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Diagnosis and Metabolic Management of Adult Refsum Disease: Guidance From the Medical and Scientific Committee of Global DARE (Defeat Adult Refsum Everywhere)

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ABSTRACT

Adult Refsum disease (ARD; OMIM 266510) is a degenerative autosomal recessive condition typically diagnosed in adulthood. It affects visual, auditory and nervous system function. It is characterised by plasma, neuro-ophthalmological and adipose tissue accumulation of the dietary-derived phytanic acid (PA). This guidance reviews the clinical aspects of ARD and discusses interventions to address various co-morbidities of the disease. This GRADE-aligned guidance is based on a review of the literature and a consensus statement reflecting the conclusions of professionals with experience in the diagnosis and management of ARD. This statement reviews clinical aspects of ARD and discusses current and potential interventions to address various symptoms of the disease. It provides an overview of the clinical phenotype, reviews the clinical, biochemical, and genetic findings in ARD, and the neurological and ophthalmological investigations needed at diagnosis and during follow-up. It highlights the importance of dietary management and its role in situations such as acute hospital admissions for inter-current illness. Furthermore, it provides guidance on the acute management of decompensation in ARD and outlines when therapeutic plasma exchange/lipoprotein plasmapheresis should be considered. Greater clinician and patient awareness will lead to early diagnosis and improved outcomes. Implementation of a low PA diet before further end organ involvement offers the best prognosis. Life-long dietary therapy, along with therapeutic plasma exchange/lipoprotein apheresis during acute decompensations, remains the mainstay of management. Patients should have access to a multidisciplinary team to ensure specialist dietary input and supportive management of comorbidities.

1 | Background

Adult Refsum disease (ARD—OMIM #266510) is a degenerative, autosomal recessive ultra-rare disease typically diagnosed in adulthood. It primarily affects visual, auditory and nervous system function [1–3] and has an estimated prevalence of one in 1 million [2, 3]. Affected individuals are unable to catabolise the branched-chain fatty acid (BCFA), phytanic acid (3,7,11,15-tetramethyl hexadecanoic acid). This leads to accumulation of phytanic acid (PA) in critical tissues, including retina, myelin sheath, adipose and organs such as kidneys, liver and skin. There is overwhelming evidence that the toxic accumulation of PA underlies the clinical manifestations of disease. Nevertheless, the mechanistic basis for PA toxicity has not yet been fully elucidated.

ARD is caused by loss-of-function (LOF) variants in the *PHYH* or *PEX7* genes required for PA catabolism via alpha-oxidation in peroxisomes [3]. ARD is distinctly different from infantile Refsum disease (IRD), a term formerly used to refer to milder cases of Zellweger spectrum disorder (ZSD), a peroxisome biogenesis disorder [4]. At least 90% of ARD cases are due to bi-allelic mutations in the gene encoding for the peroxisomal enzyme phytanoyl-CoA hydroxylase (PHYH), which, if deficient, impairs PA alpha-oxidation [3]. Most of the remaining patients with ARD have biallelic LOF variants in the *PEX7* gene [5] that partially impair PEX7 protein function [5]. This can result in phytanic acid accumulation since PEX7 transports PHYH into the peroxisome matrix, a prerequisite for phytanic acid alpha-oxidation to proceed [6]. *PEX7* pathogenic variants that cause ARD have minimal effect on plasmalogen biosynthesis. More commonly, biallelic LOF variants in the *PEX7* gene cause defects in both alpha-oxidation and plasmalogen biosynthesis and result in rhizomelic chondrodysplasia punctata type 1 (RCDP1), a disease characterised by skeletal abnormalities, intellectual disabilities, seizures and a shortened lifespan [6]. Rarely, ARD clinical phenocopies may be caused by biallelic mutations in alpha-methyl-acyl-CoA racemase (*AMACR*; OMIM 604489) [7], a peroxisomal enzyme that catalyses the conversion of R-stereoisomers of PA, pristanic acid (PrA), and C27 bile acids to their S forms to enable their further metabolism. Phenocopies are also observed with biallelic variants in the non-peroxisomal genes such as lysophosphatidylserine (lysoPS) lipase abhydrolase domain-containing 12 (*ABHD12*), which causes polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract syndrome (PHARC; OMIM 612674) without affecting PA levels [8].

A detailed description of PA metabolism is beyond the scope of this paper. A comprehensive review of the relevant pathways is described by Wanders et al. [2, 9].

2 | Objective

Experience of managing people with ARD is limited, even among clinicians with significant expertise in inherited metabolic diseases. Therefore, there is an urgent need to consolidate experience to guide management, as early diagnosis and reduction of circulating PA may improve prognosis. These guidelines are for management of ARD secondary to pathogenic variants in *PHYH* and *PEX7*.

3 | Methodology

This guideline has been developed using 'Developing NICE guidelines: the manual' as a reference and has been aligned with the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) [10, 11].

There are currently no published large-scale high-quality trials for the diagnosis and management of people with ARD. Therefore, the guidelines were developed following careful evaluation of individual case reports, small case series, review articles, and clinical experience of panel members.

R.R. (secretary; chemical pathologist/metabolic physician), A.W. (chair, chemical pathologist/metabolic physician) formed a core panellist group to coordinate organisational and content aspects of the guidelines. The panel further included neurologists (F.E., A.F.), dietitians (S.F., E.B.), a metabolic physician in training (R.B.) a clinical biochemist (R.J.W.), ophthalmologists (O.M., B.P.L, R.M.H.), clinical biochemical geneticist (S.F., J.G.H.) and expert in lipoprotein apheresis (R.K.) and two patients (K.D., S.K.), both founding members of the patient advocacy organisation for ARD—The Global DARE (Defeat Adult Refsum Everywhere) Foundation. Collaborations during guideline development occurred via video link and e-mails.

Panellists and patient representatives agreed on the scope of the guidelines (supplement 1). The literature was assigned to important outcomes and evaluated by the panel (email or online/phone meetings).

Critical outcome measures as agreed by panel members were:

1. Early diagnosis
2. Survival
3. Morbidity
4. Quality of life

Based on this, an evidence profile was developed, and recommendations—along with their strength—were formulated by a core author group (R.R., R.B., A.W., E.B., S.F.) before being circulated to the wider authorship, including two patient advocates, for review and consensus. Two additional online meetings were held to discuss differences of opinion before finalising the recommendations. Two further online meetings were held to resolve differences of opinion before the recommendations were finalised.

