Newborn Screening: Current Landscape & Future Directions

National Academies of Science, Engineering and Medicine

EVERYLIFE FOUNDATION FOR RARE DISEASES

Annie Kennedy
Chief of Policy, Advocacy & Patient Engagement

January 26, 2024

Newborn Screening Modernization Roundtable Series *(Late 2022 – Early 2023)*

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3 Roundtables held

108 Attendees at public meeting

40+ Experts identified actionable policy solutions

4 Key themes identified

Study Support Provided By:

American Society of Gene + Cell Therapy

BIOMARIN

Expecting Health

NBSTRN Newborn Screening Translational Research Network

Orchard therapeutics

PTC THERAPEUTICS

sanofi

SAREPTA THERAPEUTICS

TRAVERE THERAPEUTICS

Pioneering the New Era of Newborn Screening:
Collaborative Insights & Recommendations for Modernizing NBS Systems (Sept 2023)
https://everylifefoundation.org/nbs-white-paper/

Four Key Themes/Opportunities for Modernization that Yielded from Roundtables

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THEME 1: Increase federal leadership, accountability, and transparency within federal newborn screening programs

THEME 2: Establish a regional lab network that provides state NBS programs with the opportunity to work together to ensure efficient and faster addition of newborn screening conditions

THEME 3: Increase access to population-level data both before and after newborn screening to facilitate the development and adoption of newborn screening conditions to federal and state panels

THEME 4: Integrate next-generation, evidence-based neonatal sequencing into newborn screening in a manner that can be broadly implemented in all state newborn screening programs

https://everylifefoundation.org/nbs-white-paper/

For Today – 2 Critical Challenges in NBS for our Rare Disease Community

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- **Rare Diseases are Disadvantaged by Our Existing Processes & RUSP Evidence Review Criteria**
- **Disparities Across State Lines**

Limited State and Federal Funding

Rare Diseases are Disadvantaged by Our Existing Processes & RUSP Evidence Review Criteria

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NBS Evidence & Infrastructure Building

- Validated screen (FDA approved)
- Collaboration with federal agencies
- Collaboration with state labs
- State Pilot(s)
- Clinical Care Guidelines
- Parent resources
- Provider decision tools
- Peer-reviewed publications with clinical outcome data re: timely ID & intervention
- Sibling studies
- Longitudinal data collection

- Collaboration with provider groups (Pediatric, genetic & specialty)
- Health economic data
- Patient preference data
- ICD code
- Surveillance data/ epidemiology
- Action Sheets
- And more…

FEDERAL NOMINATION & IMPLEMENTATION PATHWAY

Evidence Development
(Screen, Tx, infrastructure, Care Standards, and more)

RUSP Nomination to Secretary's Advisory Committee on Heritable Disorders in Newborns & Children

Nomination package review by Evidence Review Committee

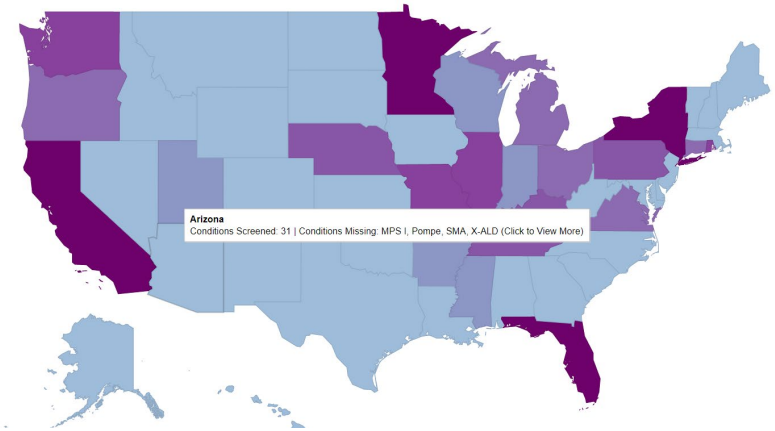
Review by Advisory Committee

If package not accepted, continue to build evidence

If not approved, continue to build evidence

Approved!

Await HHS Secretary Approval



State by State Implementation begins

Key considerations for adding conditions to the recommended universal screening panel (RUSP)

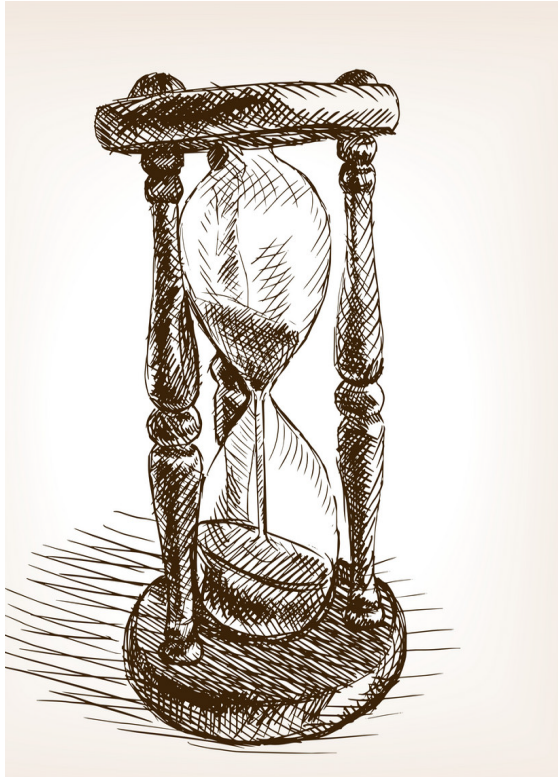
1. Screening is needed to identify all babies who may need treatment
2. There is a significant risk of illness, disability, or death if babies are not treated promptly,
3. Effective treatment is available
4. Treatment is more beneficial in the newborn period than later
5. Resources and access to treatment and counseling are widely available
6. The benefits to babies and to society outweigh the risks and burdens of screening and treatment

Duchenne Muscular Dystrophy (not currently screened for federally)

Time to diagnosis of Duchenne muscular dystrophy remains unchanged: Findings from the Muscular Dystrophy Surveillance, Tracking, and Research Network, 2000–2015 ***(Muscle and Nerve, 2022)***

- Family/primary caregivers were most commonly the first to note concerns
- Mean age at first signs and symptoms reported by the caregiver was 2.7 years, followed by first CK at 4.6 years and confirmatory testing at 4.9 years.
- The average time from first report of symptoms to diagnostic confirmation was 2.2 years.
- The ages at first concern, and subsequent testing and initial visit to a specialist, were significantly later among non-Hispanic black individuals compared with non-Hispanic white individuals In addition, the age at CK testing was significantly later among Hispanics compared with non-Hispanic whites.

