Sugar in the Arctic:

The Arctic Variant of CPT1A and Congenital Sucrase Isomaltase Deficiency

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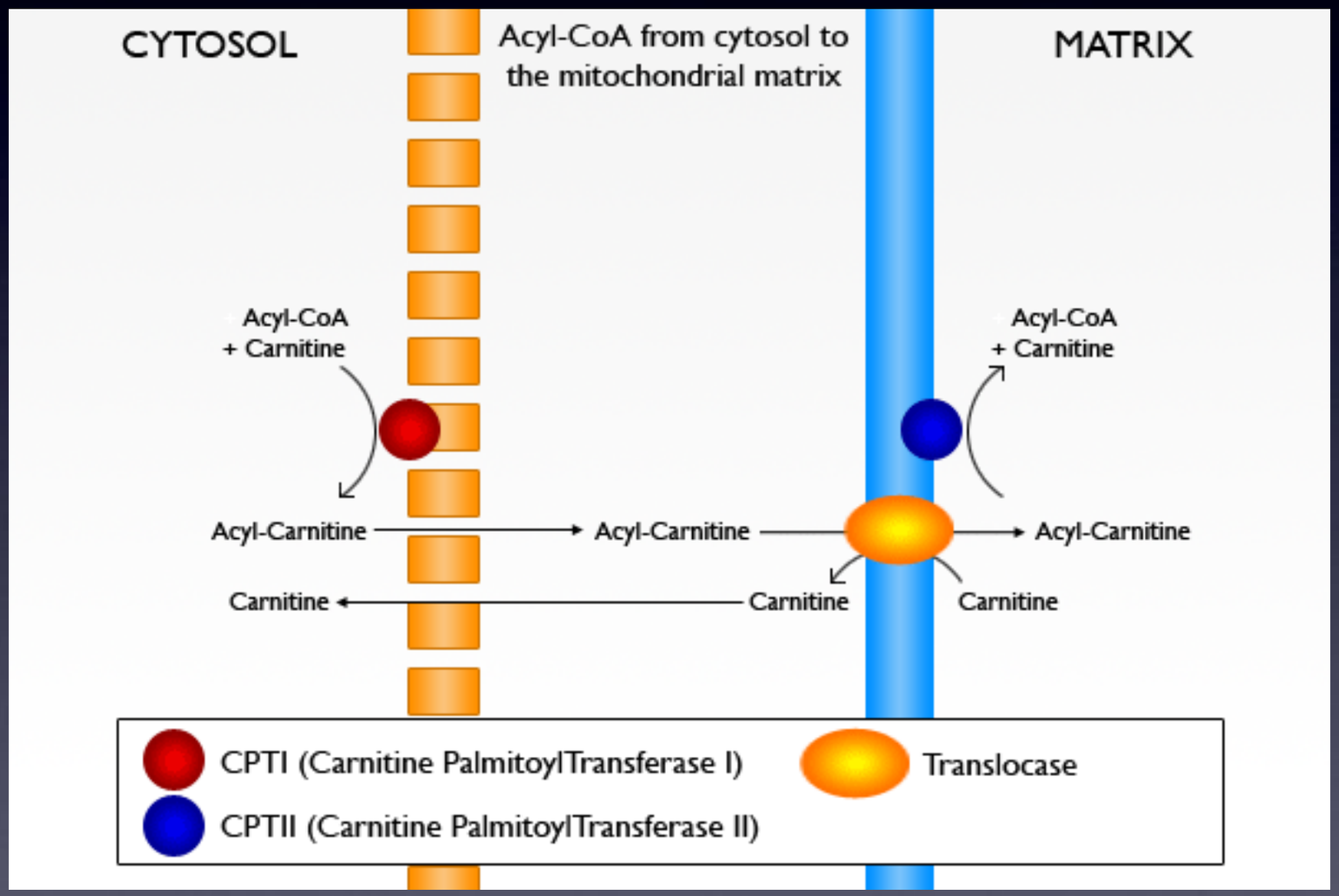
Background

- CPT1 = carnitine palmitoyltransferase type 1
  - Expressed in fibroblasts, liver, brain, skin, skeletal muscle, kidney
- CPT1A = liver isoform of CPT1
  - All reported cases of human deficiency of CPT1 are due to defect in the CPT1A isoform
  - Does not affect muscle, heart, brain, etc.

