Duchenne Newborn Screening

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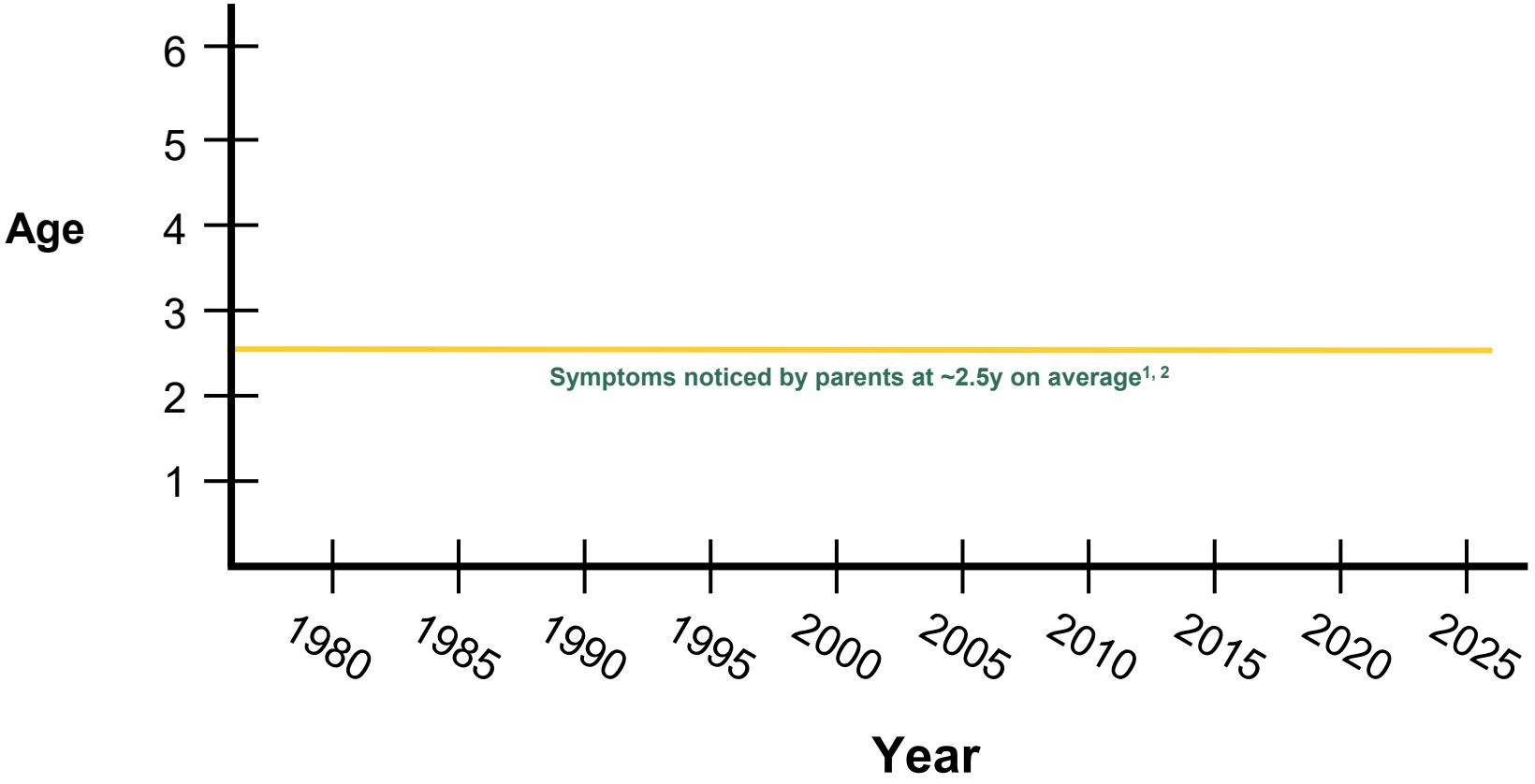
Parent Project Muscular Dystrophy

Duchenne Muscular Dystrophy

- Most common hereditary neuromuscular disease (1:5000 boys)
- Progressive muscle loss due to variants in *DMD* gene (dystrophin protein)
  - Damage starts in utero
- Loss of ambulation between 10-14y
- Loss of pulmonary and cardiac function
- Life expectancy increased in last ~10 years to nearly 30

Why newborn screening?



