purpose for use in patients with MMA
- The initial proposed scoring algorithm was confirmed to be clinically meaningful. The next steps in this research should aim to further validate the proposed scoring algorithm

References

1. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;9:130.
2. Haijes HA, van Hasselt PM, Jans JJM, et al. Pathophysiology of propionic and methylmalonic acidemias. Part 2: Treatment strategies. J Inherit Metab Dis. 2019;42:745–761.
3. Shchelochkov OA, Carrillo N, Venditti C. Propionic Acidemia. May 17, 2012 [Updated Oct 6, 2016]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92946/. [Accessed May 2022].
4. Forny P, Hörster F, Ballhausen D, et al. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. J Inherit Metab Dis. 2021;44:566–592.
5. Boulkedid R, Abdoul H, Loustau M, et al. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One. 2011;6:e20476.
6. Von der Gracht HA. Consensus measurement in Delphi studies: Review and implications for future quality assurance. Technol Forecast Soc Change. 2012;79:1525–1536.
7. Keeney S, McKenna H, Hasson F. The Delphi Technique in Nursing and Health Research. John Wiley & Sons, 2010.
8. US Food and Drug Administration. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. February 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients. [Accessed May 2022]
9. Zhou X, Cui Y, Han J. Methylmalonic acidemia: Current status and research priorities. Intractable Rare Dis Res. 2018;7:73–78.
10. Joffe H, Yardley L. Content and thematic analysis. In: Marks D, Yardley L, eds. Research Methods for Clinical and Health Psychology. London: SAGE Publications. 2004:39–55.

Acknowledgments

Editorial, layout, and formatting assistance was provided by Sarah Millard, of Caudex, a division of IPG Health Medical Communications and was funded by Moderna, Inc. This study was funded by Moderna, Inc.

Disclosures

NL has participated in an advisory board for/has received grants from Moderna, Inc. (paid to institution). VS and GB are employees of and hold stock/options in Moderna, Inc. SG and CD-V have participated in an advisory board for Moderna, Inc. OM, MAB, and EJS are employees of ICON Insights, Evidence and Value, who were paid consultants to Moderna, Inc., in connection with this study. JV has received research funding from Moderna, Inc. JdlH has been a consultant for Moderna, Inc.

Presented at ISPOR Europe, November 12–15, 2023; Copenhagen, Denmark