CPT1A Arctic Variant and COVID-19 in Kids

Matthew Hirschfeld, MD/PhD

Medical Director
Maternal Child Health Services
Alaska Native Medical Center
Anchorage, AK
mhirschfeld@scf.cc

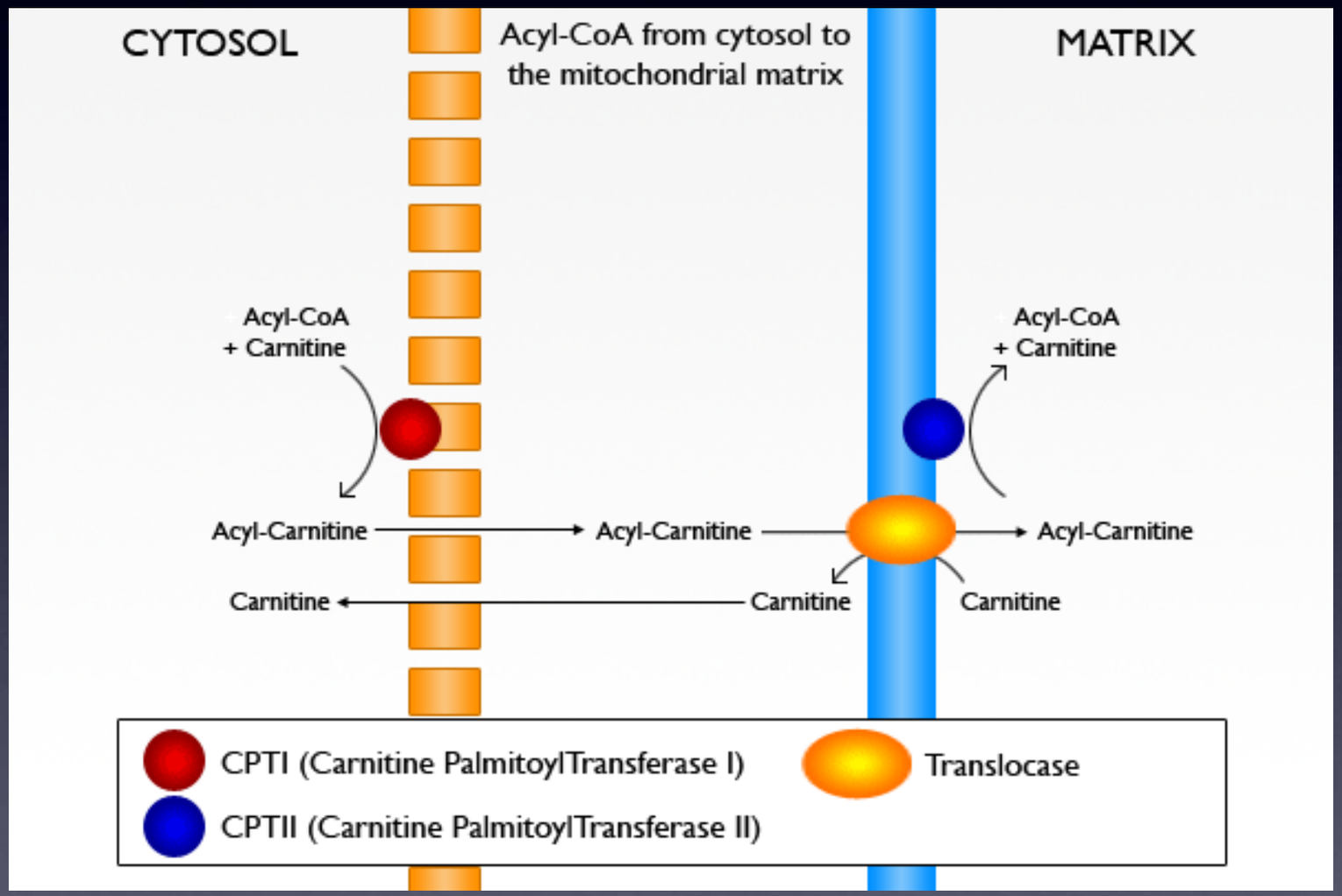
CPT1A Background

- 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

