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Review Article

Nutrition management guideline for propionic acidemia: An evidence- and consensus-based approach

Jurecki E.[a,*], Ueda K.[b], Frazier D.[c], Rohr F.[d], Thompson A.[e], Hussa C.[a], Obernolte L.[f], Reineking B.[a], Roberts A.M.[g], Yannicelli S.[h], Osara Y.[i], Stembridge A.[i], Splett P.[j], Singh R.H.[i]

[a] BioMarin Pharmaceutical Inc., Novato, CA, USA
[b] British Colombia Children's Hospital, Vancouver, BC, Canada
[c] University of North Carolina, Chapel Hill, NC, USA
[d] Boston Children's Hospital, Boston, MA, USA
[e] Greenwood Genetic Center, Greenwood, SC, USA
[f] Waisman Center, University of Wisconsin, Madison, WI, USA
[g] Valley Children's Hospital, Madera, CA, USA
[h] Nutricia North America, Rockville, MD, USA
[i] Emory University, Atlanta, GA, USA
[j] University of Minnesota, St. Paul, MN, USA

1. Introduction

Propionic acidemia (PROP) is an autosomal recessive inherited metabolic disorder (OMIM 606054) caused by defective functioning in the mitochondrial enzyme, propionyl CoA carboxylase (PCC), resulting in the accumulation of propionic acid metabolites, and dysfunction in the respiratory chain and urea cycle pathways. The reported incidence of PROP is 1 in 100,000 newborns in Europe and 1:242,741 in the United States, but as high as 1:2,000 to 1:40,000 newborns in areas of the world with higher rates of consanguinity [23,109]. PCC catalyzes the first step of the catabolic pathway for the essential amino acids, isoleucine (ILE), valine (VAL), methionine (MET), and threonine (THR). In addition, PCC drives the catabolic pathway for the odd-chain fatty acids and for the cholesterol side chain, and converts these and the amino acids to methylmalonyl-CoA which is further metabolized to succinyl CoA. Succinyl-CoA is oxidized in the citric acid cycle for ATP production. With biotin as a necessary co-factor, PCC activity may be compromised by defects in the biotin utilization pathway, as in biotinidase or holocarboxylase synthetase deficiency [135].

Similar to other inherited metabolic disorders (IMD), PROP manifests as a spectrum of phenotypes. Neonatal onset PROP is characterized by poor feeding, vomiting, and fatigue in the first days of life in a previously healthy infant, and if untreated, may be followed by lethargy, seizures, coma, and death. Neonatal onset PROP is frequently accompanied by metabolic acidosis with anion gap, ketonuria, hypoglycemia, hyperammonemia and cytopenia. Late onset PROP, in older children and adults with milder phenotypes, is less common, and may present with developmental regression, chronic vomiting, protein intolerance, failure to thrive, hypotonia, and occasionally basal ganglia infarction which may result in dystonia and choreoathetosis, and cardiomyopathy [21,22]. Metabolically unstable individuals can have an acute decompensation that resembles the neonatal presentation, often precipitated by a catabolic stress such as infection, injury, or surgery, or an excessive intake of intact (i.e., complete, dietary, or natural) protein. Long-term manifestations of neonatal and late onset PROP can include growth impairment, intellectual disability, seizures, basal ganglia lesions, pancreatitis, and cardiomyopathy [97]. Other less common manifestations include optic atrophy, hearing loss, premature ovarian insufficiency, and chronic renal failure [122]. Testing of urine organic acids in symptomatic individuals will show elevated 3-hydroxypropionate and the presence of methylcitrate, tiglylglycine, and propionylglycine that are normally not observed in the urine. Testing of plasma amino acids will reveal elevated glycine. Affected newborns identified by tandem mass spectrometry (MS/MS) newborn screening have elevated propionylcarnitine. Confirmation of diagnosis relies on detection of either deficient PCC enzymatic activity or bi-allelic gene mutations [97,109].

Individuals with PROP, at initial presentation or during illness, typically present with dehydration, hyperammonemia, and metabolic acidosis. Patients require aggressive management including removing accumulated toxic organic acids, minimizing endogenous protein catabolism, and promoting anabolism. Continuous hemofiltration has been used for rapid removal of toxins and allowing administration of larger volumes of fluids without risk of over-hydration. Insulin has been

* Corresponding author.
E-mail address: ejurecki@bmrn.com (E. Jurecki).

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administered to increase glucose tolerance, stimulate anabolism, and block catabolism. Gradual intravenous rehydration with energy sources in amounts typically exceeding maintenance requirements has helped to achieve an anabolic state prior to restarting oral intake [29,132].

The goal of medical nutrition therapy (MNT) in PROP is to reduce toxic metabolite accumulation by restricting dietary sources of propiogenic amino acids (VAL, ILE, MET, and THR) while maintaining normal plasma concentrations. Nutrient intake should be adjusted to promote normal growth and development, and to support positive clinical and patient-reported outcomes. Challenges to achieving adequate medical and nutrition management include risk of infection, metabolic crises, vomiting, anorexia, and other co-morbidities. Despite these challenges, early and aggressive medical and nutrition management can result in improved survival and clinical outcomes [12,109,135,137].

Southeast Regional Genetics Network (SERN) and Genetic Metabolic Dietitians International (GMDI) have undertaken a multi-year project to develop evidence- and consensus-based nutrition management guidelines for IMD for which there are limited peer-reviewed publications for various aspects of treatment. The goals of this project are to optimize nutritional management of affected individuals and reduce the uncertainty and variability in practice by reviewing research, developing guidelines, and directing future research. This is the third IMD nutrition guideline, following a similar method used to develop guidelines for maple syrup urine disease (MSUD) and phenylketonuria (PKU) [45,118]. Complete evidence documentation can be accessed through both the SERN (southeastgeneticsnetwork.org/ngp) and GMDI (GMDI.org) websites.

2. Methods

The methodology for development of the PROP nutrition management guideline and others in the series (MSUD [45] and PKU [118]) followed a rigorous, transparent and systematic process-based on standards for guideline development [55] with modifications to incorporate consensus methodology where research was lacking [117]. The process utilizes evidence from published peer-reviewed research and practice-based medical literature, as well as evidence derived from Delphi surveys and nominal group technique consensus processes [79].

Each step of the process including question formulation, search, critical appraisal and abstraction, consensus input, evidence summary, recommendation development, and external review is fully documented and archived on the SERN portal (southeastgeneticsnetwork.org/ngp). The topics for the evidence analysis were selected from areas of uncertainty and variation in practice by an organic acidemia working group comprised of 13 experienced metabolic dietitians. Seven practice-based questions were identified for evidence analysis and guideline development (Table 1). The practice-based questions were formulated in the PICO (population, intervention, comparison, and outcomes) format. Outcomes to be considered in each of the questions included patients' health status, metabolic stability, growth, nutritional status (i.e., protein, vitamin/mineral, bone mineral density, body composition, etc.), neurocognition and development, and quality of life. The systematic search for evidence included both published formal research and gray literature. The literature search was conducted in PubMed using key words for each question (refer to Supplement 1). Inclusion criteria were: published from 1970 to 2016, human studies, and English language; and exclusion criteria were: studies unrelated to PROP treatment and animal studies. Gray literature included non-peer reviewed articles, abstracts and presentations from scientific meetings, clinical protocols and guidelines, unpublished research, communication among experts (including listservs), professional and patient organization newsletters, and book chapters collected by work group members. Peer-reviewed published articles were assessed and graded based on criteria for sound scientific research; and gray literature was screened and prioritized for inclusion based on relevance, currency, and

Table 1
Research questions in PICO format

Topic	Question
1. Nutrient Intake	For individuals with PROP, what nutrient intakes are associated with positive outcomes?
2. Nutrition Intervention	For individuals with PROP, what nutrition interventions are associated with positive outcomes?
3. Nutrient Supplementation	For individuals with PROP, do specific nutrient supplementation or other treatment modalities improve outcomes?
4. Monitoring	For individuals with PROP, monitoring of which parameters is associated with positive outcomes?
5. Pregnancy and Lactation	For women with PROP, what nutritional therapies are associated with positive outcomes during menstruation, pregnancy, delivery and the post-partum period?
6. Secondary Complications	For individuals with PROP with secondary complications, what nutrition interventions are associated with positive outcomes?
7. Liver Transplantation	For individuals with PROP undergoing liver transplantation, what nutrition interventions pre-, during and post-transplant result in optimal outcomes?

