Newborn Screening Advisory Committee

Monday, April 29, 2024
1:00 pm - 5:00 pm

Role Call / Introductions

1. Name
2. Organization
3. Role
4. Physical Description (e.g. age, skin color, gender, hairstyle and hair color, clothes description, any distinctive accessories)*

*Please include a physical description of yourself for meeting participants who may be visually impaired. Share only those attributes you feel comfortable sharing. Thank you!

Agenda

Time	Agenda Item
1:00p - 1:30p	**Welcome & Roll Call** ● Icebreaker ● Voting & Non-Voting Members
1:30p - 1:45p	**Pompe Nomination Packet Review**
1:45p - 2:00	**Pompe Packet Discussion**
2:00p - 2:50p	**Pompe Presentations** ● SME: Dr. David Viskochil ● Family: Erin Hoch, mother and advocate ● Montana State Laboratory
2:50p - 3:30p	**Pompe Discussion** ● Question & Answer with presenters
3:30p - 3:40p	**Public Comment Period**

Agenda

Time	Agenda Item
3:40p - 3:50p	Break
3:50p - 4:20p	**Unfinished Business** ● Process Memo ● Review Member Attendance Requirements ● MT v RUSP Conditions Table ● New Forms Available on Website
4:20p - 4:40p	**Continuation of Membership** ● Rules for New Appointments ● Mandated Members Term Limit
4:40p - 4:50p	**Newborn Screening Advisory Committee Next Steps** ● Schedule next meeting
4:50p - 5:00p	**Meeting Close**

Public Comment Period (10 minutes)

- Moderator will announce comment period
- Use “raise hand” feature”
- Moderator will call your name
- Unmute yourself
- 2 minute max per comment
- Please email additional comments up to 1 hour after meeting ends to: HHSNewbornAdvisoryCommittee@mt.gov

Ground Rules

- Mute
- Video
- Clarifying questions
- Avoid interrupting
- Avoid acronyms
- Use specific examples
- Focus on the collective interests and goals
- Additional meetings or communications may be scheduled
- Next steps assigned to ensure accountability
- Facilitators may call on attendees for input
- Safe space

Ground rules adapted from Strategy Management Consulting "*Ground Rules for Effective Meetings and Strategic Planning Offsites*"

Pompe Nomination Packet Review

Packet Response Overview

Symptoms and age of onset

- Detectable as early as birth
- Cardiomyopathy, respiratory distress, muscle weakness, feeding difficulties

How is this disorder currently identified?

- Symptomatic presentation followed by a blood test

Why should it be screened at birth

- If undiagnosed, Infantile Pompe Disease can lead to death within the first year of life. Treatment can significantly reduce disease progression and prolong life.

Packet Response Overview

How is this disorder treated?

- Is there a treatment available?
  - Yes – currently 2 FDA approved Enzyme Replacement Therapy treatments, with a third approved in the EU and UK
- Is the treatment in the experimental phase?
  - No

Proposed screening test method

- First tier: GAA enzyme activity in blood sample
- Confirmatory tier: Variant detection from blood sample

Packet Response Overview

Status of condition in the United States

- States currently screening for the condition - 45
- Registries or databases currently established for the condition - 2

Selection Criteria			
	True	**Unsure**	**No**
1. It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected.	X		
2. A test with appropriate sensitivity and specificity is available.	X		
3. There is a significant risk of illness, disability, or death if babies are not treated promptly (within the recommended time frame for the condition).	X		
4. Effective treatment is available and access to follow-up care and counseling is generally available.	X		
5. There are demonstrated benefits of early detection, timely intervention, and efficacious treatment.	X		
6. The benefits to babies and to society outweigh the risks and burdens of screening and treatment.	X		

Selection Criteria			
	True	**Unsure**	**No**
7. There are minimal financial impacts on the family.	X		
8. There is a public health benefit to conducting the test.	X		
9. There exist responsible parties who will follow up with families and implement necessary interventions.	X		
10. The condition's case definition and spectrum are well described.	X		
11. FOR LAB USE ONLY - The public health laboratory can support the testing resources and expertise necessary to provide accurate and timely results.			

Pompe Nomination Packet Discussion (15 minutes)

Clinical Background from Pompe Subject Matter Experts: Dr. David Viskochil and Sabina Cook

Pompe Disease Utah Newborn Screening

Montana NSAC April 29, 2024

Dave Viskochil, MD, PhD, Professor
Medical Genetics Department of Pediatrics
University of Utah

Sabina Cook, MS, LCGC, Genetic Counselor
Utah Department of Health and Human Services

NEWBORN SCREENING

HEALTH UNIVERSITY OF UTAH

Intermountain Primary Children's Hospital

Disclosures

Dave Viskochil: Amicus, Audentus, Sanofi Genzyme

Sabina Cook: none

Objectives

- Pompe disease overview
- Utah criteria example (MPS 2)
- Utah screening for Pompe
- Follow-up data

