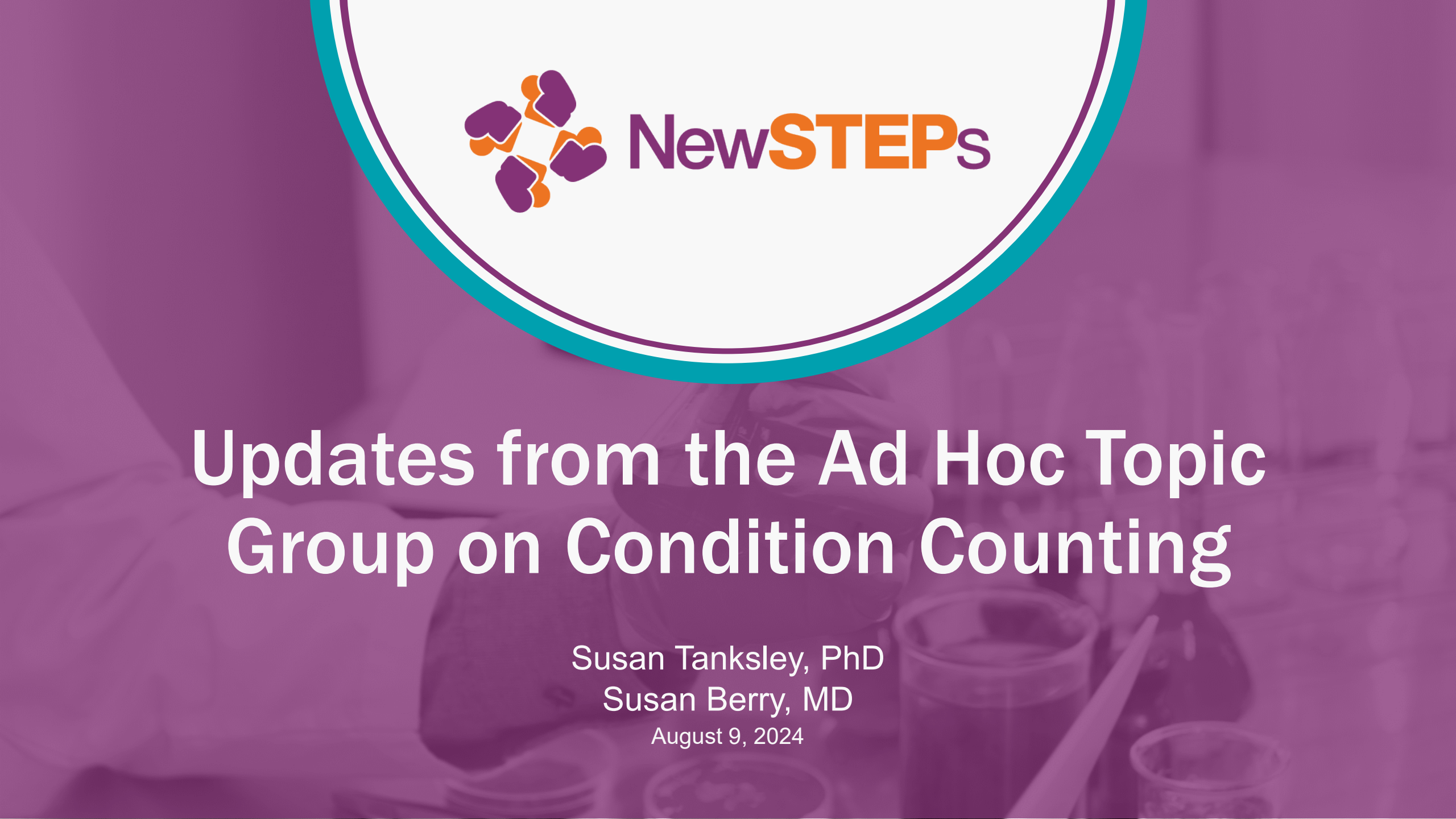


NewSTEPs

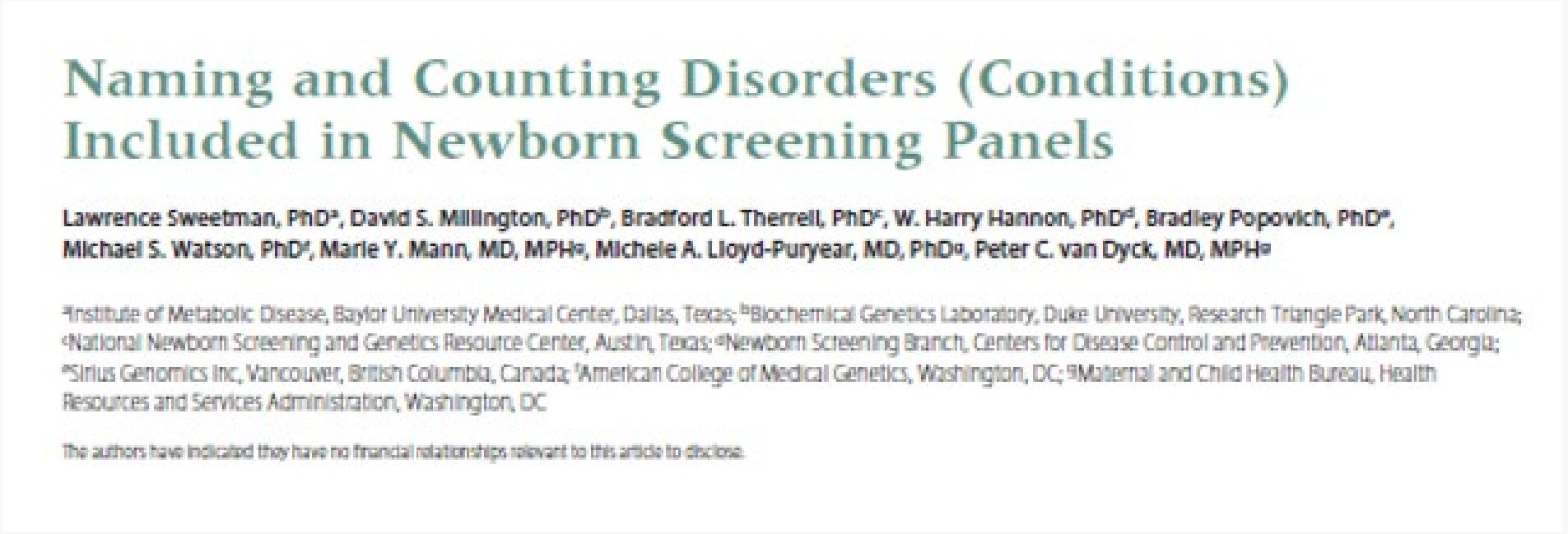
Updates from the Ad Hoc Topic Group on Condition Counting

Susan Tanksley, PhD
Susan Berry, MD

August 9, 2024

Background

16 years ago….



Naming and Counting Disorders (Conditions) Included in Newborn Screening Panels

Lawrence Sweetman, PhD[a], David S. Millington, PhD[b], Bradford L. Therrell, PhD[c], W. Harry Hannon, PhD[d], Bradley Popovich, PhD[e], Michael S. Watson, PhD[f], Marie Y. Mann, MD, MPH[g], Michele A. Lloyd-Puryear, MD, PhD[g], Peter C. van Dyck, MD, MPH[g]

