



## The financial and time burden associated with phenylketonuria treatment in the United States



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### ABSTRACT

**Background:** Phenylketonuria (PKU) imposes a substantial burden on people living with the condition and their families. However, little is known about the time cost and financial burden of having PKU or caring for a child with the condition.

**Methods and findings:** Primary data were collected with a detailed cost and utilization survey. Primary outcomes included utilization and out-of-pocket costs of medical services, medical formula, and prescribed low-protein food consumption, as well as the time and perceived effort involved in following the PKU diet. Respondents were people living with PKU or parents of children with PKU identified through a state newborn screening program database. Secondary administrative claims data were also used to calculate mean total, insurer, and out-of-pocket payments in inpatient, outpatient (office visits, emergency room, and laboratory tests), and pharmacy settings for privately insured persons with PKU. Payments were calculated for sapropterin and for PKU formula.

In primary data analysis (children  $n = 32$ , adults  $n = 52$ ), annual out-of-pocket costs were highest for low-protein foods (child = \$1651; adult = \$967) compared with other categories of care. The time burden of PKU care was high; families reported spending more than 300 h per year shopping for and preparing special diet foods.

In secondary data analysis, children 12–17 years old had the highest average medical expenditures (\$54,147;  $n = 140$ ) compared to children 0–11 years old (\$19,057;  $n = 396$ ) and adults 18 years and older (\$40,705;  $n = 454$ ). Medication costs were the largest contributor to medical costs, accounting for 61–81% of total costs across age groups. Sapropterin was the largest driver of medication costs, accounting for 85% of child medication costs and 92% of adult medication costs.

**Conclusion:** Treatment for PKU incurs a substantial time and cost burden on persons with PKU and their families. Estimated medical expenditures using claims data varied by age group, but sapropterin represented the largest cost for PKU treatment from a payer perspective across age groups.

### 1. Introduction

Phenylketonuria (PKU, OMIM 212600) is an autosomal recessive inherited disorder of amino acid metabolism, with an estimated incidence in the United States of 5.3 to 7.4 in 100,000 [1–3]. It is caused by mutations in the phenylalanine hydroxylase (PAH) gene. The body's inability to metabolize the amino acid, phenylalanine, leads to a damaging excess of phenylalanine in the body [2]. If untreated, PKU can

lead to severe intellectual disability and seizures [4]. Even slightly suboptimal phenylalanine levels can result in subtle neurocognitive deficits, such as slower information processing and memory impairments [2].

PKU treatment for life consists primarily of a strict low phenylalanine diet, including consuming medical formula that is low in phenylalanine while providing adequate amounts of other essential amino acids. As persons with PKU age, they typically replace some medical

**Abbreviations:** HPA, hyperphenylalaninemia; PKU, phenylketonuria

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formula with low protein foods, such as fruits, some vegetables, specially formulated low-protein products, and imitation dairy products [5]. Adherence to this restrictive diet can be difficult as specialty low-protein products are often expensive or difficult to obtain and require extra time to prepare. In addition, many people find the limited diet to be unpalatable and socially isolating [6,7]. Due in part to these challenges, many persons with PKU are not fully adherent to the recommended diet [8].

A newer treatment option is sapropterin dihydrochloride or tetrahydrobiopterin (BH4). Approved by the U.S. Food and Drug Administration in 2007 for people with PKU as well as those with non-PKU hyperphenylalaninemia (HPA), sapropterin is an oral medication that helps improve phenylalanine concentrations in a subset of patients with BH4-responsive PKU (20–44% in clinical trials), allowing some individuals to liberalize their diets [9]. However, the drug therapy is expensive and patient response, in terms of metabolic control, is variable [10,11]. Those with mild PKU or non-PKU HPA are more responsive to BH4 (24%–100% response rate) than those with more severe PKU (10%–40% response rate) [9,12,13].

In addition to diet and, in some cases, medications, United States clinical experts recommend that persons with PKU monitor their blood concentrations of amino acids to insure they remain in the optimal range and regularly attend a metabolic clinic [5]. The burden of having PKU or caring for a child with the condition in terms of time requirements and out-of-pocket spending has not been quantified. The objectives of this study were to identify out-of-pocket costs, time costs, and resource utilization from the family and payer perspectives associated with dietary and medical treatments for PKU to better quantify the economic burden of disease management.

## 2. Methods

This study used primary survey data from persons with PKU (or caregivers for children with PKU) and secondary data from a large administrative claims dataset to estimate costs and resource utilization from the family and payer perspectives.

### 2.1. Primary data

#### 2.1.1. Survey development

A cost and utilization survey was developed to measure out-of-pocket costs, time costs, and resource utilization associated with the dietary and medical treatments for PKU. The instrument was based on pre-existing questionnaires used in other conditions and was pilot-tested in the target population ( $n = 10$ ). The instrument included questions on utilization and out-of-pocket costs of medical services, medical formula, and prescribed low-protein food consumption, as well as the time required and perceived effort involved in following the PKU diet. Instrument sections and a summary of their content are included in the appendix (Table A1). The survey instrument and study procedures were approved by the University of Michigan and Michigan Department of Health and Human Services Institutional Review Boards.

