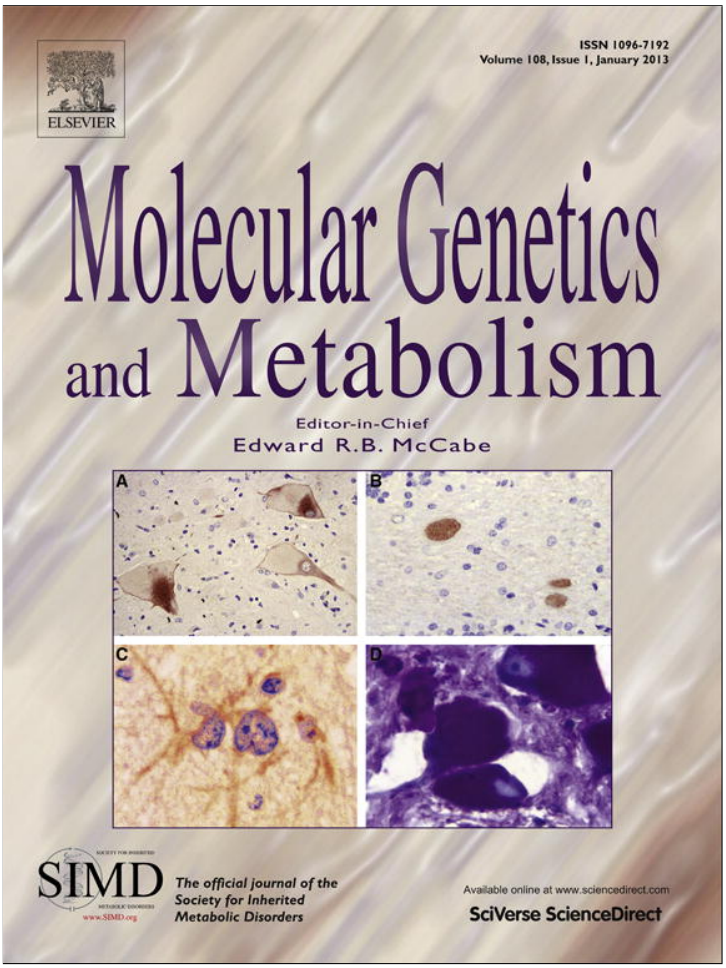

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A diversified approach for PKU treatment: Routine screening yields high incidence of psychiatric distress in phenylketonuria clinics

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ABSTRACT

Objectives: Individuals with phenylketonuria (PKU) treated early and continuously are reported to have psychiatric and executive function impairments. The feasibility of screening for psychiatric distress and executive function impairment in individuals with PKU was tested in 3 separate clinics in North America.
Methods: Individuals were offered screening for psychiatric distress using the Pediatric Symptom Checklist, the PSC–Youth Report or the Brief Symptom Inventory and executive function impairment using the Behavior Rating Inventory of Executive Function. Gender, age and blood phenylalanine (Phe) concentrations obtained most recently and during the 2 years prior to screening were assessed.
Results: More than 90% of patients with PKU accepted the screening for psychiatric distress during their routine clinic visit. The screening took 15–20 min. 32% of patients screened positive for psychiatric distress and 19% for executive function impairment. More individuals >18 years screened positive for psychiatric distress while a similar number screened positive for executive function impairment across age groups. Lower blood Phe levels correlated with negative screening for psychiatric distress. Patients positive for psychiatric distress had higher ($p = 0.009$) median and most recent blood Phe values ($p = 0.05$).
Discussion/conclusions: Routine screening for psychiatric distress of patients with phenylketonuria could be easily implemented in current clinic structures. High incidences of positive screens reinforce the need for regular psychiatric assessments of individuals with PKU. Identification and referral to local mental health providers might help to improve the standard of care for individuals with PKU.

