Review of the ACHDNC Process
Part I: Systematic Evidence Review

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

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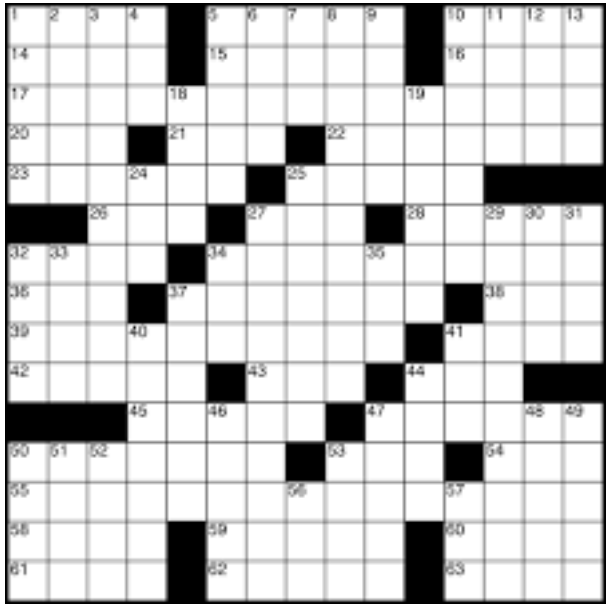
Key Issue: How can we best synthesize the available evidence to inform the Advisory Committee

- This presentation is about evidence review, not the decision process



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Background

- In March 2019, we provided a summary of an in-person meeting that was recently held to address the process through which a condition is considered for or included in the RUSP, including
  - Nomination
  - Evidence Review Process
  - Decision Making
- The meeting also included a consideration of how to review conditions already on the RUSP

Objective

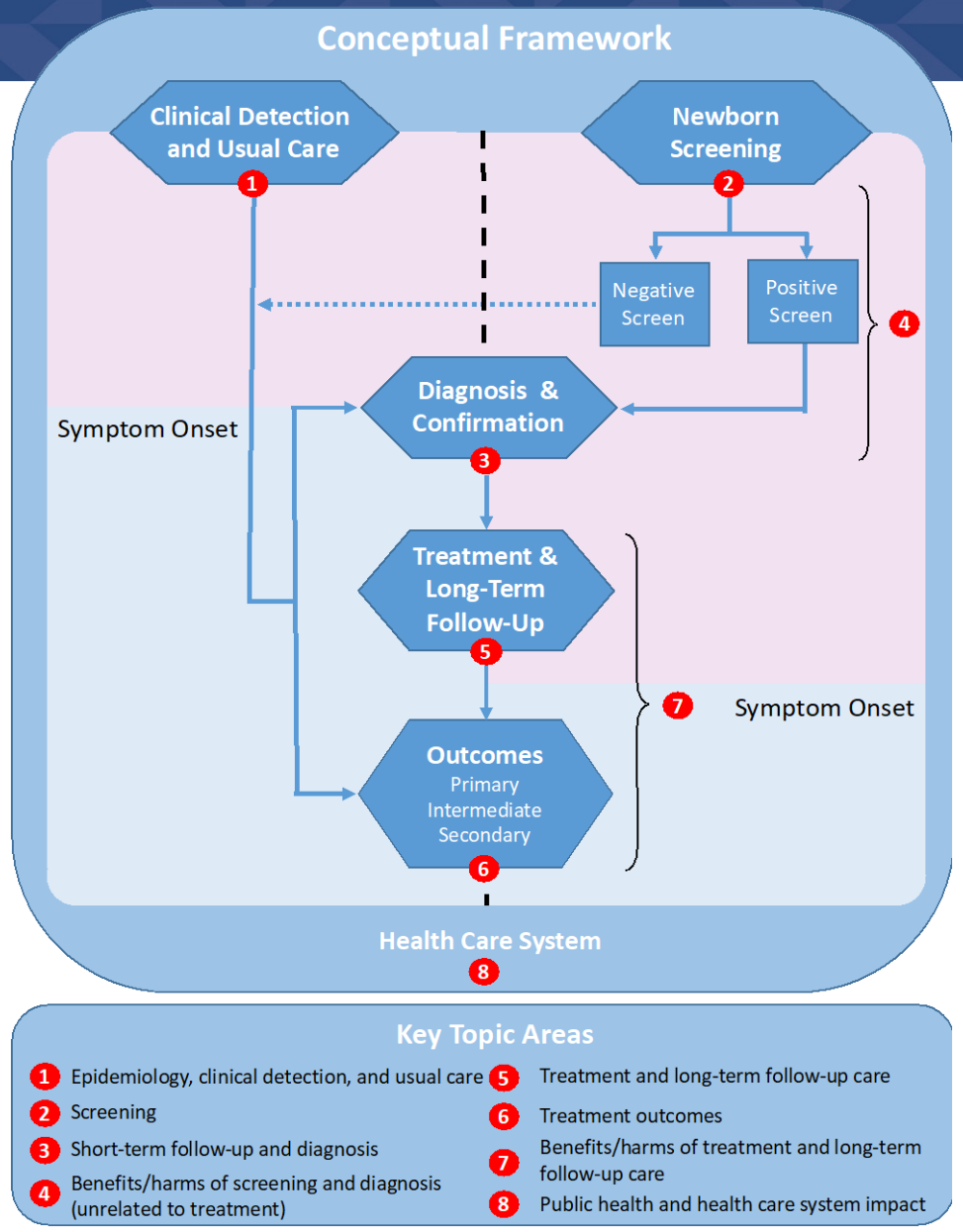
- Inform the ACHDNC about ways to strengthen the evidence review and develop a manual of procedures