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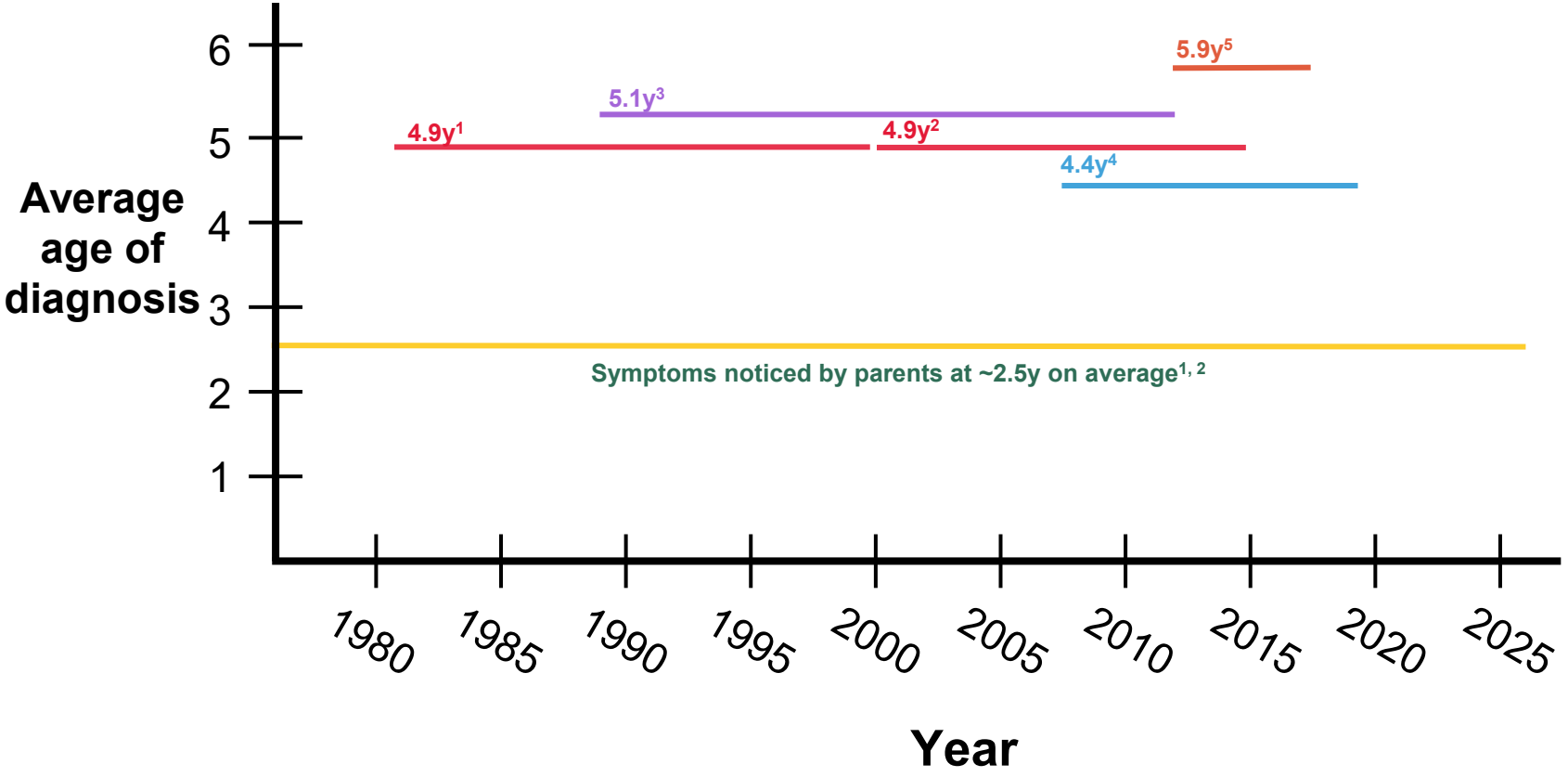


Why newborn screening?

- Years of advocacy has not changed average age of diagnosis
- Avoidable costs of delayed Duchenne diagnosis for families:[6]
  - $211,229 in medical and productivity cost
  - 20 lost days of work per year
  - 17 out-of-state trips for medical care
- Damage from delay and inappropriate testing + therapies[7-8]

Opportunity for Intervention

- **Therapeutic interventions**
  - 9 FDA-approved treatments (8 specific to Duchenne)
    - 5 available at any age
    - 2 available starting at age 2
    - 1 gene therapy
  - Early intervention
    - Speech/language therapy
    - Physical/occupational therapy
  - Clinical trial opportunity

Impact of Intervention

- **Early Intervention Symposium**
  - Earlier corticosteroids extend walking by 1-2 years[9,10]
    - Especially pronounced when comparing boys with similar expected trajectory (similar variant)
    - Losing ambulation before ~12 leads to heart failure 5+ years sooner[11]
    - Lung function declines over 2x faster once nonambulatory[12]