https://onlinelibrary.wiley.com/doi/10.1002/mus.27532



Life Altering Therapies Available – Babies Go Undetected

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Meanwhile…

- 7 FDA approved therapies for Duchenne
- All with safety & efficacy established prior to mean age of diagnosis
- Mean age of diagnosis is outside of optimal therapeutic window for timely intervention

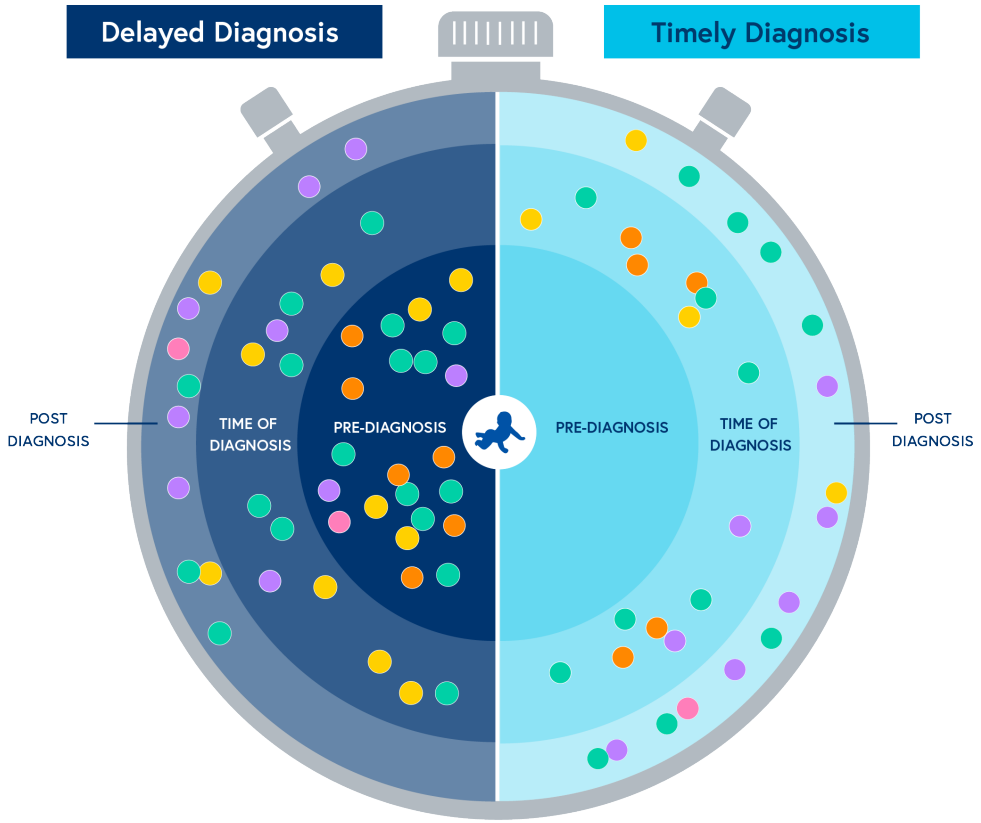
NBS Status –

- US Pilots conducted in OH and New York State
- Nomination to RUSP, accepted to evidence review after 2nd vote
- So far - Ohio and New York state-wide screening

The Impact of Delayed Diagnosis in Duchenne

Navigating a rare disease diagnosis can require more than 6 years and 17 medical interventions, on average, after symptoms begin, including emergency room visits and out-of-state specialist appointments.[1] We took a detailed look into Duchenne muscular dystrophy, a rare neuromuscular condition, to illustrate the significant economic impact of this diagnostic odyssey.

Every Minute Matters



- **TYPICAL ACCOMPANYING DIAGNOSIS:** Gait issues and muscle weakness
- **TESTING & PROCEDURES:** Genetic testing, liver biopsy
- **SPECIALISTS:** Orthopedist, Hepatologist, Gatroenterologist
- **TREATMENTS & SUPPORTING THERAPIES:** Ankle-foot orthotics (AFO)
- **EVENTS:** Unexpected hospitalizations

Examples are not exhaustive

ACTION IS KEY TO SECURING TIMELY DIAGNOSIS

The EveryLife Foundation and leading partners, including Parent Project Muscular Dystrophy (PPMD), are working to develop state and federal policies to eliminate the diagnostic odyssey in Duchenne. For more information on how you can get involved and support this effort, please visit **everylifefoundation.org** and **parentprojectmd.org.**

DELAYED DIAGNOSIS DRAMATICALLY INCREASES COSTS FOR FAMILIES*

$211,229 Total medical cost and productivity loss per family

20 Lost days of work for caregivers each year

17 Out-of-state trips for medical care across the 7 communities studied

*Across the diagnostic odyssey

How Did We Collect These Data?
- Medicare and Commercial insurance claims data, including patients with Duchenne
- Results from The Rare Disease Financial and Social Impact Survey, completed by 1,409 community members

BENEFITS OF TIMELY DIAGNOSIS

Timely diagnosis, defined as before five years old for children with Duchenne[2,3], can improve health outcomes by:

- Providing earlier access to supportive therapies and treatment
- Delaying disease complications and physical disabilities
- Lowering costs for patients and families by reducing or eliminating costly and unnecessary services or procedures

The Cost of Delayed Diagnosis in Rare Disease: *A Health Economic Study*

Parent Project Muscular Dystrophy

Reference:
1. Yang G, Cintina I, Zhou M, et al. The National Economic Burden of Rare Disease Study. The EveryLife Foundation for Rare Diseases. https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf. Published February 25, 2021. 2. Ciafaloni E, Fox D, Pandya S. Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr. 2009;155(3):380-385. 3. Families Continue to Experience Delay in Getting a Diagnosis of Duchenne Muscular Dystrophy. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention; 2023. https://www.cdc.gov/ncbddd/musculardystrophy/features/delay-in-diagnosis-of-duchenne-muscular-dystrophy.html

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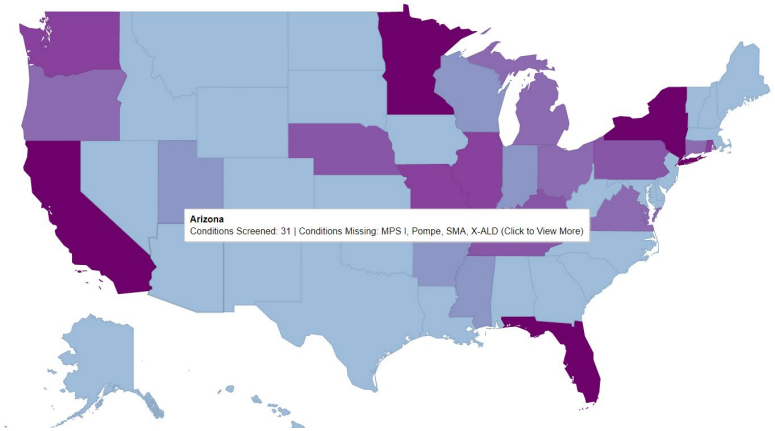


