TABLE OF CONTENTS

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ONE SWALLOW MAKES A SUMMER: CLINICAL TRIALS THAT ENROLL ONLY ONE PARTICIPANT (N-OF-1 TRIALS)

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"One swallow does not make a summer, neither does one fine day; similarly, one day or brief time of happiness does not make a person entirely happy."

Aristotle
Nicomachean Ethics, Book I, 1098a

Randomized controlled trials (RCTs) are widely acknowledged as the methodological gold standard in clinical research for demonstrating the efficacy and safety of treatments in large populations, due to their ability to minimize bias and establish robust causal relationships. However, while they remain essential, this approach is not always applicable or sufficient to answer all clinical questions – particularly when attention shifts from the general population to the individual patient. In such contexts, where treatment responses may vary considerably between individuals due to genetic, environmental or lifestyle factors, the relevance of n-of-1 studies becomes evident.

These studies apply the experimental logic of clinical trials to a single participant, offering a rigorous, scientifically grounded method for evaluating the effectiveness of highly personalized therapeutic interventions. They make it possible to determine whether a specific treatment is effective for a specific patient, thus providing valuable data for precision medicine and individualized care.

UNDERSTANDING THE N-OF-1 TRIAL

In clinical research methodology, an n-of-1 trial – where "n" refers to the number of participants, in this case, only one – is defined as a rigorously designed clinical study aimed at assessing the comparative effectiveness of different therapeutic interventions in a single patient[1].

This approach is methodologically sophisticated because the patient serves as both the treatment and the *control group*. The study design typically involves a structured and systematic alternation between treatment conditions (for example, an active drug *vs.* a placebo, or two different drugs). These alternations follow *predefined*, *randomized*, and *repeated sequences* – often using a *crossover* model – designed to eliminate bias related to the order of administration. A key element for the study's validity is the inclusion of washout periods (treatment suspension intervals), which help ensure that the residual effects of one intervention do not influence the assessment of the next[1].

The goal is not to generate results generalizable to a broader population, as in conventional randomized clinical trials (RCTs), but to identify the most effective treatment for that specific individual. In this sense, n-of-1 trials are powerful and pragmatic tools to advance controlled clinical research and support clinical decision-making in the era of precision medicine and therapy personalization.

The methodology of n-of-1 trials was first formalized in the second half of the 1980s by a group of researchers at McMaster University in Hamilton, Ontario, Canada, led by Gordon Guyatt, a prominent figure in the field of evidence-based medicine[2]. Despite their methodological soundness and clear potential, the practical use of n-of-1 trials in clinical settings and research has remained quite limited. This limited adoption can be attributed to several factors, including the logistical and statistical complexity of designing such studies, the essential need for close collaboration between physician and patient, and, above all, the lack of familiarity among many clinicians and researchers with this specific study design.

N-of-1 trials offer several significant advantages that make them particularly valuable in specific clinical and research settings – especially in areas such as rare diseases and chronic conditions:

1. **Cost Reduction**
   Unlike traditional RCTs, which require enrolling hundreds or thousands of participants and incur high costs, n-of-1 trials are inherently more economical. While they do require careful and thorough initial planning, conducting the trial on a single patient substantially reduces operational and logistical costs. This makes them a sustainable option for evaluating costly or resource-intensive interventions.
2. **Personalized Treatment**
   The main strength, and indeed the very essence, of n-of-1 trials lies in their ability to provide concrete, individualized evidence to guide therapeutic decisions. This approach is particularly useful in situations where treatment responses vary significantly from one patient to another, as often seen in chronic conditions, such as autoimmune diseases or chronic pain.
3. **A tool for Rare Diseases**
   N-of-1 trials are especially powerful, and at times essential, for research on rare diseases. By definition, these conditions affect very small numbers of individuals, often making it impractical to recruit a sufficiently large sample for a traditional RCT. In such cases, n-of-1 trials represent a valid methodological alternative for generating high-quality clinical evidence.

CHALLENGES TO BROADER ADOPTION

Despite their potential, the wider adoption of n-of-1 trials is hindered by several practical and methodological barriers that must be carefully addressed during the study design phase:

1. **Bias and Blinding Difficulties**
   Blinding – keeping the patient and/or clinician unaware of which treatment is being administered at a given time – is essential for ensuring the validity of the results. However, effective blinding is particularly challenging in non-pharmacological interventions such as nutritional, physiotherapy, or rehabilitation treatments, where the nature of the intervention is evident to the patient. This awareness increases the risk of bias in patient-reported outcomes.
2. **Logistical Feasibility and Operational Burden**
   Setting up an n-of-1 trial requires meticulous planning and execution. Elements such as randomization of treatment sequences, proper implementation of washout periods, and maintenance of blinding must be managed with consistent accuracy. These requirements pose significant logistical and operational challenges for clinicians and researchers, especially in resource-limited settings
3. **Ethical and Regulatory Issues**
   The approval process for n-of-1 trial protocols by Ethics Committees can be complex, as existing regulations are primarily designed for population-based RCTs. In some countries, this type of study falls into a regulatory grey area, particularly regarding informed consent, and requires proactive dialogue with regulatory authorities.
4. **Limited Generalizability**
   A fundamental limitation of the n-of-1 design lies in the nature of its results. Since the data are specific to the individual patient involved, their applicability to a broader population is inherently limited. The findings are “valid for me,” not necessarily “valid for us.”

CLINICAL APPLICATIONS

N-of-1 trials can be applied in a variety of clinical settings where individual variability in treatment response is high, and where personalization plays a decisive role:

- Chronic diseases: These trials are widely used in conditions such as asthma, arthritis, migraine, or neuropathic pain, where patients may respond unpredictably to different drug classes.
- Rare diseases: In ultra-rare conditions, n-of-1 trials can serve as a valuable alternative to generate the only possible clinical evidence when recruiting a standard study sample is unfeasible.
- Managing side effects and tolerability: This approach enables precise identification of treatment-related side effects or benefits, focusing on the patient's specific experience and improving treatment adherence.
- Behavioral and nutritional interventions: N-of-1 trials are increasingly used to evaluate individualized lifestyle changes, such as specific diets, physical activity programs or psychological therapies, where outcomes are highly subjective and depend on the patient's personal response.

THE ROAD AHEAD

Despite the current challenges, the future of n-of-1 trials appears highly promising. International initiatives, such as the DIAMOND Project[3], are actively developing standardized guidelines and practical tools to promote and facilitate the adoption of this methodology, helping overcome existing logistical and regulatory barriers.

Digital technologies are expected to play a crucial role. Mobile applications and wearable devices can greatly simplify the real-time collection of clinical data and patient-reported outcomes, significantly reducing the logistical burden for both patients and research teams.

In addition, statistical research is exploring advanced methods, such as aggregate synthesis, through prospective meta-analyses of multiple n-of-1 trials conducted in patients with similar profiles. This innovative approach could enhance the generalizability of findings while maintaining a strong focus on the personalized nature of interventions in precision medicine.

CONCLUSIONS

N-of-1 trials remain an underutilized tool in clinical research. By merging methodological rigor with individualized patient needs, this form of controlled experimentation offers a valuable opportunity to accelerate the development of treatments tailored to precision medicine. While barriers remain, it is our responsibility to raise awareness and foster broader use of this approach in the near future.

Conflict of Interest:
The author declares no conflicts of interest.

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Not required due to the nature of the article.

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NURSING PERSPECTIVES ON INHERITED METABOLIC DISORDERS: EXPERIENCE AND EDUCATIONAL NEEDS IN AN ITALIAN HOSPITAL SETTING

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***ABSTRACT* – Objective:** The aim of this study was to assess the clinical experience and training needs of nursing staff involved in the care of patients with inherited metabolic disorders (IMDs), a group of rare diseases that require specialized, multidisciplinary management and are currently underrepresented in nursing education.

Subjects and Methods: A cross-sectional, single-center survey was conducted at Fondazione IRCCS San Gerardo dei Tintori (Monza, Italy). An 18-item online questionnaire was distributed to 500 nurses across 23 hospital units. The survey addressed demographics, clinical experience, and educational exposure related to IMD care. Descriptive statistics were used to analyze the responses.

Results: A total of 104 nurses (21%) completed the survey. Among them, 87% had assisted at least one IMD patient, and 82% perceived the nursing care as highly complex. While routine procedures such as blood glucose monitoring and enteral nutrition were commonly performed, IMD-specific interventions (e.g., intravenous arginine administration or enzyme replacement therapy) were rarely carried out. Emotional responses to IMD care included uncertainty (53%), concern (50%), and a sense of inadequacy (46%). Formal training was limited: 54% had not received IMD-related education during their studies, and 48% had never attended relevant courses. Notably, 92% expressed a desire for further training in this area.

Conclusions: Despite frequent clinical exposure to IMD patients, most nurses reported limited formal training and low procedural confidence. These findings underscore the need for structured, IMD-focused educational initiatives to enhance nursing competence and support high-quality, multidisciplinary care for rare disease populations.

Keywords: Nursing, Inherited metabolic disorders, Training, Expertise, Education.

Abbreviations: IMD: inherited metabolic disorder; EN: enteral nutrition.

INTRODUCTION

Inherited metabolic disorders (IMDs) account for approximately 15% of rare diseases, with an overall incidence ranging from 1 in 500 to 1 in 4,000 live births[1]. Inherited metabolic disorders encompass a heterogeneous group of conditions that impair metabolic pathways responsible for the breakdown or storage of carbohydrates, fatty acids, and proteins[2].

The implementation of Newborn Screening Programs has enabled early diagnosis for many IMDs, reducing the risk of irreversible damage and allowing prompt intervention[3-6]. Dietary management remains central to IMD treatment, involving scheduled meals to prevent fasting and nutritional supplementation to avoid deficiencies[7].

The use of food for special medical purposes is often lifelong and essential in many IMDs to ensure adequate caloric intake, support growth, maintain satiety, and provide dietary variety. In addition to early diagnosis, advances in genetics and biochemistry have enhanced clinicians' understanding of the pathophysiology and treatment of IMDs, thereby increasing the life expectancy of affected individuals[8,9].

Given the growing attention to the quality of life of patients with IMDs and their families, alongside the complexity of these conditions, appropriate clinical management by a multidisciplinary team, including medical doctors, biochemists, nurses, and other healthcare professionals, is crucial to ensure comprehensive care[10-12].

Nurses play a vital role within the therapeutic team, assisting physicians in the diagnostic and treatment process, as well as providing direct patient care, including nursing procedures, medication administration, and injections[13].

As nurses are typically the first healthcare professionals to interact with patients and often spend extended periods with them, patients tend to expect not only medical knowledge but also safety, trust, and effective communication from them[13].

To foster awareness and build specific expertise in IMDs among all professionals involved in their complex management, including nurses, educational programs, and training initiatives have been developed within the European Reference Network[14].

However, the role of nurses in IMD care remains poorly defined, and the extent of their training and expertise in the specific management of IMD patients has not been thoroughly examined, particularly in the Italian context.

This survey aims to investigate, within a single-center cohort, the role of nurses in the management of IMDs, assess their level of expertise and training, and identify emerging needs to be addressed through targeted future strategies.

SUBJECTS AND METHODS

An online survey comprising 18 single- or multiple-choice questions (Supplementary Material) was developed by an expert panel composed of nurses from the pediatric day hospital and pediatric hospitalization departments, pediatric metabolist doctors and dietitians of the simple operating unit of inherited metabolic diseases. These professionals provide care for both pediatric and adult patients with IMDs. The survey was designed with Microsoft Forms, which enabled us to share it directly *via* institutional Outlook email addresses. The survey was distributed electronically to nurses from 23 Operating Units of Fondazione IRCCS San Gerardo dei Tintori between April and May 2024 *via* their respective clinical center contacts, using QR codes or direct links.

The non-validated questionnaire, developed in Italian, was structured into three sections: personal information, clinical experience, and training needs.

Ethical approval was not required, as the survey did not constitute a clinical study and did not involve clinical outcomes or patient-specific data, but was instead conducted among healthcare professionals.

Statistical Analysis

Survey responses were analyzed using descriptive statistics, with results reported as percentages (%) and absolute numbers (n). As the survey included multiple-choice questions, participants could select more than one response; in such cases, total percentages may exceed 100%.

RESULTS

Personal Information

Of the 500 nurses who received the survey, 21% (104/500) responded. Among respondents, 90% (94/104) were female.

Regarding age distribution, 43% (45/104) were under 36 years old, 27% (28/104) were aged 36-50 years, and 30% (31/104) were over 50 years.

Most participants (88/104, 85%) identified as general nurses, while 15% (16/104) reported working as pediatric nurses. With respect to the highest educational qualification, 72% (75/104) held a diploma or Bachelor's degree, 26% (27/104) had a Master's or first-level degree, and 2% (2/104) reported holding a second-level Master's degree.

The majority of respondents, about 51% (53/104), work in pediatric areas: Pediatric Unit (16/104, 15.3% of the total respondents), Pediatric Hematology Unit (15/104, 14.4%), Neonatal Intensive Care

(8/104, 7.6%), Pedatric Day Hospital (4/104, 3.8%), Pediatric Ematology Day Hospital (7/104, 6.7%) and Neonatal Clinic (3/104, 2.8%). 20% of nurses belong to critical care areas: 9.7% (10/104) in the emergency room, 4.9% (5/104) in Operating Rooms and 5.8% (6/104) in intensive care (general and neuro-intensive care). Additionally, 7.8% (8/104) were based in diagnostic departments (endoscopy and radiology).

Responses were also received from nephrology (5/104), emergency medicine (10/104), psychiatry (3/104), otorhinolaryngology (2/104), orthopedics (1/104), general medicine (5/104), and the day hospital of medicine (4/104). No responses were received from departments of the emergency medicine swab department (activated following the COVID-19 emergency), child neuropsychiatry, neurosurgery and the general critical care area.

Regarding professional experience, 14% (15/104) of respondents reported less than 5 years of total and departmental experience. A total of 24% (25/104) had 5-10 years of general experience, with 10 of these (10/25) having worked in their current department for fewer than 5 years. Among 26% (27/104) of respondents, general experience ranged from 10 to 25 years; of these, fourteen had fewer than 5 years, four had 5-9 years, and nine had 10-25 years of experience in their current department.

Finally, 36% (37/104) reported more than 25 years of overall experience. Among them, eight had spent the entire period in the same department, 14 had worked 10-25 years, eight for 5-9 years, and seven for less than 5 years in their current department.

Clinical Experience

Of all respondents, 25% (26/104) reported having cared for pediatric patients (<18 years), 20 participants reported having assisted only adult patients, and 58 respondents (56%) indicated experience with both pediatric and adult patients during their working experience in their current Unit.

When asked how frequently patients with IMDs are admitted to their unit, 12% (12/104) of participants reported daily admissions, 21% (22/104) reported approximately once a week, 24% (25/104) nearly once a month, and 25% (26/104) about once a year. Notably, 18% (19/104) stated they had never encountered IMD patients in their unit (Figure 1).

Participants were then asked to report the frequency with which they performed specific clinical tasks and activities during their professional experience with both general and IMD cases (Figure 2).

Central venous access management and capillary blood sugar control (digital therapeutics, DTX) monitoring were frequently performed by 77.9% (81/104) and 73.1% (76/104) of respondents, respectively. A majority also reported frequent administration of enteral nutrition (EN) (57.7%, 60/104) and nasogastric tube placement (56.7%, 59/104). In contrast, preparing EN mixtures was less commonly performed, with 47.1% (49/104) reporting frequent involvement.

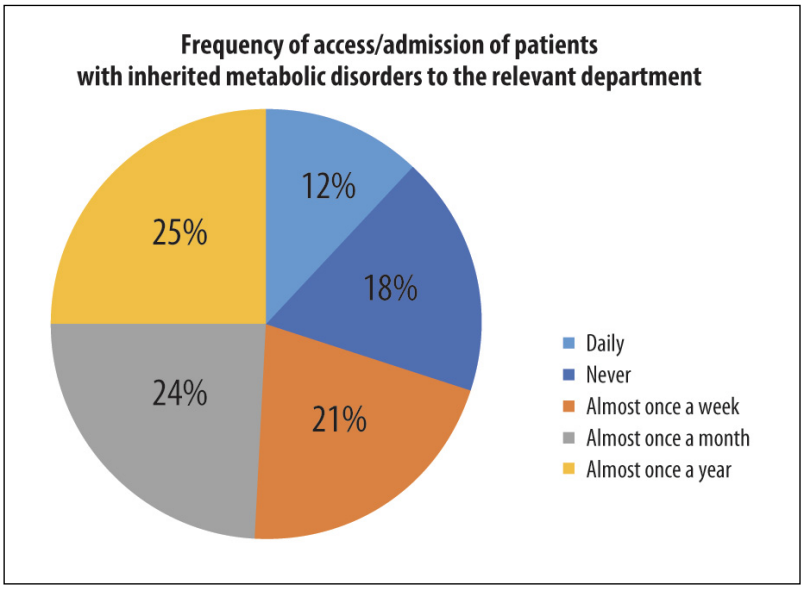

Figure 1. Frequency of access/admission of patients with inherited metabolic disorders to the relevant department.

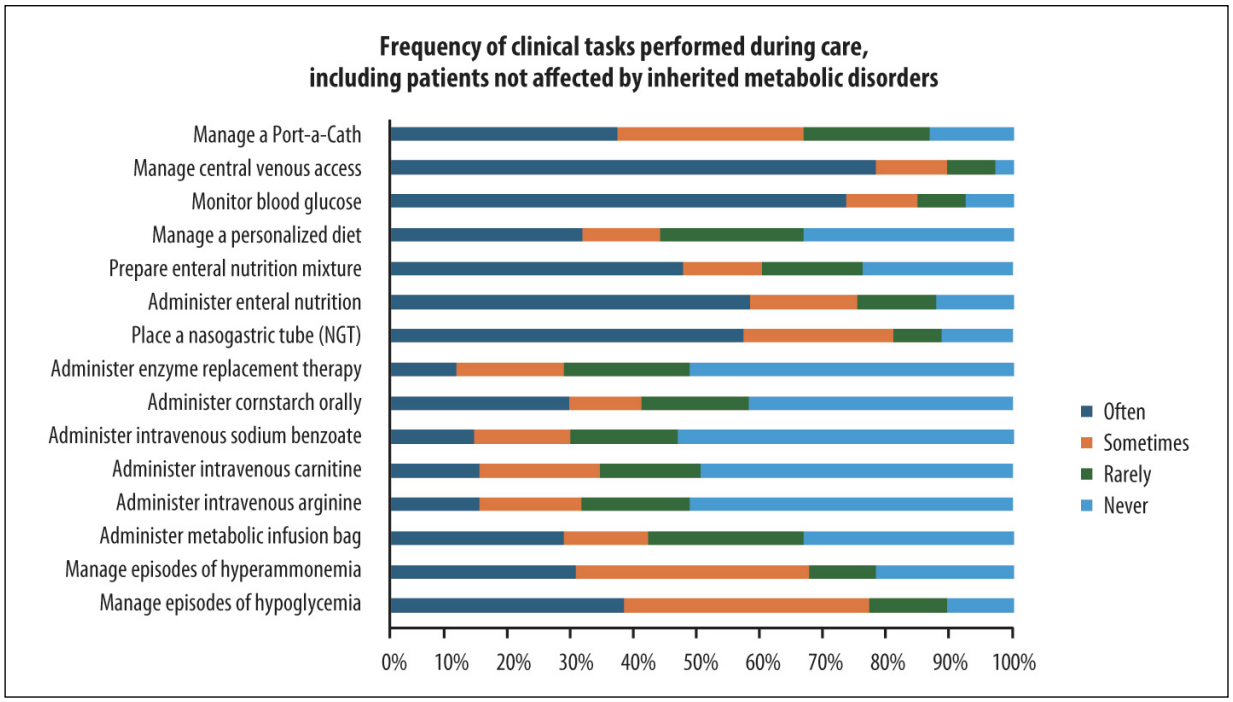

Figure 2. Frequency of clinical tasks performed during care, including patients not affected by inherited metabolic disorders.

30.8% of nurses reported having managed a diet *ad personam* (i.e., checking the delivery of the meal, the correspondence with the prescription, the time of consumption, monitoring the amount of food consumed, and managing potential substitutions), while certain IMD-specific interventions were less common. Notably, 42.3% (44/104) had never administered oral cornstarch. Specialized procedures such as intravenous administration of arginine (51.9%, 54/104), carnitine (50.0%, 52/104), sodium benzoate (53.8%, 56/104), and enzyme replacement therapy (51.9%, 54/104) were also reported as never performed by more than half of the respondents. Similarly, 33.7% (35/104) had never administered metabolic infusion bags, and 24.0% (25/104) had never prepared EN mixtures.

Conversely, episodes of hyperammonemia and hypoglycemia were more frequently managed, with 29.8% (31/104) and 37.5% (39/104) of participants, respectively, indicating frequent involvement.

Considering the subgroup of the Pediatric Area, specific interventions and therapies in management of IMD patients are performed more frequently: for istance, the management of *ad personam* diet – which consists of checking that the meal corresponds to the dietician's prescription, that the correct quantity is consumed, monitoring compliance with the timetables, and administering any substitute foods – happens "often" in 25/53 cases and "sometimes" in 12/53.

