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Abstract

Objectives: The analysis was undertaken to investigate the extent to which the frequency of blood tests is associated with control of phenylalanine (Phe) levels among children with phenylketonuria (PKU).
Methods: Multivariate and age-stratified regression analyses were run on Phe test results (N=3,015) from sixty-two sample subjects, aged eight years or younger, treated in four PKU clinics in the intermountain West over the period 1980 to 1995. More detailed regressions were run on the subset of observations (N=1,965) from the thirty-three subjects treated in the Utah clinic.
Results: Each additional week of delay between tests was associated with a 10% reduction (95% CI=0.83-0.98) in the likelihood that a subsequent Phe reading would fall below the recommended upper limit of the recommended range (#6mg/dl). The relationship was most pronounced among sample subjects three years and older (0.86, 95% CI=0.73-1.01) and in the analysis of Utah clinic subjects, which included additional sociodemographic controls (0.83, 95% CI=0.75-0.92).
Conclusions: Since the advent of universal screening for PKU nearly forty years ago, the challenge faced by patients and families as well as by health professionals, has been to improve the daily management of the condition. The significant relationship between Phe test frequency and Phe levels reported in this analysis suggest that opportunities for improvement in the management of PKU may reside with institutional and technological changes in the administration and utilization of the Phe test.

Key Words: Phenylketonuria (PKU), phenylalanine (Phe) test, self-monitoring, hazard analysis.
JEL Classification: I18, I19.

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Background

Phenylketonuria (PKU), an inborn error of metabolism that occurs in about 1 in 15,000 live births in the United States,(1) is associated with elevated blood phenylalanine (Phe) levels that result in progressive neurological impairment and mental retardation when left untreated.(1-3) Universal screening for PKU at birth has been conducted throughout the United States since the early 1960s. Strict adherence to a low phenylalanine diet through special food preparation and supplemental formula prevents the debilitating effects of PKU. Such dietary management, beginning in infancy and continuing throughout life, is central to the current protocol for treating the condition. Strict control of Phe levels is especially critical for pregnant women with PKU because of the serious consequences to the fetus exposed to elevated Phe levels in-utero.(4-7)

The treatment of PKU is complex, requiring collection of blood samples, recording of food intake, maintenance of a highly restrictive diet, and frequent visits to a PKU clinic.(1, 2) Adherence to the recommended diet tends to slacken after early childhood, leading to increased prevalence of blood Phe concentrations that exceed recommended levels.(8, 9) A growing body of evidence has demonstrated progressive decline in intellectual development,(10, 11) neurological problems(11) and behavioral problems associated with elevated Phe levels across the lifespan. The most recent guidelines issued by the Medical Research Council Working Party on PKU(12) and by a National Institutes of Health Consensus Panel(2) therefore state that in order to achieve optimal outcomes, treatment most likely will be required for all individuals with PKU for their entire lifetime.

Part of the current protocols for treating PKU includes frequent periodic testing of Phe levels so as to monitor adherence and to make adjustments to nutritional intake. Such tests require a blood draw during a scheduled visit or a lancet-derived blood sample obtained at home and mailed to the clinic. Results are typically provided to the patient within five to ten days after

the test. More frequent testing and more timely feedback could potentially help patients and their caregivers more effectively monitor and manage their condition,(13, 14) as has been the case with home glucose monitors for those with diabetes.(15)

Variation in frequency of blood Phe measurement reflects differences in clinic recommendations and in individual adherence. A formal analysis of the impact, if any, of this variation in Phe test frequency among the PKU population on management of the condition could provide insight into both the appropriateness of current recommendations as well as the potential for an intervention, such as a home Phe monitor, to improve management. Phe test data on fifty-nine PKU patients from four clinics in the intermountain west from 1980 to 1995 afforded such an analysis.

Methods

Data—Comprehensive records from four PKU clinics in the intermountain west (Montana, Salt Lake City, UT, Reno NV, and Las Vegas, NV) over the period 1980 to 1997 were made available to the researchers. These clinics served the entire population with PKU in Nevada, Utah, and much of the central and eastern region of Montana. The records were originally gathered as part of a multi-center, randomized, controlled clinical trial designed to test the impact of a new dietary regimen on Phe levels.(16) Subjects eligible for that trial included those aged eighteen years and younger with PKU treated in any of the four clinics. Of eighty-four eligible subjects, sixty-nine initially enrolled in the trial, but three withdrew, leaving historic records available on sixty-six subjects.

