Validation of a Patient Identification Algorithm to Estimate the Prevalence of Classical Homocystinuria (HCU) in the United States (US)

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Poster #B24

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METHODS

Study Design and Data Source

- This was a descriptive, retrospective analysis using the IQVIA PharMetrics® Plus and AEMR 2018-2021 databases
  - PharMetrics Plus is comprised of fully adjudicated medical and pharmacy claims, containing a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs, and enrollment information
  - AEMR comprises approximately 75 million US patient records that are sourced from an "opt-in" provider research network. The aggregated database comprises records collected across 80,000 physicians from large practices and physician networks.
- Study period: January 1, 2018-May 31, 2022
- Index date: date of the first qualifying event indicating homocystinuria
  - Date of entry for "homocystinuria" in the AEMR OR homocystinuria-associated International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code (E72.11) in the AEMR or PharMetrics Plus
  - Date of highest total Hcy (tHcy) level
- Demographics and clinical characteristics were assessed in the 1 year prior to index
- Standardized prevalence rates were estimated by projecting prevalence rates by age from this study to the 2020 US Census

Patient Identification Algorithm

- Using a previously developed algorithm[8] to identify two cohorts of patients using strict and broad definitions of HCU, patient cohorts were identified in a stepwise method, based on the presence of the term homocystinuria in the AEMR or a homocystinuria-related ICD-10 diagnosis code (E72.11) in the AEMR or PharMetrics Plus dataset, followed by the patients' highest tHcy level at any time during the study period (**Figure**)
- Clinical characteristics and phenotypic outcomes were used to further refine the cohort selection for the broad cohort
- The cohorts were used to calculate prevalence estimates, standardized using US Census Bureau data