The quality of evidence was rated (high/moderate/low/very low) based on consensus. The strength of each recommendation (very strong/strong/weak) was also rated by the panellists based on the quality of the evidence, as well as the balance of benefits and harms, values, preferences and resources. Evidence quality

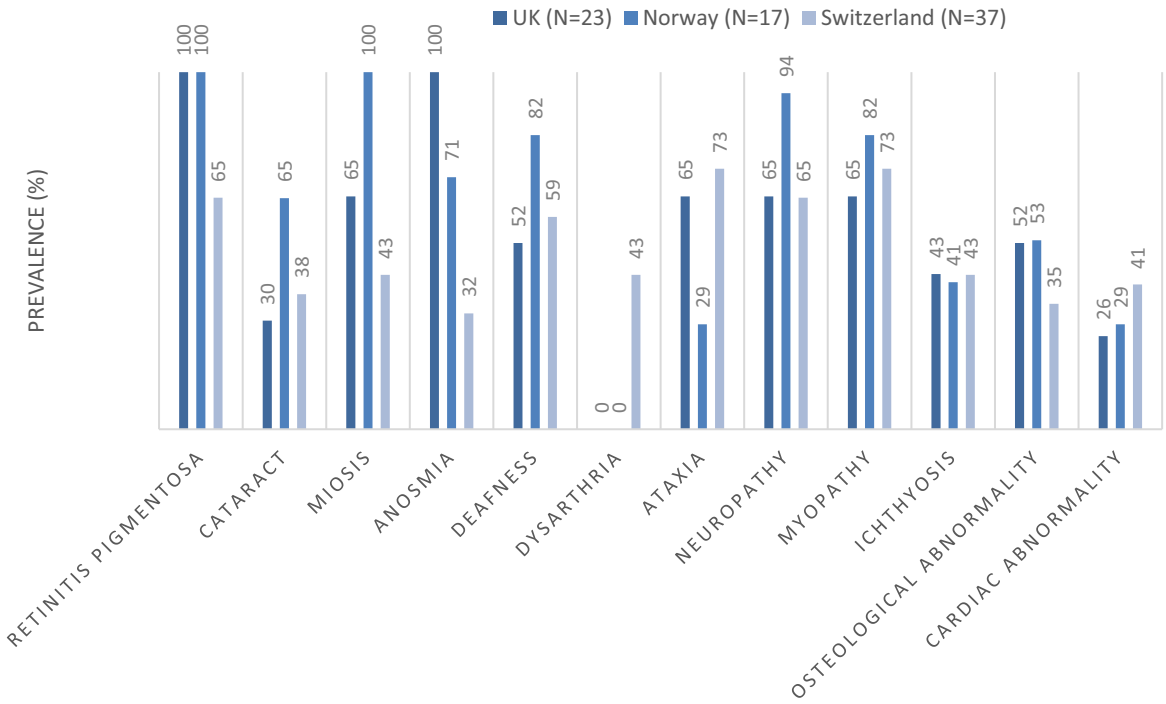

FIGURE 1 | Frequency of clinical signs in the 3 original UK, Norway, and Switzerland case series of ARD. Numbers at the top of the bar indicate percentage of patients with the symptom/sign. Of note, data may be incompletely recorded in some cases. *N* numbers for each case series are shown in the graph legend.

and other factors were evaluated according to the GRADE criteria detailed in Supporting Information.

4 | Literature Search and Evidence Grading

To gather the initial evidence base, a PubMed search was performed on 01 November 2024 to include all English language articles to date with the following search phrase: ((((phytanic) OR (refsum)) NOT ((peroxisomal) biogenesis (disorder))) AND (human)) NOT (fungi/plants/other animals). This search yielded 1172 entries. The evidence available is mostly in the form of individual case reports (337) or case series. Articles were manually sorted for evidence on clinical features (49)/diagnosis (100)/management and prognosis (61) (R.R., A.W.). Review articles ($n = 261$) filtered in the search were scanned for any extra information over and above that available in case reports/case series (R.R., A.W.). Review articles on biochemistry, clinical features or management of ARD were examined for additional insights, including personal communications on new cases, or observations relevant to these guidelines. Articles were allocated to the categories high/moderate/low quality of evidence to a certain outcome by at least two panellists.

5 | Clinical Features of ARD

Most people with ARD present with slowly progressive peripheral visual loss in adulthood and/or long standing impaired night vision [12]. In the largest 3 historic case series on the ophthalmic and other effects of ARD, almost all cases had retinitis pigmentosa (RP) diagnosed between age 2 and 55 years [12–14](Figure 1). Screening for PA conducted in one series of 52 patients with retinitis pigmentosa and two other clinical manifestations possibly related to ARD found one new case of ARD [15].

The age-related prevalence of symptoms is difficult to determine from these published series; however, data is available from a case series of 40 patients (unpublished and updated from Wierzbicki et al. 2002) from the UK Centre of Excellence for ARD [1] (Figure 2).

A recent retrospective analysis of a self-reported survey of 27 ARD patients published by Coordination of Rare Diseases at Sanford (CoRDS) Registry- Global DARE Foundation confirmed retinitis pigmentosa (RP) to be the most common presenting feature, with 96% ($N = 26/27$) patients reporting they had RP [16].

Loss of pupillary dilation and cataracts are also common ophthalmological findings [12]. Cataract surgery can improve visual acuity and subjective visual function in patients with RP, including those with ARD, but requires surgeon awareness of higher rates of zonular weakness, posterior capsular opacification and cystoid macular edema [17].

While vision loss is a hallmark characteristic of ARD, other sensory systems are also often affected. Anosmia/microsmia is a common feature of presentation, reported in 100% of participants in some studies. It is, however, often variably reported by patients and difficult to assess clinically without the use of specialised smell tests [18].

Sensorineural hearing loss was observed in 62% patients (62%) [16] but typically has a later onset than RP, often occurring

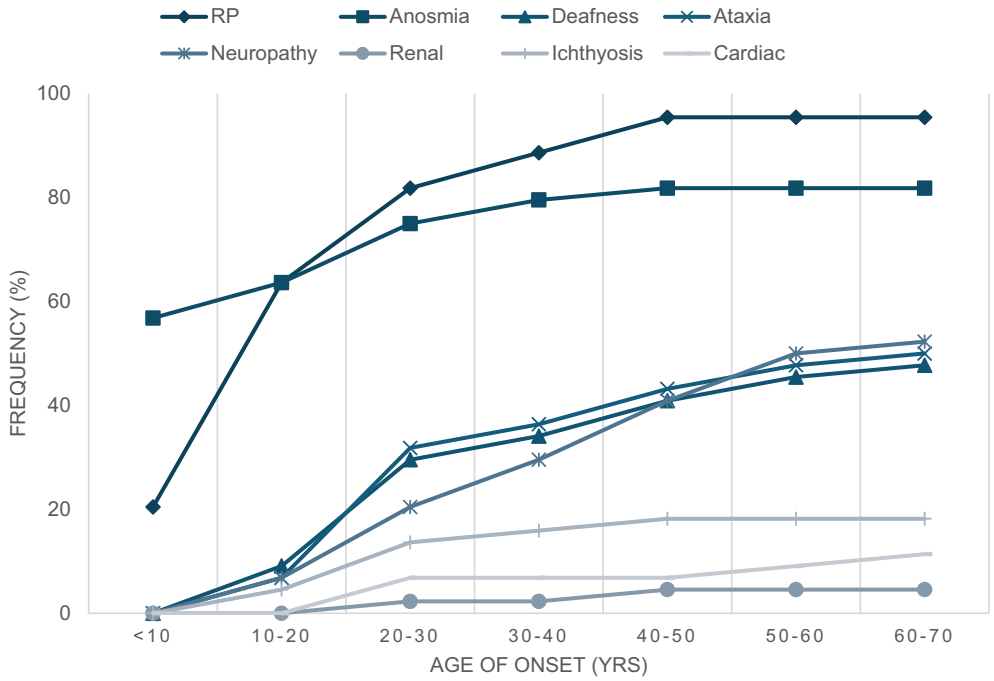

FIGURE 2 | Occurrence of symptoms (%) in a 40 patient single clinic series of ARD based on clinical database maintained at the UK Centre of excellence for ARD.

around age 50 years. Most patients require the prescription of hearing aids [19] or cochlear implant devices [20].

