

# Nomination and Prioritization Workgroup Report: Cerebrotendinous xanthomatosis (CTX)

Advisory Committee on Heritable Disorders in Newborns and Children

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# Nomination of Cerebrotendinous xanthomatosis (CTX)

## Nominator

- Andrea E. DeBarber, PhD, Research Associate Professor, OHSU

## Co-Sponsoring Organizations

- Robert Rauner, United Leukodystrophy Foundation President
- John Wolf, Marc Chevrier, MD, United Leukodystrophy Foundation
- William Rizzo, MD, Professor, University of Nebraska Medical Center
- Shailendra B Patel, MD, Professor, University of Cincinnati
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# Cerebrotendinous xanthomatosis (CTX) Overview

- Progressive metabolic leukodystrophy
- Lipid storage disease
- Onset ranges from birth to adulthood
  - infantile-onset diarrhea,
  - childhood-onset cataracts,
  - adolescent- to young adult-onset tendon xanthomas, deterioration of neurologic function
  - adult-onset progressive neurologic dysfunction
    - dementia, psychiatric disturbances, pyramidal and/or cerebellar signs, dystonia, atypical parkinsonism, peripheral neuropathy, and seizures

# Genetics and Epidemiology of Cerebrotendinous xanthomatosis (CTX)

- Autosomal recessive inheritance, variable phenotypic expression
- Deficiency in the mitochondrial enzyme sterol 27-hydroxylase that is encoded by the CYP27A1 gene<sup>1</sup>.
- More than 57 disease causing variants in CYP27A1 have been described<sup>2</sup>.
  - No genotype-phenotype correlation has been determined for CTX.
  - Onset and presentation of symptoms can be variable even for the same pathogenic CYP27A1 variant within the same family.
- ~300 CTX patients have been reported worldwide in >70 years<sup>2</sup>.
- Incidence of CTX varies significantly
  - 1:130,000 (South Asian) to 1:470,000 (African)
    - The incidence of CTX is much higher in certain Israeli populations, for example Moroccan Jews and an isolated Druze community in the Galilee region<sup>3</sup>

# Key Questions

- Is the nominated condition(s) **medically serious**?
- Is the **case definition** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
- Are **prospective pilot data** from population-based assessments available for this disorder?
- Does the screening test(s) have established **analytic validity**?
- Are the **characteristics of the screening test(s)** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
- Is there a widely available and CLIA and/or FDA approved **confirmatory test/diagnostic** process?
- Do the results have **clinical utility**? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?
- Are there defined **treatment** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

# Is the nominated condition(s) *medically serious*?

## **Yes**

- Despite range of phenotypes, CTX is a progressive neurologic disorder.
- Left untreated CTX is very serious when identified clinically.
- Very rare with only ~300 cases since the 1960s. Different incidences based on subgroups.

Is the *case definition* and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.

## No

- Suspicion index to aid in clinical diagnosis of CTX cases that takes into account indicators such as family history and common systemic and neurological features<sup>4</sup>
  - Most serious phenotype is clear
  - Lack of genotype/phenotype correlation
  - Minimal data on clinical subtypes
- No biochemical markers/profile in case definition

Are *prospective pilot data* (U.S. and/or international) from population-based assessments available for this disorder? Do these data meet the Committee's pilot study data criteria?

- 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, and the screening protocol used, should be similar to the US population and to 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.



# Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

## No

- Pilot study 1: anonymous Netherlands population newborn DBS
  - Anonymized study, N = 200
- Pilot study 2: identifiable Israeli population newborn DBS
  - Ongoing study, no prospective cases identified
  - “the screening protocol used should be similar to the US population and to state newborn screening programs with respect to known prevalence of the condition”
- Pilot study 3: anonymous Washington State population newborn DBS (study ongoing).
  - Anonymized study with no potential for diagnostic follow-up
  - Ongoing study, no screen positive results

# Does the screening test(s) have established *analytic validity*?

## Unclear

- FIA-MS/MS + LC-MS/MS
  - Supplementary data not provided
  - Only between run accuracy and precision data provided
  - Linearity and Interference results discussed but not shown
  - Data not provided for
    - LOD or LOQ
    - Recovery
  - Matrix effects indicated the need for use of stable-isotope internal standard analogue which was not available
- FIA-MS/MS
  - Very limited data provided on analytic validation