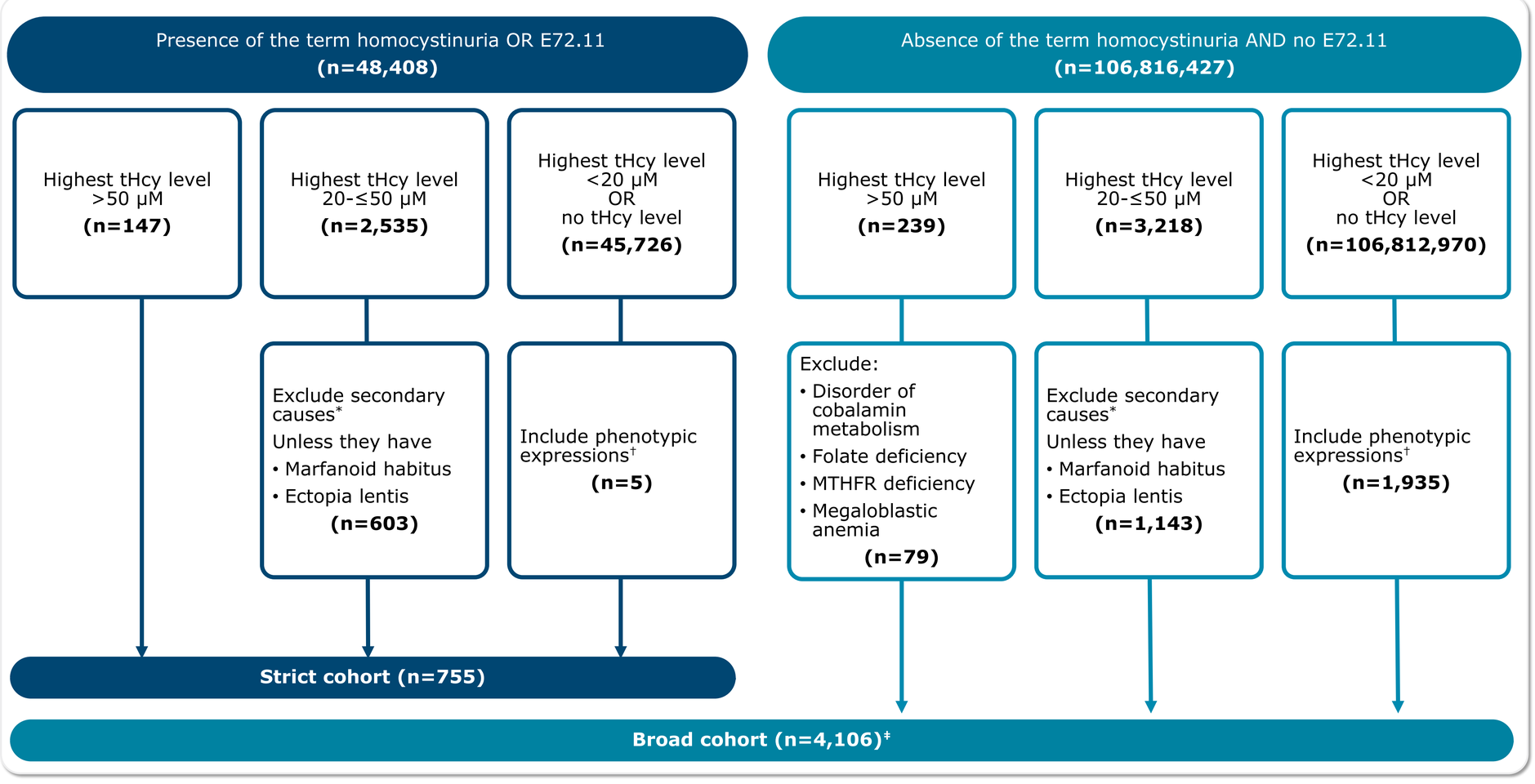
Strict cohort

- The strict cohort included patients with the term homocystinuria in the AEMR or a homocystinuria-related ICD-10 diagnosis code (E72.11) in the AEMR or PharMetrics Plus dataset, if they had:
  a) Highest tHcy level >50 µM
  b) Highest tHcy level 20-≤50 µM with no other identifiable secondary cause of elevated tHcy
  c) Highest tHcy <20 µM or no tHcy level with clinical presentations indicative of HCU
     - ≥2 Type A conditions (pectus excavatum, ectopia lentis, or marfanoid habitus); or
     - ≥1 condition listed as Type A AND ≥1 condition listed as Type B (thrombotic/thromboembolic events or neurologic features)

Broad cohort

- The broad cohort included patients within the strict cohort with the addition of:
  1. Patients without the term homocystinuria in the AEMR and no E72.11 diagnosis code, if they had:
     a) Highest tHcy >50 µM without disorder of cobalamin metabolism or folate or methylenetetrahydrofolate reductase (MTHFR) deficiency or megaloblastic anemia
     b) Highest tHcy 20-≤50 µM with no other identifiable secondary cause of elevated tHcy
     c) Highest tHcy <20 µM or no tHcy level with clinical presentations indicative of HCU (excluding patients with disorders of sulfur-bearing amino-acid metabolism [ie, sulfite oxidase, cystathioninuria, methioninemia])
  2. Patients with evidence of betaine prescriptions and without megaloblastic anemia or disorder of cobalamin metabolism or folate or MTHFR deficiency

Figure. HCU Patient Identification Algorithm



*Secondary causes; At any time:** Megaloblastic anemia, disorder of cobalamin metabolism, folate deficiency, CKD, ESKD, renal transplant, diabetes, hypothyroidism; **Within 12 mo:** Myocardial infarction. †**Phenotypic expressions:** 1. Ectopia lentis AND (cerebrovascular thrombotic/thromboembolic event OR neurologic feature) **exclude**: Marfanoid habitus, sulfite oxidase deficiency (E72.19); 2. Pectus excavatum AND (cerebrovascular thrombotic/thromboembolic event OR [any thrombotic/thromboembolic event AND neurologic feature]) **exclude**: Marfanoid habitus, sulfite oxidase deficiency (E72.19); 3. Marfanoid habitus AND cerebrovascular thrombotic/thromboembolic event AND neurologic feature AND (ectopia lentis OR pectus excavatum) **exclude**: Sulfite oxidase deficiency (E72.19). ‡The total number of patients in the broad cohort includes 3,912 patients, as shown above, plus 194 patients with 2 records of betaine at least 12 months apart (excluding those with megaloblastic anemia or disorder of cobalamin metabolism or folate or MTHFR deficiency). Index date for these patients was defined as the date of first betaine record.
CKD, chronic kidney disease; **ESKD**, end-stage kidney disease; **HCU**, classical homocystinuria; **mo**, month; **MTHFR**, methylenetetrahydrofolate reductase; **tHcy**, total homocysteine.

