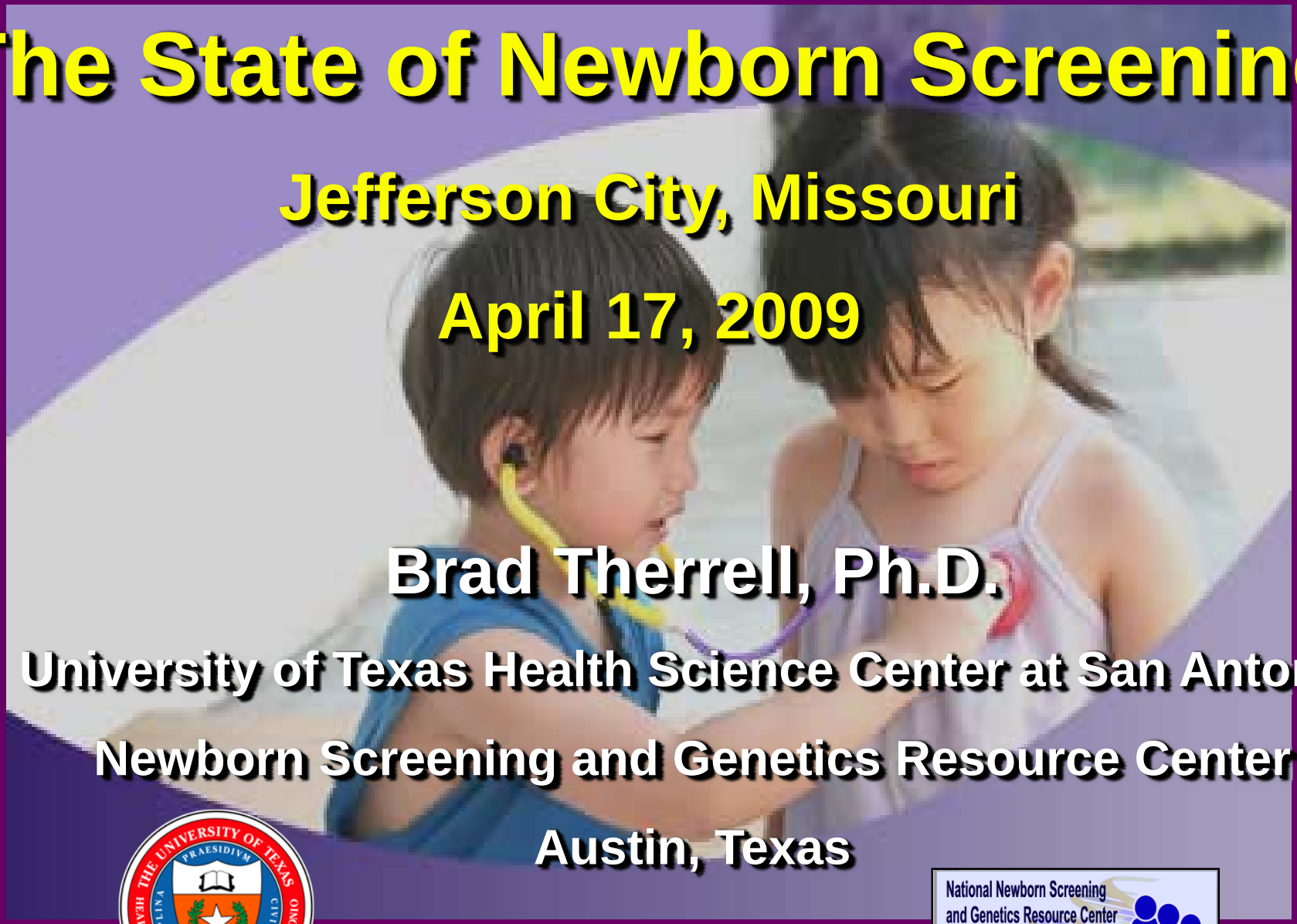
The State of Newborn Screening

Jefferson City, Missouri

April 17, 2009



Brad Therrell, Ph.D.

University of Texas Health Science Center at San Antonio

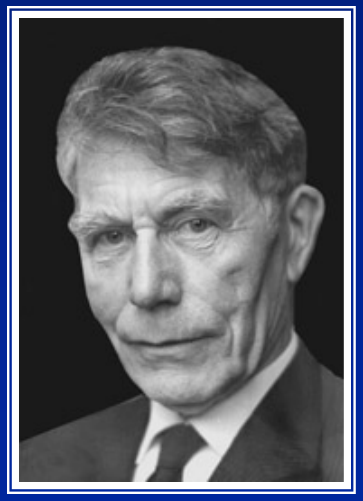
Newborn Screening and Genetics Resource Center

Austin, Texas

Newborn Screening History

The Early Days

- 1902 – Garrod - Originated the phrase “Inborn Error of Metabolism”



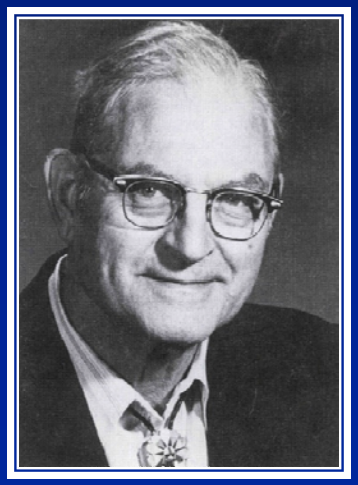
- 1934 – Følling - Identified PKU as an inborn error associated with mental retardation - diaper test - ferric chloride - presence of phenylpyruvic acid in urine

Source: http://www.pkuworldlink.org/history.html

Newborn Screening History

The Early Days

- 1953 - Bickel - PKU dietary treatment - Published the results of dietary therapy and formula treatment developed by himself, Evelyn Hickmans, John Gerrad, and Louis Woolf in the medical journal Lancet.



- 1959 - Guthrie - Filter paper test for PKU - Developed a simple, inexpensive test with blood on filter paper for early detection of PKU (and other disorders). Early detection and treatment prevents the harmful effects of PKU.

Source: http://www.pkuworldlink.org/history.html

Newborn Screening
History of PKU

- 1930's: dietary treatment was proposed
- 1950's: dietary treatment became available
  - greatest cognitive improvement seen in youngest patients

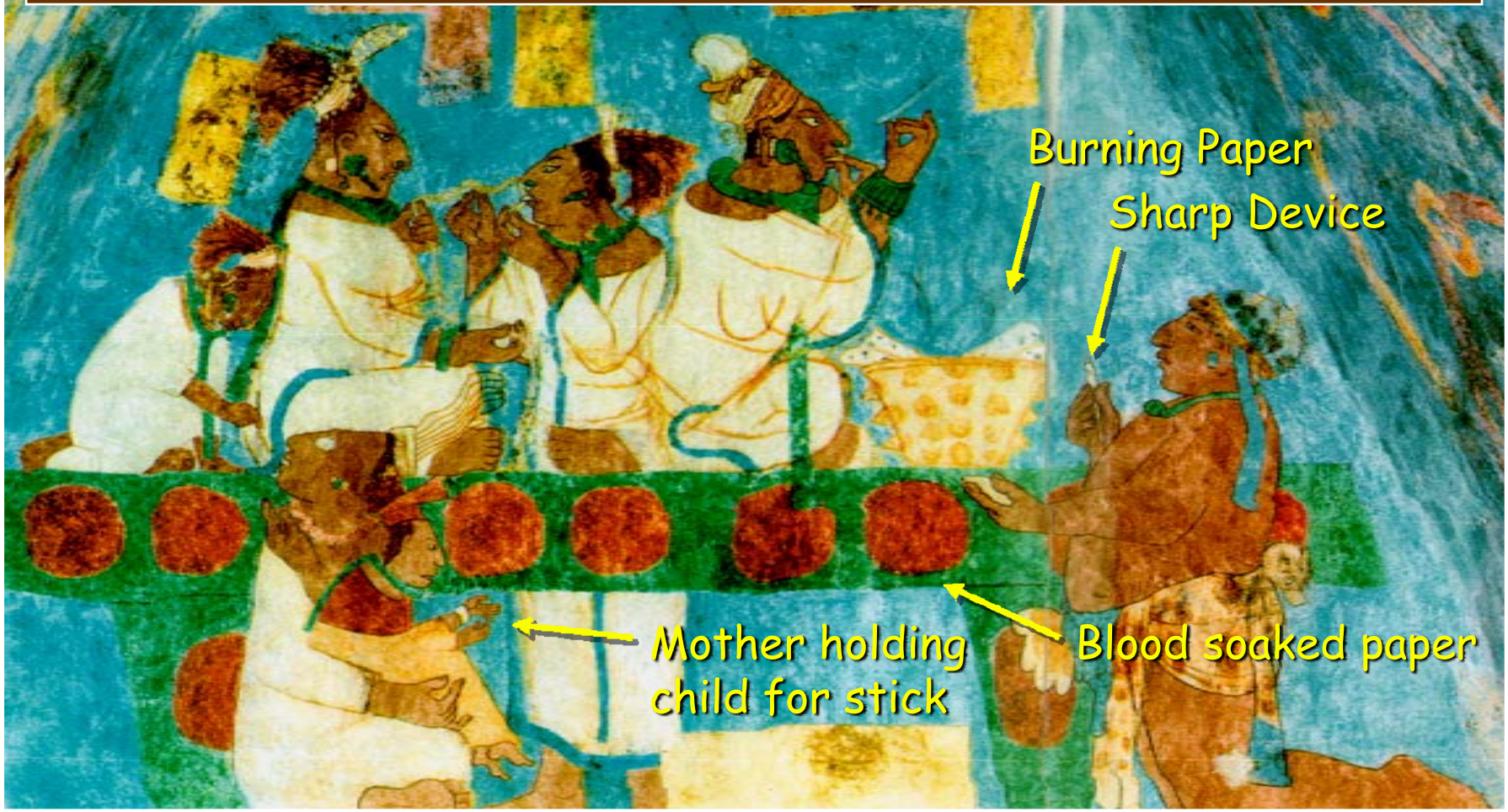
Fig 19. Contrast—untreated and treated phenylketonurics. The 11-year-old boy is severely retarded, whereas his 2½-year-old sister, diagnosed in early infancy and promptly treated with the mind-saving diet, is normal.[17]

Pediatrics, **105:**89, 2000.