State by State Implementation begins

Life Altering Therapy Available in ASMD – Babies Are Going Undetected

- Disease Progression
  - Type A: unlikely to live beyond 4yrs.
  - Type B: may live until late childhood or early adulthood with many complications.
  - Type C: Varies based on age of presentation, but ~20 years.
- ASMD Treatments:
  - Bone Marrow transplant
  - **Enzyme replacement therapy FDA approved for ASMD in 2022**
  - Statins to manage cholesterol
  - Physical and occupational therapy

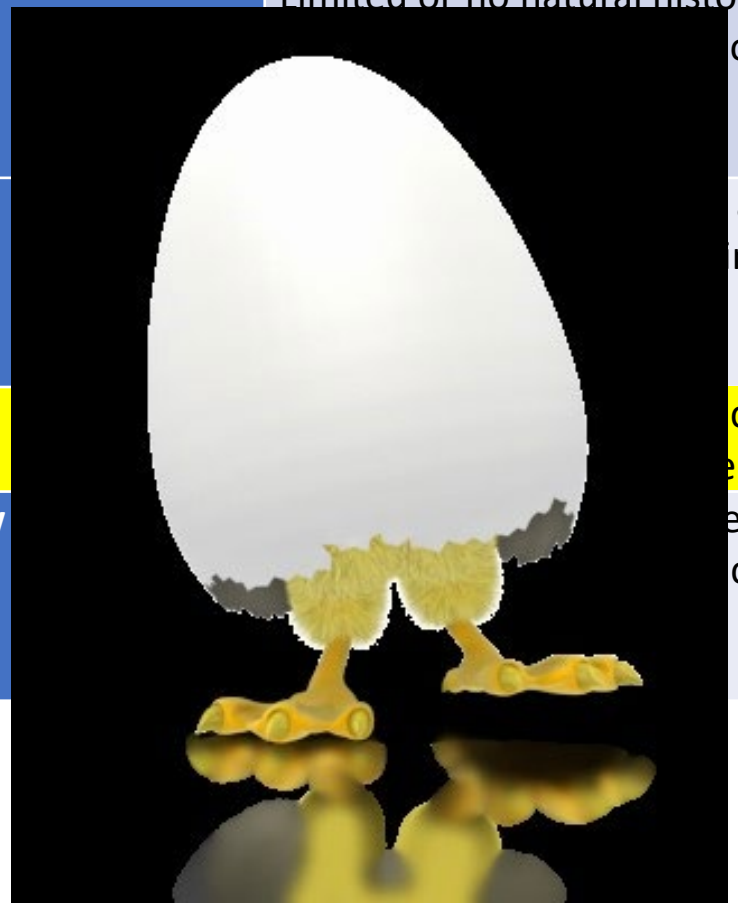
Life Altering Therapy (Soon) Available –

Disease Progression:
Infantile: ~ death by age 5
Juvenile: progressive symptoms with death ~10-20 years following onset.
Adult: progressive symptoms with death ~6-14 years following onset

Treatments:
Bone Marrow transplants
Symptomatic and supportive
BLA submitted in September for gene therapy, already authorized in EU

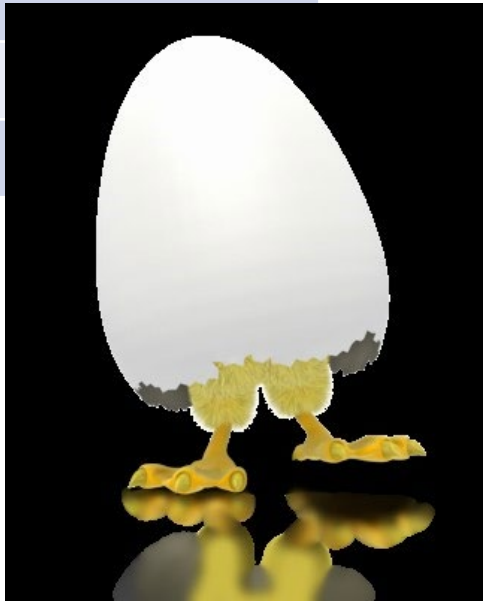
Rare Disease Therapy Development Challenges

Rare Disease-Challenges (MAGNIFIED IN 'ULTRA-RARE'	Regulatory Science-Related Challenges
Small patient populations	Limited or no natural history data; incomplete or limited understanding of otypic variability within a disease.
Limited measurement tools	and validated biomarkers or other surrogate n rare populations
Delays in receiving a diagnosis	cluding companion diagnostics, no NBS without enetic testing as first-line options
Inconsistent approaches to review disease applications	es and approaches between offices, divisions and cation of regulatory flexibility



History of Therapy Approval & RUSP Addition

Disease on RUSP	Date of Addition	Date of First FDA Approval
X-ALD	2016	Stem Cell Transplant used since the 80s
Pompe Disease	2015	2006 (late onset 2021)
MPS-1	2016	2003
SMA	2018	2016
MPS-2	2022	2006



Disease Prevalence

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RUSP conditions

- PKU: 1 in 12,000-20,000
- CF: 40,000 U.S. cases (~1 in 8,000)
- SCID: 1 in 60,000
- SMA: 1 in 11,000
- ALD: 1 in 17,000
- Pompe: 1 in 40,000
- MPS 1: 1 in 100,000
- MPS-2: 1 in 100,000-170,000
- GAMT: 1 in 550,000

Non-RUSP Conditions w/ Approved Therapies (US and EU):

Duchenne: 1 in 5000 males
Friedreich's Ataxia: 1 in 40,000
Fabry: 1 in 40,000-60,000 males
MLD: 1 in 40,000-100,000
Krabbe: 1 in 100,000
ASMD: 1 in 250,000

FDA Programs in Late Stage Development/ NBS programs be formed by PAGs:

Angelman: 1 in 12,000 to 20,000
Prader Willi: 1 in 10,000 to 30,000
CTX: 1 in 50,000
Sanfilippo: 1 in 70,000
MPS VII: 1 in 250,000

Key considerations for adding conditions to the recommended universal screening panel (RUSP)