CPT1A Function

- Responsible for the 1st and rate-limiting step in mitochondrial fatty acid oxidation
- Located in the outer (cytosolic) membrane of the mitochondrion

A Closer Look



Symptoms of “Classic” CPT1A Deficiency

- Occur after prolonged fast, when glucose and glycogen stores become depleted
- Presents with hypoketotic hypoglycemia, fatigue, vomiting, liver dysfunction, and seizures

History of “Classic” CPT1A Deficiency

- Deficiency is severe
  - Less than 5% of enzyme activity
- Deficiency is rare
  - 2004 review reported 30 cases worldwide
  - First cases in Alaska diagnosed in 2004—confirmed by skin biopsy (only method of confirming CPT1A deficiency at the time)
    - Found when Alaska changed to MS/MS to perform their newborn metabolic screens (NBMS)
    - Doubled the world’s cases in the first year of screening

Expanded NBMS

- Before 2004 in Alaska
  - Hypothyroid
  - PKU
  - Galactosemia
  - MSUD
  - Biotinidase
  - CAH

Expanded NBMS

- Utilizes tandem mass spectrometry (MS/MS) to screen for many more diseases than before
- Currently, Alaska screens for about 50 diseases

Expanded NBMS

- After 2004
  - Added amino acid and urea cycle disorders
  - Organic acid disorders
  - CF
  - Hemoglobinopathies
  - Fatty Acid Oxidation Disorders

Fatty Acid Oxidation Disorders—NBMS

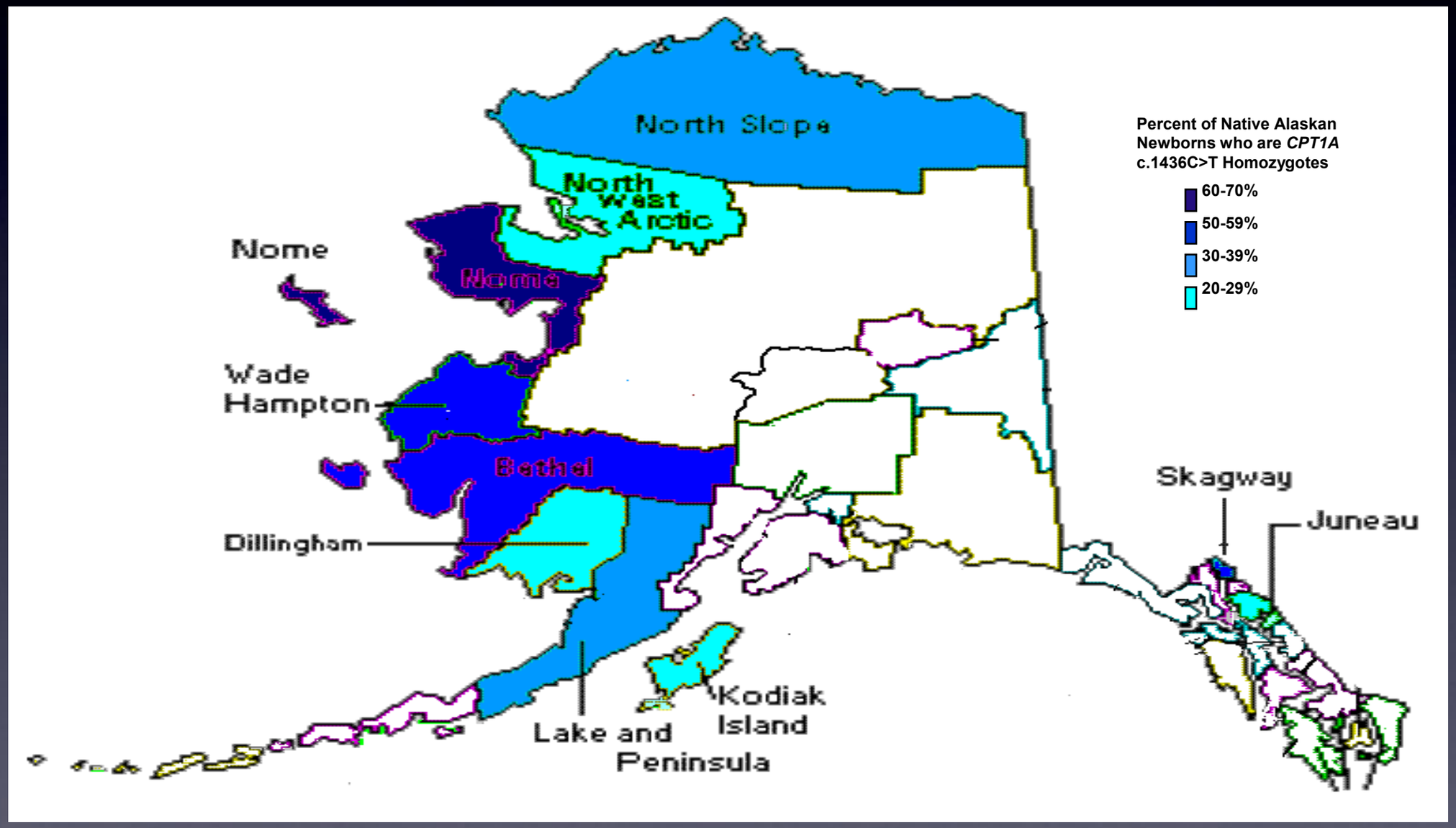
- VLCADD
- SCADD
- CPT1
- MCADD
  - One of the major drivers for expanded screening (Medium Chain Acyl CoA Dehydrogenase Deficiency)
  - Fatty acid metabolism disorder that has been linked to increased infant mortality—SIDS

