Panel Management Subcommittee – Review of Pompe disease and MPS1
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Jennifer Marcy, MS, LGC

Licensed Genetic Counselor

Iowa Newborn Screening Program

Subcommittee Activity

Met in December 2020

- **Presentation on Pompe disease and MPS1 by Dr. Bernat**

Met in February 2021

- **Presentation on LSD screening options by Tate Kappell from SHL**

Vote by email

- **2/22/21 - 3/26/21 with 1 reminder email on 3/15/21**

Pompe Disease

- Glycogen storage disease type II (AKA acid maltase deficiency)
- Caused by a deficiency of acid alpha-glucosidase (GAA) enzyme
- Symptoms are caused by build-up of glycogen throughout the body
- Inherited in the Autosomal Recessive pattern
- Wide variation in clinical presentation
- 2 clinical types

  Infantile-onset Pompe disease (IOPD)

  Late-onset Pompe disease (LOPD)

Infantile-Onset Pompe Disease (IOPD)

- Symptom onset before 12 months, can be prenatal
- Hypotonia
- muscle weakness
- feeding difficulties
- failure to thrive
- respiratory distress
- hypertrophic cardiomyopathy

Late-Onset Pompe Disease (LOPD)

- Symptom onset from late infancy (without cardiomyopathy) to adulthood
- Variable phenotype
- Progressive proximal muscle weakness, eventually leading to respiratory insufficiency

Pompe Pseudodeficiency

- Decreased enzyme level without disease
- Associated with specific genetic variant
- Higher frequency in Asian ancestries

Pompe Disease – CRIM Status

- Cross-reactive immunologic material
- CRIM-negative = no residual GAA protein

  Leads to immune response to enzyme replacement therapy
- CRIM-positive = some residual GAA protein

  Better response to ERT
- Genotype associated with CRIM status

Pompe Disease – Treatment

- Enzyme Replacement Therapy (ERT) = alglucosidase alfa
- IOPD –

  Increased survival, decreased need for ventilator, improved acquisition of motor skills

  Earlier treatment associated with better outcome
- CRIM-negative patients will also need immunomodulation to counter immune response
- LOPD –

