Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Laboratory Standards & Procedures Subcommittee

April 22, 2005

Laboratory Standards & Procedures Subcommittee

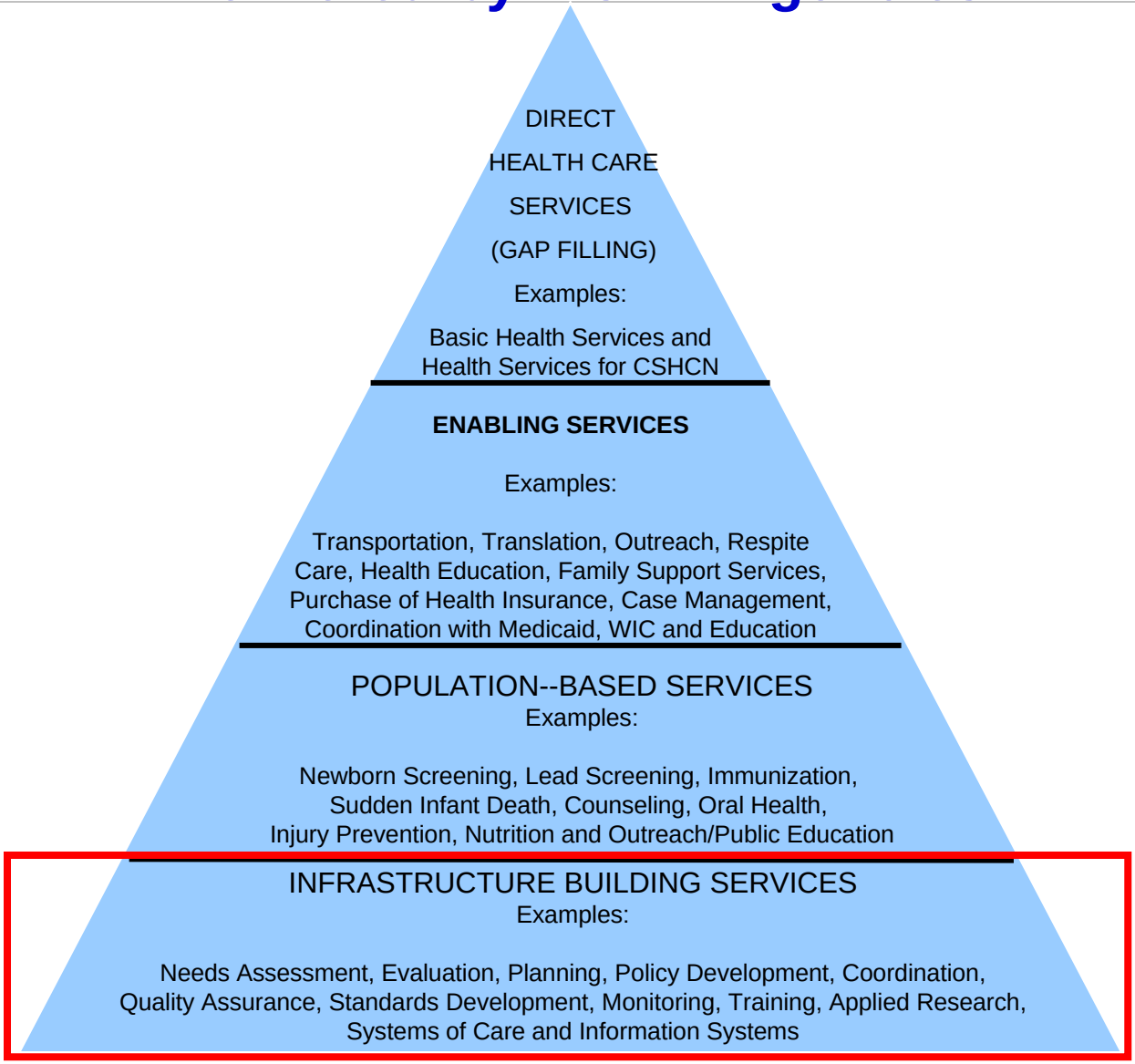
- Duane Alexander
- Amy Brower (chair)
- Peter B. Coggins
- R. Rodney Howell
- Marie Mann (staff)
- Piero Rinaldo