#### 2.1.2. Survey distribution

Survey participants were persons with either PKU or non-PKU HPA, or the parents of children with PKU, who had been identified through Michigan's Newborn Screening Program. A total of 499 individuals were mailed a paper survey by the Michigan Department of Health and Human Services in October 2014 and a subsequent follow-up mailing took place in November 2014. Eighty-five surveys were undeliverable, resulting in a total eligible sample size of 414 respondents. One hundred fourteen completed surveys were returned ( $N = 47$  child;  $N = 67$  adult) for an overall response rate of 28%. Results for the subset of respondents with PKU are presented here (32 children and 52 adults). The survey took approximately 60 min to complete and respondents received a \$50 debit card for their participation.

### 2.1.3. Analysis

Descriptive statistics were reported for primary outcomes: number and type of medical visits (annual), travel time, total visit time, and out-of-pocket costs (e.g., co-pays, parking) associated with each medical visit, and time costs. Time costs associated with medical visits were estimated by multiplying the number of visits per year by total time per visit and by the 2018 US average hourly earnings [14]. The number of primary care provider visits were calculated by subtracting the reported number of primary care visits by the recommended number of well visits by age [15]. Total costs for medical visits were calculated by summing time costs and out-of-pocket costs. 95% confidence intervals were generated by bootstrapping using STATA 12.

Primary outcomes included utilization of medical formula, low protein foods, and sapropterin. At the time the survey was conducted, the cost of medical formula for children, and some adults, was covered by the state and, therefore, many families incurred no out-of-pocket costs for formula. Medical formula prices were obtained from price lists available from regional metabolic clinics. Low protein food prices were obtained from online retailers. Formula and food prices and out-of-pocket expenses were inflated to 2018 US\$ using the Consumer Price Index. The price of sapropterin was obtained from the Redbook Average Wholesale Price [16].

Time costs of shopping for and preparing a PKU diet were calculated by summing the reported time spent shopping for the special diet and time spent preparing the special diet multiplied by US average hourly earnings [14].

## 2.2. Secondary data

### 2.2.1. Administrative claims data

We analyzed administrative claims data from the IBM MarketScan® Commercial Research Databases, which contains information on tens of millions of people with employer-sponsored insurance from a sample of US private health plans provided through employers. We accessed MarketScan data from 2010 to 2015 via version 4.0 of Treatment Pathways, an online analytic platform that includes data from both the MarketScan Commercial and MarketScan Medicare Supplemental databases, restricted to health plans with prescription drug benefits. Prices were inflated to 2018 US\$ using the Personal Consumption Expenditures Healthcare Services Index. People were eligible for our analysis if they had two or more claims at least seven days apart with the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for PKU (270.1) during the study period (2010–2015) and were continuously enrolled during 2014.

### 2.2.2. Analysis

Claims data were analyzed separately for children aged 0–11 years ( $n = 391$ ), children 12–17 years ( $n = 137$ ) and adults 18 years and older ( $n = 441$ ).

Mean total, insurer, and out-of-pocket payments during 2014 were tabulated by inpatient, outpatient, and emergency room settings, as well as for laboratory tests. Payments were also calculated for sapropterin and for PKU formula, with the latter including both pharmacy claims and outpatient procedure claims for enteral formula for inherited disease of metabolism.

## 3. Results

### 3.1. Primary data (survey of people living with PKU or their parents)

Persons with PKU were approximately 60% female and more than 90% were non-Hispanic white. Mean (SD) age was 9.1 (4.9) years for children and 29.2 (8.9) years for adults with PKU. There were some differences in demographics between children and adult respondents. More than 30% of children had an annual household income higher than \$100,000 compared with 2% of adults. Seventy-five percent of

**Table 1**  
Respondent demographics.<sup>a</sup>

	Child (n = 32)	Adult (n = 52)
	Percent (n)	Percent (n)
Gender		
Female	59.4 (19)	59.6 (31)
Male	37.5 (12)	40.4 (21)
Missing	3.1 (1)	0
Age (mean (SD))	9.1 (4.9)	29.2 (8.9)
Education (adult or parent of child)		
Less than high school	3.1 (1)	3.8 (2)
High school/GED/2-year college degree	46.9 (15)	67.3 (35)
4-year college degree	12.5 (4)	26.9 (14)
Masters/doctoral/professional degree	37.5 (12)	1.9 (1)
Employment status (adult or parent of child)		
Full time	62.5 (20)	28.9 (15)
Part time	28.1 (9)	30.8 (16)
Not employed outside of the home	9.4 (3)	40.4 (21)
Marital status (adult or parent of child)		
Married/living with partner	78.1 (25)	32.7 (16)
Single	6.3 (2)	65.3 (32)
Divorced or separated	12.5 (4)	2 (1)
Missing	3.1 (1)	0
Household income		
≤ \$25,000	12.5 (4)	44.2 (23)
> \$25,000 up to \$50,000	18.8 (6)	23.1 (12)
> \$50,000 up to \$75,000	15.6 (5)	19.2 (10)
> \$75,000 up to \$100,000	18.8 (6)	3.9 (2)
> \$100,000	31.3 (10)	1.9 (1)
Missing	1 (3)	7.7 (4)
Household size (mean (SD))	4.1 (1.5)	2.4 (1.7)
Ethnicity		
American Indian/Alaskan Native	0	1.9 (1)
Hispanic	0	0
Black, not Hispanic	0	1.9 (1)
Mixed	3.1 (1)	1.9 (1)
White, not Hispanic	90.6 (29)	94.2 (49)
Other	3.1 (1)	0
Missing	3.1 (1)	0
Diet recommended	85.7 (28)	69.2 (36)
Age 0–11 (n = 20)	95.0 (19)	-
Age 12–17 (n = 11)	72.7 (8)	-
Consume medical formula (currently)	75.0 (24)	61.5 (32)
Age 0–11 (n = 20)	80.0 (16)	-
Age 12–17 (n = 11)	72.7 (8)	-
Prescribed sapropterin	37.5 (12)	15.4 (8)
Age 0–11 (n = 20)	35 (7)	-
Age 12–17 (n = 11)	45 (5)	-