Timeline

- Summary report, due March 2020
  - Facilitated discussions, led in partnership with Dr. Powell, at each of the ACHDNC meetings over the next year
    - April 2019: Systematic evidence review
    - August 2019: Values, cost assessment, population-level modeling, public health system assessment
    - November 2019: Decision matrix
    - February 2020: Review of the RUSP, Nomination Process
  - Of course, engagement in between these meetings

For today – focus on what additional information is needed from the evidence review

Not to resolve all of the thorny and complex issues



Key components of the review:

- Effectiveness of newborn screening
- Benefits and harms of newborn screening compared to usual case detection
- Public health and health care system impact

Consider the outcomes and the time horizon

Optimized for the time constraints of the evidence-review process

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Topics for Today

- Case definition
- Key outcomes
- Treatment
- Assessing the peer-reviewed evidence
- Identifying and assessing unpublished evidence

Case Definitions

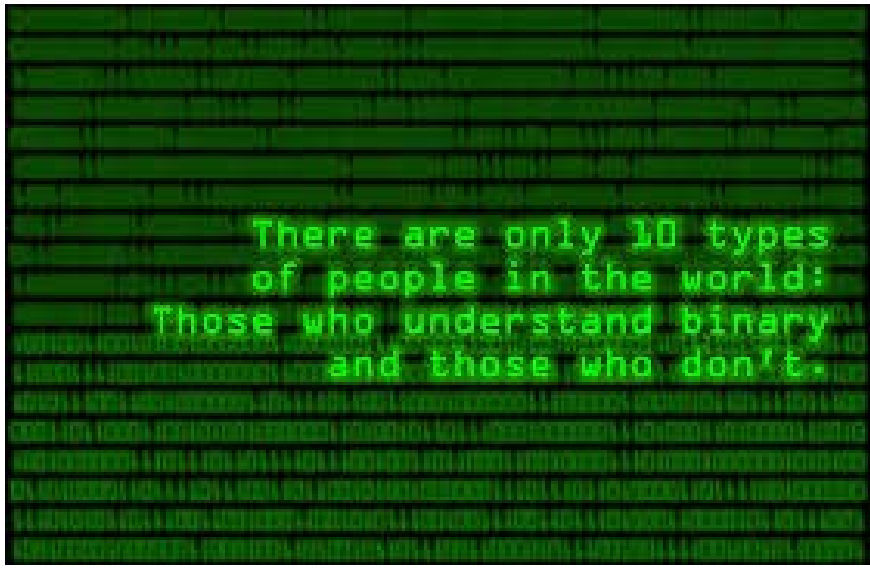
- What defines a condition detected through screening when the potentially affected individual might be asymptomatic?
  - Genotype
    - But there might not be a clear genotype-phenotype correlation or incomplete penetrance and variable expressivity
  - Biochemical
    - But there are challenges with pseudodeficiency and changes in biochemical profile over time
  - Clinical
    - But signs or symptoms might not emerge when asymptomatic and early treatment might significantly alter the course

Case Definitions

- Need to standardize terminology
  - Primary target
  - Secondary target
  - Incidental findings
- Challenges related to
  - Understanding of the condition
  - Agreement about the goal of screening (e.g., identification of carriers or late-onset disease)
  - State newborn screening program reporting requirements

Case Definitions

- As a clinician, I like case definitions to be binary, but most conditions are not
  - For example, congenital hypothyroidism or cystic fibrosis
- Significant implications for evidence review



