

The Role of Explicit and Evidence-based Processes for Making Recommendations Regarding Newborn Screening

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- U.S. Preventive Services Task Force.
 - GRADE Working Group: Grading quality of Evidence and strength of recommendations. BMJ 2004;328:1490-4.
- West and Lohr
 - Rating Systems for Strength of Scientific Evidence (www.ahrq.gov/clinic/epcsums/strengthsum.htm)
- NIH Consensus Development Conferences
- CMS Medical Coverage Advisory Committee
- GRADE Working Group
 - Grading quality of evidence and strength of recommendation. BMJ 2004;328:1490-4.

Goals of Explicit, Evidence-based Approach

- Credibility
- Transparency
 - People can understand what you did
- Reproducibility, limit bias
 - Different people would get same result
- Identify gaps in evidence
 - Highlight where we need better evidence
- Reduce the chance of “getting it wrong”

Components of Explicit Approach

- Identify target population and audience
- Identify topics for consideration
- Define outcomes of interest
- Define what evidence is relevant
- Evaluate quality of evidence
- Tie recommendations to strength of evidence

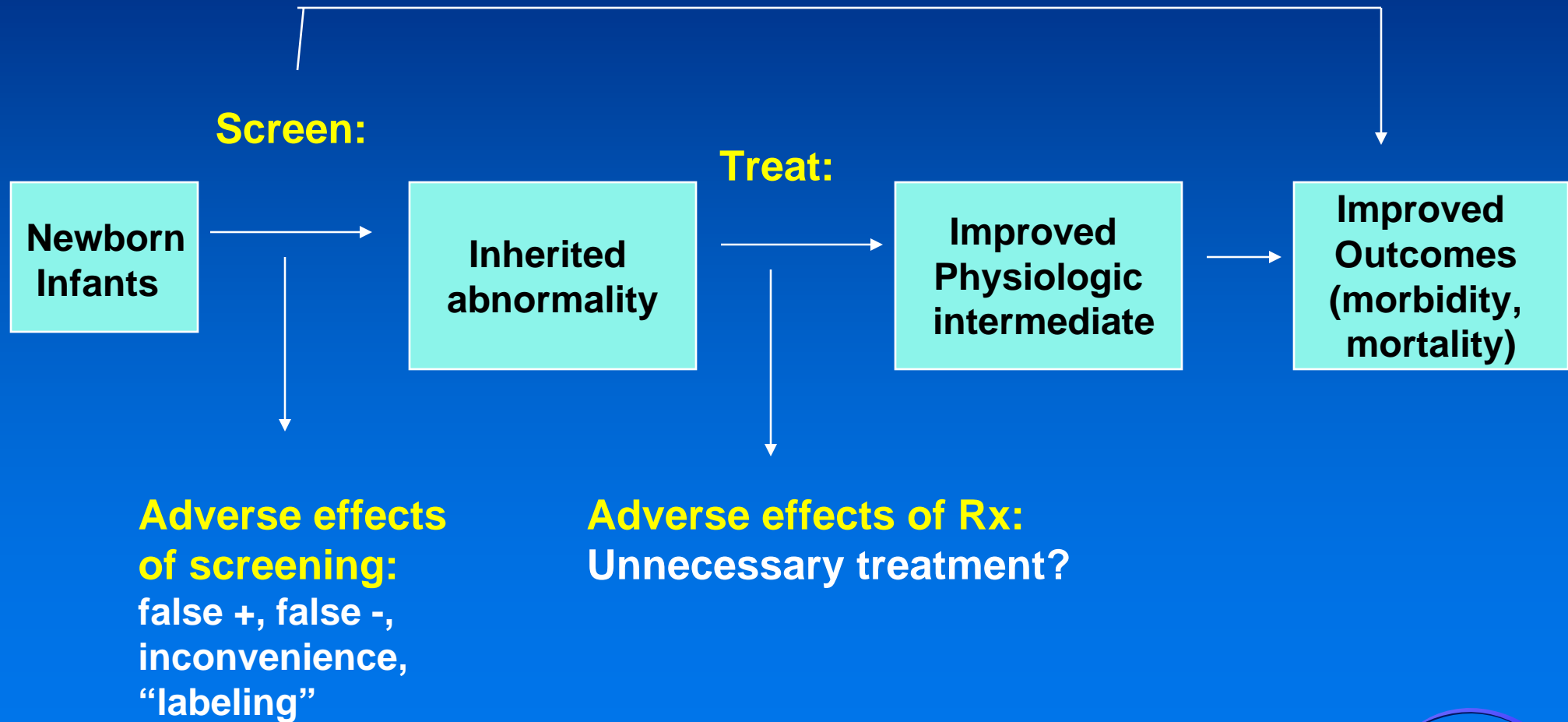
Explicit, Evidence-based Process DOES NOT:

- Require evidence from RCTs
- Exclude consideration of expert opinion
- Exclude input of other stakeholders
- Prohibit recommendations in the face of poor evidence

Explicit, Evidence-based Process DOES SPECIFY:

- Questions to be answered
- Consistent process for reviewing evidence
- Procedures to reduce bias and conflict of interest
- Role of evidence vs. other factors in recommendation
- Which recommendations based on evidence of improved outcomes vs. other considerations

Newborn Screening -Analytic Framework



1. Target Population and Audience

- Population: Infants born in the US
- Audiences:
 - State screening programs
 - Clinicians (generalists and experts)
 - Parents
 - Public health practitioners
 - Policy makers

2. Identify Topics for Consideration

- Specify criteria that would justify review
 - E.g. available test, burden of disease, etc.
- Solicit nominations of candidate topics
 - From experts, public, programs, industry
 - Request background info with nomination
- Assess each topic against criteria
- Panel votes on priorities for review

3. Specify Outcomes of Interest

- Reducing morbidity and mortality in infants with inherited disorders
- Reducing impact of inherited disorders on family and society
- ? Minimizing harms to healthy infants and their families
- ? Ensuring efficient use of resources of newborn screening programs

4. Define Relevant Evidence

- Issue: evidence is limited for many rare newborn conditions
- Need to expand review beyond most rigorous study designs without including invalid findings
- Role of panel: *define* general standards against which to judge evidence
- Evidence review: *evaluate* evidence against those standards

Setting the Bar



[D]

5. Judging Quality of Evidence

- Individual studies – Should I trust this result?
- Body of evidence – Can I answer the question at hand from the available evidence?
- Balance of benefits and harms – Can I be sure this intervention will do more good than harm?

5A. Assessing Quality of Individual Studies

- GOAL: Identify those studies least likely to be biased (*internal validity*)
- Quality is function of:
 - study design (e.g., RCT or controlled cohort vs. case series)
 - study execution (e.g., loss to follow-up)
- Critical elements vary by topic

What do we mean by “quality?”

- “Extent to which a study’s design, conduct, and analysis has minimized selection, measurement, and confounding biases.”
 - Lohr and Carey, *J Clin Qual Improvement*, 1999
- “Extent to which one can be confident that an estimate of effect is correct”
 - GRADE, *BMJ*, 2004

Assessing Individual Studies -- Treatment

- Study design – can I be sure the effects are due to treatment (control group?)
- Few controlled studies in this area
- What are sources of bias in uncontrolled case series?
- Can we be sure what clinical course would have been without treatment?
- Is population comparable?

Assessing Individual Studies - Diagnosis

- Is patient population representative of newborns who will get this test?
- Are results generalizable to typical practice in state screening programs?
- Have tests been confirmed with accepted gold-standard test?
- Can sensitivity/specificity/positive predictive value be calculated?