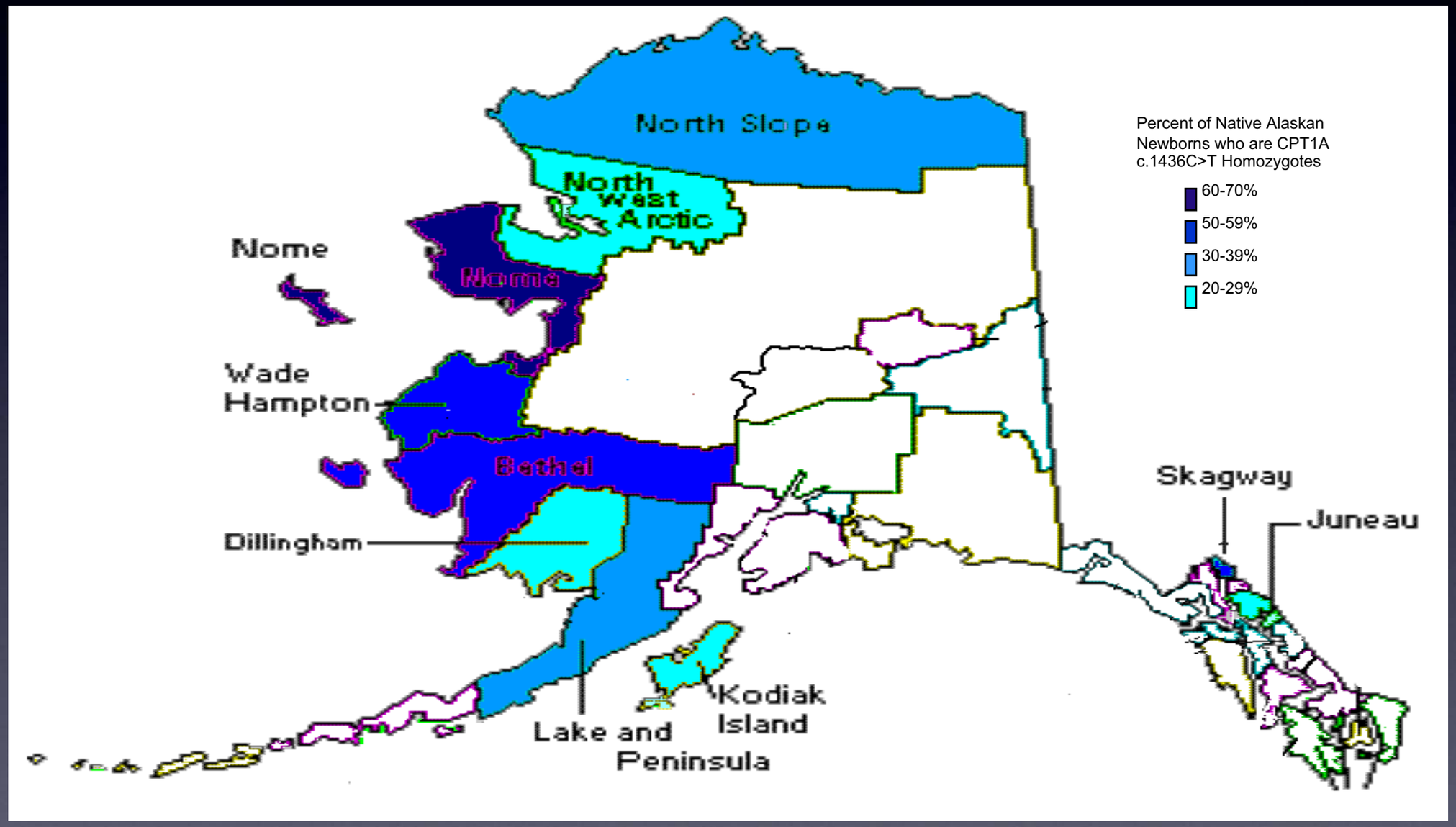
- VLCADD
- SCADD
- CPT I
- MCADD
  - One of the major drivers for expanded screening (Medium Chain Acyl CoA Dehydrogenase Deficiency)
  - Fatty acid metabolism disorder that has been linked to increased infant mortality—SIDS

