

Effectiveness of Interventions in Inborn Errors of Metabolism Affecting the CNS

**Research Challenges in CNS
Manifestations of Inborn Errors
Of Metabolism**

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Newborn Screening

- **Newborn screening developed worldwide from a keen interest and understanding of Inborn Errors of Metabolism- a term introduced by Garrod in 1908**
- **Newborn Screening has focused considerably on identifying conditions that adversely affect the CNS**
- **Newborn screening has been driven to a considerable extent by available technology, and increasingly by better understanding of conditions as well as new diagnostic technologies and treatments.**
- **In view of the close relationship of newborn screening and inborn errors of metabolism that affect the CNS, my comments will focus in this area**

Utskillelse av fenylpyrodruesyre i urinen som stoffskifteanomali i forbindelse med imbecillitet.¹

AV

Dr. med. Asbj. Folling, Oslo.

Dette er den første meddelelse om en hittil ukjent stoffskifteanomali, som jeg har iaktatt hos endel imbecille patienter. Stoffskifteanomalien viser sig ved at der utskilles fenylpyrodruesyre i urinen, og der synes å være en forbindelse mellom denne stoffskifteanomali og imbecilliteten. Jeg har nemlig hittil funnet 10 patienter med fenylpyrodruesyre i urinen, og av disse er de 9 utvilsomt åndelig defekte. Den tiende er bare 1½ år gammel, så nogen mental diagnose ennå ikke med sikkerhet kan stilles.

Jeg skal først gi en kort beskrivelse av det kliniske materiale.

1. L. E. ♀ Født 14/6—1927. Patienten er den første i en søskenflokk på 2. Hennes far har i de siste 5—6 år lidt av asthma, moren er frisk. Foreldrene er ikke beslektet. En søster av farens mor lider av dementia præcox. Svangerskap og fødsel normal. Rettidig fødsel. Normal fødselsvekt. Patienten fikk morsmelk i 8—9 mdr., de første 2½ mdr. utelukkende morsmelk. Tannfrembrudd i normal alder. Hun begynte å gå da hun var 22 mdr. Der har ikke vært brekninger og ikke kramper. Har ikke hatt andre sykdommer enn angina.

Hennes legemlige utvikling er normal. Vekt 31 kg. Høide 131 cm. Skalleomfang 51 cm. Naturalfunksjoner i orden. Hun er meget agil, vimser utvilsomt fra det ene til det andre.

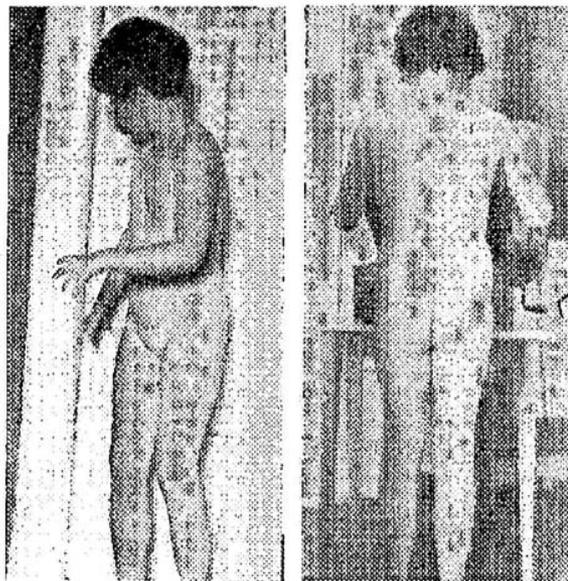


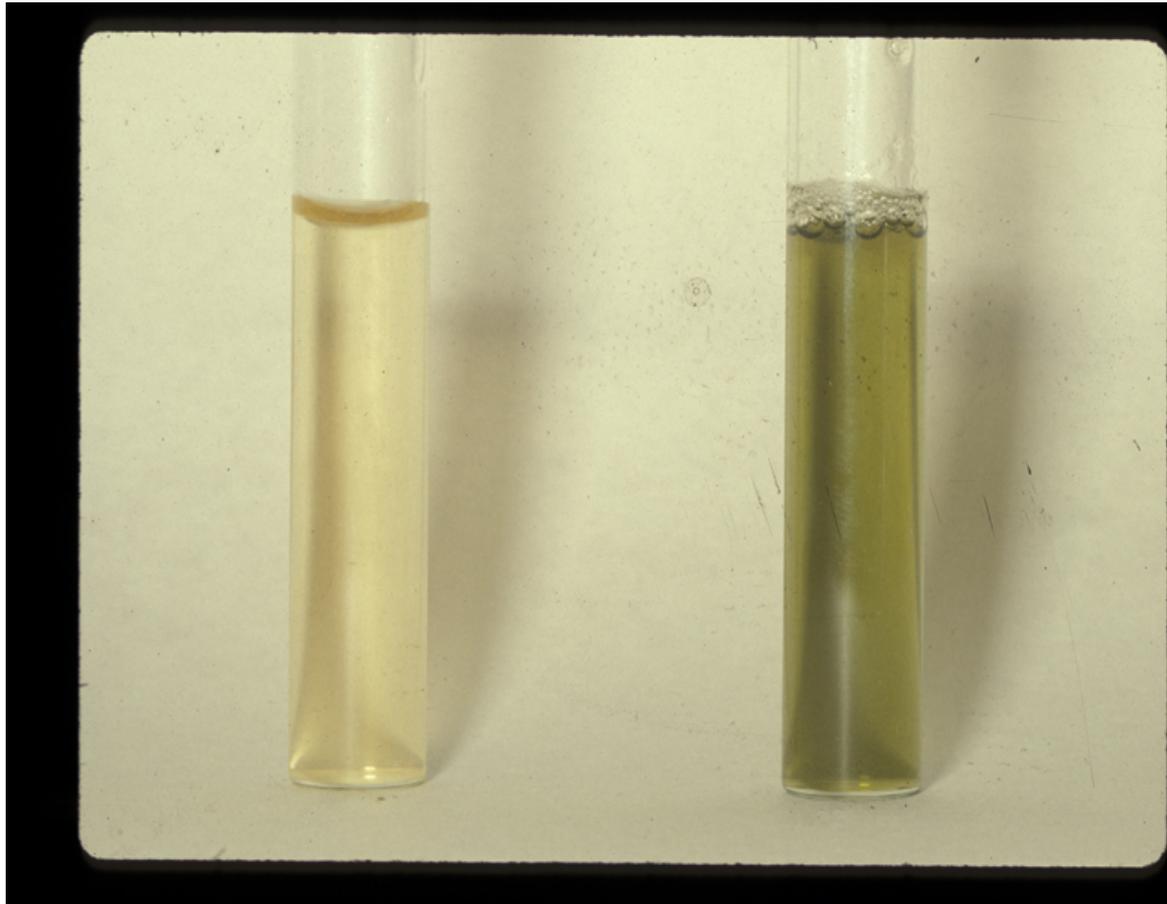
Fig. 1 a.

Fig. 1 b.

keside er ru med små hvite nupper. Alle reflexer er normale. Der er lett rigiditet av alle muskler. Ved organundersøkelsen finnes normale forhold. Fig. 1 a og 1 b.

2. D. E. ♂ Født 22/4. 1930. Han er bror av foranstående. Svangerskap og fødsel normal. Rettidig fødsel. Normal fødselsvekt. Lett icterus neonatorum. Patienten fikk morsmelk i 7 mdr., de første 4 mdr. bare morsmelk. Tannfrembrudd i normal alder. Der har ikke vært kramper. Der har delvis vært brekninger ved begynnelsen av måltidene. Har ikke hatt nogen av de almindelige barnesykdommer. Han har en recidiverende cysto-pyelit, og i juni 1933 lå han derfor en tid i hospital. Han hadde da temperatur op til 39° 7 og et rentgennomsnitt.

