Review of the Advisory Committee Process: Final Report on Proposed Next Steps

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

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By

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Background

- In February 2019, convened an Expert Advisory Panel (EAP) meeting to address the process through which a condition is considered for or included in the RUSP.

Objective

- Inform the ACHDNC about ways to strengthen the evidence review and decision-making process
- Develop consumer friendly guidance to enhance transparency about the process and any changes.

Focus Areas and Subtopics

Focus Areas	Subtopics
Nomination	Nomination Form and Process
Evidence-Based Review	• Assessing published evidence • Assessing Unpublished evidence • Assessing Public Health System Impact • Assessing Values from Different Perspectives
Decision Matrix	
Review of Conditions on the RUSP	(Not currently done regularly)

Guiding Questions

1. *What issues or changes are needed in Committee process?*
2. *Next steps? How can we address the issues?*
3. *Which actions can be done immediately*? Which need further discussion, research, or policy change?

Approach to Reviewing the Committee Process

- Convene the Expert Advisory Panel to gather expert opinion
- Present and facilitate discussion with Advisory Committee and stakeholders
- Summarize issues, propose next steps
- Categorize proposed next steps by actionability:
  - actionable now, needs further discussion, needs further research, needs policy or system change
- Convene Ad Hoc Committee Process Workgroup to review proposed next steps
- Present final proposed next steps to Advisory Committee

Timeline of Approach for the Review of Committee Process

Dates	Activity
Feb 5-6 2019	Expert Advisory Panel (EAP) convened to review the process
March 2019	Presented overview of plan to review Committee methods; summary of EAP meeting
April 2019	Presented systematic evidence review and population-level health
July 2019	Presented Public Health Impact Assessment
Sept 2019 – July 2020	*(Legislative and pandemic hiatus)*
August 2020	Presented recap of progress and considerations regarding values assessment
August 2020	Presented assessing values – approaches, newborn screening decision-making considerations
December 1 2020	Presented decision-making and decision matrix
February 11 2021	Presented evaluating conditions on the RUSP; nomination process/form
May 24, June 11 2021	Ad Hoc Committee Processes Review Workgroup reviewed preliminary next steps
August 11 2021	Presented final report on review of Committee processes; Summary of proposed next steps

Summary of Issues Identified

Revisiting the Nomination Process

Issue	Actionability
Guidance about the process from HRSA or the Committee is limited, about the process itself, or specific criteria considered for nominations.	Actionable - Consumer guidance and Nomination FAQ to be developed and posted to the Committee's website
Information requested from the nomination form does not directly link to specific and relevant information needed for the evidence review, in areas such as registries, unpublished evidence, the screening algorithm and resources, and long-term follow up, etc.	Actionable - Revisions proposed for the Nomination Form. New nomination form posted on Committee website in FY22

Revisiting the Nomination Process (cont)

Issue	Actionability
No systematic review or landscape scan in the nomination package. NPWG review relies on potentially biased presentation of evidence. Given the limited time to complete evidence reviews, and issues raised about case definitions and critical outcomes sometimes changing over the course of the interview, EAP members encouraged considering a scoping review at some point during NPWG review. A scoping review could assist in the a) systematic consideration of key evidence, removing bias from the nomination package, preliminary identification of critical outcomes for the condition, those outcomes for which evidence was available, as well as critical gaps in evidence. Challenges: • Addition of a scoping review or landscape scan would require development of new procedures. • Time and resources required for the additional review component.	No Committee Action Taken at this Time • Further discussion • Further research • Possible policy/budget implications

Evidence-Based Reviews: Assessing Published Evidence

Issue	Actionability
The case definition is not always clear for screening and clinical purposes. Case definition may evolve over the course of the evidence review re: clinical phenotype, screening, incidence/prevalence.	• Actionable – Adopted into Committee Processes FY22 The case definition should specify screening targets and any other secondary or incidental findings which may be identified. Case definitions should consider screening procedures. Changes in case definition based on evidence should be raised early in the review and presented to the Committee.
• Critical outcomes considered are dependent on availability of evidence. • No a priori specification of critical outcomes. • Patient/family or other values not considered.	• Actionable – Adopted into Committee Processes FY22 Important and critical outcomes to be identified a priori, with evidence review informing which are available and other literature gaps. • Further Discussion Ranking of stakeholder importance will require further discussion re: how rankings could be gathered, when in the process, and whose rankings. Suggested list of primary outcomes or outcomes of interest, with input on the importance of these outcomes by different stakeholder (Committee, family, general public).