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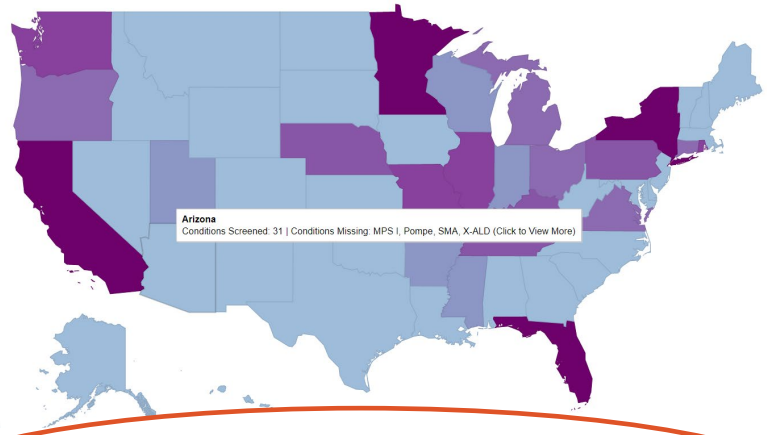

State by State Implementation begins

Disparities Across State Lines

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Disparities Across State Lines

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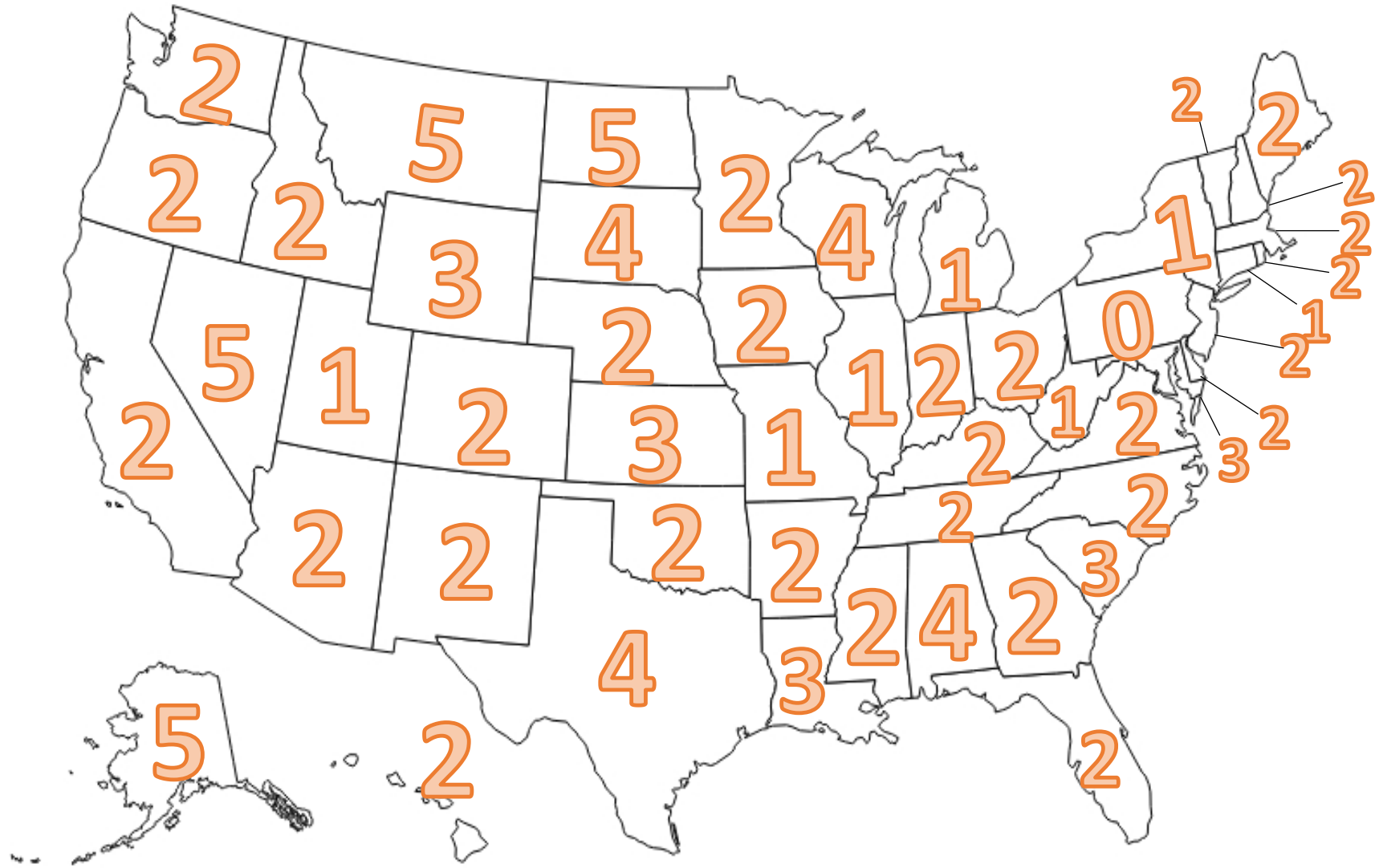