Impact of Intervention

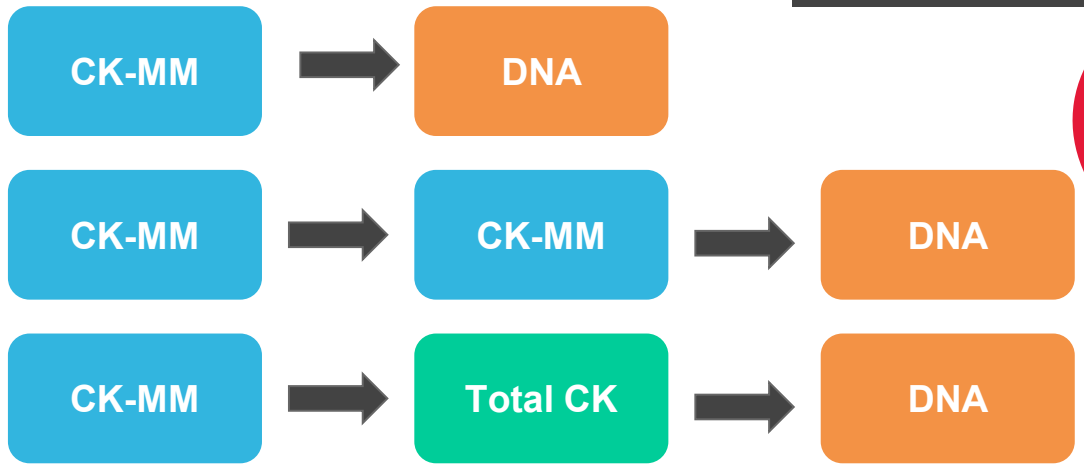
- **Early Intervention Symposium**
  - Brothers with disparate diagnostic ages[13]
    - Brother A: Diagnosed at 6y11mo
      - Steroids at 8.5 years
      - No clinical trials
      - NSAA of 14/34 at age 9, lost ambulation at 12
    - Brother B: Diagnosed at 4 months
      - Clinical trial at 4 years
      - Steroids at 5.5 years
      - Clinical trial at 7 years
      - NSAA of 32/34 at age 9, walking well
  - Differences in brothers consistently reported[14-16]

How is Duchenne NBS done?

Assay FDA authorized in 2019

Program (Iowa State Hygienic Lab) already uses the GSP machine that runs this assay for:

- Cystic fibrosis
- Congenital adrenal hyperplasia
- Congenital hypothyroidism
- Biotinidase deficiency



Available through free, sponsored testing programs:

Decode Duchenne, Detect MD

DMD or neuromuscular panel

Blood spot card, buccal, or blood sample

Protocols Will Vary By State

- Thresholds for CK levels, levels impacted by[17]:
  - Age/birth weight at collection
  - Birth trauma
  - Sex
  - Race
  - High humidity/heat
- Piloting, validation studies, refinement tools may change protocols over time

New York[18]

Age at collection (h)	Borderline cutoff (ng/mL)	Referral cutoff (ng/mL)
0-47*	≥1990	≥4000
48-71	≥1430	≥4000
72-167	≥571	≥860
≥168	-	≥571

*Repeat specimen requested if collected at <24h

New York[18]

Age at collection (h)	Borderline cutoffs (ng/mL)	Referral cutoff (ng/mL)
0-47*	~~≥1990~~ ≥3000	~~≥4000~~ ≥5000
48-71	≥1430	≥4000
72-167	≥571	≥860
≥168	-	≥571

*Repeat specimen requested if collected at <24h

Expected to reduce repeat DBS by 82%

New York Pilot Post-Hoc Analysis

Mayo's Collaborative Laboratory Integrated Reports (CLIR):

- Free for use by state labs sharing data
- Pool disease data across submitting labs
- Incorporate other analytes collected to ID false positives

With New York's Data[19]:

- False positives have higher TSH levels than true positives
- CK-MM/TSH ratio to create true and false positive profiles
- Used on 233 available borderline cases, **reduced borderlines by 93%**

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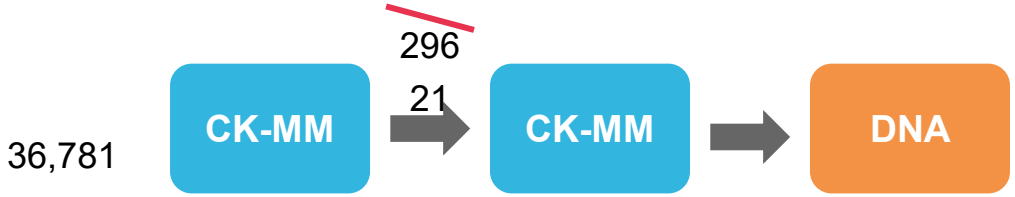