Information on sex, date of birth, PKU type, Phe test date, and Phe test results were available from these records across clinic sites. Given the literature showing a significant relationship between certain socioeconomic and demographic characteristics and dietary compliance,(8, 17-19) the authors of this study contracted with personnel at the Utah clinic to

provide additional data on income, marital status of parents, number of siblings, and number of siblings with PKU for the thirty-three sample subjects treated in that clinic, so as to afford a more comprehensive analysis of this Utah sub-sample.

Sample--The unit of observation for the empirical analysis was a Phe test, of which 6,506 were taken on the sixty-two sample subjects over the period of study. There were 1,403 observations taken during the randomized control trial between 1996 and 1997 that were excluded from the analysis because of potential distortion on Phe readings generated by the experiment. Separate analyses that included such observations, with additional controls entered for experimental status (prior to/during the experiment, control/experimental group), were not significantly different from the results reported below. Because results from each test generally take a minimum of three days to report, 542 observations followed by an interval of less than three days were deemed unreliable and deleted from the sample. Due to the relatively recent emphasis on control throughout childhood, and research demonstrating that reinstitution of diet after a sustained period of discontinuation is particularly difficult,(20) the sample was further restricted to observations on subjects eight years of age and younger, yielding 4,122 observations on 60 subjects.

In order to assess and minimize the impact of outliers on the analysis, separate specifications incorporated an upper limit on the interval between tests of 14, 30, and 60 days. For the analyses reported below, the sample was restricted to observations on individuals following a maximum thirty-day interval. Results from specifications using fourteen day and sixty-day maximum intervals are not reported, but are discussed below. There were 3,015 such tests (observations) on the fifty-nine eligible subjects within the specified age range at the four clinics between 1980 and 1995, and 1,965 such observations for the thirty-three subjects at the Utah clinic.

Model—Multiple observations on each sample subject presented the possibility that effects uncovered on measured covariates were actually attributable to unidentified characteristics of individuals. Random effects models were run so as to control for such characteristics.

Multivariate logistic regressions were run on the probability that a Phe reading would be 6 mg/dl or less, as 6 mg/dl is currently the upper limit of the recommended range in all clinics. The independent variable of primary interest was the elapsed time measured in fractions of weeks to the nearest day since the subject's previous Phe test. Other covariates incorporated into the four-clinic analyses included the subject's age as of the date of the test (in years to the nearest day); the subject's sex; a cohort variable assessed as the time elapsed (to the nearest day) between September 8, 1980, the date of the first sample test reading, and the date of the test; and PKU type (severe or moderate). It is well established that dietary compliance declines with age. With the growing appreciation for the importance of dietary compliance throughout life, and as the recommendations for compliance have become more strict over time, it was expected that those in the latter part of the analytic period would have more Phe readings within the recommended range than those tested earlier. Those with severe PKU were expected to have more difficulty maintaining Phe levels below the upper limit than those with moderate PKU, although research has suggested that such assessment of severity is unreliable.[(21, 22) Indicator variables for each clinic, with the Utah clinic serving as the referent, were also incorporated in the all-clinic analysis to capture differences in Phe test results arising from clinic-specific policies or from other unspecified characteristics associated with individual clinics.

Additional covariates incorporated in the Utah-clinic specific analysis included marital status of parents (married, not married), the number of children residing in the household, the number of PKU siblings, and a measure of household income (less than 150%, 150-300%,

greater than 300% of the poverty). Each of these characteristics was assigned based on patient records taken as close as possible to the date of each observation. Subjects residing in two-parent households and in households with higher incomes were expected to have higher probabilities of test readings within the recommended range, given the relationship of SES to Phe level (17-19). The presence of other children in the household, however, was expected to reduce the probability of compliance as additional children tend to dilute the amount of resources, both time and material, available to devote to management of the condition. A similar expectation was formed with respect to the presence of other PKU siblings, although this expectation was subject to some ambiguity since the presence of other siblings with PKU might engender greater dedication, and perhaps some economies of scale, at the household level in managing the condition.