The same occurs with the administration of some specific therapies, such as Enzyme Replacement Therapy (ERT), reported "often" and "sometimes" by 41% of nurses working in the Pediatric Area, while in the remaining areas it takes place "often" in only 4 cases (all belonging to Adult Day Hosptal) and "sometimes" in three cases, for a total of 23% of the 30 nurses who do not work in the pediatric area and who have assisted a patient with IMD at least once.

A total of 90 nurses (87%) reported having cared for at least one patient with an IMD during their professional experience. Among these respondents (n=90), 82% rated the complexity of nursing care for IMD patients as "high," while 18% perceived it as "medium." Notably, none of the participants reported the level of care complexity as "low."

In addition, when assisting patients with IMDs, respondents reported experiencing a range of emotional responses (Figure 3), including uncertainty (48/90), concern (45/90), a sense of inadequacy (41/90), anxiety (20/90), personal gratification (17/90), and confidence (6/90).

When assisting patients with IMDs in non-urgent situations that are complex to manage independently, participants reported primarily seeking support from colleagues (76%, 71/104) or nurses from other units (46%, 41/104). Additionally, 59% (54/104) indicated they may consult a physician from their department, while 49% (45/104) reported contacting the designated metabolist within their center.

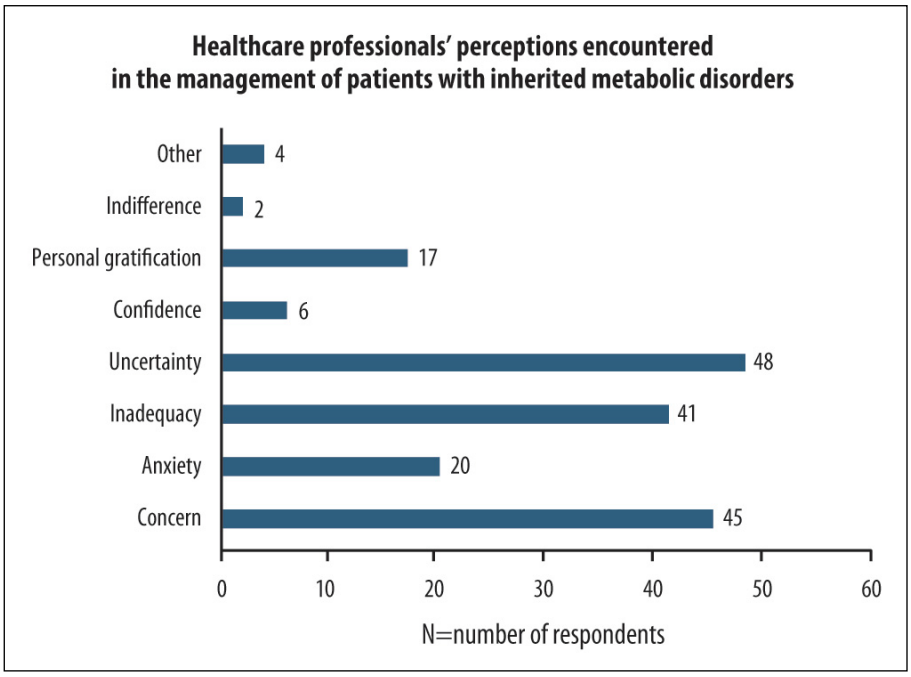

Figure 3. Healthcare professionals' perceptions encountered in the management of patients with inherited metabolic disorders.

Approximately half of the respondents (47/104) reported referring to specific protocols, and 19 participants (18%, 19/104) indicated consulting online resources such as medical books.

Formation and Training Needs

In 54% of cases (56/104), respondents reported that IMD topics were not included in their formal education. Additionally, 48% (51/104) stated they had never attended a training course or conference on IMDs.

A large majority (92%, 96/104) of nurses expressed a need for more information on IMDs and reported a desire to receive further training on the topic.

DISCUSSION

This single-center survey assessed the clinical experience and educational needs of nurses caring for patients with inherited metabolic diseases (IMDs), a growing yet underrepresented field in nursing education.

Despite follow-up reminders, the response rate was low (21%; 104/500), potentially reflecting limited awareness or interest in IMDs among nurses. Nonetheless, 87% of total respondents reported having managed at least one IMD patient in their career, with particularly high exposure among pediatric nurses (among the 53 nurses belonging to the pediatric area, 52 gave an affirmative response).

A large majority (82%) perceived IMD-related nursing care as highly complex, indicating the clinical challenges these patients pose. Consistent with this, nurses frequently performed procedures applicable to other categories of patients, such as blood glucose monitoring, enteral feeding, and central venous access management, while IMD-specific interventions (e.g., intravenous administration of arginine, sodium benzoate, or enzyme replacement therapy) were less common. This likely reflects the rarity and specialized nature of such treatments.

Pediatric departments demonstrated greater experience with IMD-specific procedures due to the higher admission rates of affected patients in these units. The example of ERT administration is significant: while in non-pediatric settings this mostly occurs in outpatient care, the administration of ERT often takes place in both pediatric departments and pediatric hematology departments, as patients with lysosomal storage diseases undergoing transplantation (Mucopolysaccharidosis patients) can be hospitalized in these settings.

Emotional responses such as uncertainty, concern, and a sense of inadequacy were commonly reported. These findings highlight the need for structured training and standardized protocols to improve preparation and professional confidence among nurses.

Significant educational gaps emerged: 54% of respondents had not received IMD-related instruction during their undergraduate education, and 48% had never attended any relevant course or conference. Notably, among the youngest age group (20-35 years), comprising 43% of respondents, only 29% had addressed IMDs during their degree program. In contrast, 92% expressed a clear need for further training in this field.

This discrepancy between the perceived complexity of IMD care and the limited basic nursing education on this subject underscores the urgency of targeted educational interventions. As supported by the literature[13,14], continuing professional development enhances diagnostic confidence, procedural competence, and communication skills in rare disease care. Nurses play a central role within multidisciplinary teams, providing both routine and emergency care for IMD patients, and directly influencing their quality of life[12].

Adequate training would allow nurses to effectively respond to patients' clinical, therapeutic and psychological needs, significantly impacting their quality of life, and would enable them to provide comprehensive health education to patients and caregivers. Informed patients and caregivers, educated in therapy administration, device use, and emergency management, can reduce hospitalizations and emergency visits. This is especially important given the high treatment burden that already disrupts daily life. Moreover, comprehensive nursing care supports daily functioning, ensures adherence to therapy and diet, manages pain, and helps prevent hypoglycemia.

A key limitation of this study is the reliance on subjective perceptions to assess the complexity of nursing care in the absence of standardized indicators, which may compromise the objectivity of the findings[15]. Additionally, being a single-center study with limited departmental participation and a predominance of pediatric responses, the generalizability of findings is restricted.

Future multicenter studies involving diverse clinical settings are needed to confirm these results and support reforms in undergraduate and continuing nursing education. Dedicated training should focus on nursing roles in metabolic emergencies, especially the preparation and administration of frequently used therapies.

Following the revision of the survey data, a SWOT analysis was conducted (Figure 4). The strengths identified include the extensive experience nurses have in the care of IMD patients working in pediatric settings. This expertise could be shared with colleagues from other departments through residency courses and the development of protocols and quality documents.

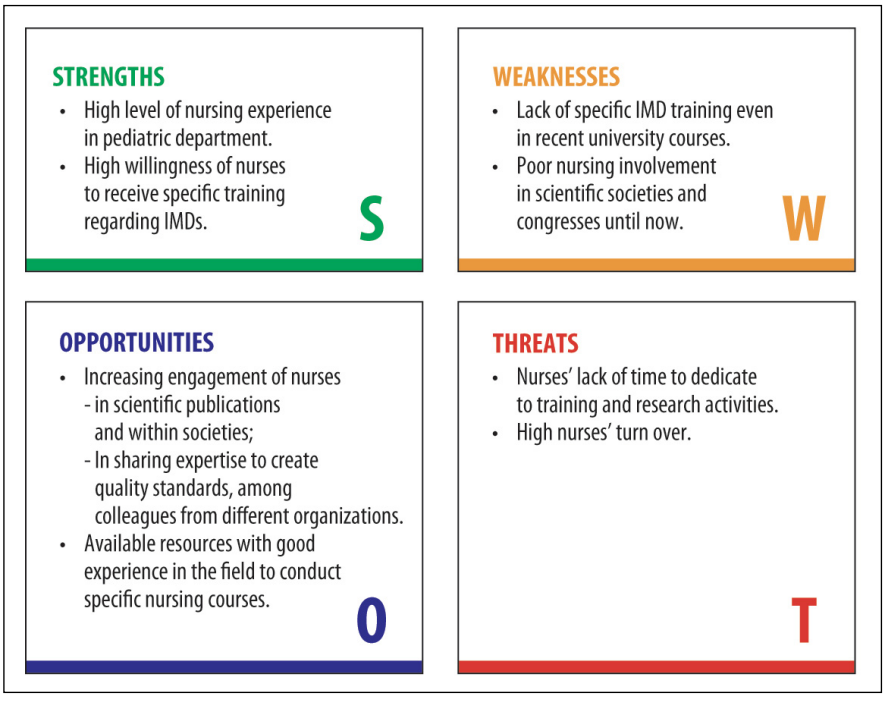

Figure 4. SWOT analysis, based on survey findings.

The lack of specific IMD training, especially in recent University curricula, as highlighted by the survey, is a significant weakness, along with the limited involvement of nurses in scientific societies and congresses up to now.

The increasing engagement of nurses in this field and scientific publications represents a valuable opportunity for enhancing nursing expertise and management of IMDs and eventually improving the quality of nursing care.

This knowledge can also be shared and expanded at both national and international levels. To achieve this, it is essential to provide experienced IMD nurses with opportunities to engage in scientific and research activities, allowing them to dedicate adequate time while balancing these commitments with their clinical duties.

Reducing staff turnover is also of fundamental importance, as it enables the development of specialized skills within specific areas, thereby improving the quality of nursing care provided.

Following this analysis shared with the working team, a dedicated residential course on IMDs is already active at Fondazione IRCCS San Gerardo dei Tintori. This course has been implemented and integrated with a nursing section focused particularly on the management of metabolic emergencies, as well as the preparation and administration of specific therapies in such cases.

Our institution, Fondazione IRCCS San Gerardo dei Tintori, has revised protocols and manuals and is developing a comprehensive handbook for managing metabolic emergencies. In parallel, the University of Milano-Bicocca has launched a Master's program in Intensive Care Nursing Sciences that includes a specific module on IMD emergency management. The nursing component addresses therapy preparation and administration and includes case-based learning.

Finally, establishing a Nursing Work Group within the Italian Society for the Study of Inherited Metabolic Diseases and Neonatal Screening (SIMMESN) could foster the exchange of expertise among national reference centers and promote clinical standardization. The present survey could serve as a foundation for a broader, multicenter investigation across Italy.

CONCLUSIONS

This single-center survey reveals substantial gaps in the training and expertise of nurses involved in the care of patients with IMDs. Despite frequent clinical encounters and a high perceived complexity of care, most respondents reported limited formal education and hands-on experience in IMD management.

These findings underscore the urgent need to better define the role of nurses in IMD care and to implement targeted training programs that address the unique, specific challenges associated with managing rare metabolic conditions.

Broader, multicenter studies are warranted to validate these results and to guide the integration of IMD-specific content into nursing curricula and continuing professional development pathways.

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Study conception and design: all; collection and interpretation of data: S. Gigante, K. Pozzi, V. Sisti, A. Cerizza; statistical analysis: S. Gigante, K. Pozzi, V. Sisti, A. Cerizza; manuscript drafting: all; manuscript editing: all; approval to submit: all.

Availability of Data and Material:
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest:
The authors declare that they have no conflicts of interest to disclose.

Ethics Approval:

Ethical approval was not required, as this survey was not classified as a clinical study, according to the most recent national regulatory framework outlined in Regulation No. 425/2024. Specifically, the survey did not involve clinical outcomes or patient-specific data but was exclusively conducted among healthcare professionals, aligning with the definition established in the current legislative reference.

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Informed Consent:

Participants were clearly informed about the study's purpose, their voluntary involvement, and data confidentiality. Consent is considered implicit, as participation was entirely voluntary and free from coercion. Responses were anonymous or de-identified, and the study did not involve interventions or pose any risk to participants.

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PEGZILARGINASE AND BEYOND: ITALIAN REAL-WORLD EXPERIENCE AND PROPOSAL OF INNOVATIVE TOOLS FOR COMPREHENSIVE MANAGEMENT OF ARG1-D

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ABSTRACT **–** Arginase 1 deficiency (ARG1-D) is a rare urea cycle disorder primarily affecting the central nervous system with progressive spasticity, cognitive decline, and variable seizures, despite often mild hyperammonemia. Conventional treatment fails to maintain optimal metabolic control, leading to irreversible functional impairment. Pegzilarginase, a pegylated recombinant human ARG1 enzyme, has recently emerged as a causal therapy capable of reducing plasma arginine and improving motor outcomes, marking a new era in disease-modifying interventions.

This expert opinion paper, authored by an Italian multidisciplinary panel – including clinicians with real-world and trial-based experience – aims to harmonize diagnostic and follow-up strategies in ARG1-D. Based on literature review, clinical experience, and evidence from the PEACE trial, the panel proposes a multidomain clinical framework integrating core, advanced, and exploratory assessments across biochemical, neuromotor, imaging, hepatic, musculoskeletal, and quality-of-life domains.

The proposed model includes essential tools such as plasma arginine and guanidino compounds monitoring, standardized motor function scales (GMFM, GMFCS), MRI, and cognitive assessments. Optional investigations like cerebrospinal fluid (CSF) arginine, proton magnetic resonance spectroscopy (^{1}H-MRS), and motor evoked potentials offer mechanistic insights, while exploratory biomarkers [e.g., growth differentiation factor 15 (GDF15), neurofilament light chain] may refine understanding of redox-autophagic mechanisms and functional recovery. The paper highlights unmet needs, including muscle fibrosis and autophagy modulation by arginine, with implications for both pathogenesis and treatment response.

This framework serves as a foundation for future national guidelines and research. By fostering standardized, evidence-based care and embedding advanced tools in routine practice, it aims to improve outcomes for current and future patients with ARG1-D, transforming the natural history of this previously relentless disorder through expert collaboration and innovation.

Keywords: Arginase 1 deficiency, Urea cycle disorders, Pegzilarginase, Real-world evidence, Multidomain clinical monitoring, Multidisciplinary management, Functional biomarkers, Real-world multidomain monitoring framework, Neurometabolic disease management, Expert consensus in rare disorders.

INTRODUCTION

Urea Cycle Disorders: General Framework and Clinical Significance

Urea cycle disorders (UCDs) are a group of rare inherited metabolic conditions resulting from defects in enzymes or transporters involved in the urea cycle, the primary pathway for detoxifying and excreting excess nitrogen in the form of urea. The disruption of this pathway leads to the accumulation of nitrogenous waste products, causing episodic or chronic hyperammonemia and associated neurotoxicity[1]. The clinical spectrum of UCDs is heterogeneous, ranging from neonatal-onset classical forms to later-onset variants characterized by intermittent hyperammonemia, gastrointestinal symptoms, cognitive decline, behavioral disturbances, or motor impairment[1,2]. While the overall incidence of UCDs is estimated to be between 1 in 35,000 and 1 in 50,000 live births, their diagnosis remains challenging due to symptom overlap with more common neurological or hepatic conditions[1]. The introduction of newborn screening (NBS) programs has improved early detection for some UCDs, although limitations persist for certain forms not reliably detectable by this approach[1,2].

Arginase 1 Deficiency: Clinical Burden and Diagnostic Challenges

Arginase 1 Deficiency (ARG1-D) is the most distal and rarest UCD, with an estimated global prevalence ranging between 1:726,000 and 1:950,000[1,2]. Unlike other UCDs, which are primarily characterized by life-threatening hyperammonemia, ARG1-D manifests predominantly during early childhood with spastic paraplegia. Additional clinical clues include slowing of linear growth, progressive neurological involvement, gait abnormalities, plateauing and subsequent regression of cognitive development, intellectual disability, and epilepsy, often mimicking cerebral palsy[2,3]. Seizures occur in over 60% of cases and may be resistant to treatment, while hyperammonemia, though possible, is typically mild and episodic[1,4]. Cognitive function is variably affected, with some patients showing intellectual disability and behavioral issues such as irritability, inattention, or hyperactivity[3,4].

Biochemically, ARG1-D is characterized by chronically elevated blood arginine levels, typically three to fourfold above the upper limit of normal. Accumulation of arginine and its downstream metabolites, including guanidino compounds (GCs), plays a central role in disease pathophysiology, contributing to neuronal dysfunction and myelination defects through mechanisms such as gamma-aminobutyric acid (GABA) receptor inhibition and oxidative stress[2,3,5].

The diagnostic process relies on biochemical evidence of persistent hyperargininemia and is confirmed by biallelic pathogenic variants in the *ARG1* gene. Additionally, reduced arginase activity in red blood cells can be detected[3]. However, diagnosis is often delayed due to the absence of specific symptoms in the neonatal period, poor disease awareness, and overlapping features with non-metabolic neurodevelopmental disorders such as cerebral palsy[1,3].

Despite current dietary and pharmacological interventions aimed at lowering plasma arginine levels and preventing hyperammonemia (i.e., protein restriction and ammonia scavengers), patients hardly achieve optimal metabolic control (blood Arg <200 µmol/L), especially due to the endogenous production of arginine[1,5]. As a result, individuals with ARG1-D face progressive loss of functional mobility, communication abilities, and independence, ultimately leading to substantial caregiver burden and impaired quality of life[2,5].

Recent data from the Pegzilarginase Effect on Arginase 1 Clinical Endpoints (PEACE) trial[5] demonstrated that pegzilarginase, cobalt-substituted, pegylated human ARG1 enzyme replacement therapy, is capable of rapid and sustained reduction of blood arginine concentrations, with meaningful clinical improvements in gross motor function. This highlights a new era in disease-modifying therapy, shifting the focus from merely slowing progression to enabling potential recovery of function and proactive long-term management.

Prior Italian Experience in Diagnosis, Management, and Follow-Up of ARG1-D

In Italy, the clinical experience with ARG1-D has progressively expanded, although the extremely low prevalence – estimated at approximately 0.61 cases per million inhabitants in 2021 – has contributed to heterogeneous awareness and clinical practices across centers and specialties[2]. Diagnosis in Italy predominantly relied on clinical recognition of hallmark neurological features of ARG1-D, including progressive lower-limb spasticity, developmental delay or regression, cognitive impairment, and persistently elevated plasma arginine levels, often prompting re-evaluation of patients initially diagnosed with cerebral palsy or hereditary spastic paraplegia[2,4].

The standard of care for Italian patients traditionally included a combination of dietary protein restriction and oral nitrogen-scavenging agents. Management also includes symptomatic treatment of seizures, spasticity, and neuromotor complications, often requiring multidisciplinary input from metabolic specialists, neurologists, and rehabilitation teams. Follow-up protocols across Italian centers have included regular biochemical assessments, clinical neuromotor evaluations, and, in select cases, neuroimaging or neurophysiological studies, although standardization of monitoring strategies remains an area of unmet need[2]. Disease follow-up includes monitoring of bone metabolism, growth, and nutritional balance, particularly in light of the markedly protein-restricted diet. From February 2025, pegzilarginase became available as an etiologic treatment for ARG1-D patients aged two years and older[2,3].

The PEACE Trial: Design, Outcomes, and Clinical Relevance

The PEACE trial[5] represented the first randomized, double-blind, placebo-controlled phase 3 study specifically designed to assess the efficacy and safety of pegzilarginase in individuals with ARG1-D. The trial enrolled 32 patients across seven countries, including Italy, and incorporated a 24-week blinded treatment phase followed by a long-term open-label extension (LTE) of up to 150 weeks. Participants were randomized 2:1 to receive pegzilarginase or placebo, in addition to individualized standard of care, including dietary and pharmacological measures.

Pegzilarginase demonstrated statistically significant and clinically meaningful reductions in plasma arginine, with mean concentrations decreasing from 354.0 µmol/L at baseline to 86.4 µmol/L after 24 weeks – a 76.7% reduction compared to placebo. Notably, over 90% of treated patients achieved normal plasma arginine levels (40-115 µmol/L), a target that is unachievable with standard therapy alone. In parallel, patients showed improvements in functional mobility assessed by validated outcome measures such as the Gross Motor Function Classification System (GMCFS), Gross Motor Function Measures – 88 (GMFM), Gross Motor Function Measure – Parts E and D (GMFM-E; GMFM-D), the Modified Ashworth Scale (MAS), the Gillette Functional assessment, the 9-PEG Hole test, the Functional Mobility Scale (FMS), the Vineland Adaptive Behaviour Scales (VABS) and the 2-Minute Walk Test (2MWT). These gains were maintained and enhanced during the LTE phase, with continued improvement observed at 48 weeks. Pegzilarginase also led to significant reductions in key neurotoxic guanidino compounds, such as guanidinoacetic acid and argininic acid, while increasing plasma ornithine, thereby targeting the pathophysiological drivers of neurologic dysfunction in ARG1-D[5].