Cutoffs in Active States

Minnesota

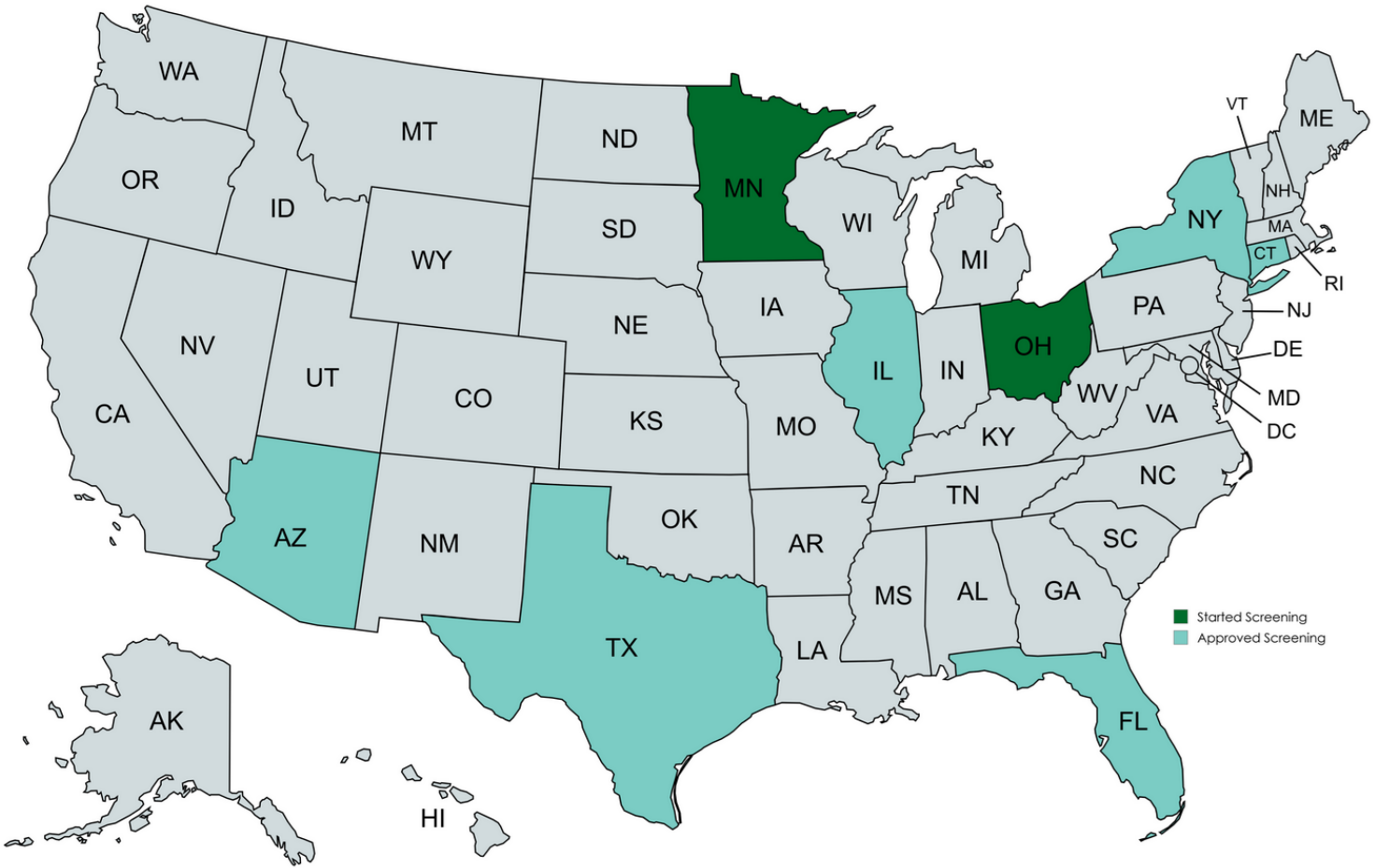
Age at collection (h)	Borderline cutoffs (ng/mL)	Referral cutoff (ng/mL)
0-47	≥1700	N/A
48-71	≥1500	N/A
72-167	≥500	N/A
≥168	N/A	≥500

2nd tier testing rate reported at APHL: 0.44%
3 referred for specialist workup

Ohio

Age at collection (h)	Borderline cutoffs (ng/mL)	Referral cutoff (ng/mL)
0-47	≥1990	≥4000
48-71	≥1430	≥4000
72-167	≥571	≥860
≥168	N/A	≥571

All babies <2000g get repeat testing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Started Screening
Approved Screening

Resources to Support Clinicians + Families

- **ACT Sheet already available**
- **Robust support resources through PPMD**
- **Free genetic testing through Decode Duchenne (PPMD) or Detect Muscular Dystrophy (Invitae)**
- **Baby Duchenne**
  - Led by Drs. Bo Hoon Lee & Emma Ciafaloni (Rochester)
  - Multi-state research network
  - Characterize natural history + long-term follow up for active states

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Thank you!