

## Breastfeeding Infants with Phenylketonuria in the United States and Canada

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### Abstract

**Objective:** This study described the prevalence and duration of mothers' breastfeeding infants with phenylketonuria (PKU) and explored factors related to duration of breastfeeding as a surrogate for breastfeeding success.

**Subjects and Methods:** Descriptive analysis as performed from an international Internet survey of mothers ( $n=103$ ) who met the inclusion criteria: (1) at least 21 years of age, (2) able to read and write in English, (3) child with PKU, and (4) living in the United States or Canada.

**Results:** Of the 103 mothers, 89 (86%) initiated breastfeeding immediately following delivery, whereas 14 (14%) chose bottle feeding. In comparison to breastfeeding after delivery, significantly fewer mothers breastfed after diagnosis (McNemar's  $\chi^2=30.33$ ,  $p<0.001$ ;  $n=72$  vs.  $n=89$ ). Breastfeeding duration ranged from less than 1 month to 24 months with one modal duration category ( $n=20$ , 22%) at less than 1 month. The timing of the addition of commercial infant formula to supplement breastfeeding or expressed mothers' milk was associated with a shorter duration of breastfeeding among infants with PKU:  $\chi^2$  (42,  $n=73$ )=88.13,  $p<0.001$ .

**Conclusions:** PKU is treated with phenylalanine (Phe) restriction. Breastfeeding infants with PKU is challenging in part because Phe intake is difficult to determine precisely. We studied breastfeeding duration in infants with PKU and factors associated with success. Further research should identify the unique needs of mothers' breastfeeding infants with PKU to guide the development of interventions specific to these mothers to support their efforts to continue breastfeeding after the diagnosis of PKU.

### Introduction

**D**URING THE EARLY YEARS of phenylketonuria (PKU) treatment, the standard of care for infants diagnosed with PKU included immediate weaning from breastfeeding and institution of phenylalanine (Phe)-free or low-Phe medical beverage in conjunction with standard commercial infant formula to maintain appropriate Phe levels (120–360  $\mu\text{mol/L}$ ).<sup>1–3</sup> At the time, this was believed to be the only effective way to monitor the infant's intake and allow for precise titration and measurement of Phe to protect the neurological and cognitive development of the infant. Consequently, this management approach precluded breastfeeding infants with PKU. However, breastmilk offers several advantages when used as a primary source of nutrition for infants with PKU. These include the benefits of breastfeeding for any infant<sup>4,5</sup> and that breastmilk is lower in Phe than standard commercial infant formulas.<sup>6,7</sup>

Studying breastfeeding in PKU is challenging. Breastfeeding in the context of PKU, defined as breastfeeding and bottle feeding of expressed mothers' milk to infants, entails the need for mothers, at each feeding, to estimate how long to breastfeed or how much breastmilk to bottle feed, as well as to estimate how much Phe-free supplementation is required to maintain acceptable blood Phe levels. Although based on relatively small samples of fewer than 50 participants due to PKU's rarity, study results comparing infants with PKU fed breastmilk and supplemented with Phe-free medical beverage versus those exclusively formula fed consistently have reported that breastmilk supplemented with Phe-free medical beverage was an acceptable dietary treatment for infants with PKU as Phe levels could be maintained within the desired range.<sup>2,3,8–11</sup> Among women with a child with PKU, there are no large-scale studies reporting the variables related to breastfeeding duration with duration taken as a measure of "breastfeeding success." Nonetheless, studies of overall

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prevalence of breastfeeding have found the following variables to be linked to duration: older maternal age, white, married status, greater social support, and normal vaginal delivery improve duration, whereas infant health problems shorten duration.<sup>12-14</sup>

Although the practice of breastfeeding infants with PKU has been discussed in the literature, there is limited research describing patterns of breastfeeding in mothers of infants with PKU.<sup>2,3,9-11,15-18</sup> It is notable that there is no published research identifying factors associated with breastfeeding duration within this unique population of breastfeeding mothers or to support clinical guidelines that specifically address the unique challenges of mothers breastfeeding infants with PKU. Therefore, the purpose of this analysis was to describe the prevalence and duration of breastfeeding among mothers of infants with PKU living in the United States and Canada and to identify factors that affected the duration and success of breastfeeding in this unique population.

