Comparison of the Estimated Prevalence of Diagnosed Homocystinuria and Phenylketonuria in the United States

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Background

- Classical homocystinuria (HCU) is a rare inherited (genetic) disorder in which the body is unable to process the toxic compound homocysteine (HCY), which is involved in several important metabolic processes. HCU is caused by mutations in the cystathionine beta synthase *CBS* gene.[1]
- At least 1 in 200,000–335,000 people worldwide, and 1 in 100,000 to 200,000 in the United States, are estimated to have homocystinuria (HCU).[2,3,4]
- However, these prevalence estimates are widely believed to be an underestimate of the prevalence of HCU. Several studies have estimated the birth prevalence of HCU to be much higher. [5,6]
- Newborn screening (NBS) typically tests for HCU by an indirect method: the concentration of methionine (a precursor to HCY) is measured rather than HCY itself, and NBS often produces false negatives.[7] HCU may be underdiagnosed at birth due to NBS that is inadequately sensitive. Moreover, NBS for HCU has only been universally performed in the U.S. since 2006.
- Symptoms of HCU vary from patient to patient and are ill-defined. Patients are often initially misdiagnosed, and plasma HCY levels are not routinely checked. Hence, diagnosis can be delayed until later in life.
- Phenylketonuria (PKU) is another rare inherited metabolic disorder. It is estimated to occur in approximately 1 in 15,000 people in the United States.[8]
- The newborn screen for PKU utilizes a direct method, and the majority of PKU patients are diagnosed at birth.[9]

Objectives

- To estimate the prevalence of diagnosed HCU in the United States (U.S.) population across age groups compared with that of diagnosed PKU in similar age groups.

Methods

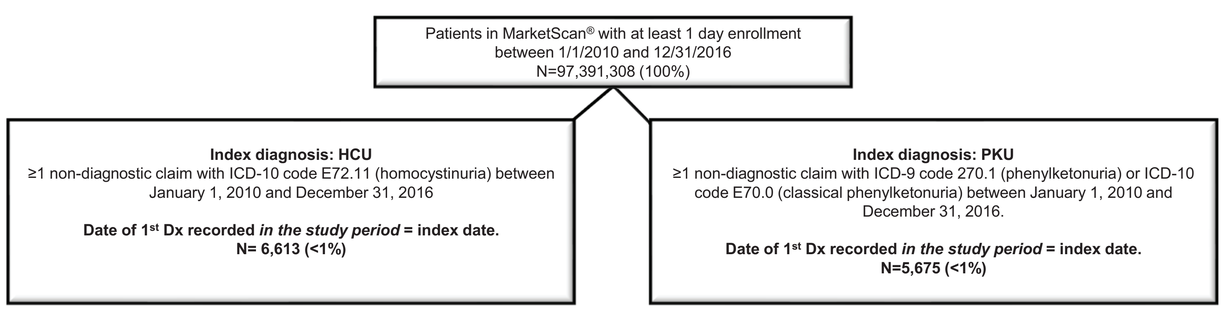
Data Source

- This study utilized patient-level de-identified US administrative claims in the IBM MarketScan® Commercial and Medicare Supplemental Database from January 1, 2010 through December 31, 2016.

Patient Selection and Study Design

- Enrolled patients with an HCU diagnosis or a PKU diagnosis between January 1, 2010 and December 31, 2016 were identified in the MarketScan® database using the following criteria:
  - **HCU cohort – Unique patients with:**
    - At least 1 non-diagnostic claim with International Classification of Diseases, 10th revision (ICD-10) code E72.11 (homocystinuria) between January 1, 2010 and December 31, 2016
      - Each patient's entire available data history during the study was included in the analysis, including ICD-9 diagnoses predating the ICD-10 system.
  - **PKU cohort – Unique patients with:**
    - At least 1 non-diagnostic claim with ICD-9 code 270.1 (phenylketonuria) or ICD-10 code E70.0 (classical phenylketonuria) between January 1, 2010 and December 31, 2016.
- The first diagnosis of HCU or PKU observed during the study time period was set as the index date.
  - Note that the patient population represents a population with prevalent disease. Patients may have been initially diagnosed prior to to the beginning of the study time period.
- Demographics were captured on the index date.

Figure 1. Patient Selection



Analysis

- Prevalence (overall and in each age group) in the MarketScan population was calculated by dividing the number of patients with HCU or PKU by the number of patients enrolled in the MarketScan® database any time between January 1, 2010 and December 31, 2016.
- National projections of prevalence were calculated by multiplying the prevalence determined from MarketScan® data by the population of the United States (overall and by age group) using U.S. Census Bureau population estimates from July 1, 2016 (latest available). Age-adjusted prevalence was further calculated.

Results

Patient Population Characteristics

- A total of 6,613 and 5,120 patients met inclusion criteria for HCU and PKU (Figure 1). The average age of HCU patients (55.5 years) was 38 years older than that for PKU patients (17.5 years). Both cohorts were slightly over 50% female, were primarily residing in urban areas, and the majority were covered by EPO/PPO plans (Table 1).

