Duke Clinical Research Institute

Newborn Screening for Pompe Disease: Preliminary Evidence Review and Public Health Impact Assessment

Alex R. Kemper, MD, MPH, MS

January 31, 2013

Condition Review Workgroup (CRW)

CRW Members	Role	Institution
Alex R. Kemper, MD, MPH, MS	Chair	Duke University
Anne M. Comeau, PhD	State NBS Public Health Program	New England NBS Program, University of Mass Medical School
Aaron Goldenberg, PhD, MPH	NBS Bioethicist	Center for Genetic Research Ethics & Law, Case Western University
Nancy S. Green, MD	Nomination & Prioritization Workgroup Liaison	Department of Pediatrics, Columbia University Medical Center
Scott Grosse, PhD	Federal Advisor, Health Economist	Nat'l Center on Birth Defects & Developmental Disabilities, CDC
Jelili Ojodu, MPH	Public Health Impact Task Leader	NBS & Genetics, Association of Public Health Laboratories
Lisa Prosser, PhD	Decision Analysis Leader, NBS Health Economist	Health Management & Policy/ SPH; Pediatrics/Univ of Michigan Med School
Susan Tanksley, PhD	State NBS Public Health Program	Newborn Screening Laboratory TX Department of State Health Services
K.K. Lam, PhD	Project Leader	Duke University

Overview: Pompe Disease

- Deficiency of acid α-glucosidase (GAA), which leads to the accumulation of lysosomal glycogen
- Autosomal recessive disorder
- GAA gene located on chromosome 17 (17q25.3)
- More than 300 mutations have been described. Not all associated with disease
  - *Some specific associations with disease phenotype, which has a wide spectrum*

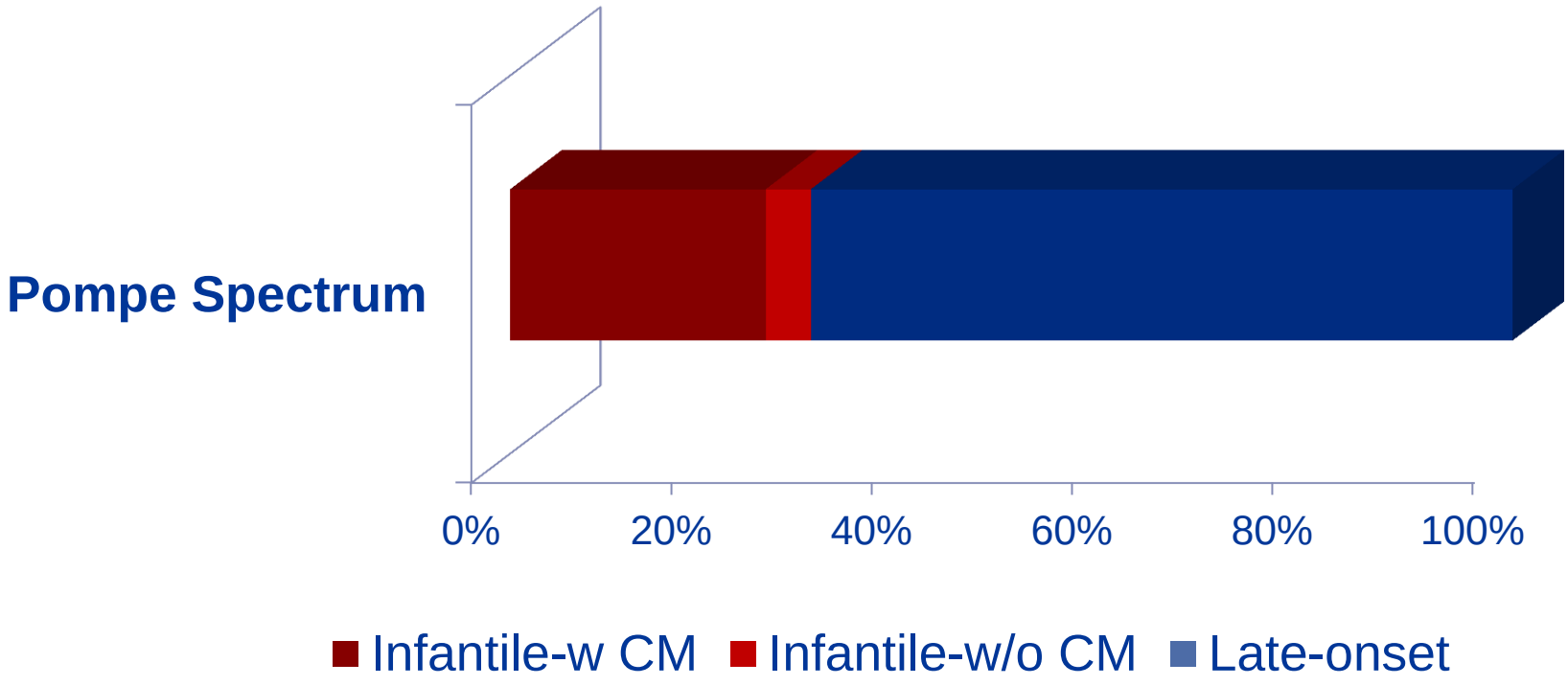
Epidemiology

Incidence, based on gene frequency

Pompe disease, overall: ~1 in 40,000 births

- *Infantile: ~1 in 133,000*
- *Late-onset ~1 in 26,466 to 1 in 57,000*
- *Gene frequency studies may underestimate epidemiology due to unrecognized mutations*
- *Actual epidemiology varies by race/ethnicity*

Spectrum of Pompe: Prevalence of Forms



Case Definition: Spectrum of Pompe Disease

Infantile: Most severe

- *Onset ≤12 months of age*
  - **Infantile Onset *with* Cardiomyopathy** (“Classic Form”) – progressive hypotonia and cardiomyopathy; without treatment, death usually within the first year of life
  - **Infantile Onset *without* Cardiomyopathy** (“Nonclassic Form”) – typically no cardiomyopathy; longer survival, but without treatment, death in early childhood