Positive Urinary Ferric Chloride Test in PKU



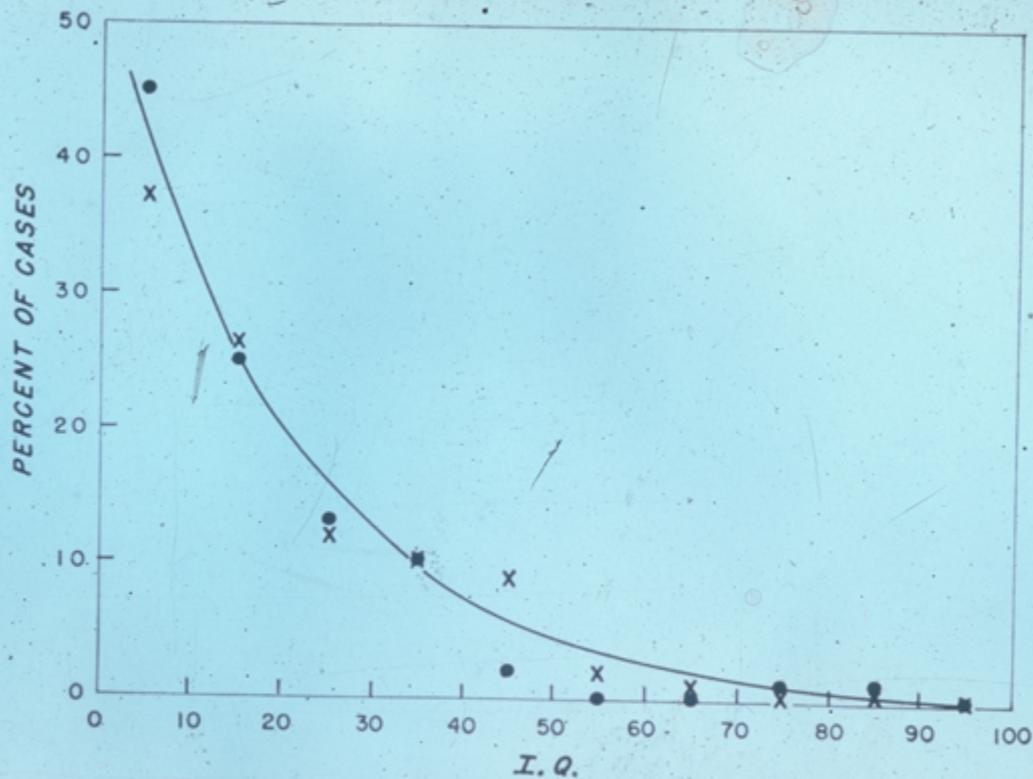
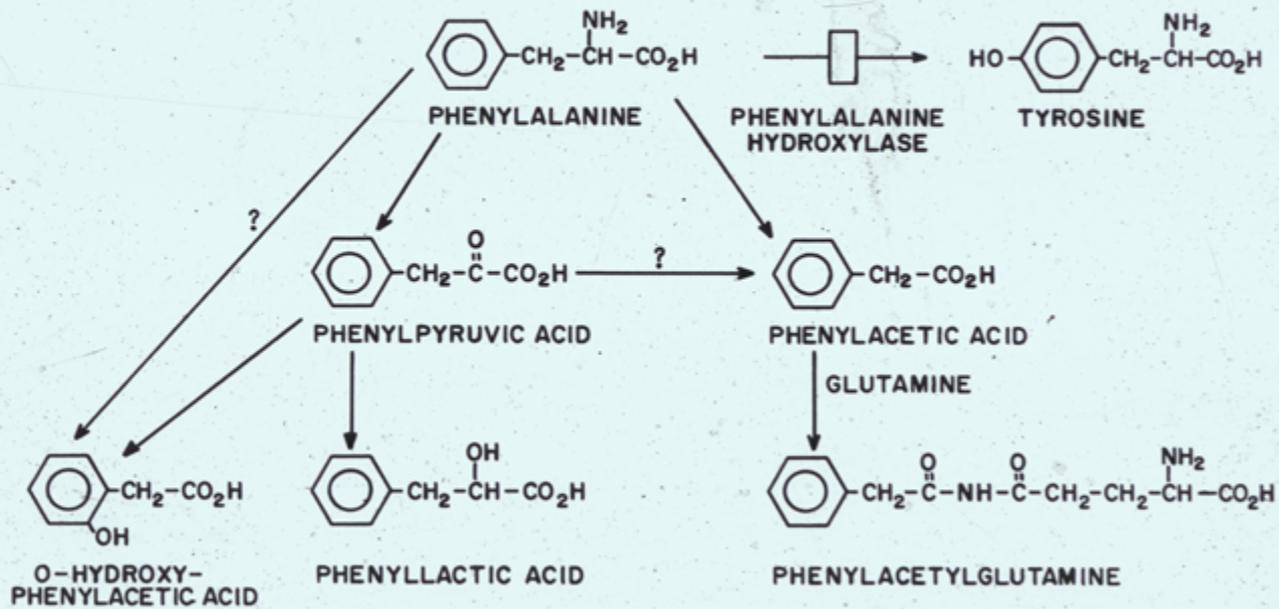
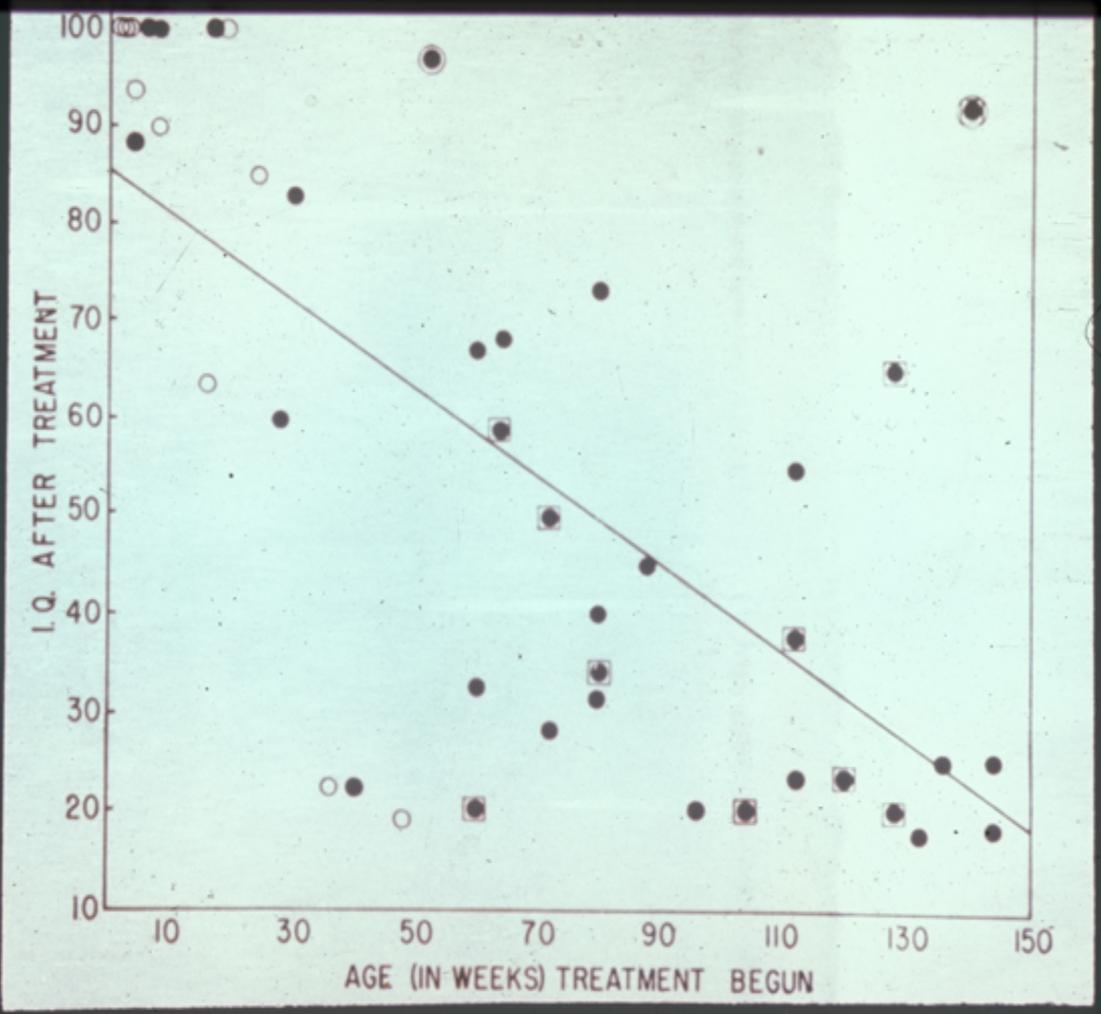