Earliest Reference Dried Blood Spots?

Mayan Mural 780 AD – Bonampak, Mexico – "Letting drops of blood fall on paper that will be burned to conjure the gods"

National Geographic 1995



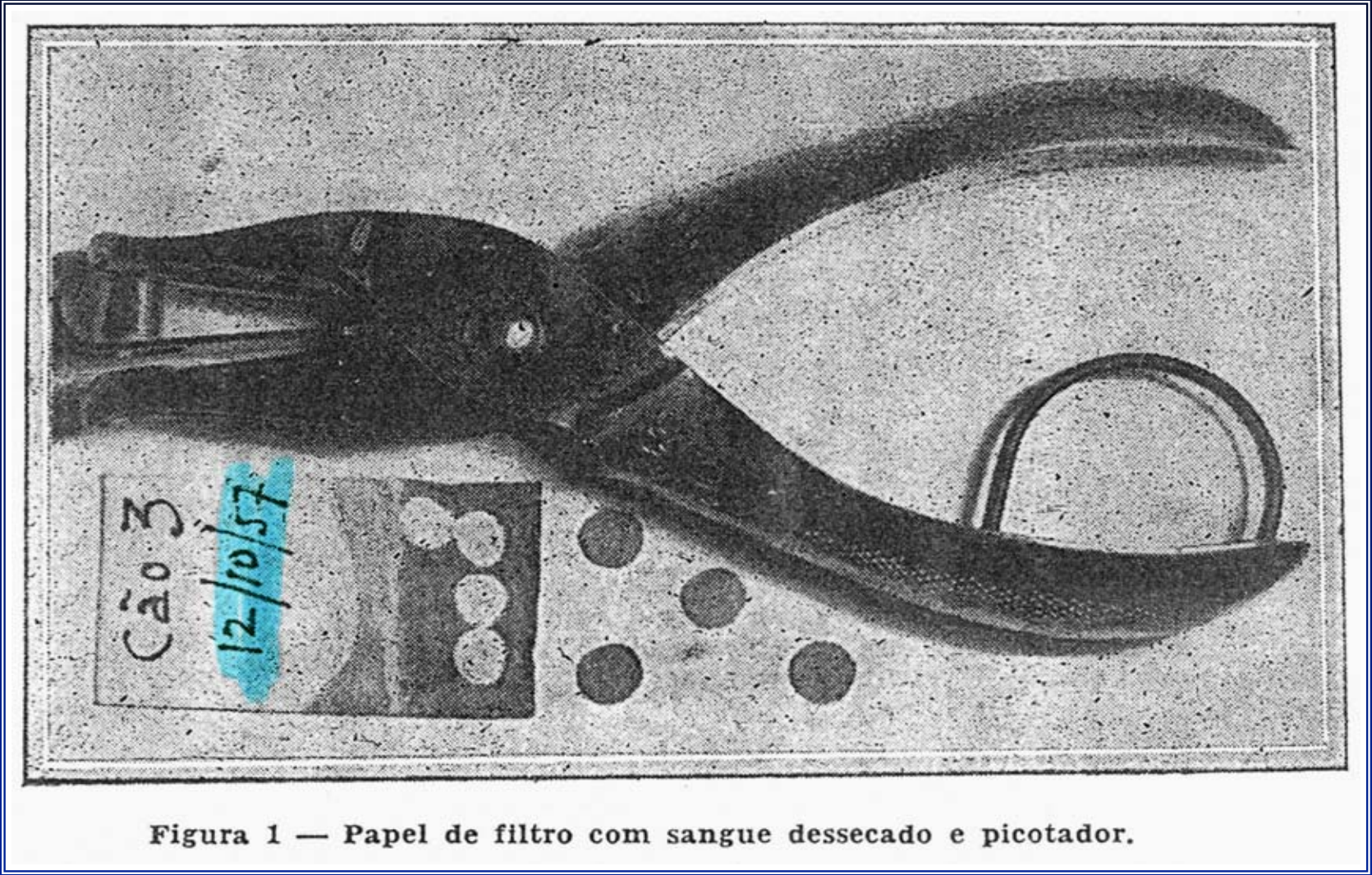


Figura 1 — Papel de filtro com sangue dessecado e picotador.

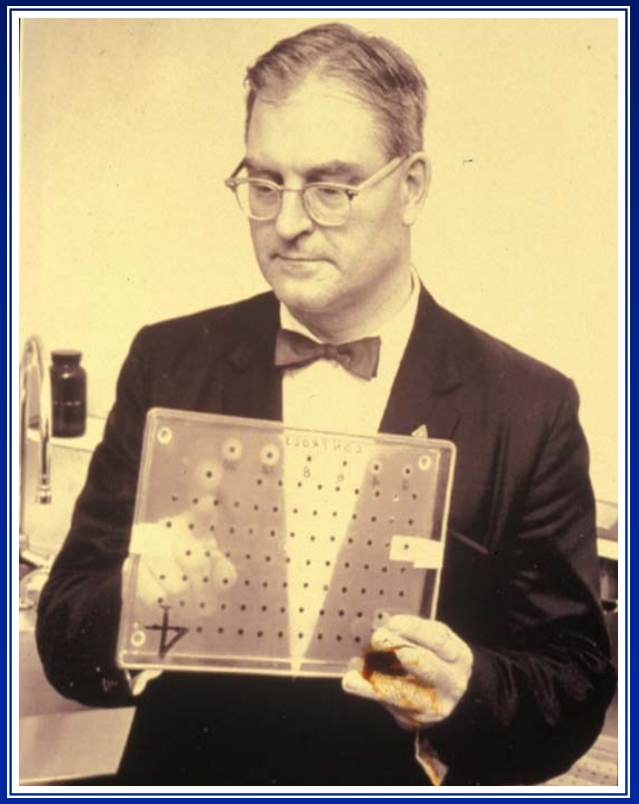
1957: First reported use of a paper punch device to obtain standardized aliquots of dried blood from filter paper.

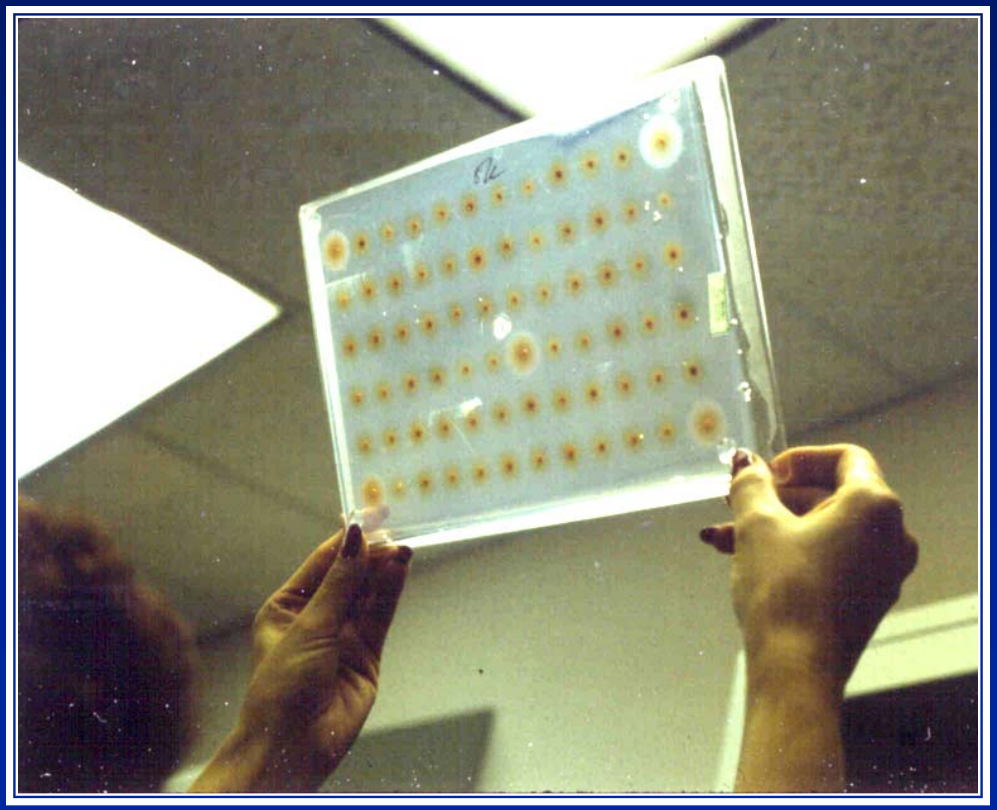
Source: Pellegrino J, Brener, Z., Revista Brasileira de Malariologia e Doencas Tropicais 1958:39-44. [Rio de Janeiro, Brazil]