## Subjects and Methods

This was a descriptive study of data from an international Internet survey conducted to explore mothers' current or retrospective experiences breastfeeding infants with PKU. The Internet survey took place between November 2010 and May 2011. The sample comprised women who met the following criteria: at least 21 years of age, able to read and write in English, had a child or children with PKU regardless of current age, and lived in the United States or Canada. In this study, breastfeeding included the bottle feeding of expressed mothers' milk.

The survey consisted of a questionnaire that contained sections about the demographic characteristics of mothers and infants and infant feeding history. Response options included both forced choice and open-ended questions. Six mothers of children with PKU pilot-tested the questionnaire and online survey, and their input was used to make final revisions in the survey in order to refine and improve the approach and wording of the questions.

After approval was received from the university's institutional review board, the study was announced on the PKU Listserv. The purpose of this listserv is to facilitate communication among families of children born with PKU and to share information, advice, and experiences of living with PKU. Subsequently, several regional and national PKU support groups ( $n=14$ ) used the original or modified university-approved announcement of the study to communicate its availability to their members. The posting included a brief description of the purpose of the study and the inclusion criteria with the instruction that interested participants should reply directly to the researcher (S.A.B.-W.) by e-mail. Mothers who responded to the recruitment post were e-mailed a copy of the research information sheet and instructions for the survey. The university's institutional review board waived the requirement for a formal written consent. The mean duration for mothers to complete the survey was 19 minutes (SD=10 minutes) with a range from 7 to 69 minutes. Mothers who completed the survey were sent a \$10 (U.S.) electronic gift certificate to a medical foods company that provides low protein items popular with families who have individuals with PKU. Of the 149 women who received the information sheet and instructions for the Internet survey, 119 completed the Internet survey for a return rate of approximately 80%.

After the Internet survey was closed, data were downloaded into an SPSS (Chicago, IL) software file and compared, and all discrepancies were resolved by checking the hard copy of each participant's data. Statistical analysis was performed with SPSS Windows (version 19.0) software. For binary dependent variables within-subjects, the  $\chi^2$  test was applied to analyze the difference between the proportion of mothers who breastfed immediately after delivery and the proportion of mothers who continued breastfeeding after the diagnosis of PKU. Pearson's  $\chi^2$  test was used to analyze the statistical relationship between duration of breastfeeding and variables known to affect breastfeeding duration. A  $p$  value of  $<0.05$  was considered statistically significant.

## Results

### Demographics

The final sample was comprised of mothers ( $n=119$ ) consisting of two groups: mothers with one child who had PKU ( $n=103$ , 87%) and mothers with more than one child with PKU ( $n=16$ , 13%). Only data from the 103 mothers with one child with PKU are included in this report. Demographic characteristics of the mothers are presented in Table 1 and those of the infants in Table 2. Mothers were from various regions across the United States and Canada (Fig. 1). Demographic features of the mothers closely match another survey of parents with children who have PKU.<sup>19</sup> In addition, this sample was consistent with the known ethnic distribution of PKU, with a higher incidence in individuals of Northern European ancestry than black, Hispanic, and Asian individuals.<sup>20-23</sup>

### *What is the prevalence of breastfeeding prior to and after diagnosis of PKU?*

Of the 103 mothers with one child with PKU, 89 mothers (86%) initiated breastfeeding, and 14 mothers (14%) began bottle feeding immediately after delivery. After diagnosis, 18 mothers switched from breastfeeding to bottle feeding formula, whereas one mother initiated breastfeeding. An ad hoc analysis using McNemar's test was performed to assess the difference between the proportion of mothers who breastfed immediately after delivery and the proportion of mothers who continued breastfeeding after the diagnosis of PKU (Fig. 2). There were significantly fewer mothers breastfeeding after diagnosis (McNemar's  $\chi^2=30.333$ ,  $p<0.001$ ;  $n=72$  vs.  $n=89$ ).