The Arctic Variant

- A missense mutation (P479L) found in all affected Alaska Native people
  - Same mutation found in Canadian and Greenland Inuit populations, Siberian arctic populations, and in Vancouver Island First Nations populations
- Skin biopsy results showed that this mutation gives 20% enzyme activity
- Genetic research shows that CPT1A is the *normal gene* in the Arctic—very highly selected for (not in the population by chance)

Where Arctic Variant Occurs

Distribution



The Arctic Variant Regulation

- P479L occurs in a region of CPT1 responsible for regulation of activity
  - CPT1A is inhibited by malonyl CoA
    - Malonyl CoA increases when carbohydrates are ingested
    - Mutation causes protein to always be “on” by not allowing malonyl CoA to bind

Newborn Screening

- NBMS has now detected over thousands of cases in Alaska since 2004
- Before July 1, 2016, we detected the minority of cases—about 15%
  - There are actually 700 infants with the P479L variant born per year in Alaska

Questions Surrounding the Arctic Variant of CPT1A

- All of the infants who had a skin biopsy had 20% residual activity—is this enough activity to eliminate symptoms?
- Could the Arctic variant be a contributing factor to the higher rate of SIDS in the rural villages in Northern/Southwest Alaska?
- Why does this variant have such high prevalence in Arctic populations?

1st Project

- 5 families with a child between the ages of 3-5 years with the Arctic Variant of CPT1A flown to Doernbecher Children's Hospital for an 18 hour fasting study
- Labs at 6, 12, 18 hours drawn: Chem7, insulin, acylcarnitines, free fatty acids, lactate, pyruvate, ketones (acetoacetate and 3-hydroxybutyrate)
  - Hourly serum glucose starting at 6 hours of fasting
- MRS done to determine if fatty deposits occur in liver

Fasting Project Continued

- 2 of the 5 kids became symptomatic with plasma glucose below 51
  - One went below 40
- Ketones were not produced at any stage of the fast in any kid
  - Suggests that fatty acid oxidation is fairly severely affected by the Arctic Variant

Fasting Project Continued

- Their livers were imaged using magnetic resonance spectroscopy. The hypothesis was that these kids will have fatty livers compared to controls because of their inability to metabolize fats efficiently—like classic CPT1A deficiency
  - Actually, completely normal livers

Conclusions

- Even healthy 5 year olds with the Arctic Variant of CPT1A can't utilize fats effectively and can become symptomatic if fasting is prolonged
  - *In children who are sick, the symptoms would occur faster and would be more severe*

