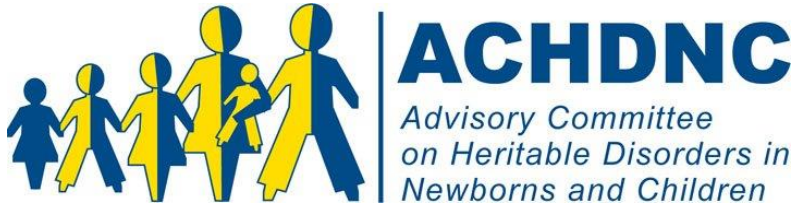

Overview of Immediately Actionable Committee Process Updates

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Background

- In February 2019 - the Committee convened an Expert Advisory Panel (EAP) meeting to address the process through which a condition is considered for or included on the RUSP.
- The Committee considered four main focus areas:
    - **Nomination**
        - Nomination Form and Process
    - **Evidence-Based Review**
        - Assessing published/unpublished evidence
        - Assessing public health system impact
        - Assessing stakeholder values
    - **Decision Matrix**
    - **Review of Conditions on the RUSP**

Background

- Proposed next steps categorized by level of actionability:
  - **Immediately actionable**
  - Needs more discussion
  - Needs more research
  - Needs policy change

Immediately Actionable Committee Process Updates: Nomination Process

Issue	Actionability
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not directly link to specific and relevant information needed for the evidence review, in areas such as registries, unpublished evidence, the screening algorithm and resources, and long-term follow up, etc.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

Condition Nomination Form Updates – Section I, Part A

SECTION I – CONDITION INFORMATION AND TREATMENT

SECTION I, PART A. CONDITION

CONDITION	STATEMENT
Nominated Condition	
Type of Disorder	
Screening Method	
Gene	
Enzyme	
Locus	Include ClinVar link if applicable.
OMIM or other names for condition	Include Genetics Home Reference link if applicable.
Case Definition	Include the specific case definition for the screening target.
Incidence	**Include U.S. incidence estimate and citation**. Determined by what method(s): pilot screening or clinical identification?
Timing of Clinical Onset	Relevance of the timing of newborn screening to onset of clinical manifestations **for phenotypes that would be detected.**
Severity of Disease	Morbidity, disability, mortality, spectrum of severity. **Include U.S. distribution/prevalence of known phenotypes if applicable.**

Condition Nomination Form Updates – Section I, Part B

SECTION I, PART B. TREATMENT

TREATMENT	STATEMENT
Modality	**Describe the medical/clinical care required. Drug(s), diet, replacement therapy, transplant, other. Identify which treatment(s) are current standard of care.** Include information about regulatory status of treatment.
Clinical Indications for Treatment and Urgency	**What are the clinical indications (e.g., ages of treatment initiation, clinical symptoms/severity, etc.) for the current standard of care treatment(s) identified above? What are the contraindications for treatment initiation?** How soon after birth must treatment be initiated to be effective?
Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability, **for known phenotypes.** Treatment limitations, such as difficulty with acceptance or adherence.
Availability	**Is treatment and follow-up available in most hospitals? Major medical centers? Describe the follow-up and specialized treatment centers which may be needed.**
Potential Harms of Treatment	Potential adverse medical events or other harms from treatment and the likelihood, if known.

Condition Nomination Form Updates – Section II, Part A

SECTION II, PART A. VALIDATION OF THE LABORATORY TEST

TEST	STATEMENT
Modality of Screening Specimen Sample	Dried blood spot, physical or physiologic assessment, other. **If not dried blood spot specimen, indicate any timing requirements in screening/specimen collection.**
Screening Test(s), Platform, and Procedures	Description of the high volume method **(number of samples run in high-throughput?), instrumentation (e.g., tandem mass spectrometry, digital microfluidics, other) and if available as part of multi-analyte platform. Disposables - Lab-based analysis or off-the-shelf (OTS) kits? If OTS Kits, FDA-approved? Vendors/suppliers if known?**
Does the screening algorithm include a second tier test? If so, what type of test and availability?	**Modality of specimen sample for tier 2 test?** (dried blood spot, physical or physiologic assessment, other) **Screening test**

Condition Nomination Form Updates – Section II, Part A (cont.)

