



Inherited Metabolic Disease in Adult Services: Nutritional Continuity After Paediatric Transition

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Abstract

Dietary treatment for inherited metabolic disease is now recommended for life, and the population reaching adult services is growing. The evidence supporting lifelong treatment is not distributed evenly across the lifespan. In phenylketonuria, the childhood relationship between phenylalanine exposure and cognitive outcome rests on a meta-analysis across 40 publications, in which each 100 umol/L difference from birth to 6 to 12 years predicted 1.3 to 3.1 IQ points. The adult recommendation rests on a follow-up comparing 17 adults who remained on diet through adolescence, median phenylalanine 496 to 707 umol/L, against 18 who relaxed it after age 10, median 750 to 1038. A cohort of 55 patients followed for two years either side of transfer to adult care reported the programme a success: only 6 per cent were lost to follow-up and clinic attendance rose from a median of 5 appointments to 11. Over the same period the proportion of samples below 480 umol/L fell from 51 to 37 per cent. Attendance and metabolic control moved in opposite directions, and the service metric captured the first.

Keywords: *Inherited metabolic disease; Phenylketonuria; Transition; Dietary adherence; Continuity of care*

Introduction

Newborn screening and early dietary treatment converted several inherited metabolic disorders from causes of severe disability into chronic conditions managed by diet [1,2]. The first fully screened cohorts are now middle-aged, and a population that did not previously exist in adult medicine has arrived in it [2,3].

Treatment in these conditions is nutritional rather than pharmacological in the main, which means continuity of care is continuity of a dietary regimen, a supply of prescribed substitutes, and a relationship with a dietitian who knows the patient [1,4,5]. None of those transfers automatically at the point of transfer [5,6].

This review examines what the evidence supports about lifelong treatment, what happens at transition, and where the two do not meet.

Objective

This review sets out to establish four things from the published literature. First, what the evidence for lifelong dietary treatment consists of and how it is distributed across the lifespan. Second, what is observed at and after transfer to adult services. Third, what a transition programme measures and what it may miss. And fourth, which elements of care actually move with the patient.

Literature Review

What the childhood evidence establishes: European guidance on phenylketonuria summarises a meta-analysis across 40 publications in which a difference of 100 umol/L in blood phenylalanine from birth to 6 to 12 years predicted a difference in IQ of 1.3 to 3.1 points, and in which each 100 umol/L increase in lifetime concentration predicted an average reduction of 1.9 to 4.1 points across a range of 423 to 750 umol/L [1]. A separate meta-analysis supported a target of 570 umol/L for ages 13 to 18 [1]. This is the strongest part of the evidence and it concerns exposure during development [1,7].

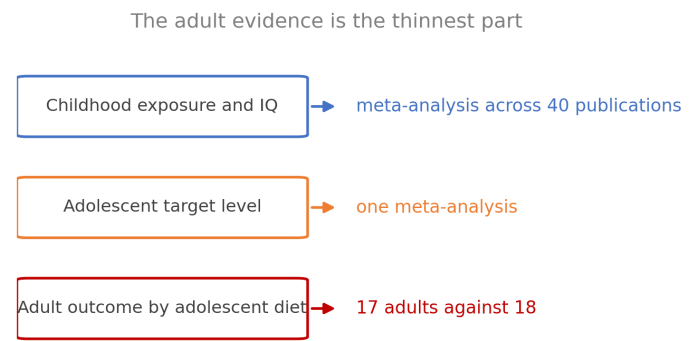


Figure 4: What each strand of the evidence rests on [1]

What the adult evidence consists of: The recommendation to continue treatment into adulthood draws substantially on a longitudinal follow-up comparing adults who remained on diet through adolescence, 17 patients with median phenylalanine between 496 and 707 umol/L, against 18 who relaxed the diet after age 10, with medians between 750 and 1038 umol/L [1,8]. The first group had better IQ (Figure 5) [1,8]. A further small study found no IQ difference between controls and four young adults with lifetime concentrations below 500 umol/L [1]. These are the numbers behind a lifelong recommendation for a growing population [1,8].