1. Introduction

Phenylketonuria (PKU, OMIM 261600) is a rare autosomal recessive metabolic disorder affecting approximately 1:15,000 live births in the United States (U.S.) [1]. PKU results from impaired conversion of phenylalanine (Phe) to tyrosine due to deficient phenylalanine hydroxylase (PAH) activity [2]. If untreated, toxic accumulation of Phe results in severe neurocognitive and neuromotor impairments [3]. With newborn screening for PKU, patients with PKU are identified and treated from birth with a Phe-restricted diet, eliminating the most severe manifestations of the disorder. However, even those individuals with PKU treated early and continuously with a Phe-restricted diet are reported to have more subtle attention and processing speed deficits [4], behavioral and emotional problems [5,6], psychiatric disorders [7] and cognitive deficits [7]. These impairments may be associated with minor elevations in Phe levels [8,9] and Phe fluctuations [8,9] and may go unrecognized even in those patients regularly attending their appointments at a PKU metabolic clinic.

The typical structure of most PKU metabolic clinics includes a physician, usually a geneticist, and dietitian, and possibly a nurse, social worker and genetic counselor. Clinic staffs do not typically include psychologists or psychiatrists, in most cases due to funding limitations, and some do not have a social worker. Without access to on-site mental healthcare professionals, integrating psychiatric screening into the standard of care for patients with PKU can be a challenge. Clinics have limited time and resources for psychiatric screening, and reimbursement for additional services may be difficult to obtain. In a recent survey of metabolic clinics in the United States, only 15% of metabolic clinics reported routinely screening for psychiatric symptoms of distress such as depression, anxiety and phobias, which are more prevalent in adults but have also been reported in children and adolescents, and executive function impairments

Abbreviations: ADAPT, "A Diversified Approach for PKU Treatment"; BRIEF, Behavior Rating Inventory of Executive Function; BSI, Brief Symptom Inventory; PSC, Pediatric Symptom Checklist; PSC-Y, Pediatric Symptom Checklist Youth Report.

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despite 56% of clinics reporting that patients' cognitive deficits may be impacting their ability to obtain regular medical care [10]. A lack of validated assessments to accurately identify symptoms in individuals with PKU is an additional barrier, with clinics believing that these assessments would require administration by a mental healthcare specialist for accurate assessment of psychiatric distress or executive function impairment.

With psychiatric distress and executive function impairment frequently reported in the literature for PKU [4–10], the metabolic clinics of the Ann and Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital, CMH) in Chicago, Illinois, the University of Utah (Utah) in Salt Lake City, Utah, and Johns Hopkins Hospital in Baltimore, Maryland, sought to determine the feasibility of screening for psychiatric distress and executive function impairment in individuals with PKU. As the three clinics have different team structures, ensuring appropriate representation of the different metabolic clinic staff structures encountered in the United States, and processes for managing their PKU patients (Table 1), the program had to be easily integrated into varying clinic structures with limited time available to do this screening by the clinic team. The results would need to be interpreted by the PKU clinic staff that did not have daily access to a psychologist or psychiatrist to assist in the interpretation.

A Diversified Approach for PKU Treatment (ADAPT) is a mental health screening study that aimed to: determine the rate and symptom profile of psychiatric distress and executive function impairment in children and adults with PKU; identify the barriers and challenges of integrating psychiatric care into the management of individuals with PKU; and develop solutions to the need for integrated mental healthcare in the current metabolic clinic structure. ADAPT was implemented by the three clinics, each with slightly different implementation processes.

2. Methods

Slightly different procedures were implemented between clinics due to institutional requirements and to differing team structures established for the ADAPT program (Table 2).

Screening was offered by the medical clinic coordinators and implemented by the clinic social worker or genetic counselor during the patient's regular clinic visit. Gender, age, type of insurance and number of siblings were recorded. Most recent Phe concentrations were taken at random time points varying from the day of and up to several months before the psychological assessments, and at CMH and Utah, blood Phe concentrations collected during the ≥2 years prior to when the screenings were done were also included for analysis. When results were positive for psychiatric distress and/or executive function impairments, patients were referred to a mental healthcare professional for further evaluation. Clinics later followed up to determine if those patients who had been referred made an appointment with a mental healthcare professional.