Newborn Screening History

1959 – Guthrie – Began working on PKU method

1961 – Guthrie – Reported his bioassay for PKU
(1963) using dried blood collected on filter paper





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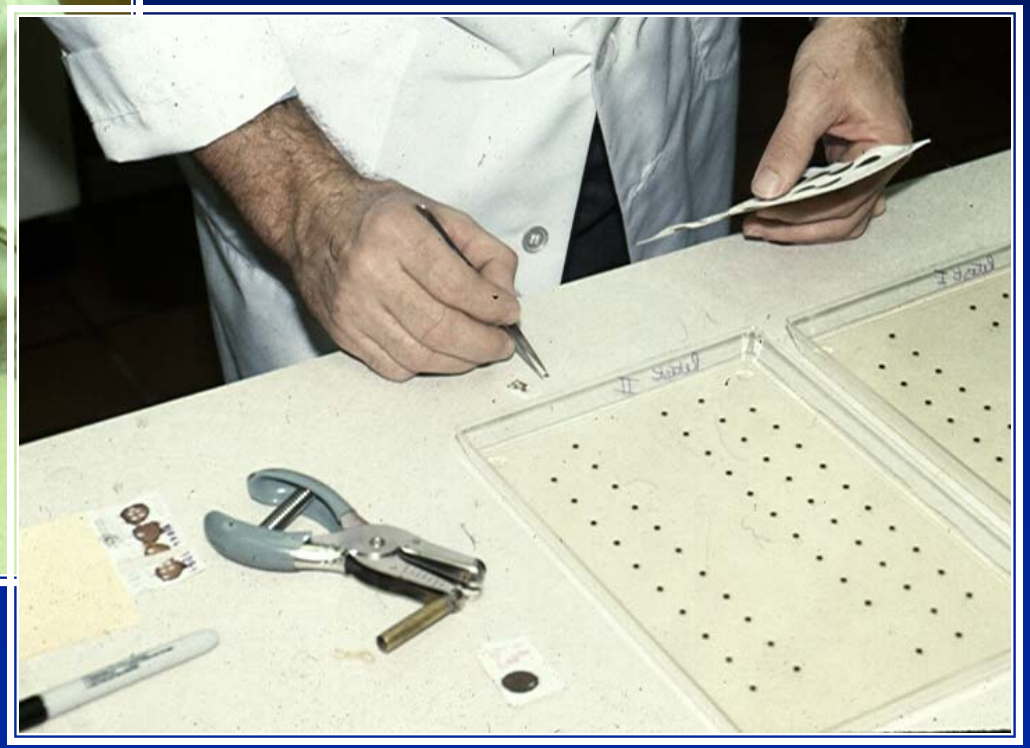
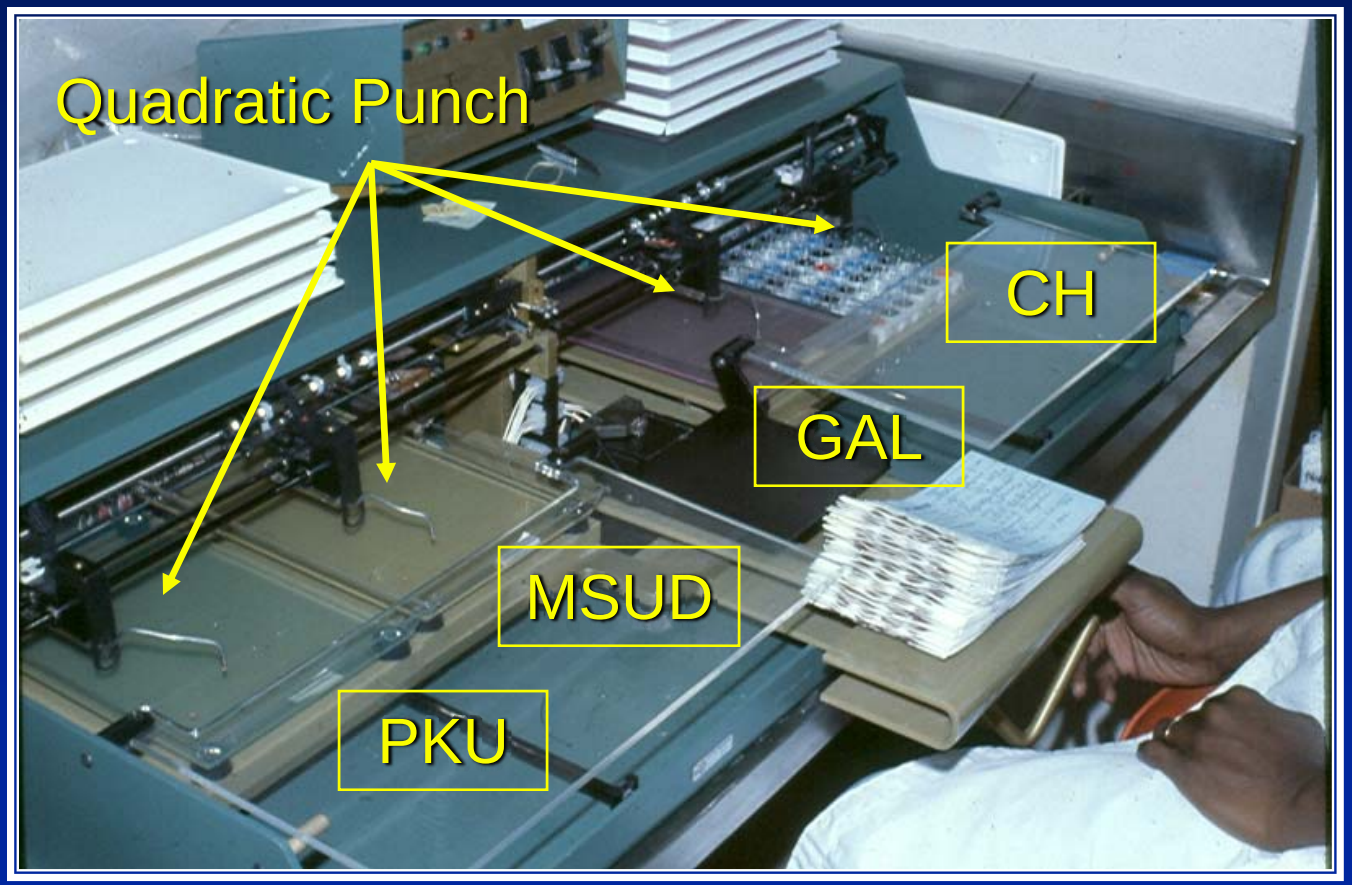
Newborn Screening History Lessons Learned

Specimens punched and transferred manually



Newborn Screening History
Lessons Learned

1960s – Phillips (USA), Thalhammer (Austria) –
Began to develop automated tray scanning



