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Living with phenylketonuria: Perspectives of patients and their families

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Summary: This study surveyed PKU patients and their primary caretakers to assess their current management practices, the barriers to effective management, and the potential utility of a home monitor in managing PKU. A survey instrument was mailed to caretakers of all 50 patients with PKU in Utah between the ages of 2 and 18 years in 1997 (response rate 64%). It included separate components for caretakers and patients aged 10 to 18 years. Although there was uneven compliance with recommended practices, caretakers universally recognized the negative consequences of not adhering to the low-protein diet. There was, however, disagreement regarding such consequences among the older children surveyed. The primary obstacles cited to better adherence were time constraints and stress associated with food preparation and record-keeping, and the restrictions imposed on social life. Phenylalanine test results were regarded as the principal signal for the need for dietary adjustment. Despite the facts that obstacles to dietary adherence are multifaceted and that no single intervention would therefore serve as a panacea, a large majority of respondents believed a home monitor would facilitate better management of PKU through more regular and timely feedback.

Phenylketonuria (PKU) is an inborn metabolic disorder caused by phenylalanine hydroxylase deficiency, which, if not diagnosed and treated at birth, causes severe irreversible mental retardation. There is a nationwide newborn screening in the United States for this condition. Treatment requires maintenance of therapeutic blood phenylalanine (Phe) levels through a low-Phe diet. Diets must be individualized and periodically adjusted to maintain adequate nutrition for physical development. A synthetic protein source (formula) is required to provide adequate nutrition intake. Several studies have shown that discontinuation of the diet results, over time, in neuropsychological and behavioural problems as well as decline in IQ (Koch et al 1987, 2002; NIH 2001; Pietz et al 1988; Ris et al 1994; Rylance 1989; Smith et al 1988; Wappner et al 1999; Weglage et al 1992). Health professionals generally agree that the patient must therefore adhere to the diet throughout life (Medical Research Council 1993b). Blood Phe levels of women with PKU must be strictly controlled

during childbearing age in order to prevent damage to the fetus. Currently, the protocol for monitoring of Phe levels requires periodic drawing of blood by the patient, followed by laboratory analysis of the sample and a report back to the patient, generally within a week.

Similarly to other chronic conditions such as diabetes and hypertension, successful management of PKU is dependent on patients and their families. However, the rate at which patients 'comply with' or 'adhere to' the PKU diet typically declines as they move into adolescence (Medical Research Council 1993b; NIH 2001; Weglage et al 1992). Given the potentially serious consequences of elevated blood Phe levels, it is critical to identify the obstacles to better management faced by patients and their families, and to devise policies and procedures to alleviate them.

Clinicians often cite the restrictiveness of the recommended diet, the palatability of medical foods, testing frequency, knowledge and perceived value of the diet, psychosocial problems, the cost of medical foods and formula, and the availability of professional support as factors that hinder adherence (NIH 2001; Seashore et al 1999; Wappner et al 1999). Little is known about these obstacles, however, from the perspective of patients and their parents. Four previous surveys collected information on various aspects of the management of PKU. A German study, based on narrative interviews with parents of 8-year old PKU patients ($n = 11$), found that parents did not follow a strict dietary regimen but compromised between the dietary recommendations and personality development of the child (Awiszus and Unger 1990). A Minnesota study ($n = 43$) focused on the effects of family functioning on the management of PKU and concluded that family cohesion and education were positively correlated with metabolic control and the patient's IQ level (Shulman et al 1991). Another study surveyed PKU clinics in the United States and Canada regarding frequency of visits, dietary control and noncompliance policies (Fisch et al 1997). The American Association of Pediatrics (AAP) Committee on Genetics surveyed parents and young adults with PKU ($n = 1064$) across the United States via the *National PKU News* in its effort to develop PKU management guidelines (Wappner et al 1999). This survey provided some summary information on PKU management practices and concluded that parents supported more stringent PKU management.