SD = standard deviation.

<sup>a</sup> Survey of people affected with PKU and their families.

children and 62% of adults consumed medical formula. Thirty-eight percent of children and 15% of adults were currently taking sapropterin (Table 1).

**3.1.1. Costs of following the recommended diet and medications - children**

Of respondents who reported using medical foods, the average annual retail cost of the diet was \$4418 for medical formula (47% of respondents) and \$1961 for low protein foods (56% of respondents, Table 2). Parents reported spending more than 300 h in the last year shopping for and preparing special diet foods for their affected children (Table 3). The annual cost of sapropterin was \$88,855 (22% of respondents), although the out-of-pocket cost was only \$302 (Table 2). Mean costs for all respondents, including those who did not report costs, are available in the appendix.

**3.1.2. Costs of following the recommended diet and medications - adults**

Among adults who reported costs, the annual retail cost of medical formula (46% of respondents) was \$7753 and low protein foods (10% of respondents) was \$1274 (Table 2). Among the two-thirds of adults that reported taking sapropterin who reported dosage taken, the

**Table 2**  
Annual cost of diet and medication for PKU treatment<sup>a</sup>, those with costs only.<sup>b</sup>

	Children 0–17 years		Children 0–11 years		Children 12–17 years		Adults 18+ years	
	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)
Medical formula								
Retail	4418 (n = 15) (3672–5179)	804–7336	4169 (n = 11) (3333–4920)	804–6539	5102 (n = 4) (3546–6659)	2748–7336	7753 (n = 24) (6558–9148)	1800–18,942
Out-of-pocket	0	-	0	-	0	-	5292 (n = 1)	-
Low protein foods								
Retail	1961 (n = 18) (1379–2594)	410–4311	2025 (n = 13) (1289–2785)	410–4311	1795 (n = 5) (906–2836)	436–3743	1274 (n = 5) (480–2498)	0–3606
Out-of-pocket	1615 (n = 22) (1106–2167)	159–5091	1761 (n = 15) (1147–2454)	318–5091	1303 (n = 7) (528–2312)	159–3819	967 (n = 20) (389–1693)	0–5091
Sapropterin								
Average wholesale price	88,855 (n = 7) (42,963–135,334)	6835–180,446	55,501 (n = 5) (22,146–86,943)	6835–114,830	172,244 (n = 2) (164,042–180,446)	164,042–180,446	191,382 (n = 5) (109,362–269,029)	54,680–328,083
Out-of-pocket	302 (n = 8) (95–525)	0–764	305 (n = 5) (25–598)	0–764	297 (n = 3) (0–636)	0–636	25 (n = 6) (0–76)	0–153

<sup>a</sup> 2018 US\$.

<sup>b</sup> Data from a survey of people affected with phenylketonuria (PKU) and their families.

**Table 3**  
Time burden of PKU, those who reported consuming special foods only.<sup>a,b</sup>

	Child		Adult	
	Mean (95% CI)	Range (min- max)	Mean (95% CI)	Range (min-max)
Time spent shopping for special diet (hr, annual)	29.3 (15.4–49.1)	4–200	9.8 (6–15)	0–36
Time spent preparing special diet (hr, annual)	289.0 (233–356)	91–730	301.8 (213–391)	0–913
Time cost of shopping/preparing food (\$) <sup>c</sup>	8789 (7055–10,697)	2635–20,107	8784 (6078–12,122)	0–25,053
Days missed from work because of PKU	3.4 (2.0–5.0)	0–20	0.6 (0.2–1.1)	0–7
Full time employees	3.0 (1.8–4.4)	0–10	1.2 (0.1–2.5)	0–7
Part time employees	4.7 (0.9–10.1)	0–20	0.5 (0.2–0.9)	0–3
Not employed outside the home	2.5 (1.0–4.0)	1–4	0.1 (0–0.3)	0–1
Number of fewer hours worked because of PKU	4.4 (1.4–8.4)	0–40	0.1 (0–0.2)	0–3
Full time employees	1.1 (0–3.2)	0–20	0	–
Part time employees	9.4 (2.9–17.1)	0–26	0.2 (0–0.6)	0–3
Ever quit or been dismissed from work because of PKU (percent (n)) <sup>d</sup>	22.6 (7)		6.3 (3)	

<sup>a</sup> 2018 US\$.

<sup>b</sup> Data from a survey of people affected with phenylketonuria (PKU) and their families.