Questions Surrounding the Arctic Variant of CPT1A

- All of the infants who had a skin biopsy had 10-25% residual activity—is this enough activity to eliminate symptoms?
- Could the Arctic variant be a contributing factor to the higher rate of SIDS in the rural villages in Northern/Southwest Alaska?
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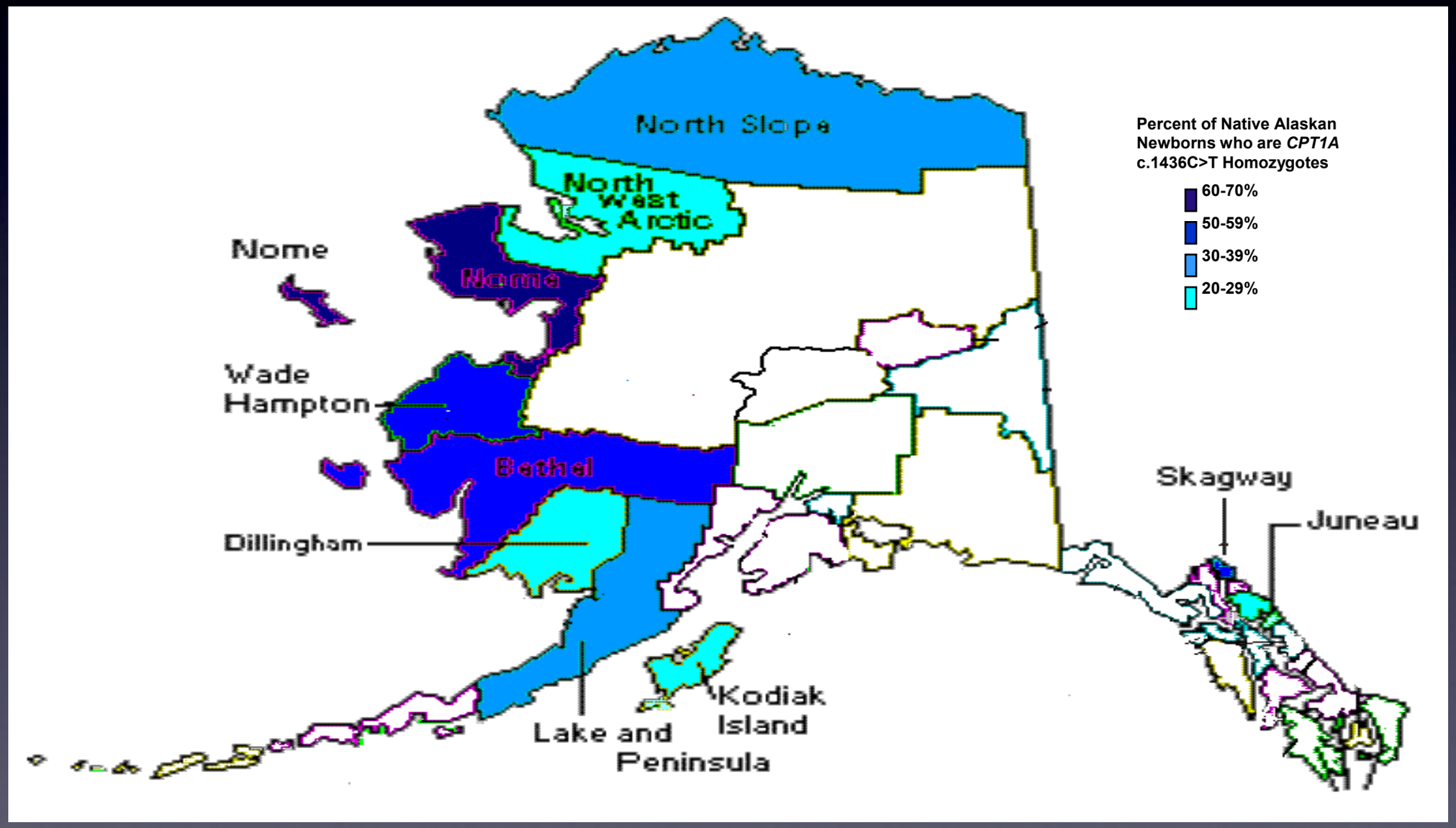
CPT1A and SIDS

Infant mortality rates (IMR) 1992-2004

Region	# Deaths	IMR
Northern	83	12.1*
Southwest	123	10.8*
Anchorage Bowl	425	6.3
Gulf Coast	84	6.2
Interior	140	6.2
Southeast	79	6.2

Distribution



Phenotype of the Arctic Variant

- Looked at all Alaska Native infant deaths from 2006-2010
  - 110 deaths
    - 46 homozygous for the Arctic Variant
  - Case control study comparing to 395 Alaska Native controls from the same time period
    - 119 were homozygous for the Arctic Variant

Arctic Variant and Cause of Death

Cause of Death	OR (95%CI)
SIDS or asphyxia of unknown etiology	0.50 (0.22 to 1.1)
Infectious disease	2.9 (1.0, 8.0)
Congenital anomaly	0.91 (0.34, 2.4)
Injury	1.2 (0.38, 3.6)

Illness Preceding Death	OR (95%CI)
Any hospitalization	5.1 (1.7, 16)
Pneumonia	15 (1.9, 125)
Sepsis or meningitis	2.9 (0.88, 9.2)