Evidence-based Reviews: Assessing Unpublished Evidence

Issue	Actionability
Develop a systematic and transparent framework for incorporating expert-derived evidence: Evidence reviews for rare diseases require adaptations to standard review approaches, to continue to assess risk of bias, particularly for inclusion of gray literature and other unpublished evidence that is reviewed.	• Actionable – Ready for Implementation The ERG will expand current procedures for assessing gray literature, and incorporate standard procedures used in GRADE to collect expert-derived evidence to supplement unpublished evidence. Once relevant meeting abstracts or other unpublished sources have been identified in the evidence review, if information available is not sufficient to assess quality and bias risk, the ERG will request further information from the investigators/authors.
Registry data and other sources of data: EAP meeting attendees agreed that conducting new analyses on unpublished data within the time frame allotted for review is challenging from a timeframe standpoint, but also poses issues due to the data and analysis not being peer reviewed.	• Actionable – Ready for Implementation Registry and other unpublished sources of data will be considered and reviewed as unpublished evidence (see above).

Evidence-Based Reviews:
Assessing the Public Health System Impact, Including Costs

Issues	Actionability
The PHSI does not capture the process of states expanding newborn screening to their panel (i.e., the challenges in obtaining authority to screen, and funding).	• Actionable – Done – Ready for Implementation • PHSI Survey revisions made • NewSTEPs Readiness Tool captures states overall readiness to expand, including start-up process
The PHSI Survey yields results that provide only limited information (e.g., limited response options do not capture full ranges of estimated time to screen)	• Actionable – Done – Ready for Implementation PHSI Survey revisions made (presented to Committee) and approved by OMB.
Current PHSI findings re: cost estimates are not widely generalizable to all newborn screening programs, especially re: resources and costs.	• Actionable – Ready for Implementation • The PHSI cost assessment results will report cost estimates in general terms (vs point estimate ranges).
The PHSI does not consider or assess long-term follow-up plans and anticipated costs for conditions nominated for addition to the RUSP. This includes the diagnostic testing, treatment, and possible longitudinal surveillance.	• Further Discussion • Further Research • Possible Policy Change

Revisiting the Decision Matrix

Issue	Actionability
Communication regarding purpose of the decision matrix is lacking, and impacting consistency and transparency. The matrix is a complex tool. How the Committee assess criteria, comes up with matrix ratings, and makes recommendations from the decision matrix is unclear. B-ratings (moderate certainty of evidence) – guidance is scant and limited for the complexity of conditions being considered by the Committee. B-ratings from last few conditions are not entirely clear. Net-benefit – also unclear exactly what should be considered in the net benefit, sum total of benefits and harms. Descriptions for each criterion within the decision matrix are limited for the complexity of conditions being considered.	• Actionable - additional guidance drafted • Further discussion is needed to develop guidance for B-ratings.

Revisiting the Decision Matrix (cont)

Issue	Rationale	Actionability
The decision matrix includes only 2 recommendation votes: Y or N. No specific recommendation covers provisional or conditional recommendations for specific evidence needed.	Recent conditions reviewed have some uncertainty, and need further research. Conditional or provisional could highlight specific gap areas to encourage research in that area.	<u>No Action Taken at this Time</u> It was also noted that the Committee has voted no to adding to the RUSP, and provided specific requirements that are needed for further consideration (e.g., SCID, GAMT). After consideration this method is appropriate.
Conditions are nominated and considered one-at-a-time.	Future reviews might include closely related conditions nomination in panels in the future (e.g., lysosomal storage disorders, intellectual disabilities) instead of one condition at a time.	<u>No Action Taken at this Time</u>

Values Assessments from Stakeholders

Issue	Actionability
• Patient/family perspectives. The Committee's process does not currently assess values of different stakeholders, particularly the patients and families most impacted. Family preferences for which outcomes are most critical/important, or how they prioritize changes in those outcomes due to screening, are not taken into account. • Assessing public perspectives: Public perspectives on expanding newborn screening are not considered by the Committee. As a public health program, the impact of newborn screening on the public should be considered. Challenges • Published data on values are limited, not usually generalizable, and have a high risk of bias. • Assessing public perspectives that are representative of the public, and also have some knowledge of newborn screening is challenging and resource intensive.	<u>No Action Taken at this Time</u> • Further discussion • Further research • Possible policy/budget implications