Late-onset: Variable Presentation

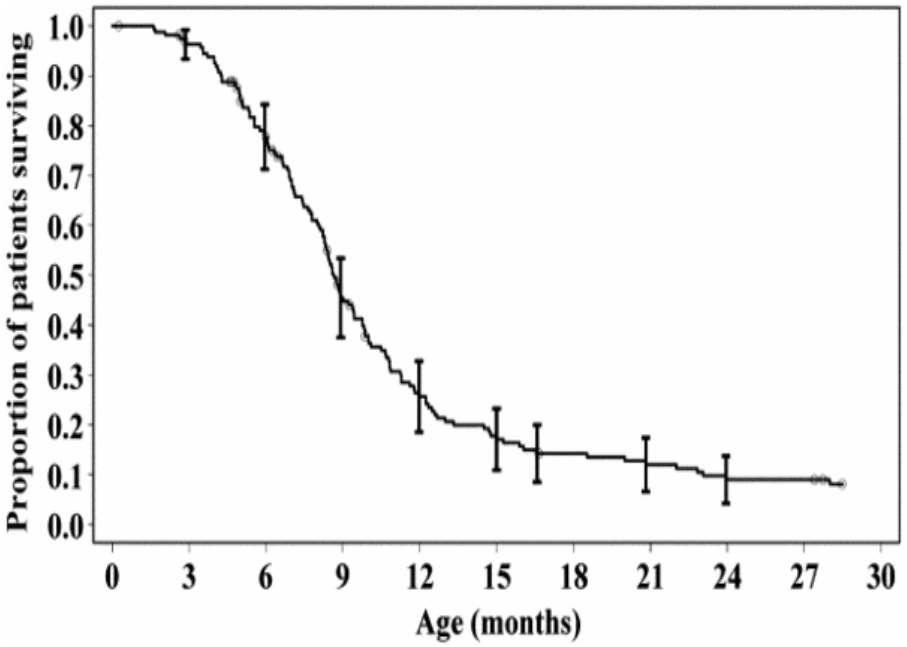
- *Onset >12 months of age*
- *Most experience symptom onset in adulthood (>18 years);*
  - ➢ *Pompe diagnosis ~8-10 years later*
- *Slowly progressive myopathy*
- *May have mild weakness in childhood that can go unrecognized*
- *Variable outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)*

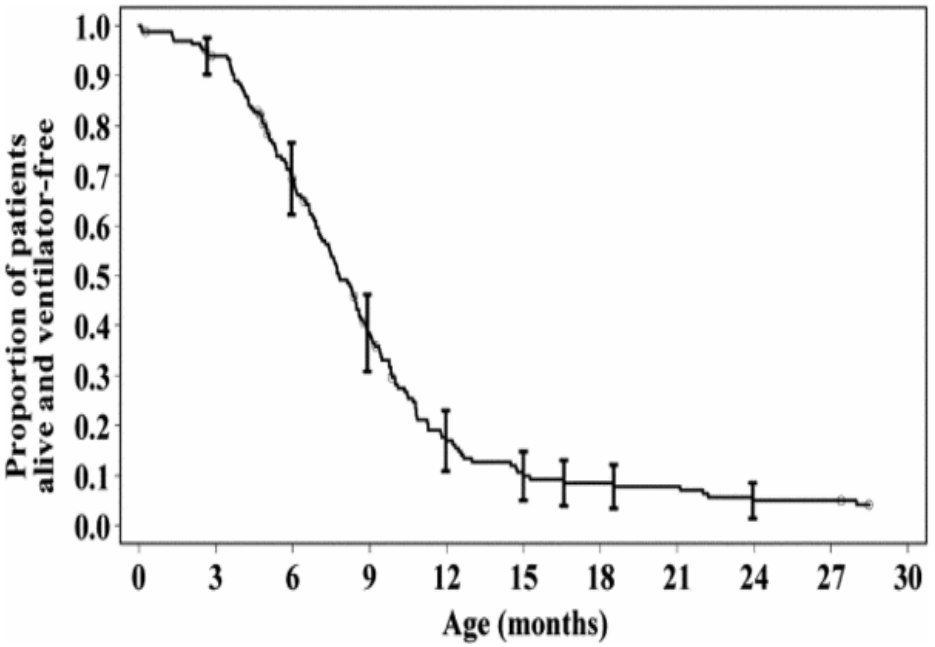
Overview: Natural History of Infantile Pompe Disease

- 2006 international retrospective study to describe the natural history of Infantile Pompe disease
  - *168 subjects clinically identified*
  - *Mostly classic (91.7% with cardiomegaly)*
  - *Median age of symptom development: 2 months*
  - *Median age of diagnosis: 4.7 months*
  - *Me\dian age of death: 8.7 months (range: 0.3-73.4 months)*

[31] Kishnani et al. (2006). A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr 148(5): 671-676.

Natural Outcomes of Infantile Pompe Disease (n=168)





Age, in months	% Surviving	% Surviving, Ventilator-Free
12	25.7	16.9
18	14.3	8.5
24	9.0	4.9

[31] Kishnani et al. (2006).

Overview: Other Considerations

- **CRIM+ vs. CRIM–**
  - *Cross-reacting immunologic material – individuals who make some endogenous enzyme, which may or may not be functional*
- **Pseudodeficiency**
  - *Not associated with disease*
  - *Individuals make active GAA, but enzyme function artificially appears very low or undetectable*
  - *Associated with 2 specific mutations*
  - *High allelic frequency in Taiwan (14.5%)*
  - *Mechanism not clear after current evidence review activities*

Overview: Genetics of Pompe Disease

- Genotype-phenotype correlation not always clear
- The impact of having one allele associated with pseudodeficiency and another allele associated with Pompe disease not clear after evidence review

Overview: Diagnosis

- Reduced GAA activity in lymphocytes, fibroblasts, or muscle cells
- <1% of normal associated with infantile form
- Must distinguish from pseudodeficiency, which can be determined by genotyping
- Genotyping can help identify CRIM status

Overview: Treatment

- alglucosidase alfa
  - *Recombinant human GAA (rhGAA) enzyme replacement therapy (ERT) licensed in 2006*
  - *An additional product was licensed in the US for patients ≥ 8 years with late-onset disease*
  - *Infusions of 20 mg/kg every 2 weeks, typically lasting 4 hours, over the lifetime (i.e., not curative)*
  - *In 2006, the wholesale price of treatment was $720 per 50-mg vial (~$7,488 X kg/year of medication alone assuming no wastage) + 104 hours of infusion time/year*