A slowly developing peripheral distal symmetrical axonal neuropathy with accompanying myopathic features was reported in 71% of all patients [16, 21–24]. Its severity varies and in some cases, symptoms resolve with lowering of circulating PA levels [25]. Nerve conduction studies show abnormalities of sensory conduction with normal or only mild slowing of motor conduction velocity. Sural nerve biopsy studies have shown a reduction in the density of myelinated fibres and no onion bulb formations. The peripheral neuropathy can be accompanied in severe cases by ataxia which may resolve with timely lowering of circulating PA levels; although it may progress to chronic disability if left untreated [25, 26]. Leukodystrophy has been reported in one patient with ARD [27].

Outside of characteristic involvement of the sensory organs and nervous system, other less common manifestations can occur in a subset of patients. Dermatological signs, including itchy scaly skin or an overt ichthyosis, occurred in 43% of affected individuals [16, 28]. These tend to correlate with circulating PA levels and resolve with reductions in levels.

Bony abnormalities, often described as pathognomic (as in the original case report), are not always present. In a case series of 17 patients, bony abnormalities were noted on radiographic investigations in 35% of patients [29]. The recent patient self-reported survey found it may be more common with approximately 74% reporting shortened toes/fingers and 52% reporting other bony abnormalities [16]. A short conical terminal phalanx of the thumb was seen in all patients with skeletal abnormalities and may represent a frequent manifestation of ARD. Some patients had shortening of the shafts of metacarpals and/or metatarsals, or of the mid-portion of phalangeal shafts. Other noted skeletal changes include chondrodysplastic changes such as epiphyseal flattening and irregular articular margins affecting knee and elbow [29]. The pathogenesis of the bony changes is unclear and independent of ARD genotype as the skeletal manifestations vary between members of the same family [30].

Likewise, renal involvement is a less common feature of ARD. Creatinine clearance (estimated glomerular filtration rate, eGFR) may be decreased in patients with ARD, especially in the presence of a high circulating PA. Tubulopathy, as evidenced by low blood potassium levels (hypokalemia), excess potassium in the urine (kaliuria), mild amino aciduria, and proteinuria, can be a feature of acute ARD [31, 32]. Hypokalaemia and kaliuria may persist despite resolution of the acute ARD episode in some patients.

5.1 | Acute Metabolic Decompensation of ARD

No standard definition of an acute metabolic decompensation of ARD exists, in terms of the severity or length of time over which symptoms develop. The development of symptoms generally follows the rate of rise of PA, suggesting that symptoms are related to circulating PA levels.

In the study by Baldwin et al. 2010, the definition of a clinical and biochemical exacerbation was a > 50% rise in circulating PA levels from the previous visit and exceeding a baseline of > 10 times the ULN for circulating PA levels [33].

People with ARD may also present to the emergency room with acute symptoms. A few case reports and series have been published of patients with acute presentations of ARD. Most frequently, patients present with acute neurological symptoms including worsening ataxia affecting all four limbs, as well as the trunk, and a rapidly developing sensorimotor neuropathy [21]. ARD is often listed as one of the possible differentials of Guillain-Barré syndrome [34]. Both proximal and distal muscles are involved, with demyelinating features on electrodiagnostic testing. Exacerbations can also be accompanied by increased neuropathic pain or loss of sensation. There may be an acute deterioration of hearing, visual changes, or widespread ichthyosis. Kidney function may also be affected; one patient had abnormal tubular function with hypokalemia, elevated urinary beta-2 microglobulin and retinol binding protein [32]. Patients may also present with cardiac involvement including cardiac arrhythmias, left ventricular hypertrophy/dilatation, and symptoms of heart failure [35]. One ARD patient has successfully received a heart transplant following heart failure with over 10 years' survival at the time of this publication (Leroy, unpublished observation). Sudden death has been reported, especially during acute deteriorations. This may be due to cardiac arrhythmias. Patients may also have a high serum creatine kinase during acute decompensation [35–37].

Acute presentations typically occur secondary to a rapid rise in circulating PA levels due to catabolic states including intercurrent illness, fasting and rapid weight loss. Acute presentations are more commonly associated with circulating PA levels > 500 μmol/L, and often > 1000 μmol/L [33].

6 | Diagnosis

Patients with ARD often experience significant diagnostic delay mostly attributed to a lack of ARD awareness amongst clinicians. In one report from 1992, an average delay of 11 years (range 1–28 years) between first presentation to an ophthalmologist and a diagnosis of ARD [12] was observed. In this series, most patients were diagnosed by neurologists after the patient presented with chronic or acute neuropathic symptoms several years after RP diagnosis. Similar information can be extrapolated from patient cohort and ARD registry data (September 2022) which report that 50% of patients had a diagnosis of RP by the age of 20 years, whereas only 9% had a diagnosis of ARD by 20 years [16]. Biochemical diagnosis of ARD is made by measuring circulating PA levels. A high circulating PA level (historically > 10 times the upper limit of normal), with a concomitant low circulating PrA level, is considered diagnostic of ARD [38].

Widespread use of genetic testing, including broad retinal dystrophy gene panels and whole genome sequencing, as first-line diagnostic tools whilst investigating patients for RP disorders, has significantly reduced lag times between presentation with visual symptoms and diagnosis of ARD. Furthermore, it is becoming increasingly clear that genetically confirmed patients with ARD related RP may, in fact, have circulating PA levels within or just above the reference range. We have previously presented 2 cases where patients with more than a 10-year history of RP had circulating PA levels just above the reference range (< 20 μmol/L; Reference range < 15 μmol/L); with levels returning to within reference range very quickly with a low PA diet [39]. The first patient, diagnosed aged 30 years, was compound heterozygous for two pathogenic variants. Biochemical enzymatic studies on patient-derived fibroblasts confirmed reduced phytanic acid alpha-oxidation activity with preserved peroxisomal beta oxidation. The second patient, diagnosed aged 48 years, had one pathogenic variant and another variant of unknown significance with conflicting reports of pathogenicity. The second patient had typical clinical features and atypical biochemical features (mildly raised circulating PA levels and undetectable to borderline normal circulating PrA levels on repeated testing). Similar variability of PA levels as well as the presence and extent of extraocular ARD findings were described in a small cohort of RP patients who shared a potentially hypomorphic variant in *PHYH* [40]. These diagnostic dilemmas are not unusual in recessive disorders [41].

The authors' recommendations for Diagnosis, Family screening and Newborn Screening are detailed below:

Recommendation #1:

Patients presenting with RP, or in any patients where ARD is considered as a differential diagnosis, should be tested for pathogenic changes in PHYH and PEX7 genes [38].

