Using Decision Modeling to Inform Newborn Screening Policy Decisions for Pompe Disease: A Case Study

Lisa A. Prosser, PhD, MS

Professor

CHEPS Seminar

October 9, 2017

UNIVERSITY OF MICHIGAN

Today's Session

- Brief Introduction to Decision Analysis
- Case Example: Newborn Screening for Pompe Disease
- Questions welcome

Decision analysis

- Systematic approach to decision making under conditions of uncertainty
- Requires explicit consideration of each aspect of the decision problem:
  - Defining full set of alternatives
  - Choices regarding timing of implementation
  - Uncertainties involved
  - Assigning relative values to full set of possible outcomes
- Identifies alternative estimated to result in maximum benefit and uncertainty associated with that projection

Advantages of Decision Analysis (DA) Approach

- Allows for extension of time horizon beyond clinical trial time frame
- Can simulate head-to-head comparisons of real and hypothetical alternatives
- Requires decision-makers to explicitly define assumptions
- Can identify sources of uncertainty and prioritize future research

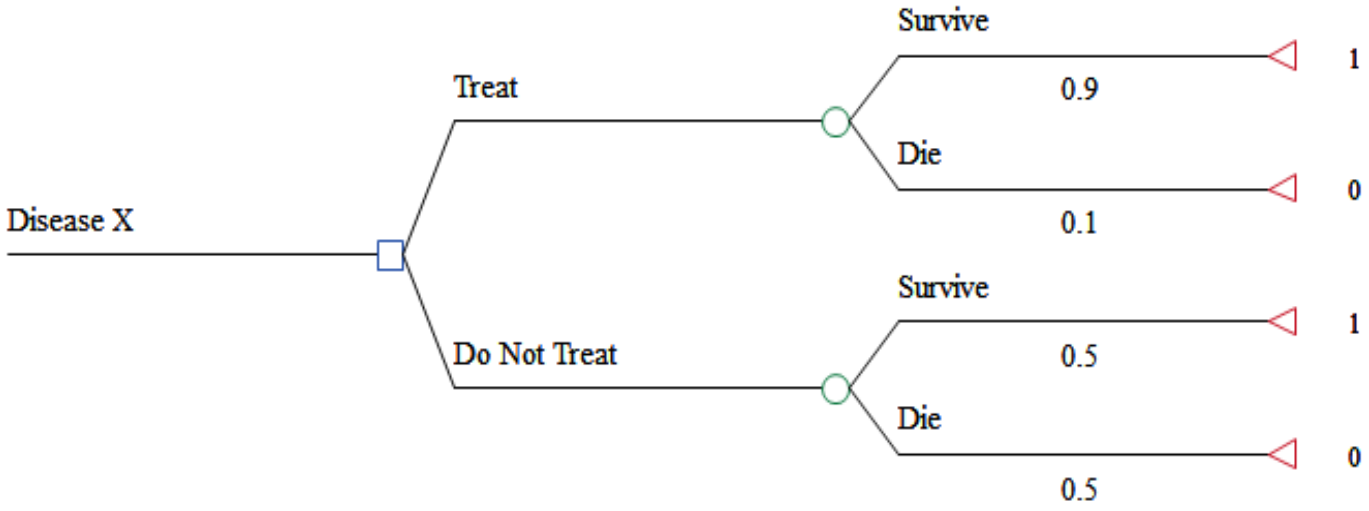
Applications of DA - Health

- Underpinning of most cost-effectiveness analyses
- Clinical guideline development
- Clinical decision making
- Patient decision aids
- FDA approval for medical devices

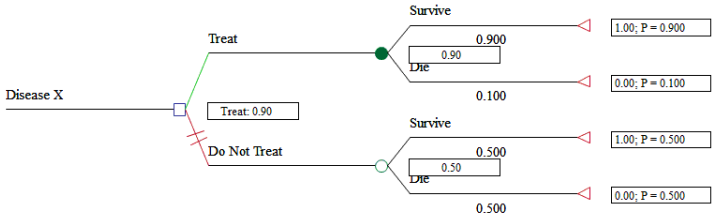
Setting up a decision tree

- Identify strategies (alternatives), including the “status quo” or “usual care”
- Decision nodes
- Chance nodes: mutually exclusive, collectively exhaustive (MECE)
- Branch probabilities
- Payoffs

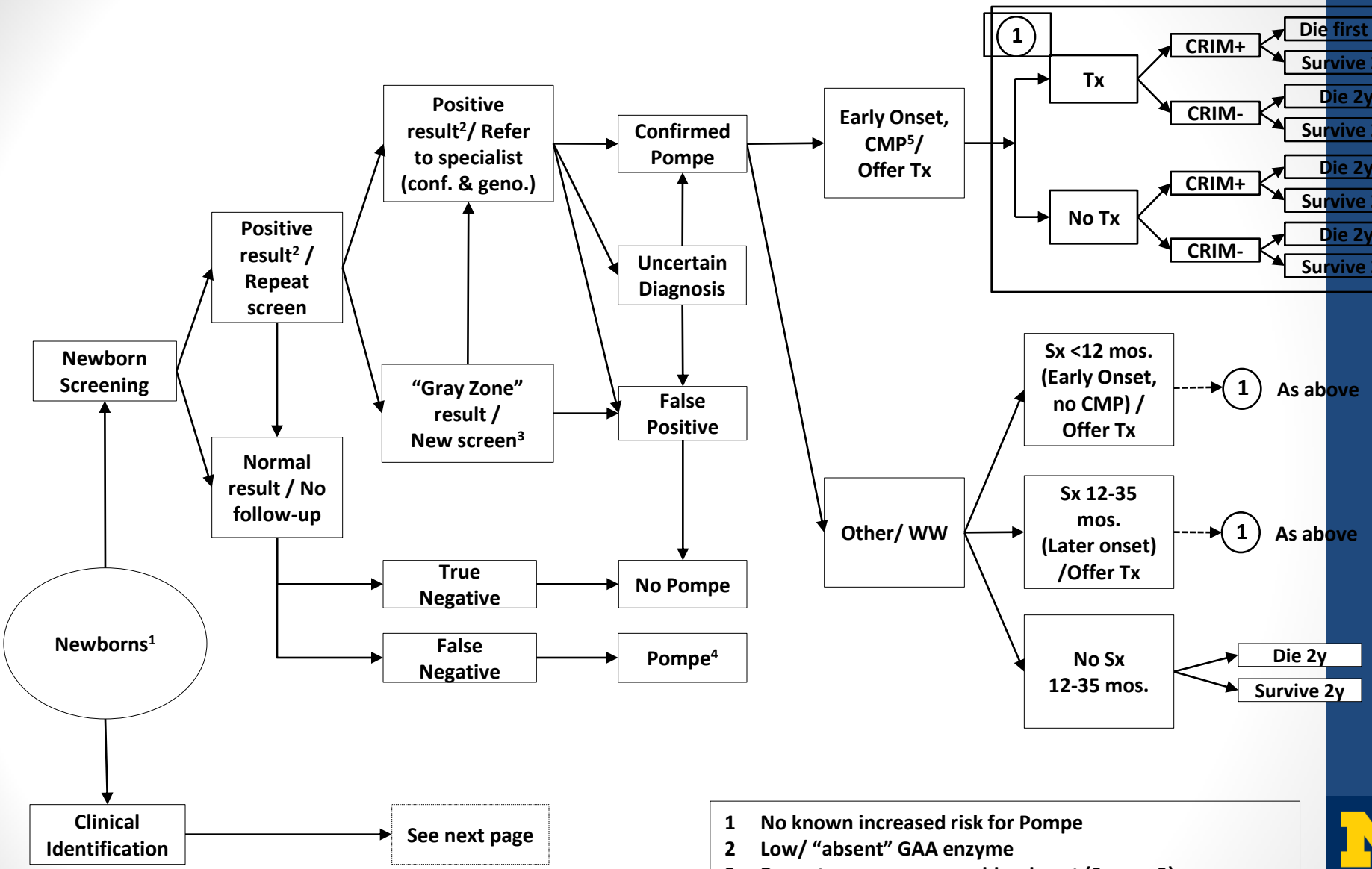
Simple Example: Decision Tree



Decision Tree: “Rolled Back”