Fig. 11-3. Frequency distribution of IQs among 330 patients [14] and 104 patients [46]. The total of 2 per cent above IQ 60 would account for 20 such patients in a total of 1,000. Table 11-3 lists the 30 such patients who are known.

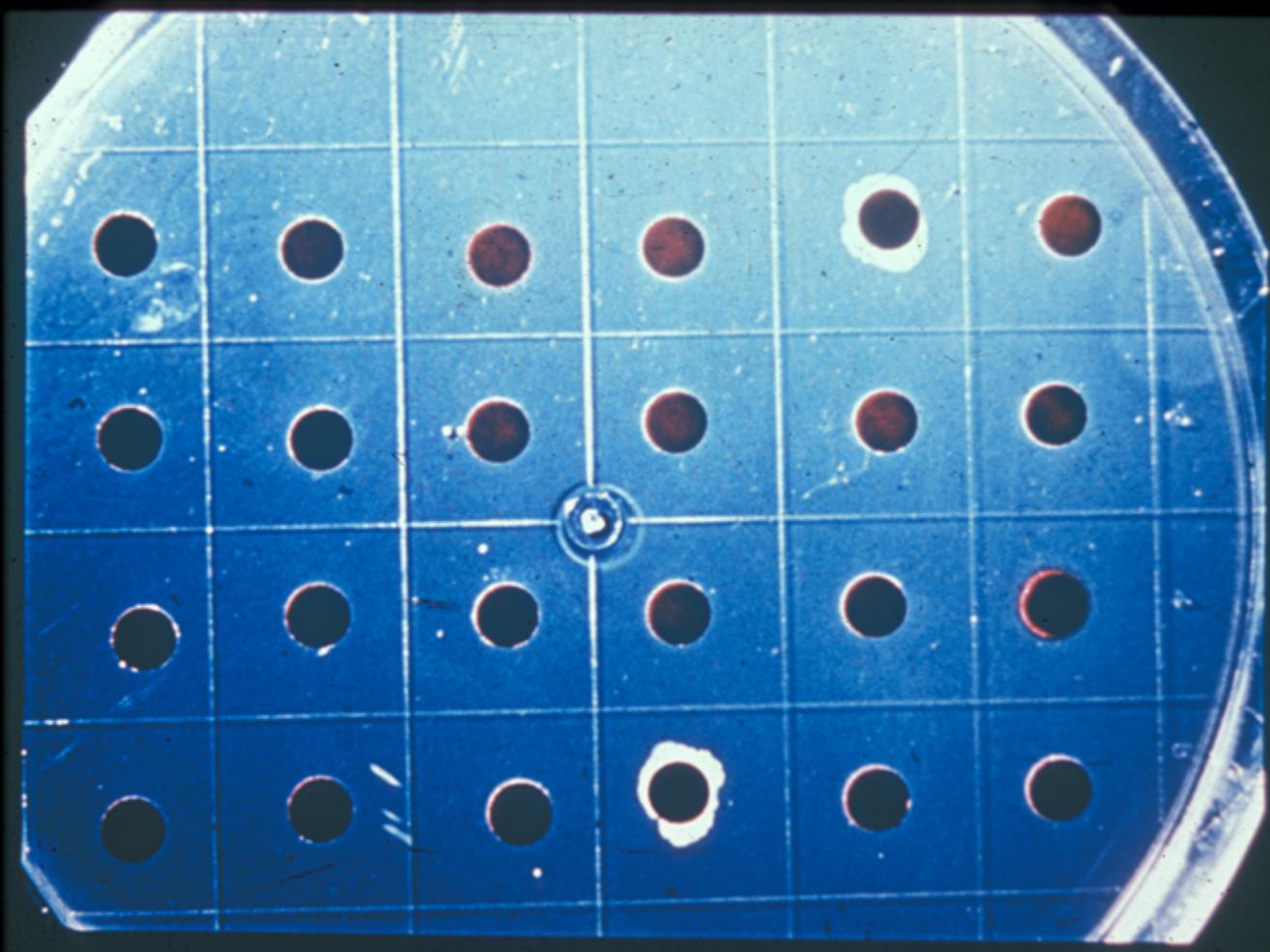
PHENYLALANINE METABOLITES

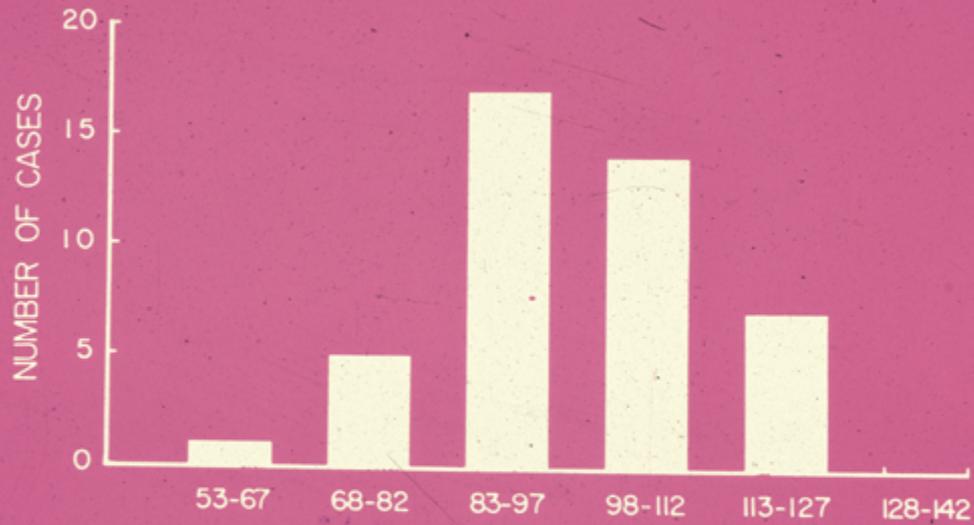












Distribution of Stanford-Binet IQs in 43 phenylketonuric patients diagnosed and treated from birth. Note normal distribution of intelligence.