The safety profile of pegzilarginase was favorable, with most adverse events being mild or moderate in severity, and no new safety signals emerged during long-term exposure. No treatment discontinuations were reported due to hypersensitivity or metabolic decompensation. Collectively, PEACE provides the first high-quality evidence that enzyme replacement therapy can modify the natural history of ARG1-D, offering a therapeutic approach that not only corrects the metabolic defect but also has the potential to restore functional capacity and improve long-term outcomes for affected individuals[5].

RATIONALE AND OBJECTIVES OF THIS EXPERT OPINION PAPER

The introduction of pegzilarginase as the first etiological therapy for ARG1-D marks a pivotal advancement in the management of this rare and progressive disorder. However, its arrival also highlights the urgent need for a harmonized national framework to guide clinical practice. Until now, the diagnosis and care of patients with ARG1-D in Italy have largely been fragmented across centers, with variability in diagnostic workups, metabolic management strategies, and functional follow-up approaches[1,2].

This heterogeneity, while partially attributable to the rarity and clinical complexity of the disease, could result in inconsistent standards of care and unequal access to optimal treatment pathways. In light of recent therapeutic developments, a nationally shared perspective is critical to ensure equitable, timely, and evidence-based care for individuals with ARG1-D.

This expert opinion paper was conceived as a platform for critical reflection and shared clinical advancement in the management of ARG1-D in the era of enzyme replacement therapy. The initiative brings together the perspectives of a diversified group of clinicians to stimulate dialogue across complementary clinical profiles. The panel also includes clinicians with direct participation in the PEACE trial[5] as well as those with real-life experience managing differently impacted patients, thereby encompassing both investigational rigor and pragmatic clinical insight.

With causal therapy now available, it becomes imperative to re-evaluate the approach to ARG1-D beyond the structured environments of controlled trials. This paper aims to lay the groundwork for national guidance on diagnosis, therapeutic decision-making, and long-term monitoring, with the goal of building consensus both on core clinical practices and on exploratory research parameters.

Ultimately, this collaborative effort aims to serve not only as a practical contribution to national clinical practice but also as a starting point for a broader scientific conversation about the evolving natural history of ARG1-D in the post-pegzilarginase era – an era where patient management must evolve alongside therapeutic innovation.

PROPOSED CLINICAL PARAMETERS AND MONITORING FRAMEWORK

Given the complexity and multisystemic nature of ARG1-D, and in light of the paradigm-shifting therapeutic availability of pegzilarginase, the panel proposes a structured, multidomain framework to support the longitudinal characterization and monitoring of affected individuals. This model integrates assessments across biochemical, metabolic, neuromotor, neuroimaging, neurophysiological, hepatic, musculoskeletal, and quality-of-life domains, aiming to capture both disease mechanisms and individual therapeutic trajectories, and ultimately to inform personalized follow-up strategies.

Importantly, the phenotypic variability of ARG1-D demands a flexible approach to clinical monitoring that should consider age-specific and stage-specific presentation. As highlighted in recent expert consensus[2], certain "red flags", such as progressive lower limb spasticity, developmental regression, seizures, and cognitive or behavioral decline, should prompt further metabolic evaluation, particularly when standard neurological diagnoses (e.g., cerebral palsy or hereditary spastic paraplegia) do not fully explain the clinical course. In pediatric patients, early signs such as tip-toe walking, frequent tripping, growth delay, and feeding difficulties with spontaneous avoidance of protein-rich foods may precede overt neurological symptoms[2]. Conversely, in adolescents and adults, the disease may present with gait disturbances, loss of functional autonomy, or spastic paraplegia misclassified under more common neurodegenerative phenotypes.

To ensure broad applicability across clinical settings, the panel has identified for each domain a set of essential core assessments, readily implementable in most centers involved in the care of patients with inherited metabolic disorders, as well as optional advanced investigations, which may provide deeper mechanistic insights or support specialized therapeutic decision-making. In addition, the framework highlights a selection of emerging or exploratory research parameters, considered promising for future validation, including biomarkers of neuroinflammation and neurodegeneration, novel metabolic readouts, and parameters of muscle damage and the reversibility of these manifestations, which may further enhance our ability to stratify patients, monitor subclinical progression, and personalize long-term care strategies.

Crucially, because many first-line encounters with ARG1-D patients occur outside of specialized metabolic settings, this proposed framework is designed to be multidisciplinary in nature and translatable to general neurology, pediatrics, rehabilitation, and neuropsychiatry. By fostering shared awareness and diagnostic readiness across specialties, we aim to improve early detection and proactive management of this underrecognized, yet treatable, condition.

A comprehensive overview of the proposed assessments across all domains, including their categorization into essential, optional, and exploratory tools, is summarized in Table 1.

1. Biochemical and Metabolic Domain

Essential Core Assessments

Peripheral arginine levels longitudinal monitoring represents the key metabolic parameter for correlating metabolic control and clinical outcomes before and after treatment with the aim of normalizing arginine plasma levels.

Moreover, assessment of guanidino compounds could be additional longitudinal informative markers of metabolic modifications during treatment. These include guanidinoacetic acid (GAA), argininic acid (ARGA), α-keto-δ-guanidinovaleric acid (GVA), and α-N-acetylarginine (NAARG), all measurable by Ultra-High Performance Liquid Chromatography – Tandem Mass Spectrometry (UHPLC-MS/MS) and previously associated with seizure risk and white matter injury in ARG1-D[6,7].

Table 1. Summary of recommended clinical parameters in ARG1-D monitoring, by domain and level of recommendation.

Domain	Category	Recommended Parameters/Tools
Biochemical and Metabolic	Essential core assessments	Plasma arginine levels; guanidino compounds (GAA, ARGA, GVA, NAARG) measured by UHPLC-MS/MS.
	Optional advanced investigations	CSF arginine quantification; neurofilament light chain (NfL) in plasma/CSF; assessment of ureagenesis.
	Exploratory research parameters	Brain-acting hepatokines: GDF15 and FGF21, associated with mitochondrial stress, inflammation, and liver-brain signaling.
Neuromotor	Essential core assessments	GMFCS; GMFM-88; GMFM-D and GMFM-E; Modified Ashworth Scale (MAS); Gillette FAQ; 9-Hole Peg Test; Functional Mobility Scale (FMS); VABS; 2-Minute Walk Test (2MWT).
	Optional advanced investigations	Motor evoked potentials (MEPs) to assess descending corticospinal conduction.
	Exploratory research parameters	Ultrasound-based elastography; muscle MRI to assess stiffness, fibrosis, and reversibility of muscle damage.
Imaging	Essential core assessments	Brain and spinal cord MRI to assess baseline and longitudinal structural integrity, particularly of the corticospinal tracts.
	Optional advanced investigations	Proton magnetic resonance spectroscopy (^{1}H-MRS) for central arginine levels; diffusion tensor imaging (DTI); tractography; NODDI.
Liver Function	Essential core assessments	Albumin, INR, AST, ALT, GGT, total/direct bilirubin; liver ultrasound with elastography (Fibroscan®) for fibrosis assessment.
Cognitive, QoL, Behavioral	Essential core assessments	Age-appropriate cognitive tools (e.g., Wechsler scales, exectuve function tests); Pediatric Quality of Life Inventory (PedsQL); SF-36 (adults); CBCL; VABS; MetabQoL 1.0.
Musculoskeletal	Optional advanced investigations	DXA/MOC and QUS of the calcaneus; biochemical markers: osteocalcin, PTH, 25(OH)-Vitamin D, serum calcium and phosphorus, bone-specific ALP, NTX.
	Exploratory research parameters	Ultrasound-based elastography; muscle MRI for structural and compositional analysis.

Guanidinoacetic acid (GAA), argininic acid (ARGA), α-keto-δ-guanidinovaleric acid (GVA), α-N-acetylarginine (NAARG), Ultra-High Performance Liquid Chromatography – Tandem Mass Spectrometry (UHPLC-MS/MS), cerebrospinal fluid (CSF), Gross Motor Function Classification System (GMFCS), Gross Motor Function Measure – 88 (GMFM-88) Gross Motor Function Measure – Parts E and D (GMFM-E; GMFM-D), Vineland Adaptive Behavior Scales (VABS), international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), Child Behavior Checklist (CBCL), dual-energy X-ray absorptiometry (DXA/MOC), quantitative ultrasound (QUS), parathyroid hormone (PTH), alkaline phosphatase (ALP), N-terminal telopeptide of type I collagen (NTX).

Optional Advanced Investigations

As part of a comprehensive baseline and follow-up assessment, the expert panel also proposes the inclusion of lumbar puncture for cerebrospinal fluid (CSF) arginine quantification as a complementary diagnostic and monitoring tool. Central arginine levels may offer a more accurate reflection of neuronal exposure to metabolic toxicity and help elucidate the relationship between biochemical normalization in plasma and clinical response. Recognizing the logistical and ethical considerations associated with lumbar puncture, the procedure could be strategically performed in conjunction with brain MRI, particularly under sedation in pediatric patients, thereby minimizing procedural burden while maximizing diagnostic yield. This approach would support a more integrative and mechanistic understanding of treatment effects, particularly in early-phase or borderline clinical cases.

Assessment of ureagenesis before and after initiation of pegzilarginase therapy is advisable[8] but not all metabolic centers have access to this test. Recently proposed biomarkers of neurodegeneration, such as neurofilament light chain (NfL), could be informative on axonal impairment and improvement, as confirmed in several other neurological disorders characterized by spastic paraplegia[9].

Exploratory Research Parameters

Additionally, the panel suggests the inclusion of brain-acting hepatokines GDF15 and FGF21 as exploratory biomarkers. GDF15, a stress-induced cytokine associated with mitochondrial dysfunction and inflammation, and FGF21, a key regulator of energy balance and metabolism by acting as a mediator for liver-to-brain communication, may offer insight into systemic energy expenditure, metabolic stress, and neuroinflammatory activation in ARG1-D[10-12].

2. Neuromotor Domain

Essential Core Assessments

To objectively monitor motor function before and during treatment, the use of validated clinical outcome measures is essential. The expert panel recommends regular assessment using the same instruments employed in the PEACE trial[5]:

- Gross Motor Function Classification System (GMFCS) to stratify overall motor impairment severity and assess functional ambulation categories.
- Gross Motor Function Measure – 88 (GMFM-88) for detailed evaluation of gross motor skills across multiple dimensions.
- Gross Motor Function Measure – Parts E and D (GMFM-E; GMFM-D) specifically targeting domains of walking/running/jumping and sitting/standing, respectively.
- Modified Ashworth Scale (MAS) for semi-quantitative assessment of muscle spasticity.
- Gillette Functional Assessment Questionnaire to capture mobility performance in everyday contexts from the caregiver's perspective.
- 9-Hole Peg Test (9-HPT) for upper limb dexterity and fine motor control evaluation.
- Functional Mobility Scale (FMS) to assess ambulatory ability across different environmental distances (5, 50, and 500 meters).
- Vineland Adaptive Behavior Scales (VABS) to measure adaptive behaviors in communication, daily living skills, and socialization.
- 2-Minute Walk Test (2MWT) as a standardized metric of functional endurance and walking capacity.

These scales have shown sensitivity in patients with ARG1-D and provide quantifiable endpoints aligned with therapeutic goals[5].

Optional Advanced Investigations

Functional neurophysiological studies, especially motor evoked potentials (MEPs), are proposed to assess the integrity of corticospinal tract pathways, offering a dynamic and objective measure of descending motor conduction over time.

3. Imaging Domain

Neuroimaging represents a crucial tool for characterizing structural and functional changes in the central nervous system.

Essential Core Assessment

The panel recommends performing brain and spinal cord MRI both before and after initiation of pegzilarginase therapy, with the aim of assessing structural involvement of the central nervous system, particularly the integrity of the corticospinal tracts. This imaging modality serves as a key tool to detect and monitor pre-existing or evolving cerebral and spinal injury, enabling clinicians to evaluate whether structural damage is present at baseline and to track its stability, progression, or potential reversibility under treatment.

Optional Advanced Investigations

As part of the optional advanced investigations suggested, the use of proton magnetic resonance spectroscopy (^{1}H-MRS) is proposed to non-invasively assess cerebral arginine levels before and after the initiation of pegzilarginase therapy. Spectroscopic sequences with intermediate echo times (TE ~144 ms) have demonstrated the capacity to isolate and quantify the arginine peak at approximately 3.8 ppm, providing a potential biomarker of central biochemical exposure in ARG1-D. This technique may be particularly valuable in exploring the relationship between plasma arginine normalization and persistent neurological symptoms, especially in patients with evidence of progressive spasticity or cognitive plateauing despite metabolic control. In this regard, ^{1}H-MRS offers a complementary and non-invasive approach to cerebrospinal fluid sampling and could be strategically integrated into routine brain MRI protocols, including during sessions conducted under sedation in pediatric patients. Previous studies[13,14] have confirmed the visibility of this peak in affected individuals and support the utility of spectroscopy as a surrogate marker of arginine neurotoxicity and treatment response.

Diffusion tensor imaging (DTI) and tractography are also advised in order to evaluate corticospinal tract integrity longitudinally. Additional functional sequences, such as neurite orientation dispersion and density images (NODDI), would be able to assess the microstructural complexity of dendrites and axons and the integrity of white matter.

All these modalities have the potential to detect subclinical changes and to correlate neuroanatomical recovery with clinical improvement in response to pegzilarginase.

4. Liver Function Monitoring

Given the impact of ARGD-1 on the liver, proposed liver function monitoring includes:

- Synthetic parameters: including albumin and international normalized ratio (INR)
- Cytolytic parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT)
- Cholestatic markers: gamma-glutamyl transferase (GGT), alkaline phosphatase, total/direct bilirubin
- Liver fibrosis assessment: Ultrasound scan with elastography (Fibroscan®)

5. Cognitive Function and Quality of Life and Behavioral Assessment

Monitoring patient-centered outcomes is essential to contextualize biochemical and functional data. The expert group recommends regular use of standardized cognitive behavioral and quality-of-life assessment tools, including:

- Standardized age-appropriate cognitive assessment tools (Wechsler scales)
- Age-specific test for executive functions
- Pediatric Quality of Life Inventory (PedsQL)
- SF-36 QoL assessment for adults
- Child Behavior Checklist (CBCL)
- Vineland Adaptive Behavior Scales (VABS)
- MetabQoL 1.0

These instruments allow for systematic evaluation of emotional regulation, attention, adaptive functioning, and caregiver-reported well-being, with high relevance in chronic adult and pediatric neurological conditions[15-17].

Particularly, to comprehensively capture the burden of disease in children and adolescents affected by intoxication-type inborn errors of metabolism (IT-IEM), the MetabQoL 1.0 questionnaire was developed within the framework of the European Network and Registry for Intoxication Type Metabolic Diseases (E-IMD). Unlike generic or chronic-generic instruments, MetabQoL 1.0 is the first disease-specific health-related quality of life (HrQoL) assessment tool tailored to this patient population. Moreover, it is positioned as a robust and responsive instrument for monitoring patient-reported outcomes in clinical trials and long-term care. It is particularly suited for evaluating the multidimensional impact of emerging therapies, such as pegzilarginase, in ARG1-D, and it represents a critical step toward integrating patient-centered endpoints into the routine management of rare metabolic diseases[18].

EXPERT OPINION AND DISCUSSION

The therapeutic advent of pegzilarginase introduces a transformational shift in the natural history of ARG1-D, allowing for the first time sustained normalization of plasma arginine levels and improvements in motor function in the majority of patients[5,7]. This unprecedented biochemical and functional efficacy has simultaneously revealed the need for a deeper and more nuanced understanding of the disease's pathophysiological heterogeneity, especially in relation to neurodegeneration, residual disease activity, and long-term outcomes.

The Italian expert group proposes a framework for interpreting the real-world clinical data that will be gathered following this publication, with the aim of informing precision medicine approaches and establishing shared national guidance for the diagnosis and longitudinal management of patients with ARG1-D.

FROM BIOCHEMICAL CORRECTION TO FUNCTIONAL UNDERSTANDING

The normalization of plasma arginine levels, as achieved in over 90% of patients treated with pegzilarginase in the PEACE trial[5], constitutes a major biochemical breakthrough in the treatment of ARG1-D. This therapeutic milestone has demonstrated clear clinical benefits, particularly in terms of functional stabilization or improvement. However, despite these advances, a wide range of pathophysiological mechanisms remain unexplored, limiting our ability to fully understand the determinants of response and long-term disease trajectory.

Indeed, the discrepancy often observed between biochemical normalization and residual neurological impairment in some patients suggests that plasma arginine may not reliably mirror CNS arginine burden. Given the bidirectional but transporter-modulated equilibrium between plasma and CSF, the expert panel underscores the importance of systematic CSF arginine and guanidino compound (GC) profiling, including GAA, ARGA, GVA, and NAARG, as an investigative tool to assess the extent of persistent neurotoxicity, despite adequate peripheral control[2,7].

In parallel, neurofilament light chain (NfL) in both plasma and CSF is proposed as a surrogate marker of axonal damage, enabling clinicians to distinguish biochemical response from true neuroprotective efficacy. This distinction may be particularly relevant in individuals with longstanding disease or incomplete clinical recovery, in whom structural CNS damage might already be established.

The optional advanced investigations and exploratory research parameters proposed in this paper were deliberately selected to probe the fundamental mechanisms of disease, extending well beyond routine clinical endpoints. These investigations aim to bridge current knowledge gaps and support the evolution of a real-world, mechanism-informed management model, paving the way toward an increasingly multidisciplinary and individualized care strategy.

One of the key challenges in ARG1-D is the observed phenotypic heterogeneity, even among patients carrying identical genotypes. This observation strongly suggests a role for epigenetic regulation and genetic modifiers, which may shape not only the severity of the neuromotor phenotype but also the capacity for recovery following treatment. The pathophysiological role of hypomobility-induced muscle damage, and its potential reversibility under therapy, also emerges as a critical but insufficiently understood dimension.

The panel proposes that future research should address whether functional improvements observed after pegzilarginase initiation are mediated by recovery of axonal integrity, white matter structure, or myelin plasticity. In this context, it can be hypothesized that both injury and repair may be governed by overlapping inflammatory and redox-sensitive pathways, which could be differentially activated across patients.

Furthermore, the paper highlights the muscle compartment as an area of unmet clinical need. In particular, a better understanding is required regarding the onset and evolution of muscle fibrosis and whether this process can be halted or reversed by targeted metabolic correction and rehabilitation strategies. To this end, the panel identifies three principal biomarker domains to guide future exploration: cellular lysis markers, reflecting direct tissue injury; inflammatory status, with a focus on GDF15 as a sensor of mitochondrial and metabolic stress; and myelin integrity, as indicated by neurofilament light chain levels, serving as a dynamic index of central nervous system structural damage.

Collectively, these lines of investigation aim to dissect the multifactorial nature of ARG1-D and provide real-world, mechanism-driven evidence that may inform both clinical decisions and the design of next-generation therapeutic strategies. The current paper, by framing these open questions, aspires to lay the groundwork for future translational research efforts in this evolving field.

UNSOLVED QUESTIONS IN ARG1-D: FROM MUSCLE STIFFNESS TO ARGININE-DRIVEN AUTOPHAGIC MODULATION

While the hallmark features of ARG1-D remain centered on progressive neuromotor dysfunction, cognitive impairment, and biochemical dysregulation, clinical observations increasingly point to a constellation of secondary manifestations, notably muscle damage and growth retardation, which, although not defining elements of the disease, may significantly contribute to long-term disability. These features are likely the result of chronic neurodisability, prolonged spasticity, nutritional compromise, and metabolic inefficiency, and deserve greater attention as part of an expanded disease model.

In particular, clinicians have reported segmental muscle weakness and acquired stiffness, especially in patients with longstanding mobility limitations[2]. Analogous findings[19,20] in cerebral palsy (CP) suggest that two pathophysiological mechanisms may underlie this phenomenon: an increase in extracellular matrix viscosity, which reduces elasticity and heightens resistance to stretch, and a fibrotic substitution of contractile muscle fibers, ultimately compromising functional output and the reversibility of motor deficits. These changes, although secondary, may become self-perpetuating and resistant to recovery even after correction of the underlying biochemical defect, especially if not detected and addressed early.

To better characterize these alterations, the expert panel highlights the potential of ultrasound-based elastography as a non-invasive technique to assess muscle stiffness and fibrosis *in vivo*. This modality, which measures the mechanical properties of tissues by quantifying their elastic response to an applied force or vibration, offers the possibility of detecting early structural changes before overt clinical symptoms arise. While elastography has shown promise in neuromuscular disorders and in the evaluation of spastic muscles, it is not yet widely available in most centers, and no established clinical experience currently exists for its application in ARG1-D. Nonetheless, the panel recommends this tool as a future implementation priority, particularly in research contexts, to better elucidate the pathophysiological mechanisms of muscle damage and remodeling in ARG1-D and to explore potential biomarkers of tissue reversibility under enzyme replacement therapy.