Staff Support – Carrie Diener

Charge of Subcommittee

- **Assessment of laboratory methodologies and standards for testing panels of inherited disorders in newborn and children**
  - **Process definition for addition/deletion of conditions to uniform panel**
  - **Evaluation of new technologies**
  - **Focus on infrastructure services**

Focus on Infrastructure Building Services: Core Public Health Services Delivered by MCHB Agencies



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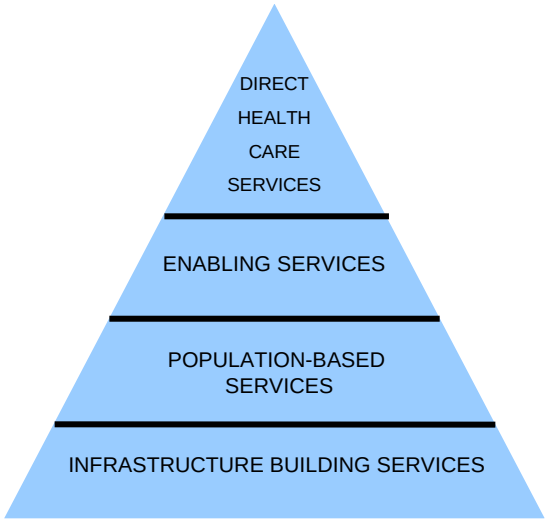
Infrastructure Building Services



- **Nomenclature**
- **Testing strategies**
- **Cut-off values**
- **Reporting** [D]
- **Performance metrics**

Nomenclature

- **Provide guidelines for standardized "counting" of conditions**
  - **Clinical phenotype**
  - **Group of conditions**
  - **Primary marker**
  - **Test platform**
  - **Response to treatment**
  - **Number of loci**
  - **Ad hoc criteria (to be established)**
- **Facilitate communication to professionals and consumers by providing structural feedback to education subcommittee**

Testing Strategies

- **Evaluation and standardization of pre-analytical, analytical, and post-analytical practices**
  - **Time of collection**
  - **2nd collection**
    - **All cases**
    - **First abnormal (repeat test)**
  - **2nd tier tests**
    - **Biochemical**
    - **Molecular**
    - **New technologies**
  - **Interpretation (profile evaluation)**
  - **Timing of confirmatory testing**

Cut-off Values

- Disease range vs. normal range
- Use of analyte ratios
- Monitoring of abnormal results
  - True positives
  - Reported abnormal, false positive
  - Interpreted as not significant
- Normalization (abnormals/10,000 cases)
- Impact of 2nd tier tests

Reporting

- Standardization of required elements
- Quantitative results
- Cut-off
- Prior experience (range)
- Interpretation
  - Differential diagnosis, if applicable
  - Recommendations for confirmatory testing

Performance Metrics

- Definition of targets
  - Detection rate
    - Cumulative
    - By condition
  - False positive rate
    - Cumulative
    - By analyte
  - Positive predictive value
    - Cumulative
    - By analyte
- Proficiency testing (beyond QC)