Conclusions

- Looks like the presence of the Arctic Variant of CPT1A could be a contributing reason for the difference in infant mortality between Northern/SW Alaska the rest of the State
  - The Arctic Variant doesn’t cause death, but contributes when the baby has an infectious issue
  - Not associated with SIDS, as originally hypothesized
- Need to identify all infants with Arctic Variant

Change the NBMS

- Since July 1, 2016, we've used PCR on all NBMS cards to truly identify all kids with the Arctic Variant

July – December 2016 First Six Months of DNA Testing

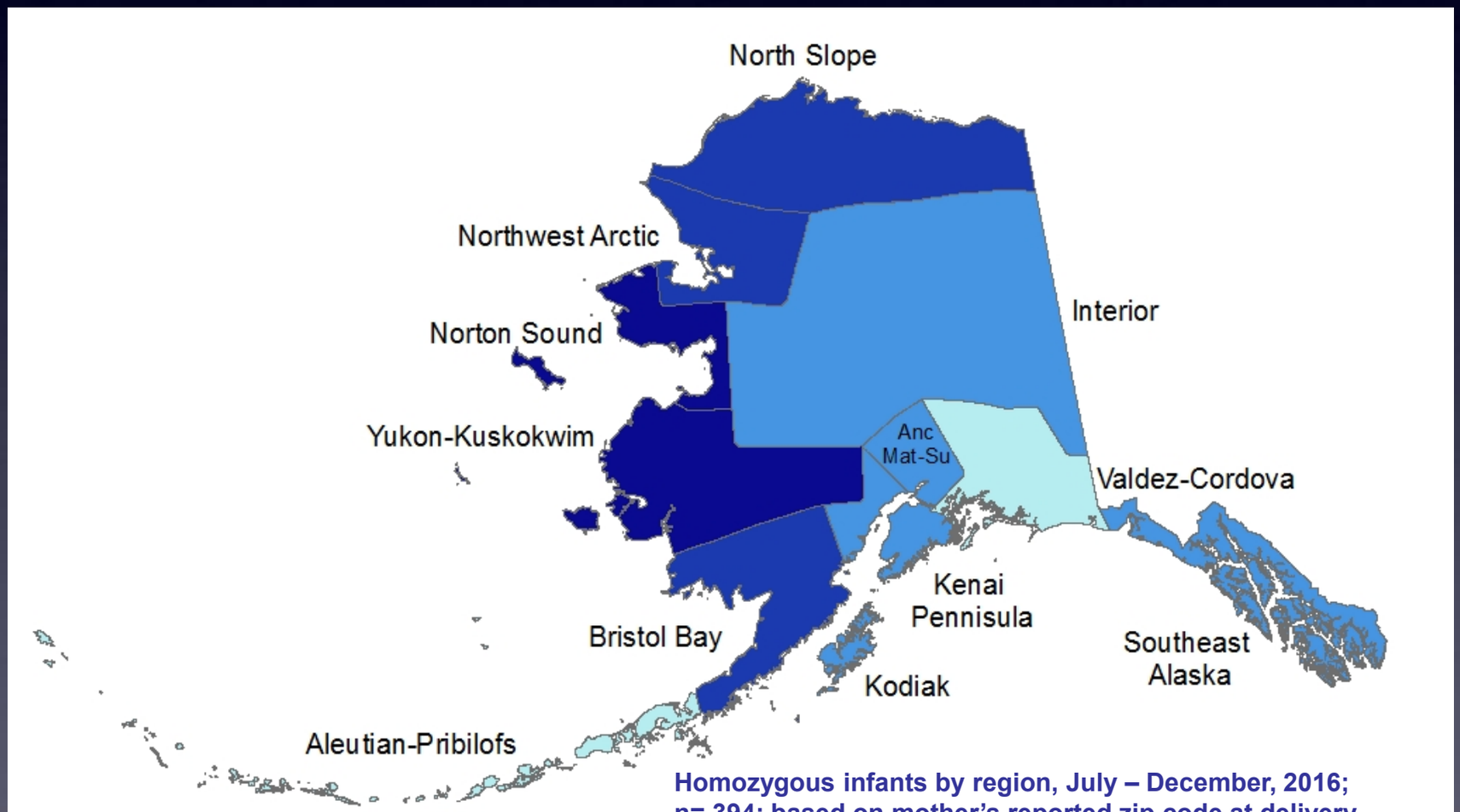
- 394 homozygous infants
- 556 heterozygous infants
- 950 infants with one or two copies

- % of all Alaska Native infants
  - Homozygous: 25.5%
  - Heterozygous: 37.5%
- % of all Alaskan infants
  - Homozygous: 7%
  - Heterozygous: 11%