Symptoms of psychiatric distress, including somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism, were assessed. The Pediatric Symptom Checklist (PSC), the PSC–Youth Report (PSC-Y) or the Brief Symptom Inventory (BSI) was completed by either the patient or the parent/guardian of the patient. For patients 5–17 years of age, the Pediatric Symptom Checklist (PSC), a 35-item self-report checklist, was completed by the parent or guardian. Cut off scores for positive screens were based on established guidelines. A positive screen on the PSC was determined by a cut off of ≥24 for children 5 years of age or younger and ≥28 for children ≥6 years. At CMH and Utah, patients 11–17 years of age completed the Pediatric Symptom Checklist–Youth Report (PSC-Y), a 35-item self-report checklist with positive screen being determined by a cut off of ≥30. The BSI was used for patients ≥18 years of age, or 17 year old patients at the discretion of the clinic. The BSI is a 53-item self-report checklist for patients. A positive screen was determined by the global severity index (GSI) T-score of ≥63 and/or T-scores of two or more symptom domains ≥63.

Executive function impairment was measured by the Behavior Rating Inventory of Executive Function (BRIEF) for children, adolescents and adults. For patients <18 years, parents were asked to complete the BRIEF–Parent Form. Children and adolescents age 11–18 were asked to complete the BRIEF-Self Report form. Patients ≥18 years were asked to complete the BRIEF Self Report for Adults (BRIEF-A). A child/parent/spouse/sibling or another person familiar with a patient ≥18 years was asked to complete the BRIEF-A Informant Report Form. When the informant-reported result differed from the self-reported result, the informant-reported result was used to identify the patient as having either a positive or negative screen for symptoms of executive function impairment.

Measures of executive function included working memory, planning, attention, and impulse control. Self-monitoring for the child version includes 86 items while the adult version has 75 items and requires 5th grade reading level to complete. These assessments are widely used, with extensive population-based norms based on age and gender and involve three validity scales on the adult version (negativity, infrequency and inconsistency) and two validity scales on the parent report version (negativity and inconsistency), 3 global scales and 8 clinical scales. Summary scores of Behavioral Regulation Index (BRI), Metacognition Index (MI) and Global Executive Composite (GEC) are positive with a T-score ≥65. This was selected as indicative of a positive screen a priori as a mean score of 50 is expected in the general population, with a score of 65 being 1.5 SD above the mean and a score of 70 being two SD above the mean. Individual scale scores for inhibit, shift, emotional control, initiation, working memory, plan/organize, organization of materials and monitor are considered positive with a T-score ≥70 [11].

Group data were analyzed for skewness and normality using Shapiro–Wilk test and summarized accordingly. Rank sum test was used to compare recent Phe levels between patients screening positive and negative for psychiatric distress.

3. Results

Patients with PKU were evaluated during their routine visits at the metabolic clinic. Psychometric screening required approximately

Table 1
Structure of the ADAPT clinics. The three ADAPT clinics have different team structures and processes for managing their PKU patients.

Patient information	CMH[a]	Utah[b]	Johns Hopkins
Clinic structure	– Attending physicians dietitians genetic counselor – Medical office coordinator – Access to social worker	– Attending physicians dietitians genetic counselor – Medical office coordinator – Limited access to social worker	– Attending physicians dietitians genetic counselor – Medical office coordinator – Limited access to social worker
On-site access to mental healthcare professional	Yes	Yes	No
Approximate number of PKU patients:			
– At the clinic N	170	160	90
–Visits N	38 monthly	12 monthly	~10 quarterly
– Visits per year N	456	153	~75

[a] Children's Memorial Hospital.
[b] University of Utah.

Table 2
Slightly different processes undertaken by each metabolic clinic during the ADAPT program.