PROP, propionic acidemia.

substantive information not available in published scientific literature. Expert input was obtained from nutrition and medical clinicians and researchers by using an initial Delphi survey. At this point, preliminary conclusion statements, evidence summaries and recommendations were prepared and submitted to a panel of experts who participated in a two-day meeting utilizing the nominal group process technique. Caregivers of affected individuals were included in the nominal group meeting. A second-round Delphi survey was conducted focusing on areas of uncertainty. Level of agreement with practice statements was quantified using a 7-point Likert scale and consensus was defined as ≥80% agreement. Evidence from these consensus processes was incorporated into the final guideline.

3. Guideline development

The final conclusion statements and recommendations for the nutritional management of individuals with PROP in each of the seven topic areas were based on the synthesis of all evidence and consensus sources. These were written, reviewed, and edited by the project core group, with input provided by a guideline consultant along with experienced health care practitioners. Each recommendation was rated with respect to strength of evidence (insufficient evidence, consensus, weak, fair or strong) supporting the conclusion, and given a clinical action rating (conditional or imperative); definitions of these terms are available on the SERN portal (southeastgeneticsnetwork.org/ngp) and in Supplements 2 and 3. In addition, the final guidelines document included background information and patient and provider resources to support implementation. The final document was reviewed by an external panel using the Appraisal of Guidelines for Research and Evaluation (AGREEII) [15]. The external panel included 10 metabolic physicians and metabolic dietitians, and an expert in guideline development and methodology, none of whom were involved in the evidence analysis nor in the development phases of the PROP guidelines.

4. Web application

A secure, web-based application was developed specifically for IMD guidelines development and is described in detail elsewhere [118]. All reference material was categorized and stored within the web-based platform. Each step of the guideline development process has been stored and tracked within the platform. These features assisted in the development of current guidelines and will provide support for future updates to the guidelines.

5. Results

The systematic literature search identified 1,131 published articles; after exclusion of 906 papers, 225 publications were available for analysis. (See flow diagram of evidence sources for development of nutrition recommendations for PROP guidelines in Supplement 4.) In addition, the gray literature search added 29 documents; 25 were adjudicated for analysis and evidence synthesis. There were 40 articles identified for nutritional intake, 95 for nutritional intervention, 98 for supplementation, 98 for monitoring, 8 for pregnancy, 48 for secondary complications, and 38 for liver transplantation. Expert input was provided from 27 physicians and researchers, 25 metabolic dietitians, and 2 patient advocates through various steps including the Delphi surveys, and nominal group meeting participation, and reviewed externally by 10 physicians and metabolic dietitians and one guideline development expert. Recommendations for each question along with ratings for the strength of the evidence are listed below followed by an evidence summary.

Question 1: Nutrient intake recommendations

Recommendation	Strength of Evidence	Clinical Action
ILE, VAL, MET, and THR requirements should be met by providing 60–100% of the age-appropriate recommended total protein requirement, as determined by the DRI from sources of intact protein	Weak	Imperative
For individuals tolerating < 100% of the DRI from intact protein, consider adding PROP medical food to meet 100–120% of total protein requirement	Weak	Imperative
Provide additional sources of intact protein, rather than supplementing single L-amino acids to individuals who have low plasma propiogenic amino acids	Consensus	Imperative
Human breast milk can be used as source of intact protein with careful monitoring for infants with PROP	Fair	Imperative
Provide 80–120% of energy requirements for age to spare protein catabolism while individualizing for physical activity, clinical status, and to support normal growth and weight management	Weak	Imperative
Meet the DRI for age for intake of essential fatty acids, fluids, vitamins, minerals, and micronutrients; consider supplementation when insufficient intake is determined by clinical, biochemical, nutritional and/or adherence monitoring	Weak	Imperative

DRI, dietary reference intake; ILE, isoleucine; MET, methionine; PROP, propionic acidemia; THR, threonine; VAL, valine.

Evidence summary

The goal of dietary propiogenic amino acid restriction is to achieve and maintain plasma concentrations as close to normal as possible while preventing and/or correcting for deficiencies. The catabolism of VAL, ILE, MET, and THR has been shown to produce on average 50% of propionate in humans [127,134]. Part of nutrition management of individuals with PROP involves limiting the intake of intact protein to reduce the intake of these propiogenic amino acids. However, because they are essential amino acids, it is also important that the intake be sufficient to meet the needs for growth and anabolism. The dietary prescription should be adjusted based on clinical and laboratory parameters [122]; individuals with more severe disease require greater restriction of intact protein and may rely on more PROP medical food as compared to those with milder disease [12,106]. The Dietary Reference Intakes (DRI) [54] for protein and energy, adapted to address the needs for well individuals with PROP, are listed in Table 2. The medical foods, restricted in propiogenic amino acids, provide a protein source rich in essential L-amino acids that can be digested and oxidized more rapidly than intact protein, and can be used to increase total protein intake [138]. Since the amino acid profiles in foods and medical foods differ, it is important to check actual content when evaluating adequacy of protein intakes.

In one report on 55 individuals with PROP from 16 metabolic clinics in Europe, the majority supplemented their intact protein intake with medical food to meet total protein needs, though the amount of medical food versus intact protein intakes were not detailed [49]. The authors noted improved survival rates compared to previous reports, but continued unsatisfactory neurologic outcomes with approximately 75% of individuals with cognitive delays, and early onset, progressive growth retardation [49]. In a report on 49 individuals with PROP from 8 metabolic clinics, patients with milder phenotypes received only intact protein restriction while patients with more severe phenotypes received two-thirds of their total protein intake from intact sources and the rest from medical foods. No difference in outcomes were observed based on degree of intact protein restriction. The authors concluded that the higher total protein intake from both intact and medical food protein had no negative effect on outcomes and may have been beneficial [106]. In another study, 17 individuals with PROP were followed over

Table 2
Recommended intakes of protein and energy for well individuals with PROP[a]

Age	Intact Protein[b] (g/kg/day)	Total Protein[c] (g/kg/day)	Energy[d] (kcal/kg/day)
0–6 mos	0.91–1.52	1.52–1.82	M: 72–109 F: 72–108
7 – < 12 mos	0.72–1.2	1.20–1.44	M: 65–97 F: 64–96
1–3 yrs	0.63–1.05	1.05–1.26	M: 66–99 F: 66–99
4–8 yrs	0.57–0.95	0.95–1.14	M: 59–88 F: 56–84
9–13 yrs	0.57–0.95	0.95–1.14	M: 43–65 F: 39–58
14–18 yrs	0.51–0.85	0.85–1.02	M: 36–53 F: 30–45
≥19 yrs	0.48–0.80	0.80–0.96	80–100% of DRI
Pregnancy	0.66–1.10	1.10–1.32	Trimester 1 – same as pre-pregnancy Trimester 2 – +340 kcal/day Trimester 3 – +452 kcal/day
Lactation	0.78–1.30	1.30–1.56	Varies

AI, adequate intake; DRI, dietary reference intake; EER, estimated energy requirement; PROP, propionic acidemia; RDA, recommended dietary allowance.
[a] Adapted from the Institute of Medicine [54]
[b] Represented 60–100% of AI/RDA
[c] If < 100% AI/RDA for intact protein is tolerated, consider adding PROP medical food to provide 100–120% of AI/RDA for protein
[d] Represents 80–120% EER for energy

an extended period of time [128], and improvement in outcomes could be attributed to better management, including extensive use of enteral nutrition, antibiotics, and careful adjustment of protein intake. Outcomes in those individuals receiving medical food and intact protein (n = 9) were similar to those who did not receive medical foods leading to the authors' conclusions that medical foods did not seem to play an important role in long-term nutritional and developmental outcomes for these individuals. Further research is needed to determine what the optimal intake of medical food is relative to intact protein. Available consensus evidence suggests the benefits of providing age appropriate total daily protein to avoid risks of developing protein deficiency, mainly for individuals requiring limited intact protein intake, to promote metabolic stability.