Mean Scores and Standard Deviations for the Demographic Measures

From Channon et al Arch Dis Child 92:213-218 (2006)

Control Group (n=45)

PKU on Diet (n=25)

Demographic and IQ Measures

Age 28.76 (7.46)

Education 13.47 (1.87)

WASI full

scale IQ 106.98 (8.9)

Demographic and IQ Measures

Age 26.68 (4.92)

Education 14.44 (1.87)

WASI full

scale IQ 107.04 (12.01)

Newborn Screening for Genetic Disease in the United States

- **Routine newborn screening has been carried out in all 50 states since the 1970s, always as a state sponsored public health program, arguably one of the most successful ones**
- **Conditions such as phenylketonuria, with simple, reliable screening tests and proven treatment efficacy have been the targets of testing**
- **Over the years, congenital hypothyroidism and a handful of other diseases were added on a state by state basis**
- **As the programs grew and developed, there was extraordinary variation from state to state and there was little systematic evaluation of either the rationale for screening and/or the outcomes of such screening**
- **Over 4,200,000 infants are screened each year, making newborn screening by far the most commonly performed genetic testing in the United States**

American College of Medical Genetics Contract with HRSA on Newborn Screening

- **In 2001, the Maternal and Child Health Bureau, HRSA/HHS contracted with ACMG to convene an expert group to evaluate the scientific and medical information related to screening for specific conditions and to make recommendations based on this evidence.**
- **Widely representative group (physicians, scientists, consumers, state laboratorians, lawyers, ethicists and others) worked over a two year period to accomplish this goal, and their report was published in 2006.**
- **The group of over 70 developed principals by which conditions were to be evaluated, reviewed available published data, expert opinion and other materials. The two major working groups were overseen by a steering committee.**
- **The developed material was then reviewed by an independent newborn screening external review group**
- **In addition to the expert group, outside input was actively solicited**

Selection Criteria of Uniform Panel

- Incidence of conditions
- Identifiable at birth
- Burden of disease
- Availability of test
- Test characteristics
- Availability of treatment
- Cost of treatment
- Efficacy of treatment
- Benefits of early intervention
- Benefits of early identification
- Mortality prevention
- Diagnostic confirmation
- Acute management
- Simplicity of therapy

Genetics
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Reporting is Now Available!
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Newborn Screening: Toward a Uniform
Screening Panel and System

- Executive summary
- Main report



Advisory Committee on Heritable Disorders in Newborns and Children

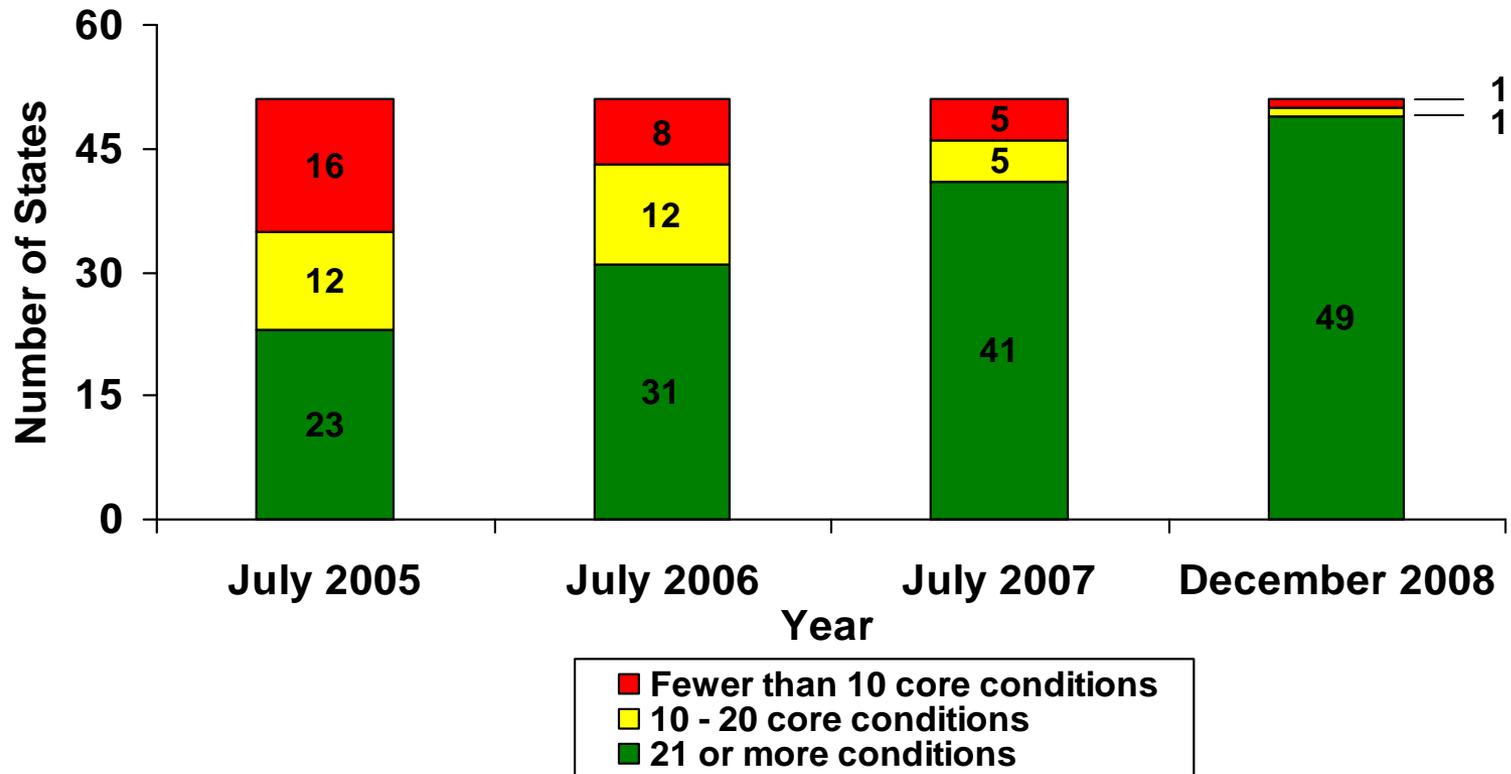
Authorizing Legislation

- **Title XXVI of the Children's Health Act of 2000 enacts three sections of the Public Health Service (PHS) Act:**
 - **Two grant programs under Sections 1109 and 1110, and established the [Advisory Committee on Heritable Disorders in Newborns and Children \(Section 1111\)](#)**
 - **Committee first met on June 7-8, 2004**
 - **Although Committee charge is broad, to date committee has focused efforts on newborn screening**

Advisory Committee for Heritable Disorders in Newborns and Children

- **During its first meetings, the Committee spent a great deal of time reviewing and discussing the HRSA-American College of Medical Genetics (ACMG) Report: Newborn Screening: Toward a Uniform Screening Panel and System**
- **After this extensive review, the Committee unanimously accepted this report and sent a letter to the Secretary of HHS recommending adoption and implementation of this report.**

Newborn Screening Tests



Source: March of Dimes. Data reported from NNSGRC.

