# Future Directions for the ERW

*Advisory Committee on Heritable Disorders in Newborns and Children*

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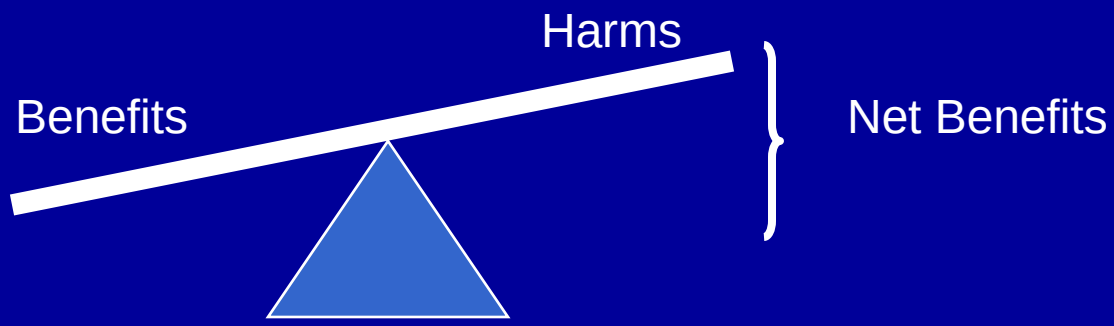
# Evidence Synthesis Around NBS

- Challenges
  - Rare conditions
  - Heterogeneity
  - Lack of data
  - Emerging technology and treatments
  - Benefits and harms not fully characterized
  - Urgency

# Weighing Potential Benefits and Risks



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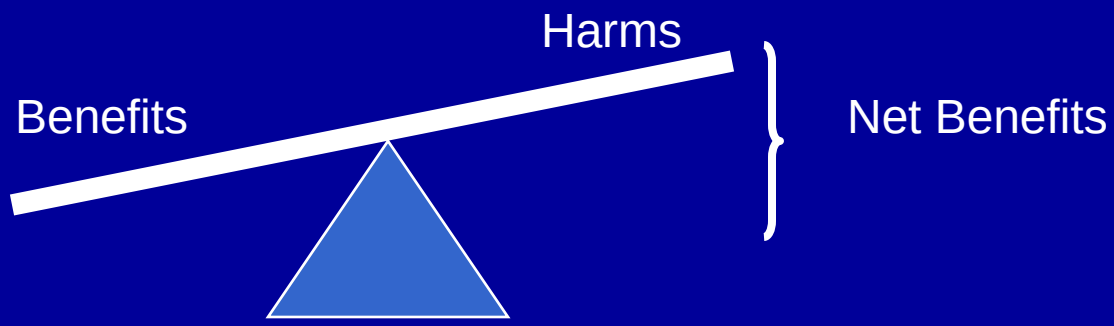


**Individual / Family Benefits**

- Decreased mortality
- Decreased morbidity
- Improved quality of life

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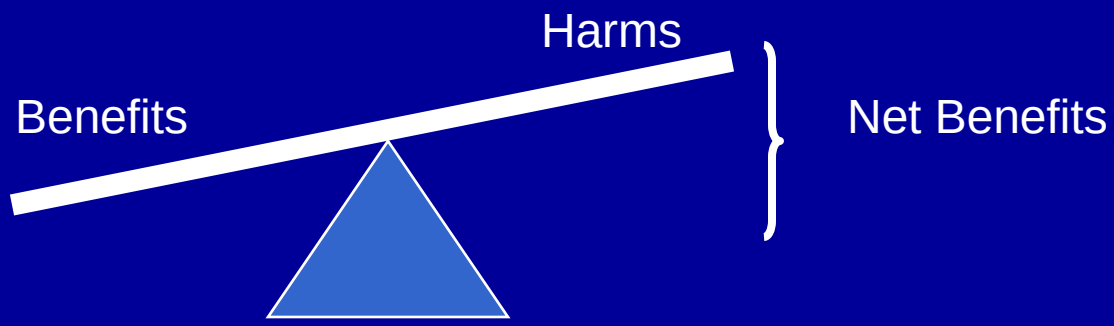