When plasma propiogenic amino acid concentrations are low, and/or signs of deficiency are detected, consensus evidence supported that repletion is better achieved using intact protein sources rather than single L-amino acids. Some individuals, treated with intact protein-restricted diets supplemented with medical food, have been noted to have low plasma ILE concentrations [115]. A case report described a 2-month-old infant on a total protein intake of 0.8 g/kg/day that included medical food, who developed skin lesions due to plasma ILE deficiency [33]. Some clinicians recommend supplementing ILE and VAL as individual amino acids, starting at doses of 100 mg/day to correct a relative deficiency [92,138]. However, there are no studies on the safety and efficacy of the combination of medical food and individual ILE or VAL supplements [12]. More recent recommendations in patients with methylmalonic acidemia (MMA), but still relevant to PROP patients given the similarities in nutrition management, provide evidence that use of intact protein to correct low concentrations of ILE and VAL may be more beneficial than individual amino acids [80].

There is limited published evidence on infants with PROP receiving human breast milk as an intact protein source. In a review of 30 individuals with PROP, 80% of whom were breastfed, no precipitating factors for metabolic decompensation were noted [73]. Consensus supported published recommendations that human breast milk (from feeding at the breast or using expressed breastmilk) may be considered as a source of intact protein for an infant with PROP if used with careful monitoring [12].

The evidence for energy needs is based on a limited amount of research, though consensus agreement supports providing 80–120% of the DRI for age [54], with some patients requiring less due to lower resting energy expenditure or physical inactivity. In one multi-center report on 13 individuals with PROP who received approximately 61–67% of total protein from intact sources and the rest from medical food meeting ≥100% of protein needs, 7 patients who received 98% of recommended energy needs demonstrated increased growth percentiles in length while 9 patients who received 87% of energy needs showed decreased length growth percentiles, suggesting that an energy intake is important to spare protein to support growth [139]. In one study, resting energy expenditure was noted to be 20% below calculated amounts as measured by indirect calorimetry in 3 healthy individuals with PROP, and did not correlate with protein intakes. The investigators concluded that calculated energy intakes should be adjusted based on clinical status [38]. Energy intake should be adequate under all circumstances to prevent catabolism and the release of propiogenic amino acids from endogenous protein and odd-chain fats from lipid stores, though specific needs may differ due to age, gender, pregnancy, breastfeeding, illness, and other factors. Energy requirement should be individually determined and balanced between promoting anabolism while avoiding overfeeding especially for less physically active individuals [2,135].

There is no evidence that the recommended intake of fluids, essential fatty acids, vitamins, minerals, and other micronutrients for individuals with PROP differs from that for the general population [12,29,31,98,137,138]. Those individuals with PROP who receive and are compliant with the prescribed medical foods that contain the recommended vitamins, minerals, and fat may not need additional supplementation. Those individuals who tolerate more intact protein, and therefore need less medical food, may need additional supplementation. A report of 5 children with PROP on intact protein-restricted diets and prescribed medical food demonstrated no significant differences in plasma or erythrocyte saturated or essential fatty acids as compared to controls [31].

Question 2: Strategies for nutritional intervention recommendations

Recommendation	Strength of Evidence	Clinical Action
During acute illness, or at first presentation, provide aggressive nutrition management to optimize energy intake, to prevent or reverse catabolism and promote anabolism, to achieve rehydration, and to minimize propionate and ammonia accumulation	Fair	Imperative
Restrict protein intake for no longer than 24–48 h, before re-introducing intact protein (in either enteral or parenteral feedings) at approximately 0.-5 g/kg/day, then increasing by increments of 0.25 g/kg/day as tolerated	Weak	Imperative
If the total protein requirement is not met [OR cannot be met] by intact protein, consider the use of propiogenic-limited amino acid medical food (enteral) or propiogenic amino acid free amino acid TPN solution (for patients requiring prolonged bowel rest) to meet the total protein requirement	Consensus	Imperative
Utilize tube feeding as necessary to supplement oral intake of nutrients and fluid, administer medications, and reduce fasting intervals	Fair	Conditional
Promote development and/or maintenance of oral skills for the tube-fed individual with use of adaptive/assistive feeding devices, behavior intervention, and positive reinforcement and guidance techniques	Weak	Imperative
For the metabolically stable individual, meet the nutrient requirements listed in Table 2, with	Fair	Imperative

adjustments of intake made for individual tolerance, growth spurts and minor illnesses		
Provide an individualized emergency home feeding plan for mild illness (i.e., episodes without GI symptoms or greater than "small" urinary ketones) including reducing total protein intake for 24–48 h, increasing energy intake from carbohydrates/fats, supplying adequate hydration, continuing medical food as tolerated, monitoring clinical signs and symptoms, and providing metabolic clinic contact information	Consensus	Imperative

GI, gastrointestinal; TPN, total parenteral nutrition.

Evidence summary

Several clinical studies and literature reviews document the importance of prevention of catabolism by administering high energy feedings enterally or parenterally [12,29,50,77,110,138]. Strategies for provisions of energy, IV dextrose, IV lipids, and insulin (outlined in Table 3) [12,41,50,61] are necessary to promote an anabolic state. Gradual rehydration over the first 48 h of initial acute presentation with fluids containing appropriate electrolytes and avoidance of Ringer's lactate solution are suggested to promote urinary excretion of toxic metabolites, essential to optimize outcomes [21,22,29,50,73,132]. Avoidance of hypotonic fluids and over-aggressive rehydration has been shown to decrease risk of cerebral edema [29,50]. Removal of total protein upon acute presentation has been suggested [21,22,44,73,77], with reintroduction within 24 to 48 h after discontinuation or sooner if decompensation is determined to be due to protein deficiency. In 30 patients with PROP in acute metabolic crisis [73], early administration of tube feedings with intact protein at 0.5–0.7 g/kg/day with careful introduction of non-propiogenic amino acids from medical foods achieved a positive nitrogen balance. Protein intake has been recommended to be advanced with intact protein by 0.25–0.5 g/kg/day as tolerated to meet minimal daily requirements, though specific amounts varied widely between patients and were determined based on disease severity, age, and growth rate, and titrated according to biochemical monitoring, with even distribution of amino acids over the course of the day [94,135]. Use of total parenteral nutrition (TPN) during acute crises minimized catabolism and improved recovery [2,12,21,22,73,94,137], though specifics on outcomes were not provided. Although TPN contains a complete source of essential amino acids including propiogenic amino acids, they were reported to be used safely by avoiding excessive amounts and titrating based on biochemical monitoring [60,61,134].