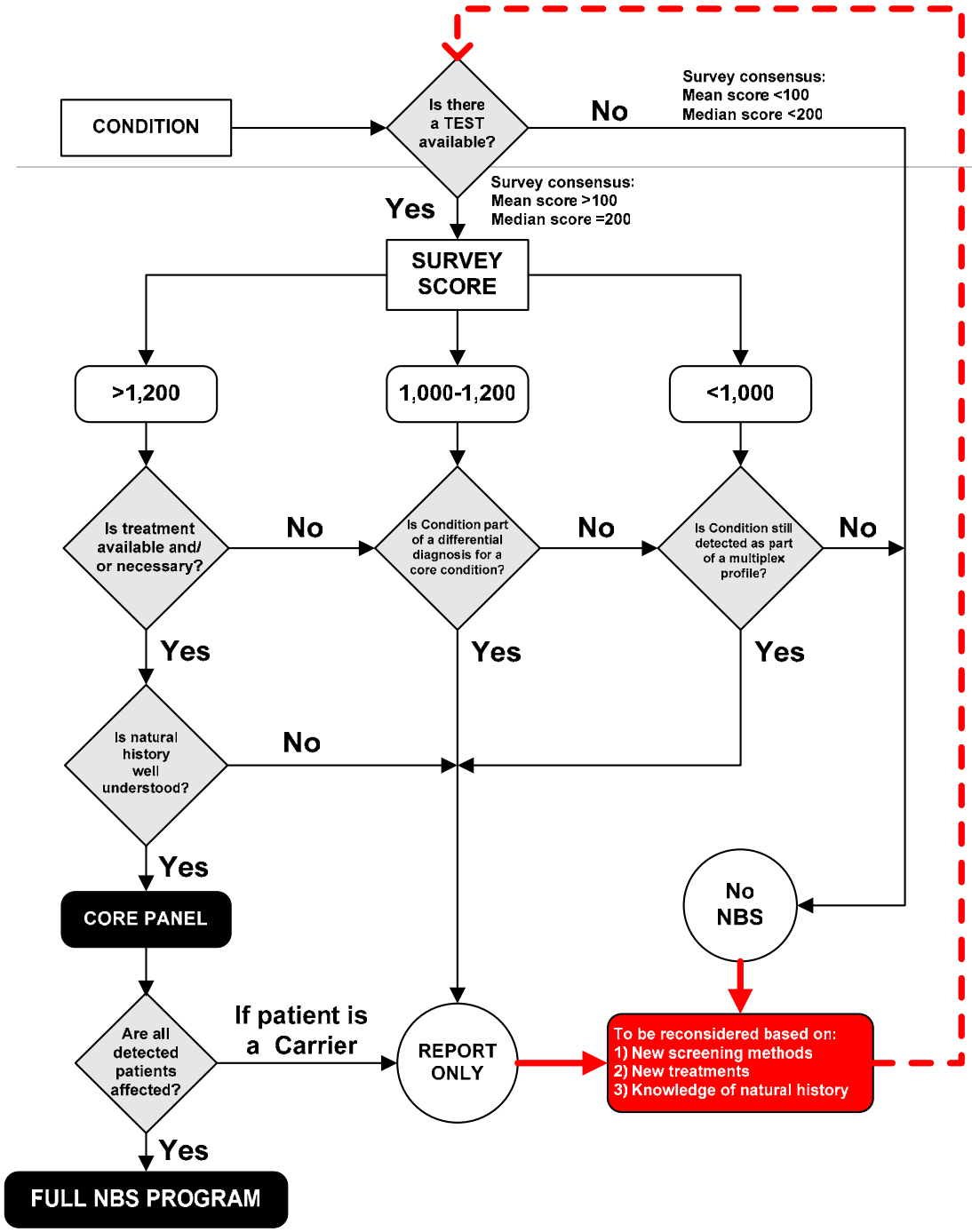
Cross Cutting Focus Areas

- Evaluation
  - Cost-effectiveness
  - Assessment methodology
    - Clinical validity and utility
  - Health outcomes
- Information technology
  - Data integration
  - Data access
  - Privacy
- Financing

Addition/Deletion of Conditions: Process Evaluation

- Dynamic, open-ended process
- Driven by stakeholders
  - Consumer advocates
  - Clinical investigators
  - Researchers (basic, transitional)
  - Providers of laboratory services
  - Industry
- Use of prospective evaluation tool