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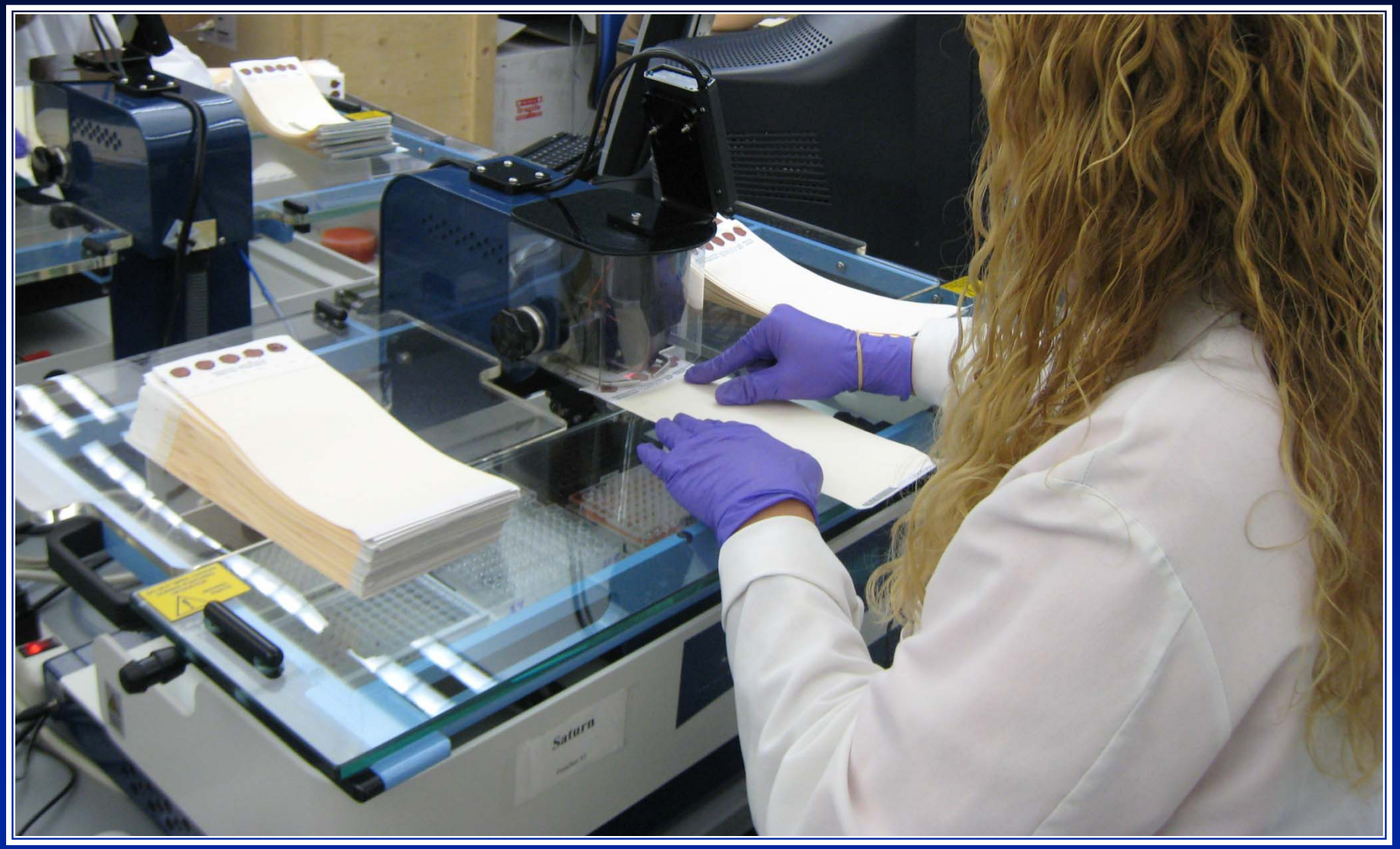
Later Generation Punch Machines



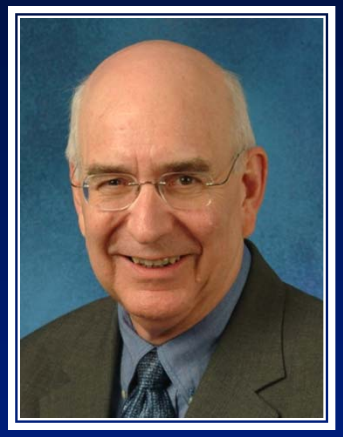
Newborn Screening History

- *1973 - Dussault -Thyroxine (T4) determination in dried blood by radioimmunoassay: a screening method for neonatal hypothyroidism.* Union Med Can 1973;102:2062-4.

- *1973 - Garrick - Sickle cell anemia and other hemoglobinopathies: procedures and strategy for screening spots of blood on filter paper as specimens.* N Engl J Med 1973; 288:1265-8.

- *1977 - Pang - Micro filter paper method for 17-hydroxy-progesterone radioimmunoassay: its application for rapid screening for congenital adrenal hyperplasia.* J Clin Endocrin Metab 1977;45:1003-8.

Brief Newborn Screening History - DNA



1987 - *McCabe - DNA microextraction from dried blood spots on filter paper blotters: potential applications to newborn screening.*
Hum Genet 75:213-216.

1993 – *Farrell - Application of DNA analysis in a population-screening program for neonatal diagnosis of cystic fibrosis (CF): comparison of screening protocols.*
Am J Hum Genet 52:616-26.

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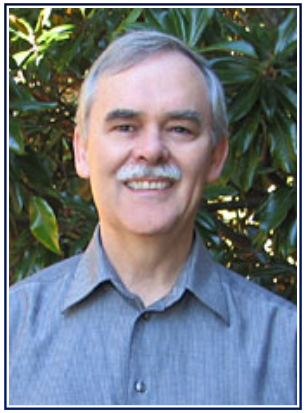
Brief Newborn Screening History – MS/MS



➢ 1990 - Milllington - *Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism.* J Inherit Metabol Dis 13:321-324.

➢ *1993 - Chace - Rapid diagnosis of phenylketonuria by quantitative analysis for phenylketonuria and tyrosine in neonatal blood spots by tandem mass spectrometry.*
Clin Chem 39:66-71.

➢ 1995 - Rashed - *Diagnosis of inborn errors of metabolism from blood spots by acylcarnitines and amino acids profiling using automated electrospray tandem mass spectrometry.*
Pediatr Res 38:324-31.

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Brief Newborn Screening History

- 1930s – Diaper Test for PKU
- 1950s – Treatment for PKU
- 1960s – Filter paper test for PKU, research, automated filter paper punching
- 1970s – Thyroid testing, sickle cell testing, CAH testing, expanded metabolic testing
- 1980s – Computerized data management and tracking, automation research
- 1990s – DNA from filter paper, MS/MS techniques, CF studies, infectious diseases (HIV), hearing.
- 2000s – Extended multiplexing, privacy (HIPAA), continued expanded screening

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The Paradigm Shift:

“Technology Driven”

Analyte Screening by Multiplex Assays –

Hemoglobins - Isoelectic Focusing, HPLC
Metabolics - Tandem Mass Spectrometry

What is a tandem mass spectrometer?

Newborn Screening Challenges - MS/MS

- Significant “paradigm shift” – MS/MS is expensive, complex and can detect disorders for which no effective treatment is available
- Sudden expansion of presumptive positive cases - Multiple disorders detected – most disorders are very rare – natural disease course poorly understood
- Confusion as to how many disorders/conditions are detectable by MS/MS – the “numbers game”
- Detection of “mild/variant” forms of diseases (e.g. SCAD, MCAD) that may not require treatment
- Staff re-training for unfamiliar and difficult roles
- Significant stress on financial and personnel resources that are already limited

Newborn Screening is a SYSTEM!

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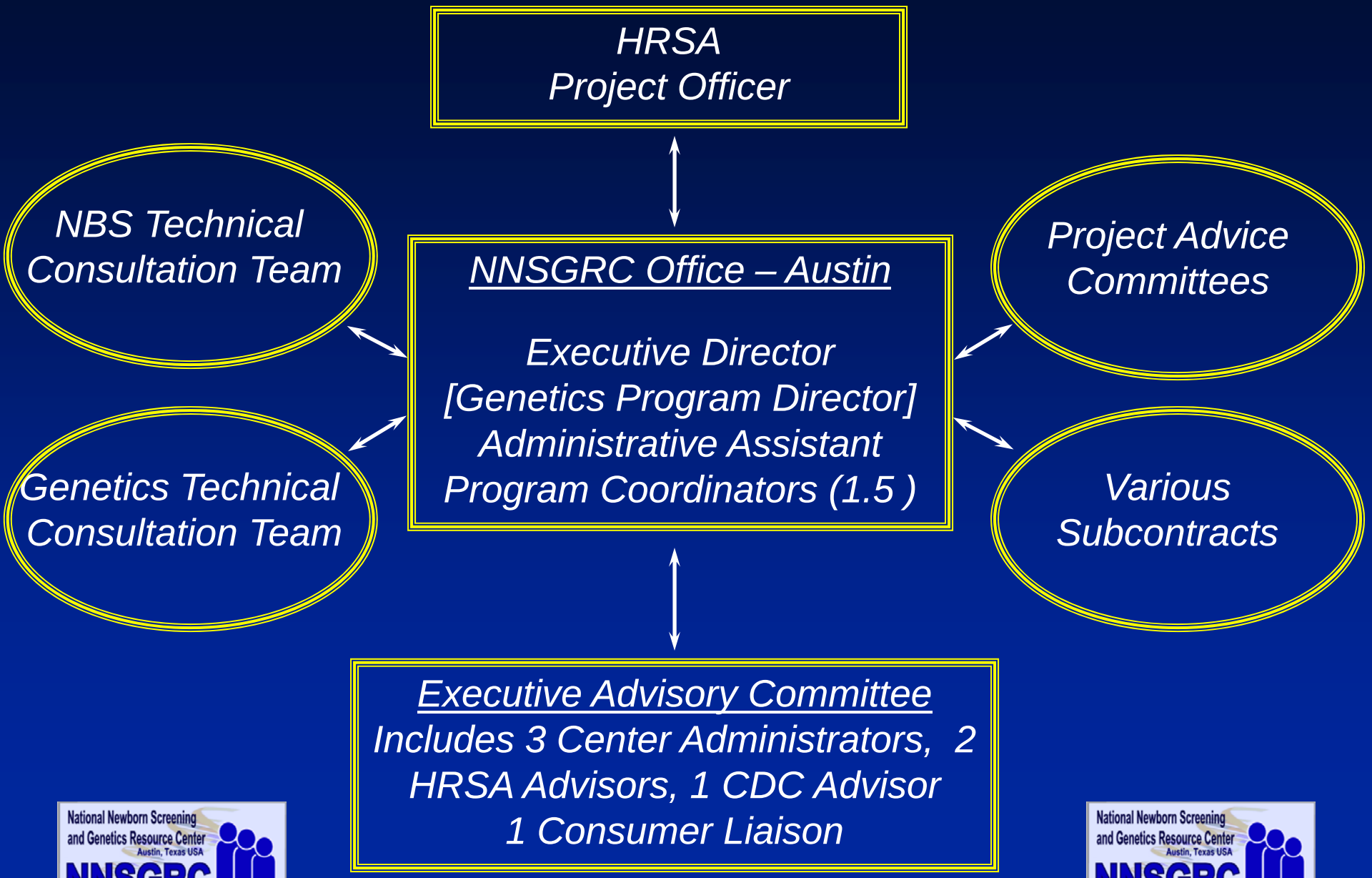
Newborn Screening Process