The easy provision of medical foods, formula, and fluids via tube feedings has facilitated nutritional management, likely with concomitant medical benefit. They allow supplementation of intake, administration of medications, reduction of the number of hours fasting when used to provide overnight feedings or more frequent daytime feedings, and provision of nutritional support during periods of anorexia and vomiting associated with compromised metabolic control [21,22,73,92,122,131]. Feeding difficulties have been noted the first 2–5 years of life due to muscular hypotonia with swallowing difficulties and developmental delay, and can lead to metabolic decompensation, illness, compromised gastrointestinal (GI) tolerance, and protein and nutrient deficiencies [65,82,92,125,128,131,138]. Tube feedings have been successfully used in cases of growth failure, anorexia, and dysphagia and in neurologically compromised patients [2,21,22,44,49,132,135]. Use of adaptive and assistive feeding devices has been recommended to compensate for feeding skill deficits and to assist with promoting oral intake [52]. Referral to feeding or speech therapy may be recommended in certain circumstances [37]. Avoidance of fasting has been reported to decrease/prevent metabolic decompensation [39,94,126,132,135,138,145]. In addition, during illnesses resting energy expenditure may increase, resulting in greater energy needs required to prevent metabolic decompensation [38]. Maximum fasting time, based on clinical experience with 12 PROP patients, was suggested not to exceed 8 h though specific outcomes associated with this recommendation was not provided [125].

A home emergency feeding regimen is suggested for mild illnesses, without GI symptoms, to provide adequate energy and prevent endogenous protein catabolism and should be done in consultation with the medical care team; the impact of this practice on clinical outcomes has not been reported [12,92,135]. Components of an individualized plan as well as factors to consider for determining appropriateness of managing individuals at home are listed in Table 3 [12,21,22,135]. Preplanning for illness management with an emergency medical treatment letter including contact information for patients' metabolic clinic has been recommended [122]. To facilitate implementation of the above recommendations for nutrition management into clinical practice, Table 3 outlines suggested actions related to the key areas of the recommendations.

For metabolically stable individuals, nutritional requirements (Table 2) should be met with adjustments made for individual tolerance, growth spurts, and minor illnesses. A diet restricted in the propiogenic amino acids, based on individual tolerance and adequate growth, and increased with medical food to optimize protein intake, has been reported to lead to more favorable outcomes. This diet can also provide a good source of vitamins and minerals missing in an intact protein-restricted diet [2,137,138]. Appropriate counseling on maintaining adequate energy and total protein intakes in amounts required to prevent growth failure and allow for catch-up growth and maintenance of adequate nutritional status has been advised, though specific outcomes were not reported [122].

Question 3: Nutritional supplementation and other treatment modalities

Recommendation	Strength of Evidence	Clinical Action
In well individuals with PROP, provide sufficient oral L-carnitine to maintain plasma free carnitine in the normal range	Fair	Imperative
Supplement biotin in newly identified individuals with PROP to rule out multiple carboxylase deficiency and discontinue biotin after the diagnosis of PROP is confirmed	Weak	Imperative
Consider, in consultation with the medical team, the use of metronidazole in acutely ill individuals with PROP in order to reduce gut production of short chain fatty acids	Weak	Conditional
Consider, in consultation with the medical team, the use of carbamylglutamate to treat secondary hyperammonemia resulting from the inhibition of NAGS by elevated propionic acid	Weak	Conditional
Discourage use of supplemental amino acids (e.g., VAL, ILE) in favor of providing additional intact protein in individuals with PROP who have low plasma concentrations of propiogenic amino acids	Consensus	Imperative
Consider the use of prebiotics and fiber to support bowel health in individuals with PROP	Insufficient Evidence	Conditional
Consider supplementation of vitamins and other agents that may enhance mitochondrial energy production	Insufficient Evidence	Conditional

ILE, isoleucine; NAGS, *N*-acetylglutamate synthase; PROP, propionic acidemia; VAL, valine.

Evidence summary

Beyond limiting the dietary intake of the propiogenic amino acids in the management of PROP, there are supplements, medications and interventions that are used to decrease propionate production, increase its excretion or limit its ability to interfere with various cellular or biochemical processes. Supplementation with L-carnitine, at doses typically of 50–100 mg/kg/day, reduces the accumulation of free propionic acid by conjugating it to form propionylcarnitine, and prevents secondary carnitine deficiency. Low concentrations of carnitine have been found in the muscle and liver [69], as well as heart tissue [81] in patients with PROP. Several case reports, including 14 patients with

Table 3
Nutritional management of individuals with PROP

Recommendation Key Points	Intervention Strategies for Management
During acute illness or first presentation	
Provide aggressive nutritional management	• Fluids and electrolytes at 1.5–2× maintenance[a] • Energy at 1.1–1.5× recommended • L-Carnitine at 100–300 mg/day • Insulin; to prevent or reverse hyperglycemia
Protein intake	• Withhold no longer than 24–48 h • Consider re-introducing at 0.5 – < 0.75 g/kg/day with intact protein and increasing by 0.25 – < 0.5 g/kg/day
Parenteral nutrition support	• Administer 10% dextrose IV at age-dependent glucose requirements to maintain blood glucose at 120–170 mg/dL (and insulin if needed) [129] • Add 20% IV lipid at 2 g/kg/day • Start with standard IV amino acid solution as per Table 2 • Consider use of propiogenic-free amino acid TPN solution when protein DRI cannot be tolerated from standard IV amino acid solution during times when prolonged bowel rest is needed
Enteral nutrition support	• Supplement oral intake and administer medications when needed • Can reduce number of hours fasting via overnight feedings or more frequent daytime feedings • Can provide nutritional support when there is anorexia due to poor metabolic control • Consider use of propiogenic-limited amino acid medical food when protein DRI cannot be tolerated from intact protein source
For ongoing management	
Do not allow extended fasting periods [126]	• Generally should not exceed 4–6 h for infants (≤12 months of age) • Generally should not exceed 8 h after infancy (> 12 months of age)
Promote oral intake to develop feeding skills	• Consider use of adaptive/assistive feeding devices • Provide extra attention and encouragement • Use of behavioral intervention and positive reinforcement and guidance techniques is suggested to address refusal, gagging, and vomiting and delays in feeding skills
For metabolically stable individuals	• Meet nutrient requirements (see Table 2) • Adjustment of intake for individual tolerance, growth spurts and minor illnesses
Home sick day plan	
Initiate and maintain contact with metabolic clinic as directed	
Provide an individualized sick day home feeding plan	• With mild illnesses without GI symptoms • When urinary ketones are small or negative
The individual plan	• Consider reduction of total protein from intact protein and medical food for 24–48 h • Increase energy intake from carbohydrates/fats • Maintain hydration • Monitor clinical signs and symptoms
Additional considerations	• Administer more frequent feedings with smaller volumes to aid enteral tolerance • Restriction of intact protein should not exceed 48 h
Factors to consider regarding the appropriateness of managing the mildly ill individual at home	• Age • Severity of illness • Distance to clinic • Caregiver's ability to accurately report, monitor and manage • History of previous illnesses and outcomes

DRI, dietary reference intake; GI, gastrointestinal; IV, intravenous; PROP, propionic acidemia; TPN, total parenteral nutrition.
[a] Adjustments needed if individual is dialyzed

PROP, reported better clinical outcomes after receiving L-carnitine, though this was given in combination with diet therapy and other interventions, making it difficult to attribute the benefit to L-carnitine alone [7,36,53,61,69,120,121,136]. Reported benefits of L-carnitine supplementation along with standard management included: lower mortality [29]; decreased incidence of metabolic decompensation [136]; better intellectual outcome [120]; and improved ability to tolerate stress caused by fasting, fever, viral infection or excessive protein loading [121]. Recommended doses for acutely ill patients range from 100 to 300 mg/kg/day divided into 2–4 doses (often administered intravenously) and for chronic management range from 100 to 300 mg/kg/day divided into 2–4 doses [12,122]. The amount of L-carnitine in medical food should be considered when dosing [122], and the total amount given adjusted based on monitoring plasma total, free and esterified (acyl) carnitine with the goal of maintaining plasma free carnitine within normal limits. The primary side effect is diarrhea when given by mouth or by gastrostomy tube, and can be avoided by administering it intravenously, the preferred route in acutely ill patients. Carnitine doses > 300 mg/kg/day may be associated with a fishy odor caused by production of methylamines by certain gut bacteria [137,138].