From EP2: DRAFT Model Schematic – Part 1



1 No known increased risk for Pompe
2 Low/ "absent" GAA enzyme
3 Repeat screen on a new blood spot (Screen 2)
4 Follow sub-tree as if diagnosed via clinical identification
5 Cardiomyopathy

WW = Watchful waiting

UNIVERSITY OF MICHIGAN

Questions

Case Study:

Using Decision Analysis to Inform Newborn Screening Policy

UNIVERSITY OF MICHIGAN

Outline

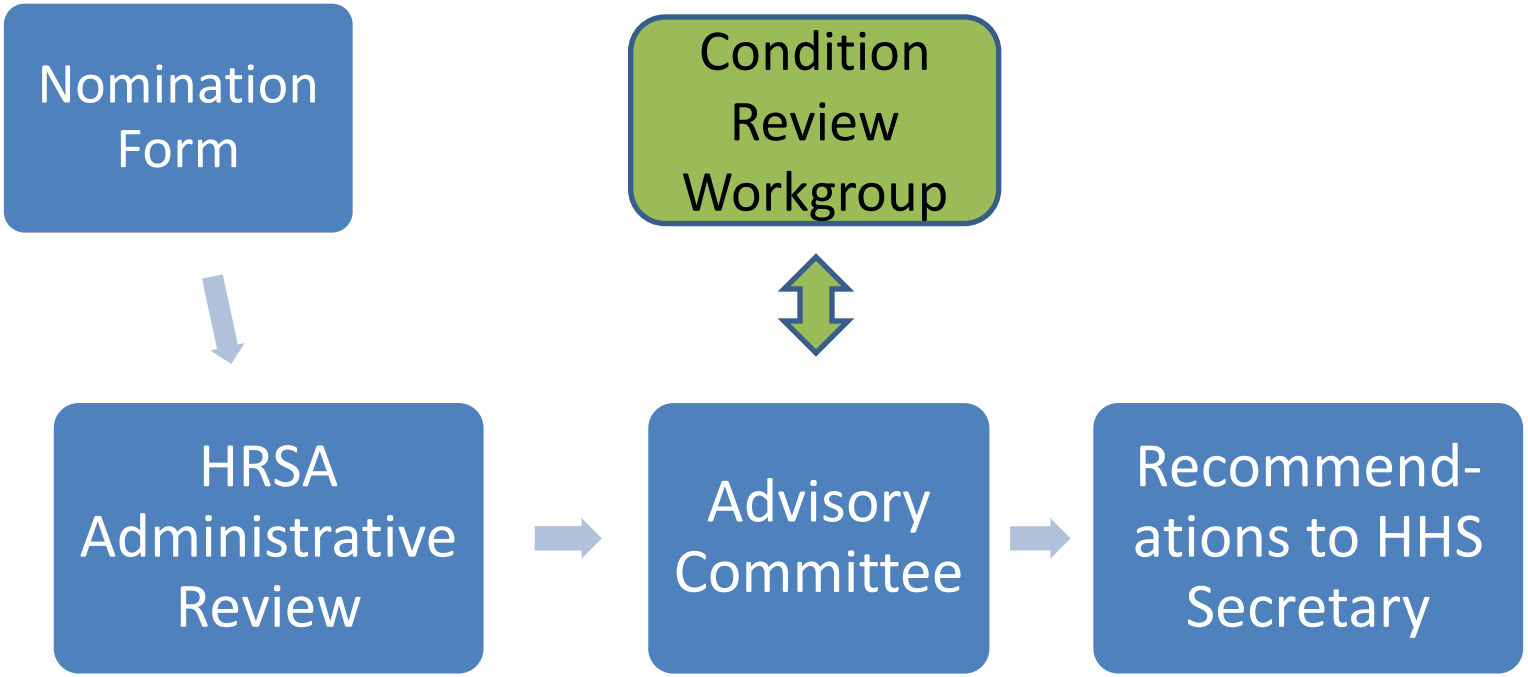
- Introduction: SACHDNC process & decision analysis
- Assessing Population-Level Benefits Using Decision Analysis (Case Example)
- Summary & Ongoing Research