<sup>c</sup> \$27.10 mean hourly earnings.

<sup>d</sup> Adult or parent of child.

estimated average annual cost was \$191,382 although out-of-pocket cost was \$25. Adults reported spending approximately 310 h shopping and preparing special foods in the past year (Table 3).

### 3.1.3. Costs of medical care (visits) - children

Of respondents who reported metabolic care visits (94%), parents reported 1.5 visits in the past year for their child (Table 4). Round trip travel time for these visits was 3.8 h with a total visit time (including travel and wait times) of 5.9 h. Total annual costs, including out-of-pocket costs and time costs, were \$499. In addition to recommended well visits, 84% of pediatric persons with PKU visited their primary care provider (PCP) 1.3 times per year with a total annual cost of \$194. Parents missed 3.4 days of work per year because of their child's PKU and 23% of parents reported that they or their partner had quit working due to their child's condition. Only 2% of children had seen a non-metabolic specialist (e.g., geneticist, neurologist) in the past year and only 3% of children had received other services (e.g., dietician, therapist, counselor).

### 3.1.4. Costs of medical care (visits) - adults

Of respondents who reported visits (52%), adults reported 1.5 metabolic care visits in the past year with 4.2 h in travel time and a total visit time of 6 h per visit (Table 4). Total annual costs, including out-of-pocket costs and time costs, were \$588. Eighty-one percent of adults visited a PCP an average of 2.1 times per year, in addition to recommended well visits. The total annual cost for PCP visits was \$153. Seventeen percent of adults had seen a non-metabolic specialist in the past year and 13.5% of adults had received other services.

### 3.1.5. Adherence and burden

Eighty-nine percent of parents and 45% of adults reported that they or their child were fully adherent to their recommended low-protein diet; 85% of parents and 56% of adults believed it was “extremely important” to follow the diet (Table 5). However, 85% of parents and 79% of adults also responded that it was difficult to follow the recommended diet due to the cost and burden of the diet as well as emotional and social factors, such as the awkwardness of packing meals for social gatherings. Similarly, 68% of parents and 60% of adults reported it was at least somewhat difficult to obtain special diet products, primarily due to financial reasons. Despite these challenges, 77% of parents responded that it was no more or a little more difficult to care for their child with PKU compared to other children.

### 3.2. Secondary data (administrative claims)

The prevalence of PKU in the administrative claims data decreased with increasing age in this privately insured population: 10 per 100,000 children aged 0–11 years, 5 per 100,000 adolescents aged 12–17 years, and 2 per 100,000 adults aged 18 years and older.

Children 12–17 years old had the highest average medical expenditures (\$54,147) compared to children 0–11 years old (\$19,057) and adults 18 years and older (\$40,705; Table A5).

Medication costs were the largest contributor to medical costs, accounting for 61–81% of the total costs across age groups. Sapropterin was the largest driver of medication costs, accounting for 85% of child medication costs and 92% of adult medication costs. The prevalence of filled sapropterin prescriptions was 24% among children and 25% among adults. Greater than 87% of medical costs and 97% of medication costs were paid by insurance across age groups.

The cost of sapropterin is a function of body weight, and consequently the cost increases with age. Among all privately insured persons with PKU, the mean cost (total of plan and out-of-pocket payments) for sapropterin was \$9312 at ages 0–11 years, \$35,835 at 12–17 years, and \$30,263 at ages 18 and above (Table A5). The mean payment for sapropterin for children and adolescents aged 12–17 years who had filled prescriptions (42.7%) was \$87,666 (Table 6). Among younger children, just 18.1% took sapropterin, at an average annual cost of \$51,286. The mean payment was \$122,440 for adults, among whom 24.7% took sapropterin.

## 4. Discussion

Treatment for PKU incurs a substantial time and cost burden, including long travel times to metabolic clinics, increased costs for special low-protein foods, and extra time spent shopping for and preparing special diets. This study provides new data to quantify the magnitude of this burden. We find that annual costs for both children and adults were likely to be high for special foods (formula or low-protein foods), on the order of \$6400 for children and \$9000 for adults, and require a substantial time commitment of over 300 h annually to shop for and prepare special foods. From the payer perspective, the cost of PKU treatment ranged by age from \$19,057 to \$54,147 annually. Over 75% of parents and adults reported that it was difficult to follow the recommended diet.

Few studies have measured family time costs or medication costs associated with PKU, and, of those, only one was conducted in the United States. In the United States, a 1982 modeling analysis in Wisconsin calculated that over 20 years, costs would total \$40,830 per

**Table 4**  
Utilization and time costs associated with PKU visits, restricted to respondents who incurred visits.<sup>a</sup>

	Visits per year			Travel time (hr, round trip)			Total visit time (hr)			Time costs <sup>b</sup> (\$, annual)			Out-of-pocket costs (\$, annual)			Total costs (\$, annual)		
	Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)	
Metabolic (n = 30)	1.5 (1.3-1.6)	1-2		3.8 (2.9-4.9)	0.66-10		5.9 (4.9-6.9)	2.5-13		227 (189-269)	268 (174-272)	32-1134	499 (381-637)					
Primary care provider <sup>c</sup> (n = 27)	1.3 (0.8-1.8)	0-5		0.4 (0.2-0.6)	0-2		0.9 (0.5-1.2)	0-2.8		52 (30-77)	150 (34-350)	0-2226	194 (63-395)					
Specialists <sup>d</sup> (n = 3)	1.6 (0.6-2.7)	1-3		-	-		2.75 (2.1-3.4)	2-3.5		75 (54-95)	125 (27-223)	27-223	200 (101-277)					
Other services <sup>e</sup> (n = 3)	12.3 (0-24)	1-24		-	-		0.54 (0-1)	0-1		114 (0-325)	0	-	114 (0-325)					