Depending on the clinical history and retinal phenotype, the gene panel used should also include genes for other causes of elevated circulating PA levels and phenocopies of ARD (see Table 1).

Outcome: Early Diagnosis, Survival and Morbidity.

TABLE 1 | ARD and clinically similar disorders which may form part of differential diagnosis.

Adult Refsum disease	Other disorders with distinct phenotypes where PA may be elevated	Clinical phenocopies of ARD
PHYH *PEX7* (*those pathogenic variants that result in elevations of PA, but with no impact on plasmalogen levels*)	Zellweger spectrum disorders (*pathogenic variants in PEX genes*) AMACR deficiency: *AMACR*–biochemistry distinct from ARD (↑ PA, Pristanic acid and di and trihydroxycholestanoic acid), Rhizomelic chondrodysplasia punctata type 1: *PEX7* mutations where plasmalogen function is also affected.	PHARC syndrome *ABHD12*–PA levels in reference range

Quality of Evidence: Moderate.

Strength of recommendation: Very strong (supported by medical knowledge).

Recommendation #2:

Patients presenting with retinitis pigmentosa with ocular and/or extraocular features suggestive of ARD should be offered biochemical testing for ARD by measuring plasma phytanic and pristanic acid levels, particularly if genetic testing is declined or unavailable to the patient, or if available genetic panels do not include PHYH or PEX7.

Outcome: Early Diagnosis, Survival and Morbidity.

Quality of Evidence: Moderate.

Strength of recommendation: Very strong (supported by medical knowledge).

In recognition of reported cases of ARD with PA within reference range, and increased availability of gene panel testing, the final consensus was to recommend genetic testing as first-line followed by biochemical testing.

Recommendation #3:

In people with symptoms of ARD and a variant of uncertain significance (VUS) in PHYH but without clear plasma biochemical changes suggestive of ARD, functional assays using biochemical analyses (i.e., *alpha-oxidation activity and peroxisomal beta oxidation measurements*) *in patient-derived primary fibroblasts may help towards confirming or excluding diagnosis of ARD.*

Outcome: Early Diagnosis, Survival and Morbidity.

Quality of Evidence: Low (evidence limited to a few case reports).

Strength of recommendation: Strong (supported by medical knowledge and consequence of missed diagnosis).

6.1 | Family Screening

Recommendation #4:

As ARD is potentially manageable via *dietary interventions, all at-risk relatives must be counselled and offered screening. This would normally include all siblings of affected patients born through a non-consanguineous partnership. In instances of consanguinity, wider screening of additional biological relatives may be required.*

Outcome: Early Diagnosis, Survival and Morbidity.

Quality of Evidence: Moderate.

Strength of recommendation: Very strong (supported by medical knowledge and consequence of missed diagnosis).

6.2 | Newborn Screening

Currently, there are no reported large-scale studies measuring PA levels in blood spots obtained from newborns. Given the exogenous dietary source of PA, it is unlikely that significant elevations will be found at birth and in babies who are exclusively breastfed using milk obtained from a person who does not have ARD. PA levels are likely to rise only after formulas containing PA or solids are introduced.

There is one report of 8 pregnancies (6 live births) in a patient with ARD where circulating PA levels were measured in all living babies soon after birth [42]. The biological father was the patient's first cousin who was a carrier of a *PHYH* deleterious variant. Of the 6 living babies, 2 had ARD. Circulating PA levels at birth in non-affected babies were within reference range. Whilst the levels in the affected babies were mildly elevated ($< 30\,\mu mol/L$) immediately after birth, they quickly normalised on a low PA feed due to the absence of exogenous PA sources. This suggests the initial circulating PA level may well have been mildly elevated due to some degree of placental transfer from the affected mother. As might be expected due to the rarity of ARD, there are no reported cases of elevated circulating PA levels in an affected baby where the mother is not affected.

Newborn screening for ARD may become more feasible with the advent of genetic screening techniques as it would be classified as a potentially treatable orphan disease [43].

Recommendation #5:

Routine newborn screening using biochemical markers such as plasma PA levels is not recommended.

Outcome: Early Diagnosis, Survival and Morbidity.

Quality of Evidence: High (despite paucity of published literature).

Strength of recommendation: Very strong (supported by medical knowledge—low sensitivity of plasma phytanic acid measurement in newborns who will not have had exposure to high phytanic acid foods, and hence diagnostic accuracy poor).

Recommendation #6:

Newborn screening may be recommended in specific groups:

1. *Newborns who may be at risk* (*siblings of patients with ARD, family history suggestive of increased risk for ARD*) *should be offered genetic screening as genetic testing for family mutation is the only reliable way to exclude ARD in this age group.*
2. *Presence of a bony abnormality that may be compatible with a diagnosis of ARD*, for example, *brachymetartarsia/metacarpia* (*for details see section 5- clinical features of ARD*) *should also prompt genetic testing for ARD in a baby or child.*

Outcome: Early Diagnosis, Survival and Morbidity.

Quality of Evidence: Low (limited to one case report).

Strength of recommendation: Very strong (supported by medical knowledge and consequence of missed diagnosis).

7 | Management

7.1 | Long Term Metabolic Management

The main aim of treatment is to maintain low levels of circulating PA. Diet remains the mainstay of management of patients with ARD. Dietary recommendations are based on current knowledge that in humans, PA is only obtained from ingesting PA or its precursor phytol, primarily in the form of phytyl fatty acid esters (PFAE) and not by any endogenous biosynthetic pathway.

While a detailed review of the low PA diet is beyond the scope of this article, we provide an overview relevant to treatment guidelines [33, 44–50].

The principles of the diet are to avoid foodstuffs rich in PA and PFAE including dairy products, meat derived from ruminant herbivores, and some types of seafood. A dairy-free vegetarian diet that includes egg, chicken, and turkey may be considered an appropriate option where access to dietetic support is limited and more detailed, personalised dietary guidance is not available. Roca-Saavedra et al.'s systematic review of the occurrence of PA in foodstuffs, its metabolism and its clinical consequences provides more information [51]. Recently more foods have been analysed for PA content using improved techniques through a project supported by the Global DARE Foundation. Dietary guidelines for ARD are evolving, and useful up to date dietary information can be found on the Global DARE Foundation website. (https://www.defeatadultrefsumeverywhere.org/diet-guide).

The effectiveness of the low PA diet has been shown in a number of studies, including a retrospective analysis of data from 25 patients with ARD attending one centre for 10 years or more [33]. Median baseline circulating PA levels at presentation to the clinic were 1631 (370–2911) μmol/L and declined by a mean of 89% ± 11% (median 85 range 10–1325 μmol/L). Circulating levels of PA were completely normalised (< 30 μmol/L) in 30%; partially normalised (30–300 μmol/L) in 50% and remained > 300 μmol/L in 15% of patients. The time required for circulating PA levels to halve was 44 ± 16 months in patients compliant with diet. No patient required admission or extracorporeal treatment with plasma exchange or lipoprotein apheresis despite occasional spikes in circulating PA levels attributable to intercurrent illness, surgery, sudden weight loss, or psychological illness. The severity of exacerbations of circulating PA levels decreased in frequency and severity over time.