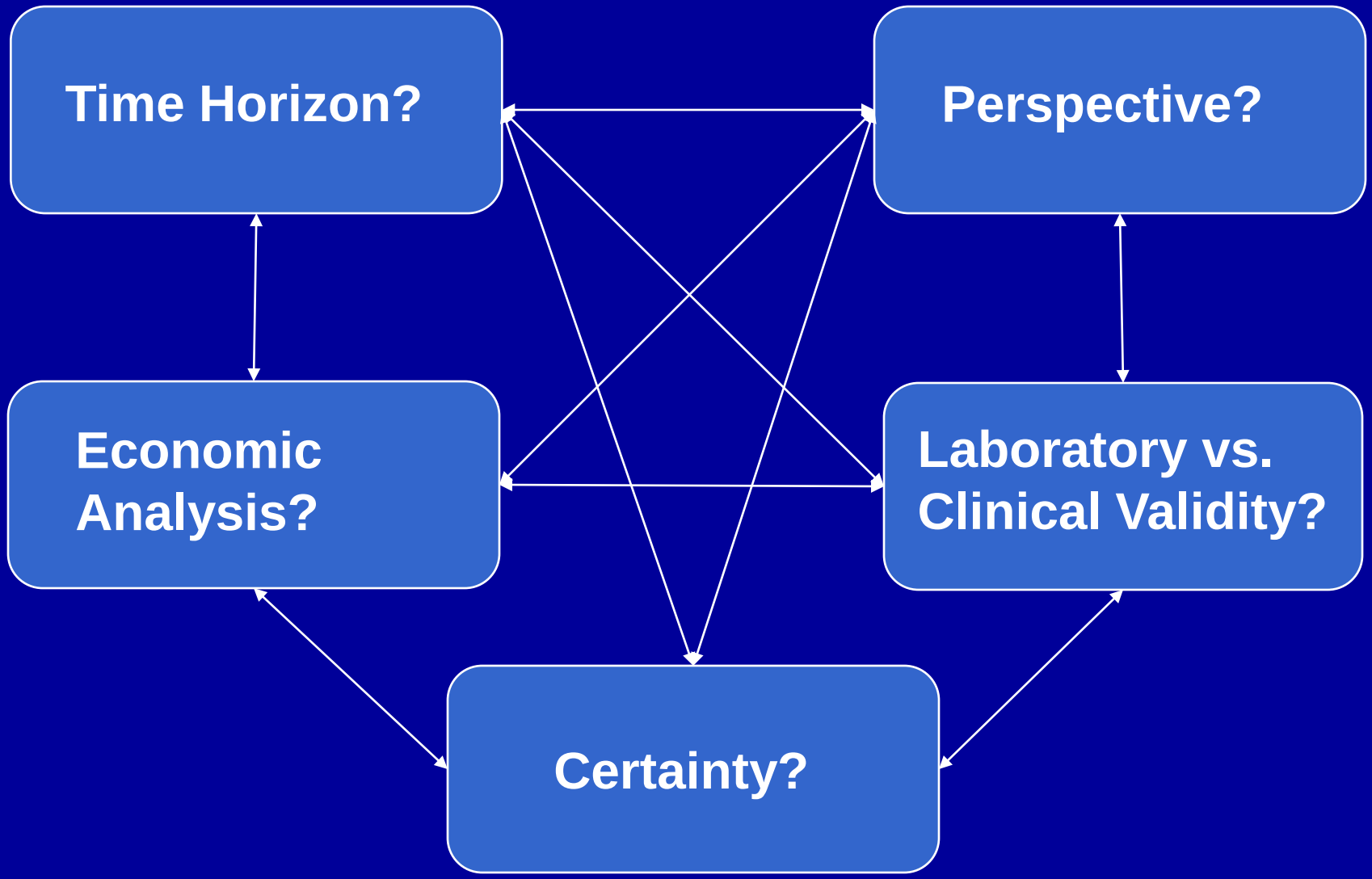

**Individual / Family Benefits**

- Decreased mortality
- Decreased morbidity
- Improved quality of life

**Individual / Family Harms**

- False positives
- Difficulty establishing the diagnosis
- Carrier identification
- Identification of an adult-onset condition
- Little prognostic information
- Lack of health services