CMH	Utah	Johns Hopkins
• Approval was obtained from the Institutional Review Board (IRB) to do a retrospective chart review to assess blood Phe levels • A waiver of consent was received so patient consent was not required • Letters were sent to all patients ≥5 years of age announcing integration of mental health screening into regular patient care • All patients ≥5 years of age were offered screening for psychiatric distress and executive function impairment during regular clinic visits • Patients who screened positive were referred to an on-site mental healthcare specialist	• Permission was obtained from the Institutional Review Board for a retrospective chart review to assess blood Phe levels • A waiver of consent was received and so patient consent was not required • On-site mental healthcare professional • Letters were sent to all patients announcing the program • All patients were screened for psychiatric distress • Patients were not screened for executive function impairment • Patients who screened positive were referred to the on-site mental healthcare specialist	• Retrospective blood Phe levels were not assessed • A waiver of consent was received so patient consent was not required. • Letters were sent to all patients announcing integration of mental health screening intro regular patient care • All patients with PKU or hyperPhe were offered screening for psychiatric distress and executive function impairment simultaneously • Patients who screened positive were referred to a mental health specialist

15–20 min to complete. Of patients offered screening during their regular clinic visit, 97% and 92% accepted at CMH and Utah, respectively, with the largest proportion accepting in the ≥18 years group. Gender was fairly evenly distributed with 42% male. The mean age of 14 years is reflective of age groups most likely to be followed in clinic. 32% screened positive for psychiatric distress and 19% for executive function impairment. A greater proportion of individuals ≥18 years screened positive for psychiatric distress as compared to younger individuals (Fig. 1). By contrast, similar proportions of patients with PKU screened positive for executive function impairment in all age groups (Fig. 2).

Patients who screened positive for psychiatric distress were referred to a mental health provider and the majority of patients with PKU accepted the referral (Table 3). However, only a minority of these patients eventually scheduled an appointment with a mental healthcare professional (Table 3).

Mean blood Phe levels were provided by all clinics and historical blood Phe levels were provided by two (CMH and Utah). There was a significant correlation between most recent blood Phe level and age across all subjects, regardless of positive or negative psychiatric screening (Fig. 3). Individuals with PKU who screened negative for psychiatric distress had significantly lower blood Phe levels (median and most recent level) than those who screened positive (Fig. 4).

4. Discussion

The ADAPT protocol was aimed at integrating screening for psychiatric distress and executive functioning impairment into metabolic clinics without impeding regular clinic flow or requiring an on-site psychologist or psychiatrist. Two tools were used to screen for psychiatric distress: PSC and BSI, both of which are self- or parent-report checklists rather than clinician-administered checklists, decreasing the time required by the clinic team for assessments. The BRIEF, used to evaluate executive function impairment, includes self- and informant-reports. The PSC is available online free of charge, while the BSI and BRIEF are available online at minimal cost to the clinic. Although these assessments are not diagnostic, each is readily available and results are consistent in revealing the presence of the symptoms of psychiatric distress, ensuring ease of use in an outpatient setting. These instruments used were selected based on ease of completion, scoring availability and evidence of validation in the non-PKU population.

The norms for general outpatient medical patients were used as the assessments are not validated for the PKU population. On average, approximately 10% of the adult general population would have a positive screen for psychiatric distress based on a T-score of ≥63 [12,13]. In the ADAPT program, 53% of the adult individuals with PKU assessed screened positive for psychiatric distress (Table 3). Among the <18 years group, 17% of individuals with PKU screened positive with the PSC, whereas the national average for unaffected individuals <18 years is approximately 13%, ranging from 5% to 20% and varying by socioeconomic and demographic factors [14]. While it's likely that psychiatric symptoms are more common in adults with PKU than in the children, the different screening tools used for children/adolescents when compared to the adult age groups could also contribute to the discrepancy in these results. In addition, individuals younger than 18 years are more likely to visit the metabolic clinic routinely when compared to older individuals. Prolonged high blood Phe concentrations [8,15–18] and fluctuating blood Phe levels [8,19] have been correlated with positive screening for psychiatric distress and neurocognitive