  

	Visits per year			Travel time (hr, round trip)			Total visit time (hr)			Time costs <sup>b</sup> (\$, annual)			Out-of-pocket costs (\$, annual)			Total costs (\$, annual)		
	Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)		Mean (95% CI)	Range (min-max)	
Metabolic (n = 27)	1.5 (1.1-2.0)	1-6		4.2 (3.4-5.1)	0.3-8		6 (4.7-7.3)	1-12		244 (153-369)	311 (183-449)	11-1049	588 (378-825)					
Primary care provider <sup>c</sup> (n = 42)	2.1 (1.5-2.7)	1-9		0.6 (0.5-0.7)	0.2-1.5		1.4 (1.2-1.6)	0.2-2.5		91 (58-129)	65 (41-94)	0-334	153 (106-214)					
Specialists <sup>d</sup> (n = 9)	1.7 (1.1-2.2)	1-3		-	-		4.5 (2.1-7.2)	0.5-12		148 (90-209)	309 (71-562)	0-763	472 (200-762)					
Other services <sup>e</sup> (n = 8)	52 (2-130)	1-317		-	-		0.9 (0.4-1.6)	0-3		549 (36-1208)	569 (30-1559)	0-3464	1044 (91-2788)					

<sup>a</sup> Data from a survey of people affected with phenylketonuria (PKU) and their families.

<sup>b</sup> \$27.10 mean hourly earnings 2018 US\$.

<sup>c</sup> Visits in excess of recommended well visits.

<sup>d</sup> Included: geneticist, pulmonologist, gastroenterologist, surgeon, cardiologist, PMR (physical medicine and rehabilitation), neurologist, dermatologist, and other.

<sup>e</sup> Included: nutrition counseling, dietitian, special education or early education, family counseling, nursing care, respite care, home health care, rehabilitation care, psychologist, speech therapist, behavioral therapist, physical therapist, respiratory therapist, social worker, genetic counselor, and other.

**Table 5**  
Perceptions of difficulty associated with the PKU diet<sup>a</sup>.

	Child (n = 32) Percent (n) <sup>b</sup>	Adult (n = 52) Percent (n) <sup>b</sup>
Have you followed special diet		
Yes- fully or daily	89.3 (25)	45.2 (14)
Yes- partially	10.7 (3)	48.4 (15)
No	0	6.5 (2)
How important is diet?		
Somewhat important	0	8.8 (3)
Important	3.9 (1)	23.5 (8)
Very important	11.5 (3)	11.8 (4)
Extremely important	84.6 (22)	55.9 (19)
How difficult is it to follow the recommended diet		
Not difficult	15.4 (4)	20.6 (7)
Somewhat difficult	65.4 (17)	26.5 (9)
Difficult	7.7 (2)	14.7 (5)
Very difficult	7.7 (2)	14.7 (5)
Extremely difficult	3.9 (1)	23.5 (8)
Reasons not able to follow recommended diet <sup>c</sup>		
Cost of diet	75 (3)	38.9 (7)
Diet requires too much time	25 (1)	50.0 (9)
Diet is burdensome	25 (1)	66.7 (12)
Emotional/social factors	50 (2)	55.6 (6)
Difficulty in getting part of the special diet		
Not difficult	32.1 (9)	40.0 (12)
Somewhat difficult	53.6 (15)	36.7 (11)
Difficult	10.7 (3)	16.7 (5)
Extremely difficult	3.6 (1)	6.7 (2)
Reasons it is difficult to get special diet products <sup>c</sup>		
Financial	73.7 (14)	70.0 (14)
Availability	63.2 (12)	20.0 (4)
Distance to retailer	26.3 (5)	5.0 (1)
Time	31.6 (6)	25.0 (5)
Health (parent/self-rating)		
Fair	0	17.7 (6)
Good	15.4 (4)	38.2 (13)
Very good	19.2 (5)	38.2 (13)
Excellent	65.4 (17)	5.9 (2)
How much more care is required because of your child's PKU?		
No more	43.3 (13)	–
A little more	33.3 (10)	–
Moderately more	16.7 (5)	–
Much more	6.6 (2)	–
How difficult is it to meet your child's healthcare needs?		
Not difficult	46.6 (14)	–
Somewhat difficult	33.3 (10)	–
Difficult	13.3 (4)	–
Very difficult	6.6 (2)	–

<sup>a</sup> Data from a survey of people affected with phenylketonuria (PKU) and their families.

<sup>b</sup> N does not sum to full sample size (n = 32 child; n = 52 adult) due to missing responses. Percentages were calculated using the number of valid responses.

<sup>c</sup> Respondents could select more than one answer.

person (approximately \$92,000 in 2018\$) [17]. Because only lifetime costs were presented and methods and context differed from recommended practice (e.g., use of a 7% discount rate, sapropterin was not available), it is difficult to compare our results to that study.