The Path to the FUTURE



Secondary targets and No NBS conditions

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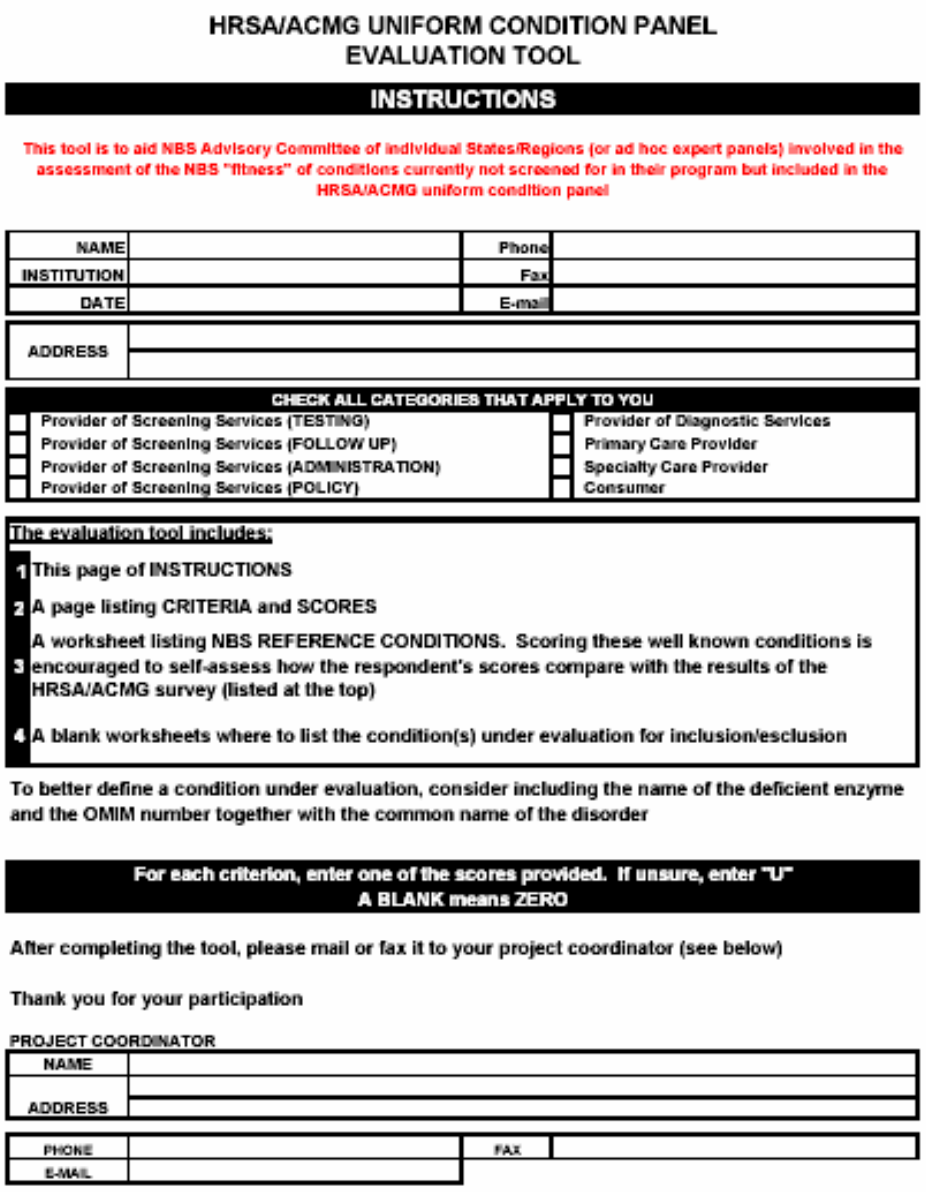
To be reconsidered based on:

1) New screening methods
2) New treatments
3) Evolving knowledge of natural history

Prospective Evaluation Tool



HRSA/ACMG UNIFORM CONDITION PANEL
EVALUATION TOOL

INSTRUCTIONS

This tool is to aid NBS Advisory Committee of individual States/Regions (or ad hoc expert panels) involved in the assessment of the NBS "fitness" of conditions currently not screened for in their program but included in the HRSA/ACMG uniform condition panel

NAME		Phone	
INSTITUTION		Fax	
DATE		E-mail	
ADDRESS			

CHECK ALL CATEGORIES THAT APPLY TO YOU

- ☐ Provider of Screening Services (TESTING)
- ☐ Provider of Screening Services (FOLLOW UP)
- ☐ Provider of Screening Services (ADMINISTRATION)
- ☐ Provider of Screening Services (POLICY)
- ☐ Provider of Diagnostic Services
- ☐ Primary Care Provider
- ☐ Specialty Care Provider
- ☐ Consumer

The evaluation tool includes:

1. This page of INSTRUCTIONS
2. A page listing CRITERIA and SCORES
3. A worksheet listing NBS REFERENCE CONDITIONS. Scoring these well known conditions is encouraged to self-assess how the respondent's scores compare with the results of the HRSA/ACMG survey (listed at the top)
4. A blank worksheets where to list the condition(s) under evaluation for inclusion/esclusion

To better define a condition under evaluation, consider including the name of the deficient enzyme and the OMIM number together with the common name of the disorder

For each criterion, enter one of the scores provided. If unsure, enter "U"
A BLANK means ZERO

After completing the tool, please mail or fax it to your project coordinator (see below)