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



Newborn Screening

- NBMS has now detected over 3000 cases in Alaska since 2004
  - Before July 1, 2016, we detected the minority of cases—about 15%
    - Positive cases before 2016 are true positives
- 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

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?
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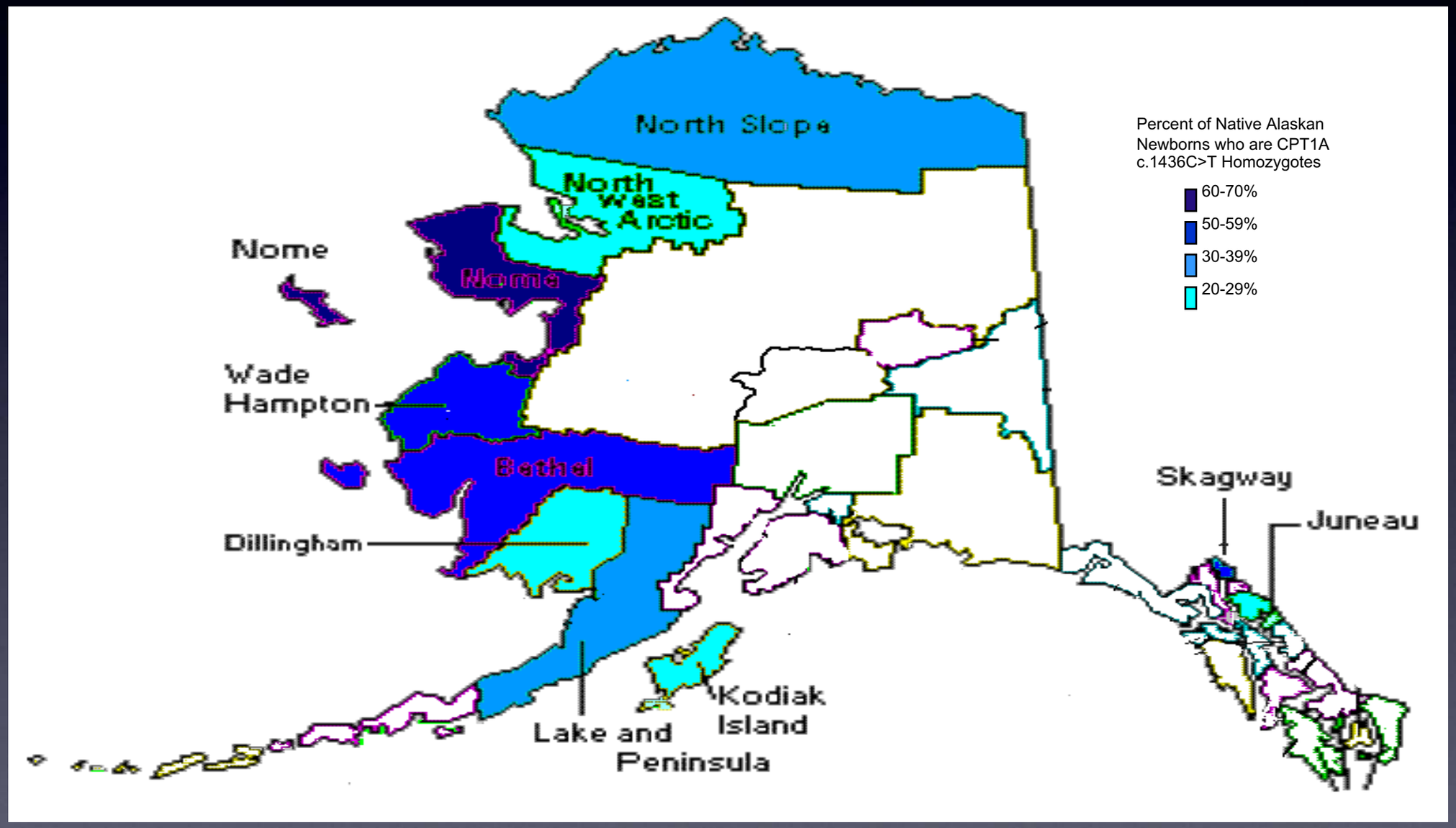
CPT1A and SIDS