Given the significance of fewer mothers breastfeeding after diagnosis, another ad hoc analysis was conducted to ascertain whether this significance differed by country, as Canadian breastfeeding rates are higher than United States breastfeeding rates for ever-breastfed (90.3% vs. 73.9%).<sup>24</sup> Of the 89 mothers who breastfed after delivery, 75 (84%) were mothers from the United States, and 14 (16%) were mothers from Canada. After diagnosis, 60 mothers (80%) from the United States continued to breastfeed, whereas 15 mothers (20%) switched to bottle feeding. In contrast, only two Canadian mothers switched from breastfeeding to bottle feeding after the diagnosis of their infants having PKU. Using McNemar's test with layering of the United States and Canada, the significant reduction in breastfeeding mothers was a function of women from the United States (McNemar's  $\chi^2=27.48$ ,  $p<0.001$ ;  $n=60$  vs.  $n=75$ ) and not from Canada (Fig. 2).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF MOTHERS OF INFANTS WITH PHENYLKETONURIA

Variable	United States (n=89)	Canada (n=14)
Maternal age (years)		
21–29	16 (18)	2 (14)
30–39	54 (61)	10 (72)
40–49	14 (16)	2 (14)
50–65	5 (5)	0
Ethnicity		
Asian/Pacific Islander	1 (1)	0
White	83 (93)	12 (86)
Hispanic/Latino	5 (6)	0
First Nation/Inuit	0	2 (14)
Marital status		
Never married or partnered	2 (2)	1 (7)
Living with partner	0 (0)	3 (22)
Married	82 (92)	9 (64)
Separated	1 (1)	1 (7)
Divorced	4 (5)	0
Education <sup>a</sup>		
High school	2 (2)	1 (7)
Some college	11 (12)	2 (14)
Associates degree	13 (15)	2 (14)
Bachelors degree	34 (38)	4 (29)
Masters degree	21 (24)	4 (29)
Doctorate degree	5 (6)	0
Professional degree	3 (3)	1 (7)
Employment (hours per week)		
0	28 (31)	3 (21)
<8	4 (4)	0
10–16	2 (2)	2 (14)
20–38	21 (24)	4 (29)
40	29 (33)	4 (29)
>40	5 (6)	1 (7)
Gross annual household income <sup>b,c</sup>		
<\$25,000	3 (4)	1 (7)
\$25,001–\$50,000	8 (9)	4 (29)
\$50,001–\$75,000	18 (21)	2 (14)
\$75,001–\$100,000	30 (35)	2 (14)
\$100,001–\$150,000	12 (14)	4 (29)
>\$150,000	14 (17)	1 (7)
Community population size		
A town with a population <10,000	17 (19)	1 (7)
A city with a population between 10,000 and 50,000	30 (34)	6 (43)
A city with a population between 50,001 and 100,000	13 (15)	1 (7)
A metropolitan area with a population between 100,001 and 500,000	10 (11)	4 (29)
A metropolitan area with a population between 500,001 to 1 million	8 (9)	2 (14)
A metropolitan area with a population >1 million	11 (12)	0

Data are n (%).  
<sup>a</sup>Highest level of education completed.  
<sup>b</sup>In U.S. dollars.  
<sup>c</sup>U.S. mothers, n=85.

*What is the duration of breastfeeding for mothers of infants with PKU who breastfeed?*

Among mothers in this study, the duration of breastfeeding (including bottle feeding of expressed mothers' milk) ranged from less than 1 month (n=20, 22%) to 24 months (n=5, 5%).

TABLE 2. DEMOGRAPHIC CHARACTERISTICS OF INFANTS WITH PHENYLKETONURIA

	United States (n=89)	Canada (n=14)
Gender (male/female)	38/51	10/4
Birth weight (kg) <sup>a</sup>	3.44 (2–5)	3.44 (1–4)
Term gestation	78 (88%)	11 (79%)
Uncomplicated pregnancies	80 (89%)	13 (93%)
Phe level (μmol/L) at diagnosis <sup>a</sup>	969 (240–2,520)	810 (252–2,400)
Age (days) at diagnosis <sup>a</sup>	4 (1–28)	4 (1–14)
Infants born between 2000 and 2011	77 (86%)	13 (93%)

<sup>a</sup>Data are mean values (minimum–maximum are given in parentheses).  
 Phe, phenylalanine.