Overview: Screening

- Measurement of GAA enzyme function
- Two steps:
  - *Enzyme assay*
  - *Measurement of enzyme function*
    - MS/MS after enzyme assay; requires separate run
    - Fluorometry (traditional, microfluidics fluorometric assay)
- Work underway to multiplex screenings with other LSDs (e.g., Fabry, Gaucher, MPS-I) and with X-ALD. This requires additional MS/MS machines
- Other strategies (i.e., measuring NAG/GAA ratio) may improve specificity

Overview: Current Population-Based Screening Programs

- Taiwan – population-based screening; data extensively reported
- US – unaware of results of population-based screening results
  - *Illinois - ~3 years ago evaluated digital microfluidics, now planning with multiplex MS/MS, including other LSDs*
  - *Missouri – Pilot testing LSDs with digital microfluidics*
  - *New Jersey, New Mexico – State mandate to screen for Pompe, but still in planning*
  - *Washington State – completed validation of multiplexed enzyme assay; developing a pilot study*
- US Commercial/Research
  - *Perkin Elmer Bridgeville – Offers screening (MS/MS)*
  - *Mayo – comparing different analytic methods, including MS/MS fluorometric assays, immuno-assay*

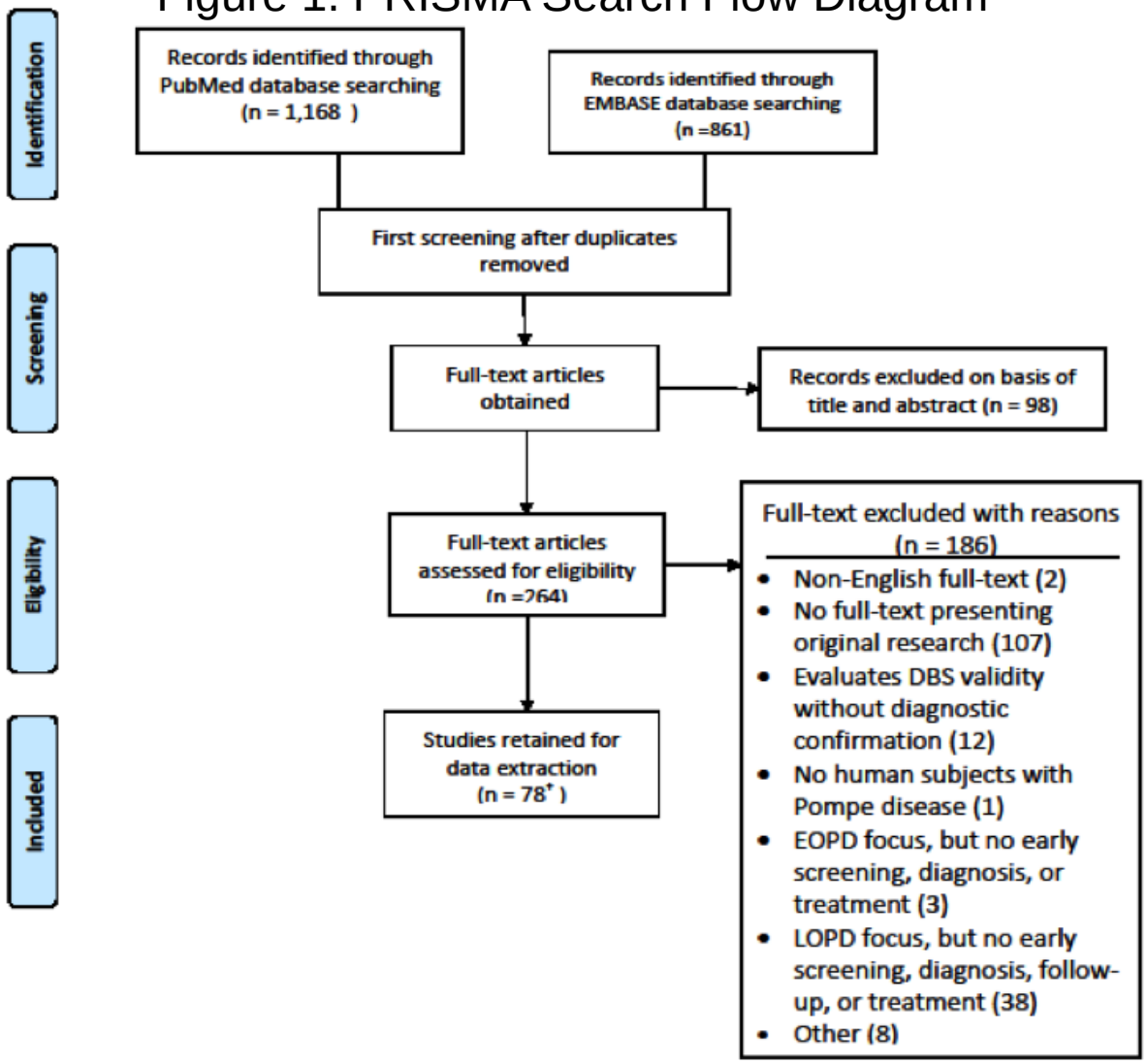
Condition Review: Pompe disease

- Systematic Evidence Review
- Decision Analysis to Project Public Health Impact of NBS for Pompe on the Population
- Assessment of the Public Health Impact of NBS for Pompe: Feasibility and Readiness of State NBS Programs

Systematic Evidence Review: Published Literature

- Articles through PubMed and EMBASE Search (1,982)
- Articles screened for eligibility & relevance (n=264)
- Articles retained for data extraction (n=78)*
- Screening by two independent reviewers

Figure 1. PRISMA Search Flow Diagram



*Note: *Final number of included articles will be reduced following final exclusion of later-onset articles not relevant to newborn screening for Pompe disease.*