Although the evidence is limited, rates and lengths of hospitalisation decrease with treatment; neuropathy, cardiac symptoms, and skin changes improve with both acute and chronic treatment; progression of eye disease and hearing loss may reduce with treatment. To date, there is no evidence of bone changes or meaningful improvement in the perception of smell with treatment; however, the latter may not have been adequately studied.

Recommendation #7:

Restrict dietary intakes of PA to < 10 mg/day. Avoid PA-containing oral nutritional supplements during periods of oral/enteral/parenteral nutritional support.

Outcome: Morbidity and survival.

Quality of Evidence: Moderate (case series, case reports).

Strength of recommendation: Very strong (supported by medical knowledge).

The recommended low PA diet is deemed adequate in micronutrients, although a study of patients on the diet found that sodium intakes were higher due to increased consumption of cured pork products, and fat-soluble vitamin levels (vitamins A, D, E, K) were possibly insufficient [52]. Mild cobalamin (vitamin B_{12}) insufficiency based on elevated methylmalonic acid levels was also suspected. The recommendations were to monitor patients' intake periodically and screen for levels of fat-soluble vitamins, B12, copper and selenium.

Recommendation #8:

Monitor micronutrient and vitamin levels (K, D, E, A and B_{12}) in patients on the low PA diet.

Outcome: Morbidity.

Quality of Evidence: Low (limited evidence in literature).

Strength of recommendation: Strong (supported by medical knowledge and clinical experience of the panel).

7.2 | Weight Loss, Fasting and Surgical Procedures

The majority of PA is stored in adipose tissue, but an acutely mobilizable pool is suspected to exist in adipose tissue or the liver. Acute decompensations correlate with circulating PA levels rather than with PA stored in adipose tissue [53]. Weight loss and fasting lead to lipolysis-related mobilisation of stored PA, thus increasing circulating PA levels. Most case reports of acute neurological deterioration cite weight loss as a trigger. Patients wanting to lose weight should do so only under strict monitoring by dietitians. Higher baseline circulating PA levels are associated with greater rises in PA levels, and therefore, greater risk of adverse events. Whilst evidence is limited, we would recommend avoiding intentional weight loss at PA levels > 200 μmol/L.

Patients are also advised to avoid prolonged fasting. Circulating PA doubling time with fasting has been noted to be 29 h, but in principle could vary according to the individual and conditions studied [53]. If patients receive adequate calories during the day

at regular intervals, overnight fast is acceptable, and overnight feeding/night-time snack is not needed.

Recommendation # 9:

Minimise risk of weight loss and consequent acute metabolic decompensation.

Outcome: Morbidity and Survival.

Quality of Evidence: Moderate (case reports).

Strength of recommendation: Very strong (supported by medical knowledge and clinical experience of the group).

Recommendation #10:

Avoid periods of prolonged fasting.

Outcome: Morbidity and Survival.

Quality of Evidence: Moderate (case series and case reports).

Strength of recommendation: Very strong (supported by medical knowledge and consequence of missed diagnosis).

Recommendation #11:

Specific recommendations for medical procedures or surgery that require fasting.

a. *We would strongly recommend clinicians performing the procedure/surgery contact the patients' metabolic teams well in advance to ensure a personalised metabolic protocol is in place prior to procedure.*
b. *The extent of metabolic intervention required is likely to depend on the nature of the procedure and restrictions with regards to pre-procedure fasting and post-procedure re-initiation of oral intake. To prevent post-surgical metabolic complications, for adult patients we recommend IV glucose 200 mg/kg/h (given as 10% glucose at 2 mL/kg/h or if fluid restriction needed—as 20% glucose at 1 mL/kg/h or 50% glucose at 0.4 mL/kg/h) to be commenced at the start of the fast and continued until the patient can eat and drink normally. For patients in the paediatric age group*, the *rate of dextrose infusion should be aligned with paediatric IV regimens for long chain fatty acid disorders.*
c. *Blood glucose should be monitored closely; if blood glucose levels remain above 10 mmol/L (180 mg/dL), consider insulin sliding scales or other regimens as per local protocols* [54] *rather than reducing the rate of glucose infusion. This ensures adequate calorie provision whilst maintaining blood glucose levels. Furthermore, insulin prevents lipolysis, further mitigating a rise in circulating PA levels.*
d. *If a patient remains nil by mouth (or is unable to maintain calorie requirements by mouth) for more than 48 h, there should be a low threshold for starting a more complete low PA enteral/parenteral nutritional regimen that meets at least safe minimum amounts of protein, full calorie requirements, and all essential vitamins and minerals.*

Outcome: Morbidity and Survival.

Quality of Evidence: Low (low for ARD; however, well established management strategy in other long chain fatty acid oxidation disorders associated with fasting associated decompensation).

Strength of recommendation: Very strong (supported by medical knowledge and consequence of acute decompensation secondary to catabolic state).

Recommendation #12:

Outpatient Emergency management when unwell due to an intercurrent illness:

a. *If unwell and unable to eat and drink normally due to loss of appetite/vomiting or diarrhoea during an inter-current illness, patients are advised to start an oral glucose polymer regimen (for details please see dietary guidance on the Global Dare Foundation website* https://www.defeatadultrefsumeverywhere.org/refsum-emergency-regimen). *Specific evidence in ARD for this advice is not available and has been extrapolated from well-established management protocols for other fatty acid oxidation disorders* (https://bimdg.org.uk/guidelines/guidelines-adult.asp).
b. *Patients with diabetes will need very regular blood glucose monitoring and their emergency regimen may need to be tailored to minimise risk of dangerous hyperglycemia.*
c. *If unable to tolerate glucose polymer orally or symptoms not improving/getting worse after 24–48 h, patients should be advised to report to the local emergency services. Moreover, they should be advised to contact their metabolic team for consideration of acute admission and in-patient management with IV glucose (as detailed in Recommendation #11 points b-d), cardiac monitoring and/or plasmapheresis and treatment of any intercurrent illness.*

Outcome: Morbidity (acute metabolic decompensation) and Survival.

Quality of Evidence: Low (low since published evidence in ARD is limited; however, a well-established management strategy in other long chain fatty acid oxidation disorders is associated with fasting-associated decompensation).

Strength of recommendation: Very strong (supported by medical knowledge and consequence of missed diagnosis).

7.3 | Exercise Advice

The principles of management are to prevent excessive lipolysis which elevates circulating PA levels. This advice is extrapolated from advice given to patients with other fatty acid oxidation disorders as specific evidence for the impact of exercise on PA in

patients with ARD is lacking [55]. Patients should discuss exercise regimen and weight loss goals with their metabolic teams to ensure tailored advice based on baseline PA levels and fitness.

Recommendation #13:

We recommend patients have a carbohydrate-containing meal or snack before exercising at moderate or heavy intensity, and to take a carbohydrate snack during exercise if the exercise lasts longer than 45 min.

Outcome: Morbidity (acute metabolic decompensation).

Quality of Evidence: Low (No published evidence for ARD; however, well-established management strategy in other long-chain fatty acid oxidation disorders associated with fasting-associated decompensation).

Strength of recommendation: Strong (supported by medical knowledge and consequence of missed diagnosis).