Results

Summary characteristics are provided separately for sample subjects (upper panel) and for sample observations (lower panel) in Table 1. Characteristics for the entire (four-clinic) sample, broken down by age group, are provided in the first three columns, while the same breakdown for the Utah-only clinic sample is provided in the final three columns. Thirty-three of fifty-nine subjects (55.9 %) were treated by the Utah clinic and nearly two-thirds of the 3,015 total test observations (65.1%) were generated from those subjects. In the group aged two years and younger, observations were provided from fifty-six of fifty-nine subjects in the all-clinic sample (column 2) and from all thirty-three subjects in the Utah sample (column 5). Approximately two-thirds of subjects in each sample also generated observations between the ages of three and eight years (columns 3 and 6) during the period of observation. The proportion of all test observations on children aged three to eight years taken at the Utah clinic (50.7%) was distinctly lower than the proportion taken at that clinic across all ages (65.1%). This lower

proportion reflected both a longer average interval between testing (2.7 versus 2.3 weeks) and fewer average years contributed by the older group (8.0 versus 9.2 years) at the Utah clinic relative to the all-clinic average. Utah subjects were also more likely to be diagnosed with "severe" PKU (84.8%) than were subjects from the all-clinic sample (72.9%).

Only 58.8% and 55.6% of Phe test results from the all-clinic and the Utah clinic samples, respectively, fell below the recommended upper Phe limit (<7 mg/dl), reflecting a high degree of unsuccessful management of the condition. The percentage of tests falling below the upper limit was smaller among the older group (50.7%) than among the younger group (61%), in accordance with the literature showing a decline in successful management with age. The average duration between Phe tests was also related to age, with longer average intervals between tests at older ages, reflecting, in part, the formal recommendations for higher test frequency in infancy and early childhood than in later childhood and adulthood. The extent to which the test interval was associated with successful management, independent of age and such recommendations, was tested in the multivariate analyses.

Odds ratios given in Table 2 were generated from multivariate logistic regressions on the probability that a phenylalanine reading was below the upper bound for the recommended range (< 7 mg/dl). The format of Table 2 follows that of Table 1, with results on the four-clinic sample reported in the first three columns and those from the Utah-only sample in the final three columns. Higher test frequency was associated with significantly higher odds of blood phenylalanine concentration falling below the upper limit of the recommended range. Results on subjects eight years old and younger (column 1) indicate that each additional week of delay between Phe tests was associated with a 10% reduction (95% CI=0.83-0.98) in the likelihood that a subsequent reading would fall below the upper recommended limit. The significance of test interval on Phe level was concentrated among those older than two years (column 3), as the

association between test interval and Phe level among those aged two years and younger failed to achieve statistical significance (column 2).

Results from the analysis conducted on the Utah-only sample showed larger effects, within more stringent confidence bands, of test frequency on phenylalanine blood concentration relative to the four-clinic sample. Among those aged three to eight years of age tested at the Utah clinic (column 6), for example, the elapse of each additional week between tests was associated with a 21% (95% CI=0.63-0.99) reduction in the likelihood of a Phe level falling below the upper recommended limit. For this sample, test frequency was also a marginally significant predictor of stricter management of Phe levels among the group aged two years and younger. These Utah-specific results, which were from equations that included controls for the additional socioeconomic and demographic characteristics noted above, were significantly stronger than in specifications excluding such controls (not shown). It is therefore unlikely that results from the all-clinic sample (columns 1-3) were attributable to confounding between test frequency and such excluded socioeconomic and demographic characteristics.

The indicator variable for PKU type was significant in none of the specifications, reinforcing both a concern that has been raised regarding this measure's value as an epidemiological concept(21, 22) and a conclusion that the Utah results were not attributable to its higher proportion of subjects diagnosed with severe PKU. With the exception of the equation run on those aged three to eight years treated in the Utah clinic (column 6), results on the cohort variable showed a significant increase in the odds of Phe levels falling below the upper recommended limit. This improvement in management over time was likely attributable to the increased awareness among health professionals and among patients and their families on the importance, as demonstrated in the most recent literature, of maintaining control of Phe levels beyond early childhood. The upper limit of the recommended Phe level was also reduced at the

Utah clinic from 10 mg/dl to 6mg/dl in 1992, partly in response to that literature. In separate equations that incorporated the higher limit on the dependent variable, results on the cohort variable were unaffected (not shown), suggesting that better management with time was not exclusively attributable to more rigid standards.

Discussion

Based on comprehensive test records from four clinics serving those with PKU in three intermountain west states between 1980 and 1995, this analysis suggests that higher Phe test frequency was associated with a significantly higher probability that Phe levels would fall below the upper limit of the recommended range. Moreover, the relationship between test frequency and Phe levels was most pronounced among older children in the sample, those at greatest risk for non-compliance.