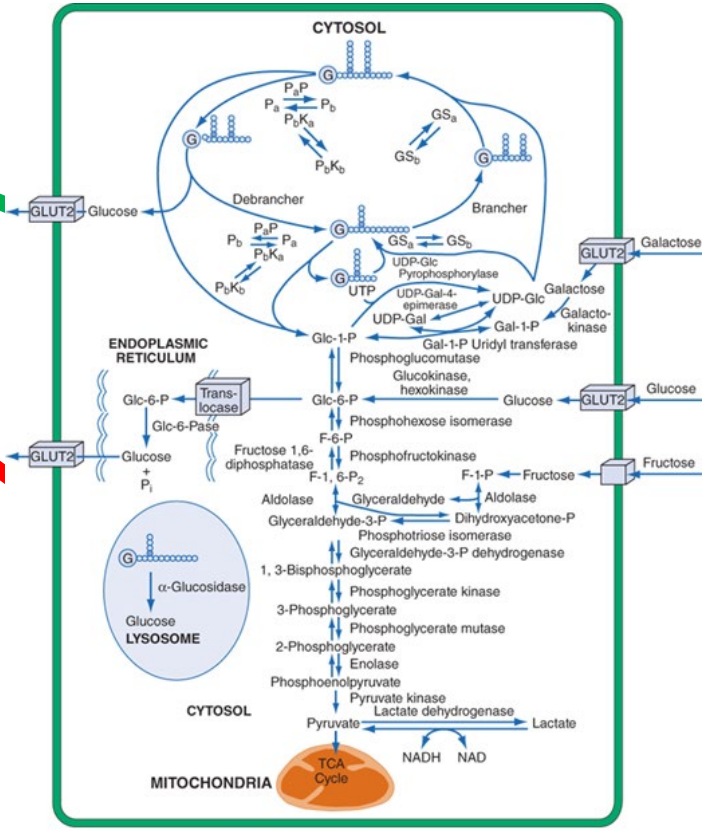
Pompe Disease

Glycogen storage disease type 2

- Deficient α-glucosidase (*GAA*) → accumulation of lysosomal glycogen → progressive damage to skeletal and cardiac muscle
- Broad spectrum of illness from infantile to adult-onset (all requiring therapy)
- Autosomal recessive
- 1:17,000 newborns
  - Infantile 1:150,000
  - Late-onset 1:19,000
  - Late onset to infantile = 8:1
- More than 300 known pathogenic variants in *GAA*

Carbohydrate Metabolism

- Glycogen metabolism occurs in cytoplasm
- Spent glycogen goes to lysosome during autophagy to be degraded via α-glucosidase
- Residual glycogen is not a major source of energy but can cause problems if it accumulate



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

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Clinical presentation

- **Infantile:** poor muscle tone, delays or respiratory symptoms due to heart failure. Patients appear able to understand their environment but cannot move or react to it. Macroglossia, hepatomegaly (due to heart failure, not glycogen storage), protuberant abdomen, death in 1-2 years

- **Juvenile:** skeletal muscle (not heart) involvement. Slowly progressive. Causes respiratory failure and death by 20 years of age

- **Adult:** Slowly progressive proximal myopathy. Most patients require respiratory support (BiPAP) at night

Diagnosis

- Cardiomegaly with cardiac hypertrophy, ECG changes (high QRS, short PR), mildly elevated (3-10X) CPK, AST, and LDH.
- Adults: proximal muscle weakness, progressive respiratory insufficiency.
- Low GAA enzyme activity in WBC
- Urine Hex4 increased.
- DNA testing of *GAA*
- Pseudodeficiency:
  - Low acid α-glucosidase (*GAA*) activity in vitro, but does not lead to disease
  - Can be identified by genotyping
- CRIM (cross reactive immunologic material) status:
  - if negative needs prolonged immune tolerance therapy.

Treatment

- Enzyme replacement therapy: given IV
  - Effective if started before irreversible muscle damage (2 weeks). Two formulations approved: alglucosidase alpha and avalglucosidase alpha. 20 mg/kg every 2 weeks, some patients require 40 mg/kg every 2 weeks.
- Many develop antibodies against ERT. CRIM negative (and possibly positive as well) patients require immumodulation with rituximab, methotrexate, and IVIG in the ERT-naïve setting
- Experimental: gene therapy, ERT associated with chaperone.