Recommendation #14:

Avoid excessive intake of caffeine and adrenergic stimulants due to association with hepatic lipolysis and therefore risk of rise in circulating PA levels [56].

Outcome: Morbidity (acute metabolic decompensation).

Quality of Evidence: Low (No published evidence for ARD specifically).

Strength of recommendation: weak.

Recommendation #15:

The use of regular LA/TPE in patients who are not in acute metabolic decompensation and when circulating phytanic acid levels are < 1000 μmol/L is not routinely recommended.

Outcome: Morbidity (acute metabolic decompensation) and Survival.

Quality of Evidence: Low (limited to case reports).

Strength of recommendation: Strong (supported by medical knowledge).

7.4 | Specific Drug Therapies for ARD

There are no currently accepted targeted drug therapies for ARD. Case reports exist of a 55% reduction of circulating PA levels and improvement in neuropathy and dermatological signs in 2 patients with the drug orlistat which inhibits gastric and pancreatic lipase and reduces intestinal triglyceride uptake [57]. This may reflect improved adherence to the low-fat diet with orlistat. A low-fat diet is naturally low in PA. No improvement was seen in circulating PA levels in 6 patients who were already highly compliant with a low PA diet in another centre (Wierzbicki; unpublished data). Therefore, it is unclear whether orlistat carries benefits beyond what has been seen via reduction in dietary fat.

Several potential therapeutic strategies have been proposed to lower PA levels in people with ARD. The provision of alternative substrates for a PhyH 2-oxo-glutarate binding site with a LOF missense variant present in some patients showed some promising effects in cell culture models but has not proved practical for development into animal or human studies [58]. Another strategy is to increase the activity of the alternative PA omega-oxidation pathway in the liver as this is highly induced in acute disease but shows rapid reduction in activity as PA levels fall [53]. In fact, the omega-oxidation pathway has been estimated to be able to catabolise up to 30 mg/day of PA [59]. Urinary 3-methyl-adipic acid levels, which can be measured as part of extended urine organic acid profiles, are a potential biomarker of PA omega-oxidation activity. The biochemistry of the omega-oxidation pathway has mostly been clarified in mice and human cell lines [60]. The first (rate-regulating) step is mediated by specific cytochrome (CYP) family members. These pathways are also involved in omega-oxidation of other very long chain fatty acids (VLCFAs) and docosahexaenoic acid (DHA) [9]. While the pharmacological enhancement of liver omega-oxidation activity provides an attractive therapeutic hypothesis to pursue to lower circulating PA levels, additional preclinical studies are required before testing in patients.

The augmentation of *PHYH* or *PEX7* activity through genetic approaches provides a promising research direction. Therapies that enhance liver peroxisomal alpha-oxidation through mRNA replacement, AAV-mediated gene augmentation, or gene editing to correct *PHYH* or *PEX7* deleterious variants can be considered in the future. These are based on the therapeutic hypothesis that the partial restoration of hepatic PA metabolism in principle could lower circulating PA levels and eventually in some tissues stores if stored PA were released into circulation by lipolysis and metabolised in the liver. Given the limited knowledge of peroxisomal alpha-oxidation in these compartments, it remains to be determined if similar approaches to restore peroxisomal alpha-oxidation in the visual or auditory systems of affected individuals could be beneficial.

Recommendation #16:

No therapies (including orlistat) exist with proven benefit/phytanic lowering properties in patients with ARD. Their use is not routinely recommended.

Outcome: Morbidity (acute metabolic decompensation) and Survival.

Quality of Evidence: Low.

Strength of recommendation: Very Strong (supported by medical knowledge and consequence of missed diagnosis).

7.5 | Drug to Be Used With Caution

No specific drug interactions with PHYH have been described. Caution is advised with drugs metabolised through racemisation

by AMACR, including naproxen [61] though no cases of exacerbation of ARD secondary to naproxen therapy have been reported. Similarly, drugs likely to promote lipolysis directly, such as glucocorticoids, or indirectly, such as amiodarone, need to be used with caution.

Recommendation # 17:

Caution is advised with drugs metabolised through racemisation by AMACR including naproxen or those likely to promote acute lipolysis (e.g., *glucocorticoids, amiodarone*).

Outcome: Morbidity (including acute metabolic decompensation).

Quality of Evidence: Low.

Strength of recommendation: weak (supported by medical knowledge and consequence of missed diagnosis).

7.6 | Management of Acute Metabolic Decompensation

Therapeutic plasma exchange (TPE): The mainstay of treatment for ARD is dietary restriction of PA, which allows both circulating and stored PA levels to slowly decrease over time. The half-life of circulating PA with dietary management is reported as 39 [20–79] months [33]. However, during acute decompensations of ARD, more rapid lowering is needed.

As therapeutic plasma exchange (TPE) [26, 62, 63] is more widely available than lipoprotein apheresis [64], we would recommend this as a first-line therapy in non-specialist centres.

Only circulating free and lipoprotein bound PA is amenable to direct extracorporeal removal by TPE [63] or LA (Lipoprotein Apheresis). Following a TPE treatment, circulating PA may rebound back to pre-treatment levels within 24–48 h due to redistribution of PA levels from storage into circulation. As a result, a series of TPE treatments may be required to achieve sustained lowering of PA plasma concentration. Whilst evidence for recommended frequency of TPE is limited, during an acute decompensation, multiple TPE 24–48 h apart may be required to clear adequate levels of PA. Patients tend to improve clinically, as their circulating PA levels decrease [26].

In one study, it was modelled that 3–4 TPE treatments removed as much PA as would be ingested by patients on a low PA diet for over a year [26]. This change was enough to lead to clinical stabilisation of their patient in terms of their cardiac arrhythmias, and it allowed the patient's appetite to increase. However, this calculation has never been confirmed prospectively.

In theory, fasting may facilitate central and peripheral lipolysis by mobilising stored PA into circulation, thus increasing the potential levels of PA amenable to removal per TPE cycle, but it is also potentially dangerous, given the risks associated with an acute rise in circulating PA. Fasting before TPE is therefore not recommended.

Proposed cut-offs for consideration of TPE in patients presenting with acute/worsening symptoms are between 900 and 1500 μmol/L [25, 26, 63]. However, in the absence of robust evidence for these cut-offs, in practice, these cut-offs may vary depending on individual clinician preference and clinical presentation. Where symptoms such as acute neurological deterioration, inter-current cardiac arrhythmias, kidney tubulopathy, or others are present, TPE may be started and continued until circulating PA levels fall to a safe level, and patients show clinical signs of improvement. Evidence for what constitutes a safe level is also limited. However, acute complications are rare in patients with circulating PA levels < 200 μmol/L.

Lipoprotein Apheresis (LA): Most circulating PA is carried in lipoproteins, with approximately 35% of PA carried in LDL particles [65]. Therefore, in specialist centres where facilities are available, LA is a viable alternative to TPE [63, 64]. LA has been reported to have equivalent efficacy to TPE, with the added advantage of very low loss of immunoglobulins and coagulation factors [63, 64]. Furthermore, TPE (particularly if the replacement fluid used is plasma) carries allergic risks associated with exposure to human plasma products.