The present study reports findings of a survey distributed to Utah PKU patients in 1999. In addition to systematically exploring how patients or their caretakers currently manage dietary control and Phe-level testing, this survey elicited information concerning barriers to adherence to the diet from the perspective of both caretakers and patients, and assessed the potential utility of new home monitoring technologies from their viewpoint.

METHODS

The survey instrument was mailed in September 1999 to all 50 classic PKU patients in Utah between the ages of 2 and 18 years, and living with a parent. While the primary care-giving parent was requested to answer all questions, patients who were aged 10 years or older were also requested to answer a subset. The survey included both closed and open-ended questions that permitted the patients and caretakers to comment in more detail on certain aspects of PKU management. As an incentive to complete and return the survey, families who responded were paid a modest compensation of $10. Patients were asked to identify

Table 1 Sample of PKU patients by sex and age—summary statistics

	Male			*Female*			*All*		
	Mean age (y)	*SD age* (y)	*n*	*Mean age* (y)	*SD age* (y)	*n*	*Mean age* (y)	*SD age* (y)	*n*
Patients <10 years of age	4.3	2.6	9	4.5	1.9	10	4.4	2.2	19
Patients ≥ 10 years of age	12.2	2.5	6	14.4	2.5	7	13.4	3.1	13
All patients	7.5	4.9	15	8.6	5.5	17	8.1	5.2	32

themselves on the return envelope but not on the survey instrument itself. Return envelopes and survey forms were separated upon receipt, in keeping with the promise of confidentiality made to respondents. A list of respondents was kept, however, in order to assess whether findings were subject to selection bias. Subjects who did not respond were contacted again by mail after 4 weeks. By mid-December 1999, 32 subjects (64%) had responded to the survey. Table 1 summarizes the age and sex distribution of patients who responded to the survey.

If parents who were better informed and more careful about PKU management were also more likely to respond to the survey, then the results could be subject to sample selection bias. Among the 2–5 year age cohort, such bias was not a problem because only one questionnaire (out of 13) was not returned. Among children older than 5 years, where the response rate was 51%, we assessed potential selection bias by comparing responding and nonresponding subjects in terms of patients' blood test frequencies and measured Phe levels from clinic records. These records indicated that the number of Phe tests over the previous 12 months averaged 6.4 (SD = 5.1) for responding patients and 4.0 (SD = 3.4) for nonresponding patients, a difference that is significant at the 10% level (two-tailed test). On the other hand, the mean measured Phe levels were respectively 10.0 mg/dl (SD = 6.5) and 10.6 mg/dl (SD = 4.3) for the responding and nonresponding groups and this difference was not statistically significant ($p = 0.39$). Thus, there is some suggestion that in the case of children older than 5 years of age the management practices of responding and nonresponding groups were significantly different, although the impact of such differences on measured Phe levels was not significantly different.

RESULTS

Adherence to management recommendations

Successful management of PKU requires patients and caretakers to be familiar with the prescribed diet, to track Phe and energy intake, to monitor the physical growth of the patient, and to periodically test blood Phe levels. Survey findings summarized in Table 2 show that knowledge concerning the diet was not a problem for the overwhelming majority of caretakers (91%). Low-protein foods were used extensively (78%). Some families, however,

Table 2 Current management practices of PKU families[a]

	Almost always	*Often*	*Some times*	*Almost never*	*No response*
The prescribed diet is known	87.5	3.1	6.3	3.1	0.0
Special low-protein foods are used	50.0	28.1	15.6	6.3	0.0
A count of the amount of Phe used is kept	37.5	25.0	25.0	12.5	0.0
Adequate calories are consumed	40.6	31.3	12.5	12.5	3.1
A count of calories consumed is kept	6.3	6.3	25.0	62.5	0.0
Child's height and weight are measured	6.3	28.1	50.0	12.5	3.1
Diet records are kept before each blood level	40.6	15.6	25.0	18.8	0.0
Each Phe test is taken at around the same time of the day	53.1	25.0	15.6	6.3	0.0
Prior to a Phe test the diet is followed more carefully	9.4	37.5	34.4	18.8	0.0

[a]Primary caretaker responses ($n = 32$). Reported figures are percentages

were more lax than others in the management practices. Phenylalanine intake was monitored 'often' or more frequently by 63% of families. Although a majority of families (72%) reported adequate energy consumption, only 13% reported that they actually kept track of energy intake 'often' or more frequently. Such a discrepancy may be explained, in part, by the fact that the calorie count was normally kept by the nutritionist. Two parents commented that this was indeed the case for them.

