DEVELOPMENT OF A PATIENT IDENTIFICATION ALGORITHM TO ESTIMATE PREVALENCE OF CLASSICAL HOMOCYSTINURIA (HCU) IN THE UNITED STATES (US)

Mahim Jain[1], Lionel Pinto[2], Kamlesh M. Thakker[3], Mehul Shah[2], Andrew Rava[4], Colette Ndiba-Markey[4], David Cork[5]

[1]Kennedy Krieger Institute, Johns Hopkins Medicine, Baltimore, MD, USA; [2]Travere Therapeutics, Inc., San Diego, CA, USA; [3]Notting Hill Consulting LLC, Celebration, FL, USA; [4]Genesis Research, Hoboken, NJ, USA; [5]Genesis Research, Newcastle upon Tyne, UK

Poster# 54

TRAVERE THERAPEUTICS

METHODS

Study Design and Data Source

- This was a descriptive, retrospective analysis using Optum's de-identified Market Clarity Data (2007-2021) and proprietary Natural Language Processing (NLP) Data
- The Optum® de-identified Market Clarity Dataset deterministically links medical and pharmacy claims with electronic health record (EHR) data from providers across the care continuum
- Study period: January 01, 2016-September 30, 2021
- Baseline period: 6 months prior to index (not applicable to prevalence calculation)
- Index date: date of first diagnosis criterion (ICD code; signs, disease, and symptoms (SDS) term; lab value; etc.)

Patient Identification Algorithm

- Expert clinical input was incorporated to develop an algorithm to identify 2 cohorts of patients using strict and broad definitions of HCU (**Figure**)
- Patient cohorts were identified in a stepwise method, based on the presence of an HCU-related ICD-10 code (E72.11) or SDS NLP term, followed by the patients' highest total homocysteine (tHcy) level at any time during the study period
- Clinical characteristics and phenotypic outcomes were used to further refine the cohort selection
- The cohorts were used to calculate prevalence estimates, standardized using US Census Bureau data

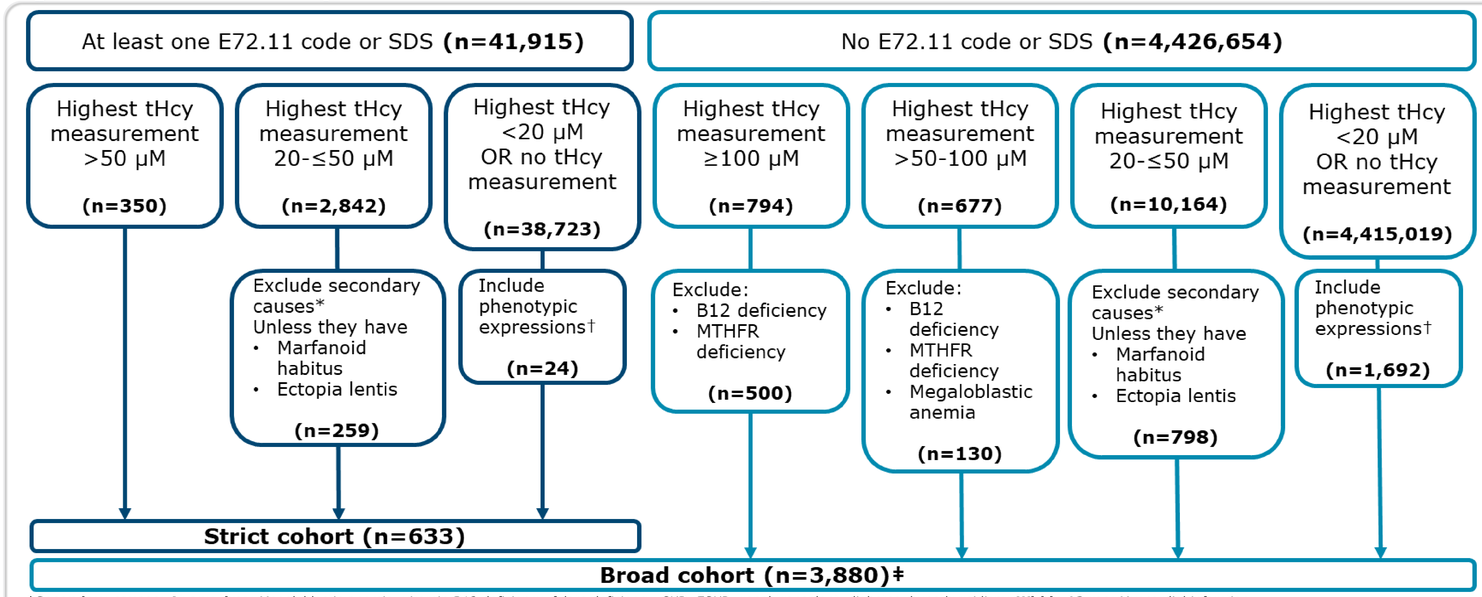
Strict Cohort (Figure)