Systematic Evidence Review: Technical Expert Panel

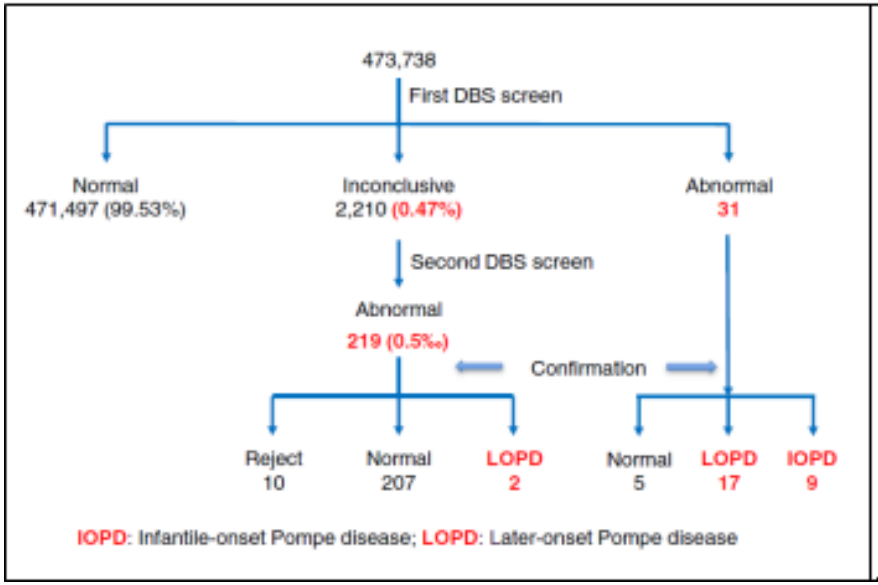
TEP for Newborn Screening for Pompe Disease: Members and Teleconference Participation

EXPERT PANEL MEMBERS	TEP 1 July 10, 2012	TEP 2 July 25, 2012	TEP 3 (Decision Tree) Dec 6, 2012	TEP 4 (Decision Tree) Jan 8, 2013
Olaf Bodamer, MD, PhD†	√			√
Barry Byrne, MD, PhD		√	√	
Sharon Kardia, PhD	√		√	
Priya Kishnani, MD, MBBS†, ±	√	√		√
C. Ronald Scott, MD	√			√
Muhammad Ali Pervaiz, MD		√		
Deborah Marsden, MBBS†			√	

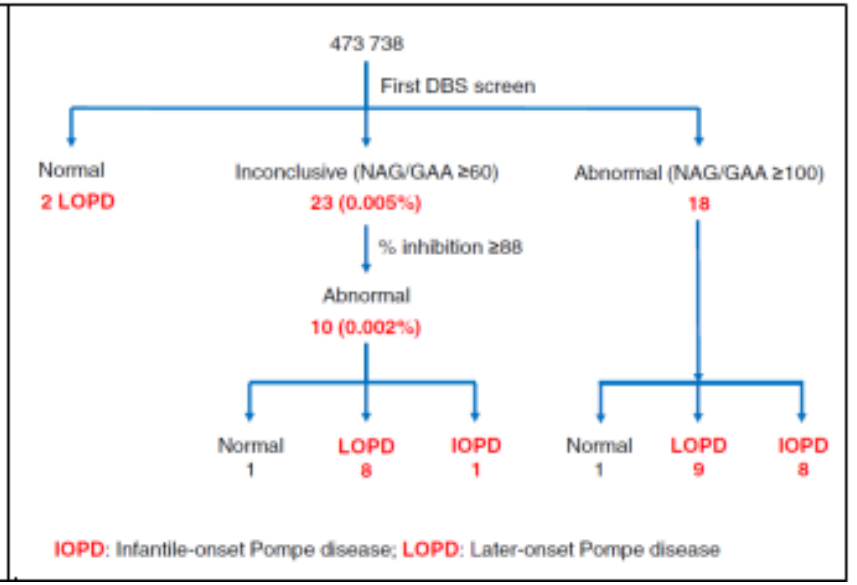
†Served on TEP for previous 2008 review of newborn screening for Pompe disease.
±Nominator of Pompe disease for consideration to be added to the RUSP.

How effective is newborn screening in identifying Pompe disease?

- Taiwan – 473,738 newborns have been screened with a fluorescence enzyme activity assay