Nomination Form (ftp://ftp.hrsa.gov/mchb/genetics/NominationForm.doc)

NEWBORN SCREENING UNIFORM PANEL

NOMINATION FORM FOR PROPOSED CONDITION

Name of Proponent	<i>(Organization, if relevant)</i>	Date	
Condition			
Type of Disorder			
Screening Method			
Treatment strategy			

CONDITION	Comment	Gene	Locus	OMIM or other names for disorder

*Note: Please reference each statement, listing references below (p.2)

Incidence	(Determined by what method(s): pilot screening or clinical identification?)
Timing of clinical onset	(Relevance of timing)
Severity of disease	(Morbidity, disability)

TEST	Comment
Screening test(s) to be used	(High volume method, platform)
Modality of screening	(Dried blood spot, physical or physiologic assessment, other)
Clinical validation	(Location, duration, type of validation)
Laboratory performance metrics	(Sensitivity, specificity)
Confirmatory testing	(Reliability, availability)
Risks	(False positives, carrier detection, invasiveness of method, other. Detection or suggestion of other disorders)

NOMINATION OF CONDITION (page 2)

TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other)
Urgency	(How soon after birth treatment needs to be initiated to be effective)
Efficacy (Benefits)	(Extent of pre-acceptance or such as difficulty with)
Availability	(Any limits of)
Risks	(Potential medical or other ill effects from treatment)

KEY REFERENCES (Specific citations – limit to 15)	
1	
2	
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Submission Check list		Submit Nominations to:
<input type="checkbox"/>	Cover letter by proponent	Michele A. Lloyd-Puryear, M.D., Ph.D. Chief, Genetics Services Branch Division of Services for Children with Special Health Needs Maternal and Child Health Bureau 5600 Fishers Lane, Room 18-A-19 Rockville, MD 20857 301-443-8604 –fax 301-443-1080 - phone
<input type="checkbox"/>	Nomination form	
<input type="checkbox"/>	Copy of references listed on this form	
<input type="checkbox"/>	Formal conflict of interest statement by proponent	
Contact information (proponent)		

Condition

Treatment

Screening Test

References

Considerations for Formal Evidence Review

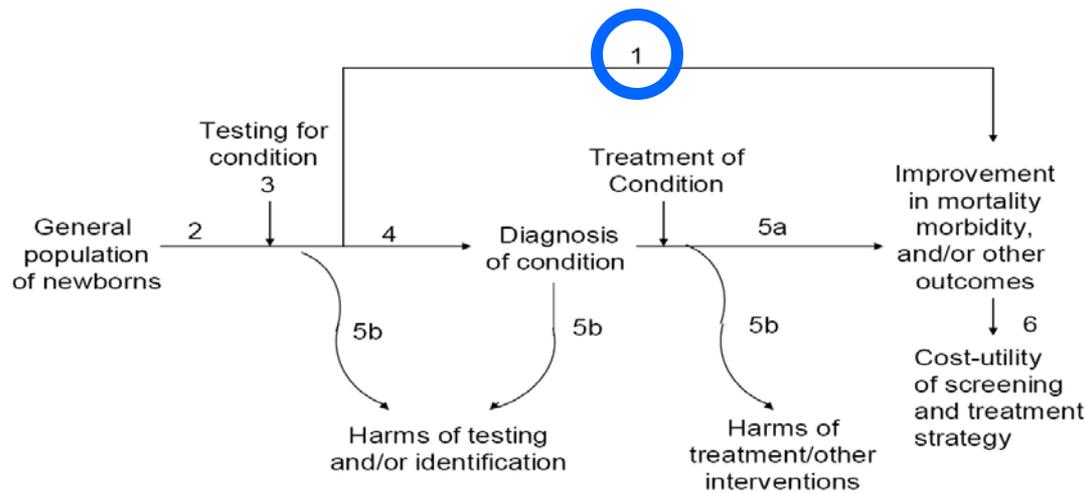
(Nomination Review and Prioritization Workgroup)

- 1. The nominated condition(s) is medically serious.**
- 2. Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder**
- 3. The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based NBS**
- 4. There is a screening test that is capable of identifying the condition**
- 5. If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky**
- 6. There are defined treatment protocols, FDA approval/ clearance (if applicable) and availability of treatment**

Process for Creating Recommendations Based on Systematic Evidence Review

- **Anticipate not having direct evidence of screening efficacy (question 1)**
- **Create chain of evidence, evaluating**
 - **Analytic validity**
 - **Clinical validity**
 - **Clinical utility**
- **Base recommendation on certainty of net benefit**

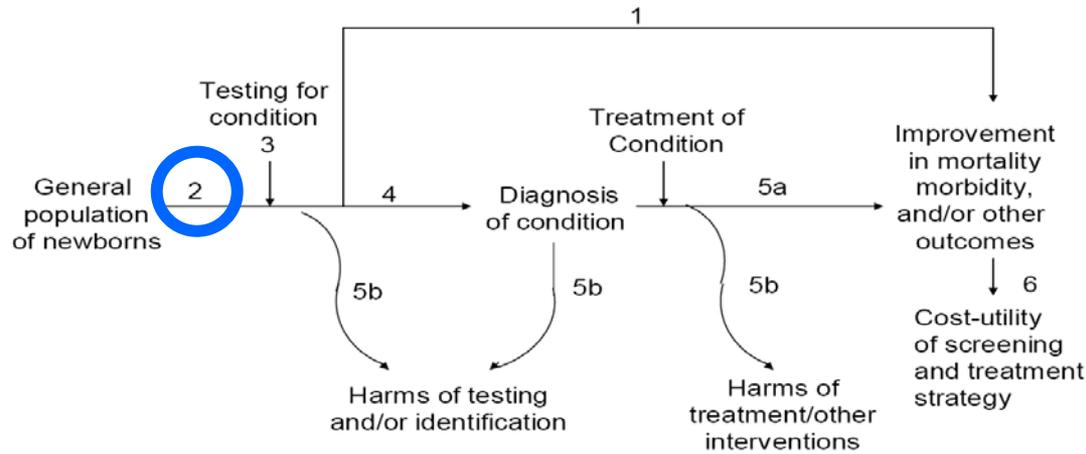
Key Question 1



Direct Evidence

Is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened, or for the child's family?

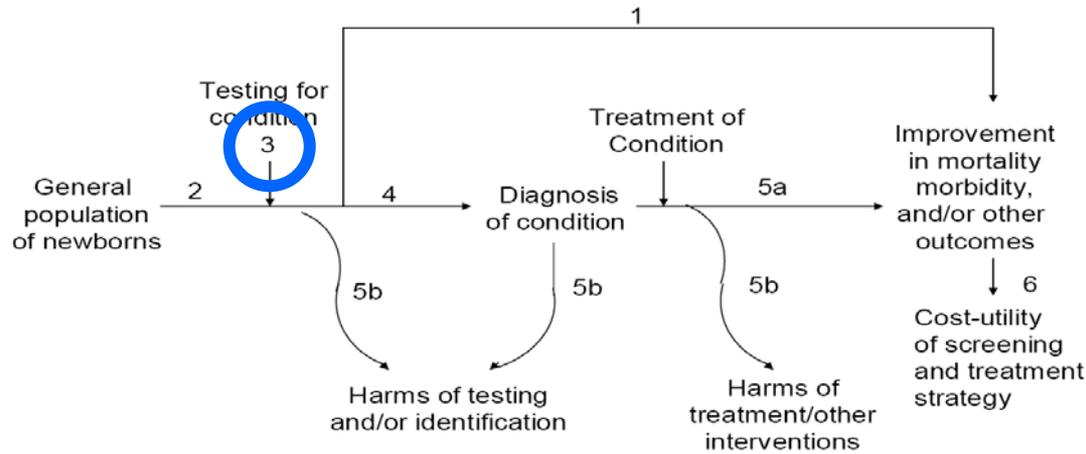
Key Question 2



Case Definition

Is there a case definition that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment?