The American Society for Apheresis (ASFA) guidelines suggest LA/TPE is accepted as a second-line therapy for ARD, either as a standalone treatment or in conjunction with other modes of treatment [66]. They acknowledge that evidence for this is limited (category II, i.e., accepted as second line treatment, Grade classification 2C (i.e., observational studies or case series only)). The guidance is based on less than 100 reported patients, with no randomised controlled trials or controlled trials. Evidence for TPE is more forthcoming with two case series (total of 12 patients) and 13 case reports (14 patients) reported. The evidence is much weaker for LA, with only 2 case series (total 8 patients) and 2 case reports (2 patients) reported [67–69].

The ASFA guidelines state that whilst approaches to therapeutic apheresis are variable, the most frequent practice, as per the guidelines, is TPE/LA once or twice weekly for several weeks/months. In our practice, when rapid lowering and clearance of PA is needed during an acute decompensation, using 3–4 treatments of TPE 24–48 h apart with 1–1.5 L of total plasma volume removal with albumin/fresh frozen plasma replacement in each treatment, facilitates adequate PA lowering and improvements in clinical symptoms.

Limitations: Whilst there is a consensus for management of acute decompensation with TPE/LA, the evidence for TPE/LA as long-term maintenance therapy is less clear. Evidence for TPE/LA as a long-term maintenance therapy for progression despite diet is limited. Two case series, each with 4 patients, have been published by the same centre in 2003 [67].

Specific considerations in ARD: Fat biopsies from 8 patients showed that PA constitutes approximately 0.2%–1.5% of the fat in abdominal adipose tissue [53]. As such, for every 1 kg of weight loss, between 200 and 1500 mg of PA may be liberated. This same study found that approximately 6.9 mg of PA can be metabolised daily via the alternate omega-oxidation pathway.

Previous studies have quoted higher values of up to 30 mg/day [59]. Nevertheless, these values are significantly lower than the amounts likely to be released with rapid weight loss. Therefore, in an acute setting, regardless of the use of TPE/LA, it is important that patients are given adequate calories to prevent catabolism and further rise in circulating PA levels. Dietetic support is a crucial part of the acute management, with a low threshold for prompt initiation of parenteral nutrition even if the gut is functioning.

Recommendation #18:

Acute metabolic decompensations should be managed with Therapeutic plasma exchange in conjunction with low phytanic acid diet and adequate energy intake to prevent/reverse catabolism.

Outcome: Morbidity (acute metabolic decompensation) and survival.

Quality of Evidence: Moderate (case series/case reports).

Strength of recommendation: Very Strong (supported by medical knowledge).

7.7 | Management of Pregnancy in ARD Patients

These principles of clinical management of ARD are pragmatically derived based on clinical experience and have been successfully applied in the 2 published cases [42, 70].

Recommendation #19:

The management of ARD in pregnancy is as follows:

Patients are encouraged to inform their metabolic teams of a pregnancy as soon as known to enable a detailed metabolic birth plan to be drawn up.

a. *The low PA diet and vitamin and omega-3 fatty acid supplementation is advised*.
b. *Calorie intake is monitored to prevent weight loss*.
c. *Increased insulin resistance may occur in the third trimester, which will predispose to lipolysis*.
d. *Hyperemesis during pregnancy may result in inadequate calorie intake and therefore acute decompensation—we recommend* a *low threshold for anti-emetics and in-patient management*.
e. *If labour is to be induced, then fasting is minimised and supplementation with oral calorie supplements* (*like oral emergency regimen*) *is advised. During acute labour, IV glucose* (*as detailed in Recommendation #11 points b-d*) *is advised*.
f. *Plasmapheresis or apheresis may be required if acute decompensation occurs*.
g. *Post-delivery weight loss should not exceed 0.5 kg per week*.

Outcome: Morbidity (acute metabolic decompensation) and Survival.

Quality of Evidence: Low (case reports).

Strength of recommendation: Very Strong (supported by medical knowledge).

7.8 | Long Term Monitoring and Surveillance of Co-Morbidities

As with many orphan diseases, since randomised controlled trials have not been conducted, treatment effects are assessed using surrogate markers such as circulating PA levels or improvements in other investigations. Monitoring recommendations are advisory based on clinical experience of the response to intervention.

7.8.1 | Visual Symptoms

No systematic data is available regarding treatment and the progression of RP as assessed by measures such as visual fields and electroretinography (ERG). Clinical anecdotes suggest a slowing of retinal disease progression with long-term treatment, and ERG improvement was reported in one patient after 3 months of diet therapy [71]. There is no data on change in cataract development and extraction rates, and dietary measures are not expected to affect miosis.

7.8.2 | Anosmia/Microsmia

Outcome data is limited often by patients' lack of recall of any detailed taste sensation, but perceived differences may reflect basic modalities or pain fibre signalling rather than osmic sensation. Data has been collected in one centre using University of Pennsylvania smell identification tests (UPSIT) comparing 10 patients at presentation and then at least 5 years later. In most patients, minimal improvement was seen but 2 reported improved taste and a greater than 5-point increase (from a random score of 10 of a potential 40 points) in scores (Wierzbicki, unpublished data).

7.8.3 | Neuropathy and Ataxia

Most descriptions are case reports of acute responses to treatment with diet and/or plasmapheresis [25, 72]. Clinical improvement is described after diet and plasmapheresis [73]. Although not systematically quantified, significant improvement is observed when PA levels are reduced to less than 500 μmol/L [33, 72, 73]. Lowering of circulating PA levels with diet can improve neuropathic symptoms; nerve conduction velocity reached the nadir at the peak of circulating PA levels, but then slowly improved as the PA level fell [74]. A similar slow improvement in nerve conduction was seen in another study, although some initial continued worsening was seen [75]. This does not seem to always be the case, and no improvement was seen in another study despite plasmapheresis [76].

It may be that symptoms related to the acute deterioration such as ataxia, acute demyelinating disease, cardiac dysfunction, and muscle weakness improve quickly, while other longstanding established neurologic symptoms do not improve [77].

Changes in surrogate outcome data using neurophysiology tests or electromyography have not been reported.

7.8.4 | Auditory and Vestibular

Most reports are from individual cases rather than systematic studies. Improvements have been reported clinically and in vestibular neurophysiology after 3 months of treatment [20, 75, 78]. An acute deterioration of hearing can improve with improvement in serum PA levels, although it may not normalise [74]. Similar findings are found in cervical vestibular evoked myogenic potentials (cVEMPs) and ocular vestibular evoked myogenic potentials (oVEMPs) to bone-conducted (BC) stimulation [75]. In other studies, hearing loss stabilises but does not improve [68]. It is likely that the differing levels of improvement may be related to the length of time that the symptoms have been present (i.e., acute vs. chronic), as well as the severity, and the way that patients were assessed and monitored. Symptomatic and audiological improvement with cochlear implants has been shown in 2 patients [20].

7.8.5 | Dermatological Signs

Improvements in skin signs have been reported in two patients with treatment [28, 72] but no systematic data has been reported. Anecdotally, patients show improvement in skin signs and resolution of ichthyosis when plasma PA levels are reduced, and signs seem to disappear when levels are below 500 μmol/L [72] (Wierzbicki, unpublished data). Though biopsy data at presentation is reported in 4 patients [79] there are no reports of repeat skin biopsy comparing post-treatment with pre-treatment changes.