  stabilization after symptom onset

  Little information about presymptomatic patients

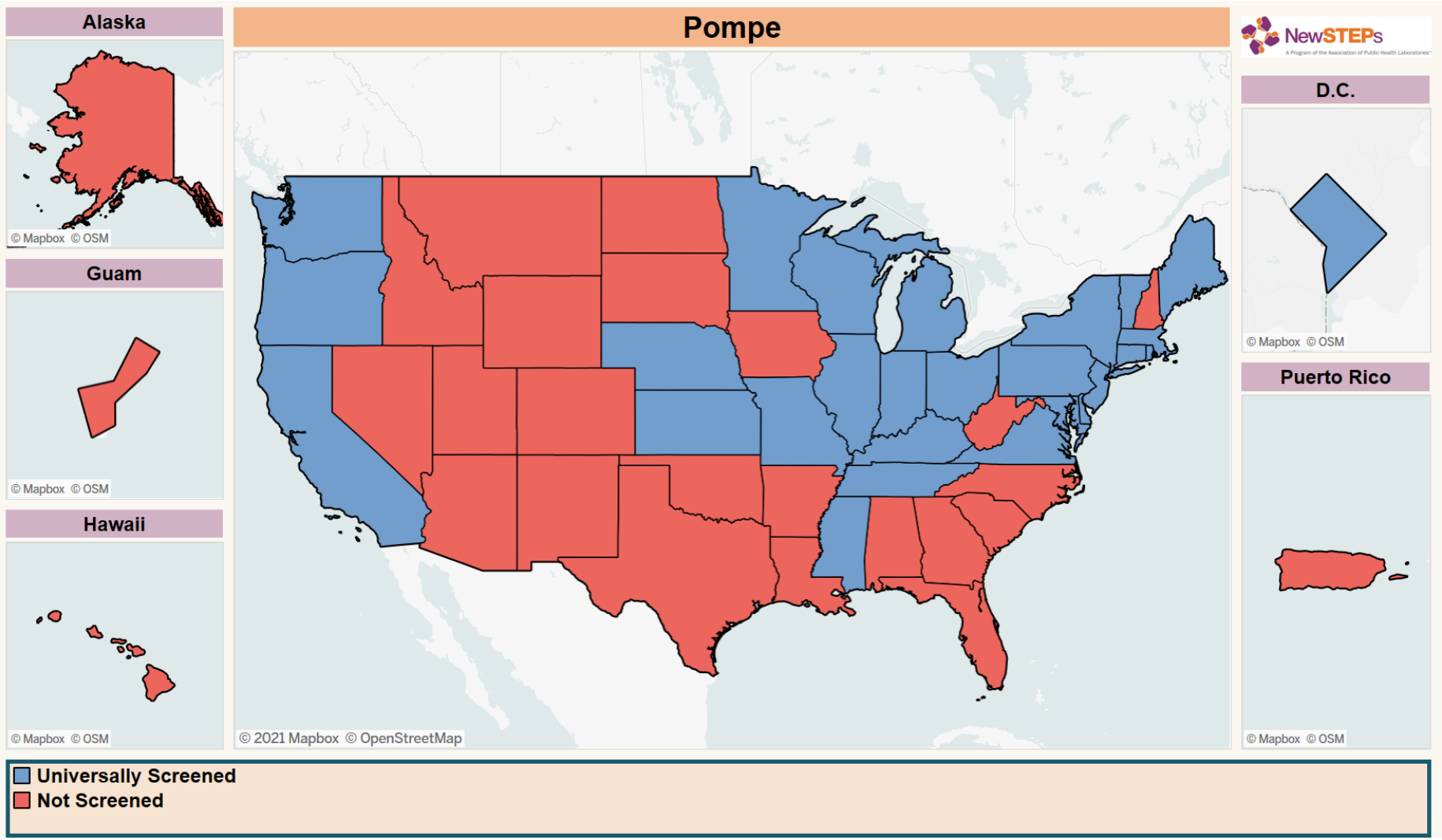
Pompe Incidence

Table 4.

Incidence of **Pompe** Disease in Different Populations

Population	Incidence	Reference
African American	1:14,000	Hirschhorn & Reuser [2001]
Netherlands	1:40,000 combined 1:138,000 infantile onset 1:57,000 adult onset	Ausems et al [1999], Poorthuis et al [1999]
US	1:40,000 combined	Martiniuk et al [1998]
South China/Taiwan	1:50,000	Lin et al [1987]
European descent	1:100,000 infantile onset 1:60,000 late onset	Martiniuk et al [1998]
Australia	1:145,000	Meikle et al [1999]
Portugal	1:600,000	Pinto et al [2004]

Leslie and Bailey. Pompe Disease. *GeneReviews* https://www.ncbi.nlm.nih.gov/books/NBK1261/



NBS

26 states & D.C.

https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders

Pompe Disease – NBS

- Several states have published findings from first years of screening

  Missouri

  Illinois

  California

- Lessons

  Options for primary screening method and for screening algorithms

  Incidence has been in line with published rates

  LOPD has higher incidence than IOPD

  2nd tier gene testing important for detecting pseudo-deficiency and limiting false positives

MPS1

- Mucopolysaccharidosis type 1
- Deficiency of lysosomal enzyme α-L-iduronidase (IDUA)
- Symptoms caused by accumulation of glycosaminoglycans (GAGs)
- Inherited in the Autosomal Recessive pattern
- Two classifications currently

  Severe MPS I

  Attenuated MPS I

  Used to be known as Hurler syndrome, Hurler-Scheie syndrome, and Scheie Syndrome

Severe MPS I

- Typically asymptomatic at birth
- Early features are non-specific: hernia, frequent upper resp infections
- Progressive coarsening of facial features, skeletal (gibbus deformity, dysostosis multiplex, short stature), intellectual disability, cardiorespiratory issues, hearing loss, corneal clouding
- Without treatment, usually die of cardiorespiratory failure by age 10

Attenuated MPS I

- Symptom onset between 3 and 10 years
- Wide variability in severity and rate of progression

  Cognitive: mild delays to normal in early childhood; learning disabilities or psychiatric issues

  Joint problems

  Cardiorespiratory disease

  Hearing loss and corneal clouding
- Without treatment prognosis ranges from death in 2nd or 3rd decade to normal life span with significant disability

Table 2.