In this context, the expert panel proposes the use of muscle magnetic resonance imaging (muscle MRI) as a non-invasive tool to evaluate the morphological and structural integrity of skeletal muscle. This includes the detection of fatty infiltration, atrophy, inflammation, or fibrosis, which may aid in differentiating primary neuromuscular involvement from secondary adaptations due to prolonged disuse or spasticity. Monitoring these parameters before and after the initiation of pegzilarginase therapy could yield crucial insights into the degree of muscle reversibility and inform targeted rehabilitation strategies.

In parallel, the potential involvement of the skeletal system must not be overlooked. Patients with ARG1-D may experience subclinical disturbances of bone metabolism, arising from chronic dietary protein restriction, reduced mechanical loading, or systemic metabolic derangements. To assess bone health, the panel recommends a dual approach combining instrumental techniques, including dual-energy X-ray absorptiometry (DXA/MOC) and quantitative ultrasound (QUS) of the calcaneus, with biochemical profiling of key markers. These include osteocalcin, parathyroid hormone (PTH), 25-hydroxyvitamin

D, serum calcium and phosphorus, bone-specific alkaline phosphatase, and N-terminal telopeptide of type I collagen (NTX). Such evaluations may uncover early signs of osteopenia or mineral imbalance, which, if identified and addressed proactively, may reduce the risk of fracture or skeletal fragility, especially during critical growth periods.

Incorporating both muscle and bone monitoring into the clinical routine expands the perspective from a purely neurological focus to a more comprehensive neuromusculoskeletal model of disease. This multidimensional approach recognizes that functional outcomes in ARG1-D are the result not only of central metabolic correction but also of peripheral tissue integrity, which may be modifiable through early intervention and longitudinal surveillance.

An additional pathophysiological dimension that deserves deeper exploration in ARG1-D is the role of arginine in the modulation of autophagic processes. Autophagy represents a fundamental cellular mechanism responsible for the maintenance, repair, and turnover of damaged organelles and proteins, playing a critical role in neuronal homeostasis and network integrity[21]. In several inborn errors of metabolism, including urea cycle disorders, disturbances in nitrogen handling and amino acid flux have been shown to alter autophagy, either activating or suppressing this pathway depending on the metabolic context.

In ARG1-D, chronic elevation of arginine and guanidino compounds may have a dual effect: while contributing directly to neurotoxicity and oxidative stress, they may also interfere with cellular regulatory pathways such as nitric oxide synthesis, protein arginylation, and lysosomal turnover, all of which are tightly connected to the autophagic machinery[21,22]. Indeed, high levels of arginine have been shown to modulate autophagy in cancer cells and neurodegenerative models, through mechanisms involving epigenetic control, argininosuccinate synthase expression, and redox signaling cascades[21].

These mechanisms are not unique to ARG1-D but appear to converge across several urea cycle disorders, including hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome and P5CS deficiency, where either arginine deficiency or ammonia excess contributes to autophagic deregulation. The shared neurodegenerative phenotype observed in these disorders, particularly in spastic paraparesis, may therefore reflect a common vulnerability of long axonal tracts to impaired autophagic flux and metabolic stress[21].

Understanding how arginine modulates autophagy is not only relevant for explaining disease progression, but also potentially critical for interpreting the functional recovery observed in some patients after pegzilarginase therapy. It is plausible that the amelioration of clinical symptoms is mediated, at least in part, by the reactivation of endogenous neuronal repair mechanisms, including remyelination and axonal regeneration, both of which depend on efficient autophagic regulation.

In this context, the expert panel underscores the importance of integrating targeted biomarker profiling into clinical follow-up protocols. Specifically, the combined assessment of markers of cellular lysis [e.g., lactate dehydrogenase (LDH), creatine-kinase (CK)], neuroinflammation (e.g., GDF15), and myelin integrity (e.g., neurofilament light chain) may offer insights into the relative contributions of necrotic, inflammatory, and redox-autophagic pathways in individual patients, guiding therapeutic expectations and supporting stratified care approaches.

Ultimately, these unresolved clinical dimensions underscore the need for ongoing observational research and interdisciplinary collaboration to refine monitoring strategies, define clinically meaningful secondary endpoints, and ensure that every aspect of disease burden, both primary and secondary, is addressed in a timely and proactive manner.

SOCIAL COSTS AND BURDEN OF DISEASE IN ARG1-D

The impact of ARG1-D extends well beyond the clinical and biochemical domains, imposing a profound burden on patients, caregivers, and society at large. Recent European cross-sectional surveys[23] have provided quantitative insight into this burden, highlighting how patients with ARG1-D, particularly those with combined mobility and cognitive impairments, experience a marked loss of autonomy, reduced quality of life, and significant reliance on formal and informal caregiving resources. From a societal perspective, the estimated annual cost per patient has been reported to exceed £68,000, with wide variation depending on functional severity: patients with severe cognitive impairment or advanced motor dysfunction (GMFCS levels 3-5) incur annual costs surpassing £100,000, compared to ~£49,000 in those with mild impairment[24]. The impact on caregiver quality of life and workforce participation is equally notable, with a significant proportion experiencing moderate-to-severe caregiver burden[23].

By mitigating clinical progression and preserving function, pegzilarginase could not only improve individual health outcomes but also substantially reduce the long-term socioeconomic impact associated with ARG1-D.

This multidomain framework has the potential to enable clinicians and researchers to:

1. Identify early biological signals of treatment response or failure, allowing timely therapeutic adjustments;
2. Correlate biochemical and imaging markers with clinical trajectories, supporting predictive modeling;
3. Uncover residual disease activity despite normalized plasma arginine, prompting reconsideration of treatment goals;

Contribute to harmonized national and international registries, like the well-established E-IMD (https://www.e-imd.org), enabling multicenter data pooling and comparative analysis.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The structured data collection proposed in this paper will allow the Italian community to generate hypothesis-driven real-world evidence, addressing key open questions in ARG1-D, like:

- What is the minimal effective reduction in arginine or GCs needed to halt CNS damage?
- When initiated early, how much does pegzilarginase positively impact patients' quality of life? And how much does it differ when compared to patients starting it later in their history?
- Can neurocognitive, neurophysiological and imaging markers guide prognosis better than static biochemical targets?

These questions are no longer theoretical. As enzyme therapy becomes accessible, there is an urgent need to match therapeutic innovation with diagnostic precision and real-world evidence. The multidimensional framework proposed here aims to ensure that clinical practice does not lag behind the therapeutic possibilities now available for this rare but increasingly manageable disorder.

CONCLUSIONS

The availability of pegzilarginase introduces a new opportunity for patients with ARG1-D. For the first time, clinicians have access to a disease-modifying therapy capable of normalizing plasma arginine, reducing neurotoxic metabolites, and translating these biochemical changes into clinically meaningful improvements in functional mobility. This shift represents not merely a therapeutic milestone, but a fundamental redefinition of what is possible, nowadays, for individuals living with ARG1-D.

However, this transformation cannot be achieved by pharmacology alone. It requires a coordinated, multidisciplinary collaboration among expert centers to redefine standards of diagnosis, monitoring, and care delivery. The consensus framework proposed in this paper serves as a foundation for a new era of proactive and precision-based management.

By fostering national alignment around real-world clinical practices and embedding advanced biomarker strategies into routine care, this initiative has the potential to impact not only the present of patients already diagnosed, but also to transform the future for families yet to receive a diagnosis. With earlier recognition, better tools for monitoring, and an effective therapy now available, we can envision a paradigm where ARG1-D is no longer a relentlessly progressive disorder, but a manageable condition with preserved function, autonomy, and hope.

This is the power of expert collaboration and scientific innovation working in synergy. As a community, we now stand at the threshold of a future where the trajectory of ARG1-D may be permanently altered for the better, benefiting generations to come.

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No AI-assisted technology was used for the production of this manuscript.

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Serena Gasperini, Diego Martinelli, and Francesco Porta contributed equally to the conception, drafting, and critical revision of the manuscript. All authors reviewed and approved the final version for submission.

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OPTIMIZING PROTEIN INTAKE IN UREA CYCLE DISORDERS: AN EXPERT OPINION

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ABSTRACT **–** Urea cycle disorders (UCDs) are rare inherited metabolic diseases caused by defects in urea cycle enzymes or transporters. The main objective of dietary management in patients with UCDs is to ensure stable metabolic control and prevent long-term complications, while supporting normal growth and development. Dietary protein restriction remains the cornerstone of long-term management, in combination with nitrogen-scavenging drugs, supplementation of arginine/citrulline, vitamins, minerals and essential amino acids if needed. However, lifelong low-protein diets raise concerns regarding growth, bone health, body composition, immune function and quality of life in patients with UCDs. Evidence on optimal protein intake in UCDs is scarce and heterogeneous, largely based on retrospective data and inconsistent nutritional methodologies. In this expert opinion, a multidisciplinary panel comprising eight inherited metabolic disease specialists from five Italian reference centers reviewed current challenges. It proposed recommendations for optimizing protein intake in UCD patients. The panel highlighted that dietary management involves not only metabolic aspects but also psycho-relational factors, both of which must be addressed to achieve optimal health outcomes in patients with UCDs. Clinical, biochemical, nutritional, instrumental, and psychological tools should be integrated to monitor outcomes, and optimization strategies should be tailored individually across all ages. The panel emphasized that all patients are potentially eligible for protein optimization, provided that individual tolerance, nutritional status, metabolic control, and psychosocial context are carefully assessed. Nitrogen-scavenging therapy may support higher protein intake, with close clinical and biochemical monitoring required during titration. This consensus represents the first expert opinion specifically addressing protein optimization in UCDs, providing a practical framework for dietary management.

Keywords: Urea cycle disorders, Low protein diet, Nutritional status, Inherited metabolic disease, Nitrogen-scavenging therapy.

Abbreviations: BCAA: branched-chain amino acid; E-IMD: European Registry and Network for Intoxication-type Metabolic Diseases, HrQoL: health-related quality of life, UCD: Urea cycle disorder.

INTRODUCTION

Urea cycle disorders (UCDs) are rare inborn errors of nitrogen detoxification/arginine synthesis due to defects in urea cycle enzymes or transporters (carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase, arginase, N-acetyl glutamate synthetase, ornithine translocase)[1]. UCDs can present at any age with acute, chronic, or intermittent symptoms. Their signature feature is the life-threatening hyperammonemic crisis, often triggered by catabolic stress, protein load, or certain drugs, leading to neurological damage[2].

The primary goal of dietary management for patients with UCDs is to maintain good metabolic control and prevent chronic complications, while enabling normal growth and development. This involves restriction of natural dietary protein in combination with nitrogen-scavenging drugs, supplementation of arginine/citrulline, vitamins, minerals, and essential amino acids if needed[3,4]. Protein intake recommendations for patients with UCDs are based on the 2007 WHO/FAO/UNU "safe levels of protein intake"[2,5]. A combination of low and some high-biological-value proteins divided between three to five meals should be provided daily. Despite the goal of the WHO/FAO/UNU safe level, considering that the population's normal protein intake on a free diet easily overcomes this level, UCD diets need to be restricted, limiting food groups like meat, fish, eggs, dairy products, and often substituting cereal-based products with special low-protein foods that have lower palatability. Essential amino acid supplementation, especially branched-chain amino acid (BCAA), is essential when protein tolerance is too low, up to 30% of the total protein intake[2]. However, optimal protein intake must be carefully individualised in every patient, according to age, severity of the disorder, protein tolerance, gender, and physical activity. Moreover, regular clinical, biochemical, and nutritional monitoring by a multidisciplinary metabolic team following an individualized schedule is recommended[2,3].

Protein aversion is a common feature of UCDs that can serve as a diagnostic clue for earlier diagnosis when investigating symptoms, such as food refusal, recurrent vomiting, and episodic altered consciousness, and it also highlights that metabolic decompensation is more frequently related to low rather than high protein intake. Protein aversion can persist or develop even after diagnosis and the initiation of a diet, making it difficult for patients to meet their prescribed protein requirements and, consequently, leading to metabolic decompensation[6].

Adherence to a protein-restricted diet can be challenging for patients with UCDs and is commonly associated with a reduced health-related quality of life (HrQoL)[7-12]. For example, a cross-sectional study[10] that included six children with UCDs reported lower general well-being than children with leukemia and lower relations with friends than healthy peers, identifying dietary constraints as a major contributing factor. Likewise, focus group interviews with nine UCD pediatric patients and parents revealed that dietary restrictions and stigmatization/social exclusion were the factors considered most relevant for HrQoL[11]. In addition, self-reports and proxy reports of HrQoL in 42 children and adolescents with UCDs showed significantly lower HrQoL total scores compared to healthy controls, as a consequence of both the burden of disease and dietary treatment[12]. A disease-specific assessment tool for HrQoL in UCDs and other intoxication-type metabolic diseases was developed (MetabQoL 1.0). It may be a promising option to study aspects specifically relevant to patients with UCDs and their caregivers, including the dietary burden[13]. Poor adherence to diet is a commonly reported problem for UCDs in all age groups, but it is known to deteriorate with age, especially from the age of 10 years onwards. The factors that could positively or negatively affect adherence across inherited metabolic disorders treated by low-natural-protein diets have been highlighted in a comprehensive review and include the burden of diet and amino acid supplement administration, patient responsibility, family characteristics, cultural and religious influences, social aspects, and information sources[14].

Nutritional complications, such as impaired growth, have been documented in children and adolescents with UCDs on low-protein diets[15-18]. However, less information is currently available in the literature regarding bone health and body composition in adult patients[18-21]. Moreover, data remain inconsistent regarding the relative importance of total protein intake, essential amino acid supplementation, and the protein-to-energy ratio in determining growth and metabolic outcomes[19,22-24]. For instance, a retrospective longitudinal study of 77 patients with UCDs found that the final height was significantly below the target height, tended to be lower in males, worsened during puberty, and was negatively associated with total protein intake. The mean total protein intake was reported to be below the recommended safe levels during the pubertal period (0.6 g/kg/day) and after reaching final height (1.2 g/kg/day). Bone demineralization and body-composition abnormalities with low lean mass were also observed[18]. On the contrary, retrospective longitudinal data from 44 patients with UCDs showed that growth patterns were within normal ranges, but median protein intake was found to meet or exceed the FAO/WHO/UNU safe

levels. A protein-to-energy ratio range of 1.5-2.9 g protein/100 kcal/day was indeed associated with optimal growth, and a significant negative correlation was observed between total protein intake and fat mass[19]. Similarly, total and natural protein intake were inversely related to fat mass percentage in a retrospective study[20] that included 12 adults affected by UCDs. The average protein intake was lower than the recommended safe levels (0.61 g/kg/day), and more than one-third of the patients were classified as overweight. On the other hand, in 307 UCDs individuals longitudinally followed by the Urea Cycle Disorders Consortium and the European Registry and Network for Intoxication-type Metabolic Diseases (E-IMD) [22], growth impairment was determined by disease severity (as reflected by early onset individuals) and associated with reduced plasma BCAA concentrations, but was not predicted by the amount of natural protein intake alone. In addition, a longitudinal study[23] of 311 UCD patients from the E-IMD found that height was positively associated with the natural protein-to-energy ratio and BCAA levels, but did not significantly differ between asymptomatic and symptomatic patients and those with and without a protein restriction.

Toxic metabolites, such as ammonia and insufficient supplies of essential nutrients and micronutrients, as in low-protein diets, may compromise the immune system function[25-29]. However, very little data has been reported on patients with UCDs in the literature to date[30-32]. For example, in a recent study[30] that enrolled 24 UCD patients, the proliferation of T cells in response to mitogens was found to be impaired, with amino acid analysis revealing distinct metabolic disruptions, emphasizing the complex interplay between metabolism and immune function. Similarly, in a case report[31] of a child with hyperornithinemia–hyperammonemia–homocitrullinuria syndrome, decreased lymphoproliferation rates in response to most mitogens were reported, and significantly decreased levels of inflammatory cytokines were detected.

This article reports the authors' advice from their best practice on the optimization of protein intake in patients diagnosed with UCDs, including the metabolic and psycho-relational issues involved in the low-protein diet, the tools used to identify these issues, the characteristics of the potential candidate for optimization, and how this could be proposed and implemented in clinical practice.

METHODS

A multidisciplinary panel of experts from five Italian inherited metabolic diseases reference centers met to identify current challenges and provide recommendations for the optimization of protein intake in UCD patients. The expert panel comprised eight inherited metabolic disease specialists, including four pediatricians (F.M., M.S., R.T., A.T.), two dietitians (A.D., S.S.), an adult endocrinologist (E.S.), and a psychologist (B.G.).

A preliminary free-response survey that included eight main questions regarding existing challenges and available tools for optimizing protein intake in UCDs was sent to all the participants two weeks before the virtual meeting. Answers to the survey were collected and summarized, and later shared with all the expert panel members during the virtual meeting.

Consensus and recommendations evolved during the virtual meeting, which was held on 25 June 2025. Experts shared their current clinical practices, highlighting the process of care and services for the dietary management of UCD patients in their centers. Following the virtual meeting, the discussion was summarized in this paper.

RESULTS

In the described process, the panel provided eight shared consensus answers to the eight initial questions proposed in the survey.

Which Metabolic and/or Psycho-Relational Domains are Involved in a Low-Protein Diet?

The panel agreed that a low-protein diet for the management of UCD patients engages both metabolic and psycho-relational domains.

Metabolic domains include maintenance of good metabolic control to prevent decompensation and hospitalization, support of normal growth and development, and achievement of optimal nutritional status in terms of protein, energy and vitamin intake.

Psycho-relational domains encompass difficulties in sustaining long-term adherence to dietary therapy, challenges in establishing and maintaining social relationships, cognitive and neuropsychological functioning, as well as family dynamics, parenting styles, and cultural or religious influences. Both individual and family-related issues should be addressed during initial and follow-up evaluations. Key areas include: emotional well-being, acknowledging that restrictive dietary therapy may constitute a vulnerability factor for dysfunctional eating patterns; social and relational dynamics, promoting coping strategies to prevent isolation; autonomy, focusing on developing patient awareness and competence in dietary self-management; and cognitive and neuropsychological functioning, considering both the risk of neurocognitive impairment and the impact of specific neuropsychological deficits on diet management. Of fundamental importance are the processes of elaboration and adaptation, including acceptance of the diagnosis, awareness of its long-term implications, and the family's adjustment to the chronic condition, all of which are crucial for adherence to restrictive dietary therapy.

The panel agreed that metabolic and psycho-related domains are interrelated and that both need to be addressed to ensure the best health outcome for the patients diagnosed with UCDs. However, it is recognized that without overcoming the psycho-relational issues through education and engagement of both the patient and the family, the metabolic goals are inevitably at risk (Figure 1).

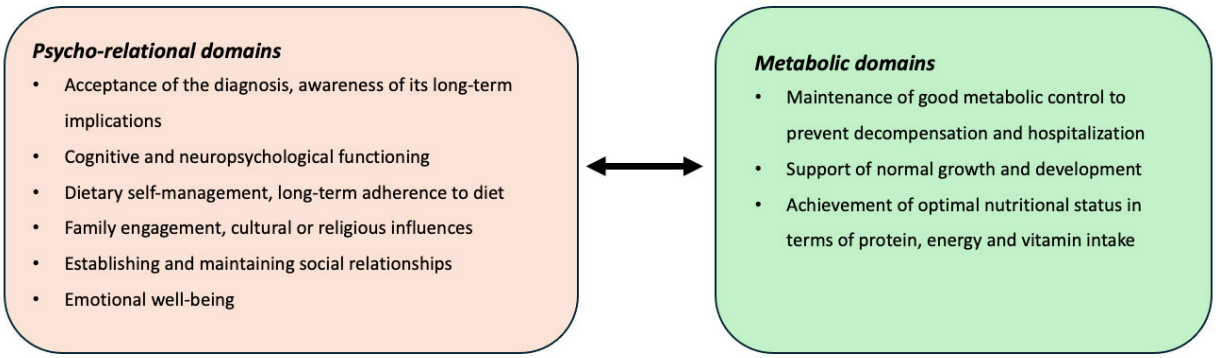

Figure 1. Issues and challenges of low-protein diet management in UCDs.

Which Tools Could Be Used in Clinical Practice to Identify Possible Issues Related to a Low-Protein Diet?

The panel agreed that clinical, biochemical, instrumental, and psychological tools should be used in clinical practice to identify possible issues related to a low-protein diet in UCD patients.

Among clinical tools, auxological measures plotted on growth charts, including the child's height/length, weight, weight-for-height, and body mass index (BMI) for age, body circumferences, and skinfold thickness measurement, together with physical examination, are mandatory to identify possible developmental issues and/or nutritional deficiencies. A careful examination of skin, hair, and nails should also be part of the diagnostic workup.

A comprehensive nutritional assessment conducted by an expert dietitian should be performed at each visit, allowing for a detailed examination of a patient's macronutrient and micronutrient intake, helping to identify potential deficiencies or excesses that may correlate with biochemical and clinical tests, or be predictive if they are not immediately apparent from standard biochemical tests. Standard dietary assessment tools, such as 3 to 7-day food diaries or 24-hour recalls, are typically self-reported by the patient, and then interpreted by the dietitian, combining diet history, and analyzed with food composition tables and software to estimate nutrient intake. Since there are no specific nutritional requirements defined for patients with UCDs, it is both necessary and appropriate to use standard nutritional guidelines to interpret dietary intakes, such as those from the WHO and the dietary reference values of nutrients and energy for the Italian population (LARN, National Recommended Energy and Nutrient Intake Levels). These values serve as a starting point for calculating individual nutritional requirements, which must then be adapted during follow-up, based on the patient's specific protein tolerance and clinical status. Ultimately, a complete dietary assessment complements other tools by providing a di-

rect, practical view of the patient's eating habits, preferences, and motivation, which is essential for the long-term management of their nutritional therapy.