7.8.6 | Cardiology

Abnormalities including cardiomyopathy, ventricular arrhythmias, and fatal heart failure during acute decompensation have been described [35–37]. Arrhythmia improves with plasmapheresis, and no cases of long-term cardiomyopathy or heart failure have been described.

Electrocardiograms (ECG) show significant ventricular dysrhythmia in 6 patients during acute presentation from a centre with 25 patients—all in the context of circulating PA levels exceeding 1500 μmol/L. Repeat ECGs from 12 patients show no significant abnormality on retesting after more than 5 years of dietary therapy (Wierzbicki, unpublished data).

7.8.7 | Renal Effects

Most reports of renal dysfunction including hypokalaemia and proteinuria have occurred with acute presentations [31, 32, 72, 80]. There are no published reports of chronic hypokalaemia though this required treatment with potassium supplements in 2 patients from one centre reviewing 25 patients with ARD (Wierzbicki; unpublished data).

7.8.8 | Osteological Effects

The bone, joint and chondrodysplastic changes show no acute change with therapy. The only report of any change is from a patient with Zellweger spectrum disorder (ZSD) rather than ARD [81]. There does not seem to be an increased rate of requirement for joint replacement surgery (e.g., knee arthroscopy or replacement) in a centre reviewing 25 patients with ARD (Wierzbicki; unpublished data).

7.8.9 | Diabetes and Glucose Tolerance

Changes in glucose metabolism through effects of PA on the peroxisomal proliferator activating receptor alpha (PPAR-α) receptor have been described in a rat hepatocyte model [82] but not in others, and no abnormalities were found in a *PhyH*-null mouse model of ARD [83]. There are no reports of impaired glycaemic control associated with acute metabolic decompensation in ARD. In a case series from one clinic with 25 patients, 2 patients developed diabetes associated with central weight gain. This may reflect risks of diabetes with age, obesity, lack of activity and dietary choices rather than being a feature of ARD.

7.8.10 | Metabolic Consequences of Low PA Diet

The low PA diet is theoretically adequate for vitamins and trace element intake [52]. However, excess salt intake has been noted in patients on a low PA diet. As with many restricted diets, deficiencies in vitamin B_{12} and trace metals such as iron, copper and selenium may occur.

Recommendation # 20:

Long term monitoring and surveillance for co-morbidities is recommended as detailed in Table 2 *below.*

Outcome: Morbidity (acute metabolic decompensation) and mortality.

Quality of Evidence: Weak (case series/case reports).

Strength of recommendation: Strong (supported by medical knowledge).

8 | Quality of Life

No published evidence found.

TABLE 2 | Co-morbidities of ARD and recommended surveillance and management.

Comorbidities	Recommended investigations	Frequency of surveillance	Management
Eye disease [12] Retinitis pigmentosa Posterior subcapsular cataracts Miosis and sluggish pupillary light response Acute angle closure glaucoma	Surveillance in specialised ophthalmology clinic Assessments may include: Visual fields Retinal imaging Electroretinogram	Annual Baseline and then as clinically indicated	Adherence to ARD dietary guidance Treatment of specific complications such cataracts Supportive measures such as low vision aids, guide dogs
Microsmia (reduced sense of smell) [18] Moderate to severe microsmia	Patient reported (awareness may be variable) The University of Pennsylvania Smell Identification Test (UPSIT) if available	Baseline and then as clinically indicated	PA restricted diet
Acute neurology [15] Acute rapidly progressive neurological symptoms (cerebellar signs, muscular weakness, demyelinating polyneuropathy; cranial nerves may also be affected)	Clinical examination Nerve conduction studies and EMG at the time of acute deterioration Baseline brain MRI	With new onset of symptoms	TPE/LA to enable rapid lowering of circulating PA levels Symptomatic management
Chronic neurology [24] Polyneuropathy—mixed sensory and motor type	Clinical neurological examination Baseline brain MRI Nerve conduction studies and EMG	Each clinic visit/ annual surveillance Baseline and then as clinically indicated	PA restricted diet Supportive management of symptoms
Auditory/vestibular [19] Sensorineural hearing loss (particularly middle and higher frequencies) Auditory neuropathy reported Cochlear abnormalities	Pure-tone audiometry, otoacoustic emissions, and Brainstem auditory evoked potentials (BAEP)/auditory brainstem response (ABR) testing.	Baseline and then as clinically indicated (ideally 5-year intervals if no exacerbation seen clinically)	PA restricted diet Supportive with hearing aids Some patients have shown a good response with cochlear implants 14 Caution with amplification in patients with absent/deranged ABR and reserved
Skin [28] Ichthyosis (resembles ichthyosis vulgaris with flexural sparing and no erythema)	Visual assessment of skin Skin biopsies not routinely indicated	Surveillance visits during acute presentation with raised PA level	PA restricted diet Supportive–hydrating creams/emollients
Cardiac [35, 36] Mostly acute presentation associated with high PA level Hypertrophic or dilated cardiomyopathy Conduction defects, sudden death Raised creatine kinase	Echocardiogram 24-h ECG holter tape.	Baseline and acute presentation with raised PA level/ presenting with cardiac symptoms	PA restricted diet Supportive management of cardiac complications Consider TPE/LA during acute presentation

(Continues)

TABLE 2 | (Continued)

Comorbidities	Recommended investigations	Frequency of surveillance	Management
Kidney [31, 32, 80] Tubulopathy and impaired glomerular filtration reported Hypokalaemia	Plasma electrolytes and creatinine (eGFR) Urine potassium and sodium Urine albumin:creatinine ratio Urine amino acids (baseline) Urine selective protein leak panel (retinol binding protein; IgG)	Annual surveillance and during presentation with acute decompensation	Supportive management of renal impairment and electrolyte imbalance
Skeletal dysplasia [29]	Clinical examination Hand, foot; knee X-rays (baseline)	At presentation	Supportive
Metabolic and vitamins [52]	HbA_{1c} Lipid Profile including Total cholesterol, Triglycerides, HDL-C and LDL-C Essential Fatty Acids Vitamins A, D, E, K Vitamin B_{12} (holotranscobalamin) Methyl-malonic acid and homocysteine (if vitamin B_{12} abnormal) Trace metals: iron (ferritin), selenium, copper	Annual surveillance Baseline, 1 year and then 2–3 yearly	Control of body weight General management of cardiometabolic risk Dietary improvement limiting refined carbohydrates Vitamin B_{12}, other vitamins and trace element supplements as required

9 | Conclusion

Increased clinician and patient awareness leading to early diagnosis and implementation of a life-long low PA diet before further end organ involvement offers the best prognosis. Life-long dietary therapy, along with TPE/LA during acute decompensations, remains the mainstay of management. Patients should have access to a multidisciplinary team to ensure specialist dietary input and supportive management of comorbidities.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The pre-determined scope of the review is provided in the Supporting Information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** jimd70201-sup-0001-Supinfo.docx.