Introduction

SACHDNC PROCESS & DECISION ANALYSIS

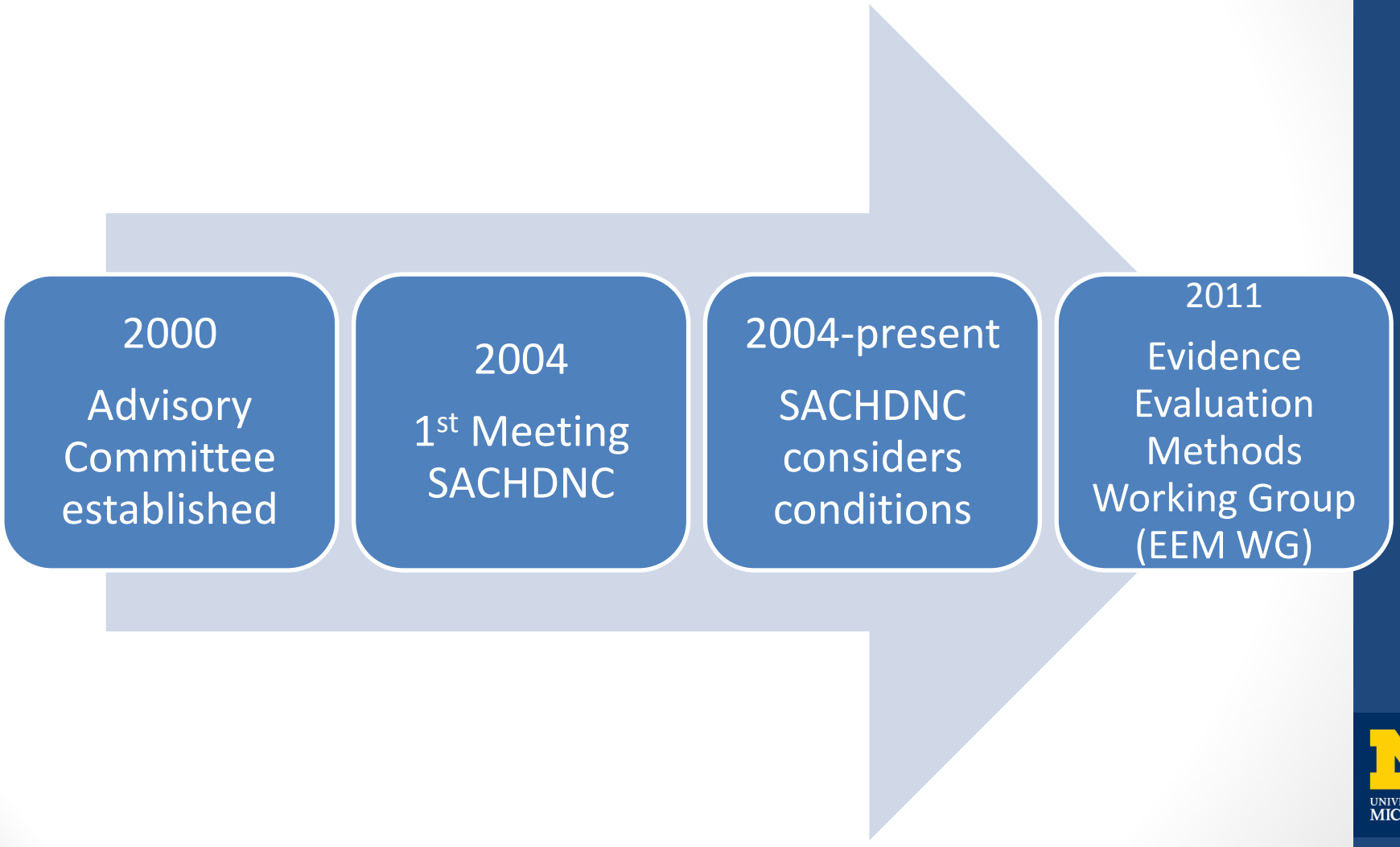
UNIVERSITY OF MICHIGAN

Process for Adding New Conditions



UNIVERSITY OF MICHIGAN

Newborn Screening Policy Process



UNIVERSITY OF MICHIGAN

Evidence Review & Synthesis

- RCT
- Cohort
- Case-control
- Observational/Descriptive
- Expert Opinion

Available Evidence

-
- Cohort
- Case-control
- Observational/Descriptive

- Expert Opinion

SACHDNC: Evidence Evaluation Methods Working Group

- Convened in April, 2011
- Charged with evaluating evidence review methods
- Considered modeling to assist in evidence synthesis and generation
- Recommended use of decision analytic modeling
- Hyperbilirubinemia case study

Decision analysis: Rationale for Application to Newborn Screening

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Identification of assumptions and key areas of uncertainty

Planned Role for Decision Analysis in Condition Review Process

- Incorporation of modeling into the evidence review process:
  - Simple models
  - Health outcomes
  - No cost-effectiveness analysis (yet)
- Initial goal is to project health benefits and potential harms

Newborn Screening for Pompe Disease: Assessing Population-Level Benefits Using Decision Analysis

Case Example

UNIVERSITY OF MICHIGAN

Acknowledgments

- **U-M Research Team**: Mia Casale, Kara Lamarand, Acham Gebremariam, Lisa Lee
- **SACHDNC/DACHDNC Condition Review Workgroup**
- **Expert Panel Participants**
- **Funding Source: HRSA**

UNIVERSITY OF MICHIGAN

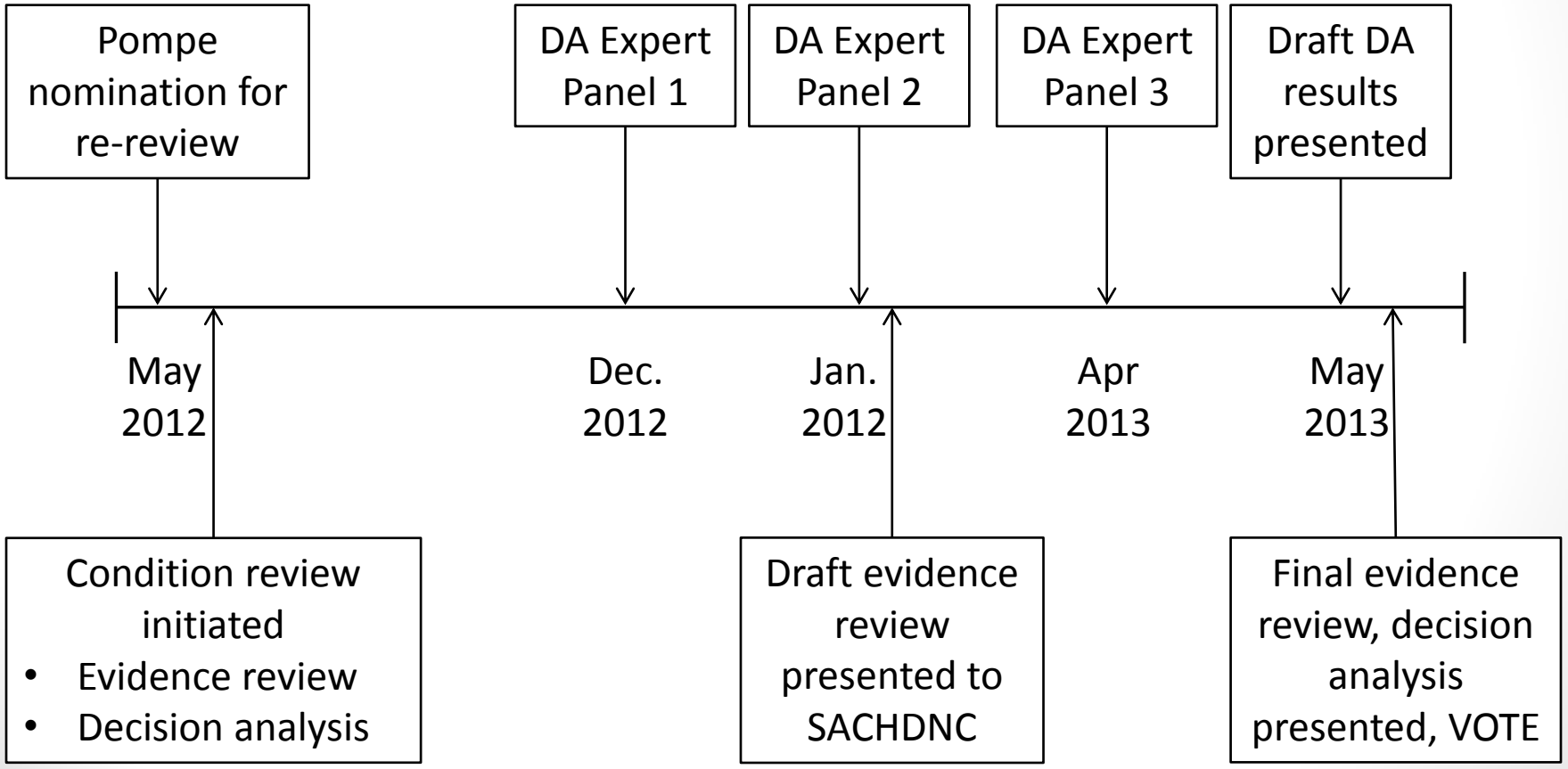
Pompe Disease

- Deficiency of acid α-glucosidase (GAA), which leads to the accumulation of lysosomal glycogen
- Broad spectrum of illness
  - **Infantile**: Most severe (<12 mos)
    - **Infantile Onset *with* Cardiomyopathy** ("Classic Form") – without treatment, death usually within the first year of life
    - **Infantile Onset *without* Cardiomyopathy** ("Nonclassic Form") –longer survival, but without treatment, death in early childhood
  - **Late-onset**: Variable Presentation (≥12 mos)
    - Variable outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)

Pompe Disease – Review Timeline

Previously nominated to the RUSP, but not added due to insufficient evidence

- May 2006 & October 2008



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

Decision analysis: Pompe disease

- Analysis:
  - Conduct base case and sensitivity analyses to obtain ranges for projected outcomes at the population level
  - Identify key areas of uncertainty and data gaps

Structured evidence review

- Literature search, gray literature, published & unpublished data
  - Key definitions
  - Natural history
  - Health outcomes
  - Available treatments (benefits, harms)
- Using information from evidence review, initial development of decision analytic model