RESULTS

Patient Demographics and Clinical Characteristics

- Strict (n=755) and broad (n=4,106) cohorts were similar in gender (41.6% and 40.6% female), while mean age was higher in the strict than broad cohort (63.6 vs 44.6 years) (**Table 1**)
- There was a higher proportion of pediatric patients (<18 years old) in the broad cohort compared with the strict cohort (28.2% vs 0.8%) (**Table 1**)
- Median highest tHcy level was 25 µM in the strict cohort and 24 µM in the broad cohort (**Table 2**)

Prevalence Estimates

- Average annual standardized prevalence estimates (2018-2021) were 0.84 per 100,000 (strict cohort) and 3.52 per 100,000 (broad cohort)
- The projected prevalence of HCU in the US is 2,800 based on the strict definition and 11,732 based on the broad definition

Table 1. Patient Demographics in the Strict and Broad Cohorts

	Strict cohort (n=755)	Broad cohort (n=4,106)
Gender, female, n (%)	314 (41.6)	1,669 (40.6)
Age at index (continuous), y		
Mean (SD)	63.6 (14.4)	44.6 (28.1)
Age at index (categorical), y, n (%)		
<18	6 (0.8)	1,156 (28.2)
18-44	80 (10.6)	594 (14.5)
45-64	237 (31.4)	1,007 (24.5)
65-74	268 (35.5)	722 (17.6)
≥75	164 (21.7)	625 (15.2)
Unknown or missing	0 (0.0)	2 (0.0)
Race, n (%)		
White	459 (60.8)	1,813 (44.2)
Black	66 (8.7)	176 (4.3)
Other	13 (1.7)	68 (1.7)
Asian	13 (1.7)	38 (0.9)
Unknown or missing	204 (27.0)	2,011 (49.0)

Because of rounding, percentages may not total 100.
SD, standard deviation; **y**, years.

Table 2. Patient Clinical Characteristics in the Strict and Broad Cohorts

	Strict cohort (n=755)	Broad cohort (n=4,106)
tHcy level available, n (%)*	751 (99.5)	1,985 (48.3)
Highest tHcy level, median, µM	25	24
Highest tHcy level, categorical, n (%)*,†,‡		
<20 µM	1 (0.1)	13 (0.7)
20-≤50 µM	603 (80.3)	1,746 (88.0)
>50 µM	147 (19.6)	226 (11.4)
≥100 µM	39 (5.2)	60 (3.0)
Charlson Comorbidity Index, mean (SD)	1.4 (1.6)	0.8 (1.4)
Baseline clinical events, n (%)		
Thrombotic/thromboembolic event	63 (8.3)	700 (17.0)
Cerebrovascular disease	60 (7.9)	357 (8.7)
Pectus excavatum	2 (0.3)	1,172 (28.5)
Ectopia lentis	0 (0.0)	39 (0.9)

*At any time during the study period. †The >50 µM group includes patients in the ≥100 µM group. ‡Percentage shown as proportion of total patients with tHcy level available.
SD, standard deviation; **tHcy**, total homocysteine.