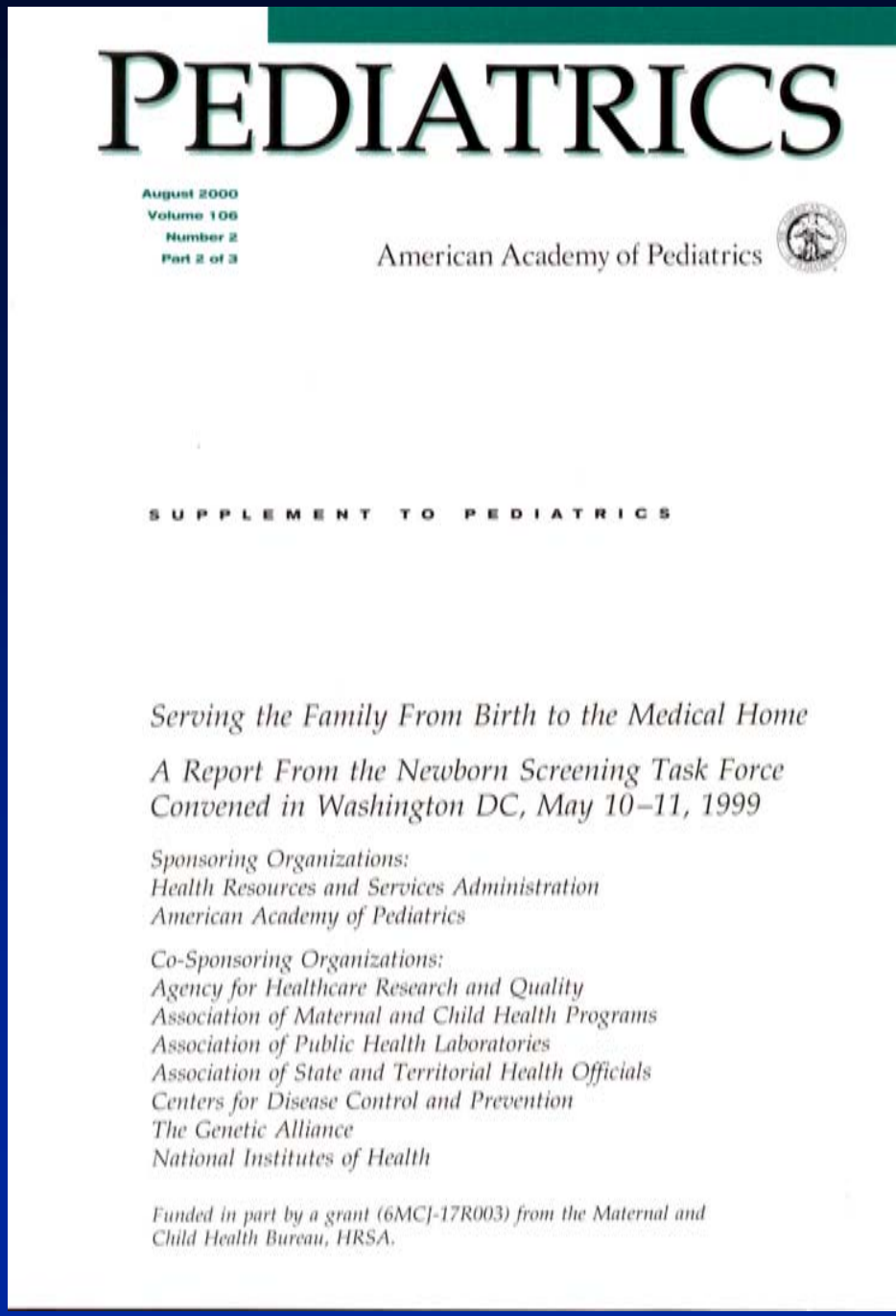
Newborn Screening Process (continued)

NNSGRC INFRASTRUCTURE



AAP Newborn Screening Task Force

- Vol. 106, Aug. 2000, Suppl.
- Approved by:
  - AAP Board of Directors
  - AAP Committee on Genetics
  - AAP Committee on Fetus and Newborn
  - Medical Home Initiatives for Children with Special Needs-Project Advisory Committee
  - AAP Task Force on Newborn and Infant Hearing



PEDIATRICS

August 2000
Volume 106
Number 2
Part 2 of 3

American Academy of Pediatrics

SUPPLEMENT TO PEDIATRICS

Serving the Family From Birth to the Medical Home

A Report From the Newborn Screening Task Force Convened in Washington DC, May 10–11, 1999

Sponsoring Organizations:
Health Resources and Services Administration
American Academy of Pediatrics

Co-Sponsoring Organizations:
Agency for Healthcare Research and Quality
Association of Maternal and Child Health Programs
Association of Public Health Laboratories
Association of State and Territorial Health Officials
Centers for Disease Control and Prevention
The Genetic Alliance
National Institutes of Health

Funded in part by a grant (6MCJ-17R003) from the Maternal and Child Health Bureau, HRSA.

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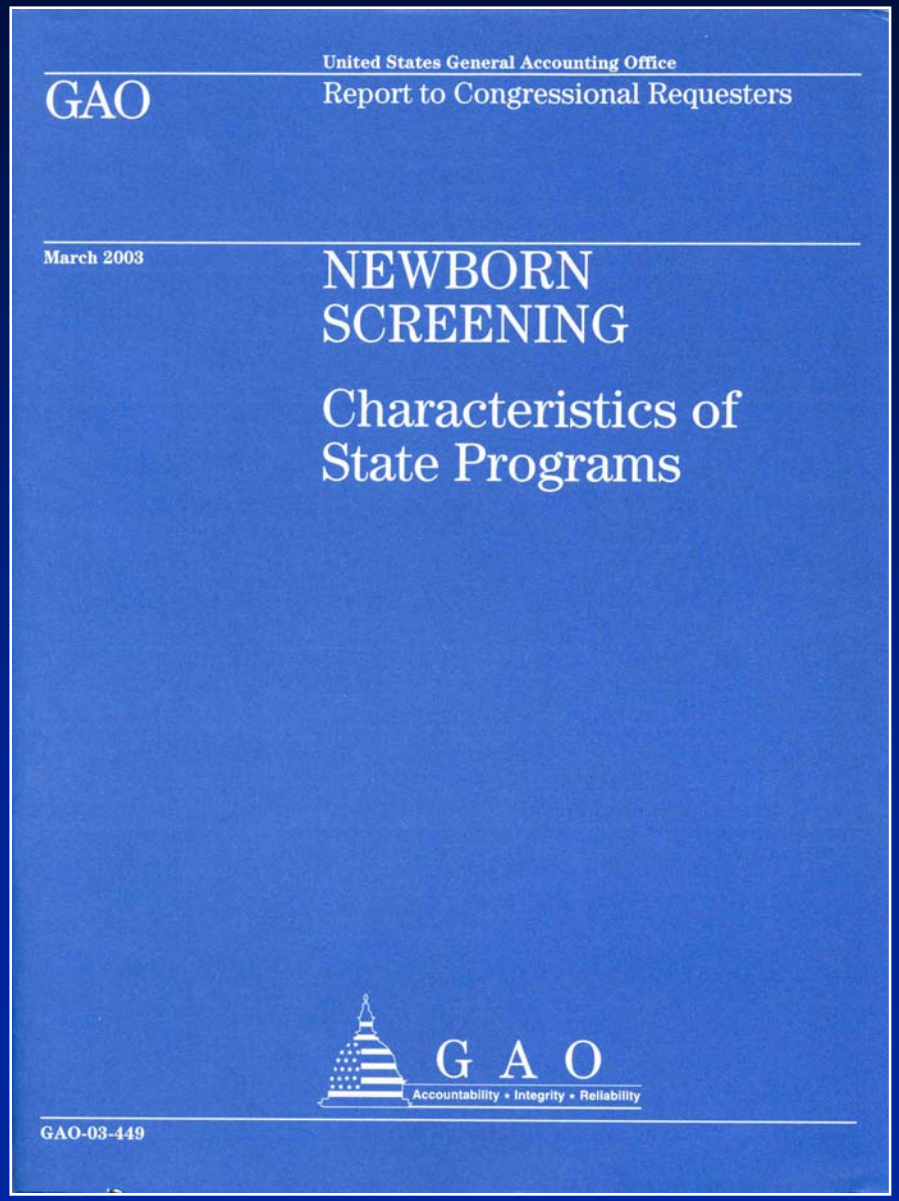
Congressional Interest - Equality