State RUSP Alignment

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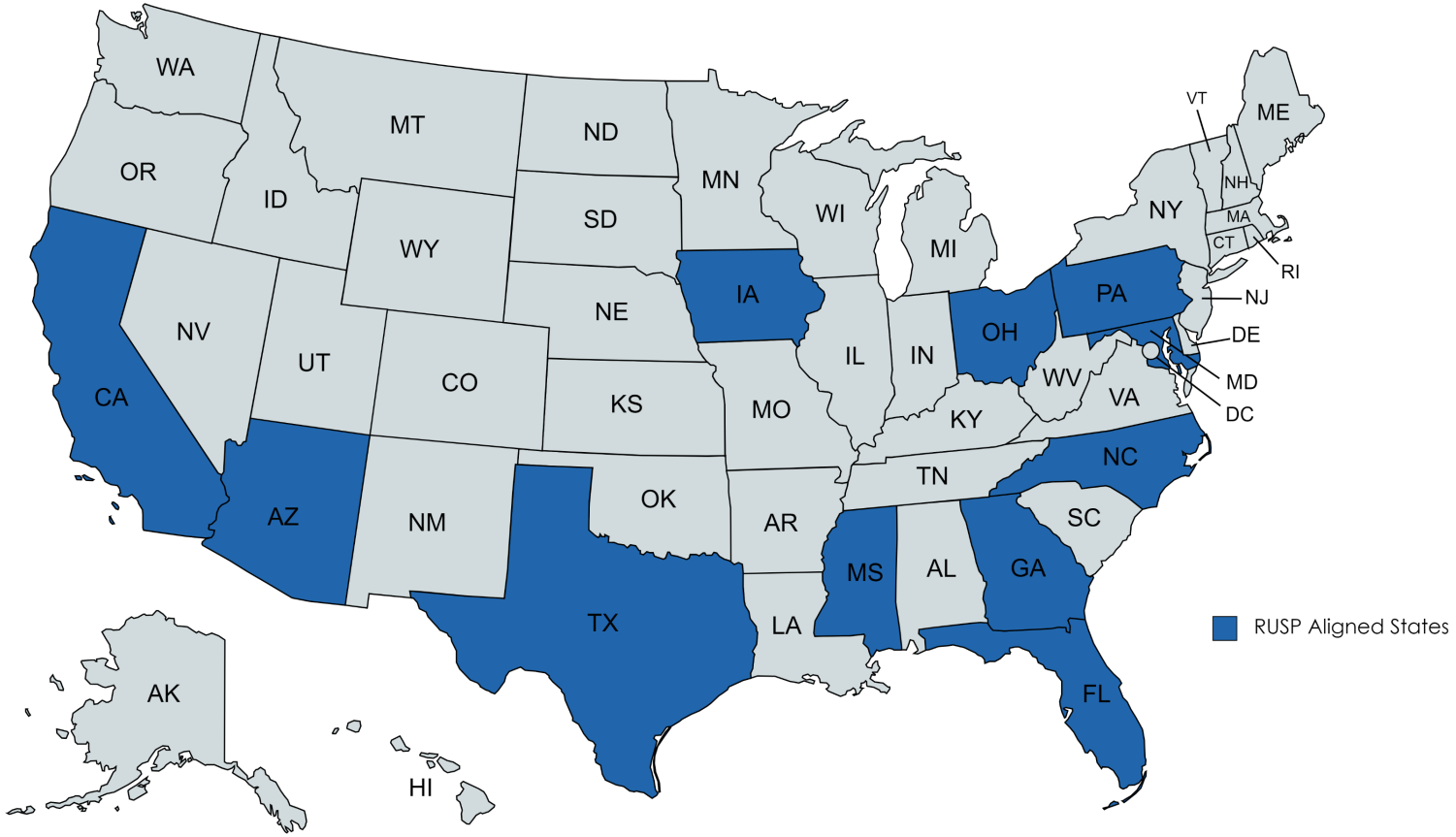

Created with mapchart.net

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Thank you to NASEM and the Committee!

- **2003** — First published full human genome
- **2008** — First passage of Newborn Screening Saves Lives Act
- **2014** — Last Reauthorization of Newborn Screening Saves Lives Act
- **2017** — First FDA approval for cell or gene therapy
- **2023** — Federal newborn screening programs remained unauthorized

Additional Data

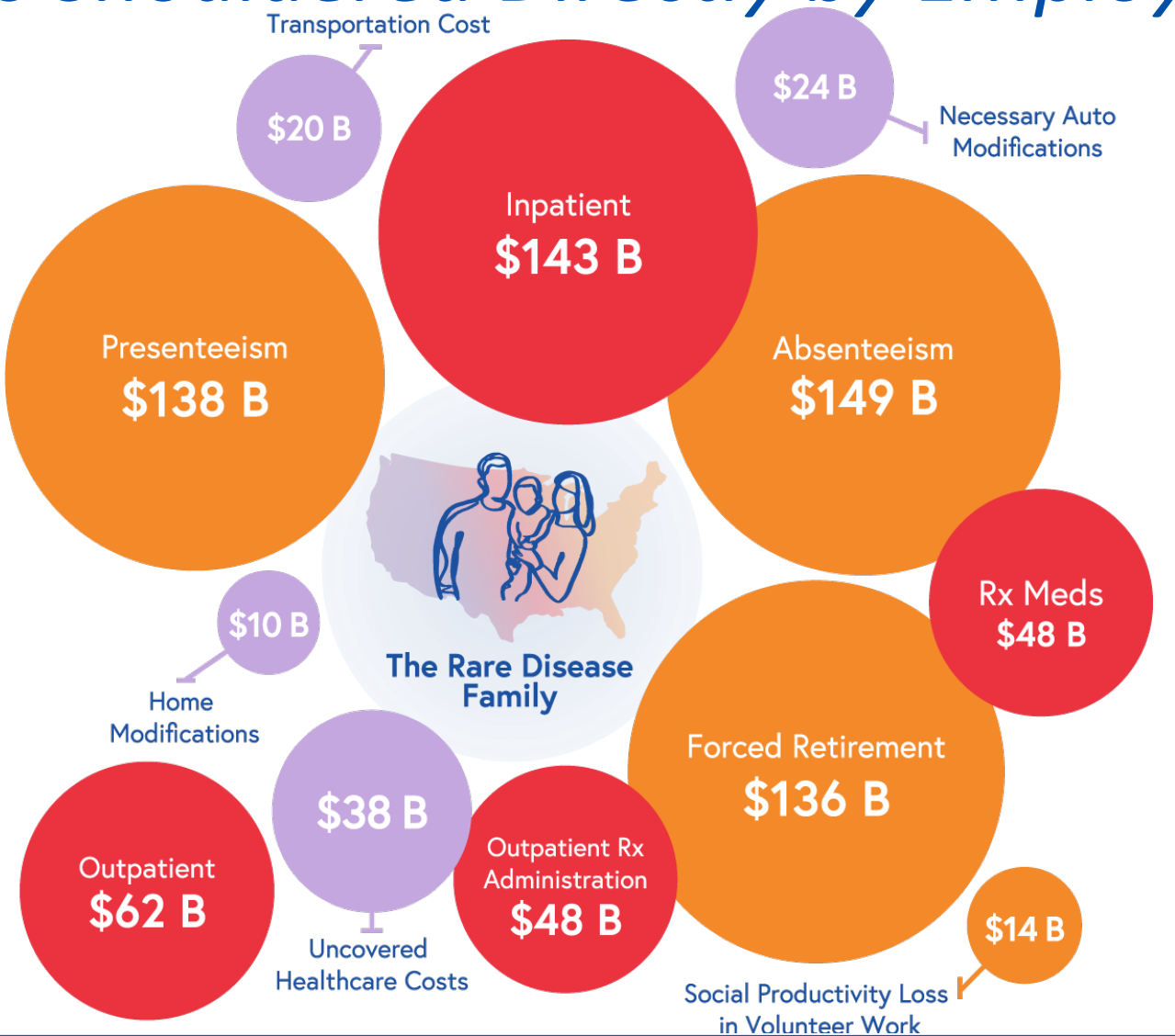
Public Health Urgency of Rare Disease

60% of Costs Shouldered Directly by Employers & Families

$437 Billion
INDIRECT COSTS: PRODUCTIVITY LOSS

$418 Billion
DIRECT MEDICAL COSTS

$111 Billion
NON-MEDICAL & UNCOVERED HEALTHCARE COSTS



Total Economic Burden of Rare Disease in the U.S in 2019:

$966 Billion

Estimated prevalence of 379 RDs

15.5 million

The National Economic Burden of Rare Disease Study

Conservative Estimate of Economic Burden Based on 379 of 10,000 RDs

Study Results:

RD Impact Survey Captures Medical Burden, Long Diagnostic Odyssey

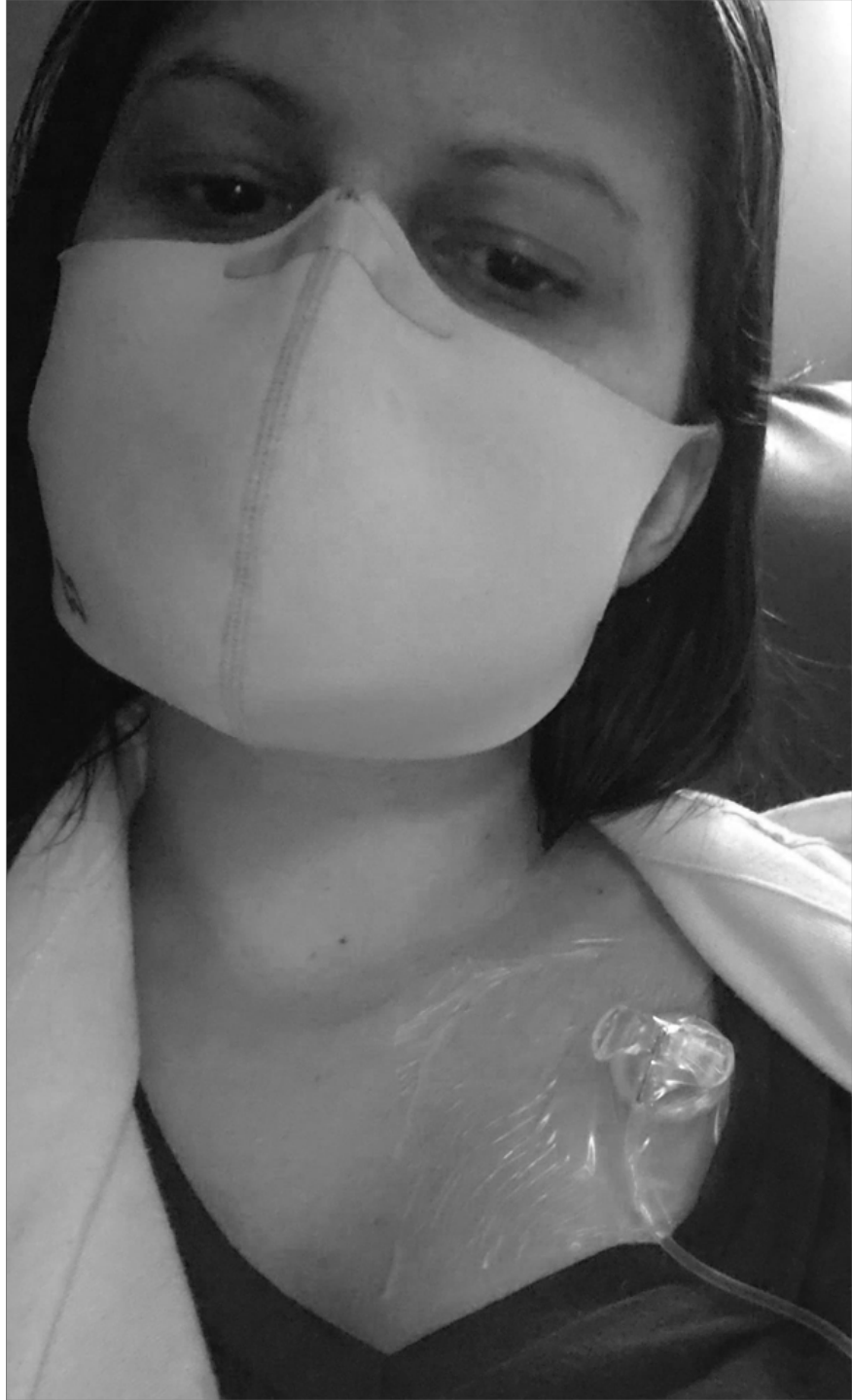
16.5 YEARS
Since first RD symptom (mean)

10.2 YEARS
Years since RD diagnosis (mean)

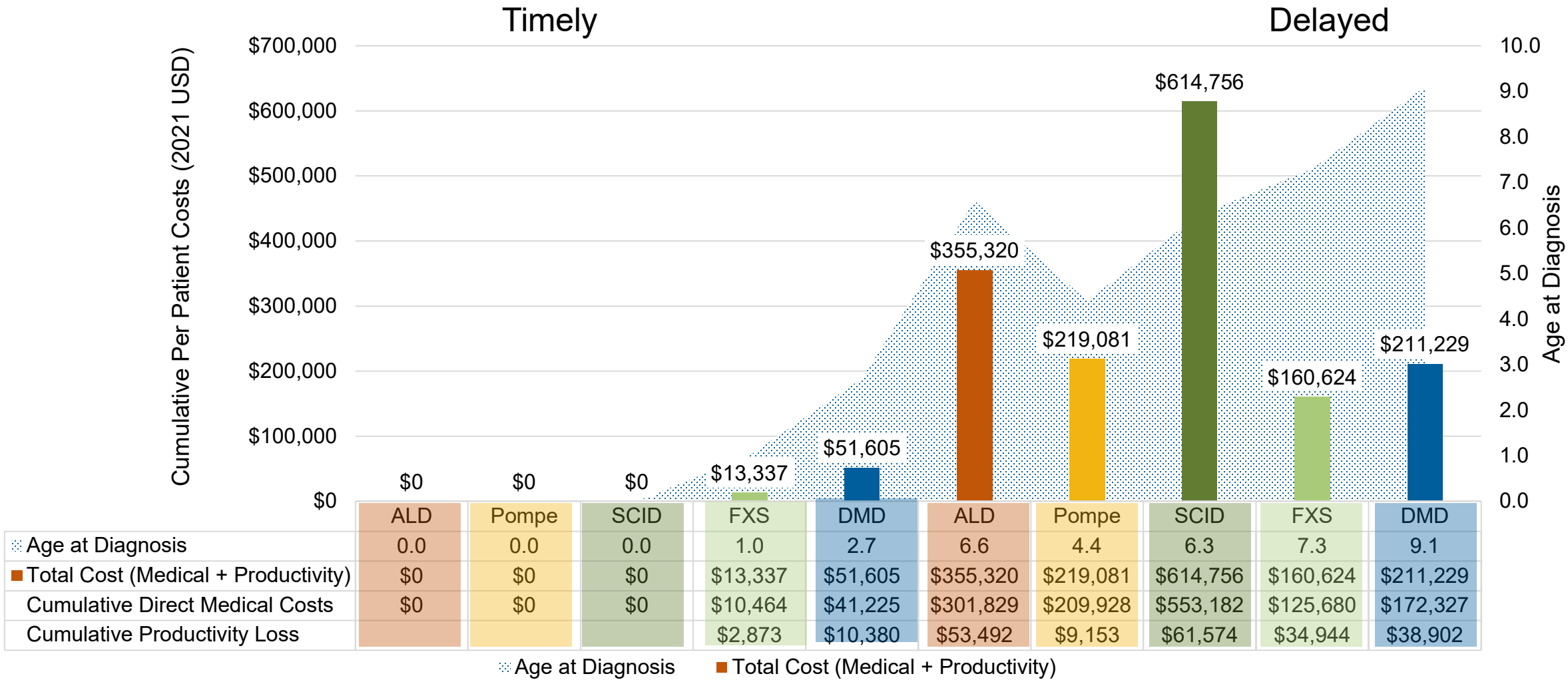
6.3 YEARS
Navigating without RD diagnosis (mean)