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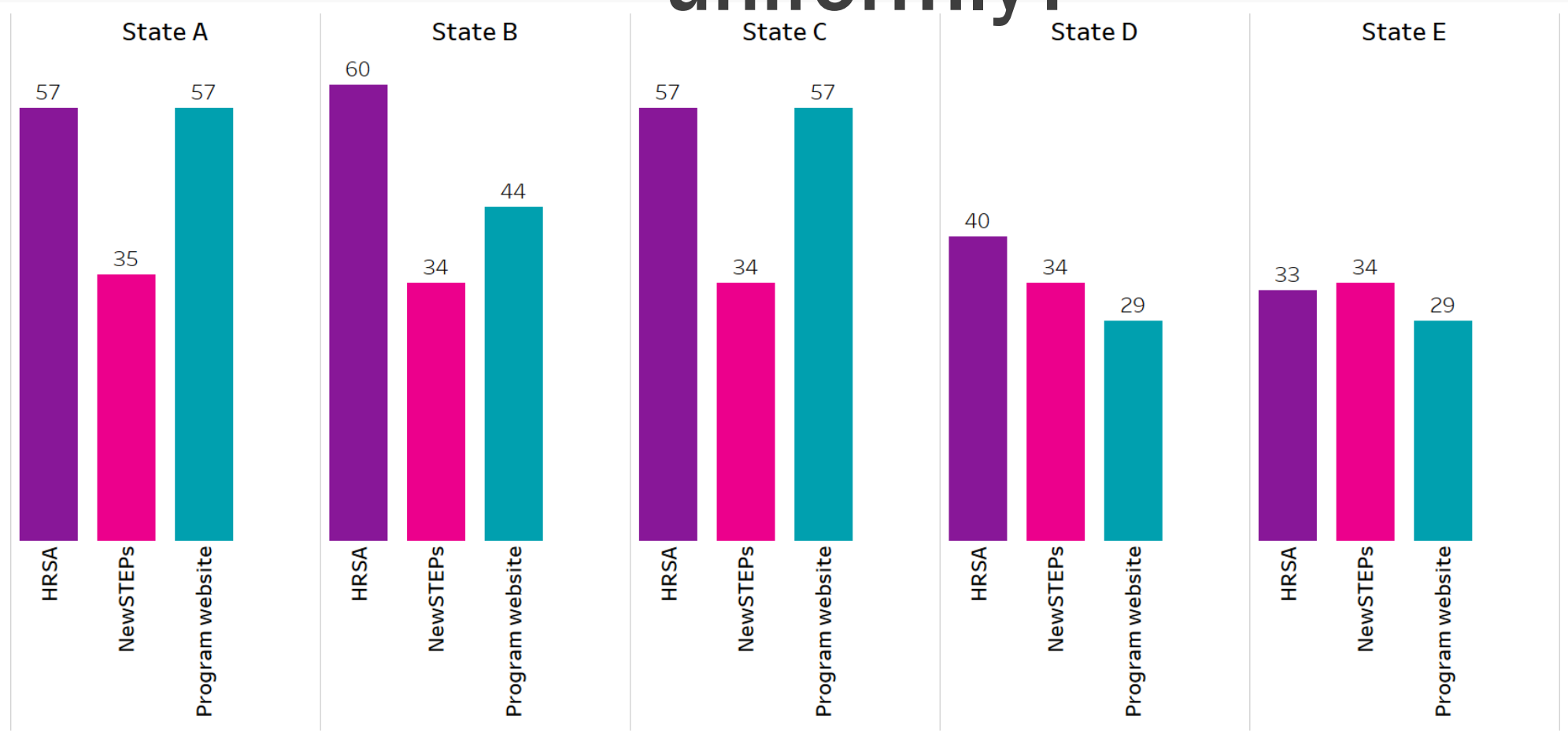
The authors have indicated they have no financial relationships relevant to this article to disclose.

Without national standards in counting or naming, competition developed between public and private labs.

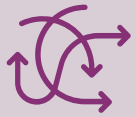
Background: Why count conditions uniformly?



Background: Why count conditions uniformly?

When differences exist in the way conditions are counted on state panels, it may appear that disparities exist…

…when NBS programs, for the most part, actually screen for the same conditions.



This leads to confusion, inaccurate comparisons and program liability.

Original Condition Counting Task Force Scope of Work

- The Association of Public Health Laboratories (APHL) and the newborn screening (NBS) community identified the need for guidance on defining screened conditions for the purpose of harmonizing how conditions are counted on NBS panels
- To improve uniformity across states and decrease confusion among the public, the standardized condition nomenclature should be promoted.
- First met June 2, 2021

Original Condition Counting Taskforce

Developed framework based on two "rules" for counting:

- Count only those conditions a program intends to identify (rather than all conditions that may be detected)
- Count all phenotypes or clinical consequences of a condition as **one** condition even if:
  - The underlying genetic cause is different (e.g., caused by a different gene)
  - The program targets more than one phenotype within the condition spectrum (e.g., infantile and late-onset)

Recommended updating nomenclature of certain conditions:

- e.g., PKU on the RUSP should be changed to phenylalanine hydroxylase deficiency (PAH deficiency)

Presented framework at 2022 NBS Symposium

Launched survey (October 2022) to assess states' ability and/or likelihood to adopt framework

- Most frequent and consistent comment mentioned alignment with the RUSP and endorsement from ACHDNC as necessary in order to adopt the framework