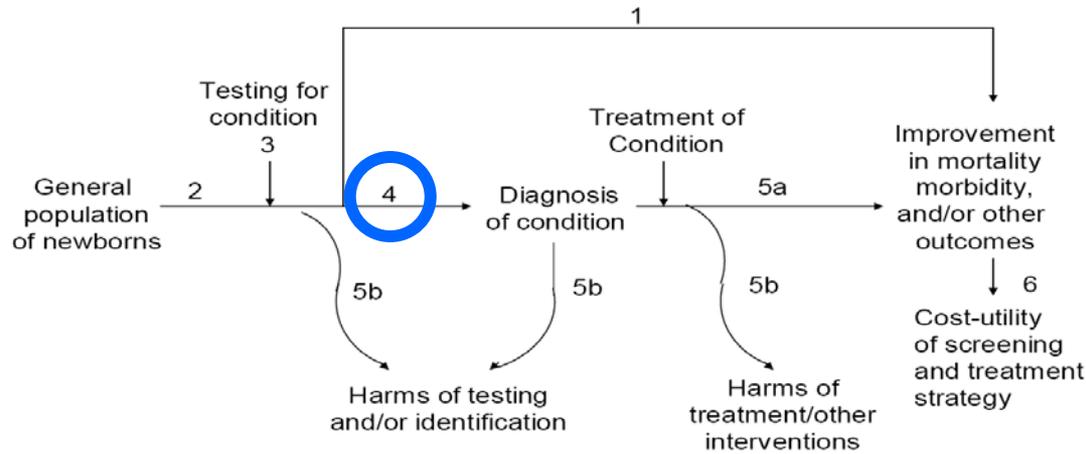
Key Question 3



Screening Test

Is there a screening test or screening test algorithm for the condition with sufficient analytic validity?

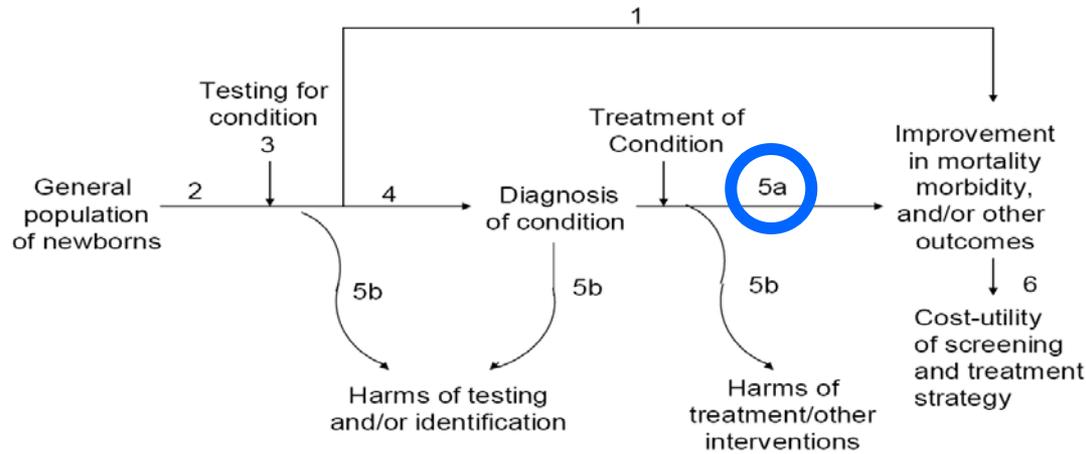
Key Question 4



Clinical Validity

Has the clinical validity of the screening test or screening algorithm, in combination with the diagnostic test or test algorithm, been determined and is that validity adequate?

Key Question 5a

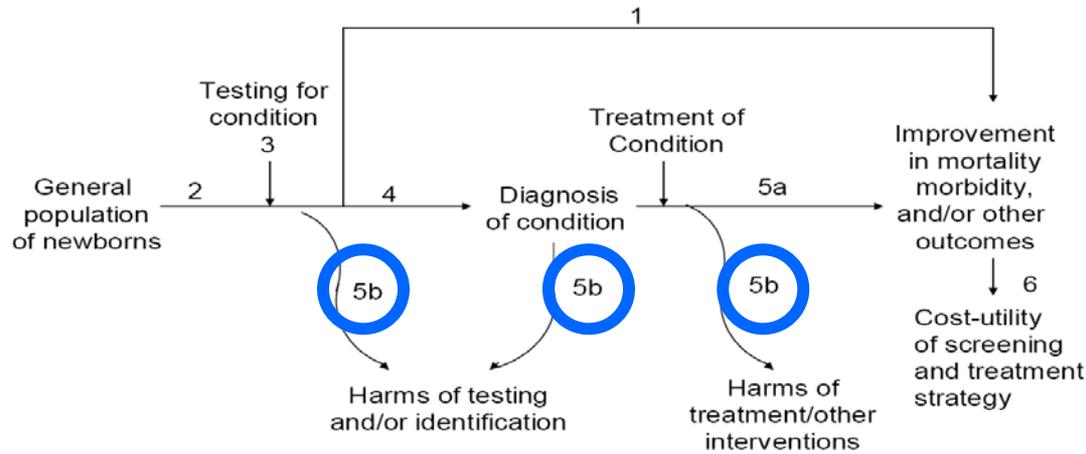


Benefits

What is the clinical utility of the screening test or screening algorithm?

- **5a**: What are the benefits associated with use of the screening test?

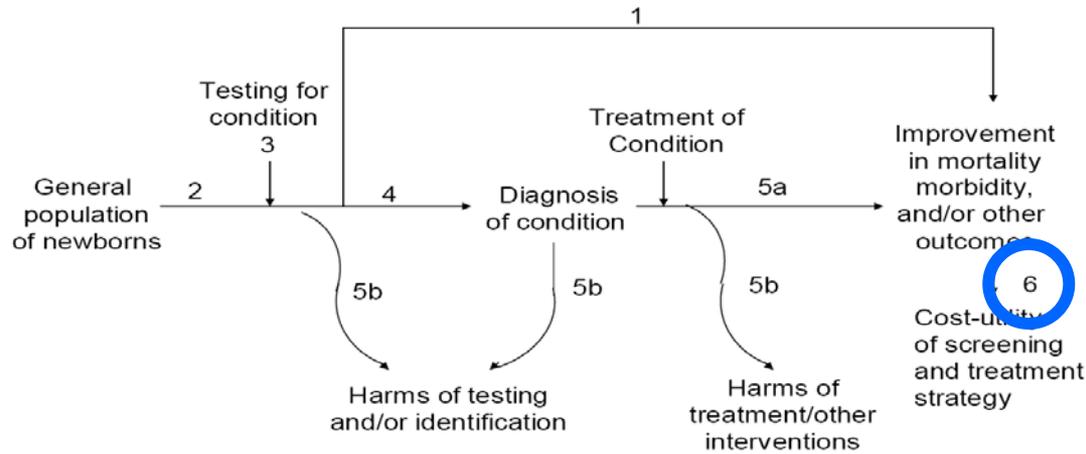
Key Question 5b



Harms

- What is the clinical utility of the screening test or screening algorithm?
 - **5b**: What are the harms associated with screening, diagnosis and treatment?

Key Question 6



Cost Effectiveness

How cost effective is the screening, diagnosis and treatment for this disorder compared to usual clinical case detection and treatment?