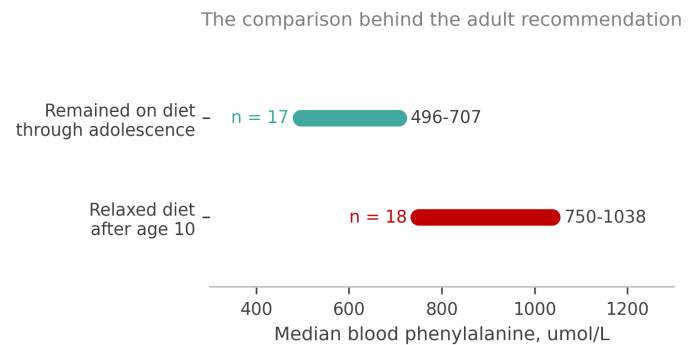


Figure 5: The two adult groups in the key comparison [1,8]

Table 1: How the evidence for lifelong treatment is distributed

Evidence strand	Basis
Childhood exposure and IQ	40 publications pooled [1]
Adolescent target concentration	One meta-analysis [1]
Adult outcome by adolescent diet	17 against 18 adults [1,8]
Adult outcome by adult control	Not established [3,9]

What happens at transfer: Adherence and attendance decline through adolescence and early adulthood across these conditions, and loss to follow-up after transfer is widely reported [4,5,10]. The reasons described are practical rather than attitudinal: the diet is socially isolating, substitutes are unpalatable and must be taken several times daily, adult clinics are less frequent and less familiar, and responsibility shifts from a parent who had managed the regimen for two decades to a young adult who has often never done so alone [5,6,11].

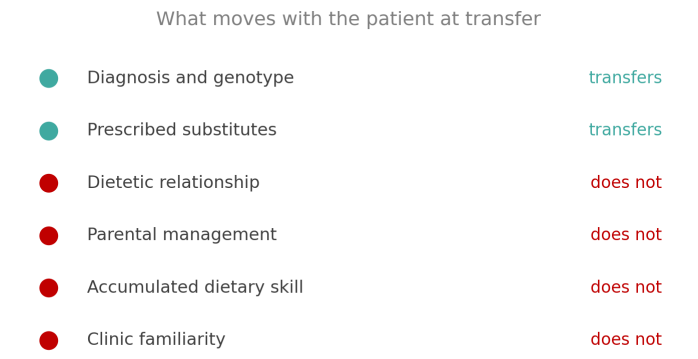


Figure 6: What moves with the patient at the point of transfer [5,6,11]

A transition programme, measured: A cohort of 55 patients with phenylketonuria was studied for the two years before and the two years after the start of adult care [12]. Three patients, 6 per cent, were lost to follow-up. The median number of clinic appointments rose from 5 to 11 ($p < 0.001$) and annual blood spots from 11 to 14 ($p = 0.002$) [12]. Median blood phenylalanine was stable at 525 plus or minus 248 against 552 plus or minus 225 umol/L ($p = 0.100$), and no parameter of protein intake differed [12].

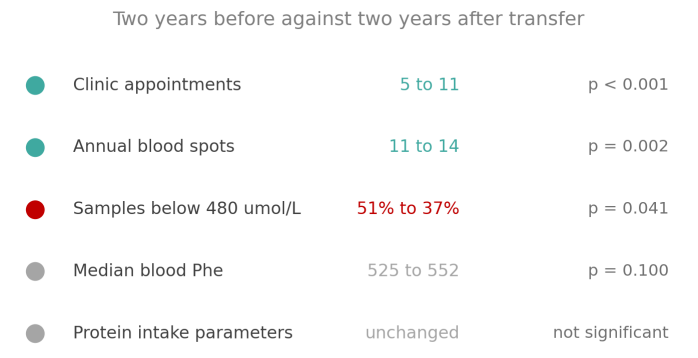


Figure 2: Measures before and after transfer in a transition cohort [12]

The honest complication: Over the same period the proportion of samples below 480 umol/L fell from 51 to 37 per cent ($p = 0.041$) [12]. Attendance more than doubled while the share of readings in range fell by a quarter of its starting value (Figure 1) [12]. The investigators reported the programme as successful because impact on metabolic control was limited and attendance remained high, which is a defensible reading of a stable median [12]. But the two measures moved in opposite directions, and the one that improved is the one a service is judged on [12,13].

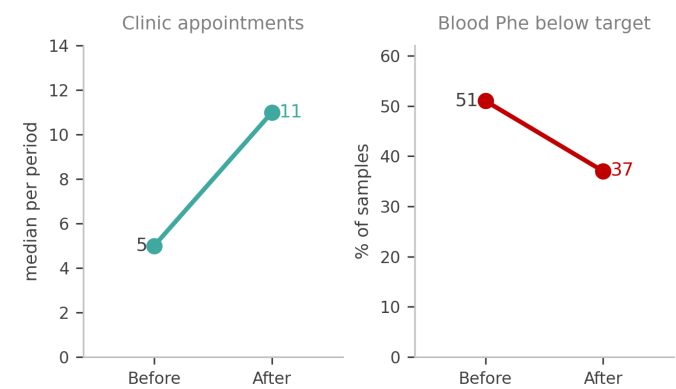


Figure 1: Attendance and metabolic control over the same period [12]