Are the *characteristics of the screening test(s)* reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

## Unclear

- 1/4" punch and 1/8" punch
- Very different generations of mass spectrometer
  - Waters Premier XE and Sciex QTRAP5500
- False positive rate acceptable
- False negative rate unknown
- Not multiplexed as presented
- Reagent availability/stability
- Other disorders detected: peroxisome biogenesis disorders, cholestatic liver disease, NPC

# Is there a widely available and CLIA and/or FDA approved *confirmatory test/diagnostic* process?

## Yes

- Measurement of elevated cholestanol in blood or elevated bile alcohol glucuronides in urine<sup>5</sup>.
- Measurement of ketosterol bile acid precursors in blood<sup>6,7</sup>.
- Genetic testing and identification of pathogenic variants in the CYP27A1 gene.
- CLIA laboratories performing confirmatory tests
  - Biochemical Genetics Laboratories at the Kennedy Krieger Institute (blood)
  - Emory University (blood)
  - Sterol Analysis Laboratory at Oregon Health & Science University (blood and urine)
  - Setchell Laboratory, Cincinnati Children's Hospital Medical Center (urine)

Do the results have *clinical utility*? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

## Unclear

- Broad spectrum with few cases
- Suspicion index is a guide
- Most serious phenotypes are clear
- Progression of other phenotypes is uncertain with limited data on variants
- Unclear how to handle cases that have high suspicion with limited findings

Are there defined *treatment* protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

## Yes

- Treatment with orally-administered chenodeoxycholic acid (CDCA)
- CDCA treatment is low risk although hepatotoxicity is a occasional side effect
  - Cholic acid has been recommended as a less hepatotoxic treatment for CTX in children (may not be as effective)
- FDA has not granted marketing approval of CDCA specifically for treatment of CTX
  - CDCA was granted orphan-drug designation for the treatment of this disorder

# Key Questions - Summary

- Is the nominated condition(s) **medically serious**? **YES**
- Is the **case definition** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening? **NO**
- Are **prospective pilot data** from population-based assessments available for this disorder? **NO**
- Does the screening test(s) have established **analytic validity**? **UNCLEAR**
- Are the **characteristics of the screening test(s)** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)? **UNCLEAR**
- Is there a widely available and CLIA and/or FDA approved **confirmatory test/diagnostic** process? **YES**
- Do the results have **clinical utility**? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky? **UNCLEAR**
- Are there defined **treatment** protocols, FDA approved drugs (if applicable) and is the treatment(s) available? **YES**

# Nomination and Prioritization Workgroup Recommendation

The Advisory Committee will provide guidance to the Nominators regarding:

1. Additional information needed to meet the Advisory Committee requirements to complete the nomination packet
2. Areas needing clarification



# References

1. J Biol Chem. 1991. 266:7779-7783. Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. Cali JJ, Hsieh CL, Francke U, Russell DW.
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3. Genet Med. 2008. 10:903-909. Population screening in a Druze community: the challenge and the reward. Falik-Zaccai TC, Kfir N, Frenkel P, Cohen C, Tanus M, Mandel H, Shihab S, Morkos S, Aaref S, Summar ML, Khayat M.
4. J Inherit Metab Dis. 2014. 37:421-429. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. Mignarri A, Gallus GN, Dotti MT, Federico A.
5. J Inherit Metab Dis. 2017. 40:771–781. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). Salen G, Steiner RD.
6. Clin Biochem. 2014. 47:860-863. A useful multi-analyte blood test for cerebrotendinous xanthomatosis. DeBarber AE, Luo J, Giugliani R, Souza CF, Chiang JP, Merkens LS, Pappu AS, Steiner RD.
7. J Lipid Res. 2014. 55:146-154. A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. DeBarber AE, Luo J, Star-Weinstock M, Purkayastha S, Geraghty MT, Chiang JP, Merkens LS, Pappu AS, Steiner RD.