Since protein is required for normal development, another part of the management protocol for PKU is the periodic measurement of the patient's physical development under the low-protein diet. Measurement of physical development did not appear to be a priority for most families, with 63% of caretakers reporting doing so 'sometimes' or less frequently. There was no relationship between such measurement practices and the age of the patient.

Careful dietary record keeping is important if the diet is to be adjusted in an informal manner. More than half of caretakers reported that they kept dietary records before each blood Phe level test and a large majority (78%) did so at a same time of day in accordance with clinic recommendations.

It has been noted that patients often 'prepare' for the test by changing diet just before testing (Weglage et al 1992). Indeed, a significant number of the Utah families (47%) reported that they altered their compliance behaviour in anticipation of testing 'often' or more frequently. This suggests that measured Phe levels kept by the clinic may frequently underrepresent the typical Phe levels of patients.

In response to other questions on management practices, only 6% of children were reportedly taken off the diet for more than a month. Many parents used nonclinical markers to assess how their children are doing; 47% reported that they could tell that the child's Phe level was high just by observing the child. In accordance with the clinical literature (Smith et al 1988), the reported symptoms were typically *'irritability'*, *'moodiness'*, or *'whining'*. (Throughout the paper, selected quotations from respondents' comments in open questions

are provided in italics.) Only one caretaker reported physical symptoms (*'pale complexion, eczema, bags under eyes'*). Sixteen percent of parents reported that their children had learning problems (*'speech delay'*, *'trouble keeping with peers in classroom'*, *'inability to pay attention in classroom'*, and *'visual and perception problems'*).

Barriers to adherence with the diet

Currently, the Utah Metabolic Clinic recommends blood Phe level testing once or twice a month for patients between ages 2 and 4 years, and once a month for patients older than 4 years. Based on independent review of clinic records, nonadherence to the recommended test frequency was widespread. The average number of tests over the 12 months preceding the survey for the younger cohort was 12. Three toddlers under age 3 years who were tested just six or nine times over this period posed particular concern because of the extensive damage associated with elevated Phe levels in early life. In the older cohort, the number of tests averaged 6.6 per year, with 25% of patients tested only once in a 3-month period or less frequently in the previous year. The yearly median measured Phe levels were above the recommended level of 6 mg/dl for 9% of the 2–4 years age cohort. The corresponding figure was 70% for patients between ages 5 and 18 years. Sex differences within either age cohort, in terms of testing frequencies or blood Phe levels, were not statistically significant.

The survey attempted to assess which factors, from the families' perspective, accounted for nonadherence to the diet and recommended test frequency. As noted above, the successful management of PKU requires special foods and formula, and frequent visits to health professionals, which could pose substantial financial burdens (Awiszus and Unger 1990; Medical Research Council 1993a; Wappner et al 1999). Special formula generally constitutes the largest single component of treatment cost, ranging from $3000 to $5000, per year, depending upon age. Utah provided payment for low-Phe formula in the past, but this policy is subject to change.