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 CPT I A 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

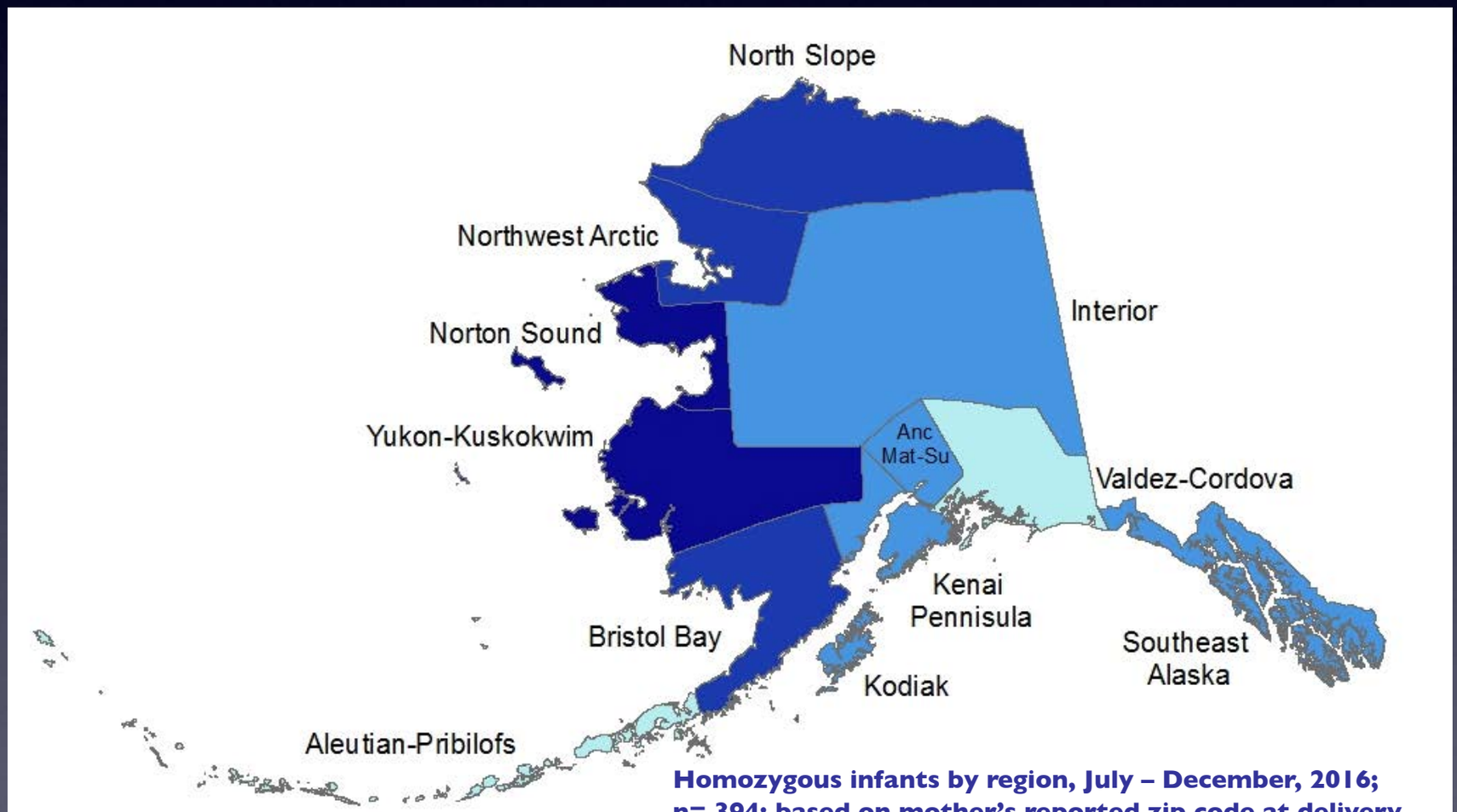
- 394 homozygous infants
- 556 heterozygous infants
- 950 infants with one or two copies