5,591 total births; 1,508 Alaska Native births

Homozygous Incidence by Region

Yukon-Kuskokwim	62%
Norton Sound	53%
Bristol Bay	43%
North Slope	41%
Northwest Arctic	39%
Kenai Peninsula	11%
Southeast Alaska	8%
Anchorage Mat-Su	7%
Interior	6%
Kodiak	5%
Aleutians-Pribilofs	0%
Valdez-Cordova	0%



Homozygous infants by region, July – December, 2016; n= 394; based on mother's reported zip code at delivery

Infants with Arctic Variant

- Homozygous results are shown as "Arctic Variant Homozygous" on the report
- Heterozygous results are noted but defined as normal
- Parents of homozygous infants are notified by Alaska NBMS Program by mail
- No notification takes place for heterozygous infants

What Families Receive

- Letter of explanation
- Card to bring to medical appointments
- DVD about Arctic Variant—
  Stopped now

How Are We Doing?

- Parents demonstrated the best understanding if they watched the DVD and spoke with a knowledgeable provider
- Parents who did not watch the DVD and did not speak to a provider had the least knowledge
- Parents who heard inaccurate information had the most fear

Children with Arctic Variant

Healthy Babies Are Not at Risk

- We have never seen hypoglycemia in babies who are able to eat normally
- Initial data shows no increase in SIDS in babies with the Arctic Variant

Parent Education

- You do NOT need to constantly feed your baby
- You do NOT need to add sugar to their formula
- Your baby should feed just like other children, with the normal volumes and spacing between feeds
- Can start solids at the normal age

Children with Arctic Variant

If An AV Baby is Sick

- Baby shouldn't go more than 6-8 hours without being able to drink breast milk, formula, or Pedialyte
- Parents should wake their baby up to check if they're sleeping through the night
- This is especially important under 2 years

If an AV Child is Having Surgery

- Tell the surgeon & anesthesiologist that the child has CPT1A Arctic Variant
- People with Artic Variant shouldn't fast for long periods of time
- Surgery should be first on the schedule
- IV Fluids during surgery should include glucose
  - Maintenance fluids are fine!!!
  - D5-NS when in doubt

Children with Arctic Variant

If An AV Baby is Sick

- Look for the same symptoms that occur in other sick infants
  - These symptoms may occur sooner in babies with the Arctic Variant
- If any of those symptoms occur (in any baby), parents need to take their baby to their clinic or ER right away

Symptoms Include

- Poor feeding or the inability to feed because they are so sleepy or ill
- Lethargy—can’t wake the baby up
- Jitteriness and shakiness
- Inconsolability
- Fast or hard breathing
- Seizures

Bottom Line Surgery

- Don’t make kids NPO more than 8 hours without glucose containing IVF
  - Especially less than 1 year old
    - For an 8am surgery
      - NPO for clears (pedialyte) = 2 hours
      - NPO for Breast Milk = 4 hours
      - NPO for solids or non-clear liquids = 6 hours

What To Do In Clinic

- If a baby with the Arctic Variant is well
  - Treat as you would any other baby
- If a baby with the Arctic Variant is sick and has not been able to eat regularly
  - Check a glucose
    - If low, try
      - Pedialyte
      - Glucose gel
      - D5NS through IV or IO

What’s Next???

Questions Surrounding the Arctic Variant of CPT1A

- All of the infants who had a skin biopsy had 10-25% residual activity—is this enough activity to eliminate symptoms?
- Could the Arctic variant be a contributing factor to the higher rate of SIDS in the rural villages in Northern/Southwest Alaska?
- Why does this variant have such high prevalence in Arctic populations?—New research study

Benefits of Genetic Prevalence

- Genetic evidence suggests the high prevalence of the Arctic Variant is the result of positive selection
- Our findings have been limited to detrimental effects on children
- What are the beneficial health effects?