Although the modal duration category was at less than 1 month (n=20, 22%), over three-fourths of the mothers breastfed their infants with PKU longer than 1 month, and over one-half breastfed to 6 months. Table 3 gives the distribution of duration of breastfeeding categories.

*What factors are related to duration of breastfeeding in mothers of infants with PKU?*

Several factors were assessed in relation to the duration of breastfeeding using  $\chi^2$  analysis. Only one variable—the timing of when standard commercial infant formula was added



FIG. 1. Geographic location of surveyed mothers of infants with phenylketonuria living in the United States and Canada.

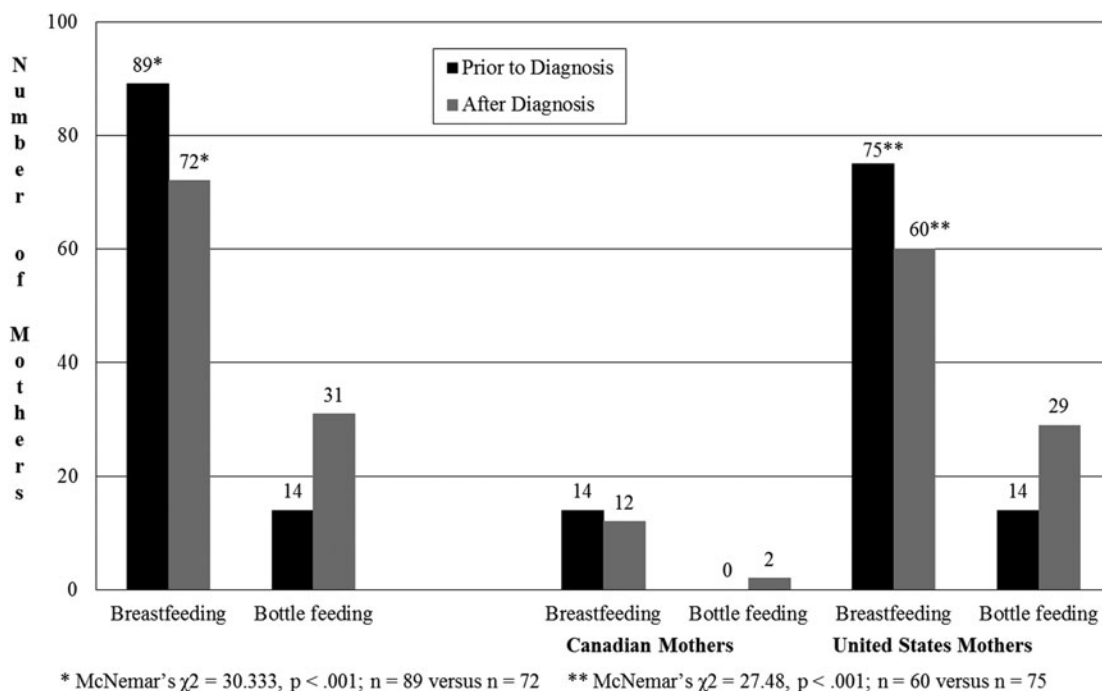


FIG. 2. Comparison of breastfeeding prevalence prior to diagnosis and after diagnosis of phenylketonuria: breastfeeding and bottle feeding (left panel) before and after diagnosis of phenylketonuria and (right panel) according to country of residence before and after diagnosis.

to diet replacing some or all breastmilk from nursing or expressed mothers' milk—was significantly associated with decreased duration of breastfeeding (including expressed mothers' milk) for infants with PKU:  $\chi^2 (36, n=71)=89.68$ ,  $p < 0.001$ . Almost one-third of mothers ( $n=26$ ) reported the challenge of decreased breastmilk supply and the need to add standard commercial infant formula. Of those identifying when standard commercial formula was added to the infant's diet, approximately 30% ( $n=21$ ) had added it by 6 months. Almost one-half of the mothers ( $n=34$ , 48%) never introduced standard commercial infant formula to their infant's diet; rather, they transitioned from breastfeeding to the introduction of solid foods with Phe-free/low-Phe medical beverage as the "milk" source.