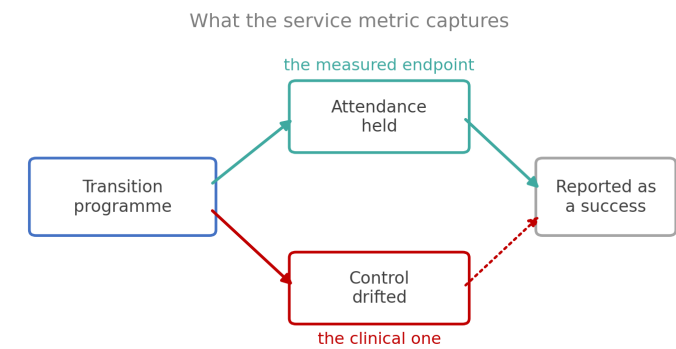


Figure 3: What a transition service metric captures [12,13]

Why the median can be stable while control worsens: A median concentration unchanged between periods is compatible with a distribution that has widened, and the proportion below a threshold is the more sensitive measure of that change [12,13]. Reporting both is what makes the divergence visible, and studies that report only a mean or median concentration cannot show it [12,14]. This is a general point about adherence outcomes in these conditions rather than a criticism of one cohort [13,14].

Table 2: The same programme on five measures [12]

Measure	Direction after transfer
Clinic appointments	Up, 5 to 11 [12]
Annual blood spots	Up, 11 to 14 [12]
Loss to follow-up	Low, 6% [12]
Median phenylalanine	Unchanged [12]
Samples in target range	Down, 51% to 37% [12]

Beyond phenylketonuria: The same structure recurs across dietary-treated inherited metabolic disease, in maple syrup urine disease, galactosaemia, homocystinuria and the urea cycle disorders, where treatment is lifelong, adult evidence is thinner than paediatric evidence, and adult services are less established [15,16,17]. Numbers in each condition are small enough that the adult literature consists largely of case series and single-centre cohorts, so the general point about evidence distribution is if anything stronger there than in phenylketonuria [15,17,18].

Maternal considerations change the calculation: In phenylketonuria the risk to a developing fetus from uncontrolled maternal concentrations is well established and is the one adult

indication where the evidence is not thin [1,19]. Guidance is explicit that longer follow-up may be necessary for girls and women for that reason [1,19]. This creates an asymmetry in which the strongest adult argument for continued treatment applies to part of the population, and is sometimes generalised to all of it without the distinction being stated [1,19,20].

What adult outcomes are actually reported: Neuropsychiatric comorbidity, executive function difficulty and reduced quality of life are described in adults with phenylketonuria, and ageing in this population is explicitly identified as understudied [3,9,21]. Whether these outcomes respond to regaining metabolic control in adulthood, as distinct from having maintained it, is the question that would justify the recommendation directly, and it has not been answered [3,9,22]. Return to diet after years off it is difficult and the studies of it are small [22,23].

Table 3: Five distinct questions often answered as one

Question	Status
Does childhood exposure affect outcome?	Established [1]
Does adolescent relaxation affect adults?	17 vs 18 adults [1,8]
Does adult control affect adult outcome?	Not established [3,9]
Does regaining control help?	Small studies only [22,23]
Does maternal control matter?	Established [1,19]

What continuity of dietetic care appears to do: The cohort authors attributed their retention to continuous dietetic care across the transfer, and this is consistent with the wider transition literature, in which retained relationships predict retained attendance better than protocols do [5,12,24]. Structured transition programmes with joint clinics, a named coordinator and overlap between paediatric and adult teams are the components most consistently associated with retention [24,25,26]. The evidence for them is observational and the outcome measured is usually attendance [24,26].

Supply is a recurring failure point: Prescribed protein substitutes and low-protein foods are the material basis of treatment, and interruption of supply at transfer is reported where funding or prescribing responsibility moves between services [4,10,27]. Availability differs markedly between countries and within them, and a recommendation to continue treatment for life presupposes a supply chain that outlasts the paediatric service [4,27,28]. This is rarely counted among clinical outcomes and is among the more actionable causes of loss of control [10,27,28].

What patients and families report: Surveys of the burden of managing phenylketonuria describe the daily labour of weighing, calculating and preparing food, the cost in time and money, and the social effects of eating differently from everyone else [29,30]. That burden is borne by parents through childhood and transfers to the patient at roughly the same moment as clinical

responsibility does [11,29,30]. Discussions of adherence that treat non-adherence as a failure of motivation rather than as a response to that burden misdescribe what is being asked [29,30].

What the adult phenotype looks like: A systematic review of the neurological and psychological phenotype in early-treated adults describes findings that are real but modest and heterogeneous across studies, against a background condition whose untreated form is severe [31,32]. Holding both in view is necessary: the treatment transformed the condition, and the residual differences in treated adults are the subject of a much smaller and less consistent literature than the original demonstration [31,32].