Pompe Disease summary

- Lysosomal disorder resulting in glycogen accumulation impairing the function of the heart and skeletal muscle
- Newborn screening identifies infantile onset (require immediate therapy) and adult onset (require close follow up) Pompe disease to allows early treatment
- Initiate treatment by 2 weeks of age in infantile onset
- Clinical evaluation for screen positive
  - WBC GAA enzyme activity, urine Hex4, DNA testing
  - Cardiology evaluation (ECG followed by ECHO, chest X-ray, CK)

Utah Newborn Screening

- 2-screen state
  - **1st NBS**: 24-48 hours of life
  - **2nd NBS:** 7-16 days of life

- As of April 2024, 44 conditions

- 2015: RUSP recommendation for Pompe disease

- July 10, 2023: Utah went live with Pompe and MPS I

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Utah NBS criteria

- Condition and screening test
- Treatment
- Screening program

Utah NBS Criteria example: MPS II

THE CONDITION	
1. The condition should be a health problem in Utah children that is associated with significant morbidity and/or mortality in affected individuals.	
2. The epidemiology and natural history of the condition, including development from latent to symptomatic disease, should be adequately understood and there should be a disease marker detectable within a latent period or early symptomatic stage.	
THE TEST	
3. There should be a reliable, safe, precise and validated screening test **with appropriate sensitivity and specificity**.	Screening completed on a dried blood spot using fluorometric assay or tandem mass spectroscopy (*MS/MS*); **Low I2S enzyme** activity indicates infant may have MPS II
4. The distribution of test values in neonates should be known and a suitable cut-off level defined. Deviations from national standards if available, must be explicitly justified.	Data available from Illinois (MS/MS) and Missouri (fluorometric). New York pilot screening with MS/MS; Taiwan pilot screening
5. There should be an agreed protocol on the confirmatory testing of newborns with a positive result.	Confirm low I2S enzyme activity in blood, test urine for elevated GAGs, genotyping and clinical referral

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Utah NBS Criteria example: MPS II

THE TREATMENT	
6.There should be an effective treatment or intervention for infants identified through early detection, with evidence of early treatment leading to better population based outcomes (such as the prevention of mental retardation or death) than late treatment.	• Effective treatment. ERT, HSCT
7.There should be evidence-based protocols about the appropriate treatment, counseling or intervention to be offered.	• Utah geneticists have been diagnosing, counseling, and treating MPS II disorders
8.All health care providers who might participate in the care of newborns affected by conditions included in the newborn screening program must have access to medical expertise necessary for the clinical management of these conditions. For the condition screened there should be an identified appropriate medical expert for consultation about management, and education to the medical home.	• Expertise is available through the Division of Medical Genetics in the Department of Pediatrics at the University of Utah

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Utah NBS Criteria example: MPS II

THE SCREENING PROGRAM	
9. There must be evidence of high quality that screening programs are effective in reducing mortality or morbidity.	In MPS II there is evidence that treatment is effective. Quality of life is improved and it prevents demise in 1st and 2nd decades.
10. The complete screening program (testing, diagnosis, short-term follow up, administration, education, and quality assurance) must be clinically, socially and ethically acceptable.	The state of Utah has specialty clinics and expertise to intervene. Screening for MPS II is being carried out in at least 2 other states and additional ones are involved in pilot programs. The HHS Advisory Committee on Heritable Disorders in Newborns and Children have recommended MPS II for screening programs.
11. The benefits to the individual and society from the screening program should outweigh the potential physical and psychological harm caused by screening and confirmatory procedures.	Improved quality of life with fewer hospital admissions and surgeries; preservation of cognition; decreased cardio-pulmonary complications
12. The incremental cost of the screening program (including testing, diagnosis, treatment, administration, training and quality assurance) should be reasonable in relation to State health expenditures. When appropriate, a new test may be implemented on a pilot basis.	The incremental costs to the screening program cannot be fully assessed until a final platform is established. This platform can be integrated into a multiplex testing panel for up to 6 other disorders, including Pompe disease and MPS I.

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Vote

Pompe screening assay

- Measure α-glucosidase activity via MS/MS in dried blood spots
  - Flow injection based and liquid chromatography coupled detection
  - Multiplexed with C26 for X-ALD and IDUA for MPS I

- Cut-off = absolute value of enzymatic activity
  - Determined via sample population analysis (~1800 1st screens, ~900 2nd screens)
  - % high = (absolute value of enzymatic activity)/(absolute value of high control) to reduce plate effects

- If GAA is low, IDUA also reviewed to determine if possible sample quality issue

Pompe screening and follow-up

Initial workflow

1st NBS
Low GAA (<2)
Low IDUA

Possible sample quality issue

- Retest on 2nd screen

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Pompe screening and follow-up

Initial workflow

1st NBS
Low GAA (<2)
Normal IDUA

Abnormal follow-up

- Request EKG
- Second-tier testing
  - Mayo: creatine, creatinine, and GAA activity ratio
  - Targeted analysis of GAA via NGS (whole exome)
- GAA activity in leukocytes

Pompe screening and follow-up

Initial workflow

1st NBS
Low GAA (<2)
Normal IDUA

Abnormal follow-up

- Request EKG
- Second-tier testing
  - Mayo: creatine, creatinine, and GAA activity ratio
  - Targeted analysis of GAA via NGS (whole exome)
- GAA activity in leukocytes

Lots of false positives!