It is possible that the observed relationship between test frequency and Phe level was partly attributable to omitted variable bias, that people who tested more frequently were simply those who were more diligent in managing their condition for other reasons. Such unobserved individual characteristics, however, were controlled for in the utilization of a random effects model. Moreover, the findings in the Utah-only regressions were robust with the introduction of other available socioeconomic and demographic controls, reinforcing the conclusion that the association between test frequency and Phe level was not a spurious one.

The finding that higher test frequency was significantly associated with lower Phe levels was also not driven by outliers, that is, excessively long intervals between tests. Results on sample observations limited to maximum test intervals of thirty days (reported in Table 2) were nearly identical to those from a sample including test intervals up to sixty days (not shown). Moreover, results from sample observations limited to test intervals of fourteen days (not shown) were also similar to those reported in Table 2.

The current recommended range for blood Phe levels includes a lower limit of 2 mg/dl in addition to the upper limit of 6 mg/dl that was exclusively used to specify the dependent variable in the reported results. The lower limit was established because phenylalanine is an amino acid that is essential in small amounts for normal growth and development. In separate analyses (not shown), the incorporation of the recommended *range* (>1 mg/dl, <7 mg/dl) in specifying the dependent variable in lieu of the *upper limit or less* (<7 mg/dl), however, failed to produce significant results with respect to test frequency. In other words, higher test frequency was sufficiently associated with a low blood Phe level of under 2 mg/dl such that the relationship between test frequency and Phe levels in the recommended range was not statistically significant. It is possible that, in order to avoid the well-publicized detrimental effects of elevated Phe associated with the condition, PKU patients and their families err in favor of too strict a low-protein diet.

However, it is also well known that patients often "prepare for the test," that is, restrict their Phe intake in the period immediately prior to a test so as to generate a result within the recommended range. Indeed, results from a survey of PKU families tied to the Utah clinic confirmed that such preparation is common.(23) When such practice translates into dietary deprivation rather than compliance, however, it is likely to produce an excessively low Phe result in the short-term than would consistent compliance with the recommended diet. To the extent that patients engage in such "preparation" for the test, the clinic, as well as patients, are uninformed about the actual extent to which Phe levels deviate from, or conform with, recommendations in daily life. While the test is also acting in these instances to change behavior, it is not necessarily promoting better long-term management of the condition.

All of the reported test results were taken using the Guthrie method. Although the test is more accurate at lower Phe concentrations than at high concentrations, test accuracy is relatively

high within the range of compliance to 20 mg/dl. The dichotomous structure of the dependent variable served to reduce distortions associated with very high readings.

As noted earlier, the recommended upper limits for Phe levels at the Utah clinic were reduced from 10 mg/dl to 6 mg/dl in 1992. To the extent that patients adjust their diet specifically to meet targets, one would expect that test frequency would be associated with Phe levels below 11 mg/dl prior to 1992 and subsequently with Phe levels below 7 mg/dl. The incorporation of such a specification on the dependent variable in our analysis, however, failed to generate significant results on test frequency. These results suggest that test frequency may be a more significant factor in meeting relatively strict guidelines (< 7 mg/dl) than in achieving moderate compliance (< 11 mg/dl).

In certain instances it is likely that the test interval was endogenous, attributable to Phe level. After a test reading above the recommended level, for example, it is not uncommon for clinics to schedule a subsequent test sooner than normal to check that Phe levels were subsequently brought under control. For the Utah sample over age two years, where the recommended testing interval was two to four weeks, the analysis was rerun dropping all tests for which the test interval was one week or less. The findings nearly replicated those reported in the table, suggesting that such reverse causation was not strictly responsible for the uncovered relationship between test frequency and Phe level. Anecdotal evidence from clinicians also suggested that at certain clinics the opposite is the case, that is, test frequency is extended subsequent to a good reading as part of a "reward" system for compliance. To the extent that low readings are responsible for such lengthening of the test interval, our results understate the effect of test frequency on Phe level.