- % 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

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 if the baby is sick
- Parents should wake their baby up to check if they're sleeping through the night if the baby is sick
- 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!!!
  - D5NS 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 2 years old
    - For surgery
      - NPO for clears (Pedialyte, apple juice) = 2 hours
      - NPO for Breast Milk = 4 hours
      - NPO for solids or non-clear liquids = 6 hours

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

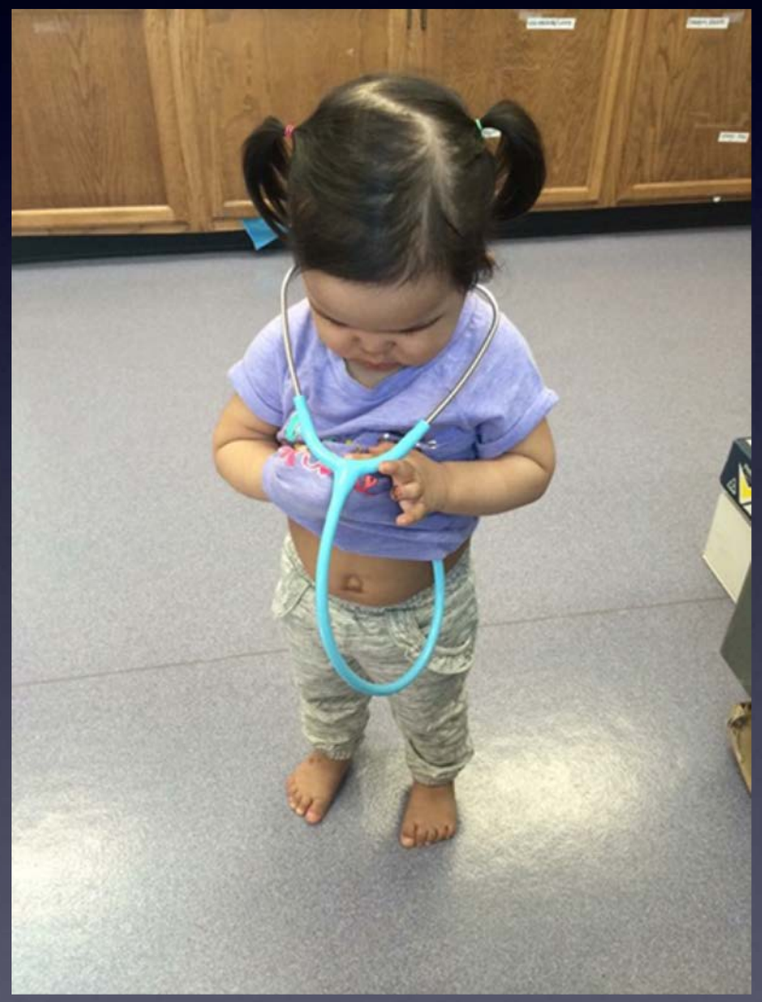
- Genetic evidence suggests the high prevalence of the Arctic Variant is the result of positive selection
  - Our findings have been limited to detrimental effects on children
  - What are the beneficial health effects?