SECTION II, PART A. VALIDATION OF THE LABORATORY TEST

TEST	STATEMENT
Clinical Validation	Location, duration, number of samples run in high-throughput, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.
Analytical Validation	Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., quality control (QC) and proficiency testing (PT) for both screening and confirmatory tests. **Has the CDC's Newborn Screening and Molecular Biology Branch (https://www.cdc.gov/nceh/dls/nsmbb.html) been contacted regarding these and other validation measures currently pending or available?**
Considerations of Screening, Diagnostic Testing and Timeliness	False positives, carrier detection, invasiveness of method, other. **Does condition qualify as "time-critical" from a timeliness perspective, requiring immediate medical attention?**
Potential Secondary or Incidental Findings	Detection or suggestion of other disorders.

Condition Nomination Form Updates – Section II, Part B

SECTION II, PART B. CONFIRMATORY TESTING AND SHORT-TERM FOLLOW-UP/DIAGNOSIS

CONFIRMATORY TESTING	STATEMENT
Confirmatory Testing Methods	**Include sample(s)/specimen(s) needed (e.g., blood, radiology tests, urine, tissue sample, biophysical test(s)**
Clinical and Analytical Validity	Quantitative or qualitative? Include sensitivity, specificity, etc. **if available.**
Regulatory Status of Confirmatory Testing	**Is test FDA cleared/approved? If so, include year/reference.** **Describe availability of confirmatory testing, information, sole source manufacturer, specialized testing centers, etc.**
List all CLIA certified labs offering testing in the US	Link to GeneTests and Genetic Test Reference if applicable.
Short-Term Follow-up and Diagnosis	**How is diagnosis confirmed? (e.g., lab or genetic tests, clinical evaluation, symptom onset, etc.)** **When is diagnosis confirmed? (time to diagnosis by phenotype)** **Who can diagnose newborns with positive screens? (e.g., primary care providers, specialists, major medical specialty centers, etc.)**

Condition Nomination Form Updates – Section II, Part C

SECTION II, PART C. PROSPECTIVE, POPULATION-BASED SCREENING (PILOT OR OTHER)

POPULATION-BASED NEWBORN SCREENING (PILOT, RESEARCH, OR LIVE NBS)	STATEMENT
Location/Program Conducting Prospective, Population-Based Newborn Screening	U.S. or international? If U.S., which site(s)/cities/regions?
Screening Method(s) and Algorithm(s) Used	Describe a) screening method and algorithm (attach flow chart with pilot outcomes), b) (prospective) confirmatory testing method(s) (e.g., genetic testing methods, other diagnostic method(s) - clinical, biochemical, molecular tests, other).
Number of Newborns Screened to Date	
Number of Screen Positive Results	Positive by primary test vs. 2nd tier test if applicable.
False Positive Rate; False Negative Rate (if known)	False positive by primary test vs. 2nd tier test if applicable.
Number of Infants Confirmed with Diagnosis	# Infants identified as 'positive screen' and referred for confirmatory testing Of those referred, # of infants confirmed with diagnosis? Time to abnormal newborn screening result obtained? Time to diagnosis confirmed? Time to treatment initiation?
Key Outcomes of Treatment	What are the key outcomes of interest? For which of these key outcomes is evidence available and what is the follow-up period? What plans are there for longer-term follow-up of newborns detected early? (e.g., studies with ongoing follow-up? Clinician follow-up? Etc.)
Population-Based Screening Contacts	Cite reference if available, and/or program contacts to follow up with about programs conducting prospective, population-based screening (pilot or other).

Condition Nomination Form Updates – Section II, Part C (cont.)

SECTION II, PART C. PROSPECTIVE, POPULATION-BASED SCREENING (PILOT OR OTHER)

STATUS OF NBS CONDITION IN THE U.S.	
State(s) currently screening for the condition	
State(s) currently mandated to screen for the condition	
States considering screening but not mandated	
PATIENT REGISTRY(IES) OR DATABASES	
List registries or databases currently established for the condition.	
Are there unpublished data that would inform newborn screening? *If yes, who holds these data?*	

Condition Nomination Form Updates – Section III

SECTION III – KEY REFERENCES

LIST OF REFERENCES
References from scientific journals to support statements in Sections I-IV. For sources based on un/non-published data, references may be written statements from clinicians, researchers, and/or investigators.

* No limit on number of references

Immediately Actionable Committee Process Updates: Evidence – Based Review

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).*

Immediately Actionable Committee Process Updates: Evidence – Based Review (Continued)

Issues	Actionability
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 ranges (vs point estimates).

Immediately Actionable Committee Process Updates: 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. *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

Summary of Immediately Actionable Updates

Nomination

- Updates to the ACHDNC condition nomination form

Evidence-Based Review

- Assessing published evidence
- Assessing unpublished evidence

Public Health Impact Assessment

- Reporting cost estimates in broad categories

Decision-Making Process

- Decision matrix guidance

Questions?