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Pompe screening and follow-up

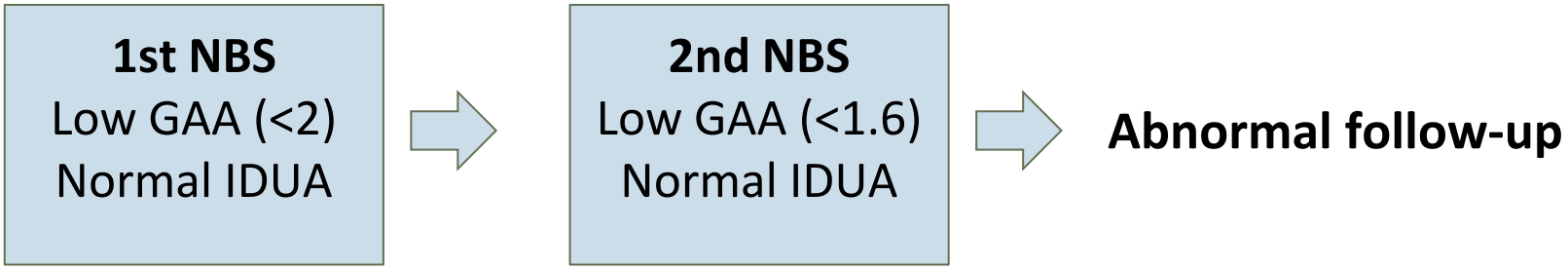
UPDATED workflow

1st NBS
Low GAA (<2)
Normal IDUA

Request 2nd screen is collected at 7-8 DOL

Pompe screening and follow-up

UPDATED workflow



Data and follow-up experience

From July 2023 - April 2024 (n ≈ 30,500)

18 first screens with low GAA activity

- 10 (56%) were in NICU
- 4 (22%) had low GAA on second screen
- 1 pseudodeficiency
- 4 carriers of late onset Pompe (LOPD)
- 1 in ongoing evaluation for possible LOPD
  (low GAA on both, normal creatine and hex4, 1 pathogenic variant)
- No confirmed cases

NEWBORN SCREENING

HEALTH UNIVERSITY OF UTAH

Intermountain Primary Children's Hospital

Contact

Sabina Cook, MS, LCGC

Newborn Screening

Utah Department of Health and Human Services

Phone: 801-584-8256

Fax: 801-536-0966

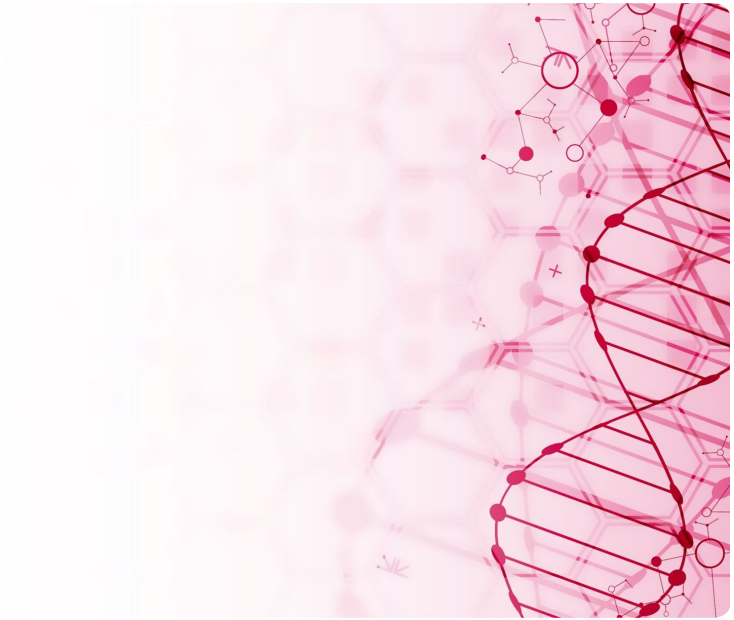
email: **sabinacook@utah.gov**

Pompe Family Story

Pompe Nomination

Family Presentation

Erin Hoch



Jaxen's Beginning

- Otherwise healthy pregnancy
- Failed two hearing tests
- Feeding issues

First Six Months

- Weekly weight checks
- Diagnosed with failure to thrive
  - Physician indicated mother's nutritional intake as cause
- Low tone
- Acid reflux
- Signs of hypoxia