- The strict cohort included patients with an HCU-related ICD-10 code (E72.11) or SDS NLP term if they had:
  1. Highest tHcy measurement >50 µM
  2. Highest tHcy measurement 20-≤50 µM with no other identifiable cause of elevated tHcy (**Figure**)
  3. Highest tHcy <20 µM or no measurement with clinical presentations indicative of HCU (pectus excavatum, ectopia lentis, or marfanoid habitus plus a thrombotic/thromboembolic event ± neurologic features)

Broad Cohort (Figure)

- Included patients within the strict cohort with the addition of:
  1. Patients with evidence of betaine prescriptions and without vitamin B12 deficiency or methylenetetrahydrofolate reductase (MTHFR) deficiency
  2. Patients without E72.11/SDS if they had:
     a) Highest tHcy ≥100 µM without vitamin B12 deficiency or MTHFR deficiency
     b) Highest tHcy >50-100 µM without vitamin B12 deficiency, MTHFR deficiency, or megaloblastic anemia
     c) Highest tHcy 20-≤50 µM with no other identifiable cause of elevated tHcy
     d) Highest tHcy <20 µM or no measurement with clinical presentations indicative of HCU

Figure. Classical Homocystinuria Patient Identification Algorithm



***Secondary causes; At any time:** Megaloblastic anemia, vitamin B12 deficiency, 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 (E72.19); 2. Pectus excavatum AND (cerebrovascular thrombotic/thromboembolic event OR [any thrombotic/thromboembolic event AND neurologic feature]) **exclude**: Marfanoid habitus, sulfite oxidase (E72.19); 3. Marfanoid habitus AND cerebrovascular thrombotic/thromboembolic event AND neurologic feature AND (ectopia lentis OR pectus excavatum) **exclude**: Sulfite oxidase (E72.19).
‡The total number of patients in the broad cohort includes 3,753 patients, as shown above, plus 127 patients with or without E72.11 or SDS and 2 records of betaine at least 12 months apart (excluding vitamin B12 and MTHFR deficiency). CKD, chronic kidney disease; ESKD, end-stage kidney disease; mo, month; MTHFR, methylenetetrahydrofolate reductase; SDS, signs, disease, and symptoms; tHcy, total homocysteine.

RESULTS

Table 1. Patient Demographics in the Strict and Broad Cohorts*

	Strict cohort (n=633)	Broad cohort (n=3,880)
Gender, female	295 (46.6)	1,862 (48.0)
Age at index (continuous), y		
Mean (SD)	50.0 (18.0)	57.2 (21.1)
Age at index (categorical), y		
<10	23 (3.6)	119 (3.1)
10-17	10 (1.6)	70 (1.8)
18-34	73 (11.5)	408 (10.5)
35-44	119 (18.8)	385 (9.9)
45-54	139 (22.0)	594 (15.3)
55-64	128 (20.2)	721 (18.6)
65-74	92 (14.5)	642 (16.5)
≥75	49 (7.7)	941 (24.3)
Race		
African American	80 (12.6)	363 (9.4)
Asian	9 (1.4)	37 (1.0)
White	502 (79.3)	3,216 (82.9)
Other/Unknown	42 (6.6)	264 (6.8)

*Expressed as No. (%) unless otherwise indicated. Because of rounding, percentages may not total 100. SD, standard deviation; y, years.