Lack of health insurance or noncoverage of certain expenses may, therefore, constitute a barrier to effective treatment. Among Utah patient families, 45% reported that PKU was not a substantial financial burden on their household. One parent qualified the response by stating that it depended on the insurance coverage, and two parents stated that they expected the financial burden to increase as the patient got older. Table 3 summarizes the extent of insurance coverage for various services and products utilized by the PKU patients. It reports only the presence or absence of insurance for various services and does not give any information on the extent of co-payment, co-insurance or deductibles. Just 6% of patients had no insurance at the time of the survey. Modified low-protein foods were not covered by insurance policies of most families (83%), a potentially serious source of financial burden. This figure is also virtually the same as that reported by the AAP national survey (Wappner et al 1999). Forty percent of families reported that all physician visits were covered by insurance, while the rest reported that some visits were covered. At least some of nutritionist and hospital visits, laboratory tests and PKU formula were also covered for most families, but 13–23% of families did not know whether their insurance covered any of these. A larger number of families (40%) were uncertain about or unaware of the coverage of their policies for psychologist visits, social worker visits and psychological testing. These

Table 3 Extent of insurance coverage of PKU patients[a]

	None	*Some*	*All*	*Don't know*
Physician visits	0.0	60.0	40.0	0.0
Nutritionist visits	3.3	46.7	26.7	23.3
Laboratory tests	0.0	40.0	43.3	16.7
PKU formula	6.6	46.7	33.3	13.3
Modified low-protein foods	83.3	0.0	10.0	6.7
Psychologist visits	10.0	30.0	23.3	36.7
Psychological testing	10.0	26.7	23.3	40.0
Social worker visits	0.0	36.7	23.3	40.0
Hospital visits	0.0	50.0	36.7	13.3

[a]Responses of 30 parents (out of the total of 32) who had some form of health insurance coverage. Reported figures are percentages

patients also met with mental health professionals and social workers significantly fewer times compared with the rest of the patients.

A separate assessment was made of the extent of total out-of-pocket medical spending on medical care (physician, nutritionist, psychologist, social worker, hospital visits, laboratory and psychological tests, formula and low-protein foods) related to PKU during the 12 months preceding the survey. The reported annual out-of-pocket spending of the insured families ranged from zero to $2400 (mean = $550, SD = $595). Out-of pocket expenses were higher, on average, for patients older than 10 years than for the younger cohort patients.

PKU diet planning and preparation is a complicated, time-consuming activity that requires knowledge of foods and recipes, and continuous measurement of ingredients (Awiszus and Unger 1990). The diet is also considered to be restrictive and comprises foods that are unpalatable (Prince et al 1997). With respect to nonfinancial problems in optimal PKU management, the instrument included a series of closed- and open-ended questions. Closed-ended questions focused specifically on the demands associated with food preparation, record keeping and Phe testing. Caretakers' and older patients' responses to these questions are provided in Table 4.

According to Table 4, there were no statistically significant differences between perceptions of parents with children younger than 10 years of age and parents with older children regarding management of PKU. The widest divergences of opinion, although statistically nonsignificant, were observed in response to statements 1 and 5. While most parents did not consider the preparation of the diet foods overly burdensome and found the Phe level testing more cumbersome, these hold true for a relatively larger number of older patient parents. These findings may be attributable to the experience of or greater involvement of patients with PKU management. Responses to other statements are more concordant. Dietary adherence required significant labour for most parents. Around 70% of parents agreed that they 'put a lot of effort into complying with the diet'. Dissatisfaction with the diet, on the other hand, was widespread. Caretakers and children who were not satisfied with the variety of foods in the PKU diet exceeded those who were satisfied by a margin of 2 to 1.

Table 4 Caretakers' and older patients' perceptions of the management of PKU[a]