Jaxen's Diagnosis

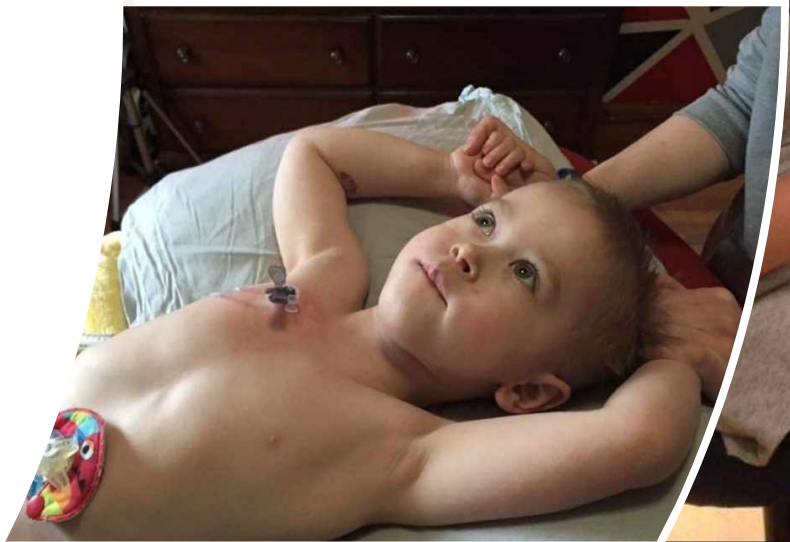
Age: 6 months

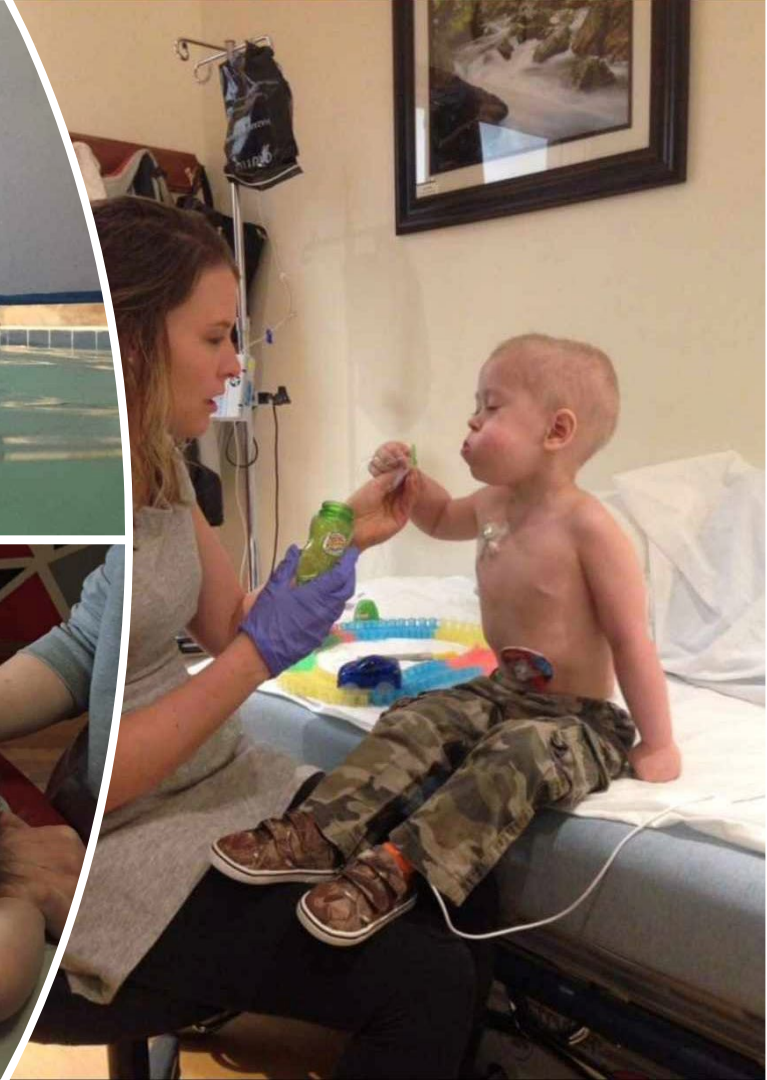
- Respiratory viral infection
- Went to urgent care
  - Chest x-ray identified an enlarged heart which contributed to respiratory issues
- Sent to hospital
  - EKG
- Sent to another hospital
  - Presumptively diagnosed with down syndrome
- Flown to Seattle Children's hospital
  - Suspicions of Pompe
  - Confirmed diagnosis with Pompe

- At Seattle Children's for 3 months
- Swallow study indicated aspiration

Care after diagnosis

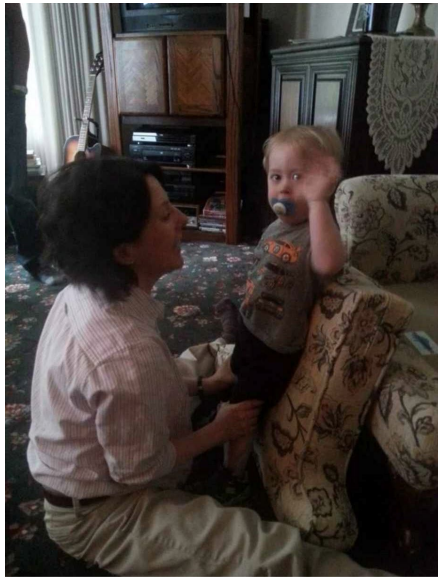
- Received a suction machine, cough assist, and vest
- Physical therapy
- Occupational therapy
- Feeding therapy
- Speech therapy
- Biweekly infusions

