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

Lisa A. Prosser, PhD, MS
Professor

CHEPS Seminar
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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

- Disease X
  - Treat: Survive 0.9, Die 0.1
  - Do Not Treat: Survive 0.5, Die 0.5
Decision Tree: “Rolled Back”
Early Onset, CMP

Offer Tx

Other/ WW

From EP2: DRAFT Model Schematic – Part 1

Newborn Screening

Positive result^2/ Repeat screen

“Gray Zone” result / New screen^3

False Positive

Confirmed Pompe

Uncertain Diagnosis

Early Onset, CMP^5/ Offer Tx

No Tx

Die 2y

Survive 2y

CRIM+

CRIM-

No Pompe

False Negative

True Negative

No known increased risk for Pompe

Low/ “absent” GAA enzyme

Repeat screen on a new blood spot (Screen 2)

Follow sub-tree as if diagnosed via clinical identification

Cardiomyopathy

WW = Watchful waiting

See next page
Questions
Case Study:

Using Decision Analysis to Inform Newborn Screening Policy
Outline

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

SACHDNC PROCESS & DECISION ANALYSIS
Process for Adding New Conditions

Nomination Form → HRSA Administrative Review → Condition Review Workgroup ↔ Advisory Committee → Recommendations to HHS Secretary
Newborn Screening Policy Process

- 2000: Advisory Committee established
- 2004: 1st Meeting SACHDNC
- 2004-present: SACHDNC considers conditions
- 2011: Evidence Evaluation Methods Working Group (EEM WG)
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
Acknowledgments

• **U-M Research Team**: Mia Casale, Kara Lamarand, Acham Gebremariam, Lisa Lee

• **SACHDNC/DACHDNC Condition Review Workgroup**

• **Expert Panel Participants**

• **Funding Source**: HRSA
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

- Pompe nomination for re-review
- DA Expert Panel 1
  - Dec. 2012
  - Condition review initiated
    - Evidence review
    - Decision analysis
- DA Expert Panel 2
  - Jan. 2012
  - Draft evidence review presented to SACHDNC
- DA Expert Panel 3
  - Apr 2013
  - Final evidence review, decision analysis presented, VOTE
- Draft DA results presented
  - May 2013
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 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

Hypothetical Cohort of Newborns

Newborn Screening Program

Health Outcomes for Pompe Disease with Screening

No Newborn Screening

Health Outcomes for Pompe Disease with Clinical Identification
From EP2: DRAFT Model Schematic – Part 1

Newborns

Newborn Screening

Positive result\(^2\)/ Repeat screen

Normal result / No follow-up

“Gray Zone” result / New screen\(^3\)

Positive result\(^2\)/ Refer to specialist (conf. & geno.)

Confirmed Pompe

Early Onset, CMP\(^5\)/ Offer Tx

Uncertain Diagnosis

False Positive

No Pompe

Pompe\(^4\)

Other/ WW

CRIM+

Die first 2y

Survive 2y

CRIM-

Die 2y

Survive 2y

Sx <12 mos.
(Early Onset, no CMP)/ Offer Tx

Sx 12-35 mos.
(Later onset)/Offer Tx

No Sx 12-35 mos.

No Pompe

See next page

Clinical Identification

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
Newborn Screening

See previous page

Early Onset, CMP\(^2\)/Offer Tx

Other / WW

1 No known increased risk for Pompe
2 Cardiomyopathy

WW = Watchful waiting
### From EP2: DRAFT Key Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Newborn Screening</th>
<th>Clinical Diagnosis</th>
<th>Screening Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positives</td>
<td>--</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>False Positives</td>
<td>--</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>True Negatives</td>
<td>--</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>False Negatives</td>
<td>--</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Repeat Screens</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Confirmed cases of Pompe (all types)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Classic early infantile</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Confirmed cases who die within 2 yrs</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Confirmed cases who are alive after 2 yrs</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>“Other” Pompe</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Confirmed cases who die within 2 yrs</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Confirmed cases who are alive after 2 yrs</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Most Likely</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.9322</td>
<td>0.9315 – 0.9329</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.9999</td>
<td>0.9993 – 1.000</td>
</tr>
</tbody>
</table>

Source: Adjusted from Chiang et al. (2012)
### Pompe disease: prevalence & subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Newborn Screening</th>
<th>Clinical Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most Likely</td>
<td>Min - Max</td>
</tr>
<tr>
<td>Pompe disease (all subtypes)</td>
<td>1/27,800</td>
<td>0.3-2.7/27,800</td>
</tr>
<tr>
<td>Infantile (&lt;12 mos)</td>
<td>0.278</td>
<td>??</td>
</tr>
<tr>
<td>Infantile with cardiomyopathy (classic)</td>
<td>0.236</td>
<td>??</td>
</tr>
<tr>
<td>Infantile without cardiomyopathy (non-classic)</td>
<td>0.042</td>
<td>??</td>
</tr>
<tr>
<td>Late-onset (≥12 mos)</td>
<td>0.722</td>
<td>??</td>
</tr>
</tbody>
</table>

Source: Chiang et al., 2012; Scott et al., 2013; Mechtler et al., 2012; Kishnani, 2006; assumptions.
# 36-month Health Outcomes