Translating Evidence into Recommendations

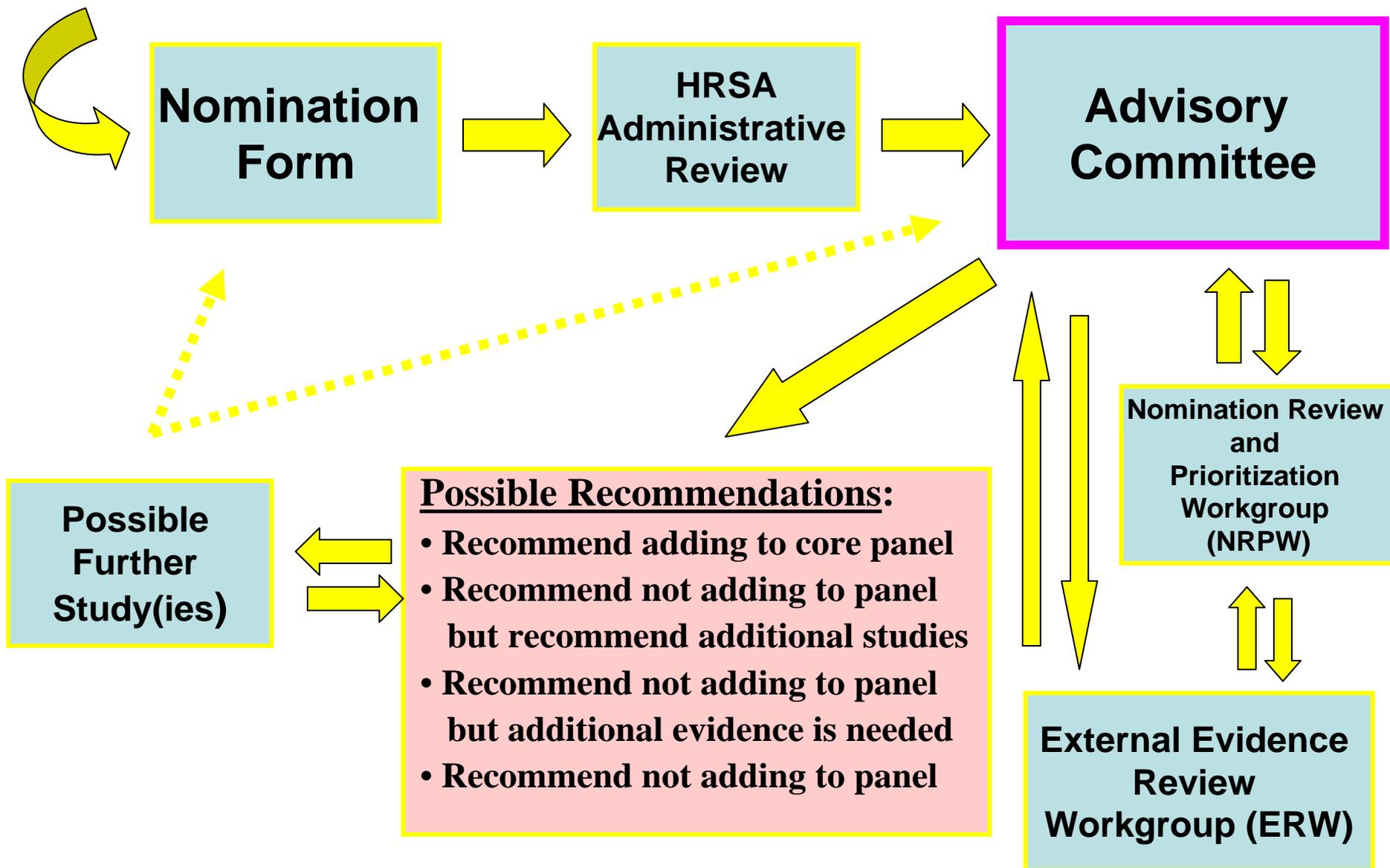
- Judgment regarding the **magnitude of net benefit** (benefits minus harms)
- Judgment of the **adequacy of evidence** in answering the key questions
- Judgment of the **certainty of net benefit**

Evidence Review Reporting

- All decisions for inclusion made by AC
- Evidence group is purely objective; ERG makes no recommendations
- Publication of evidence review and Committee recommendations:

As a Committee Report to be published on the Committee website as well as in a journal, from the workgroup, the Committee or in some combination but will be publicly available

ACHDNC Evidence Review Process: Overview



ACHDNC Progress in Considering New Recommendations as of December 2009

- **9 nominations submitted to HRSA/MCHB and reviewed by staff**
- **9 completed nominations forwarded to ACHDNC Chair, 4 conditions have been sent forward for external evidence review: Pompe, SCID, Krabbe Disease and just last month Hemoglobin H.**
- **Routine Screening for hyperbilirubinemia and critical congenital heart disease (by pulse oximetry) is now in internal review by a subcommittee**
- **Evidence and Committee review of Pompe, SCID, and Krabbe Disease are complete; All have been referred back to nominators for necessary additional studies. An NICHD-funded Committee will work with the various groups to ensure the required research is done**

Fabry, Niemann-Pick and SMA: NOT ready for evidence review, as the population-based screening test and/or treatment are not yet available

Section 1111 (ACHDNC)

- Make systematic [evidence-based](#) and [peer-reviewed recommendations](#) that include the heritable disorders that have the potential to significantly impact public health for which all newborns should be screened, including secondary conditions that may be identified as a result of the laboratory methods used for screening
- Develop a [model decision-matrix](#) for newborn screening expansion, including an evaluation of the potential public health impact of such expansion and periodically [update the recommended uniform screening panel](#), as appropriate, based on such decision-matrix

Newborn Screening Translational Research Coordinating Center

In September 2008, the NICHD awarded a 5 year contract to the American College of Medical Genetics (ACMG) to create a Coordinating Center that will establish a research infrastructure for Newborn Screening studies.

The NBSTRN Coordinating Center (NBSTRN-CC) will facilitate research to develop new screening methods and support the conduct of clinical trials for new therapeutic interventions.

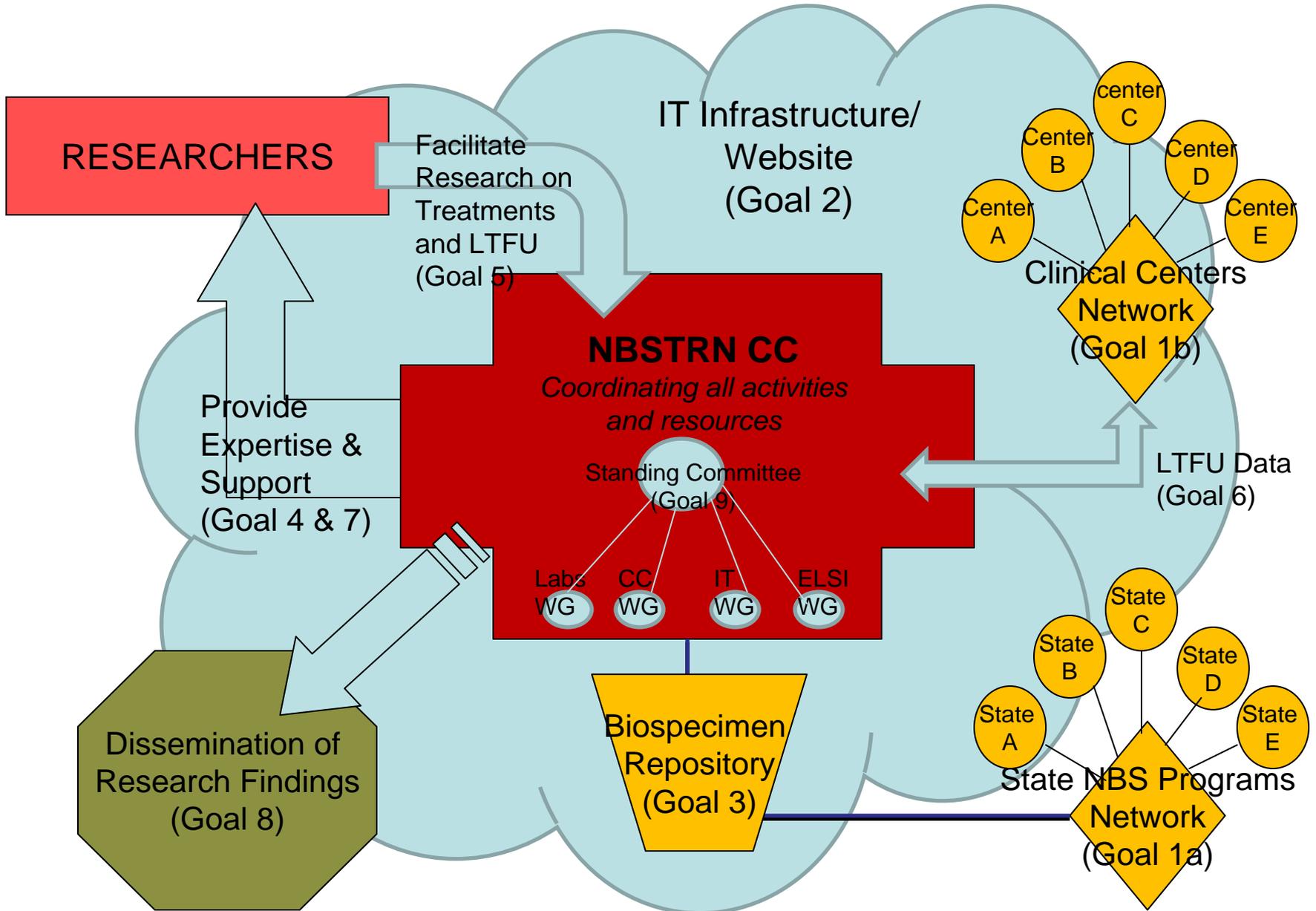
Newborn Screening Translational Research Network Coordinating Center - Objectives