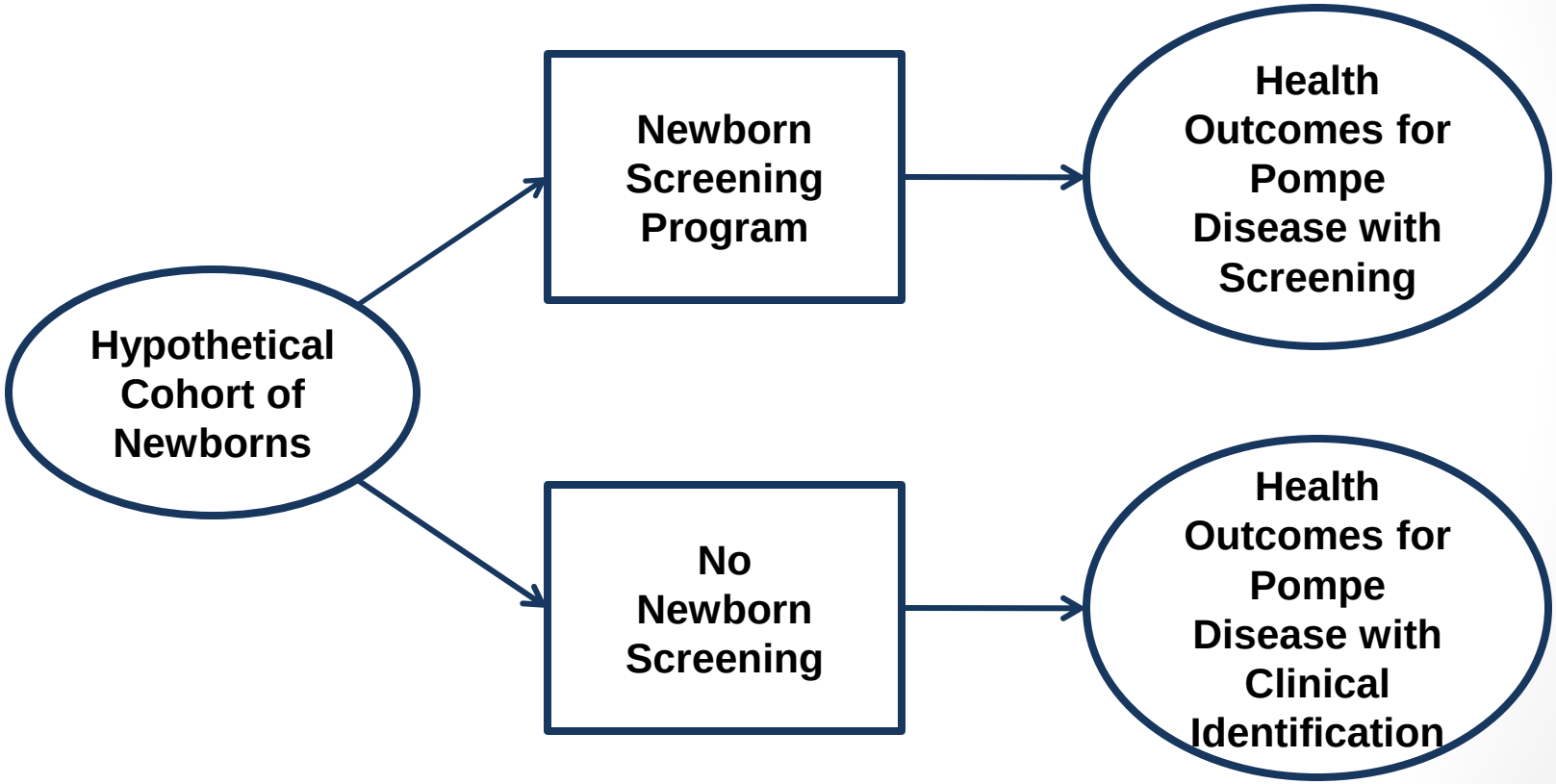
Expert Panel 1 (EP1), Dec 2012 & Expert Panel 2 (EP2), Jan 2013

- Expert panels conducted via webinar:
  - Review role of decision analysis in condition review process
  - Review draft decision tree
  - Review draft of key outcomes
  - Review modeling assumptions
- Objectives:
  - Consensus, if possible
  - Identify ranges/sensitivity analysis, if no consensus

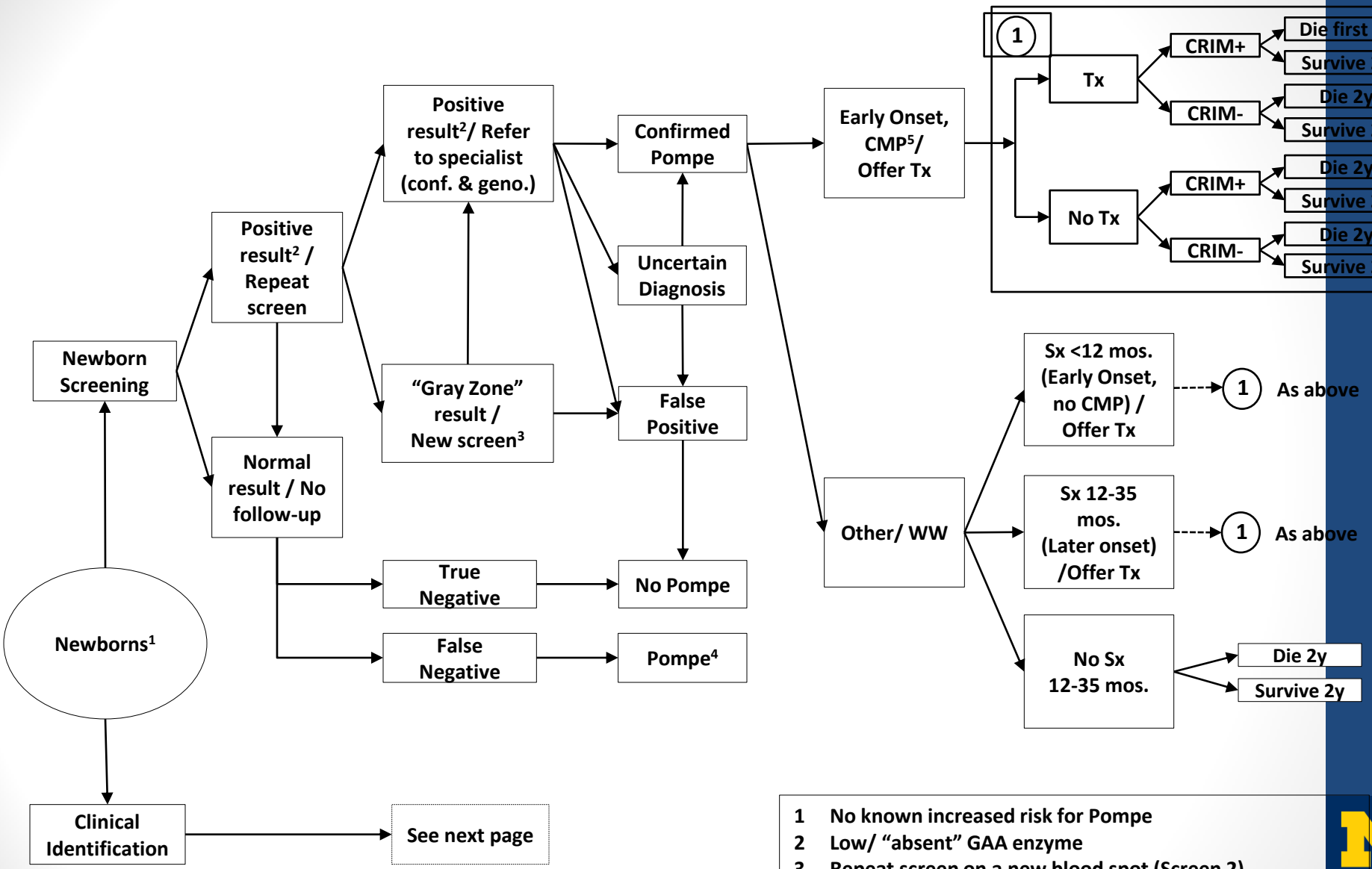
From EP1: Introduction

- Decision analysis
  - Systematic approach to decision making under conditions of uncertainty
  - Project short- and long-term outcomes (ranges)
  - Identify key parameters & assumptions
- Objectives for today's meeting
  - Review the structure of draft model
  - Review assumptions
  - Identify key outcomes