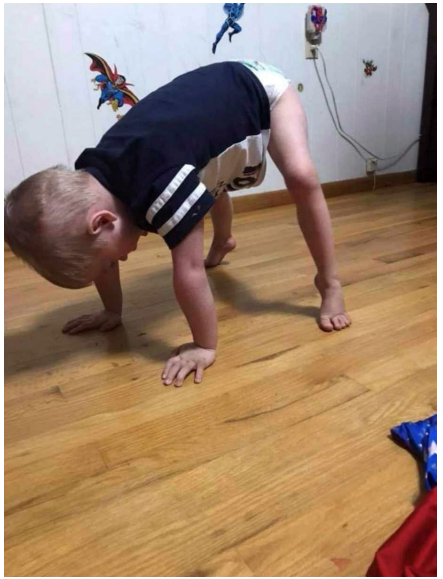




Progress with regular therapies and treatment

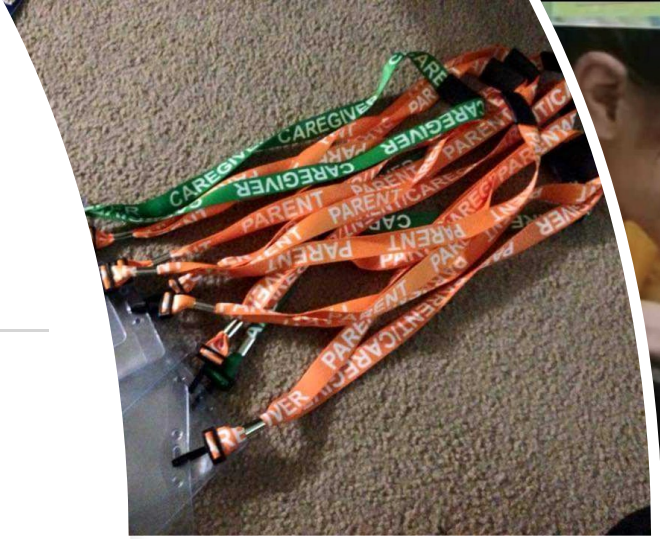
Able to transition into a supported standing position around 18 months old

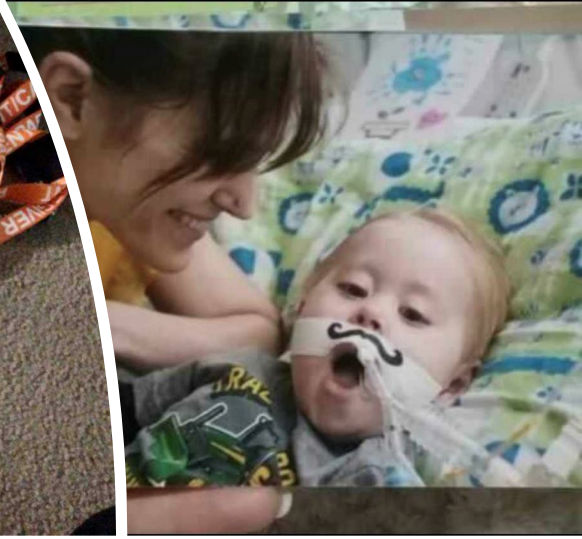


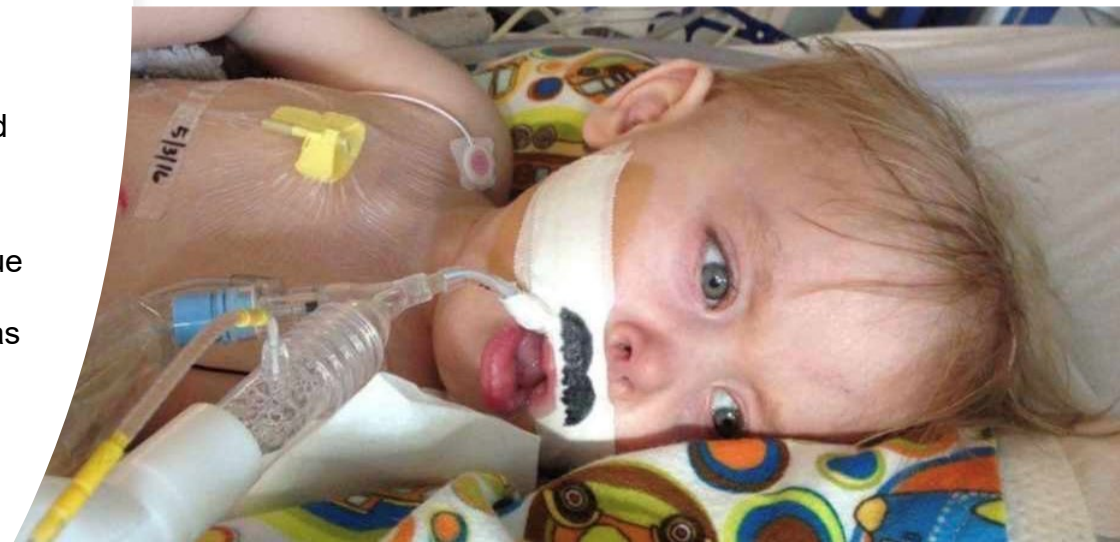


Unexpected setback

- Jaxen came down with RSV at 18 months old
- Jaxen was intubated due to complications from the infection
  - Intubated for 6 weeks
  - Almost had a tracheostomy placed due to inability to be extubated
- After RSV and hospitalization, he lost the gained strength and never regained the ability to stand
- Transitioned to weekly infusions in April 2016 due to frequent respiratory infections
  - Prior to starting weekly infusions, Jaxen was flown to Seattle 12 times for critical care