Public Comment to ACHDNC in May 2023

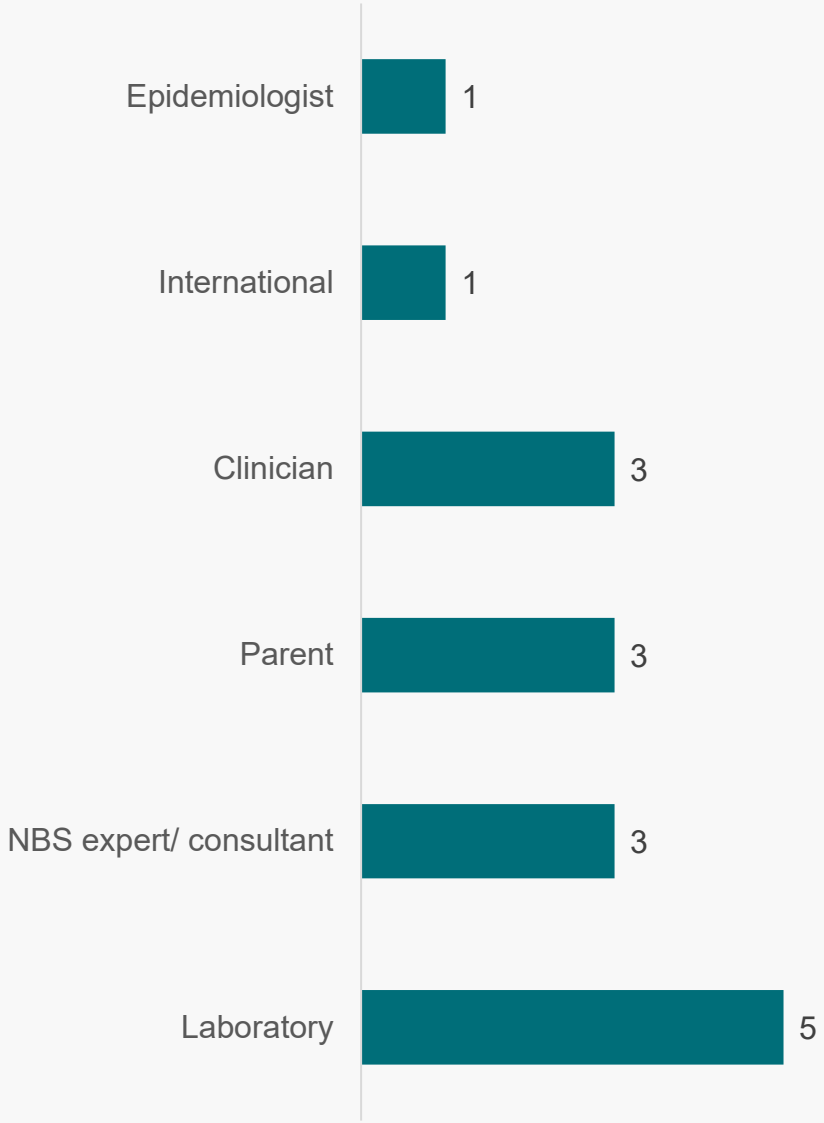
1. Remove all references to “secondary conditions” from the Recommended Uniform Screening Panel (RUSP)
2. Update certain core RUSP condition names and groupings, based on current knowledge of these conditions, in terms of nomenclature and how the conditions are specified or defined on the core panel
3. ACHDNC adoption of the recommendations and communication of the changes will facilitate states’ ability to adopt the framework.

ACHDNC Response

Decision to develop an ad hoc topic group to address uniformity or lack thereof in counting conditions in state NBS programs

Requested APHL NewSTEPs to coordinate the ad hoc topic group

Ad Hoc Topic Group Composition and Expert Advisors



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Loraine Swanson

APHL Hemoglobinopathy Laboratory Workgroup

Kathy Hassell, MD

Endocrinologists:

Ernie Post, MD

Natasha Heather, FRACP, MD

June 2024

In-person meeting

Intent to Screen
Final input

- An NBS program should say it is screening for and list a condition on its panel only when the screening process is optimized to identify the particular condition.

Definition of Optimize

- Optimization of a laboratory screening algorithm involves modifying parameters of the screening algorithm so that:
  - Sensitivity is balanced with an acceptable rate of false positives
  - Cases not identified by NBS are investigated, and the screening algorithm is evaluated to determine if a change to the algorithm would have detected the case and implement the change when feasible.
- Optimization of the laboratory screening algorithm involves a specified cadence of ongoing assessment and adjustments, including receiving screening outcomes, for the purposes of improving NBS laboratory processes.