U.S. Government Accounting Office March 2003

Response to Senate Request



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One Approach

HRSA Contract

National Policy Development for NBS Test Selection

American College of Medical Genetics

Scoring Criteria

- Incidence
- Difficulty of diagnosis (birth)
- Disease impact
- Test sensitivity/specificity
- Test characteristics
- Treatment availability & cost
- Treatment efficacy
- Benefits to individual
- Benefits to family & society
- Mortality prevention
- Diagnosis availability
- Management availability
- Simplicity of therapy

National Newborn Screening and Genetics Resource Center Austin, Texas USA NNSGRC

HRSA Contract

National Policy Development for NBS Test Selection

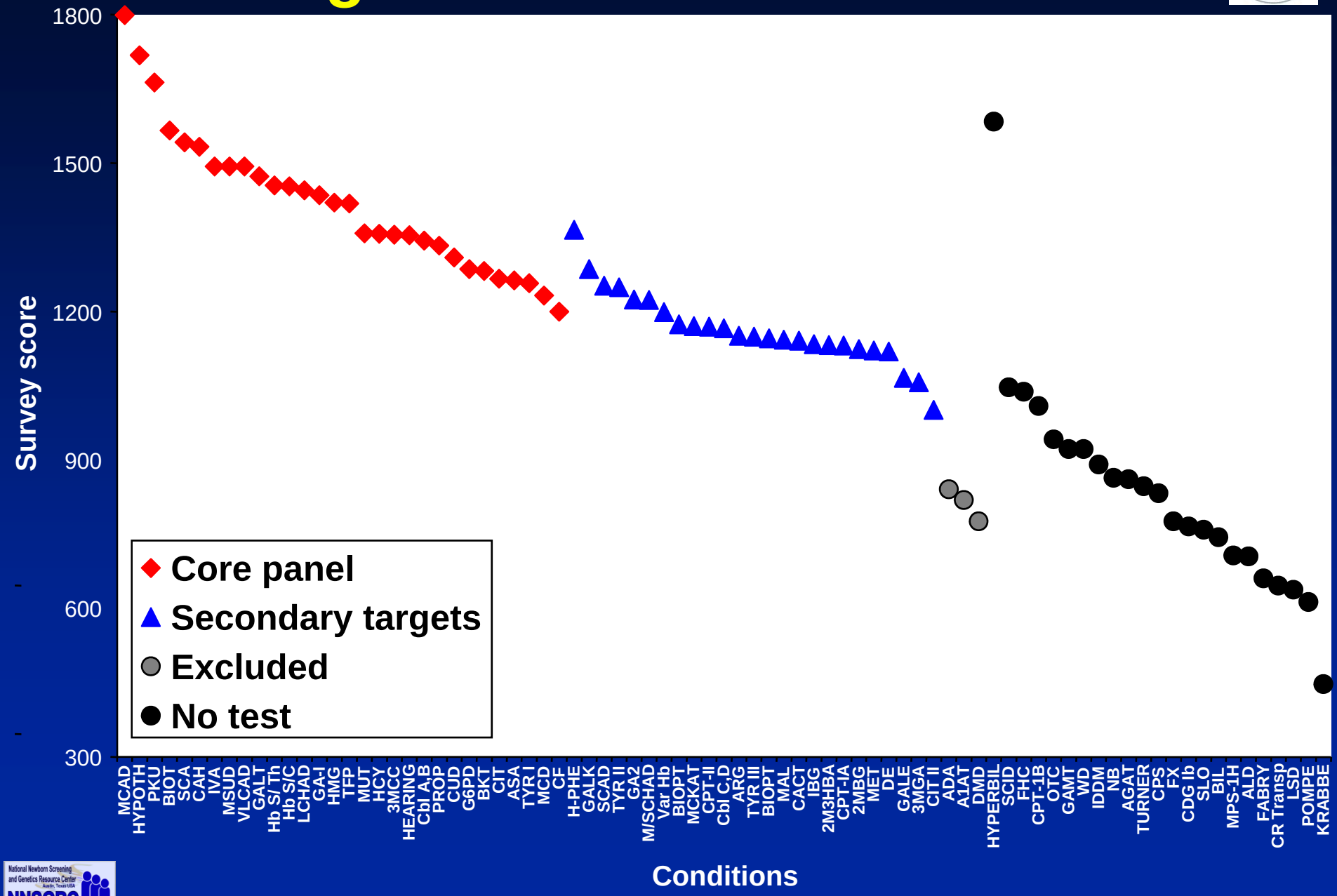
American College of Medical Genetics

Completed January 2005

CRITERIA INCLUDED IN THIS SURVEY	CATEGORIES	SCORE
Incidence of condition	>1:5,000	100
	>1:25,000	75
	>1:50,000	50
	>1:75,000	25
	<1:100,000	0
Phenotype clinically identifiable at birth	Never	100
	<25% of cases	75
	<50% of cases	50
	<75% of cases	25
	Always	0
Burden of disease 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)	Doable in neonatal blood spots **OR** by a simple, in-nursery physical method	50
	High throughput (>200/day/FTE)	20
	Cost (supplies + equipment) per test <1$	20
	Multiple markers in same analysis	20
	Detection of secondary targets	20
	Utilizes a multiplex platform	20
Availability of treatment (Expensive IF >$50,000/patient/year)	Inexpensive and widely available	100
	Expensive OR limited availability	50
	Expensive AND limited availability	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 OUTCOME)	Clear scientific evidence that intervention **IN THE FIRST WEEKS OF LIFE** maximizes outcome	100
	Early intervention improves outcome	50
	No evidence of improved outcome	0
Benefits of early intervention (FAMILY & SOCIETY)	Early intervention 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	Widely available	100
	Reduced availability	50
	Available only in a few laboratories	0
Clinical management	Widely available	100
	Reduced availability	50
	Available only in a few centers	0
Simplicity of therapy	Very high	200
	High	100
	Average	50
	Low	0
	Max score	1650