16.9
Average number of specialists seen since first RD symptom

Based on final analysis sample of 1,360 completed responses



Economic Burden of the Diagnostic Odyssey in 5 Pediatric-Onset Rare Diseases



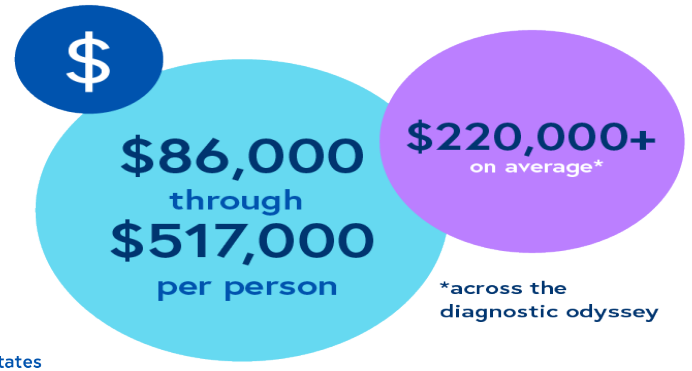
The Cost of Delayed Diagnosis in Rare Disease: *A Health Economic Study*

[a] Total cost per patient per year is the sum of direct medical costs and productivity loss in the pre-diagnosis period.
Costs are CPI adjusted to 2021 US dollars
Productivity loss is calculated as the product of work days missed and mean annual wage in 2021 (Bureau of Labor Statistics)
Missed Days' work is the weighted average of commercial and Medicaid FFS pre-diagnosis days missed work (for caregiver or patient) with delayed diagnosis; inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work (Mowitz, et al., 2022).

The Impact of Delayed Diagnosis in Rare Disease

Navigating a rare disease diagnosis can require more than 6 years and 17 medical interventions, on average, after symptoms begin, including emergency room visits and out-of-state specialist appointments.[1]

Our in-depth look at the diagnostic odyssey across seven rare diseases found the economic impact of medical costs and lost income for individuals and families totals:



Disease States

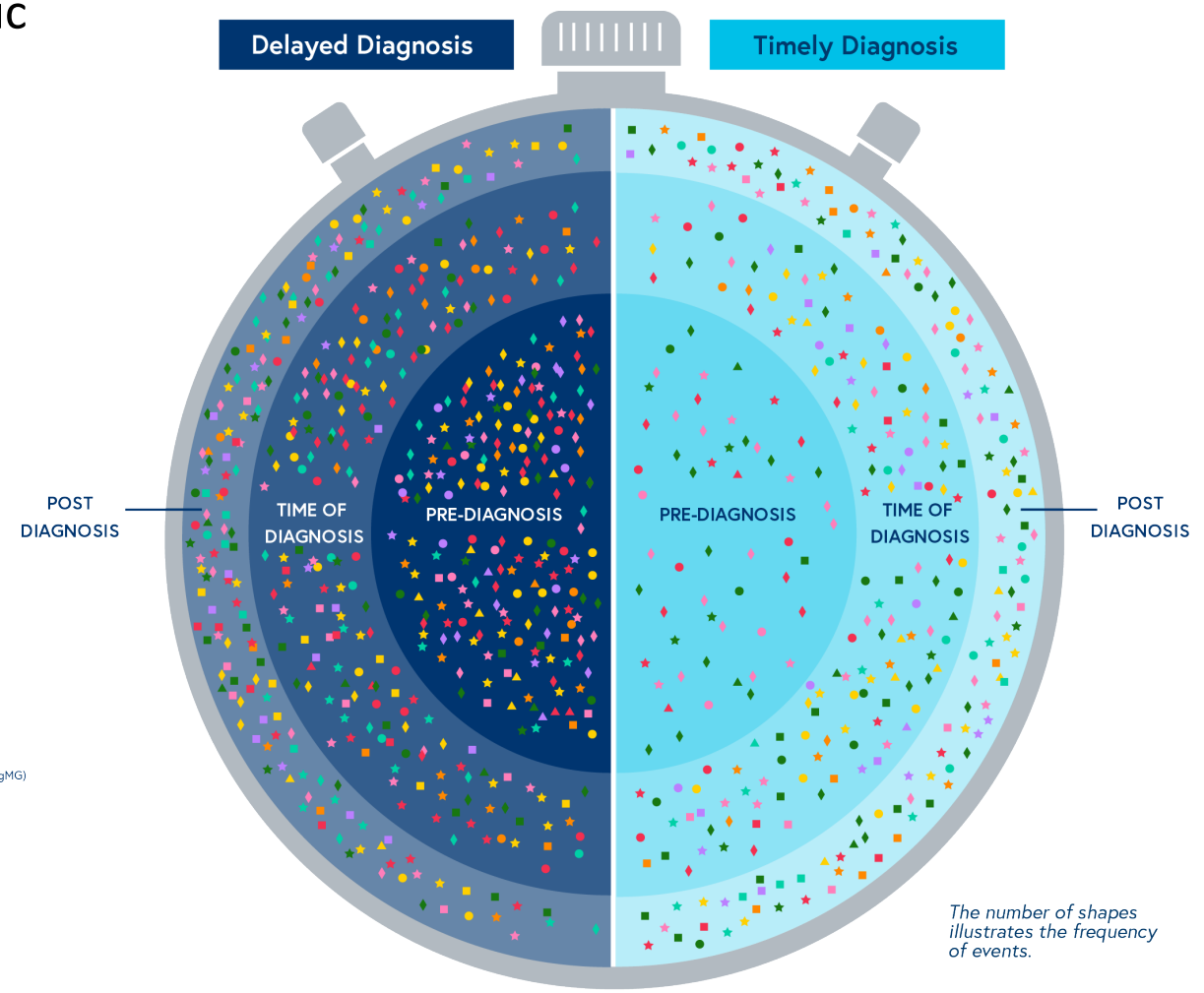
- Duchenne (DMD)
- Pompe
- Adrenoleukodystrophy (ALD)
- Severe Combined Immunodeficiency (SCID)
- Fragile X Syndrome (FXS)
- Wilson Disease (WD)
- Generalized Myasthenia Gravis (gMG)