Beneficial Effects

- Study of Greenland Inuit
  - Elevated plasma HDL and apoA-I levels
  - Suggests the AV may protect against Artherosclerosis

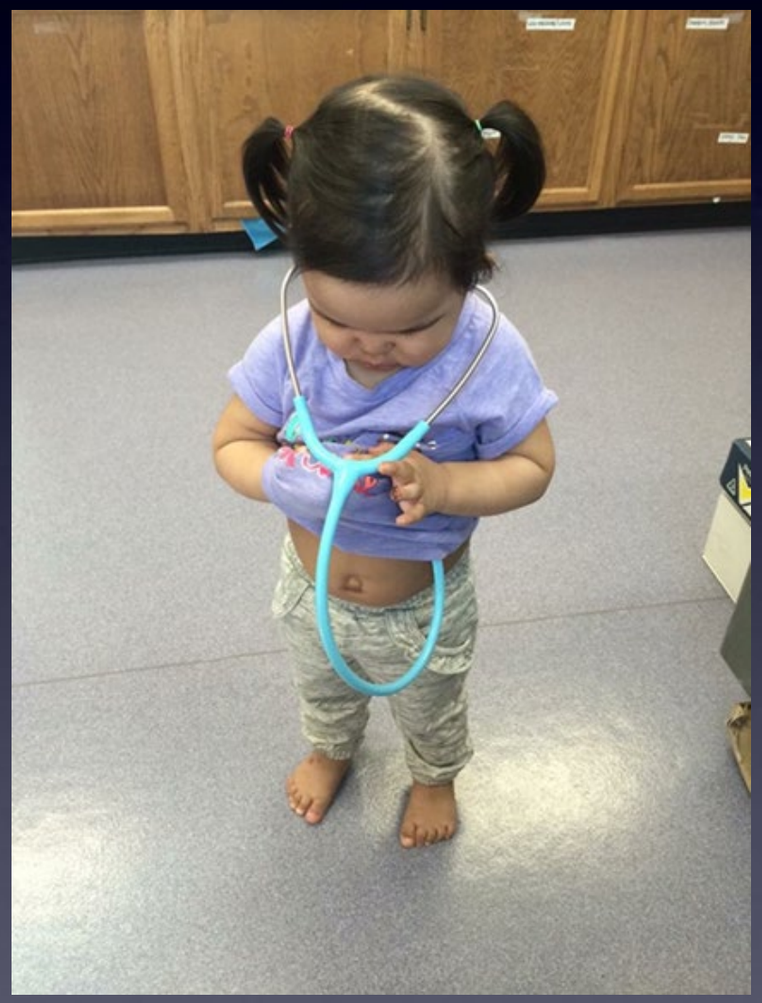
Carnitine palmitoyltransferase IA polymorphism P479L is common in Greenland Inuit and is associated with elevated plasma apolipoprotein A-I, Journal of Lipid Research, Volume 50 (2009)

Study Hypothesis

- The health effects of the CPT1A Arctic Variant are dependent on the level of intake of omega-3 fatty acids (n-3 PUFA)
  - Prenatal and postnatal n-3 PUFA intake
  - Duration of breastfeeding
  - Timing of introduction and types of solid foods given to infants

Prospective Cohort Study

- Expectant mothers will be invited to participate and enroll their child during prenatal visits around 28 weeks gestation
- Recruitment and informed consent conducted by grant supported study personnel



Prospective Cohort Study

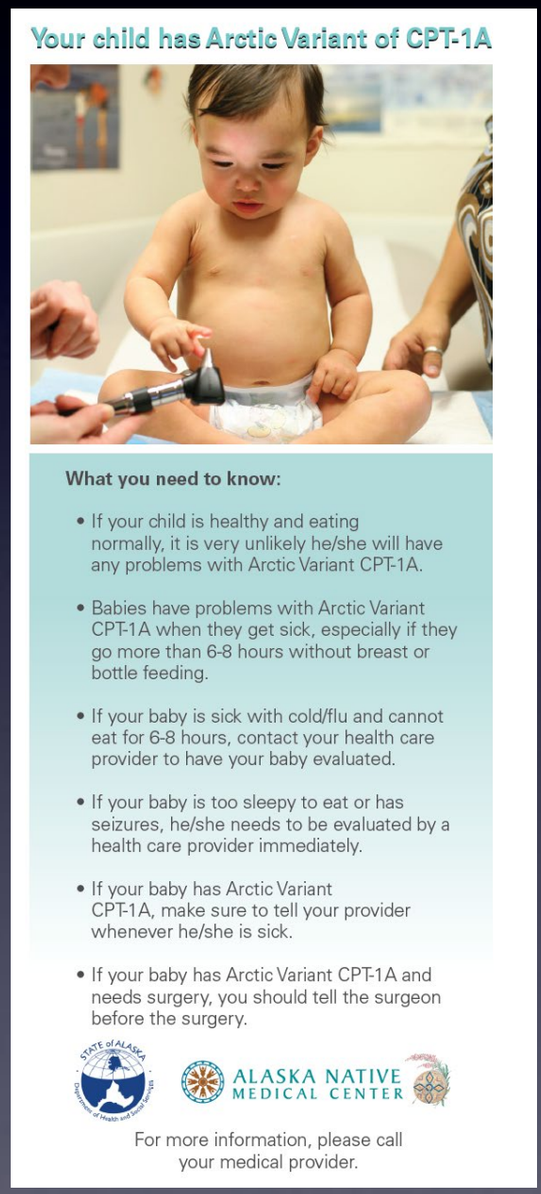
- Data on mothers
  - Health status during pregnancy
  - N-3 PUFA levels
- Data on children (0-2 years old)
  - Health, growth and developmental outcomes
  - N-3 PUFA levels
  - Known health risk factors
- Data important to community members and other stakeholders