National Newborn Screening and Genetics Resource Center Austin, Texas USA NNSGRC

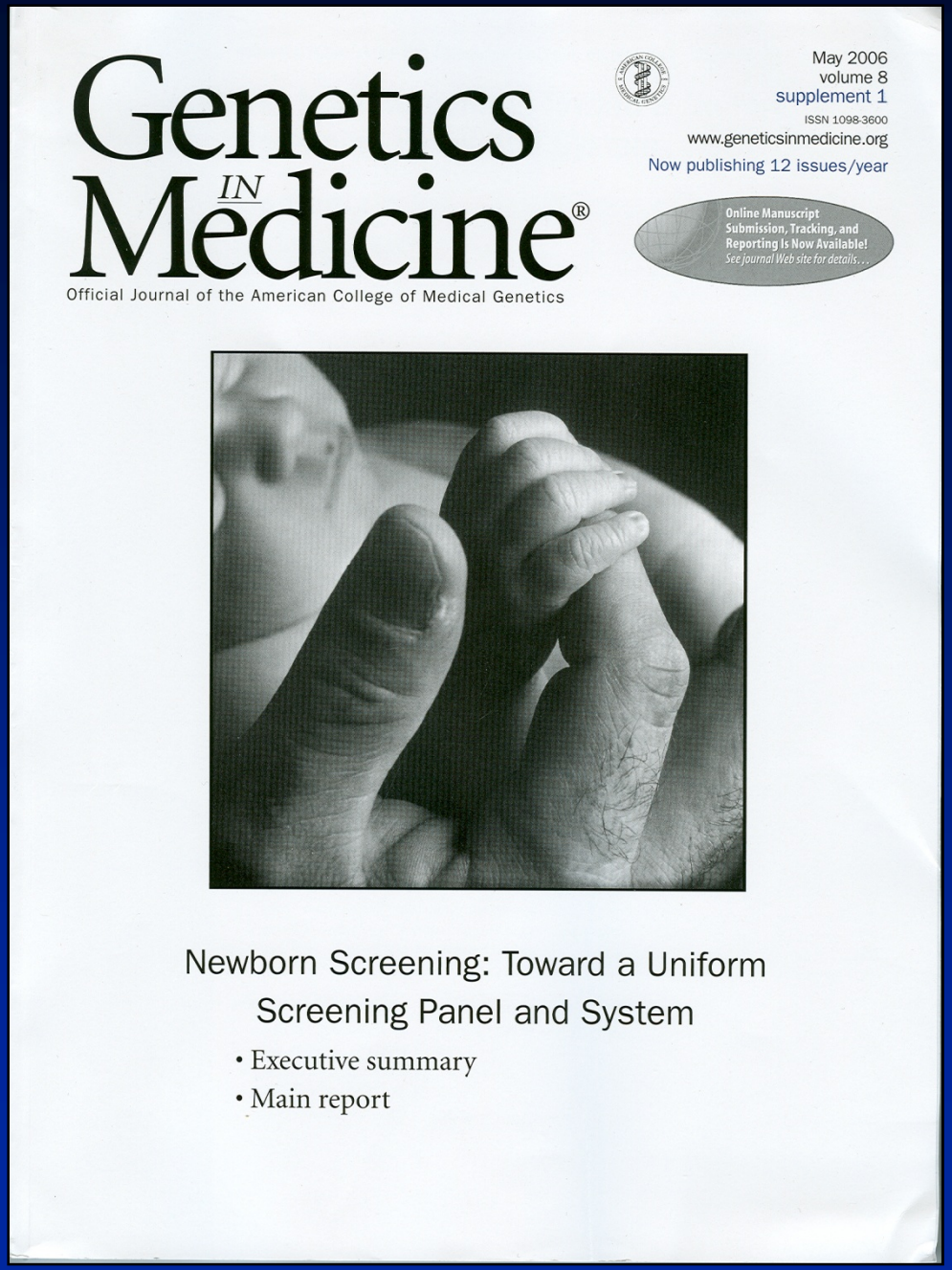
Scoring Conditions for Core Panel



Education - Policy Makers

ACMG Report on Newborn Screening

May 2006



AAP Report on Newborn Screening

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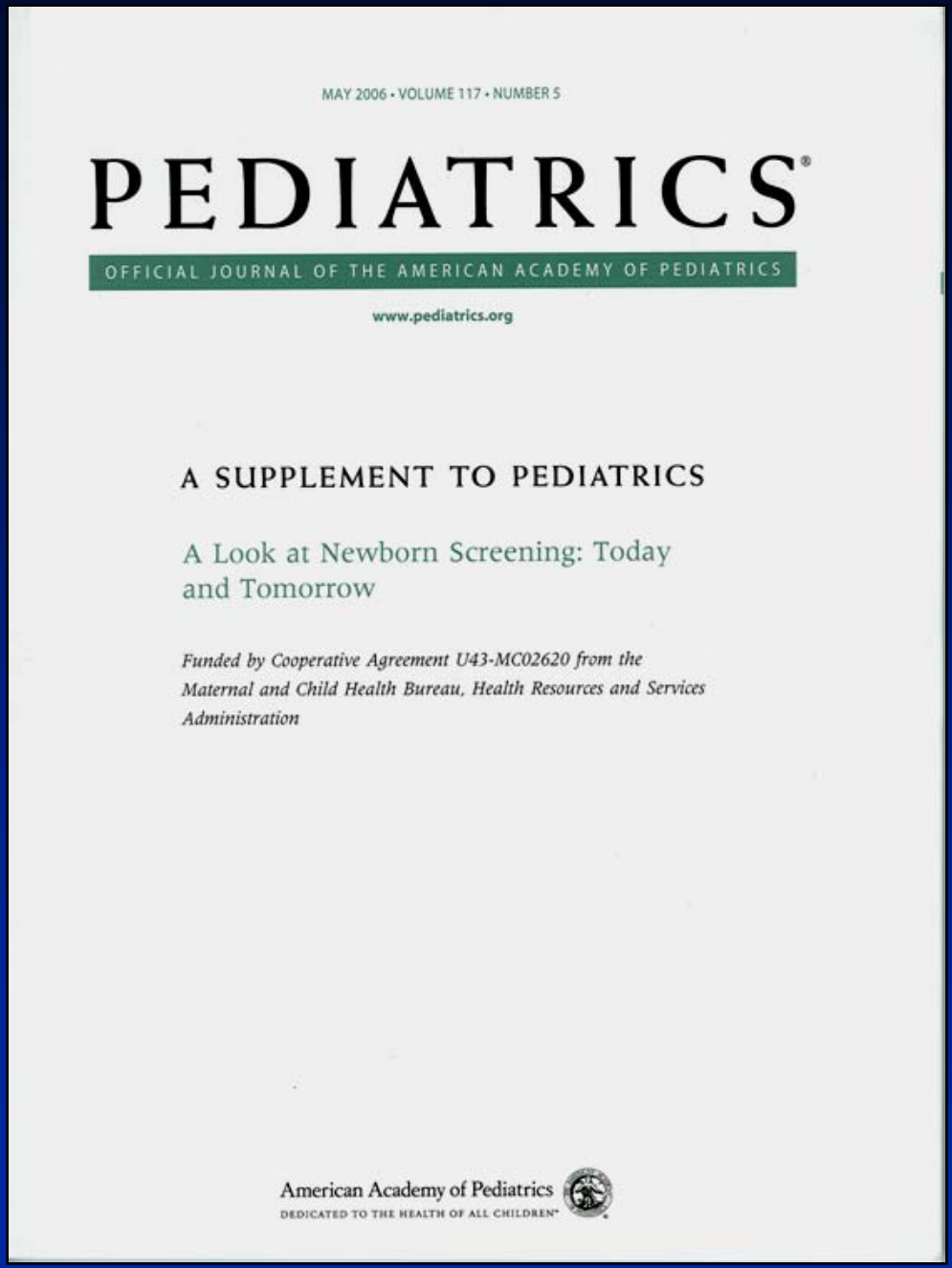

MAY 2006 • VOLUME 117 • NUMBER 5

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

www.pediatrics.org

A SUPPLEMENT TO PEDIATRICS

A Look at Newborn Screening: Today and Tomorrow

Funded by Cooperative Agreement U43-MC02620 from the Maternal and Child Health Bureau, Health Resources and Services Administration

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

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Uniform Panel (Primary Targets)				
MS/MS				
Acylcarnitines		Amino acids		
(9) OA	(5) FAO	(6) AA	(3) Hematology	(6) Others
IVA	MCAD	PKU	SCA	HYPOTH
GA-I	VLCAD	MSUD	Hb S/ Th	BIOT
HMG	LCHAD	HCY	Hb S/C	CAH
MCD	TFP	TYR I		GALT
MUT	CUD	ASA		HEAR
Cbl A,B		CIT		CF
3MCC				
PROP				
BKT				

Secondary Targets				
MS/MS				
Acylcarnitines		Amino acids		
OA	FAO	AA	Hb Pathies	Others
Cbl C,D	M/SCHAD	Hyper-PHE	Variant Hb	GALE
2M3HBA	SCAD	TYR-II		GALK
IBG	MCKAT	BIOPT (BS)		
2MBG	GA-II	TYR-III		
3MGA	CPT-IA	ARG		
MAL	CPT-II	BIOPT (REG)		
	CACT	MET		
	DE REDUCT	CIT-II		

ACMG – Developed '*Just in Time*' Guidance for Physicians – ACT Sheets

- Utilized recognized experts to develop actions to be taken upon receipt of screening results.
- Developed flow diagrams leading to diagnosis with understanding that they were templates that would likely need specialist support.
- Published on website.

NNSGRC Homepage

http://genes-r-us.uthscsa.edu

National Newborn Screening and Genetics Resource Center - Windows Internet Explorer

http://genes-r-us.uthscsa.edu/

National Newborn Screening and Genetics ...

NNSGRC

National Newborn Screening & Genetics Resource Center

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Welcome to the National Newborn Screening and Genetics Resource Center web site: GeNeS-R-US, (Genetic and Newborn Screening Resource Center of the United States).

The National Newborn Screening and Genetics Resource Center (NNSGRC) is a cooperative agreement between the Maternal and Child Health Bureau (MCHB), Genetic Services Branch and the University of Texas Health Science Center at San Antonio (UTHSCSA), Department of Pediatrics.

We provide information and resources in the area of newborn screening and genetics to benefit health professionals, the public health community, consumers and government officials.

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Search our site

ACMG ACT Sheets

Links of Special Interest

Papers and Reports----------

NEW! SACGHS Report: Oversight of Genetic Testing (2008)

ACT Sheets (ACMG)

ACMG Newborn Screening Report (2006)

Related Links----------

Brochure for Parents: Model developed for state use based on parent focus groups

Brochure for Providers: Model developed for state use based on provider focus groups

Laboratory Services: Additional non-state newborn screening laboratory services

start | National Newbor... | 08.06.21 Austin... | 5:44 AM

National Newborn Screening and Genetics Resource Center - Windows Internet Explorer

http://genes-r-us.uthscsa.edu/

National Newborn Screening and Genetics ...

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Google™ Custom Search | Search

Search our site

National Data Link

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start | National Newbor... | 08.06.21 Austin... | 5:44 AM

Resources - NNSGRC - Windows Internet Explorer

http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm

Resources - NNSGRC

NNSGRC
National Newborn Screening & Genetics Resource Center

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Resources

- General Resources
- Reports and Publications
- Newborn Screening
- Genetics
- Birth Defects

STATE MAP PAGE

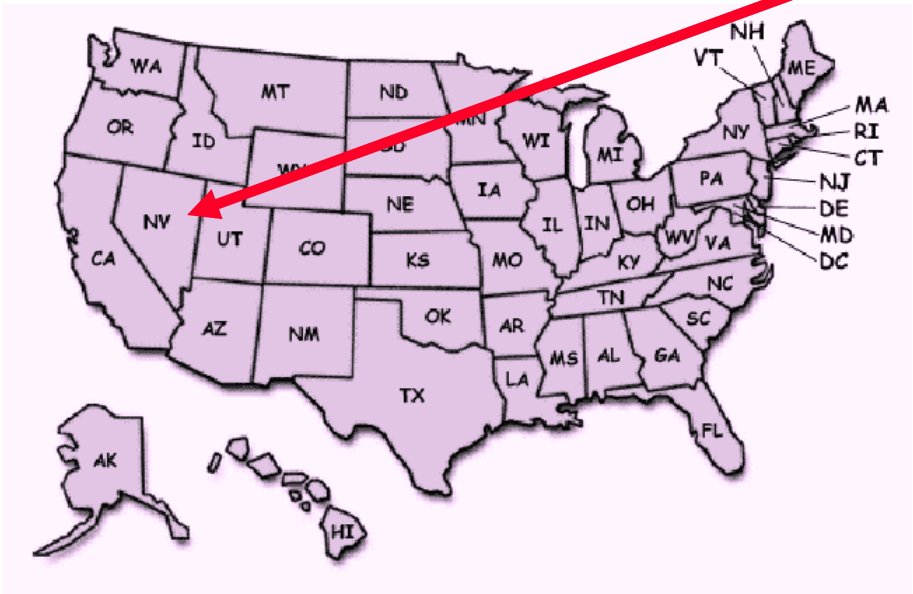
Newborn Screening

Select the state initials on the map or the state name in the table below for newborn screening information.