Biochemical examinations should include complete blood count (including differential leukocyte count), renal and hepatic function, ammonia, plasma amino acids (comprising BCAA), protein, iron, calcium, phosphorus, vitamin status, urine test with sediment and urinary biochemistry.

Among instrumental tests, dual-energy x-ray absorptiometry and bioelectric impedance analysis are useful to investigate bone status and body composition, respectively.

A patient's developmental delay may be detected during a routine clinical exam, but periodic neuropsychological evaluations with developmental and cognitive testing are often necessary. Screening and monitoring of psychopathological aspects, such as irritability, aggression, somnolence, apathy, anxiety, mood changes and social withdrawal, should also be conducted. Health-related quality of life questionnaires can be used alongside clinical evaluations to provide a comprehensive assessment that captures the patient's and caregiver's perspective, offering insight into the real-life impact of the disease and chronic dietary therapy on daily functioning as experienced by patients and families (Figure 2).

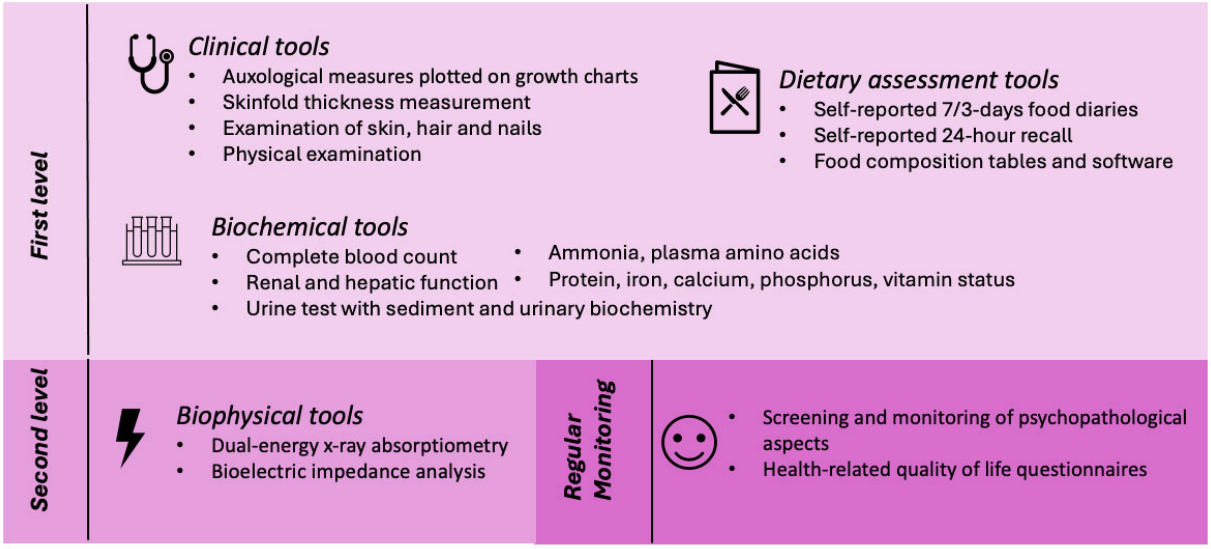

Figure 2. Identification of possible issues in metabolic and psycho-relational domains.

Which of These Tools are Used Routinely in Your Clinical Practice?

The panel concurred to divide the above-mentioned tools into first and second tiers, according to the severity of the disease, the extent of protein restriction, and the resources available in each metabolic center.

Clinical and biochemical tools should ideally be performed at every visit. However, the extent and frequency of clinical and biochemical monitoring depend on the age, severity of the disease, and metabolic stability of the patient and should be individualised by the healthcare team.

On the other hand, instrumental assessment can be performed on a less frequent basis, according to the general recommendation for the age group and the presence of established complications.

Ideally, all previously described psycho-relational variables should be regularly monitored as part of routine patient follow-up. In practice, the extent and frequency of these assessments depend on the resources available at each center, including the presence of a psychologist in the multidisciplinary metabolic team. In particular, a comprehensive evaluation of the child's developmental and emotional profile performed during the early years of childhood can promptly identify any delays in achieving developmental milestones, communicative-relational difficulties, or emotional-behavioral alterations, allowing for the early initiation of a tailored intervention (Figure 2).

At Which Stages of Life Do The Metabolic and/or Psycho-Relational Domains Have the Greatest Impact?

The panel agreed that all stages of life (childhood, preadolescence, adolescence, adulthood, pregnancy) can be profoundly impacted by the metabolic and psycho-relational domains for different reasons.

During childhood, the main metabolic issues regard the correct growth of the child during different nutritional phases, which also include breastfeeding and weaning. On the contrary, psycho-relational concerns predominantly involve caregivers and encompass acceptance of the disease, guidance on the dietary regimen, promotion of healthy eating behaviours, and development of coping skills to manage emotional stress.

During preadolescence, optimal growth remains a crucial concern, with the timely onset of puberty representing a key developmental milestone. Additionally, children start to form more complex social relationships with their peers and gradually become aware of the challenges and impact associated with their dietary treatment, which can influence both adherence and emotional well-being.

During adolescence, achievements of normal final height, weight, and peak bone mass are the main metabolic goals. At the same time, psycho-relational factors strongly influence adherence to dietary treatments during this phase. Social integration and peer acceptance are crucial for the adolescent's overall well-being. This period also marks the beginning of a gradual transition of responsibility from caregivers to the patients themselves. Therefore, it is essential to actively involve adolescents in learning more about their condition and managing their care. At the same time, typical adolescent behaviors, such as rebellion against rules, risk-seeking, impulsivity, difficulty planning for future consequences, social pressure and the drive to conform with peers, can challenge adherence and require tailored support and guidance.

During adulthood, bone and reproductive health are metabolic priorities. Periodical reinforcement of adherence to the dietary regimen is essential, as professional responsibilities and social interactions may pose potential challenges to maintaining consistent compliance.

Finally, pregnancy represents a unique physiological condition during which patient motivation is typically high, often leading to improved adherence to dietary treatment. Nevertheless, careful nutritional assessments are mandatory throughout pregnancy and the post-partum period, since protein and other nutrient requirements change significantly (Figure 3).

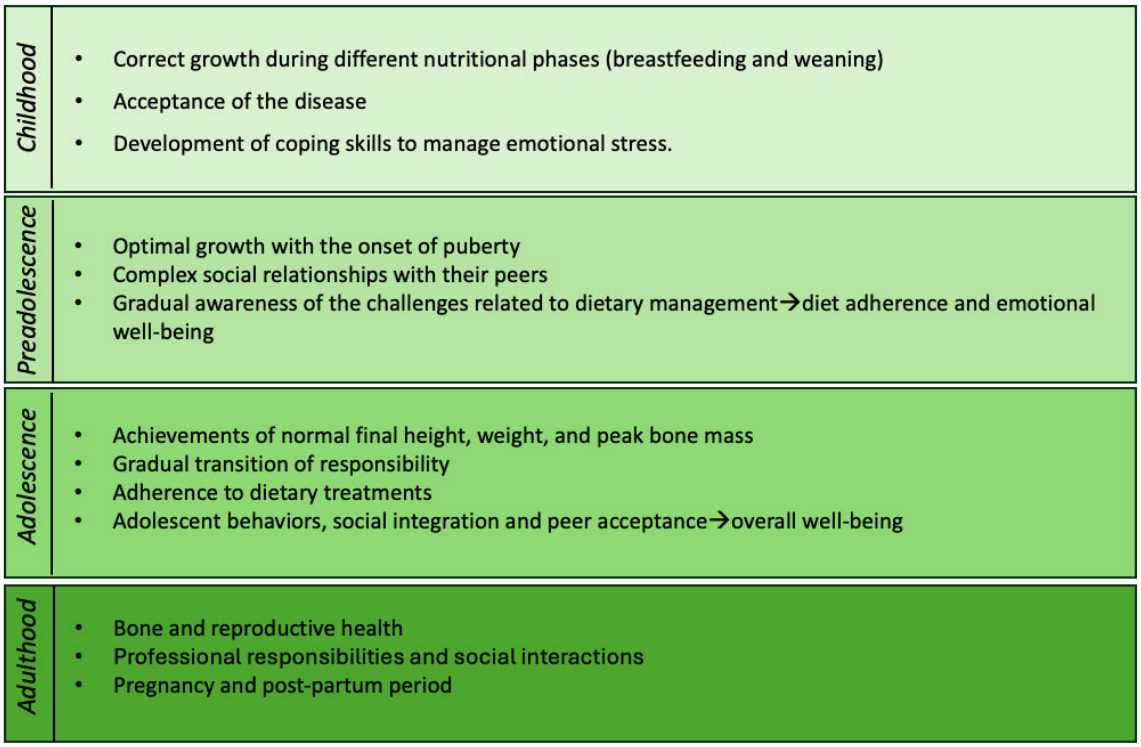

Figure 3. The impact of psycho-relational and metabolic domains at different life stages.

Which Patients Would You Consider Eligible for optimization of Protein Intake?

The panel agreed that every patient is potentially eligible for optimization of protein intake. The main motivation is that improving metabolic and psycho-relational outcomes is beneficial at every age.

Most metabolic outcomes (such as growth and development) are primarily influenced during childhood and adolescence. Metabolic stability and maintenance of a healthy body composition and bone mass are warranted throughout adulthood. Regardless of age, patients could benefit from improvements in psycho-relational aspects.

It was emphasized, however, that optimal protein intake must be carefully determined by individual titration for each individual, based on protein tolerance, nutritional status, and metabolic control.

Which Patients Would You Exclude from Protein Optimization?

For the same reason, the panel concurred that none of the patients should be excluded from protein optimization.

Nevertheless, it recognized that certain hindering factors may exist, but these do not preclude patients from being eligible for protein optimization. These factors are multiple and encompass, for example, loss of motivation, poor knowledge of the condition and its treatment, lack of trust in the healthcare team, reluctance to undergo additional monitoring, emotional stress, eating and feeding disorders, or other psychiatric conditions (e.g., anxiety and/or depression). Also, disease-related symptoms, such as protein aversion, loss of appetite, persistent nausea, and/or vomiting, can complicate the ability of patients to achieve their prescribed daily protein and energy requirements with food (Figure 4).

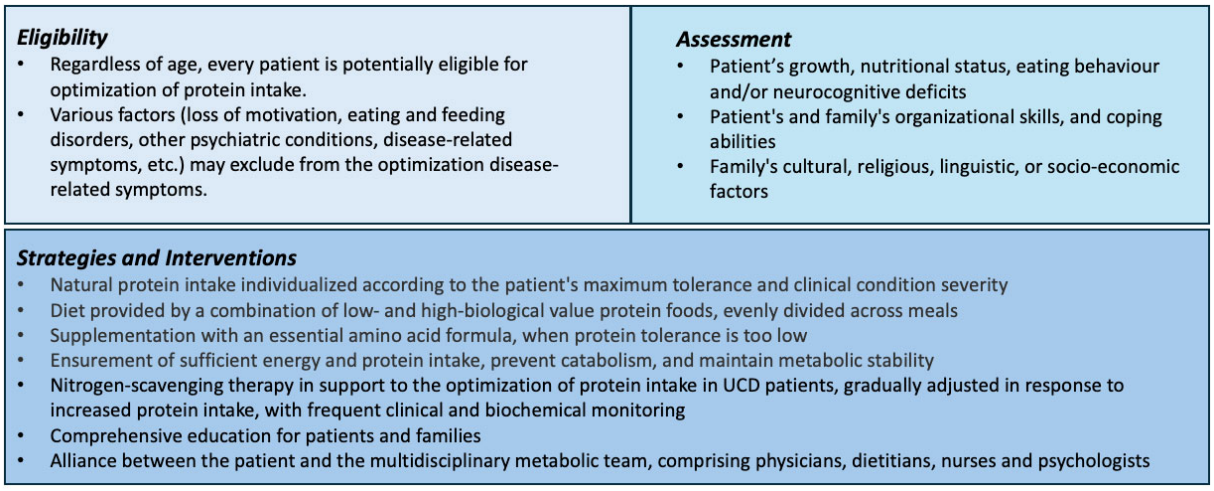

Figure 4. Framework for protein intake optimization.

How Would you Propose the Optimization of Protein Intake to the Patient and/or the Caregiver?

The panel agreed to aim for achieving, and potentially exceeding, the safe levels of protein intake recommended for each age group. On the other hand, natural protein intake should be individualized according to the patient's maximum tolerance and clinical condition severity. Ideally, diet should be provided by a combination of low- and high-biological value protein foods, evenly divided across meals. Supplementation with an essential amino acid formula is necessary when protein tolerance is too low to meet the safe intake levels through diet alone. Regular nutritional assessment and monitoring are essential, as protein requirements and tolerance may vary depending on age, growth rate, nature and severity of the disorder, and the frequency of intercurrent illnesses.

Optimizing protein intake in patients with UCD also requires a critical balance with energy intake to avoid catabolism, and must address protein aversion through individualized diets. In case of poor appetite and/or food refusal, using tube feeding (nasogastric tube or gastrostomy) can help ensure sufficient energy and protein intake, prevent catabolism, and maintain metabolic stability.

The panel also acknowledged the importance of assessing, through a multidisciplinary approach, the patient's and the family's ability to implement protein optimization in practice. Potential challenges – such as the patient's eating behaviour and/or neurocognitive deficits, and the family's cultural, religious, linguistic, or socio-economic factors – must be identified, and where present, the approach should be tailored to the specific situation of patients and caregivers. Family engagement, social support, financial and time resources, organizational skills, and coping abilities all play a key role in the success of protein optimization (Figure 4).

How Would you Set up the Optimization of Protein Intake in Clinical Practice, Also Including a Rational Use of Nitrogen-Scavenging Therapy?

The panel concurred that nitrogen-scavenging therapy may support the optimization of protein intake in UCD patients. The scavenger dose should be gradually adjusted in response to increased protein intake, with frequent clinical and biochemical monitoring recommended during this phase.

Moreover, in patients with mild urea cycle disorders identified through newborn screening, a restriction of protein foods could be avoided or mitigated by the prioritized initiation of a nitrogen-removing scanger, particularly in families with low compliance to diet and specific social issues.

Based on their clinical experience, the panel supported the preferential use of a scavenger with proven pharmacological efficacy and favorable patient response, like glycerol phenylbutyrate (Figure 4).

DISCUSSION

As reported in the most recent guidelines, a low-protein diet remains the cornerstone of long-term management for UCDs[2]. Although not supported by randomized controlled studies, mainly for ethical reasons, this assumption is strongly grounded in physiological rationale, the patient's natural aversion to protein-rich food, and extensive clinical experience[6]. However, the improved life expectancy of patients with UCDs due to early diagnosis and treatment has resulted in lifelong protein restriction, raising concerns not only about growth but also about nutritional status, body composition, bone health, immune system function, and overall well-being in both pediatric and adult patients[10-12,18-20,22,23,30,31].

In general, evidence from the literature on the optimal nutritional requirements and management in patients with UCDs, as well as their association with possible complications, is scarce and often conflicting. One possible explanation is that many available studies are retrospective, with long follow-up periods during which therapeutic options were limited and dietary management practice differed from current standards. Moreover, more recent studies have included cohorts of patients with milder forms of UCDs, such as those identified through newborn screening, who may have different nutritional outcomes. Finally, most studies lack consistency in dietary methodologies and assessment tools, and this aspect may further limit comparability and interpretation. For example, food diary-based data on protein intake are not usually available, and patients' adherence to dietary treatment is not routinely assessed, making it impossible to evaluate real nutritional intakes. Furthermore, a recent systematic review highlighted significant variability and critical deficiencies in dietary management and monitoring across nutrition-related clinical trials, comprising those for inherited metabolic disorders of protein metabolism. These included inconsistent dietary methodologies and inadequate assessment of patient adherence, which impedes accurate evaluation of actual nutrient intake and limits the reliability and comparability of study outcomes[33]. In addition, different methods to assess body composition (bioelectric impedance analysis or dual-energy x-ray absorptiometry) are generally employed, and a control group of healthy subjects is often missing.

On these bases, it is not surprising that current dietary practices among patients with UCDs differ widely. For example, cross-sectional questionnaire data collected from 464 patients with UCDs on protein-restricted diets at 41 European inherited metabolic disorder centres showed that median prescribed protein intake decreased with age across all disorders. The UK tended to prescribe higher total protein intakes than other European countries, particularly during infancy, while Italy generally prescribed lower protein intakes to children over 10 years old, although only one center was included, so this may not reflect overall Italian practices. Overall, essential amino acid supplements were prescribed to 38% of patients, especially in cases of plasma amino acid deficiencies, inadequate total protein intake,

and poor metabolic control[34]. In addition, an evaluation of dietary treatment and amino acid supplementation in 361 UCD patients from the E-IMD registry revealed that 80% received a protein-restricted diet. In general, natural protein prescriptions were often close to the recommended daily allowance, while total protein prescriptions were even above it. Protein prescriptions varied between countries, with low natural and total protein prescriptions reported in two Italian centers. Notably, plasma BCAA levels were below reference ranges in approximately 20-30% of patients. Despite lower natural protein prescriptions in patients receiving amino acid supplementation, their BCAA levels were comparable to those of patients not receiving supplementation[35] Finally, as summarized in a recent review, protein intake in patients with UCDs ranges broadly, both in children and in adults, due to differences in individual tolerance and prescribing practices between centers. Many patients do not reach safe levels of protein intake and are therefore at risk of malnutrition, with some also exhibiting micronutrient intakes below recommended values. Lean body mass was generally lower than the normal range, while fat body mass was often found to be normal or higher than reference values. Protein intake correlated inversely with fat mass in both adult and pediatric UCD patients[36].

Regarding nitrogen-scavenging therapy, a recent retrospective study involving 40 pediatric individuals with UCDs in the UK showed that almost one-third of patients had plasma BCCA levels below the lower limit of the normal range, which were inversely associated with protein intake, ammonia levels, and scavenger dose in those receiving sodium benzoate. The authors suggested that, to increase the proportion of plasma BCAA levels within the normal range, it may be necessary to adjust the biological value of protein intake, prescribe higher doses of scavengers to support safe protein intake, and provide essential amino acid supplements when indicated[24]. Glycerol phenylbutyrate is a tasteless and odourless scavenger that is administered in a small volume, and has been shown to be non-inferior to sodium phenylbutyrate[37]. Experiences in transitioning patients from either sodium benzoate or sodium phenylbutyrate to glycerol phenylbutyrate have been reported to maintain metabolic control, preserve BCAA levels, increase treatment adherence, and improve the quality of life of both patients and caregivers[38-42]. Furthermore, as suggested in a recent consensus, in mild urea cycle disorders identified through newborn screening, it is advised to base the choice of an active therapeutic approach with diet and nitrogen-scavenging therapy on the biochemical and/or genotypic profile, since beginning a low-protein diet alone after an initial period of unrestricted intake may lead to inadequate long-term adherence[43].

This expert opinion paper aims to serve as a guide for metabolic physicians on optimizing protein intake in patients with UCDs, drawing from clinical experience. The discussion focused on identifying key challenges – both metabolic and psycho-relational – associated with low-protein diets, evaluating current and ideal tools for addressing these issues, defining the profile of patients who may benefit from protein optimization, and outlining strategies for introducing and implementing such optimization in clinical practice. To the best of our knowledge, this is the first expert opinion paper specifically focused on protein optimization in UCDs. We believe that this consensus can offer a valuable framework for dietary management of UCDs and serve as a foundation for the design of specific clinical studies aimed at generating further evidence.

CONCLUSIONS

To conclude, a personalized treatment plan that includes careful dietary modification to optimize protein intake, nutrient and essential amino acid supplementation, administration of nitrogen-scavenging drugs, and comprehensive education for patients and families represents the cornerstone of UCD's management. Furthermore, initial assessment and regular monitoring of growth, nutritional status, dietary intake, neurocognitive functioning, and disease-specific quality of life are mandatory in these patients. This multifaceted approach relies on a strong therapeutic alliance between the patient and the multidisciplinary metabolic team, comprising physicians, dietitians, nurses, and psychologists.

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The authors have been involved in consultancy activities for Immedica Pharma.

Ethics Approval and Informed Consent:

This work is based on an expert consensus developed through a multidisciplinary discussion and a preliminary, non-interventional survey among healthcare professionals. No patients were involved and no sensitive or identifiable personal data were collected. Written informed consent was not required, as participation was entirely voluntary, implying consent. Ethics Committee approval was therefore not required.