Observed

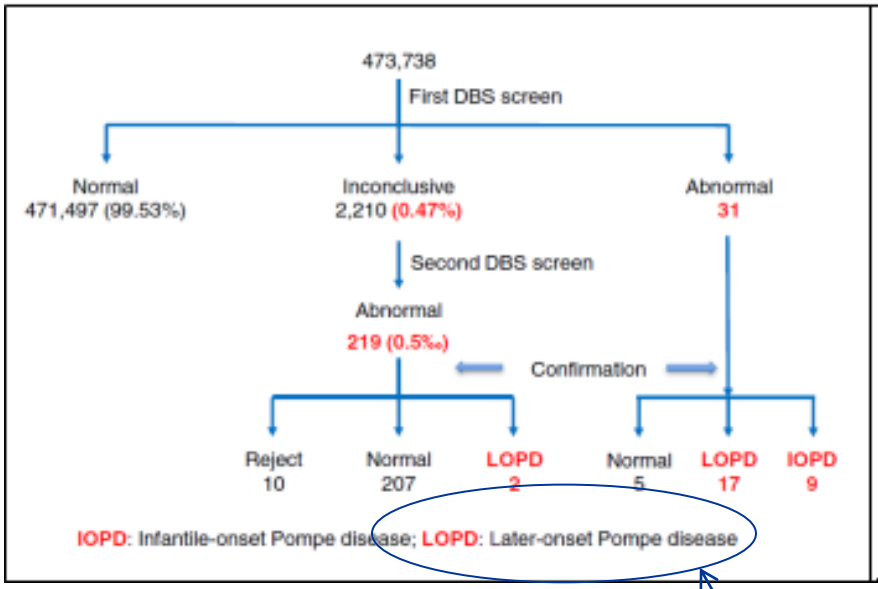


Simulated, Increased Threshold

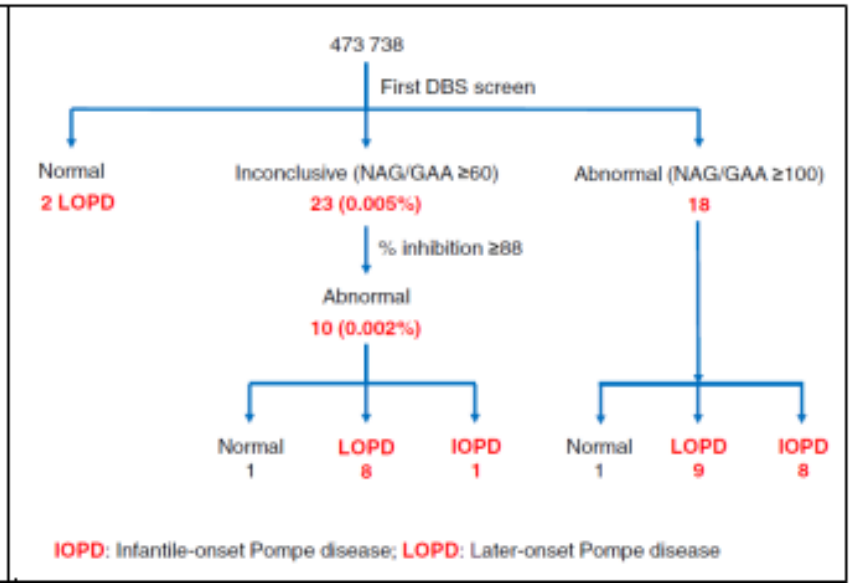
[9] Chiang et al. (2012). Algorithm for Pompe disease newborn screening: Results from the Taiwan screening program. Mol Gen & Met,106, 281-286.

How effective is newborn screening in identifying Pompe disease?

- Taiwan – 473,738 newborns have been screened with a fluorescence enzyme activity assay



Observed



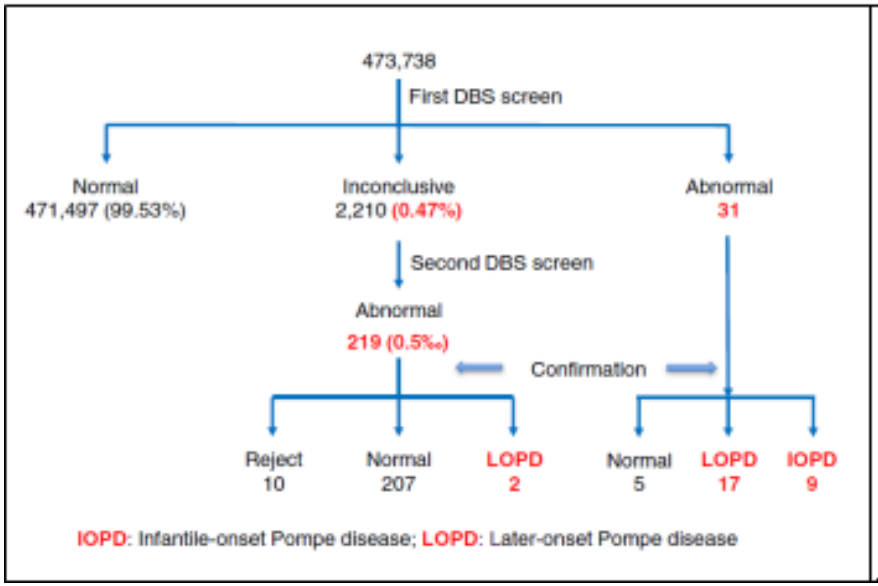
Simulated, Increased Threshold

"Later" – includes infantile-onset without cardiomyopathy

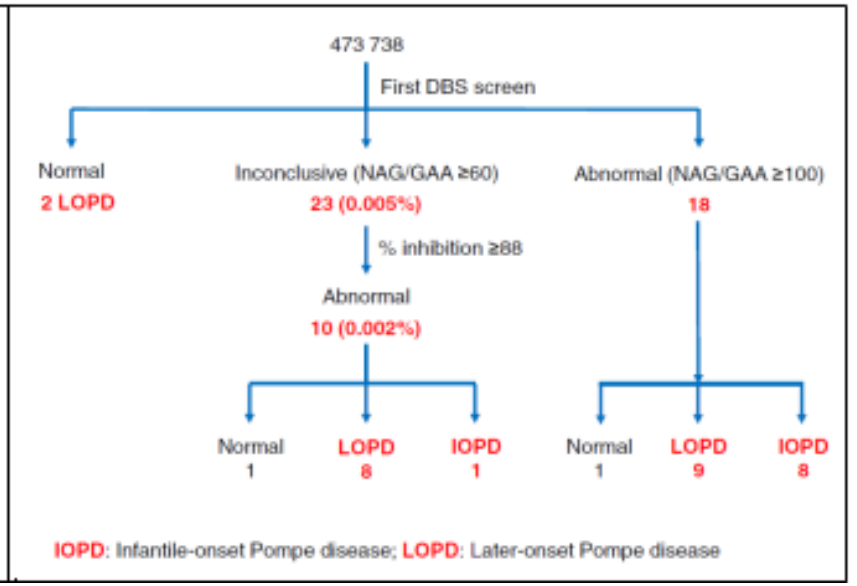
[9] Chiang et al. (2012).

How effective is newborn screening in identifying Pompe disease?

- Taiwan – 473,738 newborns have been screened with a fluorescence enzyme activity assay



Observed



Simulated, Increased Threshold

[9] Chiang et al. (2012).

Important Questions

- What findings are available from screening activities in the United States?
- In Taiwan studies, what is the difference between later-onset and late-onset disease?
- How generalizable is the Taiwan experience to the United States?