**Discussion**

In this study, a high percentage of mothers ( $n=72$ , 81%) continued breastfeeding after their infant's diagnosis of PKU. Breastfeeding an infant with PKU, who requires careful mon-

itoring of Phe intake due to the need to restrict Phe intake and titrate intake with blood Phe levels, can be challenging for mothers and healthcare providers. Difficulties arise because it is difficult to determine the quantity of Phe ingested by the infant because of variability of Phe content in breastmilk and volume of breastmilk consumed. Therefore, the high prevalence of continuation of breastfeeding after PKU diagnosis is impressive. The supports and strategies used by mothers that facilitated breastfeeding success while maintaining desired Phe levels should be incorporated into the management of breastfeeding infants with PKU and will be reported elsewhere.<sup>25</sup>

Despite the increased work associated with breastfeeding a child with PKU, a substantial number of these mothers did so, with the sample as a whole meeting or exceeding the majority of breastfeeding percentages reported in both the United States and Canada. In comparison with U.S. National Breastfeeding Percentages,<sup>26</sup> this group of mothers exceeded the expected rate of breastfeeding initiation (86% vs. 77%) and breastfeeding at 6 months (55% vs. 47%) but did not meet the expected rate of breastfeeding at 12 months (17% vs. 26%). In addition, the mothers were comparable to the Canadian 3-month breastfeeding rates for any breastfeeding (65% vs. 68%) and to the 6-month breastfeeding rate (55% vs. 54%).<sup>27</sup> Furthermore, these mothers nearly met the Canadian initiation rate for breastfeeding (86% vs. 90%). In comparison with the *Healthy People 2020* Breastfeeding Objectives,<sup>28</sup> mothers exceeded the goal for the initiation of breastfeeding (86% vs. 82%) but did not meet the breastfeeding objectives at 6 months (55% vs. 61%) or 12 months (17% vs. 34%). Almost 70% of mothers ( $n=48$ ) met the American Academy of Pediatrics<sup>29</sup> and the Canadian Paediatric Society<sup>30</sup> breastfeeding recommendation of 6 months. This drop off over time in breastfeeding by mothers of infants with PKU perhaps reflects

TABLE 3. DURATION OF BREASTFEEDING

Breastfeeding duration	United States ( $n=76$ )	Canada ( $n=14$ )
<1 month	18 (20%)	2 (2%)
1–3 months	10 (11%)	3 (3%)
4–6 months	7 (8%)	2 (2%)
7–9 months	12 (14%)	3 (3%)
10–12 months	16 (18%)	3 (3%)
13–18 months	9 (10%)	0
19–24 months	4 (5%)	1 (1%)

Data are  $n$  (%).

the ongoing demands of managing PKU therapy. A pharmacologic treatment for PKU was U.S. Food and Drug Administration approved in 2007 and might eventually be used in infants with PKU, but currently use of sapropterin dihydrochloride (Kuvan<sup>®</sup>; Biomarin<sup>®</sup>, Novato, CA) is limited to children over 4 years of age.<sup>31</sup>

In this sample, mothers' with infants who have PKU from the United States and Canada on average breastfed longer than mothers with infants who have PKU from other countries in Europe, Asia, and South America reported by other investigators.<sup>3,10,11,15-17</sup> Those studies consistently reported that the majority of mothers who were breastfeeding infants with PKU did not persist as long as mothers' breastfeeding healthy infants without PKU. Given that statistics for the incidence and duration of breastfeeding infants with PKU from countries outside North America are at least a decade old, current data might reveal more similar rates. Alternatively, the current study included mothers reporting current and retrospective experiences, and the rate and duration may reflect those who felt successful and therefore responded to the survey.