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NUTRITION IN RARE CARDIOMYOPATHIES: FROM SUPPORTIVE CARE TO TARGETED THERAPY

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ABSTRACT – Rare cardiomyopathies (CMPs) may result from infiltrative disorders, such as amyloidosis, as well as from inherited metabolic diseases, where pathophysiological mechanisms vary depending on the specific defect, including impaired energy production, accumulation of toxic metabolites, or substrate storage. Across this spectrum, nutritional factors play a dual and often underappreciated role: they may drive disease mechanisms or modulate prognosis through malnutrition, sarcopenia or cachexia. In several inborn errors of metabolism, such as glycogen storage diseases and organic acidemias, a targeted diet constitutes etiological therapy, preventing life-threatening metabolic crises and stabilizing cardiac function. In others, including systemic amyloidosis and Fabry disease, nutritional disturbances, such as malabsorption, sarcopenia and cachexia, exacerbate organ involvement and worsen survival despite disease-specific treatments. Importantly, treatable nutritional deficiencies may themselves present with CMPs: primary carnitine deficiency can cause dilated cardiomyopathy reversible with supplementation, while riboflavin has shown therapeutic benefit in ACAD9-related mitochondrial cardiomyopathy.

The interaction between nutrition and cardiomyopathy is complex and bidirectional: metabolic blocks, gastrointestinal involvement, and chronic inflammation precipitate malnutrition, while nutritional deterioration independently predicts worse outcomes. Conventional tools, such as body mass index (BMI) and serum albumin, are often inadequate; refined techniques, including bioelectrical impedance analysis, dual-energy X-ray absorptiometry and functional tests, provide a more accurate assessment.

Evidence indicates that malnutrition, cachexia, and sarcopenia are strong prognostic factors, while targeted interventions ranging from cornstarch protocols in glycogen storage disorders to cofactor supplementation in mitochondrial and metabolic CMPs can stabilize patients and improve quality of life.

This review synthesizes disease-specific paradigms, highlights cross-cutting mechanisms, and outlines principles of personalized intervention, with emphasis on the role of multidisciplinary teams. Nutrition should no longer be regarded as supportive care, but as a therapeutic axis central to rare cardiomyopathy management, with direct implications for survival, function, and patient-centered outcomes.

Keywords: Rare diseases, Nutrition, Amyloidosis, Fabry disease, Cardiomyopathies.

Abbreviations: ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); BIA: bioelectrical impedance analysis; CMPs: cardiomyopathies; GSD: glycogen storage disease.

INTRODUCTION

Rare cardiomyopathies (CMPs) represent a heterogeneous group of myocardial disorders, defined by their low prevalence but associated with substantial morbidity and mortality[1]. Although individually uncommon, they collectively account for a significant proportion of heart failure and sudden death in both children and adults. Most have a genetic or metabolic basis, often manifesting in childhood, though many are increasingly recognized later in life[2]. Regardless of their diversity, rare CMPs frequently share a common feature: a high burden of progressive disability, multisystem involvement, and reduced survival[3,4].

The management of rare CMPs has traditionally focused on genetic counselling, disease-specific pharmacological treatments, advanced heart failure therapies, and organ transplantation. Nutrition, by contrast, has long been considered supportive or marginal. This underestimation contrasts with growing evidence that nutritional status is a key determinant of prognosis, quality of life, and treatment adherence[5]. In some CMPs, dietary intervention is the cornerstone of therapy, as in glycogen storage diseases or organic acidemias[6,7]. In others, such as amyloidosis or Fabry disease, nutrition does not modify the underlying pathology but decisively influences symptoms, functional capacity, and survival[8].

Although these conditions differ markedly in pathophysiology, the examples discussed in this review reflect broader mechanistic categories in which nutritional factors influence cardiac involvement. Other inherited metabolic diseases, such as Pompe disease or fatty-acid oxidation defects, may also present with CMP through energy failure or substrate accumulation, even though nutritional therapy is not central to their management. Nutrition, therefore, emerges as a transversal dimension of care in rare CMPs, shaping both clinical presentation and outcomes. Figure 1 summarizes the overarching framework linking metabolic derangements, systemic involvement, and nutritional status. The following sections address the challenges of nutritional assessment in these patients, the prognostic implications of nutritional decline, and the principles of targeted dietary and metabolic intervention.

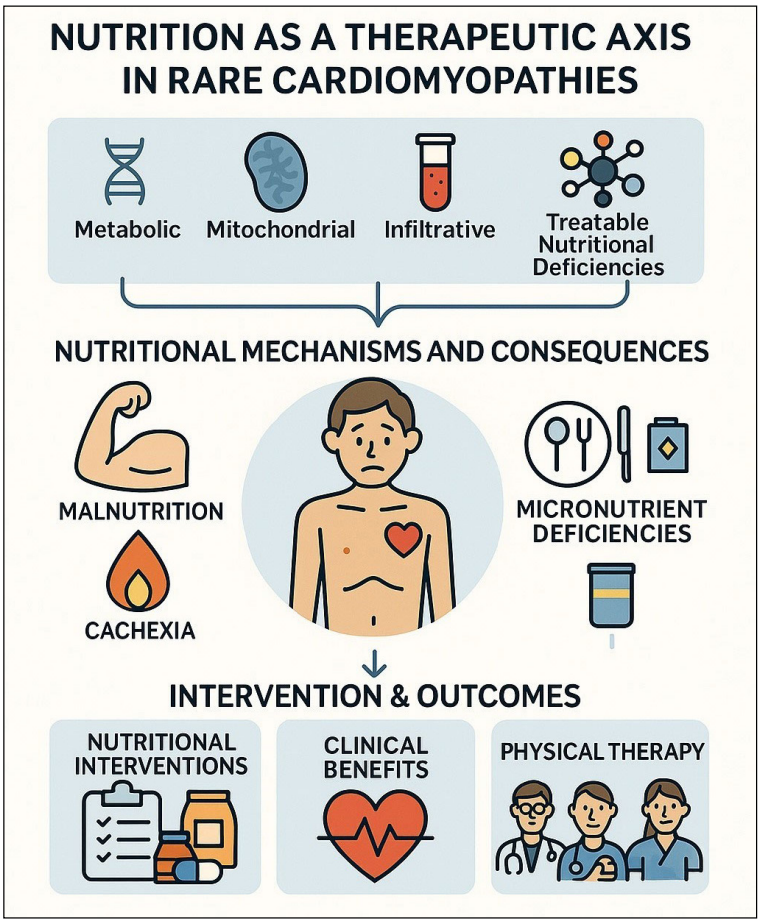

Figure 1. Conceptual framework of nutrition as a therapeutic axis in rare cardiomyopathies.
Nutrition contributes to the pathogenesis and management of rare cardiomyopathies through multiple pathways. Disease groups include metabolic, mitochondrial, infiltrative disorders, and treatable nutritional deficiencies. Nutritional mechanisms and consequences encompass malnutrition, cachexia, and micronutrient deficiencies. Interventions range from nutritional strategies and supplementation to physical therapy, with potential clinical benefits across the disease spectrum.

Methods

This article is a narrative review summarizing current evidence on nutritional mechanisms and interventions in rare CMPs. A targeted literature search was conducted in PubMed, Scopus, and Google Scholar up to September 2025, focusing on clinical studies, guidelines, position papers, case series, and mechanistic reviews relevant to nutritional assessment and management in rare cardiomyopathies and inborn errors of metabolism. Additional references were identified through citation tracking of key publications.

Studies were selected based on clinical relevance, contribution to understanding the nutritional–cardiac interface, and consistency with current metabolic and cardiology classifications. Evidence was synthesized qualitatively and organized to highlight mechanistic categories, shared nutritional features, and disease-specific paradigms.

This review is based exclusively on previously published literature and did not involve human subjects, patient data, or institutional review board approval.

NUTRITIONAL CHALLENGES IN RARE DISEASES

The nutritional consequences of rare CMPs arise from a complex interplay of mechanisms: defective metabolic pathways, chronic inflammation, gastrointestinal dysfunction, endocrine alterations, and reduced physical activity due to skeletal muscle involvement[9]. These processes often coexist, producing unique nutritional phenotypes that directly influence cardiac performance and prognosis.

In systemic amyloidosis, amyloid deposition in the gastrointestinal tract and autonomic nervous system leads to dysmotility, malabsorption and anorexia[10]. The result is a pattern of protein–energy malnutrition and cachexia that is partly nutritional and partly inflammatory[11]. In Fabry disease, abdominal pain and diarrhea restrict food intake, contributing to weight loss and selective deficiencies[12]. In mitochondrial disorders, impaired oxidative phosphorylation translates into a chronic energy deficit with fatigue, early satiety, and catabolism despite adequate intake[12,13], while the myocardium is directly affected, leading to dilated or hypertrophic CMP. Glycogen storage diseases illustrate the dual impact of nutrition on the heart: strict dietary regimens prevent hypoglycemia, but non-adherence can accelerate cardiomyopathy progression[14]. Importantly, treatable deficiencies such as primary systemic carnitine deficiency can cause dilated CMP reversible with supplementation[15], while ACAD9-related cardiomyopathy may respond to riboflavin therapy[16].

A common theme emerges: nutritional disturbances are not secondary or trivial but integral components of the CMP phenotype, shaping prognosis and interacting with therapies. Nutritional needs evolve over time, often changing dramatically during disease progression, initiation of new treatments, or the transition from pediatric to adult care (Supplementary Table 1)[16].

The Problem of Assessment

Assessing nutritional status in rare CMPs is deceptively complex. Traditional tools such as body mass index or serum albumin often fail to capture the true picture[8]. For example, a patient with amyloidosis and edema may appear “normal weight” on BMI yet be profoundly malnourished. Similarly, albumin levels fall not only with malnutrition but also with inflammation[17].

More refined tools, such as bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry, and CT/MRI-based muscle assessment, offer deeper insights into body composition and prognosis[18]. Functional measures such as hand grip strength or timed walking tests provide meaningful prognostic data[19]. Laboratory markers can reveal deficits in vitamin D, B12, folate, zinc, and thiamine, or identify disease-specific abnormalities such as elevated ammonia in organic acidemias[20].

Even so, no single tool is universally reliable in rare CMPs. Cut-off values validated in oncology or geriatrics may not apply to a young adult with mitochondrial cardiomyopathy. What matters most is longitudinal monitoring: progressive weight loss, declining grip strength, or a drop in bioelectrical impedance analysis (BIA) phase angle frequently anticipate clinical deterioration (Supplementary Table 2)[18].

Nutritional Status as a Prognostic Determinant

Evidence increasingly shows that nutritional deterioration is a driver of prognosis, not a bystander, in rare CMPs. Protein–energy malnutrition independently predicts higher mortality and hospitalization in chronic rare diseases[21]. Cachexia, with inflammation-driven catabolism, is an adverse prognostic factor in amyloidosis, reducing survival even when cardiac or renal involvement is not advanced[17]. Sarcopenia predicts functional decline and mortality in Fabry disease, hereditary myopathies, and cardiac amyloidosis[22].

Obesity also carries risks. In glycogen storage disorders (GSDs), obesity may coexist with metabolic fragility, masking malnutrition ("sarcopenic obesity"). In GSD types I and III, two of the most common hepatic glycogen storage disorders, obesity and insulin resistance may also arise from overtreatment, particularly excessive cornstarch or carbohydrate administration intended to prevent hypoglycemia[23]. This phenotype predisposes to cardiovascular and metabolic complications, accelerating disability and worsening cardiac remodeling[24]. Micronutrient deficiencies add further risk. Vitamin D deficiency is linked to fractures and cardiovascular mortality, while B12 and folate deficits exacerbate neurological dysfunction[25,26]. In metabolic CMPs, uncorrected deficiencies of cofactors such as carnitine, riboflavin, or thiamine can precipitate rapid deterioration or trigger life-threatening crises[15,16].

Composite indices such as the Prognostic Nutritional Index, the Geriatric Nutritional Risk Index, and the CONUT score have shown prognostic utility in systemic and infiltrative CMPs[17]. These indices, though not designed for rare CMPs, reinforce the concept that nutrition is a measurable and modifiable determinant of survival (Supplementary Table 3).

Principles of Nutritional Intervention

Effective management requires a personalized, dynamic, and multidisciplinary approach. Three principles stand out:

Adequate support

Ensuring sufficient caloric and protein intake, tailored to disease stage and comorbidities, is fundamental. Oral nutritional supplements are preferred, with escalation to enteral or parenteral nutrition when needed. Micronutrient monitoring and supplementation (vitamin D, B12, folate, iron, zinc, thiamine) should be systematic[27].

Targeting mechanisms

Nutritional support must address underlying drivers. In cachexia, anti-inflammatory strategies can enhance efficacy. In metabolic CMPs, strict control of substrate load (e.g., protein restriction in propionic acidemia, a prototypical organic acidemia, and timed cornstarch regimens primarily in glycogen storage disease type I, with occasional use in type III) is essential. Supplementation with cofactors such as L-carnitine or riboflavin can support mitochondrial metabolism, while other compounds such as coenzyme Q10 and thiamine may stabilize function in selected subgroups[28].

Rehabilitation and empowerment

Adapted physical activity is crucial to counteract sarcopenia, restore function, and improve autonomy. Nutritional rehabilitation integrates diet, exercise, and psychological support. Education of patients and caregivers sustains adherence, particularly during the transition from pediatric to adult care, where discontinuity often leads to nutritional decline[29].

These principles illustrate how nutrition moves from a supportive measure to a therapeutic axis, influencing outcomes across rare disease populations.

Setting the Stage for Disease-Specific Paradigms

The general framework highlights a recurring theme: nutrition is central to rare CMP management. It shapes prognosis, modifies therapy, and determines quality of life. Its role becomes clearest in specific conditions where nutritional intervention exemplifies broader principles: in amyloidosis, cachexia reflects inflammatory catabolism; in Fabry disease, gastrointestinal dysfunction undermines intake; in glycogen storage disorders, diet is the therapy; in mitochondrial disease, cofactors and caloric modulation support energy balance; in propionic acidemia, protein restriction prevents metabolic crises; in primary systemic carnitine deficiency and ACAD9 deficiency, supplementation with L-carnitine or riboflavin can reverse or stabilize cardiomyopathy.

The next sections, therefore, examine these paradigms in detail, using them as models for understanding the role of nutrition across the rare CMP spectrum.

DISEASE-SPECIFIC PARADIGMS OF NUTRITION IN RARE DISEASES

Systemic Amyloidosis

Nutritional impairment in amyloidosis is frequent but often underestimated, especially early in the disease course (Table 1). Cardiac amyloidosis typically presents with a restrictive cardiomyopathy characterized by increased wall thickness, diastolic dysfunction, and progressive heart failure; however, the degree of cardiac involvement varies markedly across amyloidosis subtypes[30]. When present, this cardiac phenotype further worsens nutritional vulnerability because reduced cardiac output, venous congestion, gastrointestinal dysmotility, and autonomic dysfunction synergistically impair appetite, nutrient absorption, and metabolic reserve. In variant transthyretin amyloidosis (ATTRv), weight loss, diarrhea, and early satiety due to gastrointestinal dysautonomia may precede the diagnosis by years. Amyloid fibril deposition in the gastrointestinal tract and autonomic nervous system disrupts motility and absorption, leading to malnutrition and micronutrient deficiencies[31]. In wild-type *ATTR* (ATTRwt), prevalent in the elderly, cachexia is compounded by reduced appetite, systemic inflammation, and visceral congestion due to heart failure. AL amyloidosis is even more complex: beyond fibril deposition, circulating light chains and chemotherapy toxicity further impair liver, gut, and muscle metabolism[32].

The nutritional phenotype typically evolves from subtle weight loss to sarcopenia and cachexia, with edema often masking true lean mass loss. Malnutrition is an independent predictor of mortality, sometimes preceding biomarker deterioration[33]. When cardiac amyloidosis is present, progressive heart failure (HF) contributes substantially to morbidity, hospitalization burden and overall prognosis[34]. Early recognition of hypoalbuminemia, falling BIA phase angle, or reduced hand grip strength enables timely intervention[35].

Supportive protocols emphasize high-calorie, high-protein diets, texture adaptation for dysphagia, and early use of enteral nutrition when intake becomes insufficient. In refractory cases, parenteral nutrition stabilizes patients through critical periods. Adjunctive strategies, such as omega-3 fatty acids for catabolic modulation or midodrine for postprandial hypotension, may facilitate tolerance and improve intake. Integration of dietitians into amyloidosis centers is therefore crucial[36].

Fabry Disease

Fabry disease, a lysosomal storage disorder, exemplifies the interplay between gastrointestinal dysfunction and nutrition (Table 1). Abdominal pain, bloating, and diarrhea affect more than half of patients, often leading to avoidance of meals, reduced caloric intake, and selective micronutrient deficiencies. These alterations are further aggravated by renal impairment and chronic inflammation, resulting in weight loss and sarcopenia[8].

Although enzyme replacement therapy improves the systemic phenotype, nutritional disturbances frequently persist. Dietary management, therefore, requires a dual strategy:

- Symptom-oriented: low-FODMAP regimens to reduce diarrhea and bloating, texture adaptation for dysphagia.
- Supportive: adequate energy and protein intake aligned with enzyme replacement therapy, regular monitoring of lean mass, and supplementation of renal-sensitive nutrients (e.g., vitamin D, iron, folate).

Educational interventions such as Fabry's Kitchen and Rare Book projects (https://www.rare-bz.net/it/news/il-progetto-fabrys-kitchen-e-il-ricettario-rare-book) have provided patients with culturally tailored recipes and evidence-based dietary advice, improving adherence and quality of life.

Table 1. Nutritional aspects across groups of rare diseases.

Disease group	Nutritional mechanism	Typical manifestations (including cardiac)	Dietary intervention	Key challenges
Systemic protein-depositing CMPs (cardiac amyloidosis) and lysosomal storage disorders (Fabry disease – sphingolipidosis)	GI infiltration, autonomic dysfunction, chronic inflammation	Malabsorption, dysmotility, anorexia, sarcopenia; HF progression; HF hospitalization	High-protein, high-calorie diet, supplements, enteral/parenteral nutrition	Early detection, poor tolerance, variable response to ERT or chemotherapy
Energy metabolism disorders (GSD I/III, mitochondrial CMP, ACAD9 deficiency)	Defects in glycogenolysis, gluconeogenesis, or oxidative phosphorylation	Hypoglycemia, fatigue, lactic acidosis, skeletal myopathy; dilated/ hypertrophic CMP	Strict cornstarch/glucose regimens; cofactor supplementation (thiamine, riboflavin, CoQ10, carnitine)	Compliance, nocturnal regimens, risk of overfeeding or obesity; variable riboflavin response
Organic acidemias (propionic, methylmalonic)	Enzyme block in amino acid catabolism → toxic metabolite accumulation	Metabolic crises, growth delay, neurologic impairment; dilated CMP in severe forms	Controlled protein restriction, specific precursor-free formulas (restriction of Ile, Val, Thr, Met), emergency protocols; carnitine, B12 in responsive methylmalonic acidemia	Balancing restriction *vs.* growth needs, recurrent crises, and sarcopenia
Primary systemic carnitine deficiency	Defective carnitine transport → impaired fatty acid oxidation	Dilated CMP, hypoketotic hypoglycemia, skeletal myopathy	Oral L-carnitine supplementation	Early diagnosis is essential; rapid deterioration without treatment
Other metabolic/lysosomal disorders (Pompe – lysosomal glycogenosis, Wilson disease – copper metabolism disorder, others)	Myopathy, hepatosplenomegaly, cholestasis	Dysphagia, early satiety, vitamin deficiencies, sarcopenia; CMP reported in Wilson and late-onset Pompe	High-protein diets, vitamin supplementation, supportive nutrition	Multisystemic involvement, transplant phases, variable cardiac expression

ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); CMPs: cardiomyopathies; CoQ10: coenzyme Q10; ERT: enzyme replacement therapy; GI: gastrointestinal; GSD: glycogen storage disease; HF: heart failure.

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are paradigmatic because nutrition is integral to their management (Table 1). Among classical hepatic GSDs, CMP is most consistently associated with glycogen storage disease type III (Cori/Forbes disease), particularly the IIIa subtype with skeletal muscle involvement, in which glycogen accumulation in the myocardium can lead to hypertrophic or dilated cardiomyopathy. By contrast, cardiac involvement is not typical in GSD type I, while PRKAG2-related cardiomyopathy and Danon disease represent distinct glycogen storage cardiomyopathies that are not primarily modified by dietary therapy.

In type I GSD, fasting hypoglycemia, due to defective glucose-6-phosphatase activity, requires frequent use of carbohydrates. Uncooked cornstarch is the cornerstone, administered every 3-4 hours, including during the night, and extended-release starch preparations reduce nocturnal dosing and improve sleep quality[37].

Pediatric regimens may require continuous gastric infusion, whereas in adulthood, strict adherence to timed starch intake remains essential. The macronutrient profile revolves around increased complex carbohydrates to provide sustained glucose release, restriction of simple sugars to limit hyperlactacidemia and hyperlipidemia, and maintaining normal protein intake to support growth and metabolic needs[38]. Despite these strategies, obesity and sarcopenic obesity may arise from chronic overfeeding and overtreatment aimed at preventing hypoglycemia.