Mucopolysaccharidosis Type I: Comparison of Phenotypes by Select Features

Feature	% of Persons w/Feature [1]	
	Severe MPS I	Attenuated MPS I
Course facial features	100%	10%
Macrocephaly	50%	20%
Hepatosplenomegaly	100%	80%
Dysostosis multiplex	100%	100%
Ophthalmologic issues	100%	100%
Cardiac involvement	100%	100%
Hearing loss	100%	50%
Upper airway involvement	100%	80%
Hydrocephalus	25%	5%
Intellectual disability	100%	10%

1. The age of the affected individual considerably affects the phenotypic features.

MPS I - Incidence

- Severe – 1/100,000
- Attenuated 1/500,000

Clarke. Mucopolysaccharidosis Type I. *GeneReviews* https://www.ncbi.nlm.nih.gov/books/NBK1162/

MPS I - Treatment

- Enzyme replacement therapy (ERT) – Laronidase (Aldurazyme)

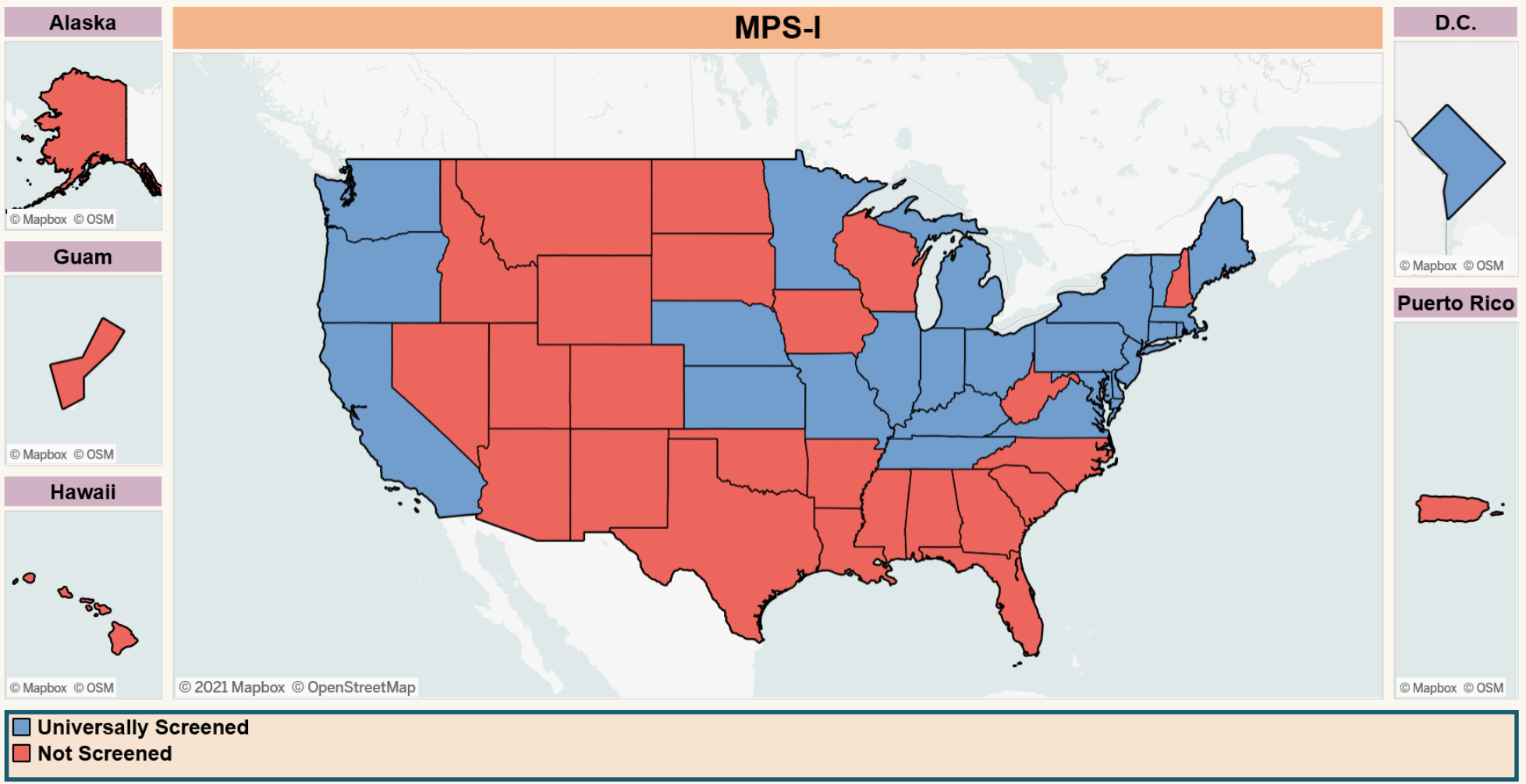
  Does not cross the blood-brain barrier- does not impact intellectual symptoms