As PCC is a biotin-dependent enzyme, biotin supplementation is often recommended. Until a definitive PROP diagnosis is made, biotin should be provided as treatment of a potential multiple carboxylase deficiency. While 5–40 mg per day of biotin has traditionally been used in PROP, review articles suggest that no one with PROP has been found to be biotin responsive with any clinical benefits [9,12,94,122,137].

While metronidazole is associated with significant reduction in enteral propionate production and increased urinary propionate output [29,30,85], no studies have compared outcomes between patients with PROP receiving metronidazole and those patients managed without this medication. The suggested dose of metronidazole in PROP is 10–20 mg/kg/day, given in a cyclical fashion [21,22,30,39,44,94,135,138]. Alternative regimens include 20 mg/kg/day in 2–3 doses for 1–2 weeks alternating with 2–3 weeks off or alternating every month with other antibiotics, such as polymyxin E [21,22,49]. Potential negative effects associated with metronidazole therapy include anorexia [137] and risk of dystonia with toxicity [122].

Several case reports, which represented a total of 15 patients, investigated the effect of carbamylglutamate therapy on reducing secondary hyperammonemia in PROP [1,41,42,47,59,74,75,119]. Dosing ranged from 21 to 300 mg/kg, administered in conjunction with

Table 4
Nutritional monitoring schedule

Stage (Domains / Measures)	Infants (0–1 yr)	Children (> 1–7 yrs)	Children (8–18 yrs)	Adults	Pregnancy	Post-partum/ Lactation
Nutrition visit in clinic[a]; dietary intake, nutrient analysis, nutrition-related physical findings, feeding skills, nutrition counseling, diet education, activity level	Weekly to monthly	Monthly to every 6 mos	Every 6–12 mos	Every 6–12 mos	Monthly to per trimester	At 6 wks post-partum then every 6 mos while breastfeeding
Anthropometrics	Every clinic visit, include weight, length, and OFC	Every clinic visit, include weight, length or height, and OFC through 36 mos	Weight, height, and BMI at every clinic visit	Weight and BMI at every clinic visit	Weight and BMI at every clinic visit	Weight and BMI at every clinic visit
Developmental / Psychomotor function and neurocognitive assessment	Neurocognitive testing appropriate for age					

BMI, body mass index; OFC, occipitofrontal circumference.
[a] Interval nutritional contact between nutritional clinic visits as needed

Table 5
Biochemical monitoring schedule

	Infants	> 1–7 yrs	8–18 yrs	Adults	Pregnancy	Post-partum/Lactation
Biochemical (routine)						
Amino Acids, plasma	1–3 mos	At every clinic visit or every 6 mos	At every clinic visit or every 6 mos	At every clinic visit or at least annually	Weekly to monthly	At every clinic visit
Carnitine, free & acyl, plasma	1–3 mos	At every clinic visit or every 6 mos	At every clinic visit or at least annually	At every clinic visit or at least annually	Weekly to monthly	At every clinic visit
Ketones, urine	Daily for baseline; Weekly to every other week; More frequent if unstable	Monthly; Daily when clinically unstable	Monthly; Daily when clinically unstable	Monthly; Daily when clinically unstable	Monthly; Daily when clinically unstable	Monthly; Daily when clinically unstable
Prealbumin	6–12 mos	6–12 mos	6–12 mos	At every clinic visit or at least annually	Monthly to per trimester	Monthly
Alb / t protein	6–12 mos	6–12 mos	Yearly	At every clinic visit or at least annually	Per trimester	Yearly
CBC with differential	6–12 mos	Yearly	Yearly	Yearly	Per trimester	Yearly
Vit $D_{25\text{-}OH}$	N/A	Yearly	Yearly	Yearly	Per trimester	Yearly
Biochemical, conditional						
NH_3	Baseline, then every 3–6 mos	Every 3–6 mos	Every 6 mos	Every 6 mos	Baseline	As indicated
Comprehensive metabolic panel	Yearly or as indicated	Yearly or as indicated	Yearly or as indicated	Yearly or as indicated	At 1st visit then as indicated	As indicated
Acylcarnitine profile, plasma	Confirm diagnosis; Every 6 mos	Annually, if indicated	Annually, if indicated	Annually, if indicated	As indicated	As indicated
Organic Acids, urine	Confirm diagnosis; Every 6 mos	Annually, if indicated	Annually, if indicated	Annually, if indicated	As indicated	As indicated

CBC, complete blood count.

standard acute management strategies, making it difficult to attribute reduction in hyperammonemia solely to carbamylglutamate. However, in most cases the investigators stated that the reduction in serum ammonia was more rapid with the carbamylglutamate than they would have otherwise expected. Side effects included vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache, though carbamylglutamate has been reported to be tolerated without significant adverse effects in newborns [27].

The use of prebiotics, non-digestible substances in food (usually fibers), has been controversial because of the concern that they may promote the growth of bacteria that enhance production of short chain fatty acids, including propionic acid. There is no direct evidence of the effect of prebiotic use in PROP; however, there is indirect evidence that their use is safe and possibly beneficial. Prebiotics and/or fiber may be prescribed for bowel health to promote fecal output and reduce the chance of overproduction of gut propionate secondary to constipation. Fructo-oligosaccharides and galacto-oligosaccharides are prebiotics added to some medical foods for PROP that have been well tolerated and have shown to produce higher acetate and lower propionate in healthy infants [66]. In either case, there is currently insufficient evidence on use of these in the management of patients with PROP.

Anaplerotic therapy with the use of vitamin supplementation and other agents that may enhance mitochondrial energy production has been suggested, though the evidence supporting their use is limited. Reversal of cardiomyopathy with administration of hydroxybutyrate, riboflavin, thiamin, and Coenzyme Q10 (CoQ10) was reported in one case [10]. Low serum tocopherol concentrations despite adequate intakes were noted in patients with IEM, including one individual with PROP [87]. Approximately half of the respondents to the Delphi survey most commonly prescribed CoQ10, thiamin, vitamin E and mitochondrial cocktails, though observed benefits were noted by ≤25% of the respondents.

Question 4: Monitoring nutritional intervention

Recommendation	Strength of Evidence	Clinical Action
Conduct nutrition assessment (e.g., dietary history, nutrient analysis, feeding skills and schedule, activity level and nutrition-related physical findings) to determine adherence and nutritional adequacy of MNT	Strong	Imperative
Monitor age-appropriate anthropometrics	Strong	Imperative
Assess developmental, psychomotor, and neurocognitive status	Weak	Imperative
Use biochemical indicators (e.g., plasma amino acid profile; albumin, transthyretin; complete blood count/differential; plasma acylcarnitine profile and plasma carnitine; and urinary ketones) to assess nutritional adequacy and response to dietary intervention and consider additional indicators during acute illness or when secondary complications are present	Fair	Imperative
Consider additional biochemical parameters and more frequent monitoring when clinically indicated (-e.g., long-term poor adherence, signs and symptoms of nutritional inadequacy, intercurrent illness, acute metabolic decompensation, pregnancy, secondary complications of PROP, and transplantation)	Fair	Conditional

MNT, medical nutritional therapy; PROP, propionic acidemia.