The recommended interval between tests by age group was subject to some inter-clinic variation. While clinic indicator variables were included in our model to adjust for such

variation, the correlation between clinic-specific recommendations and test interval could have confounded our results. Separate regressions were therefore also run with the interval between tests specified as the deviation from clinic recommendations rather than as the actual elapsed time between tests, as reported in Table 2. Results from the alternative specification (not shown) nearly replicated the reported results, reinforcing the conclusion that clinic characteristics were not responsible for the results on test interval. Furthermore, the significant findings on test interval from the Utah-only specifications, for which clinic recommendations were uniform, eliminated such concern about multicollinearity between clinic recommendations and test interval.

In several analyses conducted both in the United States and abroad, the benefits associated with screening programs for PKU at birth have been found to outweigh program and treatment costs.(24-26) These analyses, however, assumed successful management of the condition through strict dietary compliance. This assumption was unrealistic, based in part on the prevailing (incorrect) view at the time that such management would be required through only a limited period of early childhood. While the benefits of maintaining a low phenylalanine diet throughout adulthood are better understood today, it is also well known that compliance with the recommended dietary regimen is not complete at any age and that such compliance generally deteriorates with age. This pattern of non-compliance is clearly evident in the statistics on Phe test results by age reported in Table 1. Facilitating compliance for stricter control is among the major challenges in improving the outcomes for patients with PKU.(2, 27) The findings of this analysis suggest that variation in dietary management of PKU may be due, in part, to variation in frequency of Phe testing. Since part of such variation is attributable to established recommendations, one implication that flows from the analysis is that recommended test intervals be reevaluated to determine the optimal frequency of testing. Indeed, the

recommendation of test frequency by the Medical Research Council, which has been adopted by many of the clinics in the United States, was not based on any formal analysis of the effect of test frequency on Phe management.(28)

The results of the current analysis also suggest, however, that the introduction of other methods of monitoring that permit greater ease and efficiency for testing Phe levels, such as a home monitor, may improve the management of PKU. Of course, the current analysis addressed only the frequency of testing, whereas a home monitor may affect dietary management through other avenues as well. For example, the current delay of several days between Phe test and test result does not permit the patient and the family to make an immediate assessment of the association between dietary intake and Phe level. The value of the test for daily management is therefore not as great as it might be if feedback were more immediate. Indeed, PKU patients and their families have indicated that a home monitor would be valued for the timely feedback it would provide and for the higher level of involvement it would permit in the daily management of the condition.(23)

Since the advent of universal screening for PKU nearly forty years ago, the challenge faced by patients and families as well as by health professionals, has been to improve the daily management of the condition. The significant relationship between Phe test frequency and Phe levels reported in this analysis suggest that opportunities for such improvement may reside with institutional and technological changes in the administration and utilization of the test.

Table 1. Summary statistics by sample and age group

	Four-Clinic Sample			Utah-only Clinic Sample		
	Ages 0-8 years	Ages 0-2 years	Ages 3-8 years	Ages 0-8 years	Ages 0-2 years	Ages 3-8 years
Subjects						
Male (%)	59.3	60.7	60.0	57.6	57.6	65.2
Severe PKU (%)	72.9	75.0	72.5	84.8	84.8	87.0
Las Vegas (%)	15.2	16.1	12.5			
Montana (%)	13.6	10.7	15.0			
Reno (%)	15.2	14.3	15.0			
Utah (%)	55.9	58.9	57.5			
N	59	56	40	33	33	23
Phe Test Statistics						
Phe #6 mg/dl (%)	58.8	61.0	50.7	55.6	57.7	45.0
Weeks since previous test	1.7 (1.1)	1.6 (1.0)	2.3 (1.2)	1.7 (1.1)	1.5 (0.9)	2.7 (1.2)
Age at test (years)	1.8 (1.9)	1.0 (0.8)	5.0 (1.5)	1.6 (1.8)	0.9 (0.7)	5.1 (1.6)
Trend (years)[+]	10.7 (4.1)	12.1 (4.2)	9.2 (3.6)	11.5 (4.0)	11.2 (4.1)	13.1 (3.2)
Male (%)	62.3	64.0	56.4	64.9	63.4	72.5
Severe PKU (%)	77.2	80.8	64.1	90.0	90.3	88.5
No. of children in family				2.4 (1.4)	2.3 (1.4)	2.6 (1.4)
No. of siblings with PKU				0.1 (0.4)	0.1 (0.4)	0.1 (0.3)
Parents married (%)				93.2	92.2	98.2
Income > 150% and < 300% of poverty (%)				46.5	49.2	32.9
Income > 300% of poverty (%)				28.3	25.9	39.9
Las Vegas clinic (%)	6.8	7.5	4.3			
Montana clinic (%)	12.6	10.6	19.6			
Reno clinic (%)	15.5	12.7	25.4			
Utah clinic (%)	65.1	69.2	50.7			
Number of observations	3015	2362	653	1965	1634	331

Note: Entries are sample means unless otherwise noted. Standard deviations are provided in parentheses.