Newborn Screening Model



From EP2: DRAFT Model Schematic – Part 1

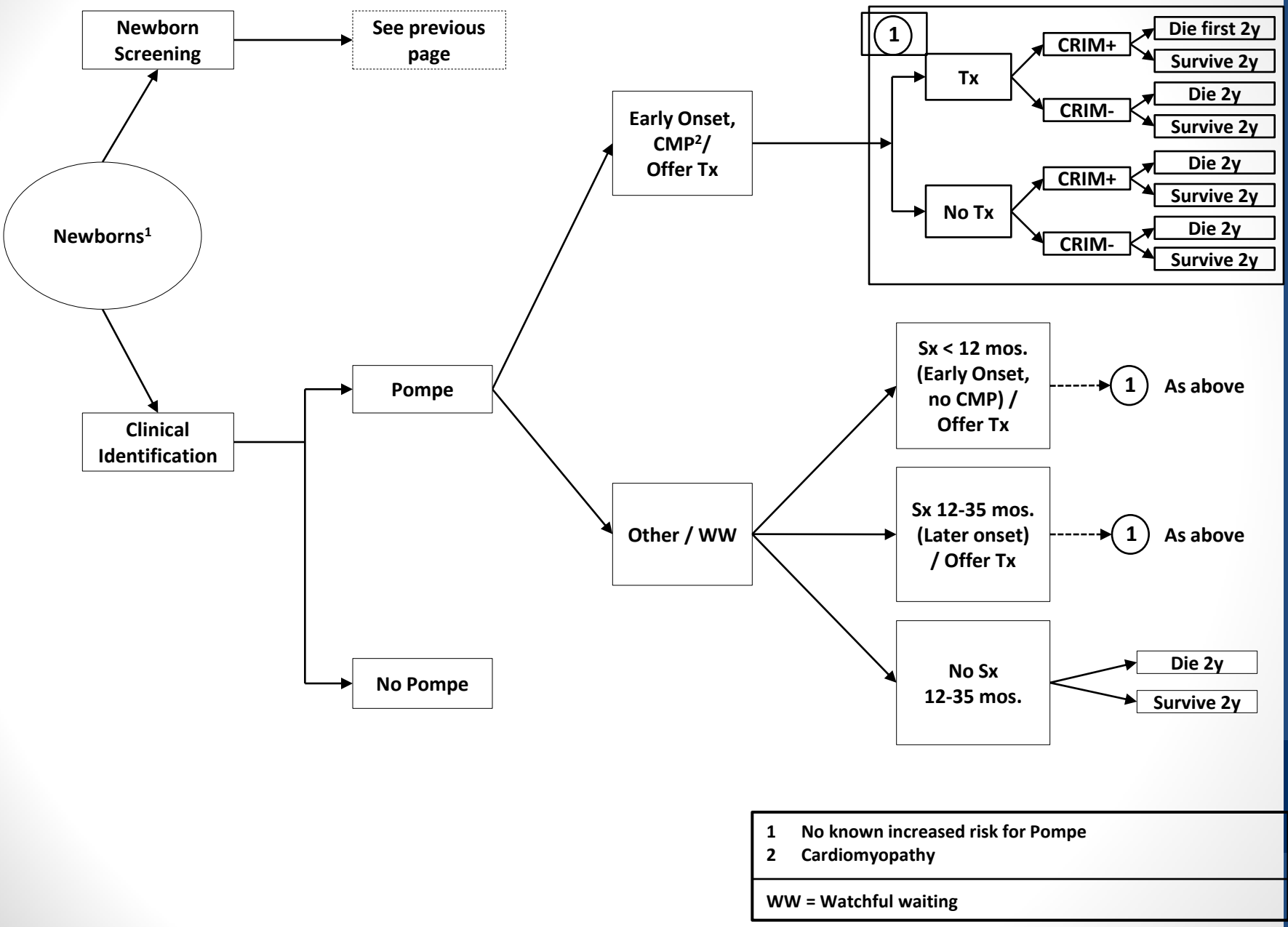


1 No known increased risk for Pompe
2 Low/ "absent" GAA enzyme
3 Repeat screen on a new blood spot (Screen 2)
4 Follow sub-tree as if diagnosed via clinical identification
5 Cardiomyopathy

WW = Watchful waiting

UNIVERSITY OF MICHIGAN

From EP2: DRAFT Model Schematic – Part 2



UNIVERSITY OF MICHIGAN

From EP2: 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	--	--	--
Confirmed cases of Pompe (all types)	--	--	--
Classic early infantile	--	--	--
Confirmed cases who die within 2 yrs	--	--	--
Confirmed cases who are alive after 2 yrs	--	--	--
“Other” Pompe	--	--	--
Confirmed cases who die within 2 yrs	--	--	--
Confirmed cases who are alive after 2 yrs	--	--	--

UNIVERSITY OF MICHIGAN

From EP2: Modeling Assumptions – for discussion

Screening

1. A newborn with initial screening results “Low/Low “ will be treated the same as a newborn with “Gray zone/Low”

2. All children diagnosed as Classic Early Infantile will initiate treatment

3. Treatment initiation is not assumed for other Pompe subtypes.

4. Individuals can only be classified as Classic Early Infantile, or not. There is no way to differentiate Non-Classic Infantile from Later Onset Pompe disease during the initial screening protocol.

Iterative Process

- After EP1/EP2
  - Revised decision tree
  - Reviewed updated decision tree, assumptions, with EP members

EP3 (April 2013)

- Reviewed updated decision tree
  - Simplified CRIM +/-
- Reviewed modeling assumptions and outcomes
  - Added ventilator-dependence
  - Added 36-month outcomes
- Reviewed estimates for key parameter inputs

Test Characteristics

	Most Likely	Min - Max
Sensitivity	0.9322	0.9315 – 0.9329
Specificity	0.9999	0.9993 – 1.000

Source: **Adjusted** from Chiang et al. (2012)

Pompe disease: prevalence & sub-types

	Newborn Screening		Clinical Identification	
	Most Likely	Min - Max	Most Likely	Min - Max
Pompe disease (all subtypes)	1/27,800	0.3-2.7/27,800	??	1-2.5/100,000
Infantile (<12 mos)	0.278	??	0.25	??
Infantile with cardiomyopathy (classic)	0.236	??	0.235	??
Infantile without cardiomyopathy (non-classic)	0.042	??	0.015	??
Late-onset (≥12 mos)	0.722	??	0.75	??

Source: Chiang et al., 2012; Scott et al., 2013; Mechtler et al., 2012; Kishnani, 2006; assumptions.

36-month Health Outcomes

Mortality

Infantile-onset	Screened/Treated	Clin Dx/Treated	Clin Dx/Untreated
w/CMP	<0.001 (0-0.029)	0.351 (??-??)	0.979 (??-??)
w/o CMP	<0.001 (0-0.029)	0.080 (??-??)	0.289 (??-??)