5B. Assessing Quality of a Body of Evidence

- **Internal validity** – are studies designed to minimize bias?
- **External validity** – are populations and interventions generalizable to typical practice?
- **Consistency** – are results of different studies are consistent?
- **Quantity** – Adequate number and size of studies?
- **“Directness”** – Do studies directly address intervention and outcome of interest?

Considering Harms Of Screening

- All screening tests have harms
- “False positive” results from:
 - Technical limitations of the test
 - Errors in lab process
 - Variability in clinical consequences
- Harms include:
 - Psychological harms to parents
 - Downstream testing
 - Unnecessary and possibly harmful treatment
 - Economic costs (without benefits)
- Need to consider “real world” harms

6. Link Recommendation to Strength of Evidence

STRENGTH OF RECOMMENDATION (FROM GRADE):

The extent to which one can be confident that ... a recommendation will do more good than harm.

- **quality of the evidence (for benefits and harms)**
- **trade-offs** (the relative value attached to the expected benefits, harms and costs)
- **ability to translate evidence** into practice in a specific setting

US Preventive Services Task Force

A - Strongly recommend

good evidence, benefits substantially outweigh harms

B - Recommend

at least fair evidence, benefits outweigh harms

C - Insufficient evidence

Uncertain balance of benefits and harms -- lack of evidence on clinical outcomes, poor quality of existing studies, or conflicting results – may make recommendations based on other grounds

7. What other considerations are relevant to recommendations?

- Equity
- Prevailing practice
- Parent/society preferences
- Feasibility
- Costs
- Resources

Economic evaluation

- Rarely used explicitly in recommendations
- Can't ignore costs in current environment
- Use of cost analysis often superficial or misleading
 - Can't tell cost impact from cost of test alone
 - Can't compare simply to cost of undetected case
- Need to consider downstream costs of testing, including follow-up testing, referral and treatment

Obtaining Input From Families and Public

- Need to consider input from affected families
- Need to balance against interests of all children
- Difficult to get representative sample of both

Obtaining Expert Opinion

- Might consider in face of poor evidence
- Need unbiased sample of opinion
- DON'T only consider those who feel strongly
- Content experts may be better at assessing components (e.g. is test accurate?) than in integrating tradeoffs (is screening worthwhile?)

Making Recommendations in the Face of Poor Evidence

- "Expert consensus"
- Extrapolations from other data
- Magnitude of problem
- Potential benefits vs. harms
- Clinical tradition

Approaches to Recommendations in Face of Poor Evidence

- “Primum non nocere” – First do no harm
 - Large majority of infants have much higher chance of being harmed than of benefiting
- Recommend on other grounds
 - Expert opinion, potential benefits, patient family preference,

Possible levels of recommendation for newborn screening

- Good evidence on accuracy of test, clinical implications of positive test, and effectiveness and safety of intervention -- RECOMMEND
- Some evidence but important limitations in evidence on prognosis or effectiveness -- CONSIDER IN PILOT PROGRAM
- Insufficient evidence - DEFER DECISION, IDENTIFY RESEARCH NEEDS

Conflict of Interest

- “Is this person predisposed to a certain outcome?”
- Perceived as well as real conflict
- Committee: deal with conflicts through disclosure, balance of conflicts, recusal if needed
- Conflicts should be avoided as much as possible in review process
- Challenge: incorporate appropriate content expertise without such close involvement that it may pose a conflict

Recommendations

- Clarify standards for evidence and for recommendations
 - If costs are relevant, do appropriate analysis
 - Consider methodologist on committee
- Separate process for evidence review from process for recommendations
- Ensure representation of all stakeholders
- Formalize process for outside review

Role of Committee

- To represent all key stakeholders
- Develops criteria for recommendations
- Identify key questions to be addressed
- Review summary of evidence
- Weigh other considerations
- Make recommendations

Role of Evidence Review

- Systematic search for relevant information
- Objective synthesis of evidence
 - Predetermined criteria
 - Avoid conflict of interest
- Combine expertise in research methodology and in content area
- Address criticisms from peer review