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

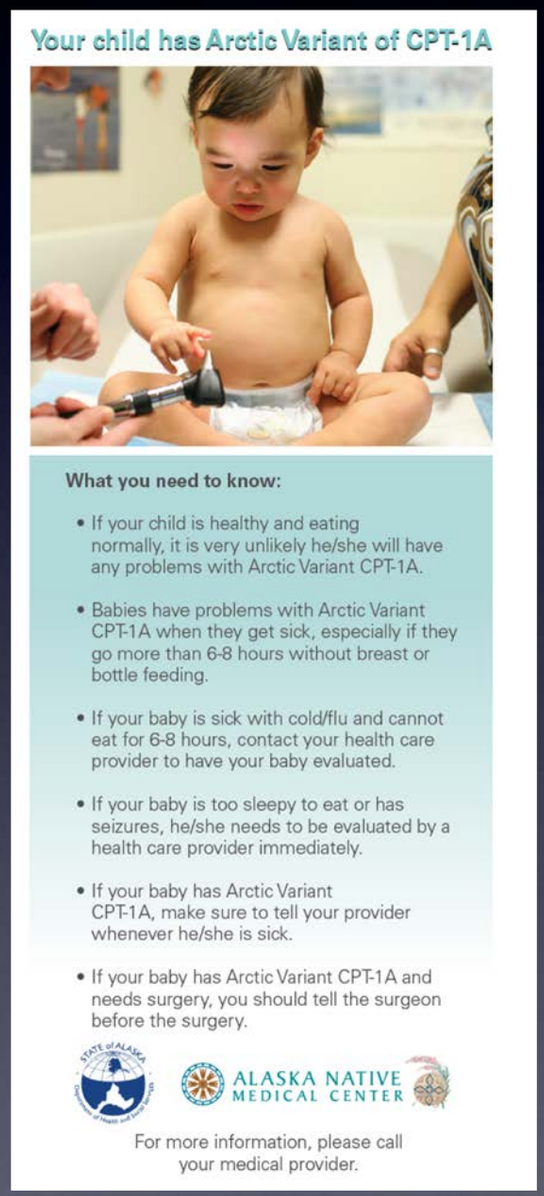
- Data on mothers
  - Health status during pregnancy
  - N-3 PUFA levels
- Data on children (0-2 years old)
  - Health, growth and developmental outcomes
  - N-3 PUFA levels
  - Known health risk factors
- Data important to community members and other stakeholders