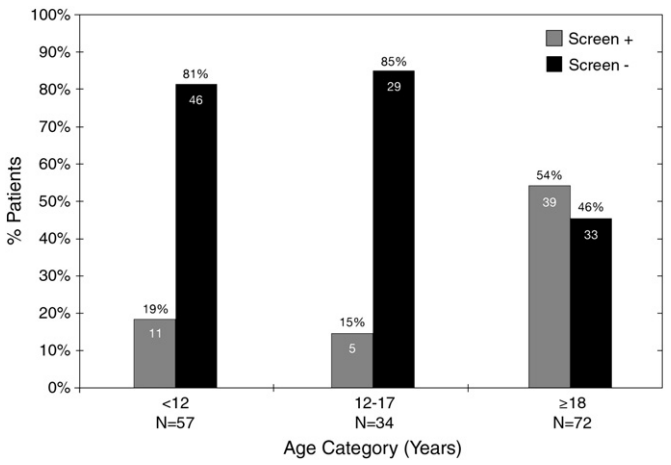

Fig. 1. Psychiatric screening results by age category for CMH, Utah and Johns Hopkins.

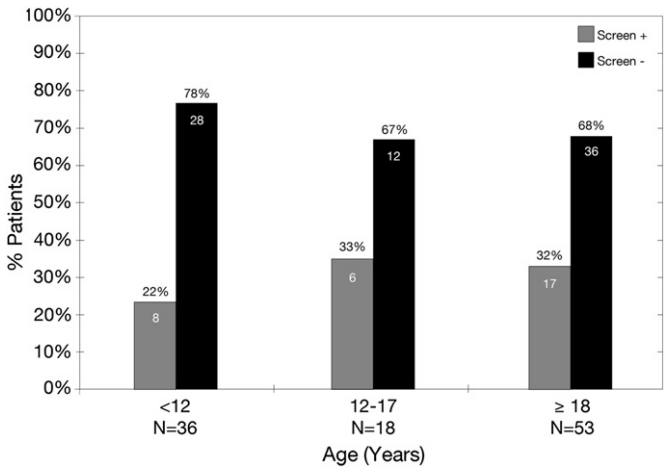

Fig. 2. Executive function screening results by age at CMH and Johns Hopkins.

Table 3
Results of the adapt program providing insight into psychiatric and executive function implications of PKU.

Patient information	CMH[a]	Utah[b]	Johns Hopkins	All sites
Offered screening N	92	65	n/a	157
Accepted screening N (%)	89 (97%)	60 (92%)	18 (n/a)	167
– <12 years N (%)	33 (37%)	22 (37%)	3 (17%)	58 (35%)
– 12–17 years N (%)	14 (16%)	19 (32%)	4 (22%)	37 (22%)
– ≥18 years N (%)	42 (47%)	19 (32%)	11 (61%)	72 (43%)
Gender–male N (%)	41 (46%)	22 (37%)	7 (39%)	70 (42%)
Age in years median (range)	17 (5–38)	14 (5–49)	23 (4–52)	15 (4–52)
Total positive screens for psychiatric distress and/or executive functioning deficit N (%)	31 (35%)	18 (30%)[c]	9 (50%)	58 (35%)
Positive for psychiatric distress N (%)	26 (29%)	19 (32%)	9 (50%)	54 (32%)
– <12 years N (% of age category screened)	6 (18%)	3 (14%)	2 (67%)	11 (19%)
– 12–17 years N (% of age category screened)	2 (14%)	3(16%)	0 (0%)	5 (14%)
– ≥18 years N (% of age category screened)	18 (43%)[d]	13 (68%)	7 (64%)	38 (53%)
Positive for executive functioning deficit N (%)	27 (30%)	n/a	4 (22%)	31 (19%)
– <12 years N (% of age category screened)	8 (24%)	n/a	0 (0%)	8 (14%)
– 12–17 years N (% of age category screened)	6 (42%)	n/a	0 (0%)	6 (16%)
– ≥18 years N (% of age category screened)	13 (31%)	n/a	4 (36%)	17 (24%)
Positive for psychiatric distress and executive functioning deficit N (% of screened)	20 (22%)	n/a	4 (22%)	20 (12%)
– <12 years N (% of age category screened)	6 (18%)	n/a	0 (0%)	6 (10%)
– 12–17 years N (% of age category screened)	2 (14%)	n/a	0 (0%)	2 (5%)
– ≥18 years N (% of age category screened)	12 (29%)	n/a	4 (36%)	16 (22%)
Accepted referral N (% of positive screens)	22 (71%)	16 (89%)	8 (89%)	46 (79%)
Scheduled appointment with mental HCP N (% of positive screens)	6 (19%)	9 (50%)	6 (67%)	21 (36%)