Five studies from other countries (two from the United Kingdom and one each from Spain, China and the Netherlands) have evaluated costs associated with PKU for patients and families. One study, from the Netherlands, collected data on family out-of-pocket costs and found that costs for low protein foods totaled 600 euros, or approximately \$883 (2018 US\$), per year [18]. That is substantially less than the average \$1147 of expenses per year found in our study, which likely reflects price differences between the two countries. Conversely, total

out of pocket costs in the Chinese study were much higher than in our study, ranging from \$3956 for infants to \$5872 for children 9 years and older. [19]

Two studies reported on the time spent preparing low protein diets. One study from the Netherlands reported that caregivers of children with PKU spent 1.4 h per day managing their child's low-protein diet. Adults estimated that management required an extra 0.5 h per day [18]. A UK study found that parents reported spending 2.7 h per day on dietary management [20]. Our data show a time burden of 0.9 h per day for both caregivers and adults, which is comparable to the Dutch study but much lower than in the UK study.

Finally, one UK modeling study calculated total treatment costs from the payer perspective. Over the first 36 years of life, persons with PKU were expected to incur on average healthcare costs of 89,000 pounds, or 2500 pounds per year [21]. Healthcare costs included medical foods and supplements, prescribed drugs, general practitioner and other outpatient visits, laboratory tests, and diagnostic procedures. When restricted to those who adhered to a restricted diet, average annual cost was estimated to be 4150 pounds per year, equivalent to approximately \$9829 in 2018 US dollars purchasing power. However, because medical prices in general and prescription drug prices in particular are much higher in the United States, the equivalent US cost might be twice as high. Also, since presumably none of the UK respondents were prescribed sapropterin, the two sets of cost estimates are not comparable.

Most parents and adults found it difficult to maintain the PKU diet due to costs and increased burden of obtaining and paying for the needed foods. Despite this, most parents responded that it was no more or a little more difficult to care for their child with PKU compared to other children, suggesting that they may have found the necessary support they needed in their communities to overcome these challenges.

In claims data, sapropterin and other medications accounted for 61–81% of total healthcare costs. Twenty-four percent of children and 25% of adults received sapropterin at an average annual cost of \$67,328 for children and \$122,440 for adults. In primary data, the annual cost of sapropterin was reported to be \$88,855 for children and \$191,382 for adults, with 38% and 15% of children and adults reporting receiving treatment, respectively. Estimated annual costs were similar for children between the two data sources but adults in the survey had much higher estimated costs compared to the secondary data sample. The higher medication costs in the primary data may reflect greater adherence in the two-thirds of surveyed adults who reported sapropterin dosage, although we did ask about adherence in our survey. We used the average wholesale price of sapropterin to impute the annual cost of medication doses taken by survey respondents; however, insurance plans may not pay this amount. On average, U.S. payers in 2017 received discounts and rebates totaling 28% of the amounts paid for outpatient pharmaceuticals [22], potentially accounting in part for the lower cost of medications in the administrative data.

This study has some limitations relating to the size and setting of the two samples, the multi-disciplinary nature of PKU treatment, and limitations of administrative data. Results from the primary data are limited by a small sample size and lack of geographic diversity as all respondents were from the state of Michigan. We also did not collect information on non-responders and their characteristics may have differed from our survey sample. However, we compared demographic characteristics of respondents in our study to participants in a national PKU registry and found our survey sample had a higher percentage of female respondents compared to the registry (60% vs 50%) but a similar proportion of non-Hispanic white respondents (92% vs 89%) [23]. It is possible that non-response bias has impacted our results, especially if females may be more likely to seek medical care and adopt health behaviors that decrease their disease risk [24].

At the time the survey was conducted, the cost of medical formula

**Table 6**  
Claims database analysis, among insured individuals with phenylketonuria who incurred costs.

	Children 0–17 years n = 528 <sup>a</sup>		Children 0–11 years n = 391		Children 12–17 years n = 137		Adults 18+ years n = 441	
	Mean	% paid by insurance	Mean	% paid by insurance	Mean	% paid by insurance	Mean	% paid by insurance
Outpatient	7094	90.8%	5665	87.8%	11,160	95.1%	5838	87.9%
Inpatient	45,217	97.5%	34,850	96.3%	73,727	99.1%	25,722	96.1%
Emergency	1412	75.5%	1253	77.9%	1885	70.7%	2988	85.6%
Labs	618	79.2%	707	79.1%	363	79.9%	538	79.8%
Medication								
Formula	2968	58.4%	4287	57.9%	329	71.3%	–	–
Sapropterin	67,328	97.9%	51,286	97.6%	87,666	98.2%	122,440	98.6%

<sup>a</sup> Sample size for any positive payments in 2014. Sample size for positive payments in each category differ.

for children and home blood monitoring tests were covered by the state. Therefore, families incurred no out-of-pocket costs for formula and out-of-pocket costs are likely not generalizable to other states which may not offer as much support to patients with PKU. For example, after the conclusion of this study, Michigan discontinued the provision of medical formula for patients with PKU and out-of-pocket costs for medical formula are likely to be more similar to retail costs for many patients. Out-of-pocket costs might also differ for other patient populations with different insurance policies, especially in the child sample, which reported parent incomes trending higher than the general population. Additionally, in Michigan, there is one primary state-funded PKU medical management clinic and three satellite clinics around the state. This structure may differ in other states, affecting travel and visit times. Although respondents reported few visits to specialists, metabolic clinics are often multi-disciplinary and may include visits with a dietician, genetic counselor, social worker, and a psychologist. Patients may therefore be receiving specialist services as part of their metabolic clinic visit, and not reporting their visits separately in our study. Finally, the administrative claims data analysis was limited by the accuracy of the billing codes in the database. It is also possible that some persons with PKU did not have a PKU-related insurance claim within the study period and, therefore, would not have been included in our analysis.