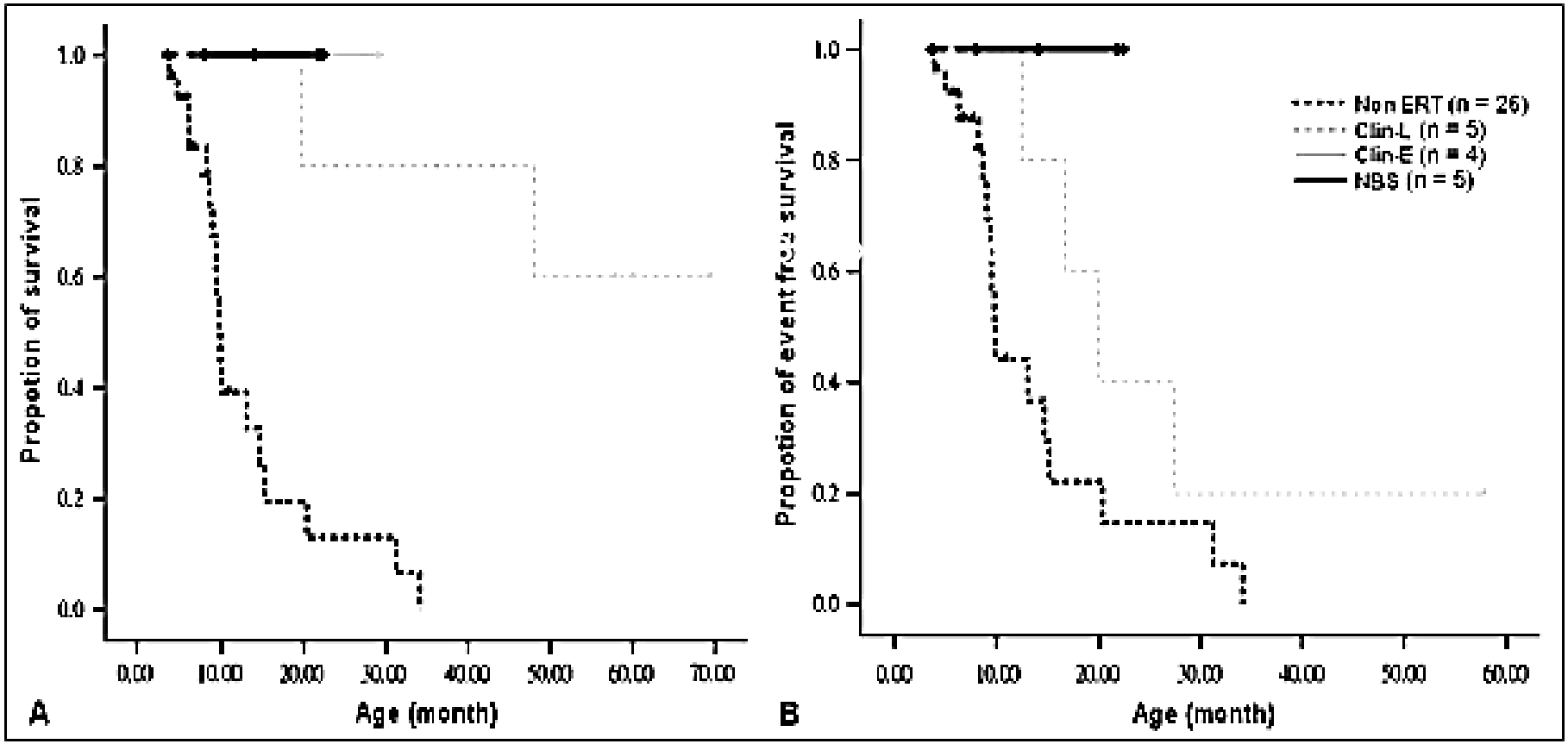
What benefits and harms are associated with the treatment of infantile Pompe disease?

- Pivotal Trial: 3 Reports describe outcomes of a 52-week trial of ERT (different doses) for 18 subjects with classic infantile-onset Pompe disease confirmed by 26 weeks of age
  - *Improved survival compared to historical controls (1 death shortly after the trial completed)*
  - *Most developed IgG antibodies, regardless of CRIM status*

[29] Kishnani et al. (2007). Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease, Neurology, 68, 99-109.
[28] Kishnani et al. (2009). Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res, 66, 329-35.
[48] Nicolino et al., (2009). Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease, Genet Med, 11, 210-9.

What benefits and harms are associated with the treatment of infantile Pompe disease, *if detected early*?

Comparative ERT Outcomes: NBS vs. Clinical ID vs. No ERT



Proportion of Survival

Proportion of Event-free Survival

Chen et al. (2009). Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease. J Pediatr, 155(2), 271-275.

Important Questions

- What is the current approach to CRIM- status? How important is this?
- How significant is the development of antibodies to ERT in those who are CRIM +?
- How do outcomes vary by genotype?
- What other harms have been identified?
- How does the net benefit of screening change based on CRIM status or classic vs. nonclassic type?

What benefits and harms are associated with presymptomatic detection of late-onset Pompe disease?

- Unclear
- Critical question
- What are the psychosocial implications for parents of early identification of late-onset Pompe disease?

What are the costs associated with newborn screening for Pompe disease?

- Critical Question:
  - *If more Pompe cases are diagnosed earlier through newborn screening, can patients be assured access to ERT treatment?*

- No recent published data identified to address this question

Next Steps: Systematic Evidence Review

- Complete evidence tables and quality scores
- Review unpublished data
- Expert interviews