[+]Time elapsed between the current test and the birth date of the oldest sample subject (9/8/80).

Table 2. The effect of test frequency on the odds of a Phenylalanine (Phe) level #6 mg/dl by Sample and Age Group

	Four Clinic Sample						Utah Clinic					
	Ages 0-8		Ages 0-2		Ages 3-8		Ages 0-8		Ages 0-2		Ages 3-8	
	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
Intercept	1.02	0.48-2.19	1.24	0.58-2.67	0.27	0.04-1.71	0.22***	0.07-0.69	0.39	0.11-1.43	0.86	0.03-26.43
Weeks since previous Phe test	0.90**	0.83-0.98	0.96	0.86-1.08	0.86*	0.73-1.01	0.83***	0.75-0.92	0.87*	0.75-1.00	0.79**	0.63-0.99
Age at test (years)	0.81***	0.76-0.87	0.61***	0.52-0.71	0.89	0.75-1.05	0.84***	0.78-0.91	0.68***	0.56-0.83	1.12	0.87-1.43
Trend (years)[+]	1.13***	1.07-1.19	1.12***	1.06-1.18	1.20***	1.05-1.37	1.16***	1.10-1.22	1.15***	1.09-1.21	0.98	0.81-1.19
Male	0.68*	0.45-1.02	0.64**	0.43-0.97	1.21	0.48-3.07	0.69	0.44-1.09	0.66*	0.41-1.08	1.66	0.51-5.42
Severe PKU	0.68	0.41-1.13	0.74	0.44-1.24	0.52	0.17-1.64	0.77	0.38-1.55	0.70	0.34-1.48	5.40	0.57-51.65
No. of children							0.94	0.80-1.12	0.92	0.76-1.11	0.77	0.52-1.16
No. of PKU sibling							1.08	0.61-1.92	1.46	0.72-2.98	0.27	0.06-1.35
Parents Married							3.26***	1.63-6.55	2.86**	1.23-6.68	0.18	0.01-2.67
Income > 150%, < 300% of poverty							1.08	0.71-1.65	0.99	0.60-1.64	3.24	0.70-14.92
Income > 300% poverty							1.72*	0.98-2.99	1.65	0.87-3.16	2.73	0.63-11.82
Las Vegas clinic	0.85	0.44-1.63	1.04	0.55-1.96	0.08**	0.01-0.62						
Montana clinic	0.99	0.53-1.85	1.27	0.66-2.43	0.99	0.29-3.40						
Reno clinic	1.34	0.70-2.59	1.26	0.65-2.45	2.05	0.46-9.14						
N	3015		2362		653		1965		1634		331	

Note: Results are from logistic regression models run for those tests where the testing interval was between three and thirty days.
*, **, and *** indicate statistical significance at the 10, 5, and 1 percent levels, respectively.

[+]Time elapsed between the test and the birth date of the oldest sample subject (9/8/80).

References

1. Wappner R, Cho S, Kronmal RA, Schuett V, Seashore MR. 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 1999;104(6):e68.

2. NIH. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16-18, 2000. In.; 2000.

3. Medical Research Council Working Party on Phenylketonuria. Phenylketonuria due to phenylalanine hydroxylase deficiency: an unfolding story. BMJ 1993;306(6870):115-119.

4. Koch R, Levy H, Hanley W, Matalon R, Rouse B, Trefz F, et al. Outcome implications of the International Maternal Phenylketonuria Study (MPKUCS): 1994. Eur J Pediatr 1996;155(Suppl.1):S162-164.

5. Hanley WB, Koch R, Levy HL, Matalon R, Rouse B, Azen C, et al. The North American Maternal Phenylketonuria Collaborative Study, developmental asessment of the offspring: preliminary report. Eur J Pediatr 1996;155(Suppl.1):S169-172.

6. Michals K, Acosta PB, Austin V, Castiglioni L, Rohr F, Wenz E, et al. Nutrition and reproductive outcome in maternal phenylketonuria. Eur J Pediatr 1996;155(Suppl.1):S165-168.