Resources

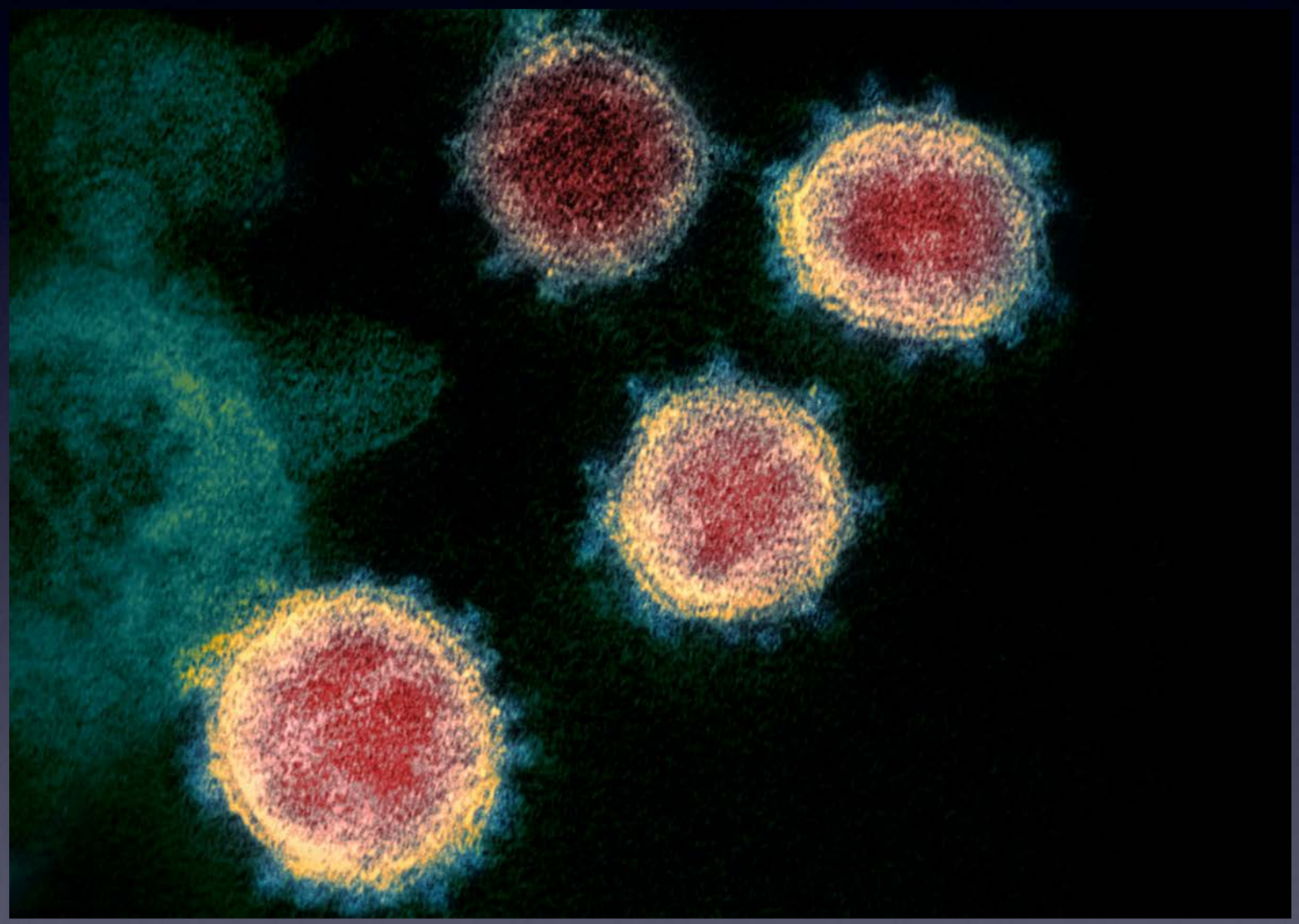
- You Tube video—sent by the State to all families with a child diagnosed by NBMS
  - https://www.youtube.com/watch?v=gE8CnQjZDak
  - Handout—very detailed for providers
    - http://www.newbornscreening.info/Parents/fattyaciddisorders/CPT1AV.html
- Alaska Dispatch News articles
  - http://www.adn.com/article/20141129/clues-emerging-about-arctic-gene-diet-and-health
  - https://www.adn.com/arctic/2016/10/29/arctic-gene-that-poses-risks-when-fasting-is-found-in-many-more-infants-now-that-dna-testing-has-begun/
- American Indian Living with Dr. David DeRose
  - http://stream.publicbroadcasting.net/production/mp3/nv1/local-nv1-1039242.mp3

Resources

- Pocket Guide to Alaska Native Pediatric Diagnoses
- http://anmc.org/files/Pocket-Guide-to-Alaska-Native-Pediatric-Diagnoses_web.pdf



SARS-CoV-2



Coronavirus

- Large family of enveloped, single-stranded, RNA viruses
- They infect a variety of animals
- In humans, CoVs mostly cause respiratory and gastrointestinal symptoms (4 major viruses)
  - Common cold to more severe disease such as bronchitis and pneumonia
  - Cause about 5% of hospitalizations in children per year
  - Often found as co-infections with other viruses