Ventilator-free survival

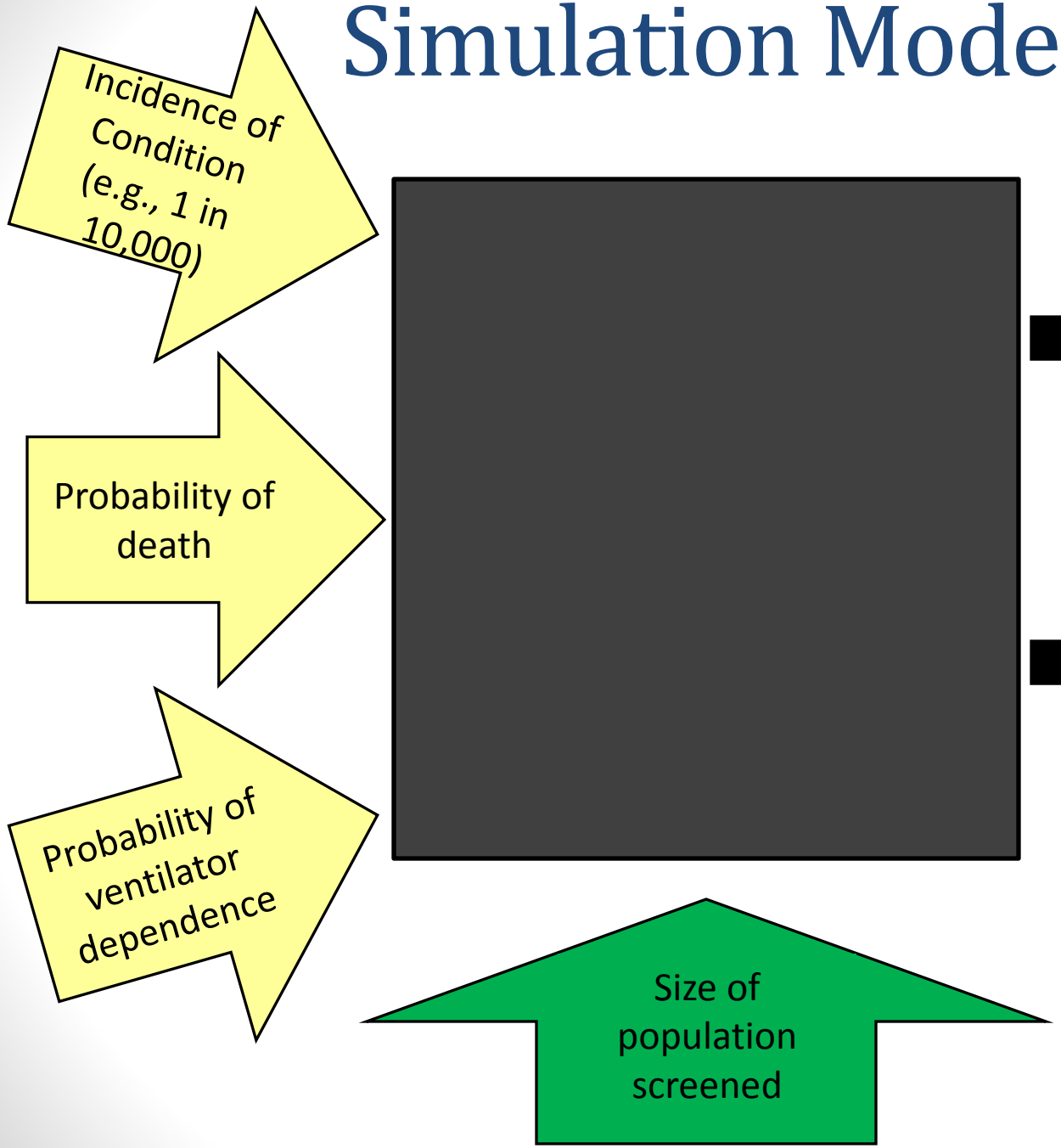
Infantile-onset	Screened/Treated	Clin Dx/Treated	Clin Dx/Untreated
w/CMP	<0.999 (0.971 – 1)	0.590 (??-??)	0.010 (??-??)
w/o CMP	<0.999 (0.971 - 1)	0.843 (??-??)	0.524 (??-??)

Source: Chen et al., 2009; Kishnani et al, 2006; Winkel et al., 2005; primary data; assumptions.

Results of EP3

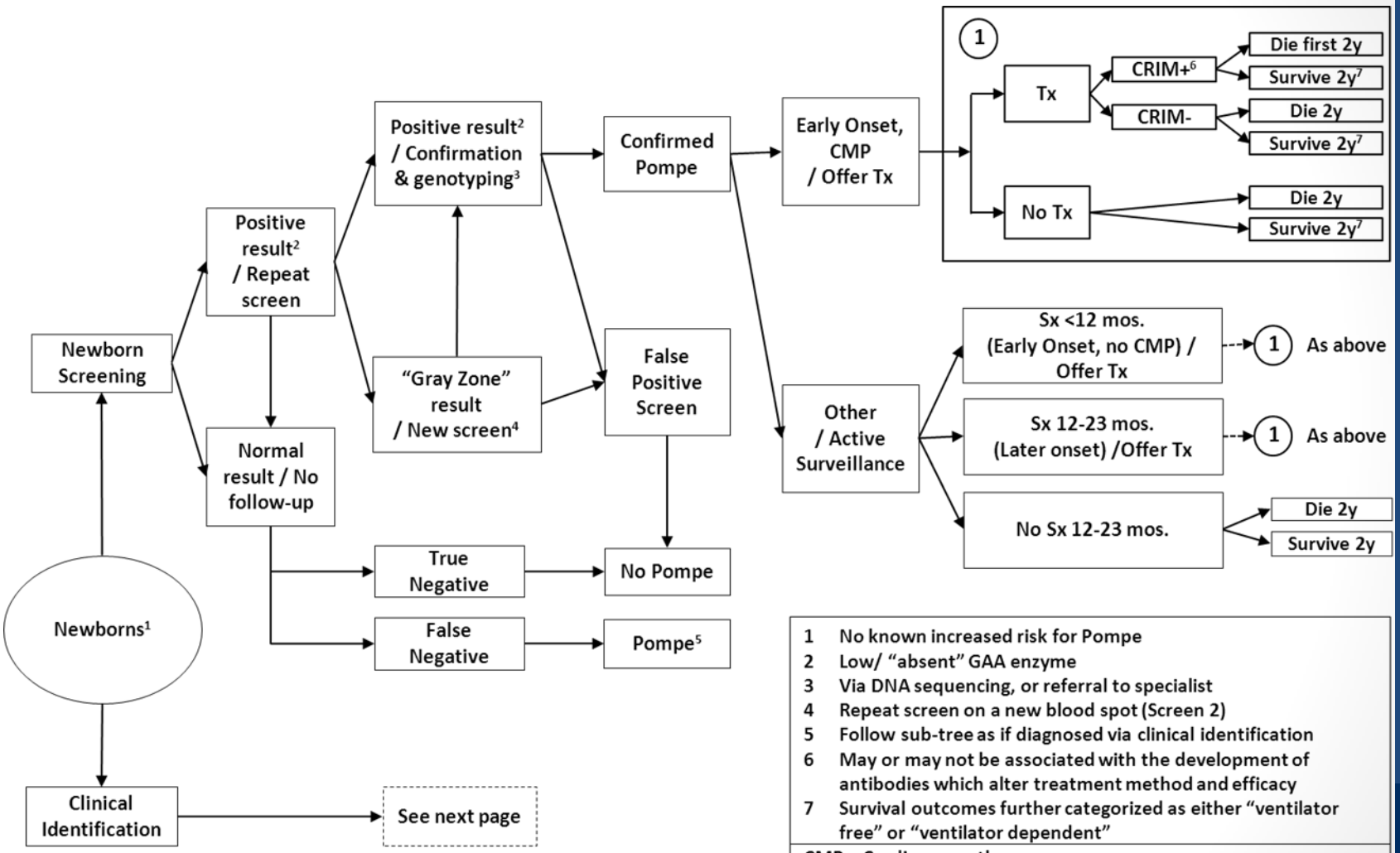
- Further simplified decision tree
- Confirmed set of key health outcomes:
  - Cases identified
  - Cases ventilator-free
  - Deaths

