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

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Background: Classical homocystinuria (HCU) is a rare genetic disorder caused by cystathionine β-synthase deficiency, which can increase risk for complications including ectopia lentis, myopia, intellectual disability, elongated arms and legs (marfanoid habitus), developmental delays, and thromboembolic events. Newborn screening primarily tests for methionine, not homocysteine, and has poor sensitivity for detecting HCU. Historical US prevalence estimates, based predominantly on newborn screening, were approximately 1 per 100,000–200,000, but a more recent study suggested the prevalence may be up to 10 times higher. To improve understanding of the true prevalence of HCU, we developed a patient identification algorithm which, in addition to diagnosis codes, considered total homocysteine (tHcy) values combined with specific clinical presentations indicative of HCU.

Methods: This was a descriptive, retrospective analysis using Optum's de-identified Market Clarity Data (2007-2021) and proprietary Natural Language Processed (NLP) Data. Expert clinical input was incorporated to develop a patient identification algorithm. The strict cohort included patients with an HCU-related ICD-10 code (E72.11) or signs, disease, and symptoms (SDS) NLP term if they had: 1) highest tHcy measurement >50 µmol/L; 2) highest tHcy measurement 20-≤50 µmol/L with no other identifiable cause of elevated tHcy; 3) highest tHcy <20 µmol/L or no measurement with clinical presentations indicative of HCU (pectus excavatum, ectopia lentis, or marfanoid habitus plus a thromboembolic event ± neurologic features). The broad cohort additionally included patients with evidence of betaine prescriptions and patients without E72.11/SDS if they had: 1) highest tHcy ≥100 µmol/L without vitamin B12 deficiency or methylenetetrahydrofolate reductase (MTHFR) deficiency; 2) highest tHcy >50-100 µmol/L without vitamin B12 deficiency, MTHFR deficiency, or megaloblastic anemia; 3) highest tHcy 20-≤50 µmol/L with no other identifiable cause of elevated tHcy; 4) highest tHcy <20 µmol/L or no measurement with clinical presentations indicative of HCU. The cohorts were used to calculate prevalence estimates, standardized using US Census Bureau data.

Results: Average annual standardized prevalence estimates (2016-2020) were 1.04 per 100,000 (strict cohort) and 5.29 per 100,000 (broad cohort). Strict (n=633) and broad (n=3,880) cohorts were similar in sex (53.4% and 52.0% female), while mean age was lower in strict than broad cohort (50.0 vs. 57.2 years), and median highest tHcy measurement was higher in the strict than broad cohort (52.5 vs. 27.3 µmol/L). Among patients in the strict cohort with elevated tHcy (≥20 µmol/L), 43% had tHcy ≤50 µmol/L, suggesting their condition may be well managed. The broad cohort may indicate that many HCU cases go undetected; 83% of patients did not have E72.11/SDS, of which 53% had multiple clinical presentations indicative of HCU, and among patients without E72.11/SDS who had available tHcy measurements, 42% had a highest value >50 µmol/L and 33% had a highest value ≥100 µmol/L.

*Conclusion*s: 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.

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