  Improvement in other findings

- Hematopoietic stem cell transplant

  Does not impact skeletal or cardiac symptoms

  Stabilizes cognitive function when done before significant issues (by 12-18 months)



NBS

24 states and D.C.

https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders

MPS I - NBS

- Published state experiences
  - **Illinois**
  - **Missouri**
  - **North Carolina**
  - **New York**
- Lessons
  - **Successful screening is reproduceable in multiple programs**
  - **Multiple screening algorithms available to review/borrow**
  - **Higher rate of pseudo-deficiency than expected**
  - **2nd Tier testing – needed to reduce follow-up burden**
  - **IDUA gene testing or heparan & dermatan sulfate derived disaccharides in DBS**

From ACHDNC Meeting

Aggregated Summary of Published Screening Results*

*(*reported in final evidence review reports)*

	SCID	CCHD	Pompe	MPS I	X-ALD	SMA
Date	2008-2017	2013 - 2018	2013– 2017	2013– 2017	2017 – 2018	2018-2019
Total Infants Screened	3,946,037 (3 programs)	176,819 (6 programs)	594,979 (4 programs)	681,424 (5 programs)	120,136 (2 programs)	225,093 (1 program)
Positive Screens	1,165	145	308	318	26	8
True Positives	65	10	45	5	12 (males)	8
Positive Predictive Value	5.5%	6.9%	14.6%	1.6%	46.2%	100%
By Phenotype *(if applicable or provided)*	NR	NR	10-IOPD 33-LOPD (2 NR)	3 severe MPSI (1 NR)	NR	3 with 2 *SMN2* 3 with 3 *SMN2* 2 with ≥4 *SMN2*
Other Positive Screen Results	277 other T-cell lymphopenia 769 unaffected	NR†	56 carriers 49 pseudodeficiency 137 unaffected 13 undetermined	19 carriers 126 psuedodeficiency 133 unaffected 6 undetermined	7 carriers/heterozygote females 4 other disorders	0
State programs Source *(1st author and pub year)*	WI - Verbsky (2011) CA - Amatuni (2019) NY - Vogel (2014)	GA - Diller (2018) NJ – Garg (2013) TX – Guillory (2017) MA – Johnson (2014) MN – Kochilas (2013) CO – Wright (2014)	NY – Wasserstein (2018) KY – Minter Baerg (2018) IL – Burton (2017) MO – Hopkins (2018)	NC – Taylor (2019) NY – Wasserstein (2018) KY – Minter Baerg (2018) IL – Burton (2017) MO – Hopkins (2018)	NC – Taylor (2019) MN – Wiens (2019)	NY – Kay (2020)