# Web of Considerations



# Unique Challenges

- Case definitions
- Describing and evaluating harms
- Describing benefit outside of early childhood
- Economic evaluation
- Grading the evidence

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# Case Definition

- Guides the review
  - What is in
  - What is out
- Previous approach – Nominations Workgroup and decisions by the ERW
- New approach – Technical Expert Panel, with final approval from the Nominations Workgroup

# Grading the Evidence

- Assessing:
  1. Analytic validity
  2. Quality of data sources
  3. Study quality
  4. Adequacy of the evidence or the strength of linkages in the chain of evidence

- Calonge N, Green NS, Rinaldo P, et al. Committee report: Method for evaluating conditions nominated for population-based screening of newborns and children. *Genet Med*. 2010;12:153-159.

# Analytic Validity

- Consider separately
  - Preanalytic phase
  - Analytic Phase
  - Postanalytic phase

# Quality of Data Sources

- Level 1 – usually good quality evidence
- Level 2 – usually fair quality evidence
- Level 3 – usually fair or poor quality evidence
- Level 4 – usually poor quality evidence
- Level 5 – usually poor quality evidence

# Assessing Study Quality

1. Clear description of test or disorder/phenotype and outcomes
2. Adequate description of study design and methods
3. Interventions clearly identified, scientifically sound, consistently provided
4. Adequate description of the basis of the “right answer”
5. Avoidance of biases
6. Appropriateness of the data analysis

# Other Approaches

- USPSTF
- AAP – variable
- IOM – in development
- Cochrane
- EPC http://www.ahrq.gov/clinic/epcpartner/
- GRADE

# GRADE

- Grading of Recommendations Assessment, Development and Evaluation Working group: http://www.gradeworkinggroup.org
- Goal: single system to avoid confusion

# GRADE

- High – further research is very unlikely to change our confidence in the estimate of effect
- Moderate – further research is likely to have an important impact on our confidence in the estimate of effect
- Low – further research is very likely to have an important impact on our confidence of effect
- Very low – any estimate of effect is very uncertain

# GRADE

| | |
|---|---|
| Type of evidence | Randomized trial = high<br>Observational study = low<br>Any other evidence = very low |
| Decrease grade if | • Serious or very serious limitation to study quality<br>• Important inconsistency<br>• Some or major uncertainty about directness<br>• Imprecise or sparse data<br>• High probability of reporting bias |
| Increase grade if | • Strong evidence of association—significant relative risk of > 2 ( < 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)<br>• Very strong evidence of association—significant relative risk of > 5 ( < 0.2) based on direct evidence with no major threats to validity (+2)<br>• Evidence of a dose response gradient (+1)<br>• All plausible confounders would have reduced the effect (+1) |

# GRADE

- Challenges for the ERW
  - Most evidence will be low or very low
  - A document to help with diagnostic testing is under development

# Potential Solution

- Approach – modifed from the EPC
  - Technical Expert Panel to help guide evidence abstraction
  - Publishing analytic framework, key questions, includes/excludes on a website for comment
  - Final approval from the Nominations Workgroup
- Advantages – transparency, broader considerations before developing the report
- Disadvantages - time

# Harms

- Often not reported in reports
  - Not recognized
  - Judgments made about their impact relative to potential benefits before they are reported in reports
  - Cateloging harms based on expert opinion is challenging and prone to bias
- Unable to model without denominator information

# Future Plans

- TEP to clarify
  - Case definitions
  - Analytic Framework
- Embase
- Posting on the web
- Manual of procedures
- Modeling (when possible)