Simulation Model



UNIVERSITY OF MICHIGAN

Expert Panel 3 Model Schematic, Part 1

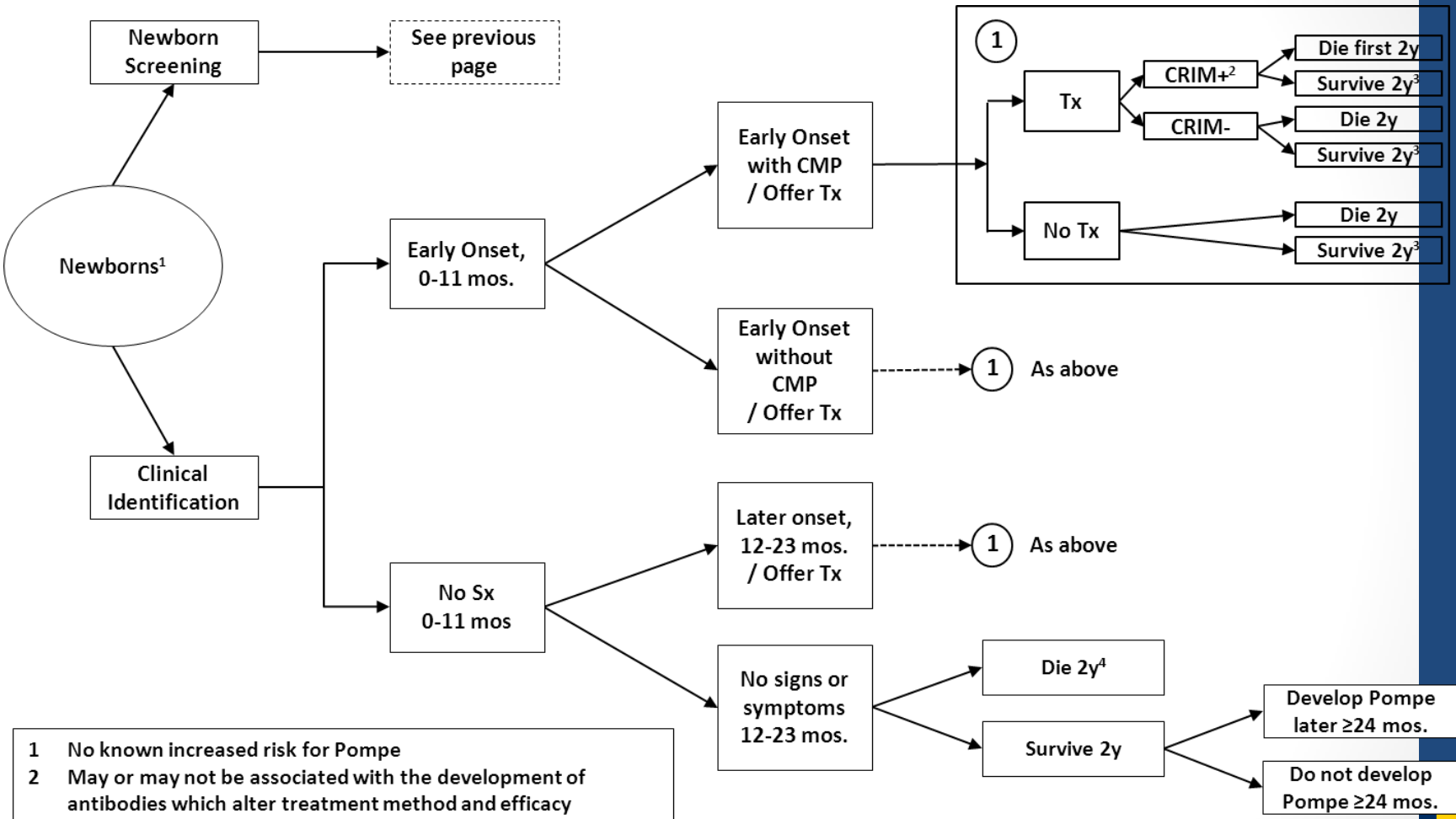


1 No known increased risk for Pompe
2 Low/ "absent" GAA enzyme
3 Via DNA sequencing, or referral to specialist
4 Repeat screen on a new blood spot (Screen 2)
5 Follow sub-tree as if diagnosed via clinical identification
6 May or may not be associated with the development of antibodies which alter treatment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

UNIVERSITY OF MICHIGAN

Expert Panel 3 Model Schematic, Part 2

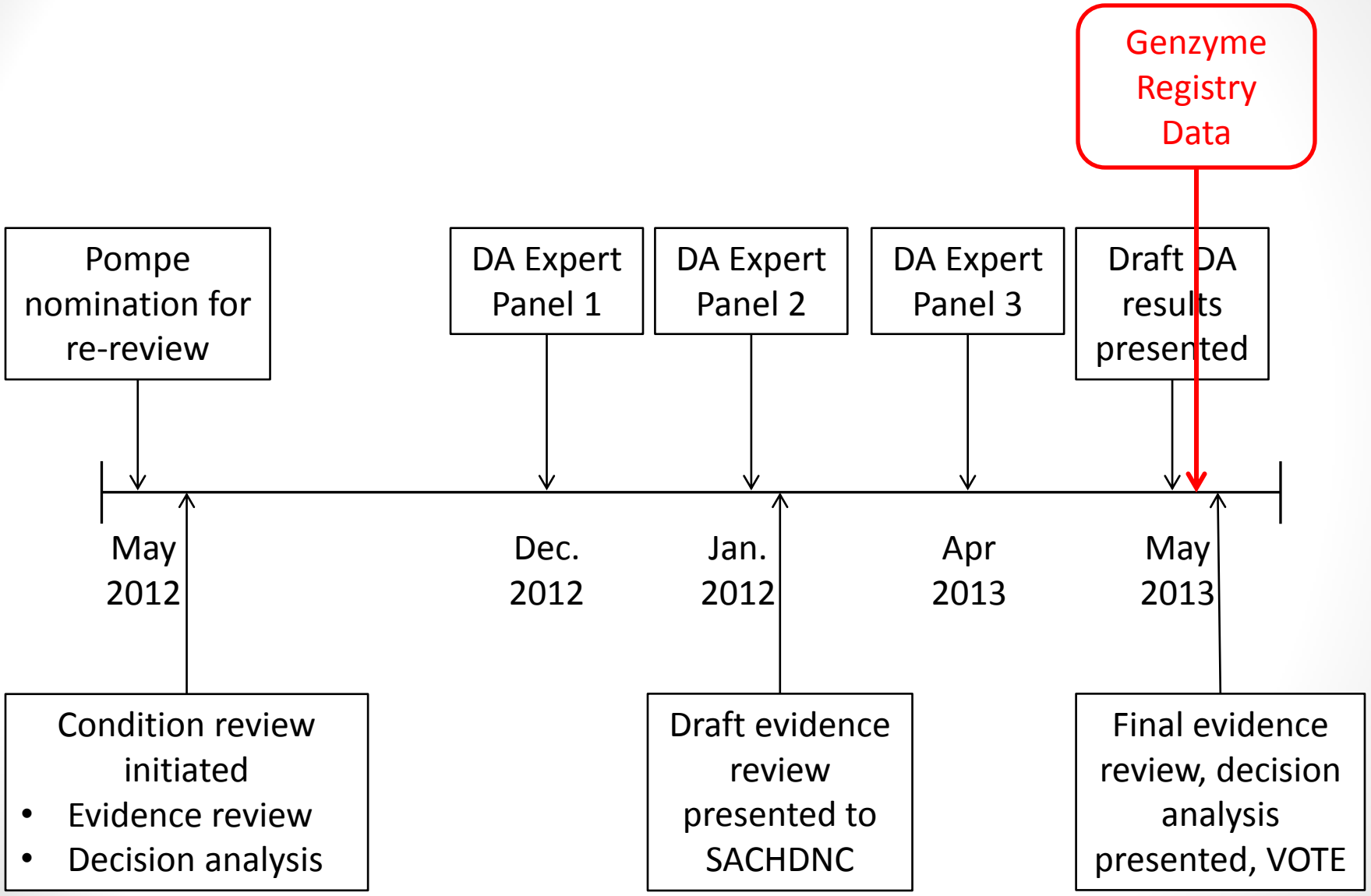


1 No known increased risk for Pompe
2 May or may not be associated with the development of antibodies which alter treatment method and efficacy
3 Survival outcomes further characterized as either "ventilator free" or "ventilator dependent"
4 Non-Pompe related mortality