Resources

- You Tube video—sent by the State to all families with a child diagnosed by NBMS
  - https://www.youtube.com/watch?v=gE8CnQjZDak
- Handout—very detailed for providers
  - http://www.newbornscreening.info/Parents/fattyaciddisorders/CPT1AV.html
- You Tube video-–for providers
  - https://www.youtube.com/watch?v=ZBJB6gLAr4Q

Resources

- Pocket Guide to Alaska Native Pediatric Diagnoses
  - https://anmc.org/files/Pocket_Guide_to_Diagnoses_web-1.pdf
- Rack Card
  - https://health.alaska.gov/media/4gnp2q3i/information-handout.pdf
- Letter from SOA
  - https://health.alaska.gov/media/1csg53ta/cpt1a_av_parentletter.pdf



Your child has Arctic Variant of CPT-1A

What you need to know:

- If your child is healthy and eating normally, it is very unlikely he/she will have any problems with Arctic Variant CPT-1A.
- Babies have problems with Arctic Variant CPT-1A when they get sick, especially if they go more than 6-8 hours without breast or bottle feeding.
- If your baby is sick with cold/flu and cannot eat for 6-8 hours, contact your health care provider to have your baby evaluated.
- If your baby is too sleepy to eat or has seizures, he/she needs to be evaluated by a health care provider immediately.
- If your baby has Arctic Variant CPT-1A, make sure to tell your provider whenever he/she is sick.
- If your baby has Arctic Variant CPT-1A and needs surgery, you should tell the surgeon before the surgery.

STATE of ALASKA Department of Health and Social Services

ALASKA NATIVE MEDICAL CENTER

For more information, please call your medical provider.

But Wait…..
Congenital Sucrase Isomaltase Deficiency (CSID)

- Sucrase Isomaltase enzyme complex is missing from small intestine
  - Can’t break down sucrose into fructose and glucose
  - Can’t break starch down completely due to decreased isomaltase activity

CSID

- Autosomal recessive
  - Frameshift mutation that causes absence of enzyme
- Results in osmotic diarrhea when table foods are introduced at 4-6 months
  - Has a varied phenotype, ranging from severe diarrhea with FTT to more of an irritable bowel syndrome picture

More CSID

- Prevalence
  - 0.2% of the general population
  - 5-10% of Greenland/Canadian Inuit people
- Unknown at this time in Alaska Native people—but we're finding out it's probably similar to the Greenland/Canadian Inuit people

CSID Treatment

- Diet control—Avoid foods with processed sugar and foods high in sucrose and starch
  - Peas, beets, onions, pastas, breads, potatoes, honey
  - Alaska Native Traditional Diet is actually perfect for CSID control
  - Ross Carbohydrate Free—Call Sam Maloney (Director of Nutrition Services) at ANMC for the recipe
- In the absence of diet control—Sucraid
  - Very expensive, and needs to be taken with every meal and snack

CSID Program

- A program at ANMC that is making access to Sucraid easier for families
  - Database of CSID positive people
  - Educational outreach
  - Resource for families
  - Change in Sucraid distribution for rural Alaska

Claire Siekaniec, RD

- (907) 729-3628
- clsiekaniec@anthc.org

CSID Resources

- Sam Maloney—ANMC Medical Nutrition Therapy Manager: smaloney@anthc.org
- Matt Hirschfeld: mhirschfeld@scf.cc
- ADN article
  - http://www.adn.com/article/20150119/sugar-intolerance-northern-populations-linked-specific-gene-researchers-say
- CSID Cares
  - http://csidcares.org/
- Lab test at UW
  - http://depts.washington.edu/moleclab/available/csid.html
- Pocket Guide to Alaska Native Pediatric Diagnoses
  - http://anmc.org/files/Pocket-Guide-to-Alaska-Native-Pediatric-Diagnoses_web.pdf

Thank you