Draft Plan

- Case definitions, stratified by whether they reflect primary or secondary targets, should be specified when evidence review begins
- The evidence review will continue to focus on the primary and important secondary targets and catalog incidental findings as they are identified during the review

Deciding on Key Outcomes

- Goal: Prespecify expected outcomes of interest
  - Harms
  - Benefits
- Will continue to be open to new outcomes of interest identified during the review

Benefits We Have Considered in Previous Evidence Reviews

- Mortality
- Morbidity
  - Length of life
  - Ventilator-free survival
  - Neurological and motor function
    - Mobility
    - Communication

Harms We Have Tried to Consider in Previous Evidence Reviews

- Screening
  - Pain or other adverse impacts from screening or diagnostic testing
  - False positives
  - False negatives
- After diagnosis
  - Earlier exposure to treatment adverse effects
  - Psychosocial harm from uncertainty of outcomes

What About Other Benefits and Harms?

- Intermediate outcomes – consider the link to patient-centered outcomes
  - Biomarkers (e.g., phenylalanine, bilirubin)
  - Imaging findings (e.g., head MRI)
- Quality of life
- Outcomes for the family
  - Avoidance of the diagnostic odyssey
  - Diagnosis in other family members
  - Ability for families to develop plans for the future

What About Other Benefits and Harms?

- The search will describe outcomes included in previous research
- Beyond the scope of the review to develop new evidence on outcomes that have not been previously described

Draft Plans

- Will continue to look at full range of benefits and harms to the individual as reported in publications
- Focus on the comparison group
- The time horizon will depend on the available data
  - Is there a minimum time horizon?
- The Committee may need to consider how to weigh evidence in the decision process related to outcomes to families

Treatment

- We have focused on FDA-approved indications
- What about
  - Therapies in development?
  - Supportive therapies for the affected individual or for the family?
- How should availability of treatment be considered in the review?

Draft Plans

- Will include specific treatments identified at the start of the review and catalog other treatments
- The review describes what is involved with specific treatments. However, availability may not be clear through systematic evidence review. Other approaches will be needed.

Assessing Peer-Reviewed Published Evidence

- For screening and treatment:
  - Number of studies and observations for each study design
  - Summary of findings
  - Consistency/precision
  - Estimates of potential reporting bias
  - Overall study quality
  - Body of evidence limitations
  - Applicability
  - Overall Strength of evidence

Adequacy of Evidence for Screening and Treatment

1. Do the studies have the appropriate research design (e.g., RCTs, population-based observational studies, etc.)?
2. To what extent are the existing studies of sufficient quality? A key consideration will include having an appropriate comparator.
3. To what extent are the results generalizable to newborn screening?
4. How many and how large are the relevant studies? Are the results precise?
5. How consistent are the results of the studies?
6. Are there additional factors that assist in drawing conclusions (e.g., fit within a biological model)?

https://www.uspreventiveservicestaskforce.org/Page/Name/section-6-methods-for-arriving-at-a-recommendation

Rating the Quality of the Evidence

- GRADE: "…a particular level of quality does not imply a particular strength of recommendation…"
  - High – Very confident that the true effect lies close to the estimate
  - Moderate – Moderately confident
  - Low – limited confidence
  - Very Low – Very little confidence
- Small case series are difficult to rate

Draft Plans

- Assess quality of evidence for RCTs and observational studies
- Case series will be included
  - Strengths and weaknesses summarized qualitatively but not assigned a specific quality rating

Gray Literature

- Has been most helpful for
  - Accuracy of Screening and process for diagnostic confirmation
  - Treatment
- Examples of gray literature
  - Newborn screening program data
  - Regulatory documents
  - Study protocols
  - Research in progress

Where to Find Gray Literature

These can be found through searches:

- ClinicalTrials.gov and the International Clinical Trials Registry Platform
- Funding agencies (e.g., NIH Research Portfolio Online Reporting Tools)
- Cochrane Central Register of Controlled Trials
- FDA and European Medical Agency
- Conference abstracts and proceedings
- Authors (standard approach needed)
- Study sponsors (standard approach needed)
- Registries (standard approach needed)

https://www.ncbi.nlm.nih.gov/books/NBK174882/

Assessing Gray Literature

- Lowest risk of bias: primary data from newborn screening programs
- We will develop a broad categorization of the risk of bias for gray literature

Draft Plans

- Continue to review trial registries, conference proceedings, and seek information provided to FDA regarding specific treatments
- Develop a standardized form to collect gray literature from those in the field

Questions?