Thank you for your participation

PROJECT COORDINATOR

NAME			
ADDRESS			
PHONE		FAX	
E-MAIL			

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INTRODUCTION

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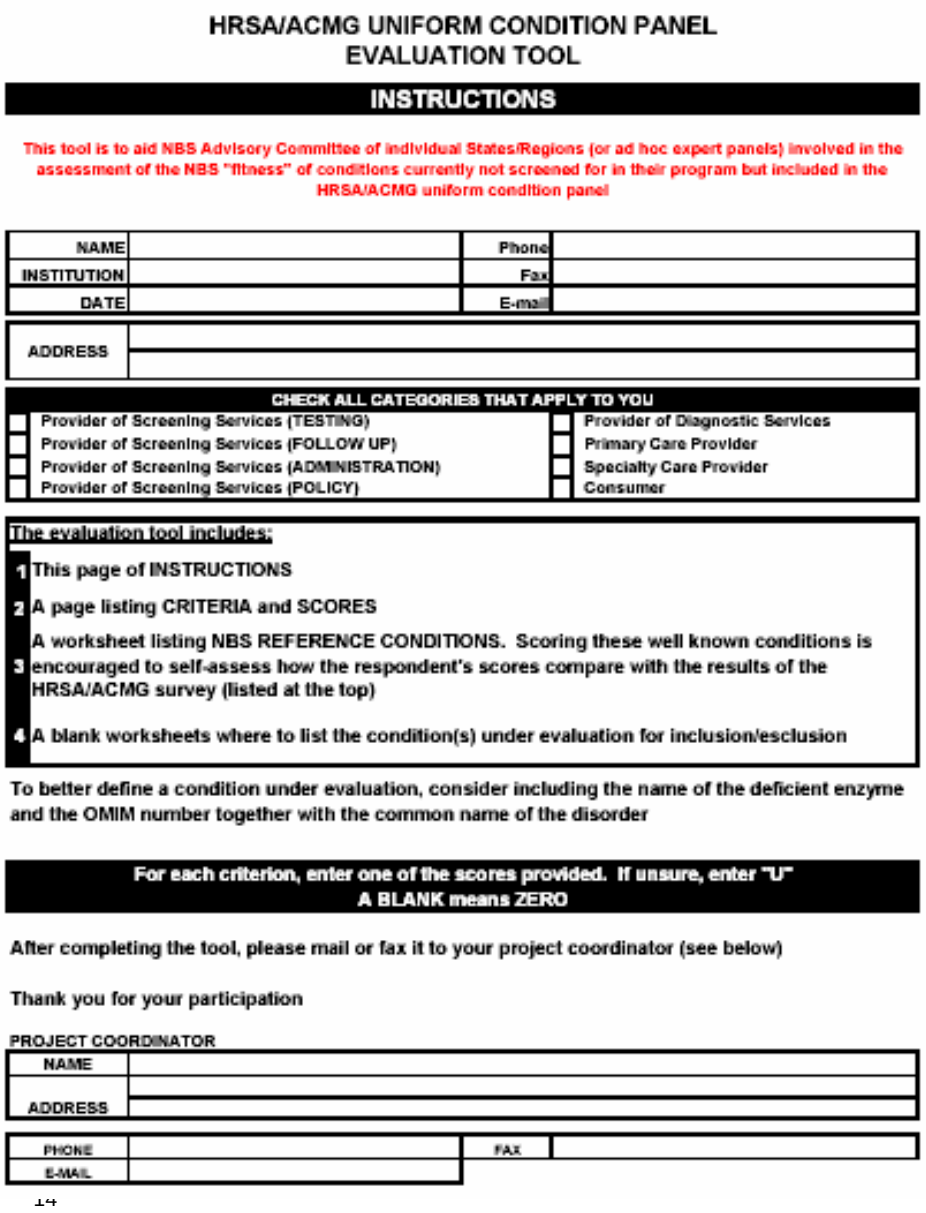
Prospective Evaluation Tool



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CONTENT

- Instructions
- Respondent profile
- CRITERIA
- SCORES
- A worksheet listing NBS REFERENCE CONDITIONS

Scoring these well known conditions is encouraged to self-assess how the respondent's scores compare with the results of the HRSA/ACMG survey (listed at the top)

- A blank worksheets where to list the condition(s) under evaluation for inclusion/exclusion [D]