Decision Analysis & Newborn Screening

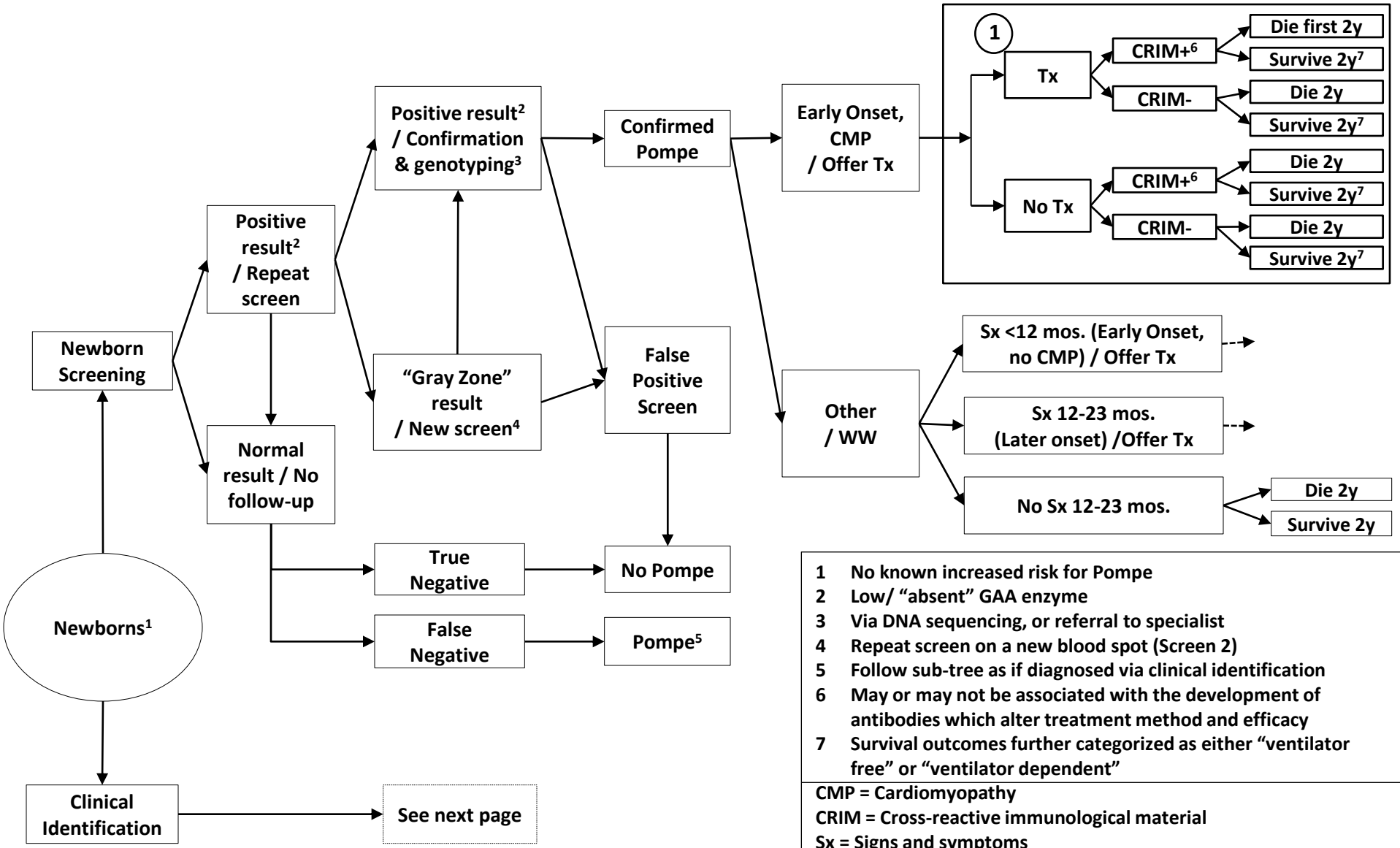
- Decision analysis (DA) as part of the condition review process can provide:
  - *Approach for evidence synthesis*
  - *Method for specifying assumptions*
  - *2011 recommendation to add decision analytic modeling to condition review process*
- Application of DA modeling:
  - *Simple models*
  - *Health outcomes*
  - *No cost-effectiveness analysis (yet)*
- Goal is to project health benefits and potential harms

Decision Analysis: Pompe disease

- Objective: To project key outcomes (ranges) for newborn screening of Pompe disease compared with clinical identification
- Methods:
  - *Design decision analytic model*
  - *Identify key outcomes*
  - *Identify key parameters and assumptions*
  - *Conduct expert panels to review model structure, assumptions, and key outcomes*

*Experts: Olaf Bodamer, MD, PhD; Barry Byrne, MD, PhD; Sharon L.R. Kardia, PhD; Priya Kishnani, MD, MBBS; Deborah L. Marsden, MBBS; C. Ronald Scott, MD;