Evidence summary

Regular monitoring of clinical and nutritional status, to determine adequacy of nutritional intake and to guide modifications in the dietary prescription, is central to management of individuals with PROP. Guidelines for monitoring diet history, activity level, anthropometric, and biochemical data at each clinic visit are listed in Tables 4 and 5. The clinician should keep in mind the timing of the blood draw relative to when medicines or meals were consumed or if in a fasting state when evaluating laboratory results. A comprehensive dietary history, conducted by a metabolic dietitian [2,44,65,128,138], is critical to assessing nutritional adequacy and adherence to the current nutrition prescription, and may include: nutrient analysis based on oral intake, tube feedings and supplements; feeding schedule and home-monitored urinary ketones; nutrition-related physical assessment; and psycho-social factors [2,44,49,122,128,137,138]. A plasma amino acid profile is commonly assessed to ensure an appropriate balance to assure nutritional adequacy to support tissue synthesis and growth [12,65,114,128,137–139]. Low concentrations of LEU [108,128], VAL [128,139] and ILE [14,128] have been reported as have deficiencies of other amino acids, including methionine, threonine and glycine [143]. Signs of deficiencies may include acrodermatitis, with erythematosquamous patches and thinning hair [14,20,123,143]. Measures of protein status, including total protein, albumin, and prealbumin (transthyretin), are recommended for routine monitoring to assess adequacy of energy and protein intakes for metabolically stable patients with PROP [2,12,21,22,44,122,137–139]. Monitoring plasma free-, esterified-, and total carnitine is recommended to assess the ratio of free: acyl carnitine and to identify deficiency of the free carnitine pool [40,44,73,135,138]. Periodic monitoring of serum ammonia is also recommended [2,67,122,138,144]. Routine testing of urinary ketones is recommended to monitor metabolic stability at home [21,22,44,94,138]. Urine ketones provide an indicator of beta oxidation and are a surrogate marker for propionate metabolites [126]. When monitored along with other signs and symptoms such as vomiting and food refusal, urine ketones may indicate impending illness and the need to initiate home emergency management [12,21,22]. Blood tests, including complete blood count (CBC) with differential, should be completed during clinic visits and especially in any individual with suspected anemia [17,44] given the increased risk of thrombocytopenia and neutropenia [48,49,51]. Monitoring for hematologic changes, including nutritional anemias, may prevent hematologic diseases and improve prognoses [73,124]. Monitoring serum selenium (with glutathione peroxidase) and zinc may be warranted in patients with insufficient intakes as deficiencies have been reported [137,140,143]. In one study, low bone mineralization was found in most patients while bone metabolism markers, including plasma calcium, phosphorus, osteocalcin, and 25-OH vitamin D were reported in normal reference ranges [128]. Monitoring bone status through DXA and 25-OH vitamin D is conditional and indicated in at-risk patients.

Neurologic manifestations in PROP, such as hypotonia and cognitive deficits, impact nutrition through altered energy needs based on level of physical activity, feeding ability, and intellectual capacity and need to be addressed as part of nutritional management [49,122]. Assessments of neurocognitive development and quality of life provide objective measures of clinical outcome [46,49,82,108]. Assessment of early-life psychomotor skills may be helpful in predicting neurologic involvement later in life [16]. Monitoring for psychomotor function, muscular hypotonia, and speech delays can influence management by providing the proper interventions to promote positive clinical outcomes [16,82].

Careful and vigilant monitoring is essential during acute metabolic decompensation [3,21,22,35,67,73,94,135,144]. A wide range of biomarkers are used to manage metabolic alterations and system consequences during metabolic decompensation, including hydration, glucose, acid-base balance, electrolytes, plasma amino acids, and bicarbonate, with the overriding goal of adjusting therapy according to patient responsiveness. Blood methylcitrate may be a useful biomarker in measuring degree of metabolic control [34,76], and has been associated with rising blood ammonia concentrations [34,40,122]. Urinary methylcitrate has also been shown to correlate with plasma ammonia in acute illnesses [34,40]. During acute crises, urine ketones, blood gases, electrolytes, ammonia and lactate should be closely monitored [12,21,22,73,104,135,144]. Blood pH has been reported to be an unreliable indicator of acid-base status [51]. Biochemical parameters

found to discriminate best between balanced metabolic state and (impending) metabolic decompensation in PROP are ammonia, anion gap, and acid-base balance [144]. A combination of ammonia and anion gap alone has been associated with 63.3% accuracy in classification of "metabolic decompensation" [144].

Question 5: Nutritional intervention before, during and after pregnancy

Recommendation	Strength of Evidence	Clinical Action
Consider, in consultation with the medical team, the use of hormonal birth control in a woman who has signs and symptoms of metabolic decompensation that coincide with her menstrual cycle	Consensus	Conditional
Advise women who are considering pregnancy to meet with both the metabolic and obstetric teams to establish good metabolic control prior to conception, and to understand the frequency and type of monitoring necessary to optimize outcome	Consensus	Imperative
Provide dietary guidance throughout gestation to help the woman with PROP meet the nutrient intake goals for pregnancy and avoid catabolism	Weak	Imperative
Monitor maternal weight gain, fetal growth, and biochemical, nutrition and clinical markers throughout pregnancy	Consensus	Imperative
Have a plan in place for monitoring and preventing catabolism during labor and delivery (including IV access for provision of fluids, nutrients and medications should labor be prolonged and/or complicated), and during the post-partum period	Weak	Imperative

IV, intravenous; PROP, propionic acidemia.

Evidence summary

Menstruation, fertility, pregnancy, labor/delivery, post-partum recovery and lactation pose challenges in the management of women with PROP. Some women with IMD, including PROP, have symptoms of metabolic decompensation that correspond to their menstrual cycles [12]. The use of hormonal birth control has been effective and shown to be safe in helping to regulate menstrual cycles [12]. There are relatively few publications on the management of pregnancies in women with PROP [71,113,130]; one of which specifically describes a woman with mild PROP [130]. Infertility does not appear to be an issue in this disorder [88]. In the few documented pregnancies, the infants born to women with PROP have had normal growth and development, and elevated maternal propionate appears to have no teratogenic effect on fetal development [71,72,88,130]. Successful pregnancy outcomes for both mother and infant have been observed in women with PROP who were in good metabolic control prior to conception and when both the metabolic and obstetrical teams worked together closely [71,113]. The possibility of maternal neurocognitive delays may make understanding the treatment and compliance to therapy difficult [71,88].

Pregnancy does present some challenging issues as the maternal and fetal nutrient requirements increase over the course of gestation. There is a need to balance the increased nutrient intake to support pregnancy while limiting propiogenic amino acids. Recommended protein and energy intakes by trimester are included in Table 1 [34,71,76,130]. Intact protein may need to be increased by > 50% over the course of the pregnancy [130] necessitating more frequent monitoring of the amino acid profile, protein status, maternal weight gain, and fetal growth [71,138]. Significant increases in oral L-carnitine supplementation, to maintain plasma free carnitine concentrations in the 20–30 μM range, have been reported [71,130,138]. The recommended intake of vitamins and minerals is based on the DRI for pregnant women. Supplementation may be necessary if these nutrients are not provided in adequate amounts in the medical food and/or shown to be inadequate by laboratory testing.