To the best of our knowledge, this study represents the first US estimates of the financial and time burden of PKU on affected individuals and their families. These estimates can be used as inputs into cost-effectiveness analyses of the value of PKU treatment or newborn

screening for PKU and also inform persons with PKU and their families about aspects of treatment and care for planning purposes. Future studies could use these methods to evaluate patient- and family-level costs and time burden of PKU in a national sample.

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### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The authors have no competing interests to declare.

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## Appendix A

**Table A1**  
Categories of cost and utilization included in the patient diary.

Section	Content
Initial and follow-up tests & diagnosis of phenylketonuria (PKU) <sup>a</sup>	When and how did you find out you/your child has PKU, follow-up tests conducted, cost of follow-up testing
Treatments <sup>a</sup>	Cost of hepatocyte transplantation
Metabolic visits	Costs and time required for visits to metabolic clinic and blood draws
Special formulas or formula replacements	Amount of and types of medical formula consumed
Your child's diet	Amount and type of special foods consumed, difficulty in obtaining special foods, extra time spent preparing special foods, perceived importance of following diet
Medications, vitamins, or supplements	Amount and costs of medications, vitamins, or supplements consumed
Emergency room visits <sup>a</sup>	Cost and time required for emergency room visits related to PKU
Hospitalizations <sup>a</sup>	Cost of hospitalizations related to PKU
Primary care provider visits	Cost and time required for primary care provider visits
Medical specialists	Cost and time required for medical specialist (e.g., geneticist, neurologist) visits
Special services	Cost and time required for medical specialist (e.g., dietician, therapist, counselor) visits
Insurance and reimbursement <sup>a</sup>	Insurance type, reimbursements, and time spent interacting with insurance
Special devices <sup>a</sup>	Costs of special devices for PKU (e.g., feeding tube, wheelchair)
Modifications and renovations <sup>a</sup>	Costs of modifications or renovations to home for PKU (e.g., video monitor, widening doorways)
Your child with PKU	Child grade in school, child in daycare, how much care your child requires

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Table A1 (continued)

Section	Content
Pregnancy <sup>a</sup>	Costs and time required for metabolic care during pregnancy; diet compliance during pregnancy
How having a child with PKU affects parents' lives <sup>a</sup>	Delivery complications, other children with disabilities
Child demographics	Child demographics
Demographics	Parent/adult demographics

<sup>a</sup> Data from this section not reported in this manuscript.

Table A2

Annual cost of diet and medication for phenylketonuria (PKU) treatment (US\$), all respondents.

	Children 0–17 years (n = 32) <sup>a</sup>		Children 0–11 years (n = 20)		Children 12–17 years (n = 11)		Adults 18+ years (n = 51)	
	Mean (95% CI)	Range	Mean (95% CI)	Range	Mean (95% CI)	Range	Mean (95% CI)	Range
Medical formula								
Retail	2651 (1720–3618)	0–7336	3057 (1986–4109)	0–6539	2268 (434–3782)	0–7336	4135 (2848–5509)	0–18,942
Out-of-pocket	0	–	0	–	0	–	112 (0–338)	0–5292
Low protein foods								
Retail	1218 (718–1762)	0–4311	1385 (753–2065)	0–4311	896 (228–1713)	0–3743	148 (20–352)	0–3606
Out-of-pocket	1147 (692–1666)	0–5091	1391 (782–2054)	0–5091	482 (204–1445)	0–3891	380 (126–694)	0–5091
Sapropterin								
Average wholesale price	23,036 (6531–42,504)	0–180,446	15,417 (2734–31,859)	0–114,830	43,060 (0–95,923)	0–180,446	19,138 (4265–39,589)	0–328,083
Out-of-pocket	86 (14–173)	0–764	85 (0–205)	0–764	99 (0–216)	0–636	3 (0–8)	0–153

<sup>a</sup> Age was not available for one child.

Table A3

Time burden of phenylketonuria (PKU), all respondents.

	Child (n = 31)		Adult (n = 51)	
	Mean (95% CI)	Range (min- max)	Mean (95% CI)	Range (min-max)
Time spent shopping for special diet (hr, annual)	21.1 (10–37)	0–200	3.6 (1.7–6.0)	0–36
Time spent preparing special diet (hr, annual)	211.9 (149–280)	0–730	138.3 (82.6–201.7)	0–913
Time cost of shopping/preparing food (\$) <sup>a</sup>	6315 (4519–8266)	0–20,107	3366 (1932–4959)	0–25,053

<sup>a</sup> \$27.10 mean hourly earnings 2018 US\$.