In GSD type III, nutritional therapy serves different objectives: reducing glycogen accumulation in the liver, muscle, and heart, particularly in adulthood. This includes a relative reduction in total carbohydrate intake, increased protein consumption to support gluconeogenesis, and, in selected cases, higher lipid intake, including ketogenic or medium-chain triglyceride (MCT)-enriched regimens. Several reports have shown that providing alternative energy substrates, especially higher-protein or ketogenic approaches, can lead to significant improvement or stabilization of GSD III-associated cardiomyopathy[39-43]. Long-term complications such as hepatic adenomas and renal dysfunction are strongly influenced by nutritional control.

Ongoing clinical trials (e.g., NCT03970278) are evaluating modified starches with prolonged release profiles, aiming to improve compliance, maintain euglycemia overnight, and reduce treatment burden. These developments highlight how nutritional innovation continues to reshape the therapeutic landscape of GSDs[44].

Mitochondrial Disorders

Mitochondrial dysfunction leads to defective oxidative phosphorylation, chronic energy deficits, and lactic acidosis. Nutritional decline is driven by both impaired intake (due to gastrointestinal dysmotility and early satiety) and increased metabolic demands. Patients often develop sarcopenia and cachexia despite apparently adequate diets (Table 1).

Management focuses on caloric adequacy while avoiding overfeeding. Supplementation with cofactors (thiamine, riboflavin, carnitine, coenzyme Q10) forms the so-called “mitochondrial cocktail”. Although evidence remains largely observational, many patients report improved energy tolerance and quality of life. Ketogenic diets have been explored in selected subgroups (particularly mitochondrial epilepsies), though long-term safety is debated[45].

Adjunctive physiotherapy and psychosocial support are essential components of “nutritional rehabilitation”, preserving autonomy and slowing decline. Clinical studies such as MMPOWER-3 (NCT03308764), which evaluated the efficacy and safety of elamipretide in primary mitochondrial myopathy using functional performance, patient-reported outcomes, and biochemical markers of mitochondrial function as key endpoints, illustrate the growing integration of metabolic and nutritional parameters in mitochondrial research.

Organic Acidemias

Propionic and methylmalonic acidemias illustrate the delicate balance between protein restriction and anabolic preservation. Propionic acidemia is the organic acidemia most consistently associated with cardiomyopathy, with dilated cardiomyopathy, arrhythmias and conduction disease reported from infancy

to adulthood. Methylmalonic acidemia appears to carry a lower but clinically relevant risk of cardiac involvement, with cardiomyopathy and heart failure described in a subset of patients. Protein intake must be carefully limited to avoid accumulation of toxic precursors, while maintaining adequate essential amino acid provision to support growth and prevent catabolism. In both disorders, management relies on specific precursor-free amino acid formulas that exclude isoleucine, valine, threonine, and methionine, combined with carnitine supplementation and, in B12-responsive forms of methylmalonic acidemia, parenteral or high-dose oral vitamin B12 (Table 1).

Emergency protocols are critical: during illness or surgery, rapid institution of glucose infusion and temporary protein restriction prevent catabolic decompensation. Without such measures, hyperammonemia and metabolic acidosis rapidly progress to life-threatening crises. Long-term therapy requires vigilant metabolic monitoring and frequent adjustments, particularly during growth or puberty. Sarcopenia, growth delay, and micronutrient deficiencies remain significant risks, highlighting the need for continuous nutritional supervision[46].

Primary Systemic Carnitine Deficiency

Carnitine plays a central role in long-chain fatty-acid oxidation, and deficiency, whether primary or secondary, can impair myocardial energy production. While primary systemic carnitine deficiency is a well-recognized cause of reversible dilated cardiomyopathy, secondary forms may also present with cardiac involvement. These include nutritional deficiency (e.g., strict vegetarian or vegan diets with low carnitine intake), malabsorption, nephrotic-range urinary losses, or chronic use of valproate, which increases carnitine depletion.

Several case reports and small series have described complete reversal of dilated cardiomyopathy after carnitine supplementation in secondary deficiency, confirming its pathogenic relevance[47,48]. This example illustrates that, even outside genetically defined metabolic pathways, nutritional deficiencies can occasionally act as primary drivers of cardiomyopathy rather than mere modulators of disease severity[15].

ACAD9 Deficiency

ACAD9 deficiency, a disorder of mitochondrial fatty acid β-oxidation and respiratory chain complex I assembly, is increasingly recognised as a cause of mitochondrial cardiomyopathy. Patients typically present with dilated or hypertrophic CMP, exercise intolerance, and lactic acidosis. Muscle biopsy often reveals lipid accumulation, providing early diagnostic clues. Importantly, riboflavin supplementation has shown therapeutic benefit in several cases, improving cardiac function and stabilizing disease course. Empirical treatment with riboflavin and carnitine may be justified based on biopsy findings, even before genetic confirmation[16,49]. This highlights how targeted nutritional interventions can have disease-modifying effects in selected rare CMPs.

Other Rare Disorders with Nutritional Relevance

Beyond amyloidosis, Fabry disease, glycogen storage disorders, mitochondrial dysfunctions, and organic acidemias, several additional rare conditions demonstrate how nutritional disturbances significantly affect clinical course and quality of life. The common denominators across these disorders are malabsorption and metabolic imbalance, which act as primary mechanisms driving deterioration. By contrast, sarcopenia and cachexia are downstream consequences of these metabolic and gastrointestinal abnormalities rather than mechanisms themselves.

Urea cycle disorders exemplify the delicate balance between substrate restriction and anabolic preservation. Preventing catabolism, such as by avoiding fasting and ensuring adequate non-protein energy intake, is essential to reduce the risk of hyperammonemic crises. Dietary management relies on Foods for Special Medical Purposes (FSMPs) specifically designed to provide essential amino acids while limiting nitrogen load. Long-term follow-up must include frequent metabolic reassessment, particularly during periods of rapid growth or intercurrent illness[50].

Pompe disease illustrates another scenario in which nutritional factors interact with multisystem involvement. In infantile-onset Pompe disease, hypertrophic cardiomyopathy is a hallmark feature and contributes significantly to early morbidity and mortality. By contrast, in late-onset Pompe disease, cardiac involvement is usually mild or absent, while dysphagia, respiratory muscle weakness, and increased energy expenditure often lead to malnutrition and sarcopenia. High-protein, energy-enriched diets integrated with enzyme replacement therapy can support functional maintenance and improve tolerance to rehabilitation[51].

Gaucher disease presents a different nutritional profile, where hepatosplenomegaly causes early satiety and malabsorption. Despite the transformative impact of enzyme replacement therapy, structured nutritional support remains necessary to prevent secondary malnutrition[52].

Metabolic liver diseases, such as Wilson's disease and progressive familial intrahepatic cholestasis, also illustrate the nutritional dimension of systemic dysfunction. In Wilson's disease, copper overload leads primarily to hepatic and neurological manifestations, but case reports describe dilated cardiomyopathy, arrhythmias, and conduction defects[53]. Malnutrition is common, driven by liver dysfunction, gastrointestinal symptoms, and poor dietary intake. Malabsorption of fat-soluble vitamins and protein–energy malnutrition complicate growth, bone health, and, in advanced cases, eligibility and recovery after transplantation. Nutritional support, including specialized supplementation of vitamins A, D, E, and K and tailored high-protein, high-calorie regimens, is therefore integral to management, with potential benefits not only for systemic outcomes but also for cardiac function in selected patients[54].

Taken together, these examples demonstrate that nutritional care is not confined to metabolic or mitochondrial cardiomyopathies. Rather, it is a cross-cutting theme across the rare disease spectrum, where nutritional decline magnifies vulnerability and appropriate intervention can stabilize patients even when disease-specific therapies are limited (Table 2).

CROSS-CUTTING THEMES, RESEARCH ADVANCES, AND FUTURE PERSPECTIVES

Cross-Cutting Clinical Themes

Despite the heterogeneity of rare CMPs, several nutritional issues recur across conditions. Sarcopenia is perhaps the most universal, arising from reduced intake, systemic inflammation, immobility, and anabolic resistance. It independently predicts mortality, hospitalization, and loss of autonomy, and often persists even in patients who appear to have adequate caloric intake. Managing sarcopenia requires integrated strategies: adequate protein and energy supply, resistance training, and, potentially in the future, targeted anti-catabolic therapies[55].

Malabsorption and secondary malnutrition also represent common denominators. In amyloidosis, infiltration of the gastrointestinal tract impairs motility and absorption; in Fabry disease, neuropathic diarrhea limits intake; in Gaucher disease, hepatosplenomegaly reduces meal capacity; and in cholestatic liver disorders, fat-soluble vitamin deficiencies are frequent. These mechanisms highlight the need for routine screening for deficiencies of vitamin D, iron, folate, thiamine, and cofactors such as carnitine and riboflavin, which may otherwise remain clinically silent until cardiac deterioration occurs[56].

Artificial nutrition, though rarely discussed in guidelines, plays a crucial stabilizing role in advanced cases. Enteral or parenteral support can bridge patients through crises, improve treatment tolerance, or serve as a pre-transplant intervention. Initiating such measures requires a careful balance between medical necessity and quality of life, ideally within a multidisciplinary framework[57].

Finally, multidisciplinary care itself is indispensable. Cardiologists, dietitians, metabolic specialists, physiotherapists, psychologists, and patient organizations each contribute to a holistic model of care. Particular attention is required during transitions, such as the shift from pediatric to adult follow-up, where adherence often declines, and nutritional deterioration accelerates.

Ongoing Studies and Clinical Trials

Research in this field is expanding, though still constrained by small cohorts and clinical heterogeneity (Box 1).

Table 2. Consolidated dietary protocols in selected rare diseases.

Disease	Standard dietary intervention	Level of evidence	Key limitations
Glycogen storage disease type III	High-protein, relatively lower-carbohydrate diet; in selected cases, high-fat or MCT-enriched/ketogenic regimens to provide alternative cardiac energy substrates	Low–moderate (case series, small cohorts) tolerability of high-fat regimens	Heterogeneous phenotype; limited prospective data; variable
Primary systemic carnitine deficiency	Oral L-carnitine supplementation (100-400 mg/kg/day) with regular meals and avoidance of fasting	Moderate–high (case series, pathophysiological evidence; cardiomyopathy often reversible)	Delayed diagnosis may lead to irreversible myocardial damage; adherence to lifelong supplementation required
Propionic / Methylmalonic acidemia	Controlled protein restriction, precursor-free amino acid formulas (Ile, Val, Thr, Met), carnitine supplementation, and emergency regimens; B12 in responsive methylmalonic acidemia	Moderate (observational studies, expert consensus)	Growth failure, recurrent metabolic crises, sarcopenia; limited prospective trial data; cardiac involvement often under-recognized
Mitochondrial disorders (including ACAD9 deficiency)	Caloric adequacy with mitochondrial cofactors (thiamine, riboflavin, carnitine, CoQ10); ketogenic diet in selected subgroups	Low-moderate (case series, pilot trials)	High heterogeneity; lack of RCTs; variable riboflavin response (notably in ACAD9-related CMP); limited long-term data
Urea cycle defects	Low-protein diet with specific FSMP formulas and nitrogen scavengers (sodium benzoate, phenylbutyrate)	Moderate (registries, consensus guidelines)	Balancing growth with ammonia control, frequent hospitalizations, limited cardiac involvement, but nutritional lessons relevant to CMP care

ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); CMP: cardiomyopathy; CoQ10: coenzyme Q10; Phe: phenylalanine; 3–4 h: Every 3–4 hours; RCTs: randomized controlled trials.

Box 1. Methodological challenges in nutrition research for rare cardiomyopathies.

- Small sample sizes – due to fragmentation of patient populations and limited multicenter collaboration.
- Marked clinical heterogeneity – variable phenotypes and nutritional needs, even among patients carrying the same mutation.
- Lack of standardized endpoints – survival, quality of life, body composition, and metabolic markers are rarely harmonized across studies.
- Limited randomized trials – most available data derive from case series, registries, or expert consensus rather than controlled designs.
- Under-reporting of long-term outcomes – especially regarding adherence to dietary regimens, functional independence, and impact on cardiac prognosis.
- Translational gaps – promising nutritional biomarkers and cofactor therapies (e.g., riboflavin in ACAD9 deficiency) are seldom integrated into trial design or clinical guidelines.

In amyloidosis, ongoing observational studies (NCT05721676; NCT04685871) are validating the prognostic role of phase angle and nutritional indices such as the Prognostic Nutritional Index. If confirmed, these markers may become part of standard risk stratification.

In Fabry disease, a multicenter study (NCT04622676) integrates dual-energy X-ray absorptiometry and BIA into routine follow-up, exploring how enzyme replacement therapy modifies body composition and basal metabolism. Parallel efforts are investigating low-FODMAP approaches for gastrointestinal symptoms.

In glycogen storage diseases, trials such as NCT03970278 are assessing extended-release starches to reduce nocturnal dosing and improve sleep quality while maintaining normoglycemia.

In mitochondrial disorders, pilot studies (e.g., MMPOWER-3, NCT03308764) combine metabolic therapies with nutritional interventions. Although pharmacological agents, such as elamipretide, remain the primary focus, dietary cofactors (riboflavin, carnitine, coenzyme Q10, thiamine) continue to play a central role in patient management.

For organic acidemias, structured dietary protocols and emergency regimens are being harmonized across European networks, though randomized trials remain lacking. Registries are beginning to capture longitudinal nutritional data, laying foundations for future intervention studies.

Together, these initiatives illustrate a paradigm shift: nutrition is being recognized not only as supportive care but as a measurable and testable therapeutic variable in clinical research.

Local Experiences and Integrated Models

Beyond trials, innovative local projects demonstrate how nutrition can empower patients and enhance adherence. The Fabry's Kitchen initiative, developed in collaboration with clinicians and patient associations, translated dietary recommendations into culturally adapted recipes, producing the Rare Book to guide low-FODMAP diets. This approach improved both symptom control and treatment adherence.

Building on this, the Pizza Mara project linked rare disease nutrition to a universally recognizable cultural symbol. By using pizza as a platform for awareness and inclusion, the initiative promoted dialogue between patients, caregivers, and the wider community, showing how nutrition can bridge clinical care with social identity.

Such experiences underscore that nutritional support extends beyond the clinic. When integrated into cultural contexts and supported by patient organizations, nutrition becomes a tool for education, empowerment, and public awareness. Combining these models with emerging tele-nutrition platforms may further enhance access, especially for patients living far from referral centers.

CONCLUSIONS

Nutrition is a critical yet underappreciated determinant in rare CMPs. Across diverse conditions, from amyloidosis and Fabry disease to glycogen storage disorders, mitochondrial dysfunctions, organic acidemias, and treatable deficiencies such as carnitine and ACAD9 deficiency, altered nutritional status both reflects disease mechanisms and independently shapes prognosis. In some disorders, diet is the cornerstone of therapy; in others, it mitigates complications, preserves function, and improves quality of life.

Early recognition of malnutrition, sarcopenia, or micronutrient deficiencies, combined with personalized interventions and multidisciplinary care, can significantly influence outcomes. Emerging studies highlight the prognostic value of body composition and the efficacy of tailored nutritional strategies, while local initiatives and digital tools show how nutrition can also enhance adherence and patient empowerment.

Moving forward, integration of nutrition into routine CMP care, research protocols, and rare cardiomyopathy registries will be essential to shift its role from a supportive measure to a therapeutic axis, with direct benefits for survival and patient-centered outcomes.

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No artificial intelligence-assisted technologies were used in the production of this article.

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DESCRIBING THE SELF-REPORTED COGNITIVE AND EMOTIONAL FUNCTIONING OF ADULT PATIENTS WITH UREA CYCLE DISORDERS

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***ABSTRACT* – Objective:** This study aims to describe the self-reported cognitive and emotional functioning in adult patients with late-onset urea cycle disorders (LO UCDs), highlighting the neuropsychiatric burden of the condition.

Materials and Methods: An observational, retrospective, archival, multicenter study was conducted on 11 female patients' medical records aged 21.5-41 years. Data were extracted from the psychodiagnostic evaluation conducted during routine clinical practice. The psychodiagnostic assessments included the Adult Self-Report (ASR/18-59), the State-Trait Anxiety Inventory – Form Y (STAI-Y), and the Beck Depression Inventory – Second Edition (BDI-II). Descriptive statistics were applied to analyze the findings.

Results: Adult LO UCD patients exhibited significant challenges in emotional and cognitive functioning, with frequent self-reported symptoms related to both cognitive and emotional functioning. Pathological levels of internalizing behaviors, particularly withdrawal, were observed, as well as a high prevalence of self-reported cognitive dysfunction, such as attention problems and lethargy, anxiety and depressive symptoms. Externalizing issues were present but less prevalent. Anxiety and depressive symptoms were also commonly reported, with depressive symptoms impacting both somatic and cognitive domains.

Conclusions: This study underscores the high prevalence of cognitive and emotional dysfunctions in adult LO UCD patients. Future research involving larger cohorts and the combined use of self-report measures and objective neuropsychological assessments is essential to better understand and manage the cognitive and emotional impacts of UCDs.

Keywords: Urea cycle disorders, Behavioral disorders, Cognitive problems, Anxiety, Depression.

Abbreviations: AD_H_prob_T: Attention Deficit/Hyperactivity Problems (T-score); ASEBA: Achenbach System of Empirically Based Assessment; ASR: Adult Self-Report (part of the ASEBA system); BDI-II: Beck Depression Inventory - Second Edition; BDI_FC_p: Beck Depression Inventory Cognitive Factor (percentile score); BDI_SA_p: Beck Depression Inventory Somatic-Affective (percentile score); EO: early-onset; EXT_prob_T: Externalizing Problems (T-score from ASR/18-59); INT_prob_T: Internalizing Problems (T-score from ASR/18-59); IQR: interquartile range; LO: late-onset.

INTRODUCTION

Urea cycle disorders (UCDs) are a set of rare inherited metabolic conditions concerning dysfunctions of urea cycle proteins, which are responsible for removing excess ammonia from the body[1]. Such urea cycle dysregulation affects the detoxification processes of ammonia to urea conversion. Consequent ammonia accumulation in the brain and other tissues, together with the increase of glutamine levels, causes astrocyte swelling and cytotoxic brain edema[2].

UCDs are often diagnosed during the newborn period; however, it is important to highlight that three UCDs [N-acetylglutamate synthase (NAGS), Carbamoyl phosphate synthetase 1 (CPS1), and ornithine transcarbamylase deficiency (OTC) deficiencies] are not detectable through newborn screening. Therefore, UCD cases have also been identified in later childhood or adult age with mild or isolated psychiatric symptoms[3,4]. Early-onset disease (EO) is defined as when hyperammonemia is diagnosed prior to 28 days of age. Individuals often present with life-threatening symptoms, a high risk of mortality and poor neurological outcome in case of survival[5,6]. Otherwise, late-onset disease (LO) is diagnosed when individuals present with symptoms after the newborn period, whose phenotype is variable and typically less severe than in individuals with EO[7,8].

Specific extent and duration of hyperammonemia have been reported to have a crucial impact on cognitive functioning[9]. This results in specific patterns of neurological deficiencies in EO cases, including impaired motor capacity and speed, difficulties in non-verbal intelligence, visual memory and attention deficit[10]. In contrast, LO individuals typically show IQ in the normal range, but may exhibit difficulties in motor planning and executive functioning could be observed[11].

Presumably, as a result of neurological perturbations or the experience of having a chronic illness[12], behavioral and emotional difficulties have also been noticed, including both internalizing (e.g., anxiety, depression, and withdrawal) and externalizing symptoms (e.g., aggression and conduct issues)[10], attention-deficit/hyperactivity disorder and behaviors associated with autism spectrum disorder[12]. Attention problems, dysphoric emotionality, followed by dissocial behavior and difficulties in the management of self or social relationships, can interfere with family life and may impact patients' quality of life[13].

The treatment of UCDs involves a diet with reduced protein intake and pharmacological treatment with ammonium chelating drugs.

Investigations of behavioral disorders in UCD patients, during both diagnostic and therapeutic phases, appear, therefore, to be important. Moreover, compared to children and adolescents, the cognitive and behavioral complications of UCD diagnosis and management have been poorly investigated in adult patients.

Accordingly, we conducted a multicenter, retrospective, observational study utilizing archival data to examine the impact of late-onset UCDs (LO UCDs) on self-reported cognitive and emotional functioning in adult patients affected by LO UCDs who underwent routine psychodiagnostic evaluation at the involved centers, aiming to fill the gap in current knowledge.

MATERIALS AND METHODS

Setting and Patients

An observational, retrospective, archival, multicenter study was carried out between May and June 2025 at IRCCS – Istituto Giannina Gaslini (Genova) and Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" (Catania). The study received ethical approvals from the Institutional Review Board of IRCCS Istituto Giannina Gaslini (protocol number 0033844/2024) on 22/10/2024 and from the Comitato Etico Locale Catania 1 - Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" - Catania (protocol number 0015160/2025) on 10/03/2025. The study was performed in accordance with the revised version of the Declaration of Helsinki.