The risk for catabolism-induced metabolic decompensation is increased if the woman has nausea with poor intake or *hyperemesis gravidarum* during her pregnancy [71,72,88]. Catabolism may also be a risk if there is a prolonged labor and/or complicated delivery. Several authors have reported successful administration of IV 10% glucose at 2 cc/kg/h during labor and delivery [71,88]; while one individual was given D10, 0.45% NaCl at 1.5 times maintenance along with infusion of intralipid 20% at 2 g/kg/day [113]. Energy intakes at these levels prevented metabolic decompensation. Intravenous L-carnitine use was reported in one case [113]. There is a decrease in total protein needs of women with PROP after delivery. In addition, there is an endogenous protein load from catabolism following the involution of the uterus. Several authors have suggested that this places women with PROP at risk for serious post-partum decompensation [12,71,88]. However, this has not been seen in any of the pregnancy case studies reviewed [71,113,130]. As these studies may be describing women with milder forms of PROP, providers should still be cognizant of the theoretical possibility of post-partum decompensation. Intravenous access should be maintained until sufficient post-partum enteral feeds are established. While there are no documented cases of women with PROP breastfeeding their infants, for those who want to breastfeed, nutrient demands will be theoretically similar to that prescribed for the third trimester of pregnancy (listed in Table 2); careful monitoring of both the mother and infant is important.

Question 6: Nutritional interventions for secondary complications

Recommendation	Strength of Evidence	Clinical Action
In individuals with PROP who develop acute pancreatitis, utilize jejunal and/or parenteral feeding to provide the appropriate "recommended intake during illness" and to rest the GI track	Weak	Conditional
Consider the use of antioxidants and additional L-carnitine to supplement the usual dietary management of individuals with PROP to prevent the onset, or lessen the severity, of cardiomyopathy.	Insufficient Evidence	Conditional
Consider the use of antioxidants and ammonia scavengers (during episodes of hyperammonemia) to supplement the usual dietary management of individuals with PROP to prevent/delay the onset, or lessen the severity, of optic neuropathy.	Insufficient Evidence	Conditional
Consider the contribution to total protein intake when intravenous gamma globulin is administered for the treatment of cytopenia or immunodeficiency in individuals with PROP.	Insufficient Evidence	Conditional
Routinely monitor and adjust intake in all individuals (well or ill) with PROP of all ages to help prevent or delay the development of secondary complications.	Weak	Imperative

GI, gastrointestinal; PROP, propionic acidemia.

Evidence summary

Individuals with PROP have an increased risk for certain secondary complications including pancreatitis and cardiomyopathy. Other less common but serious risks include cytopenia, optic neuropathy, and late onset renal disease. While no specific nutritional interventions have been shown to prevent these complications, overall good adherence to recommended dietary management and aggressive intervention during intercurrent illnesses may be associated with better outcomes.

A patient/family survey [96] suggested a prevalence rate of pancreatitis of approximately 20% in individuals with PROP, with additional reports suggesting recurring episodes [4,18,19,96]. Pancreatitis should be suspected in individuals presenting with vomiting, anorexia, abdominal tenderness/pain and unexplained acidosis, and can present with or without metabolic decompensation [96]. Suggested evaluations may include serum amylase and lipase measurements and abdominal X-ray [94,122]. Acute episodes have been treated with bowel rest for up to 2–5 weeks [18], jejunal feeds, and pain management [122]. Nutrient intakes during pancreatitis should be guided by the considerations listed in Table 3.

Retrospective analyses have suggested a 19–33% estimated risk of developing cardiomyopathy in individuals with PROP [83,96,103,122].

Neither age at diagnosis nor amount of residual PCC activity have been shown to impact the risk of developing cardiomyopathy [103]. Cardiac evaluation should be part of the periodic monitoring of individuals with PROP. Although presentation of cardiomyopathy has been reported to occur at any age from neonate through adulthood [10,13,25,32,35,43,56,57,70,86,97], the risk increases with age [11]. Presenting symptoms include shortness of breath, arrhythmias, decreased level of consciousness, and other signs of cardiac involvement [122]. While management of cardiomyopathy is mainly through medical and pharmacologic interventions, nutritional support provided by enteral and/or parenteral feedings is an important adjunct for the individual's health [86]. Autopsy analysis of cardiac tissue of an individual with PROP who died as a result of cardiomyopathy revealed a decrease in myocyte carnitine even with normal plasma carnitine concentrations [81]. It has been suggested that the usual L-carnitine dose should be doubled when treating cardiomyopathy [103], although long-term outcome studies have not been reported. Oxidative phosphorylation (OXPHOS) deficiency, with reduced levels of complex I and III activity, has been documented in at least one individual who succumbed to cardiomyopathy [43]. The results are consistent with the hypothesis that there is secondary mitochondrial dysfunction in PROP [12,32,97]. It has been suggested that antioxidant/CoQ10 supplementation could replete the mitochondrial stores and may prevent cardiac involvement [43,116]. The use of CoQ10 has been documented in individuals with PROP and cardiomyopathy, but no assessment of outcome has been published [10,13]. Symptoms of cardiac involvement have been reversed in several individuals with PROP who have received a liver transplant [21,22,32].

Optic neuropathy has been reported as a late complication of PROP [7,68,93] with an estimated prevalence of 7–11% [49,96]. Tight metabolic control may lessen or forestall development of optic neuropathy as illustrated by several case reports where individuals with PROP developed optic neuropathy after episodes of metabolic decompensation and/or decreased dietary compliance [7,93]. There are similarities between optic neuropathy in individuals with PROP and MMA and those with Leber hereditary optic neuropathy which suggests a secondary mitochondrial dysfunction [68]. Visual acuity was increased after supplementation with the antioxidants vitamin E and CoQ10 in a single report of an individual with MMA and optical neuropathy [12].

Cytopenia and recurrent infections are prevalent among individuals with PROP [49,95,99]. Among 24 patients with PROP in Saudi Arabia, 17% had pancytopenia during metabolic crises [100]. In a survey of 58 patients and their families, the following were reported: anemia (32%), leucopenia (31%), thrombocytopenia (17%), and immunodeficiency (15%) [96]. One case of abnormal B-cell production was treated with IV gamma globulin at 400 mg/kg. A reduced dietary intake of intact protein was prescribed for two days pre- and post-infusion, and prophylactic antibiotics were given during hospitalizations [99]. Another report described the use of IV gamma globulin at 1 g/kg/day for two days. No modifications of dietary protein intake were noted in this later case [17].

Routine monitoring and adjustment of dietary intakes in all individuals (well or ill) with PROP of all ages is necessary to help prevent or delay the development of secondary complications.

Question 7: Nutritional intervention for liver transplantation

Recommendation	Strength of Evidence	Clinical Action
Consider liver transplantation as a potential treatment modality for individuals with PROP	Weak	Conditional
Before transplant surgery, establish and maintain good metabolic control and continue appropriate and usual medical nutrition therapy	Fair	Imperative
During transplant surgery, provide continuous D10 infusion with electrolytes, with close monitoring for metabolic decompensation or other complications	Weak	Imperative
After liver transplantation provide intact protein at approximately the DRI and advance protein intake beyond the DRI as tolerated. Continue carnitine supplementation post-transplant as a precaution against metabolic decompensation. Continue clinical and biochemical monitoring of individuals post-transplant	Consensus	Imperative
Continue lifelong routine biochemical, nutritional and clinical monitoring of individuals who have undergone liver transplant, with the understanding that liver transplantation does not fully correct the metabolic abnormality of PROP (see Tables 4 and 5)	Weak	Imperative

DRI, daily reference intake; PROP, propionic acidemia.