Journey Map Categories

- Typical Accompanying Diagnosis: Anemia, liver failure (Wilson), cognitive impairment, seizures (ALD), Gait issues (Duchenne)
- Testing & Procedures: Cognitive deficit testing (Fragile X), muscle biopsy (gmG)
- Events: Cardiac Failure (Pompe), Hospitalization, Death (multiple diseases)
- Specialists: Palliative care, total care team (ALD), orthopedist (gMG)
- Treatments & Supporting Therapies: Auditory therapy, feeding tube (SCID)

Examples are not exhaustive

Every Minute Matters



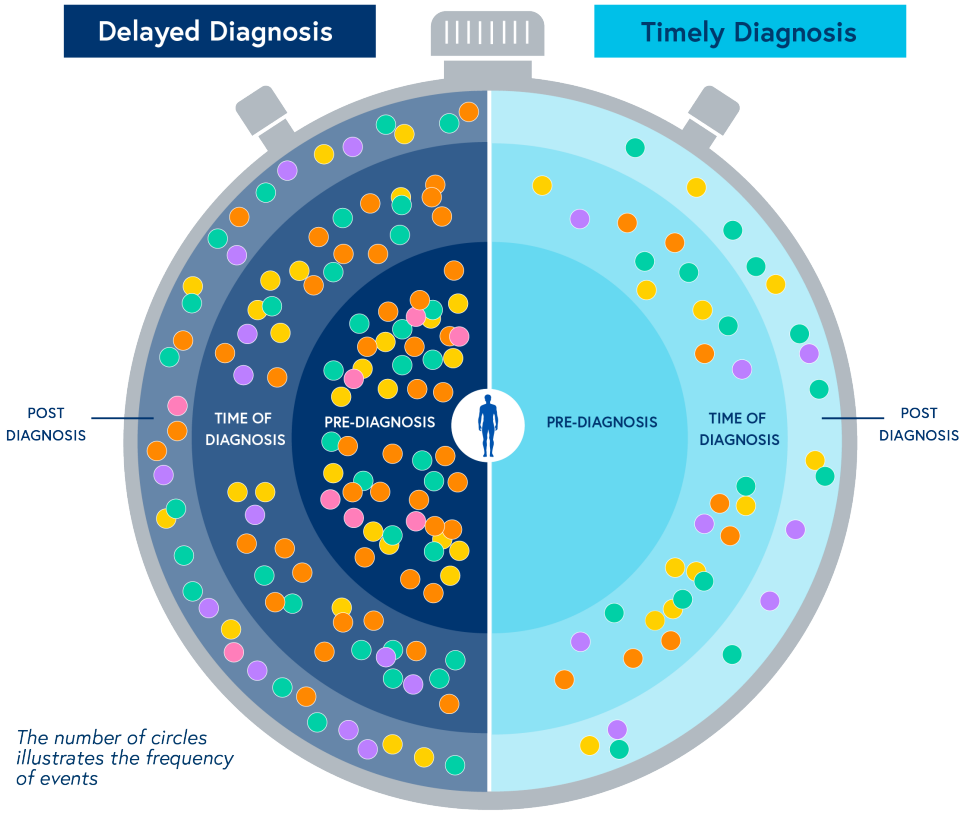
The number of shapes illustrates the frequency of events.

The Cost of Delayed Diagnosis in Rare Disease: *A Health Economic Study*

The Impact of Delayed Diagnosis in Pompe

Navigating a rare disease diagnosis can require more than 6 years and 17 medical interventions, on average, after symptoms begin, including emergency room visits and out-of-state specialist appointments.[1] The EveryLife Foundation and our partner the Lewin Group took an in-depth look into Pompe disease, a rare neuromuscular condition, to illustrate the significant economic impact of this diagnostic odyssey.

Every Minute Matters



The number of circles illustrates the frequency of events

TYPICAL ACCOMPANYING DIAGNOSIS:
Severe muscle weakness, respiratory distress

TESTING & PROCEDURES:
Biopsy (muscle, liver, skin), lumbar puncture (spinal tap)

SPECIALISTS:
Cardiologist, ophthalmologist, gastroenterologist

TREATMENTS & SUPPORTING THERAPIES:
Ventilation, movement, and developmental support

EVENTS:
Cardiac failure, death

Examples are not exhaustive

ACTION IS KEY TO SECURING TIMELY DIAGNOSIS

The EveryLife Foundation is working to develop policies at the state and federal levels to reduce time to diagnosis. For more information on how you can get involved and support this effort, please visit **everylifefoundation.org** or contact us at **info@everylifefoundation.org.**

DELAYED DIAGNOSIS DRAMATICALLY INCREASES COSTS FOR FAMILIES*

$219,081 Total medical cost and productivity loss per family

9+ Lost days of work for caregivers each year

41 Additional hospital visits, physician appointments, and other medical interventions

*Across the diagnostic odyssey

How Did We Collect These Data?
- Medicare and Commercial insurance claims data, including patients with Pompe
- Results from The Rare Disease Financial and Social Impact Survey, completed by 1,409 community members

BENEFITS OF TIMELY DIAGNOSIS

Timely diagnosis, defined as before age one for children with Pompe,[2] can improve health outcomes by:

- **Providing earlier access to supportive therapies and treatment**
- **Delaying disease complications and physical disabilities**
- **Lowering costs for patients and families by reducing or eliminating costly and unnecessary services or procedures**

In states where newborn screening has been implemented for Pompe, timely diagnosis eliminates the diagnostic odyssey, resulting in no costs incurred before the year of diagnosis.

References:
1. Yang G, Cintina I, Zhou M, et al. The National Economic Burden of Rare Disease Study. The EveryLife Foundation for Rare Diseases. https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf. Published February 25, 2021. 2.Infantile-onset Pompe disease: Diagnosis and management. Arch Argent Pediatr. 2019;117(4). doi:10.5546/aap.2019.eng.271