	Caretaker with child <10 years of age[b]			*Caretaker with child ⩾10 years of age*[c]			*Child ⩾10 years of age*[d]		
	Agree	*Disagree*	*Don't know*	*Agree*	*Disagree*	*Don't know*	*Agree*	*Disagree*	*Don't know*
1. Preparation of the PKU diet takes too much time and effort	38.9	50.0	10.5	25.0	75.0	0.0	23.1	50.0	12.5
2. I put a lot of effort into complying with the diet	73.7	26.3	0.0	69.2	30.8	0.0	66.7	33.3	0.0
3. I am satisfied with the variety of foods in the special diet	31.6	57.9	10.6	30.8	69.2	0.0	33.3	66.7	0.0
4. Testing the Phe level is no longer necessary at the child's current age	0.0	100.0	0.0	0.0	100.0	0.0	22.2	55.6**	22.2
5. Testing the blood Phe level is time-consuming and cumbersome	31.6	68.4	0.0	7.7	92.3	0.0	33.3	55.6*	11.1
6. It takes too long to find out the blood Phe test results	42.1	52.6	5.3	53.8	38.5	7.7	66.7	22.2	11.1
7. The wait for Phe test results makes compliance with the PKU diet difficult	31.6	63.2	5.3	30.8	53.8	15.4	44.4	22.2	33.3
8. The PKU diet would be followed more carefully if the blood Phe levels could be tested regularly at home	73.7	21.1	5.3	61.5	23.1	15.4	66.7	11.1	22.2

[a] Entries are percentages of responses.
[b] $n = 19$. Number of responses: 18 to statement 1 and 19 to all other statements
[c] $n = 13$. Number of responses: 12 to statement 1 and 13 to all other statements
[d] $n = 13$. Number of responses: 8 to statement 1 and 9 to all other statements
* and ** indicate that the response of patients ≥10 years of age is significantly different from that of their parents ($p < 0.05$ and $p < 0.01$, respectively). None of the responses of the two groups of caretakers were statistically significantly different at $p < 0.10$

There were some notable differences between the views of caretakers and older patients concerning some aspects of the Phe testing protocol. Patients were less sure of the need for continuation of testing and more likely to be bothered by the testing protocol. Caretakers were aware of adverse consequences associated with elevated blood Phe levels and the need for a programme of sustained testing to monitor such levels. They universally believed that Phe testing at their child's current age was necessary. Older patients who were surveyed, however, were more ambivalent; a much smaller fraction (56%) of patients than their caretakers disagreed with the statement that Phe testing was still necessary at their age ($p < 0.01$). They were also less likely than their parents to disagree with the statement that blood Phe level testing is time consuming or cumbersome ($p < 0.05$). According to the responses to the survey, the average lag between the collection of the blood sample and obtaining test results is 5 days (range 3–10, SD = 2.2), which is shorter than the 7 day lag time observed AAP national survey (Wappner et al 1999). Patients were more likely than their parents to maintain that the waiting period was a factor that made diet compliance more difficult.

Phenylalanine testing ranked very high among families with respect to gauging the success of, and the need for, alterations in management. In their open-ended comments, provided by 84% of respondents, caretakers universally concurred that the Phe test was the primary and most important indicator of how well they were doing. Most parents (78%) indicated that they utilized the Phe test results to make adjustments in the diet. They found Phe test results useful for other reasons as well. One noted that Phe test results helped in *'work[ing] with the clinic to obtain the best results'*. Several parents reported that the Phe results gave them *'peace of mind'*. Two parents stated that Phe results were helpful in encouraging dietary compliance.

Some research has documented significant psychological and social challenges to parents in the management of PKU and the attendant struggle to find a balance between strict dietary control and flexible developmental goals for the child (Awiszus and Unger 1990), but this research has not explored how the management of PKU affected family life. When asked to comment on the overall impact of PKU on the quality of their lives, Utah parents expressed varying degrees of adjustment to living with PKU, with responses ranging from *'[it is] hell'* and *'it's a mess'* to *'positive'*. The two major sources of stress related to food planning/preparation and ramifications of the diet for social life. Difficulties in finding low-protein foods, in finding time to prepare different meals for different members of the family and in record keeping were mentioned frequently. Problems encountered in social life included the child's interaction with peers and the planning of family events such as eating out or holidays. While acknowledging the time-consuming nature of PKU management, some caretakers seemed to accept that such management was a necessary and even worthwhile part of their lives that they had integrated into their daily routine. One parent simply stated that they *'haven't let (PKU) affect our quality of life'*. Another parent was *'[now] eating healthier, more organized in planning meals and more empathic with anyone who has a disability or a medical problem'*. Maturation of the patient can have both positive and negative effects on the management of PKU. According to one parent, *'early in life I felt [management] was more difficult—but since [my child] has taken control of the diet herself I see her making wise choices and eating "normally" as a vegetarian'*.