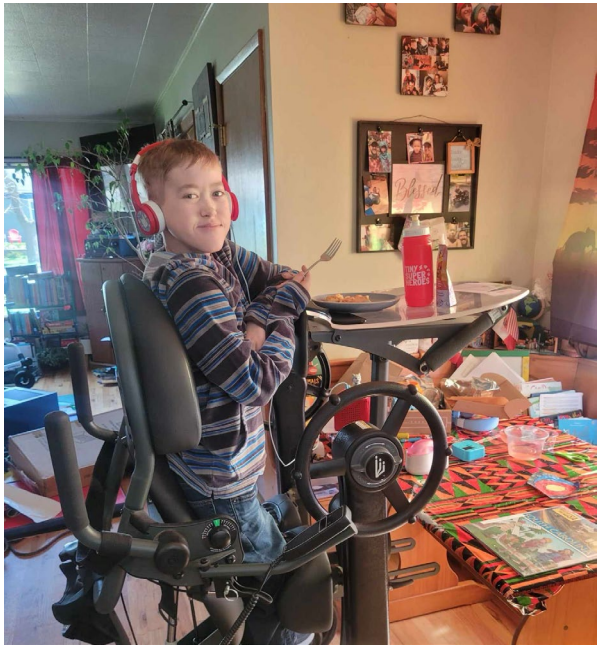






Today

- 32 providers manage Jaxen's care
- Jaxen is homeschooled
- PT at home twice a week
- Managing fatigue
- At-home equipment
- ADA bathroom
- He is now eating orally
  - 30% of feeds through G-tube
- Began talking around 5 ½ years old
- Speech and feeding therapies every other week



This has been a glimpse into our journey

Up next: others' experiences

Lathen Jr

- **Late-onset Pompe Disease**
- 15 months old
- **Diagnosed in 2023 via newborn screening in Washington**
- Has not started treatment
- No obvious symptoms
- Regular monitoring since birth

Marshall

- **Late-onset Pompe Disease**
- 4 years old
- **Diagnosed in 2019 via newborn screening in Ohio**
- Started treatment at 2 months
  - Elevated CK value that continued to rise
  - Subtle weaknesses noticed
    - Weak suckle with mild aspiration issues
    - Unable to bring his legs to midline
    - Poor head control
- Labs have since normalized and weaknesses improved
- Marshall has not missed a developmental milestone

Joe

- **Late-onset Pompe Disease**
- 45 years old
- Lives in Montana
- Symptoms started in childhood with a noticeably weak core
- Diagnosed clinically in 2018
  - Promptly started a clinical trial

Grant

- **Infantile-onset Pompe Disease**
- 3 years old
- **Diagnosed in 2021 via newborn screening in Indiana**
- Started treatment at 3 weeks old
- Grant is now a wild and active boy with no observable symptoms