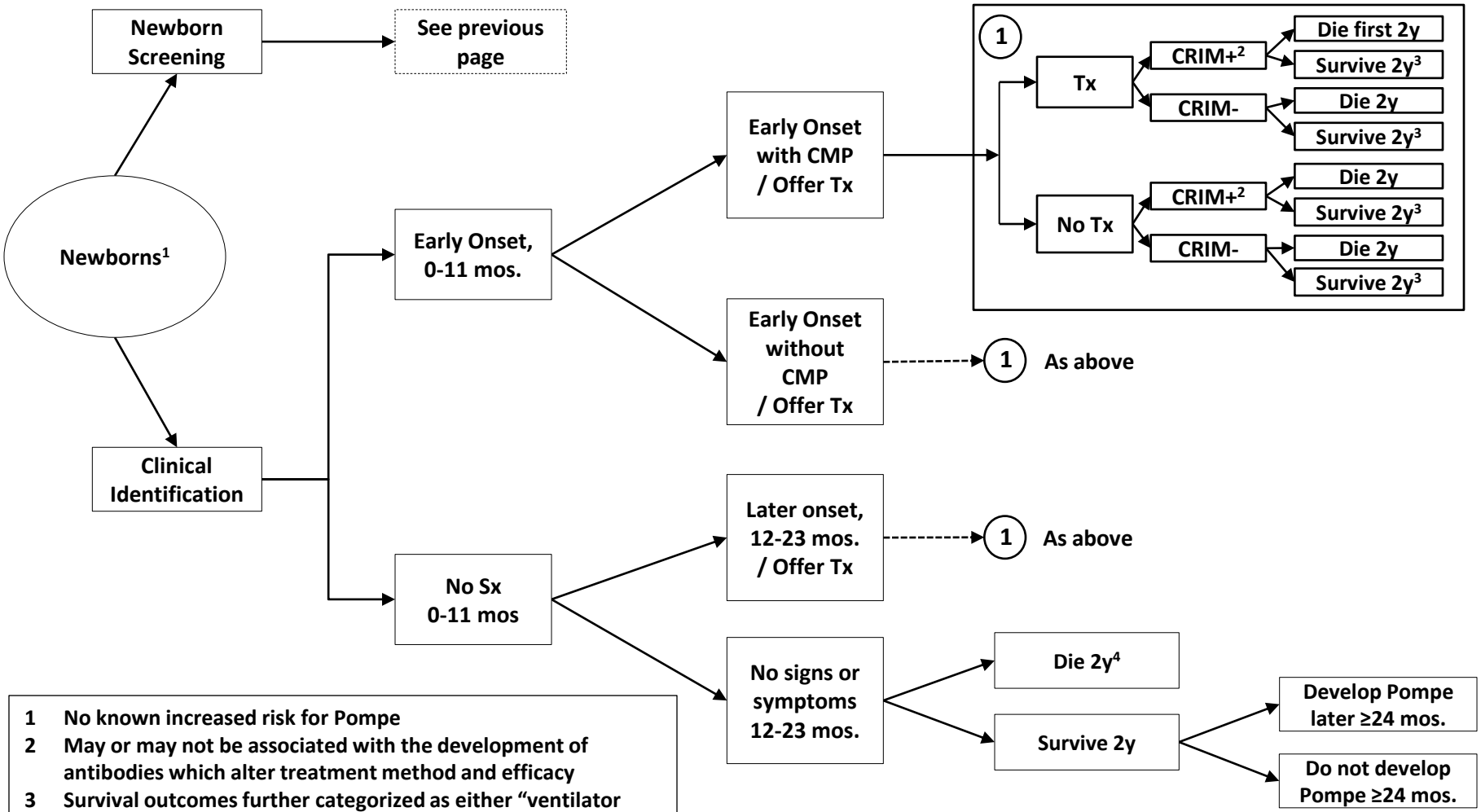
DRAFT Model Schematic – Part 1



1 No known increased risk for Pompe
2 Low/ "absent" GAA enzyme
3 Via DNA sequencing, or referral to specialist
4 Repeat screen on a new blood spot (Screen 2)
5 Follow sub-tree as if diagnosed via clinical identification
6 May or may not be associated with the development of antibodies which alter treatment method and efficacy
7 Survival outcomes further categorized as either "ventilator free" or "ventilator dependent"

CMP = Cardiomyopathy
CRIM = Cross-reactive immunological material
Sx = Signs and symptoms
Tx = Treatment
WW = Watchful waiting

DRAFT Model Schematic – Part 2



1 No known increased risk for Pompe
2 May or may not be associated with the development of antibodies which alter treatment method and efficacy
3 Survival outcomes further categorized as either "ventilator free" or "ventilator dependent"
4 Non-Pompe related mortality

CMP = Cardiomyopathy
CRIM = Cross-reactive immunological material
Sx = Signs and symptoms
Tx = Treatment
WW = Watchful waiting

DRAFT Key Outcomes

	Newborn Screening	Clinical Diagnosis	Screening Impact
True Positives	--	N/A	N/A
False Positives	--	N/A	N/A
True Negatives	--	N/A	N/A
False Negatives	--	N/A	N/A
Repeat Screens	--	N/A	N/A
Projected cases of Pompe (all types)	--	--	--
Classic early infantile	--	--	--
Late/later onset Pompe	--	--	--
Projected cases who die within two years	--	--	--
Projected cases who are alive after two years	--	--	--
Requiring ventilator assistance	--	--	--
Ventilator-free	--	--	--

Decision Analysis: Anticipated Results

- **Modeling results:**
  - *Projected health outcomes and associated ranges*
  - *Identification of key parameters (when varied over plausible ranges, these have the greatest impact on projected net benefits)*
- **Use of results**
  - *Transparency regarding assumptions on health benefits and potential risks of screening and treatment*
  - *Identification of knowledge gaps to prioritize future data collection/research activities*

Decision Analysis: Next Steps

- Develop estimates for modeling parameters (via systematic evidence review and expert interviews)
- Review parameter inputs with expert panel
- Conduct base case and sensitivity analyses to obtain ranges for projected outcomes

Public Health Impact Assessment
Readiness and Feasibility Survey

Objectives

- To review the potential public health impacts of adding new heritable disorders under consideration for the Recommended Universal Screening Program (RUSP) on state newborn screening programs.
- To assess the feasibility and readiness of selected states to add Pompe Disease to their panels.

Administration

Conducted by Association of Public Health Laboratories (APHL) in collaboration with the Condition Review Workgroup.

Sample: 10 state public health NBS programs selected to represent the NBS public health system.

Selection Criteria

General Program Characteristics

- Regional Collaborative
- Newborn population size
- State mandate to screen for RUSP conditions
- State laboratory facilities vs. outsourcing
- Second screen requirements

Condition-Specific NBS Screening Factors

- Laboratory and analytic requirements
- Equipment
- Experience with NBS screening for similar conditions

Selected Sample and Program Characteristics

State	Regional Collaborative	State Mandate for RUSP	Outsource NBS Lab Testing	Newborn Population (2009)	Academic Affiliation	NBS for Pompe
Massachusetts	Region 1	No	No	75,445	Yes	
Delaware	Region 2	No	No	11,989	No	
South Carolina	Region 3	No	No	57,884	No	
Illinois	Region 4	No	No	167,659	No	X
Minnesota	Region 4	No	No	70,426	No	
Iowa	Region 5	No	No	39,640	Yes	
Nebraska	Region 5	No	Perkin Elmer Genetics	27,198	No	
Texas	Region 6	Yes	No	408,391	No	
Oregon	Region 7	No	No	47,685	No	
Washington	Region 7	No	No	89,200	No	

Data Collection

Stage 1: Surveys administered electronically (Qualtrics) to assess generic program and condition-specific characteristics.

Status: Completed (90% response rate)

Stage 2: Semi-structured, in-depth interviews will be conducted with representatives from the selected states.

Status: Not Started

Preliminary Survey Findings

- 56% of NBS programs surveyed (n=9) take between 6 months to 1 year to make a decision to implement a condition once the process is started.
- 22% of NBS programs surveyed (n=9) currently test for Pompe disease with anonymous samples.
- 11% of NBS programs surveyed (n=9) are investigating the theory of screening for Pompe disease but are not yet testing samples.

Preliminary Survey Findings (cont'd)

- 78% of NBS programs surveyed (n=9) do not screen for Pompe disease in any fashion.
  - *67% (n=9) are not currently investigating routine screening for Pompe disease.*
  - *6 of 9 do not have authority to implement screening for Pompe disease.*
- Top challenges to implementing Pompe disease screening are funding, staffing, laboratory space, and equipment/ instrumentation.
- 56% of NBS programs surveyed (n=9) could implement screening for Pompe disease in 6 months to 1 year once aforementioned hurdles are cleared.

Questions?