[a] Children's Memorial Hospital.
[b] University of Utah.
[c] These results represent psychiatric distress only as the University of Utah did not screen for cognitive deficits.
[d] Two 17 year old individuals with PKU were screened using the BSI as the clinics felt it to be a more appropriate assessment than the PSC for these individuals. One of the 17 year old patients screened positive and one negative for psychiatric distress.

impairment, which may also contribute to the larger percentage of adults with PKU screening positive in the ADAPT program and the higher mean and median blood Phe levels founds in the group with positive screens (Fig. 4).

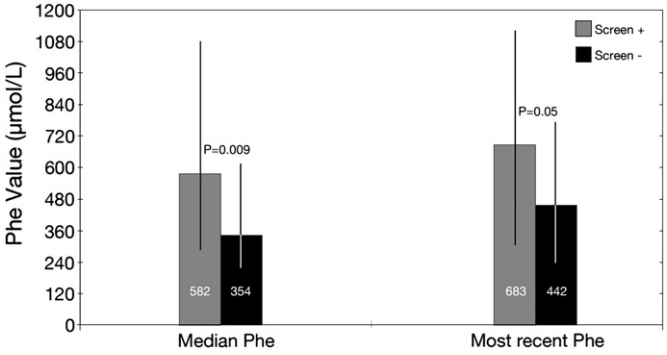

Fig. 4. Median and most recent Phe values by psychiatric screen results for CMH and Utah and mean blood Phe values from Johns Hopkins. Median blood Phe values were not available from Johns Hopkins.

Of those screened for executive function impairment, 29% overall were positive for impairment (Table 2), with a rate of 22% among children ≤12 years. This is consistent with Anderson et al. who also used the BRIEF and found that 21% of children with early treated PKU screened positive for executive function impairment whereas 18% of children with early treated hydrocephalus and 5% of an unaffected control group had similar degrees of dysfunction.

Although frequently reported in individuals with PKU [4–7,9,20,21], evaluating for executive function impairment in the regular PKU clinic appointment proved challenging due to the additional and more time consuming assessment required, as well as the need for special training or a mental healthcare professional to accurately evaluate the results of a positive screen. However, most of those who screened positive for psychiatric distress at CMH and Johns Hopkins also had a positive screen for symptoms of executive function impairment (Table 3). There was only one adult patient with a positive screen for executive function and negative screen for psychiatric distress; the remaining 6 patients were pediatric. This finding suggests that the PSC tool may not be sensitive enough to capture the psychiatric issues leading to executive function impairment, or that it is important to screen children for executive function impairment. The data reinforce the hypothesis that psychiatric distress and executive function impairment may be inter-related [11], particularly in adult subjects. However, as the tools used are not diagnostic and data are not available regarding the number of patients with an eventual diagnosis of a psychiatric disorder or disorder of executive function, conclusions about the relationship cannot be drawn. Therefore if screening for executive function impairment is not possible within the metabolic clinic, psychiatric screening should be performed and any resulting referral to a mental healthcare