Phenotype Spectrum
Final input

Input	Examples
A condition should only be listed and counted once, even when a spectrum of severity or multiple subtypes exist	**List and count as one:** Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) and trifunctional protein deficiency (TFP) should be **LCHAD/TFP**
However, programs should indicate when their laboratory algorithm is optimized to detect certain types/phenotypes	i.e., infantile versus later-onset Krabbe Disease
	infantile versus later-onset Pompe Disease
	classic PKU versus hyperphe

Secondary Conditions
Final input

- Apply phenotype spectrum rule to group or rename certain core conditions;
  - Then, ensure that any related conditions not named on RUSP are listed as differential diagnoses or other detectable disorders that can be found in the related ACT sheets for each RUSP condition.
- Request ACHDNC review of all conditions on the secondary list to review evidence or consider for addition to the core list.
- Remove all designations or distinctions between “core” / “primary” and “secondary” conditions so there is just one list of conditions comprising the recommended uniform screening panel.

Review of Core Conditions
Final input

- Consider a standing workgroup to determine how to remove conditions from the RUSP, as well as which conditions should be removed.

Input on specific conditions:

Conditions expected to need counting clarification

Condition Naming
Final input

Input		Current Name or Proposed Name Change
ACHDNC regular review of condition names is necessary to ensure nomenclature matches currently accepted condition naming.	Align naming with currently recommended nomenclature for disorders	e.g., phenylalanine hydroxylase (PAH) deficiency (PKU)
	Otherwise, use the disorder name based on biology or phenotype	e.g., tyrosinemia type I,
		Pompe Disease
	When multiple enzymes can cause the same disease, the disorder name should be based on the enzyme that is the target of the screen	e.g., methylmalonic acidemia (MMA) caused by methylmalonyl Co-A mutase deficiency,
		galactosemia caused by GALT deficiency,
		homocystinuria (HCU) caused by CBS deficiency,
		congenital adrenal hyperplasia (CAH) caused by 21-OH deficiency
	When the analyte used may detect multiple underlying causes of a single phenotype, list the single phenotype as the condition	e.g., severe combined immunodeficiency (SCID)

Hemoglobinopathies Final input

- Apply phenotype spectrum rule
  - Four conditions would encompass the following possible genotypes/ phenotypes listed in the table
  - “Other clinically significant variant hemoglobins” allows a state to list the possible genotypes/ phenotypes as one condition
  - Optimization to screen for these genotypes/phenotypes would be necessary

Condition to be listed	Included genotypes/phenotypes
Sickle cell disease	S/S, S/B0, S/C, S/D, S/E, S/B+
α-thalassemia	Highly Elevated Bart’s Hb: HbH, HbH/HbCS, HbH with other non-deletional α-thalassemias
β-thalassemia	None, very little or indeterminate HbA in full term baby: F-Only, F/weak A thalassemia intermedia, thalassemia major, triplicated α-genes
Other clinically significant variant hemoglobins	No Hb A with two variants: E/E, C/C and V,V Altered affinity, unstable, etc. E β+ and E β-0 thal

Galactosemia
Final input

- If using a first tier with both GALT enzyme and total galactose, programs may list two conditions on their panel as “galactosemia due to GALT deficiency” and “non-classic galactosemia” (which includes GALK, GALE, and GALM).
  - Rationale: follows definition of “optimize”

Congenital Hypothyroidism (CH) Final input

- If using a first-tier T4 with the intent to detect central CH, the program may list two conditions on their panel (primary and central CH).
  - Rationale: follows definition of “optimize”