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

UNIVERSITY OF MICHIGAN

Two weeks prior to DACHDNC Vote



Results Presented via WEBINAR

DACHDNC Meeting

May 17, 2013

UNIVERSITY OF MICHIGAN

Analytic Approach

- Computer simulation model to evaluate outcomes for universal newborn screening for Pompe disease compared with clinical identification
- 3 expert panels: Dec 2012, Jan & April 2013
- Key health endpoints:
  - # cases identified
  - # deaths averted
  - # ventilator-dependent cases averted

Modeling Assumptions

- All identified cases of infantile-onset Pompe disease are eligible for ERT
- Key outcomes assessed for infantile-onset cases only
- Additional number of late-onset cases identified with newborn screening is unknown

Results: Infantile & Late-Onset Cases

- Assuming an annual **US newborn cohort of 4 million***, newborn screening is projected to identify **134 cases**, including both infantile and late-onset Pompe disease
- Of these 134 cases,
  - **40 cases** are expected to be **infantile-onset**
  - **94 cases** are expected to be **late-onset** (40-70% of which may be undetected with clinical identification)
- ~10 false negative results (late-onset only)

* not at increased risk for Pompe disease

Results: Infantile-Onset Cases Identified

	NBS	Clinical Identification
Infantile onset (all)	40 (19-61)	36 (16-56)
Infantile onset with cardiomyopathy	34 (28-36)	34 (28-36)
Infantile onset without cardiomyopathy	6 (4-12)	2 (0-8)

Results: Health Outcomes

- Benefits of newborn screening:
  - Infantile-onset with cardiomyopathy:
    - Earlier identification and initiation of treatment (~22 days compared to 4-5 months of age on average)
  - Infantile-onset without cardiomyopathy:
    - Identification and treatment of 4 additional cases
- Key health outcomes, per year:
  - **13 averted deaths (range: 8-19)**
  - **26 additional individuals who would not require invasive ventilation** (range: 20-28)

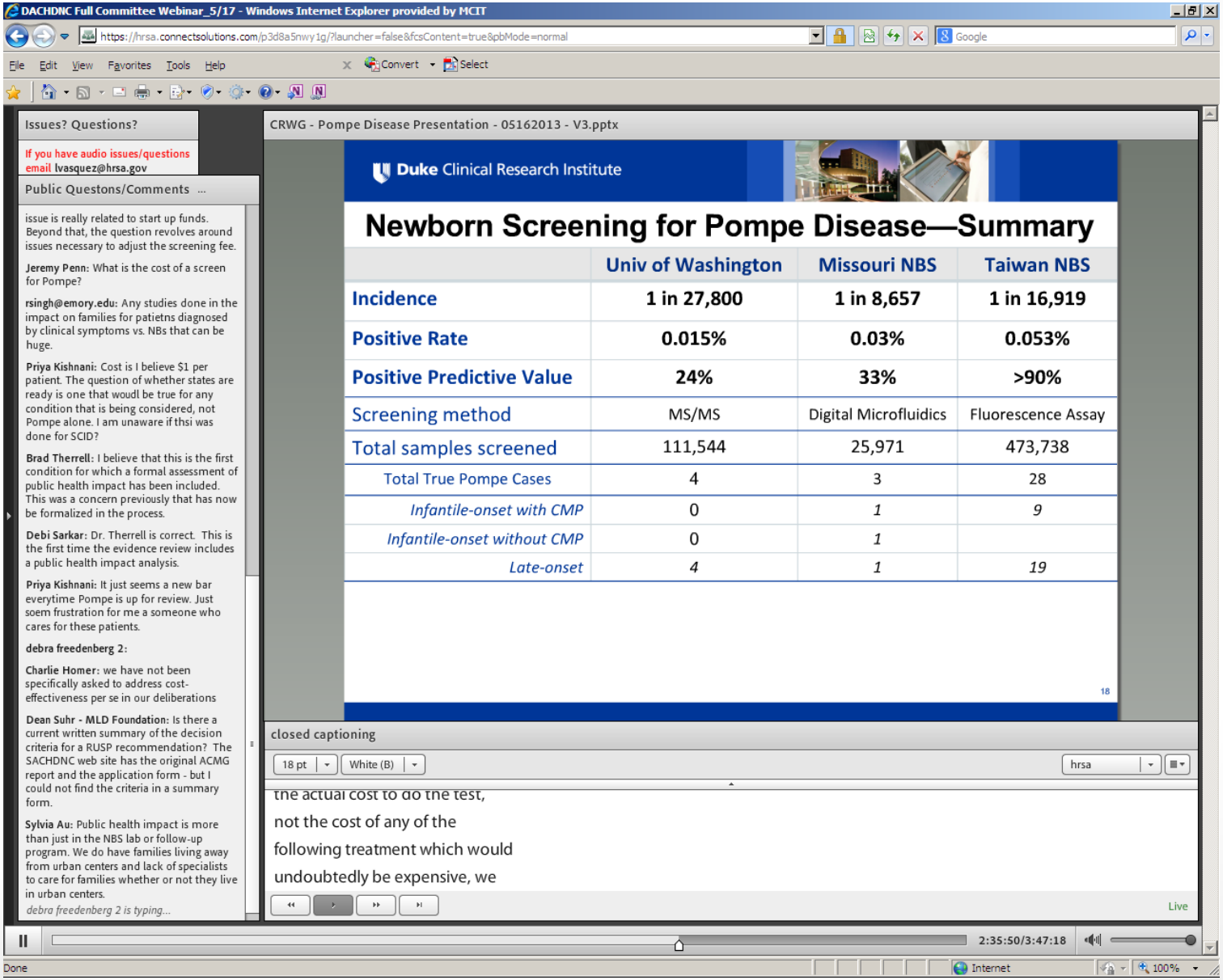
Summary

- Projected health benefits for identified cases
  - Infantile-onset only
  - Increased survival
  - Fewer individuals with invasive ventilation
- Benefits and harms of identifying late-onset cases is not included

DACHDNC Process (May 2013)

- Reports:
  - Evidence Review
  - Population Impact Modeling
  - Feasibility (APHL)
- Rating of Benefits & Harms w/r/t Decision Matrix
- Recommendation
- VOTE

DACHDNC Discussion



UNIVERSITY OF MICHIGAN

Case Example Wrap-Up: Using DA

- Transparency regarding assumptions
  - Identification of the appropriate comparator strategy: “clinical identification WITH enzyme replacement treatment” not “untreated”
  - Timing of initiation of treatment
- Identification of knowledge gaps to prioritize future data collection/research activities
  - DACHDNC Discussion focused on late-onset
  - Benefits/harms for this group unknown
  - Long-term treatment effects

Summary

- Limitations of applying DA to expanded newborn screening:
  - No cost assessment
  - Short-term outcomes only
  - Heterogeneity in severity of illness – large numbers of "patients in waiting"
  - Very scant data
- Strengths of using DA
  - Allowed for estimation of population level outcomes: both screening outcomes & health benefits
  - Identified parameters associated with uncertainty

Ongoing Research

- **Pompe disease** (separate research study)
  - Data collection: costs, health outcomes
  - Lifetime simulation model
  - Anticipated results: long-term costs, health outcomes, and cost-effectiveness to inform state-level decisions, planning
- **Reviewed and added:** MPS-1, X-ALD
- **reviewed and not added**: Hyperbilirubinemia
- **Currently under review:** Spinal muscular atrophy (SMA) nominated May 2017 (9-month timeline)
  - Vote scheduled for Feb 2018

Discussion/Questions

- Follow-up questions, please email: lisapros@umich.edu

UNIVERSITY OF MICHIGAN