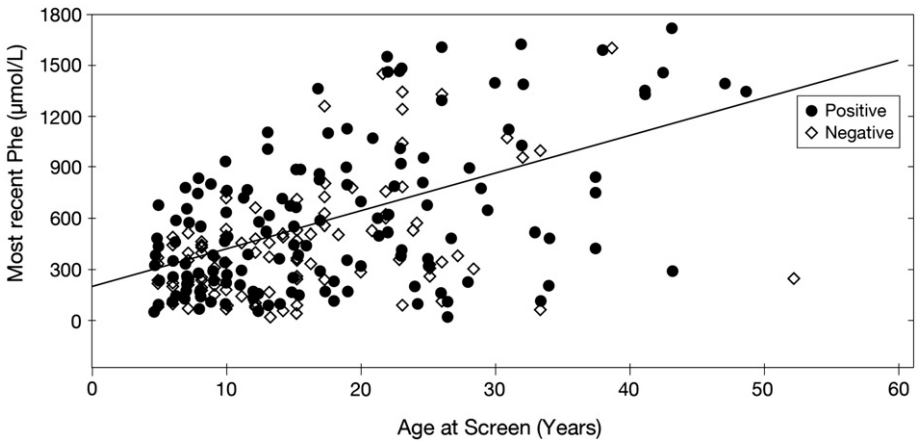

Fig. 3. Most recent Phe value at time of screening by age of all individuals screened.

professional due to a positive screen for psychiatric distress should also include a request for appropriate executive function evaluation. However, if the pattern demonstrated at CMH and Johns Hopkins is reflective of patients attending US PKU clinics, excluding the executive functioning tool from regular mental health screening could result in missing 7% of individuals with executive function impairment.

During the ADAPT program, several patients who screened positive had difficulty accessing mental healthcare professionals. Patients have been reported to "not care" [10], perhaps perceiving the psychiatric symptoms as not causing a level of functional impairment significant enough to pursue mental healthcare support. There are a limited number of mental healthcare professionals with experience supporting the special requirements of patients with PKU, yet patient follow-up was low even in metabolic clinics with on-staff mental healthcare professionals.

Cost was prohibitive for some due to lack of insurance or unaffordable co-payments and deductibles, consistent with reports in the literature [10]. As well, scheduling conflicts between mental healthcare business hours and patients' work hours were encountered, as was the stigma associated with receiving mental healthcare services. Other clinics have also cited the lack of transportation and poor experiences with mental healthcare professionals for patients failing to follow through with a mental healthcare referral [10]. Despite the challenges, the information gained from the neurocognitive and psychological assessments conducted during the ADAPT program provides insights into areas in which improvement is needed for the management of individuals with PKU.

5. Conclusion

The ADAPT protocol has been proven effective for assessing the psychiatric distress and executive function impairment frequently reported in individuals with PKU. The psychiatric distress assessment tools are easily implemented in current, differing metabolic clinic structures. The high incidence of positive screens for psychiatric distress and executive function impairment in this population reinforces the need for regular, ongoing assessments of individuals with PKU, especially for those with the highest or most variable blood Phe levels who may be at the greatest risk for impairment. However, difficulties are still encountered for individuals with PKU accessing mental healthcare services. Regular screening for psychiatric distress and executive function impairment is necessary to identify those individuals with PKU who are suffering from these impairments before the impairment significantly interferes with the individual's functioning and self-care. Establishing local protocols for navigating the mental health system across the various third party payer systems to identify accessible providers with strong clinical skills may be a tedious but necessary task to improve the standard of care for individuals with PKU.

Conflicts of interest

Barbara K. Burton, MD, Nicola Longo, MD, and Deborah Bilder, MD, have received research funding and consulting fees from BioMarin Pharmaceutical Inc. Lauren Leviton and Hazel Vespa received consulting fees from BioMarin Pharmaceutical Inc.

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