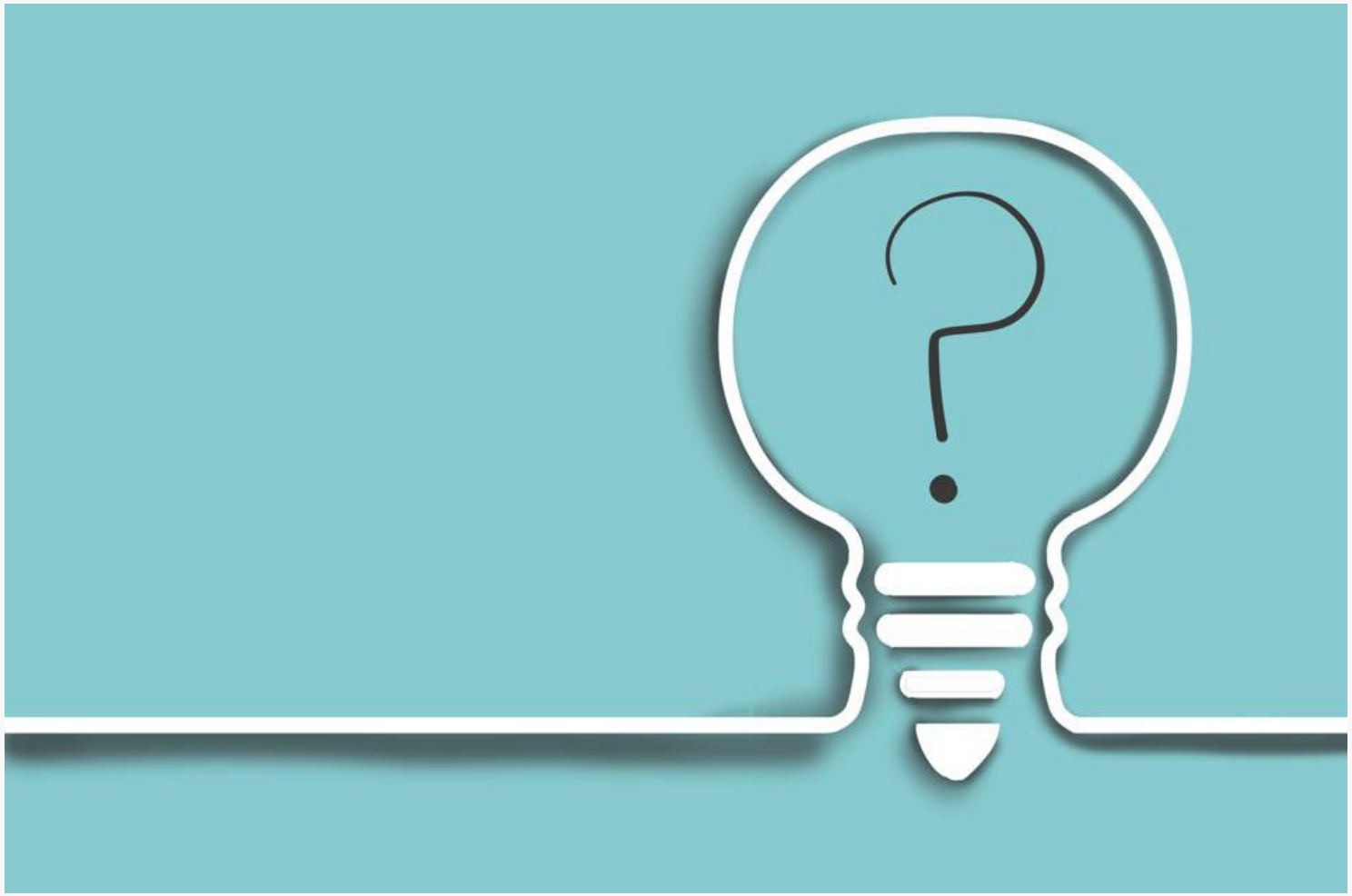
Questions for the Committee Discussion

- In thinking about the difference between a condition we are “screening for” and one we “may detect” :
  - What is the target condition intended for screening?
  - What role does optimization play in decision-making regarding screening vs. detection (and how they are listed)?
- Does the Committee agree that a condition should only be listed and counted once, even when a spectrum of condition severity or multiple subtypes exist?
- In considering nomenclature:
  - Would nomenclature rules provide clarity of intended targets for screening?
  - Could the committee create standard procedures to facilitate consistency?

Questions for the Committee Discussion

- Is there utility in distinguishing Core vs. Secondary conditions?
  - What are the benefits vs. the risks in doing so?
- Is there sufficient evidence to add conditions on the current Secondary list to the Core list?
  - Could this be done in an expedited fashion?
- Could the committee establish procedures on how to remove conditions from the RUSP, and develop processes to determine which conditions should be removed?

Questions



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