Reconsideration of Conditions on the RUSP

Issue	Actionability
More evidence is available post-RUSP regarding epidemiology (changes in incidence and phenotype distribution), net benefit, unforeseen harms, and ongoing costs to implement and follow up newborns who screen positive, or advances in screening or treatment over time – BUT <u>we do not assess this routinely</u>. Would inform states, overall committee recommendations, and further inform needs re: LTFU. Challenges • NBS outcomes not followed up or centrally collected. • What would be the recommendations if newborn screening benefits are not realized?	<u>No Action Taken at this Time</u> • Further discussion • Further research • Possible policy/budget implications

Identify Priority Research & Development Activities

Issues	Actionability
Many issues will require more research and planning. Recommend the Committee identify a list of research priority areas related to newborn screening and its evaluation. • Conditions potentially appropriate for newborn screening • Possible inclusion of values assessment into the evidence reviews • Important research areas related to values, costs, and long-term follow-up.	<u>No Action Taken at this Time</u> • Further discussion • Further research • Possible policy/budget implications

Proposed Next Steps for Each Focus Area

Presented by Dr. Cindy Powell
Committee Chairperson

Key Issues identified with Actionable Next Steps:
Nomination

I. Consumer-friendly Guidance and FAQ on Nomination Process (Available FY22)

II. Revise the Nomination Form (will be adopted FY22)

- Section I – Condition Information and Treatment
  - **Enzyme**
  - Case Definition – **Include the specific case definition for the screening target**
  - Incidence – **Include U.S. incidence estimate and citation**
  - Timing of Clinical Onset – **for phenotypes that would be detected**.
  - Severity of Disease – **Include U.S. distribution/prevalence of known phenotypes if applicable.**
  - Modality – **Describe the medical/clinical care required**. **Identify which treatment(s) are current standard of care**.

Key Issues identified with Actionable Next Steps:
Nomination: Revise Nomination Form (continued)

Section I – Condition Information and Treatment (continued)

- **Clinical Indications for Treatment and** Urgency- **clinical indications for the current standard of care treatment(s) identified above? Contraindications for treatment initiation?**
- Efficacy (Benefits) – **known phenotypes**.
- Availability – **Treatment and follow-up available in most hospitals? Major medical centers? Describe the follow-up and specialized treatment centers which may be needed**.

Key Issues identified with Actionable Next Steps
Nomination/Revise Nomination Form (continued)

- Section II – Evidence-Based Information
  - **Modality of Screening Specimen Sample**
  - **Screening Test(s), Platform, and Procedures – Description of the high volume method, instrumentation and if available as part of multi-analyte platform. Disposables – Lan-based analysis or off the shelf kits? FDA approved?**
  - Does the screening algorithm include a second tier test (type of test, availability)? – **Modality of specimen sample for tier 2 test? Screening test.**
  - Clinical Validation – **number of samples run in high-throughput**
  - Analytical Validation – **Has the CDC NBS and Molecular Biology Branch been contacted regarding validation measures**
  - Considerations of Screening, Diagnostic Testing and **Timeliness – critical condition (timeliness perspective?)**
  - **Confirmatory Testing Methods – Include sample(s)/specimen(s) needed**
  - **Clinical and Analytical Validity – Quantitative or qualitative? Sensitivity, specificity**

Key Issues identified with Actionable Next Steps:
Nomination/Revise Nomination Form (continued)

- Section II – Evidence-Based Information
  - **Regulatory Status of Confirmatory Testing – FDA approved? Availability of confirmatory testing, specialized testing centers for referrals?**
  - Location of Prospective Pilot(s) – **U.S./International, if U.S. site, cities/regions**
  - **Screening Method and Algorithm Used in Pilot – Describe screening method, provide flow chart with pilot outcomes, (prospective) confirmatory testing methods**
  - Number of infants Confirmed with Diagnosis **and Outcome - # infants with positive screen vs diagnosed, NBS timeliness information. Evidence about outcomes, time duration of follow-up period, describe plans for longer-term follow-up of newborns detected early.**
  - **Pilot contacts**
  - **States Considering Screening for the Condition/States Currently Screening/Information on State mandates**
  - **Patient Registries or Databases – contact information**
  - **Unpublished data that would inform NBS**