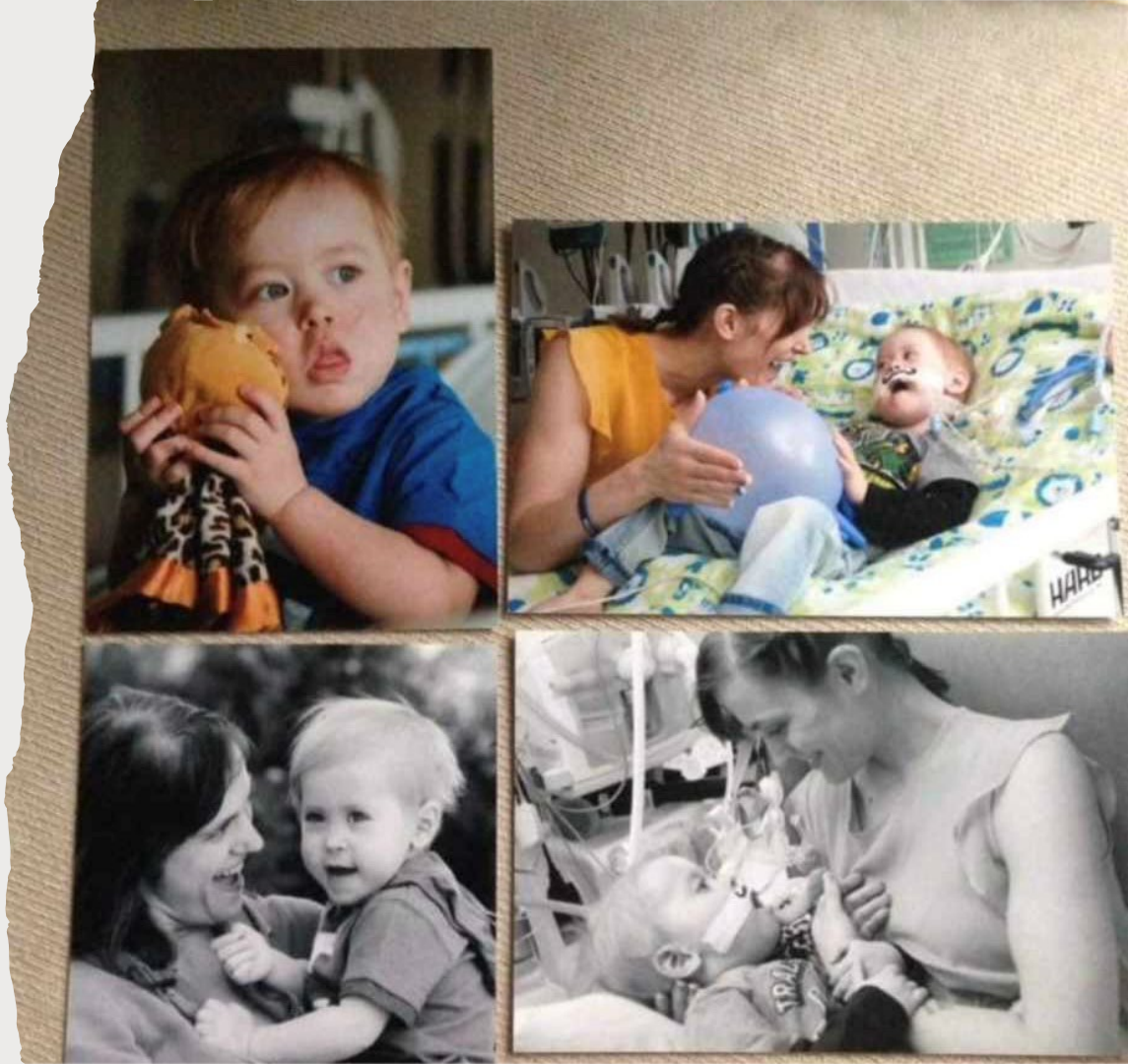
Vaun & Koen

- Vaun started treatment at 23 days old
- Koen was diagnosed in utero and started treatment at 3 days old

In closing…

- “Being born in one state or another should not be the reason that one child has access to better outcomes.”
  – *Paloma Juarez*
  mother, caregiver, advocate

Thank you



Laboratory Background

Pompe Cost Analysis

Wisconsin: (Jan 2024) cost is **$11 per specimen.**

Montana PHL:

Purchase Instrument

Instrument $380,000.00 / 132,000 babies (10 years) = **$2.88**

Service contract $50,000/ 13,200 (1 year) = **$3.79**

Kits $6,930 x 15/year = $103,950 / 13,200 = **$7.88**

Total = $14.55/screen if we amortize the instrument over 10 years

Instrument $380,000.00 / 66,000 babies (5 years) = **$5.76**

Service contract $50,000/ 13,200 (1 year) = **$3.79**

Kits $6,930 x 15/year = $103,950 / 13,200 = **$7.88**

Total = $17.43/screen if we amortize the instrument over 5 years

Pompe Cost Analysis

Reagent Rental

1 QSight and everything needed to operate: Approximate cost per kit = $14,535

$14,535/kit x 15 kits = $218,085/ 13,200 = $16.51/screen

2 QSight's would be ~$23,521 per kit

$23,521 x 15 kits = $26.73/screen

Pompe Discussion

Public Comment Period (10 minutes)

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- 2 minute max per comment
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10 Minute Break

Unfinished Business

MT vs RUSP Conditions

Continuation of Membership

Continuation of Membership

- **Member Attendance Requirements**
  - Regular attendance is expected of all Committee members.
  - Members may not send a substitute to attend a meeting in their place.
  - If a member fails to attend two (2) consecutive meetings without proper notice, an inquiry shall be made of that member concerning their continued participation. The results of the inquiry, together with recommendation of the Committee, shall be forwarded to the Director of DPHHS for a decision on the member's status.

Continuation of Membership

- Membership Continuation Form
- Proposed Bylaws Updates - Vote
  - Rules for New Appointments
  - Mandated Members Term Limit

Next Steps

- Follow Up from this Meeting
  - Meeting materials will be shared
  - Public website will be updated

- Next Meeting
  - Doodle Poll will be sent out to determine dates for Fall meeting
  - Will include Pompe vote and Gaucher disease presentation

Follow Up & Thank You

Please email if you have any questions, comments, or need anything

HHSNewbornAdvisoryCommittee@mt.gov