## Mortality

<table>
<thead>
<tr>
<th>Infantile-onset</th>
<th>Screened/Treated</th>
<th>Clin Dx/Treated</th>
<th>Clin Dx/Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/CMP</td>
<td>&lt;0.001 (0-0.029)</td>
<td>0.351 (?)-??</td>
<td>0.979 (?)-??</td>
</tr>
<tr>
<td>w/o CMP</td>
<td>&lt;0.001 (0-0.029)</td>
<td>0.080 (?)-??</td>
<td>0.289 (?)-??</td>
</tr>
</tbody>
</table>

## Ventilator-free survival

<table>
<thead>
<tr>
<th>Infantile-onset</th>
<th>Screened/Treated</th>
<th>Clin Dx/Treated</th>
<th>Clin Dx/Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/CMP</td>
<td>&lt;0.999 (0.971 – 1)</td>
<td>0.590 (?)-??</td>
<td>0.010 (?)-??</td>
</tr>
<tr>
<td>w/o CMP</td>
<td>&lt;0.999 (0.971 - 1)</td>
<td>0.843 (?)-??</td>
<td>0.524 (?)-??</td>
</tr>
</tbody>
</table>

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

- Incidence of Condition (e.g., 1 in 10,000)
- Probability of death
- Probability of ventilator dependence

Population Level Outcomes

With **Newborn Screening**:
- Cases identified
- Cases, ventilator dependent
- Deaths

With **Clinical Identification**:
- Cases identified
- Cases, ventilator dependent
- Deaths
Expert Panel 3 Model Schematic, Part 1

Newborn Screening
- Newborns
- Clinical Identification
- See next page

Positive result / Confirmation & genotyping
- Positive result / Repeat screen
- Confirmed Pompe
- Early Onset, CMP / Offer Tx
- No Tx

"Gray Zone" result / New screen
- Normal result / No follow-up
- False Positive Screen
- Other / Active Surveillance
- Sx <12 mos. (Early Onset, no CMP) / Offer Tx
- Sx 12-23 mos. (Later onset) / Offer Tx
- No Sx 12-23 mos.

False Negative
- No Pompe

True Negative

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
Expert Panel 3 Model Schematic, Part 2

Newborn Screening → See previous page

Newborns
Clinical Identification

Early Onset, 0-11 mos.

Early Onset with CMP / Offer Tx

No Tx

Early Onset without CMP / Offer Tx

Later onset, 12-23 mos. / Offer Tx

No signs or symptoms 12-23 mos.

No Tx

CRIM+

Survive 2y

CRIM-

Die 2y

Survive 2y

Die first 2y

Survive 2y

Survive 2y

Develop Pompe later ≥24 mos.

Do not develop Pompe ≥24 mos.

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
Two weeks prior to DACHDNC Vote

Pompe nomination for re-review

- May 2012
  - Condition review initiated
    - Evidence review
    - Decision analysis

DA Expert Panel 1
- Dec. 2012
  - Draft evidence review presented to SACHDNC

DA Expert Panel 2
- Jan. 2012
  - Final evidence review, decision analysis presented, VOTE

DA Expert Panel 3
- Apr 2013

Draft DA results presented
- May 2013

Genzyme Registry Data

- May 2012
- May 2013
- Nov. 2012
- Dec. 2012
- Jan. 2013
- Feb. 2013
- Mar. 2013
- Apr. 2013
- May 2013
Results Presented via WEBINAR

DACHDNC Meeting
May 17, 2013
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

<table>
<thead>
<tr>
<th></th>
<th>NBS</th>
<th>Clinical Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile onset (all)</td>
<td>40 (19-61)</td>
<td>36 (16-56)</td>
</tr>
<tr>
<td>Infantile onset with cardiomyopathy</td>
<td>34 (28-36)</td>
<td>34 (28-36)</td>
</tr>
<tr>
<td>Infantile onset without cardiomyopathy</td>
<td>6 (4-12)</td>
<td>2 (0-8)</td>
</tr>
</tbody>
</table>
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
Newborn Screening for Pompe Disease—Summary

<table>
<thead>
<tr>
<th></th>
<th>Univ of Washington</th>
<th>Missouri NBS</th>
<th>Taiwan NBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1 in 27,800</td>
<td>1 in 8,657</td>
<td>1 in 16,919</td>
</tr>
<tr>
<td>Positive Rate</td>
<td>0.015%</td>
<td>0.03%</td>
<td>0.053%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>24%</td>
<td>33%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Screening method</td>
<td>MS/MS</td>
<td>Digital Microfluidics</td>
<td>Fluorescence Assay</td>
</tr>
<tr>
<td>Total samples screened</td>
<td>111,544</td>
<td>25,971</td>
<td>473,738</td>
</tr>
<tr>
<td>Total True Pompe Cases</td>
<td>4</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>Infantile-onset with CMP</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Infantile-onset without CMP</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Late-onset</td>
<td>4</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

DACHDNC Discussion

Issues? Questions?

If you have audio issues/questions
email lausger@hsa.gov

Public Questions/Comments ...
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