Evidence summary

Liver transplantation is recognized as a viable treatment modality for PROP as the liver is the major site of branched-chain amino acid (BCAA) metabolism and propionic acid (PA) production. Indications for liver transplant have included neonatal onset, frequent metabolic decompensation, uncontrolled hyperammonemia, poor growth, and sibling death, along with consideration of risks and benefits of medical treatment for the patient who is a potential candidate [84,105]. Liver transplantation does not fully correct the biochemical profile, as only hepatic PCC is restored, and since PCC is a mitochondrial enzyme, it is also found in non-hepatic locations. Propionylcarnitine [8,111,141], 3-OH propionate [8,111], urine methylcitrate [8,111,141], and/or acetylcarnitine [141] were reported to remain elevated post-transplant. Correction of the hepatic PCC deficiency has been shown to progress towards clinical normalization and milder biochemical phenotype [5,8,94,102,112,135,141,142].

Improved metabolic control following transplant has been shown to slow and stabilize neurological decline, as well as improve cardiac function, growth and quality of life [103,133]. Multiple case reports have noted decreased metabolic decompensation after transplant [21,22,24,28,107,111,133,142]. Reports of complications post liver transplant in PROP patients included: hepatic artery thrombosis in 4 of 22 patients; steroid responsive acute cell rejection in 3 of 5 patients; metabolic decompensation in 1 patient 3 years after the transplant after having an asthma attack; metabolic stroke in 1 of 17 patients; and two reports of insulin dependent diabetes, though only persisting in one of these patients [64,84,111,112,133,141].

Effects of liver transplant on neurocognitive status are still unclear [133]. In reviews of 14 cases post-transplant, neurologic decline slowed and stabilized [21,22,102,107], and in 3 cases there was no change reported after transplant [62]. In several other studies, improved development and neurocognition were reported in 6 individuals [8,90,141,142], and improvement on MRI in brain mass in both gray and white matter was reported in 3 other individuals [28,90]. A separate study reported that 1 of 8 patients experienced continued complications associated with basal ganglia involvement [29].

The metabolic team input, including contributions from the metabolic dietitian, is integral in the pre-, peri- and post-transplant period for the individual with PROP. The recommended diet and supplementation for an individual with PROP who is preparing for liver transplant does not differ from the MNT recommendation for other similar individuals with PROP [107]. Recommendations for continuous IV dextrose at 5–10% concentration along with bicarbonate infusion, as needed, during the transplant procedure have been described in a limited number of reports [64,105].

Many individuals with PROP have been able to tolerate a higher intact protein intake after a successful transplant. The specific change in intact protein recommendation post-transplant has not been reported [133]. Several studies supported an “adequate” [90] or mild intact protein restriction [107,111,112,135,141], or avoidance of high protein foods [21,22]; however, some studies reported the ability of PROP individuals to tolerate a “normal level of protein intake” [102] or

unrestricted diet [5,24,62,142] after liver transplant. A case series of 3 post-transplant individuals with PROP reported that one patient experienced severe episodes of acidosis when carnitine (and protein restriction) recommendations were not followed [141]. Evidence points to the need for appropriate carnitine supplementation post-transplant to prevent metabolic decompensations and late onset complications [12,141]. Further evidence is needed to determine the best approach in managing PROP individuals who have received a liver transplant to help support optimal outcomes. Lifelong routine biochemical, nutritional and clinical monitoring of individuals who have undergone liver transplant is necessary given that liver transplantation does not fully correct the metabolic abnormality of PROP.

6. Discussion and conclusion

PROP is considered an ultra-orphan disease with incidences of 1:100,000–242,741, though higher incidence rates have been noted in the Middle East (1:2,000–40,000) [23,109]. Consequently, much of the data published in this area consist of case studies and case series, with a lack of age-matched, case controlled studies or prospective trials to more appropriately assess treatment strategies. Most clinicians in metabolic clinics will see only a few individuals with PROP, and patient registries for managing this disorder currently do not exist. There is a need for multi-center collaboration to gather enough evidence to determine the best treatment and management for these individuals. Previous published guidelines on PROP have been based on expert opinion of a defined number of clinicians having experience managing these individuals.

The PROP Nutrition Management Guideline project addresses the deficiencies identified in the peer-reviewed published literature with the addition of systematic review of gray literature and consensus data from two Delphi surveys and one nominal group session. All of these sources of information were combined to develop the guideline followed by systematic ratings for the resulting recommendations. The limited number of studies and the use of weaker research designs led to many recommendations being rated as fair to weak. Recommendations with minimal published research and emerging primarily through consensus processes were assigned consensus or insufficient evidence ratings, although still make up an important part of the guidelines to inform best practices. A significant limitation with formulating recommendations is the lack of prospective randomized controlled clinical studies to definitively evaluate various treatment approaches on outcomes, which is a common occurrence in ultra-orphan diseases. These guidelines are intended to help decision making in PROP patient care. Although based on the best available evidence, the consensus recommendations often only represent expert opinion and are meant to be followed flexibly applying the reader's experience and considering the individual patient. Guidelines cannot guarantee satisfactory diagnosis and outcome in every patient. Furthermore, although as exhaustive as possible, these guidelines cannot include all possible methods of diagnostic work-up and care and may inadvertently omit some acceptable and established procedures. Although they should help to optimize the care of individual patients and assist decision making by basing clinical practice on scientific and medical knowledge, the guidelines should not substitute for well-informed, and prudent clinical practice.

The complete guideline (accessible on the websites Southeastgeneticsnetwork.org/ngp and GMDI.org) provides a comprehensive resource of information including background information on PROP, nutrition intake recommendations by age, nutrition monitoring recommendations, and links to appropriate resources. Consumer summary and frequently asked questions handouts summarizes key recommendations for patients, caretakers and others. A companion toolkit, currently under development, provides tools to help implement the recommendations. The electronic platform used to support and document development of guidelines provides an accessible, robust, and thorough foundation for review of existing evidence. This platform will also enable clinicians and researchers to continue to efficiently update and build on these practices.

Relatively newer therapies are being used in the treatment of PROP including carbamylglutamate to manage hyperammonemia [1], altering the amino acid ratios particularly of the branched-chain amino acids [89], and various supplements, such as citrate [78], to enhance mitochondrial energy production, and other treatments may soon be used, such as hepatocyte transplant [6]. There is limited data at this time on how new therapies will impact outcomes in individuals with PROP or change nutrition management, and consequently will be addressed in future updates of the guidelines. The guidelines reported will be updated as warranted by developments in research and clinical practice for individuals affected by this metabolic disorder.

The electronic platform which includes not only the recommendations but also background information and tools to facilitate implementation of the guidelines will greatly support clinicians with accessing and implementing them and contribute to the goals of reducing uncertainty and variation of practice and improved outcomes. The dynamic and systematic process for development of these IMD nutrition guidelines, and inclusion of many metabolic experts promotes greater harmonization of care and research collaboration between centers following individuals living with PROP.

Conflict of interest

Dianne Frazier, Lisa Obernolte, Yetsa Osara, Anne-Marie Roberts, Patricia Splett, Adriana Stembridge, and Keiko Ueda have no conflicts of interest.

Elaina Jurecki, Christie Hussa, and Bridget Reineking are employees and stockholders of BioMarin Pharmaceutical Inc.

Steven Yannicelli is an employee of Nutricia North America.

Rani Singh served on global medical advisory boards for BioMarin Pharmaceutical Inc., Nutricia and SOBI, and medical advisory boards for Horizon.

Amie Thompson is on the speaker's bureau for BioMarin Pharmaceutical Inc.

Fran Rohr has services as a consultant for BioMarin Pharmaceutical Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2019.02.007.

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