The utility of a new home monitoring technology

It has been suggested that providing rapid feedback with home monitoring of Phe levels would help to maintain metabolic control and increase compliance with the PKU diet (NIH 2001; Peterson et al 1988; Seashore et al 1999; Wappner et al 1999; Wendel and Langenbeck 1996). Although the majority of parents did not consider the current protocol for testing burdensome, there was a nearly uniform perception that a home monitor could make management of the condition easier and more effective. When asked about the relationship between dietary compliance and testing, the majority of caretakers and older children who responded agreed that 'the PKU diet would be followed more carefully if blood Phe levels could be tested regularly at home' (Table 4). In their open-ended comments, the underlying rationale behind these responses was made clear. Parents regarded the prospect of home testing as a tool for more efficient management. They maintained that the primary utility of the monitor resided in the immediacy of feedback, so that Phe levels could be maintained consistently through quick dietary adjustment. Parents also indicated a willingness to pay an average per test of \$7.06 (range = \$0.75–15.00, SD = \$4.37, median \$5.00). One diabetic parent stated that he or she would be willing to pay *'as much as a diabetic'*.

DISCUSSION

Controlling ingestion of Phe is currently the only effective means to successfully manage PKU. The results of a survey of Utah PKU families reported here provide some insights into the multitude of challenges PKU families face in following the recommended low-Phe diet, particularly as patients reach adolescence.

While all Utah PKU families recognized that there were long-term negative consequences of not complying with the diet, it is not clear how detailed their understanding of these consequences was. Although no single factor emerged as dominant, the primary obstacles to successful management of PKU cited by caretakers were time constraints and stress related to preparation of the diet foods, the keeping of records, and the restrictions imposed on social life by PKU. The significant discordance between caretakers and older patients regarding the value and inconvenience of Phe level testing provides insight into the difficulties of PKU management as patients age. Given the multitude of problems, there is no a panacea to the difficulties faced by patients and caretakers in adherence to the diet. Even so, modification of Phe testing technology may have some potential to improve management. Caretakers recognized the test as the principal indicator that dietary adjustment was necessary. About two-thirds of the respondents agreed that a home-monitoring technology would be desirable. The primary attraction of such a monitor would be the timeliness of feedback that permitted the isolation of sources of Phe level changes and immediate remedial action.

These findings were elicited from families in Utah but are likely to be generalizable to the general PKU population. First, the evidence for sample bias within the Utah population is not strong. Secondly, a multivariate analysis of determinants of blood Phe levels of patients in Utah, Nevada and Montana showed that there were no statistically significant differences among the patients across these three states in terms of testing frequency and measured blood Phe levels (Waitzman et al 2004). Finally, the Utah and the AAP national survey samples exhibited certain similarities in terms of the willingness expressed to change current

practices—to adopt a new technology and to adopt more stringent diet or more frequent Phe testing (Wappner et al 1999), respectively—for more effective management of PKU. A larger sample would certainly provide more definitive results, particularly in the case of older patients as the paucity of young adolescents in the sample and their low response rate made findings concerning their views especially tentative.

In many chronic conditions like diabetes, it is increasingly accepted that better self-management requires collaboration between patient and clinician, where the responsibility of daily management of the condition resides with the patient and his or her family while the clinician supplies the necessary expertise and support (Glasgow and Anderson 1999). The expressed willingness and desire of patients and caretakers in Utah to adopt a home monitor to test Phe levels and to take a more active role in the management of PKU fits within this emerging paradigm of a less-hierarchical relationship between the patient and the clinic and a more active role for patients in managing their chronic conditions.

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REFERENCES

Awiszus D, Unger I (1990) Coping with PKU: results of narrative interviews with parents. *Eur J Pediatr* **149**: S45–51.