7. Rouse B, Azen C, Koch R, Matalon R, Hanley W, de la Cruz F, et al. Maternal Phenylketonuria Collaborative Study (MPKUCS) offspring: facial anomalies, malformations, and early neurological sequelae. Am J Med Genet 1997;3(1):89-95.

8. Weglage J, Funders B, Wilken B, Schubert D, Schmidt E, Burgard P, et al. Psychological and social findings in adolescents with phenylketonuria. Eur J Pediatr 1992;151(7):522-5.

9. Fisch RO, Matalon R, Weisberg S, Michals K. Phenylketonuria: Current dietary treatment practices in the United States and Canada. J Am Coll Nutr 1997;16(2):147-151.

10. Azen CG, Koch R, Friedman EG, Berlow S, Coldwell J, Krause W, et al. Intellectual development in 12-year-old children treated for phenylketonuria. Am J Dis Child 1991;145(1):35-39.

11. Koch R, Azen C, Friedman EG, Fishler K, Baumann-Frishling C, Lin T. Care of the adult phenylketonuria. EurJ Pediatr 1996;155(Suppl.1):S90-92.

12. Medical Research Council Working Party on Phenylketonuria. Recommendations on the dietary management of phenylketonuria. Arch Dis Child 1993;68(3):426-7.

13. Wendel U, Langenbeck U. Towards self-monitoring and self-treatment in phenylketonuria--a way to better diet compliance. Eur J Pediatr 1996;155(Suppl 1):S105-7.

14. Peterson K, Slover R, Gass S, Seltzer WK, McCabe LL, McCabe ER. Blood phenylalanine estimation for the patient with phenylketonuria using a portable device. Biochem Med Metab Biol 1988;39(1):98-104.

15. Schiffrin A, Belmonte M. Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. Diabetes Care 1982;5(5):479-84.

16. Prince AP. Palatable varied foods for hyperphenylalaninemia. In.: Department of Health and Human Services Grant Application (RFA-FDA-OP-91-1); 1997.

17. Shulman S, Fisch RO, Zempel CE, Gadish O, Chang PN. Children with phenylketonuria: The interface of family and child functioning. J Dev Behav Pediatr 1991;12(5):315-321.

18. Schmidt H, Burgard P, Pietz J, Rupp A. Intelligence and professional career in young adults treated early for phenylketonuria. Eur J Pediatr 1996;155(Suppl 1):S97-100.

19. Rey F, Abadie V, Plainguet F, Rey J. Long-term follow up of patients with classic phenylketonuria after diet relaxation at 5 years of age. The Paris Study. Eur J Pediatr 1996;155(Suppl 1):S39-44.

20. Schuett VE, Brown ES, Michals K. Reinstitution of diet therapy in PKU patients from twenty-two US clinics. Am J Public Health 1985;75(1):39-42.

21. Kayaalp E, Treacy E, Waters PJ, Byck S, Nowacki P, Scriver CR. Human phenylalanine hydroxylase mutations and hyperphenylalaninemia phenotypes: a metanalysis of genotype-phenotype correlations. Am J Hum Genet 1997;61(6):1309-1317.

22. Guldberg P, Rey F, Zschocke J, Romano V, Francois B, Michiels L, et al. A European multicenter study of phenylalanine hydroxylase deficiency: classification of 105 mutations and a general system genotype-based prediction of metabolic phenotype. Am J Human Genet 1998;63(1):71-79.

23. Bilginsoy C, Waitzman N, Leonard CO, Ernst SL. Living with phenylketonuria: Perspectives of patients and their families. University of Utah; 2001.

24. Alm J, Larsson A, Rosenqvist V. Health economic analysis of the Swedish neonatal metabolic screening programme. Med Decis Making 1982;2(1):33-45.

25. Barden S, Kessel R, Schuett VE. The costs and benefits of screening for PKU in Wisconsin. Social Biology 1984;31(1-2):1-17.

26. Dhont JL, Farriaux JP, Sailly JC, Lebrun T. Economic evaluation of cost-benefit ratio of neonatal screening procedure for phenylketonuria and hypothyroidism. J Inher Metab Dis 1991;14(4):633-639.

27. Seashore MR, Wappner R, Cho S, de la Cruz F. 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 1999;104(6):e67.

28. Smith I. (Medical Research Council Working Party on Phenylketonuria; contact) Personal communication. May 6, 1999.