Whether services can absorb the population: Surveys of adult metabolic services report capacity that has not grown in step with the cohort reaching them, and coverage gaps in the registries that would track long-term outcomes [17,33,34]. Those two shortfalls compound: a population followed inconsistently is one whose adult outcomes cannot be characterised, which is the same gap this review identifies in the evidence [3,33,34]. Improving registry coverage would address the evidence problem and the service problem with one instrument [33,34].

Method

This is a narrative review of published literature. Sources were assembled by searching the indexed literature for clinical guidelines, cohort studies, systematic reviews and transition-service evaluations concerning dietary treatment of inherited metabolic disease in adolescents and adults, with precedence given to guidance stating its evidence base and to cohorts reporting both attendance and biochemical measures [1,12].

Findings are reproduced as their authors published them, with the sample size attached, because in this literature the number of patients behind a recommendation is frequently the most informative quantity [1,8,12].

No new patient data were collected and no search protocol was registered, so this is not a systematic review. Target concentrations and dietary regimens are described as those stated in published guidance and are not directed at any individual.

Concluding Remarks

The recommendation to continue dietary treatment for life is reasonable and is what most services follow. Its evidence is heavily weighted towards childhood exposure, and the adult component rests on a comparison of 17 patients with 18. That is worth stating plainly to a young adult being asked to continue a demanding regimen indefinitely.

The transition literature has a related problem. A programme that doubles attendance while the share of readings in target falls from half to just over a third has succeeded on the measure it reports and not on the one that motivates the treatment. Both

findings come from the same cohort and only the first is in its conclusion.

What follows is not that treatment should be relaxed, but that services should measure control rather than contact, report the distribution rather than the median, and be honest with adult patients that the case for continuing is strong for maternal phenylketonuria, reasonable by extrapolation elsewhere, and not established by adult outcome data.

Newborn screening created the population and not the service: Screening programmes were established with paediatric treatment in view, and the adult services now required were not part of the original design [2,17,33]. Each cohort that ages out of paediatric care arrives at a service configured for a smaller and different population, and the mismatch grows rather than resolves as screening cohorts accumulate [2,17,33]. Framing the transition difficulty as a failure of individual services understates a problem that is demographic in origin [17,33].

The comparison with other lifelong conditions: Transition research in type 1 diabetes, congenital heart disease and cystic fibrosis is more developed, and the components identified as effective there are the ones the metabolic literature has begun to adopt [24,25,26]. What does not transfer directly is the centrality of diet: in those conditions dietary advice supports a treatment, while here it is the treatment [4,5]. A transition model imported without that adjustment will optimise the wrong component [5,24,26].

Study Limitations

The adult evidence base is small and largely observational, and the transition cohort described here is a single centre with 55 patients, so its findings are illustrative rather than generalisable. Conditions other than phenylketonuria are represented by smaller literatures still and are treated here only in outline.

Attendance, adherence and metabolic control are measured differently across studies and are not directly comparable. Absence of demonstrated benefit from adult metabolic control reflects the absence of studies designed to detect it rather than evidence that control in adulthood does not matter.

What a better transition metric would measure: If attendance and control can move in opposite directions, a service evaluated on attendance alone can improve while the thing the treatment exists to achieve deteriorates [12,13]. Reporting the proportion of samples within target alongside attendance costs nothing, since both are already collected, and it is the pairing rather than either measure that carries the information [12,13,14]. Registries positioned to collect both across centres would turn single-cohort observations of this kind into something generalisable [33,34].

Where this leaves the clinician: A young adult asking why the diet must continue deserves an answer that distinguishes what is established from what is extrapolated [1,3,9]. For a woman of

childbearing age the maternal evidence is strong and specific [1,19]. For everyone the childhood evidence is strong and concerns a period already past. For adult outcomes contingent on adult control, the honest answer is that the question has not been studied adequately, and that the recommendation rests on continuity with what is known rather than on a direct demonstration [1,3,9,22].

A structural observation: Conditions treated by diet rather than by drug sit awkwardly in services organised around prescribing, and the elements that determine outcome here are dietetic time, food supply and a sustained relationship [4,5,27]. These are the components least visible in service specifications and the first to be lost when a patient moves between services [5,10,27]. The transition problem described throughout this review is, in that sense, a problem of what health systems are configured to count [13,27,33].

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A note on numbers in rare disease: Criticising an adult recommendation for resting on 35 patients invites the response that no larger study is available, which is correct [1,8,17]. The point is not that the investigators should have recruited more, but that the size of the evidence should travel with the recommendation rather than being lost as it is restated [1,20]. Rare disease guidance is frequently the best available synthesis of a small literature, and presenting it as though it rested on the same footing as guidance in common conditions serves neither clinicians nor patients [17,20,34].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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