Fisch RO, Matalon R, Weisberg S, Michals K (1997) Phenylketonuria: current dietary treatment practices in the United States and Canada. *J Am Coll Nutr* **16**: 147–151.

Glasgow RE, Anderson RM (1999) In diabetes care, moving from compliance to adherence is not enough. Something entirely different is needed [letter; comment]. *Diabetes Care* **22**: 2090–2092.

Koch R, Azen CG, Hurst N, Friedman EG, Fishler K (1987) The effects of diet discontinuation in children with phenylketonuria. *Eur J Pediatr* **146**: A12–16.

Koch R, Burton B, Hoganson G, et al (2002) Phenylketonuria in adulthood: a collaborative study. *J Inherit Metab Dis* **25**: 333–346.

Medical Research Council Working Party on Phenylketonuria (1993a) Phenylketonuria due to phenylalanine hydroxylase deficiency: an unfolding story. *BMJ* **306**: 115–119.

Medical Research Council Working Party on Phenylketonuria (1993b) Recommendations on the dietary management of phenylketonuria. *Arch Dis Child* **68**: 426–427.

NIH Consensus Development Panel (2001) National Institutes of Health consensus development conference statement. Phenylketonuria: screening and management, October 16–18, 2000. *Pediatrics* **108**: 972–982.

Peterson K, Slover R, Gass S, Seltzer WK, McCabe LL, McCabe ER (1988) Blood phenylalanine estimation for the patient with phenylketonuria using a portable device. *Biochem Med Metab Biol* **39**: 98–104.

Pietz J, Benninger C, Schmidt H, Scheffner D, Bickel H (1988) Long-term development of intelligence (IQ) and EEG in 34 children with phenylketonuria treated early. *Eur J Pediatr* **147**: 361–367.

Prince AP, McMurray MP, Buist NR (1997) Treatment products and approaches for phenylketonuria: improved palatability and flexibility demonstrate safety, efficacy and acceptance in US clinical trials. *J Inherit Metab Dis* **20**: 486–498.

Ris MD, Williams SE, Hunt MM, Berry HK, Leslie N (1994) Early-treated phenylketonuria: adult neuropsychologic outcome. *J Pediatr* **124**: 388–392.

Rylance G (1989) Outcome of early detected and early treated phenylketonuria patients. *Postgrad Med J* **65**: S7–9.

Seashore MR, Wappner R, Cho S, de la Cruz F (1999) Development of guidelines for treatment of children with phenylketonuria: report of a meeting at the National Institute of Child Health and Human Development held August 15, 1995, National Institutes of Health, Bethesda, Maryland. *Pediatrics* **104**: e67.

Shulman S, Fisch RO, Zempel CE, Gadish O, Chang PN (1991) Children with phenylketonuria: the interface of family and child functioning. *J Dev Behav Pediatr* **12**: 315–321.

Smith I, Beasley MG, Wollf OH, Ades AE (1988) Behavior disturbance in 8-year-old children with early treated phenylketonuria. Report from the MRC/DHSS Phenylketonuria Register. *J Pediatr* **112**: 403–408.

Waitzman NJ, Bilginsoy C, Leonard CO, Ernst S, Prince A (2004) The effect of phenylalanine test frequency on management of phenylketonuria (PKU). University of Utah.

Wappner R, Cho S, Kronmal RA, Schuett V, Seashore MR (1999) Management of phenylketonuria for optimal outcome: a review of guidelines for phenylketonuria management and a report of surveys of parents, patients, and clinic directors. *Pediatrics* **104**: e68.

Weglage J, Funders B, Wilken B, et al (1992) Psychological and social findings in adolescents with phenylketonuria. *Eur J Pediatr* **151**: 522–525.

Wendel U, Langenbeck (1996) Towards self-monitoring and self-treatment in phenylketonuria—way to better diet compliance. *Eur J Pediatr* **155**: S105–107.