- Establish an organized network of State newborn screening programs and clinical centers**
- Develop, implement and refine a national research informatics system for investigators and policy makers**
- Establish and administer an efficient and reliable repository of residual dried blood spots**
- Provide expertise and support to researchers related to regulatory requirements associated with informed consent, IRBs and state and local research policy associated with NBS.**

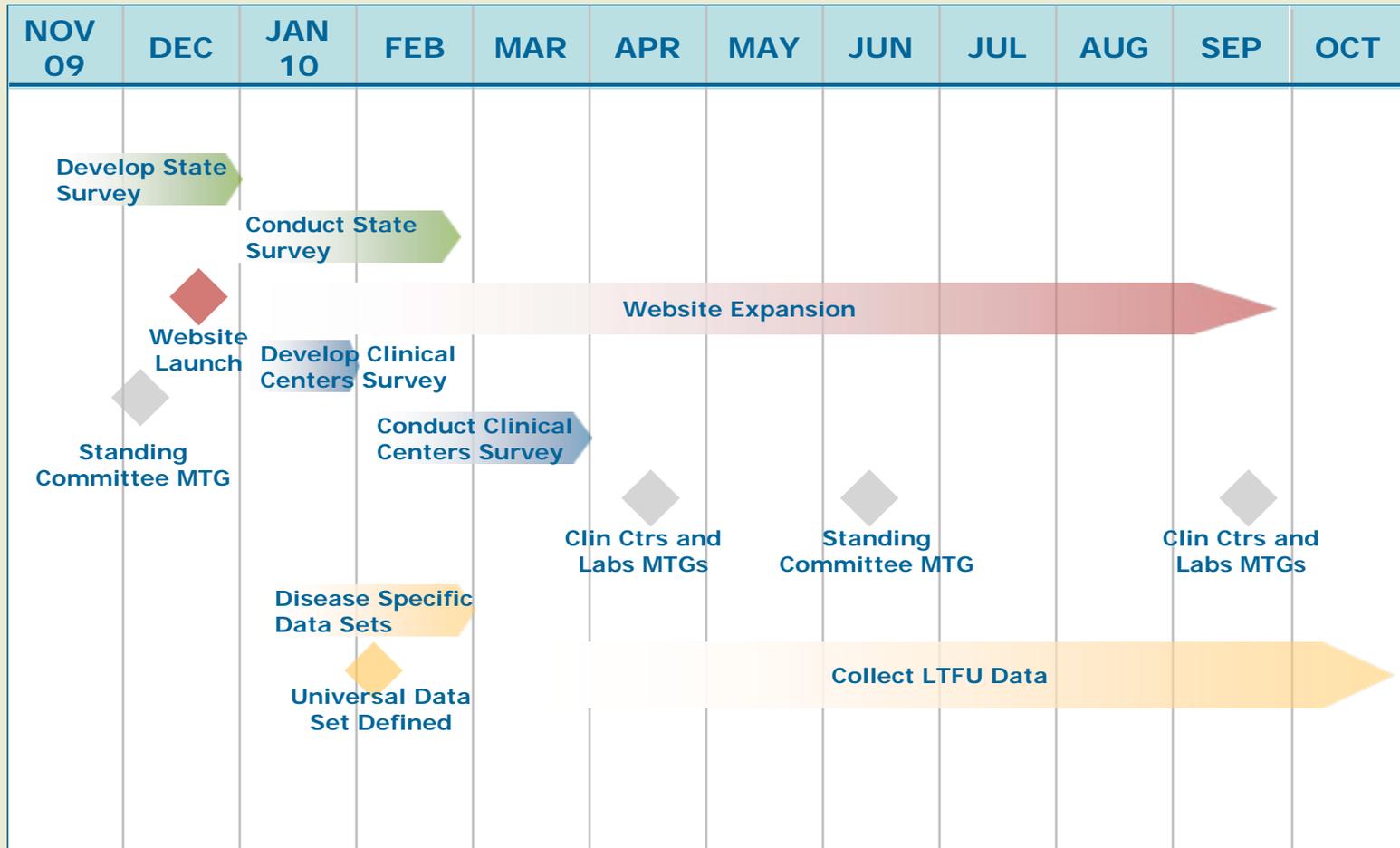
Newborn Screening Translational Research Network Coordinating Center - Objectives

- Facilitate research on the development of new methods and technologies**
- Facilitate research on screened and treated patients to define effectiveness of treatments and long-term outcomes**
- Provide statistical leadership and clinical trial design expertise for the individualized needs of researchers through the NBSTRN Coordinating Center**
- Facilitate the timely dissemination of research findings**

Newborn Screening Translational Research Network



NBSTRN Project Timeline



Goal 1a

Goal 1b

Goal 2

Goal 6

Statement of Work/ Objectives

- 9) Establish a steering committee comprised of knowledgeable healthcare professionals, public health professionals, ethicists and scientists to make recommendations to NIH program regarding research proposals to have access to NBSTRNCC
 - Review consistent with NIH standards
- 10) NIH-supported researchers, in conjunction with their Institutes program officer, will nominate research projects for consideration by the network in order to gain access to the NBSTRNCC

Why an Organized System for Collaborative Research in Rare Genetic Disease is Needed

- **Thousands of rare genetic diseases**
 - **Low statistical power at best; less at worst**
 - **Currently testing in 1500+ genes; 4000+ tests**
 - **Mostly children**
- **Clinical trials networks on a company by company basis are very expensive**
- **Multidisciplinary nature and varied symptoms specific to diseases**
- **Almost no evidence based care**
- **Little information on long-term outcomes whether in NBS or not**
- **Need protocol-driven work to ensure compatibility of data**

Why an Organized System is Needed for Newborn Screening

- **Evidence base is in disarray; expert opinion and observational studies**
- **Quality of evidence varies over aspects of the disease**
 - **Condition**
 - **54 conditions covering over 150 genes**
 - **Numerous candidates for expansion are emerging**
 - **Incidence/prevalence data and full understanding of range of burden is tenuous until screening**
 - **Screening test evidence is hard to compare across states due to variability**
 - **Diagnostic conformation data is often cleaner**
 - **Treatment data is usually good if therapeutics went through FDA required clinical trial + phase 4 surveillance is done**

Some Existing Systems for Organized Translational Research in Genetics

- **National Cancer Cooperative Study Groups**
 - **Many parallels to genetic needs of diseases**
- **NIH/ORD Rare Disease Centers**
- **GWAS studies**
- **Human Variome Project**
- **Numerous unconnected but existing registries and data collection projects +/- curation**