†Other conditions identified through POX, though not included here due to variability in reporting

Options for Lysosomal Storage Disease Screening

- Baebies: Seeker Platform
- Perkin Elmer: NeoLSD Kit
  - **QSIGHT**
- Lab Developed Test

Baebies: Seeker Platform

- Microfluidics
- Pompe, MPS I, (Gaucher, Fabry)
- Turn around time 3 hours
- 2nd Tier testing available through Baebies – Turn around time?
- Potential for adding new disorders
- Would have a minimal impact on SHL space
- Expect large upfront cost

Perkin Elmer: NeoLSD Kit

- Flow injection analysis tandem mass spec (FIA-MS/MS)
- Pompe, MPS I, (Gacher, Niemann-Pick A/B, Fabry, Krabbe)
- Turn around time up to 22 hours
- 2nd Tier only available for Pompe through PerkinElmer – 3 to 5 week turn around
- FDA approved on PerkinElmer instruments only
- SHL can accommodate additional MS/MS instruments; new automation option available
- Large up-front cost
- PerkinElmer also has QSIGHT but it comes at an even higher cost – would make the new MS/MS obsolete

Lab Developed Test

- Liquid chromatography tandem mass spectrometer (LC-MS/MS)
- Estimated turn around – up to 24 hours
- Development would take more time than bringing in a method from an outside company
- Might need facility upgrades, but space available for new instruments
- Large up-front cost

SHL Bottom Line

- Regardless of method

  Large up-front cost

  Additional FTE requirement(s)
- Variable set up, validation timelines
- Variable turn around for initial screen
- Options for 2nd Tier testing
- MS/MS methods would require an experienced TMS Research Specialist

Short Term Follow Up – Bottom Line

- Typical needs to develop SOP, education materials/plan
- Staffing needs would depend on methodology chosen

  Can always use additional FTE for education

  If 2nd tier is not included, would need additional 0.5 FTE

  If in-house testing includes genetic testing, would need additional GC effort

Long Term Follow Up – Bottom Line

- UIHC already has a robust Lysosomal Storage Disease program and are currently capable of providing diagnostics and clinical care for infants detected through NBS in neighboring states
- UIHC pediatric cardiology can absorb any patient load from LSD NBS

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IDPH – Bottom Line

- Would require an update to the data system – cost $15,000
- Overall cost of piloting and implementing could be restrictive

  Locating sources of funding may be difficult

  Development fund will be more limited than for recent panel additions

Subcommittee Vote

Subcommittee Vote

Pompe: "**Pompe disease is an appropriate addition to the Iowa newborn screening panel and I support CIDAC requesting an Implementation Assessment.**"

- Agree
- **Disagree**
- Undecided
- **Declined to Vote**

MPS1: "**Mucopolysaccharidosis type I (MPS 1) is an appropriate addition to the Iowa newborn screening panel and I support CIDAC requesting an Implementation Assessment.**"

- Agree
- Disagree
- Undecided
- Declined to Vote

Subcommittee Vote

Pompe: "**Pompe disease is an appropriate addition to the Iowa newborn screening panel and I support CIDAC requesting an Implementation Assessment.**"

- Agree 9
- **Disagree 0**
- Undecided 0
- **Declined to Vote 4**

MPS1: "**Mucopolysaccharidosis type I (MPS 1) is an appropriate addition to the Iowa newborn screening panel and I support CIDAC requesting an Implementation Assessment.**"

- Agree 8
- Disagree 1
- Undecided 0
- Declined to Vote 4

References

- Burton et al. Newborn Screening for Pompe Disease in Illinois: Experience with 684,290 Infants. *Int. J. Neonatal Screen*. 2020, 6, 4;
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- Wasserstein et al. The New York Pilot Newborn Screening Program for Lysosomal Storage Diseases: Report of the First 65,000 Infants. *Genet Med* . 2019 March ; 21(3).