Coronavirus

- Mutations in CoVs can spread from animals to humans.
  - China in 2002 when a novel CoV causing severe acute respiratory syndrome (SARS-CoV) emerged—thought to have been transmitted from civet cats or bats to humans
  - Another novel CoV emerged in Saudi Arabia in 2012—Middle East respiratory syndrome coronavirus (MERS-CoV), which is transmitted from dromedary camels to humans

COVID-19—History

- Caused by novel coronavirus—SARS-CoV-2
  - Initially identified in Wuhan, China—December, 2019
  - Adults with severe pneumonia progressing to respiratory failure
  - Virus identified January, 2020
    - Sequencing shows that the genome is most closely related (87%–89% nucleotide identity) to the bat SARS-related CoV found in Chinese horseshoe bats
  - WHO declares pandemic 3/11/20
  - Approximately 2% of positive results are kids less than 18 years old

COVID-19—Pandemic

- On 7/9/20
  - Cases / Deaths
    - Worldwide 12,128,406 / 551,521
    - US 3,088,913 / 132,934
    - Alaska 1,272 / 17

https://coronavirus.jhu.edu/map.html

Symptoms—Adults

- Fever, cough, malaise
  - Results in relatively frequent hospitalizations
    - Many other symptoms can occur
      - Diarrhea, headache, rhinorrhea
- Incubation period 2-14 days
  - Same in kids

Symptoms—Children

- Similar symptoms as adults
  - Typically milder symptoms with less hospitalizations
  - Similar to adults, most children who get severe disease have underlying medical conditions or are under 1 year/old
    - Most common: Immunosuppressed, respiratory issues, cardiovascular issues, or medically complex children
    - 3% of COVID-19 kids require PICU admission

Symptoms—Children

- Most common symptoms
  - Asymptomatic: 19%
  - Fever: 59%
  - Cough: 56%
  - Runny nose / congestion: 20%
  - Myalgia: 19%
  - Sore throat: 18%

Hoang et al, EClinicalMedicine, June 26, 2020

Imaging and Labs

- Chest X-ray
  - Normal Chest X-ray: 24%
  - Patchy infiltrates: 21%
- Labs
  - CBC, LFTs, Renal function all normal
  - Inflammatory markers procalcitonin, creatinine kinase, D-dimer, IL-6 elevated

Hoang et al, EClinicalMedicine, June 26, 2020

Co-Infections

- Most often seen with mycoplasma (58%) or influenza (11%)

Hoang et al, EClinicalMedicine, June 26, 2020

COVID and Kids

- Looking for the same things you look for in any sick kid
  - Unable to eat or drink
  - Dehydrated
  - Abnormal vital signs
  - Increased work of breathing
  - If under 2 and has CPT1A Arctic Variant, should be able to drink glucose containing fluids every 6-8 hours
  - Follow PPE guidelines for suspected COVID-19 with any kid with respiratory symptoms or fever

COVID and Neonates

- Likely transmission after birth, although vertical transmission is possible
- Test all babies born to COVID-19 + moms
- ANMC allows breastfeeding with COVID-19 + moms
  - Mom must wear a mask
  - Wash hands and chest
  - If possible, maintain 6 feet of separation if not feeding

Multisystem Inflammatory Syndrome in Children MIS-C

- Some aspects similar to Kawasaki Disease
  - Coronary artery aneurisms
- Present with a persistent fever (>24 hours), fatigue, and a variety of signs and symptoms including multiorgan (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic) involvement, and elevated inflammatory markers.
- MIS-C may begin weeks after a child is infected with SARS-CoV-2. The child may have been infected from an asymptomatic contact and, in some cases, the child and their caregivers may not even know they had been infected.
- Treatment is to decrease inflammation--IVIG

Thank you