Table A4

Utilization and time costs associated with phenylketonuria (PKU) visits, all respondents (both with and without reported utilization)<sup>a</sup>

a. Children.										
	Visits per year		Travel time (hr, round trip)		Total visit time (hr)		Time costs <sup>a</sup> (\$, annual)	Out- of-pocket costs (\$, annual)		Total costs (\$, annual)
	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Mean (95% CI)	Range (min-max)	Mean (95% CI)
Metabolic (n = 32)	1.4 (1.2–1.6)	0–2	3.6 (2.7–4.5)	0–10	5.5 (4.4–6.5)	0–13	212 (171–256)	248 (156–354)	0–1135	462 (341–597)
Primary care provider <sup>b</sup> (n = 31) <sup>c</sup>	1.1 (0.8–1.8)	0–5	0.4 (0.2–0.6)	0–2	0.8 (0.5–1.2)	0–2.8	45 (25–69)	129 (26–302)	0–2226	166 (51–354)
Specialists <sup>d</sup> (n = 30)	0.2 (0–0.4)	0–3	–	–	0.3 (0–0.6)	0–3.5	7 (0–17)	13 (0–31)	0–223	20 (0–48)
Other services <sup>e</sup> (n = 27)	1.4 (0–3.6)	0–24	–	–	0.1 (0–0.2)	0–1	13 (0–37)	0	–	13 (0–37)
b. Adults.										
	Visits per year		Travel time (hr, round trip)		Total visit time (hr)		Time costs <sup>a</sup> (\$, annual)	Out- of-pocket costs (\$, annual)		Total costs (\$, annual)
	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Mean (95% CI)	Range (min-max)	Mean (95% CI)
Metabolic (n = 52)	0.8 (0.5–1.1)	0–6	2.2 (1.5–3.0)	0–8	2.7 (1.7–3.8)	0–12	111 (58–177)	126 (63–203)	0–1049	238 (118–378)
		0–9		0–1.5		0–2.5	73 (45–107)	52 (31–74)	0–334	121 (81–172)

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Table A4 (continued)

	Visits per year		Travel time (hr, round trip)		Total visit time (hr)		Time costs <sup>a</sup> (\$, annual)		Out-of-pocket costs (\$, annual)		Total costs (\$, annual)
	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	Mean (95% CI)	Range (min-max)	Mean (95% CI)	
Primary care provider <sup>b</sup> (n = 52)	1.7 (1.2–2.2)		0.5 (0.4–0.6)		1.1 (0.9–1.3)						
Specialists <sup>d</sup> (n = 50)	0.3 (0.1–0.5)	0–3	–	–	0.8 (0.4–1.7)	0–12	27 (10–48)	39 (2–90)	0–763	60 (11–125)	
Other services <sup>e</sup> (n = 52)	7.9 (0–22)	0–317	–	–	0.1 (0–0.2)	0–3	83 (1–206)	72 (0–214)	0–3464	136 (1–395)	

<sup>a</sup> \$27.10 mean hourly earnings 2018 US\$.

<sup>b</sup> Visits in excess of recommended well visits.

<sup>c</sup> Sample size varies due to non-response.

<sup>d</sup> Included: geneticist, pulmonologist, gastroenterologist, surgeon, cardiologist, PMR (physical medicine and rehabilitation), neurologist, dermatologist, and other.

<sup>e</sup> Included: nutrition counseling, dietician, special education or early education, family counseling, nursing care, respite care, home health care, foster care, rehabilitation care, psychologist, speech therapist, behavioral therapist, physical therapist, respiratory therapist, social worker, genetic counselor, and other.

Table A5

Claims database analysis, full cohort.

	Children aged 0–17 (n = 536)			Children aged 0–11 (n = 396)			Children aged 12–17 (n = 140)			Adults aged 18+ (n = 454)		
	Mean	% of total costs	% paid by insurance	Mean	% of total costs	% paid by insurance	Mean	% of total costs	% paid by insurance	Mean	% of total costs	% paid by insurance
Outpatient	7081	25.1%	90.8%	5652	29.7%	87.8%	11,160	20.6%	95.1%	5665	13.9%	87.9%
Inpatient	1284	4.6%	97.6%	980	5.1%	96.3%	2153	4.0%	99.1%	1342	3.3%	96.0%
Emergency	232	0.8%	75.6%	208	1.1%	77.9%	303	0.6%	70.6%	413	1.0%	85.6%
Labs	477	1.7%	79.2%	548	2.9%	79.0%	279	0.5%	79.8%	436	1.1%	79.9%
Medication	19,085	67.8%	97.5%	11,669	61.2%	97.1%	40,253	74.3%	97.8%	32,848	80.7%	98.1%
Formula	17	0.1%	58.5%	22	0.1%	57.5%	2	0.0%	100.0%		0.0%	
Sapropterin	16,131	57.3%	98.3%	9312	48.9%	97.6%	35,835	66.2%	98.2%	30,263	74.3%	98.6%
Other Rx	2937	10.4%	93.3%	2335	12.3%	95.5%	4416	8.2%	95.2%	2585	6.3%	91.4%
Total medical costs	28,160		88.1%	19,057		87.6%	54,147		88.5%	40,705		89.5%

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