Key Issues identified with Actionable Next Steps:
Evidence-based Review

- Assessing Published Evidence (ready for implementation)
  - Clarify case definition
  - Specify a priori outcomes, identify those available and not available in evidence
- Assessing Unpublished Evidence (ready for implementation)
  - Formalize current procedures and framework for inclusion and assessing
  - Continue to consider registry or unpublished ~~data~~ evidence, applying formal assessment framework (above)
- Public Health System Impact
  - Revised the PHSI Survey (done, ready to implement, i.e., with MPS II)
  - Developed a New Disorder Readiness Tool (done)
  - Will report cost estimates in broad categories rather than point estimates (will be adopted FY22)

Key Issues identified with Actionable Next Steps:
Decision-making Process/Matrix

- **Additional guidance drafted*** re: decision matrix purpose, how to use in deliberations, considering each criterion individually, and how to incorporate into matrix rating (done)
- **Additional guidance drafted*** re: describing each criterion and individual matrix ratings (e.g., high vs. *moderate* vs. low certainty of evidence) (done)

*(*for further discussion)*

Key Issues identified as Needs Discussion, Research, or Policy/System-Wide Change

- **Establish a Plan to Conduct Regular Review of Conditions on the RUSP (further discussion in FY22)**
  - Decisions needed to define the process including:
    - Frequency
    - Process for prioritizing
    - Nominating or selection
    - Considerations and criteria
    - Goals and outcomes
- **Assess Long-term Follow-Up of Newborn Screening (further discussion in FY22)**
  - Impact of NBS
  - Treatment and clinical outcomes, short and longer term
  - Costs of implementation, treatment
  - Impact on health care system and providers
  - Equity and access long term

Key Issues identified as Needs Discussion, Research, or Policy/System-Wide Change (cont)

- **Determine Values of Stakeholders and Include in Decision-Making (further discussion in FY22)**
  - Preferences for NBS, esp. patients/families, public
  - Values and preferences/attitudes re: Critical Outcomes
- **Establish a Priority List of Research and Development Issues (ongoing)**
- **Revisiting the Decision Matrix (further discussion in FY22)**
- **Long-Term Follow-up in Newborn Screening (further discussion in FY22)**

Revisiting the Decision Matrix: Further Discussion

Issues	Actionability
• Communication regarding purpose of the decision matrix is lacking, and impacting consistency and transparency. The Matrix is a complex tool. How the Committee assess criteria, comes up with matrix ratings, and makes recommendations from the decision matrix is unclear. • B-ratings (moderate certainty of evidence) – guidance is scant and limited for the complexity of conditions being considered by the Committee. B-ratings from last few conditions are not entirely clear. • Net-benefit – also unclear exactly what should be considered in the net benefit, sum total of benefits and harms. • Descriptions for each criterion within the decision matrix are limited for the complexity of conditions being considered.	• (Further Discussion in FY22) • Confirm the process of using the decision matrix for the Committee to determine recommendations and set actions. • Additional description of the B-rating can be developed using past reviews with a B-rating and the reasons for the rating, creating a tracker or 'scorecard.' • Consider additional guidance be provided re: Decision Matrix procedures with draft final report, in prep for final presentation, discussion and vote. (done) • Consider further transparency efforts by requiring scoring or rating of each matrix criterion and overall rating be collected with vote. Examples: NIH grant review scoring, the EVIDEM scoring rubric.

Long-term Follow-up in Newborn Screening

(theme across all four focus areas)

Issue	Actionability
Long-term follow-up information is not collected re: plans or screening outcomes or costs. The meeting attendees underscored the importance of describing long-term follow-up plans for conditions nominated for addition to the RUSP. This includes the diagnostic testing, treatment, and possible longitudinal surveillance.	• Further Discussion (FY22) • Further Research • Possible Policy Change
Conduct follow-on assessments screening outcomes, costs, and treatment access and follow up for reviews of RUSP conditions: The meeting attendees further underscored the importance of continuing to assess the cost implications and outcomes after a condition is added to the RUSP. This information could help state public health programs prioritize and budget new screening programs, provide feedback re: the Committee's activities with newborn screening, and also help inform whether treatment access maintains equity of newborn screening, or if gaps and issues need to be addressed.	• Further Discussion (FY22) • Further Research • Possible Policy Change

Key Issues Identified but Removed From Consideration for Feasibility

- Scoping review during NPWG review to address nomination package bias
- Expansion of decision matrix to include conditional or provisional recommendation
- Consideration of multiple conditions concurrently

Questions?