Patient Identification

- Nearly all patients (99.5%) in the strict cohort had tHcy results (**Table 2**)
- In the broad cohort, 81.6% of patients did not have a diagnosis code for homocystinuria; among these patients, 2.4% had tHcy >50 µM and 34.1% had tHcy between 20 and 50 µM, with clinical presentation indicative of HCU (**Figure**)
- In the strict cohort, among patients with elevated tHcy (≥20 µM), 80.4% had tHcy ≤50 µM (**Figure**)
- Overall, 57.4% of patients without a diagnosis code for homocystinuria had no tHcy results available but had multiple clinical presentations indicative of HCU (**Figure**)
- Overall, 54.1% of patients had any lab results (not limited to tHcy) available in the AEMR database during the study period

INTRODUCTION

- Classical homocystinuria (HCU) is a rare, monogenic, autosomal recessive inborn error of metabolism, caused by cystathionine β-synthase deficiency and characterized by marked accumulation of homocysteine (Hcy) and methionine (Met) in plasma and tissues[1-3]
- HCU is associated with risk of severe multisystemic complications including stroke, cognitive impairment, developmental delays, and ocular and skeletal abnormalities[1,2,4]
- Newborn screening primarily tests for elevated Met, not Hcy, and has limitations in detecting HCU[5,6]
- Historical United States (US) prevalence estimates were based predominantly on newborn screening and were approximately 1 per 100,000 to 200,000.[1,7] A more recent study reported that the prevalence may be up to 10 times higher.[5]
  - The global prevalence of HCU has been estimated at 1 per 200,000 to 335,000[4]
- Using US administrative claims data, limited research exists on identifying patients with HCU beyond the diagnosis code

Objectives

- To validate an algorithm designed to identify patients with HCU based on diagnosis codes, lab values, and clinical presentations
- To estimate the prevalence of HCU using the IQVIA PharMetrics Plus and Ambulatory Electronic Medical Record (AEMR; 2018-2021) databases

DISCUSSION

- Using a previously developed algorithm[8] to identify patients with HCU based on presence of the E72.11 ICD-10 code, highest tHcy levels, betaine use, and clinical presentation, we determined a projected prevalence of HCU in the US using the IQVIA PharMetrics Plus and AEMR 2018-2021 databases
- A previously published analysis[8] of the Optum Market Clarity Dataset revealed that the projected US prevalence of HCU is 3,466 based on the strict definition and 17,631 based on the broad definition
  - These estimates are similar to the ones found in our current study and noted differences are likely due to variations in data sources
- In the broad cohort, there were many patients with elevated Hcy levels and a combination of clinical presentations indicative of HCU that did not have a diagnosis of HCU

Limitations

- The findings are mainly generalizable to a commercially insured population residing mostly in the East Coast of the US
- Just over one-half of patients in the AEMR database had any lab results during the study period. Missing data or errors in detection of HCU-related terms and codes in patient records may introduce bias into the analyses, including potential underestimation of US prevalence.
- For some patients, the index date may not represent the date of first diagnosis, as the analysis was restricted to more recently available data (2018-2021)

CONCLUSIONS

- ✓ HCU prevalence estimates vary based on the identification criteria, cohort definitions, and database used
- ✓ A large proportion of patients with clinical presentations suggestive of HCU did not have a corresponding diagnosis of HCU, potentially indicating underdiagnosis and/or underreporting
- ✓ Future research to explore additional methods to better understand the true prevalence of HCU is warranted

DISCLOSURES

MJ: has received consultancy fees from Travere Therapeutics, Inc. **LP and MS:** are employees and stockholders of Travere Therapeutics, Inc. **MG, WK, DT, KH:** are employees of IQVIA, Inc. and received compensation from Travere Therapeutics, Inc. for conducting this study and providing medical writing support. **AR, CNM, DTA:** are employees of Genesis Research and received compensation from Travere Therapeutics, Inc. for conducting this study and providing medical writing support.

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ABBREVIATIONS

AEMR, Ambulatory Electronic Medical Record; **CKD**, chronic kidney disease; **ESKD**, end-stage kidney disease; **HCU**, classical homocystinuria; **Hcy,** homocysteine; **ICD-10**, International Classification of Diseases, Tenth Revision; **Met,** methionine; **MTHFR,** methylenetetrahydrofolate reductase; **mo,** month; **SD**, standard deviation; **tHcy**, total homocysteine; **US,** United States; **y**, years.

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