DEPARTMENT OF HEALTH AND HUMAN SERVICES

Advisory Committee on Heritable Disorders
in Newborns and Children
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https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html

December 17, 2018

Andrea DeBarber, PhD
Research Associate Professor
Physiology & Pharmacology Department (L334)
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239-3098

Dear Dr. DeBarber:

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) appreciates your nomination of cerebrotendinous xanthomatosis (CTX) for inclusion on the Recommended Uniform Screening Panel (RUSP). As part of the Committee's formal review process, a review of the nomination package was conducted and the results of that review were presented at the November 2018 Committee meeting. A copy of the presentation is enclosed.

The Committee recognizes CTX as a medically serious condition that deserves thorough consideration. It was also concluded that there is a CLIA approved confirmatory test for CTX, a treatment is available through an orphan-drug designation by the Food and Drug Administration of chenodeoxycholic acid, and there are defined treatment protocols.

However, the Committee will require additional information in the following areas before a decision can be made as to whether the nomination can go to the next step of evidence review:

A. **Prospective population-based pilot study data** – At least one CTX case must be prospectively identified through a newborn screening system. Specifically, the Committee requires the following:
    - Data should be available from pilot studies involving population-based screening of identifiable newborns.

- The study should evaluate the newborn screening process from collection through diagnosis and identify at least one screen-positive newborn with confirmation of presence of the condition under consideration.
- The population included in the pilot study should be similar to the US population and to the populations evaluated by state newborn screening programs with respect to known prevalence of the condition, and the timing and approach to screening.
- The screening modality used in the pilot study should be comparable to the method proposed in the application.

The Committee encourages the nominators to follow the results of ongoing pilot studies as well as look into additional pilot study options.

B. **Case definition** – Add clarification regarding what is considered a true positive CTX case. Include relevant biochemical markers if applicable. Provide references or documentation of consensus among experts in the field.

C. **Characteristics of the screening test/analytic validity –** In the data submitted, many of the characteristics of the screening test are unclear. Data should be available on the analytical validation of one or more of the screening modalities being proposed for use in population-based screening in newborns. The sensitivity, specificity, positive predictive value, and negative predictive value of the screening test must be determined. It is also helpful to identify whether the screening methodology could be multiplexed (e.g. combined with a screening method that is already in use for other newborn screening conditions) and if the screening method could potentially identify conditions other than the nominated condition.

D. **Clinical Utility –** The Committee is interested in understanding how screening can inform treatment and how early treatment can impact health outcomes. Although the suspicion index provides a guide to recognition of cases, and the most serious phenotypes are clear, the progression of other phenotypes is uncertain due to limited data. If additional data are available on the spectrum of CTX, please include. If there are data available that describe the impact of early identification through screening, please provide.

E. **Net benefit -** Data should be available on the net benefits of clinical interventions following early detection compared to clinical diagnosis.

The Centers for Disease Control and Prevention (CDC) is available to provide technical input to researchers interested in nominating new conditions to the RUSP. CDC is developing in-house screening methods for the detection of CTX as well as appropriate quality assurance materials to evaluate method performance. If you have any questions, please contact Carla Cuthbert, Chief of the Molecular Biology Branch at the Centers for

Disease Control and Prevention, ijz6@cdc.gov, for technical assistance regarding the screening methodology and quality materials.

The Committee encourages you to resubmit the nomination when the above items have been addressed. Upon receipt of the completed nomination package, the Committee will review the updated nomination package to determine if the required information is present to enable consideration by the full Committee as to whether CTX will move forward for a full evidence review.

If you have any questions about the additional information requested or when you are ready to submit an updated package, please contact Dr. Catharine Riley (criley@hrsa.gov).

Thank you for your nomination of CTX for inclusion on the RUSP. I look forward to hearing from you soon.

Sincerely yours,

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Joseph A. Bocchini, Jr., M.D.
Chairperson

Enclosure:
ACHDNC Nomination and Prioritization Workgroup Presentation: CTX

cc: Catharine Riley, PhD, MPH
Designated Federal Official
Health Resources and Services Administration