Biological and social demographic characteristics that might have influenced breastfeeding duration were likely not manifested in this study because of the homogeneous demographic characteristics of the sample, which was predominantly white, well-educated, and older mothers, who characteristically have been associated with higher rates of breastfeeding.<sup>12-14</sup> Yet, breastfeeding duration rates were remarkable considering the substantial effort required to breastfeed for these mothers. These mothers breastfed, bottle fed Phe-free medical beverage, breast pumped after bottle feeding Phe-free medical beverage to maintain their breastmilk supply, and obtained once to twice weekly in-home infant Phe blood samples for laboratory analysis.

The only variable that was linked to breastfeeding duration was when standard commercial infant formula was added into the infant's diet, thereby replacing breastfeeding or pumped expressed mothers' milk. This finding is consistent with the observations of other researchers,<sup>32</sup> who identified formula supplementation in breastfed infants as a strong predictor for the discontinuation of breastfeeding in other healthy non-PKU populations. It is also possible that challenges maintaining breastmilk supply necessitated supplementation, which in turn further diminished breastmilk supply and encouraged discontinuation of breastfeeding.

Less is known about factors that affect the duration of breastfeeding infants with PKU. In this study, approximately one-third of the mothers ( $n=33$ ) breastfed to their infant's first birthday, suggesting these mothers were able to maintain lactation and further adapt their breastfeeding with the introduction of solid foods. Yet, more than 20% of mothers ( $n=20$ ) stopped breastfeeding prior to their infant being a month of age; by 6 months, more than 45% of mothers ( $n=41$ ) stopped breastfeeding. This is consistent with other researchers who have found that the majority of all mothers who stop breastfeeding healthy infants without PKU do so in the first 6 months.<sup>33,34</sup> This suggests that mothers who are breastfeeding infants with PKU may need more support during the early weeks after diagnosis and again when low-Phe table foods are introduced at around 6 months. Although some barriers and challenges to breastfeeding infants with PKU<sup>35</sup> have been identified, the role that metabolic clinics

play in the continuation or discontinuation of breastfeeding infants with PKU should be investigated further.

This study has several limitations and strengths. Even though this convenience sample population was drawn from the Internet with mothers living in various regions across the United States and Canada, from small rural communities to large metropolitan cities, the sample was representative of highly educated, married/partnered mothers who may not be representative of the larger population of mothers with children who have PKU in the United States and Canada. In addition, the sample ethnicity was overwhelmingly white, but this is consistent with the known ethnic distribution of PKU having a higher incidence in individuals of Northern European ancestry than black, Hispanic, and Asian individuals.<sup>14,20-22</sup> Furthermore, the sample characteristics were consistent with those who use the Internet for health and other purposes as they tend to be more educated and affluent than those who do not.<sup>36</sup> Consequently, mothers who read and post to the PKU Listserv may be more educated regardless of geographic residence than the general population of mothers with children who have PKU, a population for whom demographic characteristics are not known. Further research is needed to include mothers of breastfeeding infants with PKU across the socioeconomic spectrum, especially those with incomes less than \$50,000 per year, who are of non-Northern European heritage, and have limited computer access.

This was a quantitative descriptive study with an unequal distribution between United States and Canadian mothers (89 vs. 14, respectively) who have infants with PKU. This unequal distribution could be the result of the population difference between the United States and Canada and most likely reflects the fact the United States has a 10-fold larger population<sup>37,38</sup> and a somewhat higher reported incidence of PKU<sup>39</sup> (1:10,000–1:20,000) than Canada<sup>22,40</sup> (1:15,000–1:22,000), resulting in a difference of 400 infants with PKU born in the United States each year versus only 26 infants with PKU in Canada. In addition, there was the difference in the announcement of the study in the United States and Canada. The study was originally announced on the PKU Listserv. Afterward, the study was announced on the Canadian PKU and Allied Disorders Web site and newsletter. In the United States, the study was announced on several regional PKU organizations Web pages ( $n=5$ ) and Facebook pages ( $n=3$ ), while other regional PKU organizations ( $n=6$ ) e-mailed or twittered their members along with announcements in regional newsletters ( $n=2$ ). Future studies need to have improved recruitment strategies for Canadian mothers to participate.

