U.S. States Urged to Follow Expert Guidance, Revise Newborn Screening Protocols for Classical Homocystinuria

Experts estimate that up to half of babies born with Classical Homocystinuria (HCU), a rare, genetic disorder of the metabolism, are currently being missed by newborn screening (NBS) across the US[1].

Diagnosed later, which is when symptoms typically appear, people with HCU are more likely to experience severe and even life-threatening health consequences. The most serious risks of a late diagnosis include strokes and blood clots, which, sadly, have proven fatal for many young children with HCU. These patients are also at higher risk of scoliosis and osteoporosis starting in early childhood.

The devastating health issues people with HCU can experience from being missed by newborn screening are unacceptable and largely preventable. **HCU Network America urges states to follow expert guidance and revise their HCU newborn screening protocols**. We are here to help. Work with us to eliminate false negatives and improve health outcomes for babies born with HCU.

> "We know if patients get diagnosed at birth and put on a treatment plan, then we mitigate the possibilities of the red-flag symptoms. Some patients might have less severe symptoms, but overall, it's controlled."
>
> - Danae' Bartke, Executive Director of HCU Network America and HCU patient

HCU prevents the body from breaking down certain amino acids, causing a harmful build-up of substances in the blood and urine.

Signs and Symptoms of HCU that can be seen include:

- **Blood clots** (thrombosis) anywhere, including the brain
- **Optic lens dislocation** (ectopia lentis)
- **Tall stature** with long arms and legs
- **Increased risk of broken bones** due to more fragile bones (osteoporosis)
- **Curved spine** (scoliosis)
- **Cognitive problems** and mental health issues

Homocystinuria has a mortality rate of **18%** by age **30** if not initially diagnosed at birth.

[1] Naughten et al 1998; Gan-Schreier et al 2010. https://onlinelibrary.wiley.com/doi/full/10.1007/s10545-016-9979-0

Although HCU officially became part of the Recommended Uniform Screening Panel in 2009 and is screened in all states, issues with varied screening protocols continue to result in missed cases.

By implementing the changes listed below, states could significantly lower the number of false negatives and increase the likelihood of identifying HCU in newborns.[2,3]

THE PROBLEM

Why are so many babies being missed?

The biomarker used to screen for HCU, Methionine (MET), is not as sensitive as another biomarker called total plasma homocysteine (tHCY) – **yet many newborns are only being tested for MET.**

Additionally, it is mandatory in the US to carry out newborn screening within 24–48 hours after birth – yet this **is too soon to detect HCU in many affected newborns**, who typically do not have positive bloodwork for or show signs of increased MET until after this period.

There is no harmonized cut-off level for elevated Methionine.

Each state set its own cut-off parameters, which has led to missed cases of HCU because many states use a cut off that is 1.5 - 3 times higher than the recommended value.

POSSIBLE SOLUTION

Experts recommend a second-tier test for tHCY using the same dried blood spot[4]. The CDC is finalizing first- and second-tier assays for tHCY that will be made available to the state labs.

U.S. and international experts in newborn screening for HCU have recommended a revised process that includes a lower cut-off for MET or a corresponding ratio of MET to Phenylalanine (PHE). The recommended lower cut-off for MET can range from 39 to 50 uM1, depending on lab median.

State NBS Labs and HCU Stakeholders:

Join us to better ensure babies born with HCU are diagnosed at birth. We are here to partner and help. Please contact Danae' Bartke, executive director of HCU Network America, to discuss the specific situation in your state and how we can work together toward needed revisions and improved health outcomes.

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[2] Matern D, Tortorelli S, Oglesbee D et al. Reduction of false-positive rate in newborn screening by implementation of MS/MS-based second-tier tests: The Mayo Clinic experience (2004-2007). J Inherit Metab Dis. 2007; 30: 585-592; [3] Chace D, Hannon W. Impact of Second-Tier Testing on the Effectiveness of Newborn Screening. Clin Chem. 2010; 56: 1653-1655 https://doi.org/10.1373/clinchem.2010.153494; [4] Keller R, Chrastina P, Pavlíková M et al. Newborn screening for homocystinurias: Recent recommendations versus current practice. J Inherit Metab Dis. 2019; 42: 128– 139. https://doi.org/10.1002/jimd.12034;