

Newborn Screening for Carnitine Palatoyl Transferase Deficiency Type 1A (CPT-1)  
Summary of Issues, April 23, 2008

**Background:** Classic CPT-1 is a serious disorder of fatty acid oxidation that can cause liver and neurological damage and possibly death. However, it is also extremely uncommon. Prior to mass screening there were perhaps less than 50 affected individuals known world wide, with a clustering of cases in the Hutterite religious group. This infrequency figured in its failure to meet the criteria to be included among the 29 conditions recommended to be included in all newborn screening programs in a 2004 report commissioned from the American College of Medical Genetics.

Shortly after Oregon (which provides newborn screening tests for Alaska) began screening the Alaskan population for an expanded panel of disorders in the fall of 2003 they began identifying a number of infants with abnormal screening results who were ultimately diagnosed with CPT-1 through measurement of enzyme activity in cultured skin cells. However, in contrast to those with the classic form of the condition who have zero or near zero enzyme activity, these infants had an average residual enzyme activity of 20%. All of the infants were of Alaskan Native heritage. Subsequently it was found that all of the steadily increasing number of Alaskan infants found to have CPT-1 had a single, unique variant in the gene that codes for the enzyme. Between October 2003 and June 2006, 38 infants with CPT-1 were identified among approximately 7,200 Alaskan Native infants screened.

Based largely on this high frequency among Alaskan Natives, coupled with Washington's proximity to Alaska, and the assumption that affected infants would benefit from early identification and treatment, CPT-1 was included among 16 conditions recommended by Washington's Newborn Screening Advisory Committee for inclusion in an expanded newborn screening panel.

However, in response to notification of the proposal to add the new conditions, Dr. Wylie Burke, Chair of the Department of Medical History and Ethics at the University of Washington submitted a comment noting concern about CPT-1 screening among some of her medical colleagues in Alaska and British Columbia and among Alaska Native organizations. They noted a very high frequency of the unique genetic variant among native populations but a lack of clear information about the health effects of the condition. Dr. Burke's comments prompted further investigation into the issues.

**Findings:** DNA testing of 550 newborn screening cards from infants identified as "Alaskan Native" revealed 21% were homozygous for the Alaskan CPT-1 genetic variant. If this is characteristic of the entire Native Alaskan population, it means that 250 to 350 infants are born with the condition each year in Alaska. Based on 2000 census data on Alaskan Natives resident in Washington and population birth frequency, the data suggests that 20 to 100 infants who are homozygous for the variant may be born in Washington each year. Although there are a few reports from Alaska and Canada of children who are homozygous for the variant who have also had clinical symptoms

consistent with CPT-1, the frequency is very low suggesting that correlation between homozygosity for the variant and clinical risk is low.

Further, it appears that the ability of the screening test to detect infants with the condition is very low since only 20 to 30 of the likely 250 – 350 affected infants are detected through screening each year. Also the screening markers that indicate the disease in affected infants are typically normal for several days after birth and only rise later. Thus, most of the children detected in Alaska have ‘normal’ results on their first screening specimen, which is collected in the first few days of life. They are only detected if subsequent specimens are submitted at later ages. Applying these figures to the Washington population suggests that while 20 to 100 affected infants may be born in the state each year, only 2 to 10 of these may be detected through screening.

Finally, there is a feeling among some Alaskan Native leaders that their people have not been sufficiently consulted and involved as the issues surrounding CPT-1 screening in their newborn population have unfolded.

**Summary:** Based on the new information gathered in response to Dr. Burke’s comments:

- The uncertain, but likely low correlation between CPT-1 and health risk in the native population raises the question whether the condition meets the Board of Health’s criteria for adding conditions to the screening panel, Prevention Potential and Medical Rationale: *“Identification of the condition provides a clear benefit to the newborn: preventing delay in diagnosis; developmental impairment; serious illness or death.”*
- The seemingly poor sensitivity of the screening test to detect affected infants raises the question whether the condition meets the Board of Health’s criteria Available Technology: *“Sensitive, specific and timely tests are available that can be adapted to mass screening.”*
- The apparent high frequency of the condition among the Alaskan Native population and extreme rarity among others raises the question about its concurrence with the Board’s criteria: Public Health Rational: *“Nature of the condition (symptoms are usually absent, such that diagnosis is delayed and treatment effectiveness is compromised) and the prevalence of the condition justify population-based screening rather than risk based screening.”*
- Although there was not complete consensus among those consulted for this investigation, many indicated their belief that current information does not support adding newborn screening for the condition at this time. Efforts are underway in Canada and Alaska to try to provide greater insight into the frequency of the condition in different native populations and correlation between the unique CPT-1 variant and health risks.

**Conclusion:** In light of this information, which was uncovered since the Newborn Screening Advisory Committee made its recommendations; it seems prudent to remove CPT-1 from the list of conditions under consideration for inclusion on the Washington Newborn Screening Panel at this time.

### **Key Individuals Consulted**

Wylie Burke, M.D., Ph.D. Professor and Chair, Department of Medical History and Ethics. Adjunct Professor of Medicine (Medical Genetics) and Epidemiology, University of Washington.

Laura Arbour, M.D., Clinical Geneticist and Assistant Professor in the Department of Medical Genetics at the University of British Columbia. Her clinical practice and research focuses on northern and aboriginal health issues as they pertain to genetics.

Ruth Etzel, M.D., Ph.D., FAAP pediatrician and epidemiologist with the US Public Health Service at the Alaska Native Medical Center in Anchorage. Research Director for the Southcentral Foundation, an Alaska Native health organization

Terry Powell, Alaskan Native and Administrator, Institutional Review Board, Indian Health Service at the Alaska Native Medical Center.

Michael Raff, M.D., Children's Hospital and Regional Medical Center Seattle, also provides services for the Biochemical Genetics Clinics for the state of Alaska.

Sihoun Hahn, MD, Ph.D., Head of the Biochemical Genetics Section, Children's Hospital and Regional Medical Center Seattle.

C. Ronald Scott, M.D., Clinical Biochemical Genetics, Clinical Genetics, and Pediatrics, University of Washington, Seattle. Provided services to the Biochemical Genetics Clinics for the state of Alaska over 20 years.

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