Reference Conditions

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Conditions to be evaluated

NEWBORN SCREENING CONDITION EVALUATION TOOL — Reference Conditions			MCAD	CH	PKU	SCA	CAH
		Deficient enzyme	Medium chain acyl-CoA dehydrogenase	various	Phenylalanine hydroxylase	Hemoglobin S	21-hydroxylase
		[illegible] survey score	1799	1718	1663	1642	1633
		Your score					
		Common name	MCAD deficiency (MCAD)	Congenital Hypothyroidism	Phenylketonuria (PKU)	Sickle cell anemia (SCA)	Congenital Adrenal Hyperplasia (CAH)
Incidence of condition	>1:5,000	100					
	>1:25,000	75					
	>1:50,000	50					
	>1:75,000	25					
	<1:100,000	0					
Signs & Symptoms clinically identifiable in the first 48 hours	Never	100					
	<25% of cases	75					
	<50% of cases	50					
	<75% of cases	25					
	[illegible]	0					
Burden of disease if untreated (Natural history if untreated)	Profound	100					
	Severe	75					
	Moderate	50					
	Mild	25					
	Minimal	0					
Does a sensitive AND specific screening test currently exist?	YES	200					
	NO	0					
Test characteristics (Yes = apply score No = zero)	[illegible] physical method	100					
	High throughput (>200/day/FTE)	50					
	Overall analytical cost [illegible] per condition	50					
	Multiple analytes relevant to one condition [illegible]	50					
	Other conditions identified by same analysis	50					
	Multiple conditions detected by same test (multiplex platform)	200					
Availability of treatment	Treatment exists and is widely available in most communities	50					
	Treatment exists but availability is limited	25					
	No treatment available or necessary	0					
Cost of treatment	Inexpensive	50					
	Expensive (>$50,000/patient/year)	0					
Potential efficacy of existing treatment	To prevent ALL negative consequences	200					
	To prevent MOST negative consequences	100					
	To prevent SOME negative consequences	50					
	Treatment efficacy not proven	0					
Benefits of early intervention (INDIVIDUAL OUTCOMES)	Clear scientific evidence that intervention resulting from screening optimizes outcome	200					
	Some scientific evidence that early intervention resulting from screening optimizes outcome	100					
	No scientific evidence that early intervention resulting from screening optimizes outcome	0					
Benefits of early identification (FAMILY & SOCIETY)	Early identification maximizes benefits (education, understanding prevalence and natural history, cost effectiveness)	100					
	Early intervention improves benefits	50					
	No evidence of benefits	0					
Early diagnosis and treatment prevent mortality	YES	100					
	NO	0					
Diagnostic confirmation	Providers of diagnostic confirmation are widely available	100					
	Limited availability of providers of diagnostic confirmation	50					
	Diagnostic confirmation is available only in a few centers	0					
Clinical management	Providers of acute management are widely available	100					
	Limited availability of providers of acute management	50					
	Acute management is available only in a few centers	0					
Simplicity of therapy	Management at the primary care or family level	200					
	Requires periodic involvement of a specialist	100					
	Requires regular involvement of a specialist	0					

NEWBORN SCREENING CONDITION EVALUATION TOOL — Conditions to be evaluated			SCID	Pompe	Krabbe	Wilson	HyperBIL
		Deficient enzyme					
		[illegible] survey score					
		Your score					
		Common name					
Incidence of condition	>1:5,000	100					
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Outline of Process

- **Collect survey data from local group**
  - Providers of services
  - Consumers
- **Calculation of score(s)**
- **Application of evaluation flow chart**
- **Review updated literature evidence**
- **Make recommendations**

New Technologies

- Type
  - Molecular
  - Expression
  - Proteomics
- Uses
  - New approach to existing panel
  - Testing of additional conditions
  - Identification of new conditions
- Other
  - Multiplex testing
  - Point of Care (POC)
  - Direct to Consumers (DOC)

Subcommittee Invitees (Preliminary)

- **Participation confirmed**
  - **Don Chace, Pediatrix**
  - **Harry Hannon – Biochemical Branch, CDC**
  - **Gary Hoffman – WI State Laboratory of Hygiene**
  - **Jana Monaco, Parent**
  - **Larry Sweetman – Baylor University Medical Center**
- **Participation under consideration**
  - **John Sherwin, Genetic Disease Branch, California Department of Health Services**