Following the receipt of ethical approval, eleven adult female patients diagnosed with LO UCDs were identified at the two participating centers. Patients were included in the study if they met the following criteria: diagnosis of UCDs in childhood and being adults at the moment of the psychodiagnostic assessments. All identified patients had previously undergone comprehensive psychodiagnostic assessments as an integral part of their routine clinical care. Subsequently, these individuals were contacted to inform them about the study's objectives and to obtain their explicit informed consent for the retrospective use of their existing clinical data, which had already been documented in their medical records, solely for research purposes.

Materials/Instruments

Psychodiagnostic assessment comprised three self-report questionnaires. The Adult Self-Report/18-59 (ASR/18-59), part of the Achenbach System of Empirically Based Assessment (ASEBA)[14], is a self-report tool designed to evaluate a wide array of emotional, behavioral, and cognitive issues in adults aged 18-59 years. The ASR/18-59 assesses both general functioning and specific problem behaviors, providing insights into an individual's psychological well-being, interpersonal functioning, and potential psychopathology.

Broadband Scales

- Total Problems: represents the overall level of problem behavior and emotional distress, encompassing all items from each ASR/18-59 problem scale;
- Internalizing Problems: aggregates scores from anxious/depressed, withdrawn, and somatic complaints subscales, reflecting internalized symptoms like anxiety, social isolation, and psychosomatic complaints;
- Externalizing Problems: composed of the aggressive behavior and rule-breaking behavior subscales, this scale captures outwardly directed behaviors, including impulsivity, hostility, and defiance of social norms.

Syndrome scales are empirically derived categories that evaluate specific types of behavioral and emotional difficulties:

- Anxious/Depressed: measures symptoms such as pervasive sadness, anxiety, and worry
- Withdrawn: assesses social disengagement and a preference for isolation
- Somatic Complaints: includes physical symptoms related to psychological distress, such as chronic pain or fatigue
- Aggressive Behavior: captures hostile or confrontational behaviors, including physical and verbal aggression
- Rule-Breaking Behavior: focuses on behaviors indicating a disregard for rules, often associated with impulsivity
- Intrusive: measures socially intrusive and impulsive behaviors, which may disrupt social interactions
- Attention Problems: evaluates difficulties in maintaining concentration and task focus, reflecting issues with distractibility
- Thought Problems: assesses unusual thought patterns and perceptual disturbances that may suggest psychotic-like symptoms or obsessive thinking

Additional Scales

Sluggish Cognitive Tempo: reflects symptoms associated with a slower mental pace, such as lethargy and daydreaming, which can affect attention and motivation

Attention deficit/hyperactivity problems: measures symptoms associated with ADHD, including impulsivity and hyperactivity, which may affect social and occupational functioning.

The State-Trait Anxiety Inventory – Form Y (STAI-Y)[15,16] is a validated self-report measure commonly employed to assess anxiety in both clinical and research settings, differentiating between state anxiety and trait anxiety.

- State Anxiety: measures a transient emotional state, capturing the individual's experience of anxiety in response to specific situations or stress-inducing events. This subscale assesses how anxious the individual feels at a particular moment, influenced by external or immediate factors.
- Trait Anxiety: evaluates a stable personality characteristic, reflecting the individual's general tendency to perceive various situations as threatening or stressful over time. It measures an enduring predisposition toward anxiety.

The Beck Depression Inventory - Second Edition (BDI-II) is a self-report instrument designed to assess the severity of depressive symptoms in adolescents and adults aged 13 years and older[17,18]. Structured to capture both a Total Scale score and two primary factors of depression – Somatic-Affective and Cognitive, the BDI-II assesses a comprehensive range of depressive symptoms, capturing cognitive, affective, and somatic dimensions and consists of 21 items, each reflecting a specific symptom of depression (e.g., sadness, pessimism, fatigue, and sleep disturbances).

Data Analysis

Data analyses were conducted *via* the R Studio software (Vienna, Austria), using descriptive statistics. Given the small sample size, the median value was chosen as a measure of central tendency, while the interquartile range (IQR) was chosen as a measure of dispersion. Categorical variables were reported as absolute frequency and percentage.
Further details have been reported in the Supplementary Material.

RESULTS

The sample comprised eleven adult female patients with LO UCDs. The median age of the patients was 26 years (IQR: 21.5-41 years), with the onset of symptoms ranging from 6 months to 40 years. All patients, except one, were born before the implementation of the newborn screening program in Italy. At the time of the evaluation, all patients were undergoing both pharmacological therapy (ammonium chelating drugs) and a protein-restricted diet. Symptoms presented at onset included: refusal of high-protein foods, vomiting, headache, hypertransaminasemia, episodes of lethargy, coma during pregnancy, mental confusion, hyperammonemia, mild psychomotor retardation (present in only three cases), asthenia, drowsiness, abdominal pain, and coagulation alterations. The specific types of UCDs present in the cohort were: carbamoyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, citrullinemia (argininosuccinate acid synthetase deficiency), argininosuccinate lyase deficiency, argininemia (arginase deficiency), and hyperornithinemia–hyperammonemia–homocitrullinuria syndrome.

ASR/18-59 Questionnaire

According to the ASR/18-59 questionnaire (Table 1 and Figure 1), the median T-score on the Total Problems scale was 60 (IQR: 57.5-70), with five patients (45%) exceeding the pathological threshold. On the Internalizing Problems scale, the median T-score was 63 (IQR: 53-68.5), with five patients (45%) scoring above the threshold. In contrast, the Externalizing Problems scale had a median T-score of 60 (IQR: 57.5-64.5), with three patients (27%) scoring in the pathological range.

Table 1. Median scores for the 11 patients from the scales of the ASR questionnaire.

ASR questionnaire scales	Median (IQR)	Patients above pathological threshold, n (%)
Total Problems	60 (57.5-70)	5 (45%)
Internalizing Problems	63 (53-68.5)	5 (45%)
Externalizing Problems	60 (57.5-64.5)	3 (27%)
Anxious Depressed	61 (54-66.5)	3 (27%)
Withdrawn	65 (59-74)	6 (55%)
Somatic Complaints	53 (52.5-59)	0 (0%)
Thought Problems	51 (50-58)	0 (0%)
Attention Problems	62 (60-74)	5 (45%)
Aggressive Behaviour	61 (56-67)	5 (45%)
Rule-Breaking Behavior	58 (53-61)	1 (9%)
Intrusive	53 (50-57)	1 (9%)
Attention Deficit Hyperactivity Problems	65 (54-74)	6 (55%)
Sluggish Cognitive Tempo	67 (60-73)	6 (55%)

T-scores ≥65 are considered in the pathological range.

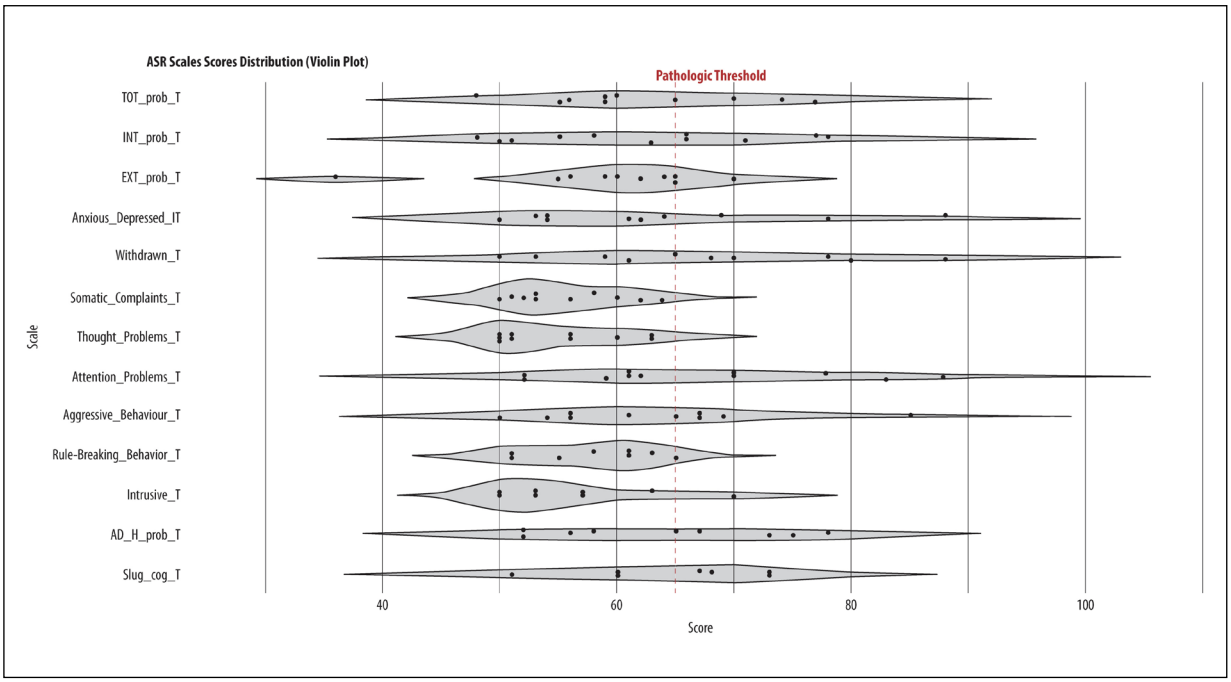

Figure 1. ASR/18-59 scales T scores distribution (Violin plot).

More specifically, regarding the Internalizing Problems sub-scales, the following results were obtained. On the Anxious/Depressed scale, the median T-score was 61 (IQR: 54-66.5), with three patients (27%) scoring above the pathological threshold. The Withdrawn scale showed a higher proportion of patients exceeding the clinical threshold, with six patients (55%) scoring in the pathological range, while the median score was 65 (IQR: 59-74). In contrast, no patients (0%) exceeded the clinical threshold in the Somatic Complaints scale, where the median score was 53 (IQR: 52.5-59).

Regarding the Externalizing Problems sub-scales, for the Aggressive Behavior scale, five patients (45%) reported clinically elevated scores, and a median score of 61 (IQR: 56-67). One patient (9%) scored pathologically on the Rule-Breaking Behavior scale with a median score of 58 (IQR: 53-61). Additionally, one patient (9%) showed a pathological score on the Intrusive scale and a median score of 53 (IQR: 50-57).

Concerning the two remaining sub-scales, in the Attention Problems scale, five patients (45%) reported clinically significant scores, with a median T-score of 62 (IQR: 60-74). However, none of the patients (0%) exceeded the clinical threshold in the Thought Problems scale, where the median score was 51 (IQR: 50-58) (Figure 1).

DSM-Oriented Scales

Regarding the additional DSM-oriented scales, on the Attention Deficit/Hyperactivity Problems scale, the median T-score was 65 (IQR: 54-74), with six patients (55%) exceeding the clinical threshold. Similarly, six patients surpassed the threshold on the Sluggish Cognitive Tempo scale, with a median score of 67 (IQR: 60-73) (Figure 1).

State-Trait Anxiety Inventory – Form Y

Regarding the STAI-Y (Table 2 and Figure 2), on the State Anxiety scale, the median T-score was 48 (IQR: 45.5-70.5), with four patients (36%) exceeding the clinical threshold. Similarly, on the Trait Anxiety scale, four patients (36%) also exceeded the threshold, with a median T-score of 63 (IQR: 45.5-76) (Figure 2).

Table 2. Scores for the 11 patients obtained from the STAI-Y and BDI-II scales.

STAI-Y and BDI-II scales	Median (IQR)	Patients above pathological threshold, n (%)
STAI-Y State Anxiety scale T scores	48 (45.5-70.5)	4 (36%)
STAI-Y Trait Anxiety scale T scores	63 (45.5-76)	4 (36%)
BDI-II Full scale percentile scores	80 (60-99)	5 (45%)
BDI-II Somatic-Affective subscale percentile scores	70 (65-88.5)	5 (45%)
BDI-II Cognitive Factor subscale percentile scores	80 (60-99)	5 (45%)

T-scores ≥65 or percentiles ≥85 are considered in the pathological range.

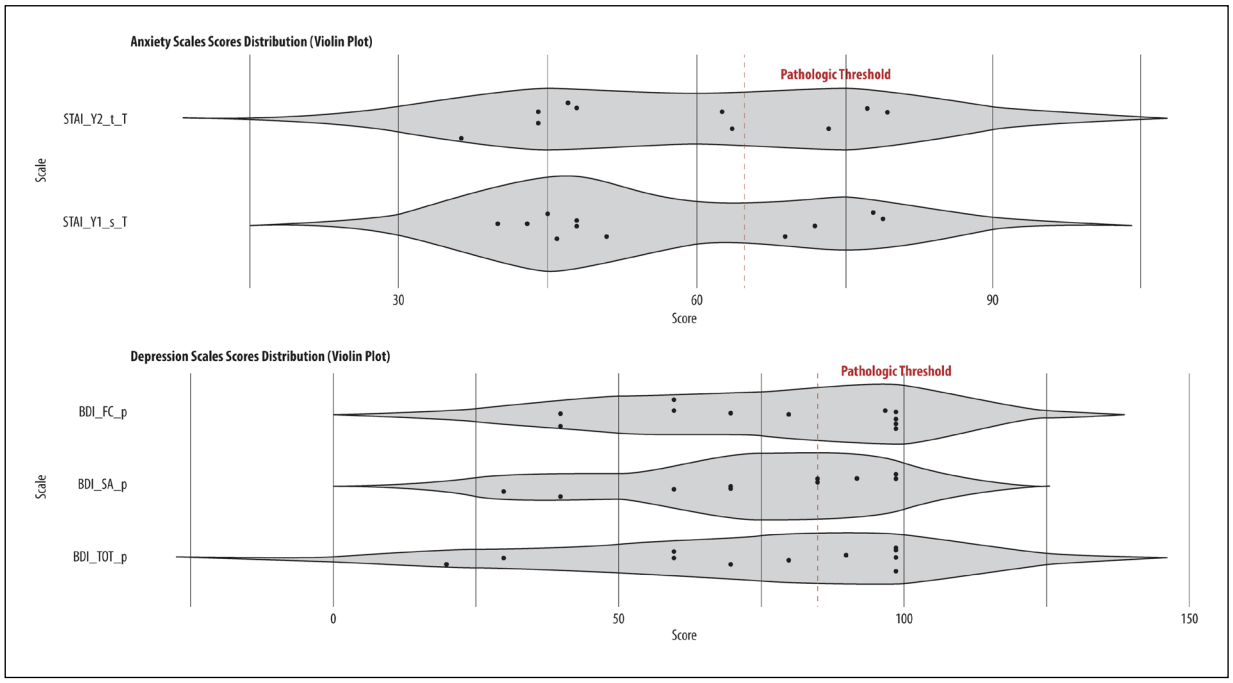

Figure 2. STAI-Y (above) and BDI-II (below) scales scores distribution (Violin plot).

Beck Depression Inventory - Second Edition (BDI-II)

Finally, based on the self-reported BDI-II (Table 2 and Figure 2), the median Total BDI-II score was 80 (IQR: 60-99), with five patients (45%) scoring above the pathological threshold of 85. Among these, four patients exceeded the threshold on both the Somatic-Affective subscale and the Cognitive Factor subscale. One patient surpassed the threshold on the Total BDI and the Cognitive Factor subscale (score: 99) but not on the Somatic-Affective subscale (score: 70). Additionally, one patient exceeded the threshold on the Somatic-Affective subscale (score: 85) while remaining below the threshold on both the Total BDI (score: 80) and the Cognitive Factor subscale (score: 80). More specifically, the median percentile for the Somatic-Affective subscale was 70 (IQR: 65-88.5), with five patients (45%) scoring above 85. Similarly, on the Cognitive Factor subscale, five patients exceeded the threshold, with a median score of 80 (IQR: 60-99) (Figure 2).

DISCUSSION

This study aimed to shed light on the cognitive and emotional impacts of LO UCDs in adults, a condition characterized by high variability in presentation and challenging management across the lifespan. Consistent with previous literature that identifies substantial psychosocial and cognitive impairments in metabolic disorders[10,11], we observed widespread emotional and behavioral disturbances among patients with LO UCDs. In this sample, 45% of patients scored above the clinical threshold on the Total Problems scale of the ASR/18-59, indicating a substantial emotional burden. This aligns with previous findings highlighting how neurological perturbations and the experience of having a chronic illness can be associated with heightened emotional dysregulation and behavioral issues[12].

The Internalizing Problems scale, which captures key symptoms of anxiety, depression, and withdrawal, was clinically significant in 45% of patients, reinforcing the notion that patients with LO UCDs experience heightened social isolation, anxiety, and depressive symptoms as the disease progresses[19,20]. Withdrawal symptoms, particularly prominent in our study (55% above the clinical threshold), suggest a distinct tendency towards social disengagement, which has been documented in the literature as a response to chronic illness-related stressors and decreased quality of life[19]. Despite these findings, only 27% of patients met clinical thresholds for anxious/depressed syndrome scale of ASR/18-59 specifically, and no patients exceeded the threshold for somatic complaints, suggesting that somatic symptoms may be less central to the UCDs experience. This pattern highlights that emotional burdens in UCD patients may manifest more distinctly in social and internalized patterns rather than physical symptoms.

On the Externalizing Problems scale, fewer patients reported clinically significant issues, with only 27% exceeding the threshold. Aggressive behavior was reported in 45% of patients, whereas other externalizing issues, such as rule-breaking and intrusive behaviors, were infrequent. These patterns may reflect a tendency for behavioral dysregulation to manifest more as internalizing than externalizing symptoms in adult UCD patients.

Furthermore, attention deficits, reported by 45% of the sample, represent another prominent aspect of UCD symptomatology, which is consistent with the documented neurotoxic impact of hyperammonemia on cognitive functions, especially attention and executive processes[9]. Complementary assessment with the ADHD and Sluggish Cognitive Tempo subscales further confirmed that five patients experienced clinically significant mental slowing, impulsivity, and inattention. These findings align with prior research highlighting the susceptibility of cognitive functions to metabolic disruptions, especially attentional regulation, as ammonia accumulation impacts the prefrontal cortex and other neural areas responsible for executive functioning[11].

Anxiety and depressive symptoms were further assessed through the STAI-Y and BDI-II scales, where 36% of patients reported both state and trait clinically significant anxiety, and 45% reported depressive symptoms, underscoring the psychological toll of the disorder. Interestingly, four patients exhibited elevated scores on both the somatic-affective and cognitive subscales of the BDI-II, suggesting depressive symptoms in metabolic disorders can encompass both physical and cognitive dimensions.

Moreover, at the time of the evaluation, all patients were undergoing both pharmacological therapy (ammonium chelating drugs) and a protein-restricted diet. Collectively, our findings underscore the intricate link between cognitive impairments and emotional dysfunctions in adult LO UCD patients, with a notable prevalence of attention deficits, anxiety, depression, and social withdrawal. Such impairments are not only compromising individual productivity and quality of life but also affecting family members and the broader social network[13]. The critical need for early identification and integrative, multidisciplinary approaches to address the cognitive and emotional challenges in UCD patients is evident, and our results underline that systematic psychological screening using validated tools should be integrated into the routine clinical care of adult LO UCD patients. This would facilitate early identification of neuropsychiatric issues, allowing for timely intervention and ongoing monitoring of their progression and response to treatment.

The limitations of this study, particularly its small sample size, warrant larger investigations to validate these findings. The study included exclusively females, which may limit the generalizability of the findings to male patients, given the potential for gender-related differences in cognitive and emotional functioning. Moreover, the cognitive aspect of the study is based solely on self-reported questionnaires, which may introduce subjectivity. While these instruments offer useful subjective data, they are inherently limited by potential bias and do not fully capture the complexity of patients' cognitive and neuropsychological functioning. Therefore, incorporating objective neuropsychological assessments is strongly recommended in future studies to improve the comprehensiveness and accuracy of cognitive assessment. Also, future studies should consider the influence of socio-demographic variables, such as educational and socioeconomic status, to deepen the understanding of the factors shaping cognitive and emotional functioning in this population.

CONCLUSIONS

In this study, adult patients with LO UCDs reported self-perceived cognitive impairments, such as attention deficits, alongside emotional issues, including anxiety, depression, and social withdrawal, underscoring the neuropsychiatric burden of UCDs. Future investigations should include larger patient cohorts and incorporate socio-demographic factors (e.g., educational attainment, socioeconomic status) along with objective neuropsychological assessments to enhance our understanding of the cognitive and emotional implications of UCDs in adulthood.

Artificial Intelligence-Assisted Technologies:

No artificial intelligence-assisted technologies were used in the production of this article.

Authors' Contributions:

Study conception and design: PC and GMTL; data collection and analysis: PC, GMTL, MCS, SP, FNP, CV, CM, ACA and MR; manuscript drafting: PC and GMTL; manuscript editing: SP, MCS, CV, FNP, CM, ACA, and MR; correspondence with Comitato Etico Locale Catania 1: CM; approval to submit: PC, GMTL, MCS, SP, FNP, CV, CM, ACA and MR.

Availability of Data and Material:

All data generated or analyzed during this study are included in this published article and its supplementary material.

Conflicts of Interest:

The authors declare that they have no conflict of interest to disclose.

Ethics Approval:

The study received ethical approvals from the Institutional Review Board of IRCCS Istituto Giannina Gaslini (protocol number 0033844/22-10-2024) and from the Comitato Etico Locale Catania 1 - Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" - Catania (protocol number 15160/10-3-2025).

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