Patient Characteristics

- Strict (n=633) and broad (n=3,880) cohorts were similar in gender (46.6% and 48.0% female), while mean age was lower in the strict than broad cohort (50.0 vs. 57.2 years) (**Table 1**) and median highest tHcy measurement was higher in the strict than broad cohort (52.5 µM vs. 27.3 µM) (**Table 2**)
- Among patients in the strict cohort with elevated tHcy (≥20 µM), 43% had tHcy ≤50 µM, suggesting their condition may be well managed

Prevalence

- Average annual standardized prevalence estimates (2016-2020) were 1.04 per 100,000 (strict cohort) and 5.29 per 100,000 (broad cohort)

Patient Identification

- Eighty-three percent of patients did not have E72.11/SDS, of which 53% had multiple clinical presentations indicative of HCU
- Among patients without E72.11/SDS who had available tHcy measurements, 42% had a highest value >50 µM and 33% had a highest value ≥100 µM

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

	Strict cohort (n=633)	Broad cohort (n=3,880)
tHcy measurement available†	582 (91.9)	1,700 (43.8)
Highest tHcy measurement, median (Q1, Q3), µM†	52.5 (24.8, 81.5)	27.3 (21.8, 60.0)
Highest tHcy†,‡,§		
<20 µM	5 (0.9)	99 (5.8)
20-<50 µM	258 (44.3)	1,058 (62.2)
≥50 µM	319 (54.8)	543 (31.9)
≥100 µM	111 (19.1)	204 (12.0)
Charlson Comorbidity Index, mean (SD)	0.7 (1.4)	1.2 (1.9)
Baseline clinical events		
Thrombotic/thromboembolic event	136 (21.5)	841 (21.7)
Cerebrovascular disease	69 (10.9)	701 (18.1)
Ectopia lentis	9 (1.4)	62 (1.6)
Pectus excavatum	3 (0.5)	23 (0.6)

*Expressed as No. (%) unless otherwise indicated. †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 measurement available. Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation; tHcy, total homocysteine.

CONCLUSIONS

- ✓ HCU prevalence estimates vary widely based on the approach and cohort definitions
- ✓ A large proportion of patients with high tHcy levels and clinical presentations indicative of HCU did not have a corresponding diagnosis of HCU, suggesting potential underdiagnosis and/or underreporting
- ✓ Future research should explore alternative methods to better understand the true prevalence of HCU

DISCLOSURES

MJ: has received consultancy fees from Travere Therapeutics, Inc.; **LP:** is an employee and stockholder of Travere Therapeutics, Inc.; **KMT:** has a consulting contract with Travere Therapeutics, Inc. and does not have any equity interest in Travere Therapeutics, Inc.; **MS:** is an employee and stockholder of Travere Therapeutics, Inc.; **AR, CNM, DC:** 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

CKD, chronic kidney disease; **EHR,** electronic health record; **ESKD,** end-stage kidney disease; **HCU,** classical homocystinuria; **ICD,** International Classification of Diseases; **ICD-10,** International Classification of Diseases, Tenth Revision; **mo,** month; **MTHFR,** methylenetetrahydrofolate reductase; **NLP,** Natural Language Processing; **No.,** number; **Q1,** 1st quartile; **Q3,** 3rd quartile; **SD,** standard deviation; **SDS,** signs, disease, and symptoms; **tHcy,** total homocysteine; **US,** United States; **y,** years

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INTRODUCTION

- Classical homocystinuria (HCU) is a rare genetic disorder caused by cystathionine β-synthase deficiency[1,2]
- HCU is associated with a risk of complications, including thrombotic/thromboembolic events, cognitive impairment, developmental delays, ectopia lentis, myopia, and elongated arms and legs (marfanoid habitus)[1,2]
- Newborn screening primarily tests for methionine, not homocysteine, and has poor sensitivity for detecting HCU[3,4]
- Historical US prevalence estimates, based predominantly on newborn screening, are approximately 1 per 100,000-200,000, but a more recent study suggested the prevalence may be up to 10 times higher[4]
- Limited research exists on identifying patients with HCU beyond the diagnosis code

Objectives

- To develop an algorithm to identify patients with HCU based on diagnosis codes, lab values, and clinical presentations
- To estimate the prevalence of HCU using the Optum® Market Clarity Dataset

DISCUSSION

- We developed an algorithm to identify patients with HCU based on presence of the E72.11 ICD-10 code, highest tHcy levels, betaine use, and clinical presentation
- The projected prevalence of HCU in the US is 3,466, based on the strict definition, and 17,631, based on the broad definition
- The data suggest that many patients are diagnosed later in life (based on age at index diagnosis) and others remain undetected or undiagnosed for a long time despite presenting with conditions indicative of HCU

Limitations

- This study was limited to data in the Optum® Market Clarity Dataset and may not be representative of the broader US population
- 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 (2016-2020)

Contact information: Medinfo@Travere.com

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