In this sample, the majority of breastfed infants with PKU ( $n=82$ , 92%) were born at term, with only seven breastfed infants who were born premature, which could have affected breastfeeding duration due to trouble with latching and suckling.<sup>41</sup> Re-analysis of the data excluding these seven infants did not change the results.

In this study, the purpose was to describe the prevalence and duration of breastfeeding for infants with PKU in the United States and Canada regardless of their metabolic clinic location. Consequently, comparison of Phe levels between breastfed and formula-fed infants with PKU was not conducted. Previous studies<sup>2,3,8-11,18</sup> have consistently reported that breastmilk supplemented with Phe-free medical beverage is an acceptable dietary treatment for infants with PKU as Phe levels could be maintained within the desired range.

Breastfeeding and feeding expressed mothers' milk were used by mothers to provide breastmilk to their infants with PKU. In addition, these mothers were bottle feeding Phe-free medical beverage, breast pumping after bottle feeding in order to maintain breastmilk supply, and performing in-home heel-stick blood sampling once to twice weekly and sending dried, blood-soaked filter paper to a laboratory for Phe analysis. With blood Phe results, adjustments are made in Phe intake by altering the ratio of breastfeeding/feeding expressed mothers' milk to Phe-free medical beverage feeding. In this study, then, "breastfeeding in the context of PKU" was used to describe the work of providing breastmilk to infants with PKU. The survey did not ask mothers to clarify how they provided breastmilk, but rather whether they did provide breastmilk and how long they provided breastmilk to their infant with PKU. In the future, clarification of how infants with PKU receive breastmilk, by breast or bottle, should be obtained to further explore the breastmilk feeding issues that arise from different methods of providing breastmilk.

Our estimates of breastfeeding were based on maternal recall of breastfeeding experiences with infants who have PKU, which ranged between 7 months to 27 years after the birth of the child with PKU. For some mothers, the length of time after birth may have affected their ability to recall their experiences.<sup>42</sup> Despite the varying lengths of time since birth of the child with PKU, a review of the literature revealed no information regarding the prevalence and duration of breastfeeding infants with PKU from countries in North America. This study provided the first exploration of the prevalence and duration of breastfeeding in the context of PKU from North America.

## Conclusions

This study provides further evidence that mothers of infants with PKU can successfully breastfeed, allowing exposure to the benefits of breastmilk and, in many cases, breastfeeding. Consequently, mothers with newly diagnosed breastfeeding infants with PKU and who had planned to breastfeed should be supported and encouraged to continue breastfeeding. It is imperative that healthcare providers who provide metabolic and nutritional care to mothers of infants with PKU reinforce that mothers' breastmilk remains the optimal base feeding for their infants with PKU. Additional research is needed to explore the types of supports these mothers need to successfully maintain breastfeeding in the context of managing the disorder of PKU for their infants. Such research will provide the needed information to contribute to the identification of effective strategies for improved clinical management of breastfeeding in the context of PKU.

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## Disclosure Statement

R.D.S. has received modest honoraria for advisory board participation for Biomarin. S.A.B.-W., N.P., K.A.K., and G.M.K. declare no conflicts of interest exist.

## Author Contributions

S.A.B.-W. conceptualized and designed the study, carried out the initial analyses, and drafted, revised, and approved the final manuscript as submitted. N.P. contributed epidemiological expertise for the analyses, critically reviewed the manuscript, and approved the final manuscript as submitted. K.A.K. contributed to the design of the study, critically reviewed the manuscript, and approved the final manuscript as submitted. R.D.S. contributed metabolic expertise for the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted. G.M.H. contributed to the conceptualization and design of the study, supervised the quantitative data collection and analyses, critically reviewed and edited the manuscript, and approved the final manuscript as submitted.

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