Table 1. Demographic Characteristics at First Recorded Diagnosis in Study Period

	HCU N=6,613	PKU N=5,120	p-value
Average age (years)	55.5 (SD 14.8)	17.5 (SD 21.0)	<0.001
Male	49.2%	47.0%	0.019
Region			1.000
Northeast	12.4%	17.7%	
North Central	23.8%	19.8%	
South	43.5%	34.2%	
West	20.0%	27.1%	
Missing	0.3%	1.2%	
Residence in an urban area	90.4%	85.1%	<0.001
Plan Type			1.000
Comprehensive	12.9%	2.7%	
HMO	6.5%	10.9%	
EPO/PPO	56.1%	64.0%	
POS/POS with capitation	7.4%	6.5%	
Other	14.8%	9.9%	
Unknown	2.2%	6.0%	

HCU vs. PKU Prevalence Comparison, Overall and by Age

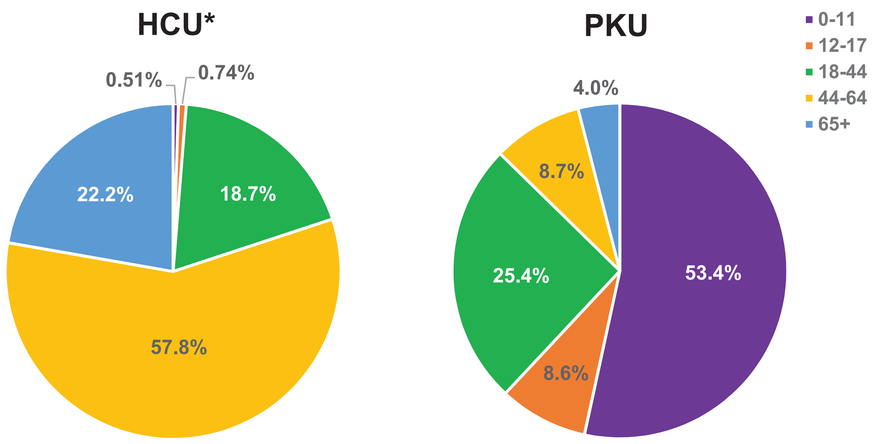
- Overall prevalence in the MarketScan® database during the study time period was higher for HCU than for PKU (0.068 per 1000 [95% CI: 0.066-0.070 per 1000] vs. 0.053 per 1000 [95% CI: 0.051-0.054 per 1000]) (Table 2).

Table 2. MarketScan Prevalence of HCU and PKU Per 1000 Study Population, 1/1/2010 - 12/31/2016

	Enrolled in MarketScan®	Evidence of HCU	Prevalence per 1000	Lower 95% C.L.	Upper 95% C.L.	Evidence of PKU	Prevalence per 1000	Lower 95% C.L.	Upper 95% C.L.
All ages	97,291,308	6,613	0.068	0.066	0.070	5,120	0.053	0.051	0.054
Age groups									
0-11	16,542,800	34	0.002	0.001	0.003	2,734	0.165	0.159	0.171
12-17	7,777,807	49	0.006	0.005	0.008	439	0.056	0.051	0.062
18-24	10,834,667	119	0.011	0.009	0.013	381	0.035	0.032	0.039
25-34	15,880,249	339	0.021	0.019	0.024	569	0.036	0.033	0.039
35-44	14,762,262	778	0.053	0.049	0.056	348	0.024	0.021	0.026
45-54	14,999,423	1,596	0.106	0.101	0.112	232	0.015	0.013	0.017
55-64	11,799,674	2,227	0.189	0.181	0.197	211	0.018	0.015	0.020
65-74	2,760,936	810	0.293	0.273	0.314	121	0.044	0.036	0.052
75-84	1,478,383	480	0.325	0.296	0.354	58	0.039	0.029	0.049
85+	555,107	181	0.326	0.279	0.374	27	0.049	0.030	0.067

- At the time of the first recorded diagnosis during the study period, 0.51% of the HCU cases were ages 0–11 years and 80% were 45 years or older. For PKU cases, 53% were ages 0–11 years and 13% were 45 years or older (Figure 2).

Figure 2. Age at First Recorded Diagnosis during Study Period



*p<0.001 for all comparisons of HCU to PKU in each age group

- Overall, the projected the number of age-adjusted prevalent cases in the United States calculated from MarketScan® prevalence rates was 31,162 people (0.096 per 1000) for HCU and 17,005 people (0.051 per 1000) for PKU.

Limitations

- This study was limited to only those individuals with commercial health coverage or private Medicare supplemental coverage. Results of this analysis may not be generalizable to individuals with other insurance or without health insurance coverage.
- The data in this study was limited to data found in administrative claims, which may be subject to data coding limitations and data entry error.
- Prevalence was only assessed during patients' MarketScan® enrollment between January 1, 2010 and December 31, 2016. Any temporal differences that may exist were not captured in this study.

Conclusions

- While HCU and PKU are both inherited metabolic disorders, the observed prevalence in the United States showed a dramatically different age distribution.
- As expected, the highest proportion of diagnosed PKU patients was observed in the youngest age group (ages 0–11 years), likely due to infants being diagnosed through universal newborn screening.
- Conversely, the prevalence per 1000 for HCU cases among the younger age group was dramatically lower than among older persons, implying that HCU patients are not diagnosed primarily at birth or during early childhood, even though HCU is a lifelong genetic disease.
- This suggests that newborn screening fails to capture the vast majority of HCU cases, with patients diagnosed late in life, including adulthood, when they present with symptoms or comorbid conditions indicative of HCU.

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