Please contact Sue Triesch with questions, or with updates/corrections to state information. (512-454-6419) E-mail: triesch@uthscsa.edu

Click here for information on Regional Genetics and Newborn Screening Regional Collaboratives

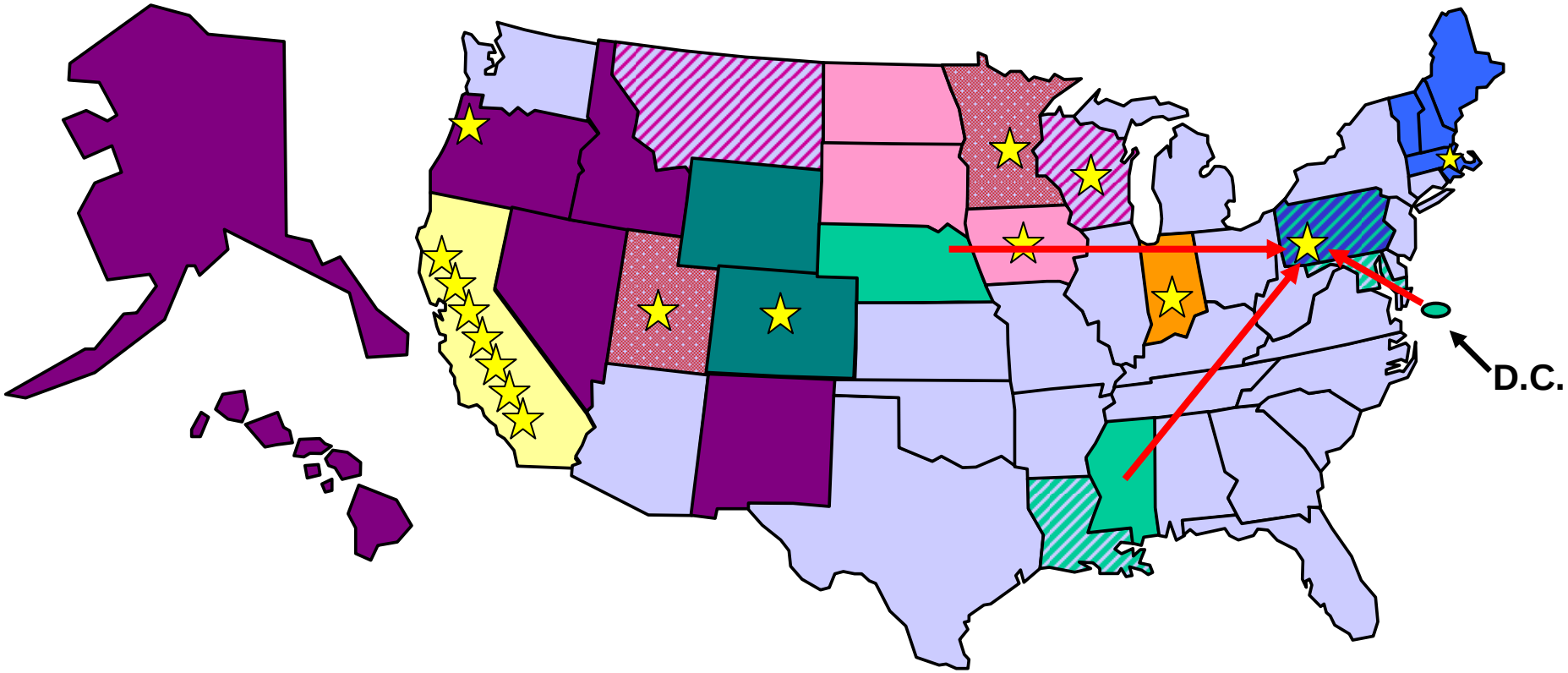
NBS Program Summary Information



start | 08.06.28 Colum... | Presentation2 | Resources - NN... | Visio-Leucine-(4-... | 5:59 AM

National Project

Update Training on Added Conditions
[MS/MS, DNA (CF)]



- OR Public Health Lab
- WI Public Health Lab
- IA Public Health Lab
- CO Public Health Lab
- U Mass Lab
- Allows Commercial Lab Competition
- 7 Contracted Labs
- 1 Pathology Lab
- 1 Med Ctr Lab
- 1 Commercial Screening Lab
- 2 Contracted Labs
- Share – Public Health/Med Ctr

Laboratory Service Delivery Models
States Using Contract Screening Laboratories
(Public and/or Commercial/Non-profit)

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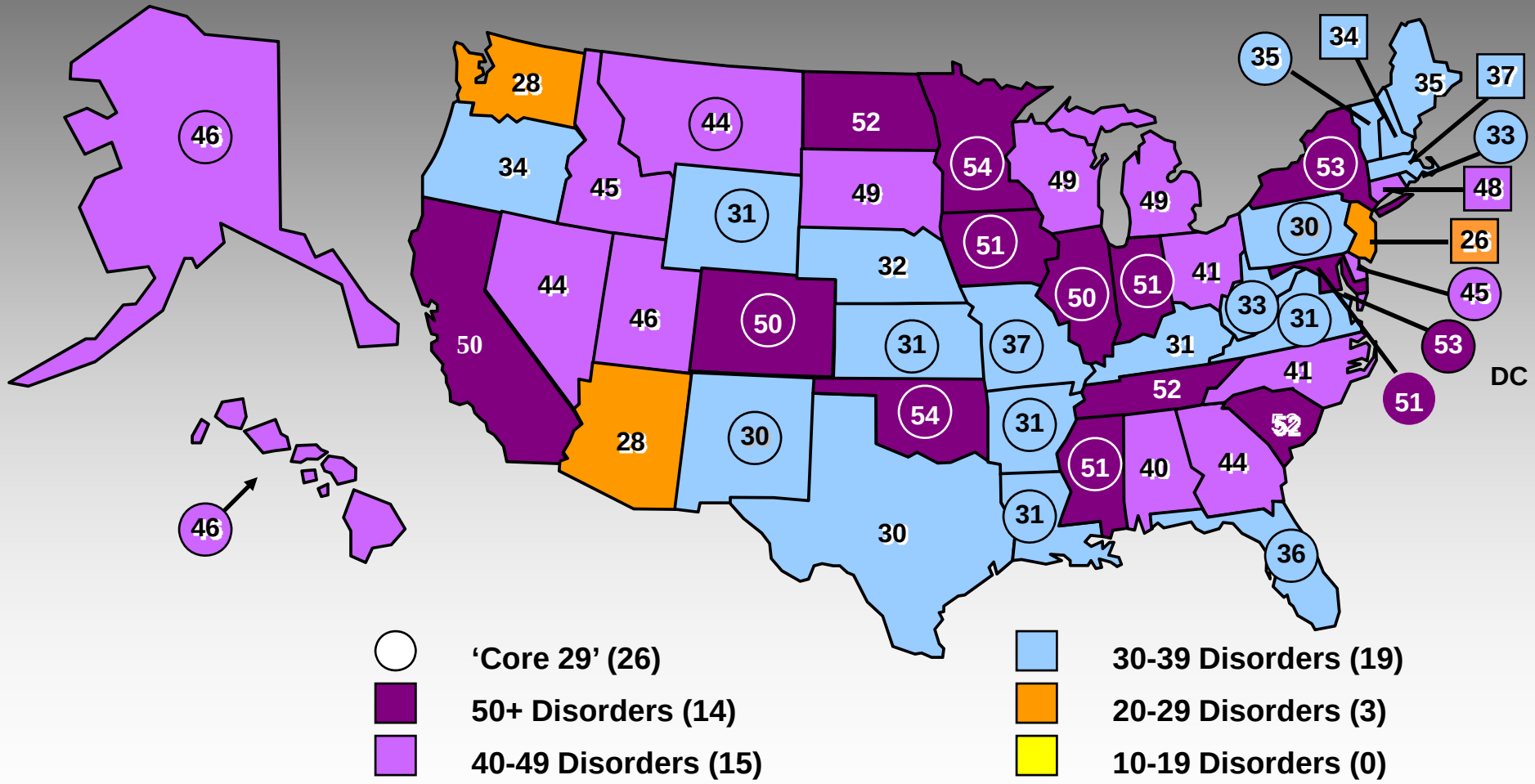
U.S. Newborn Screening

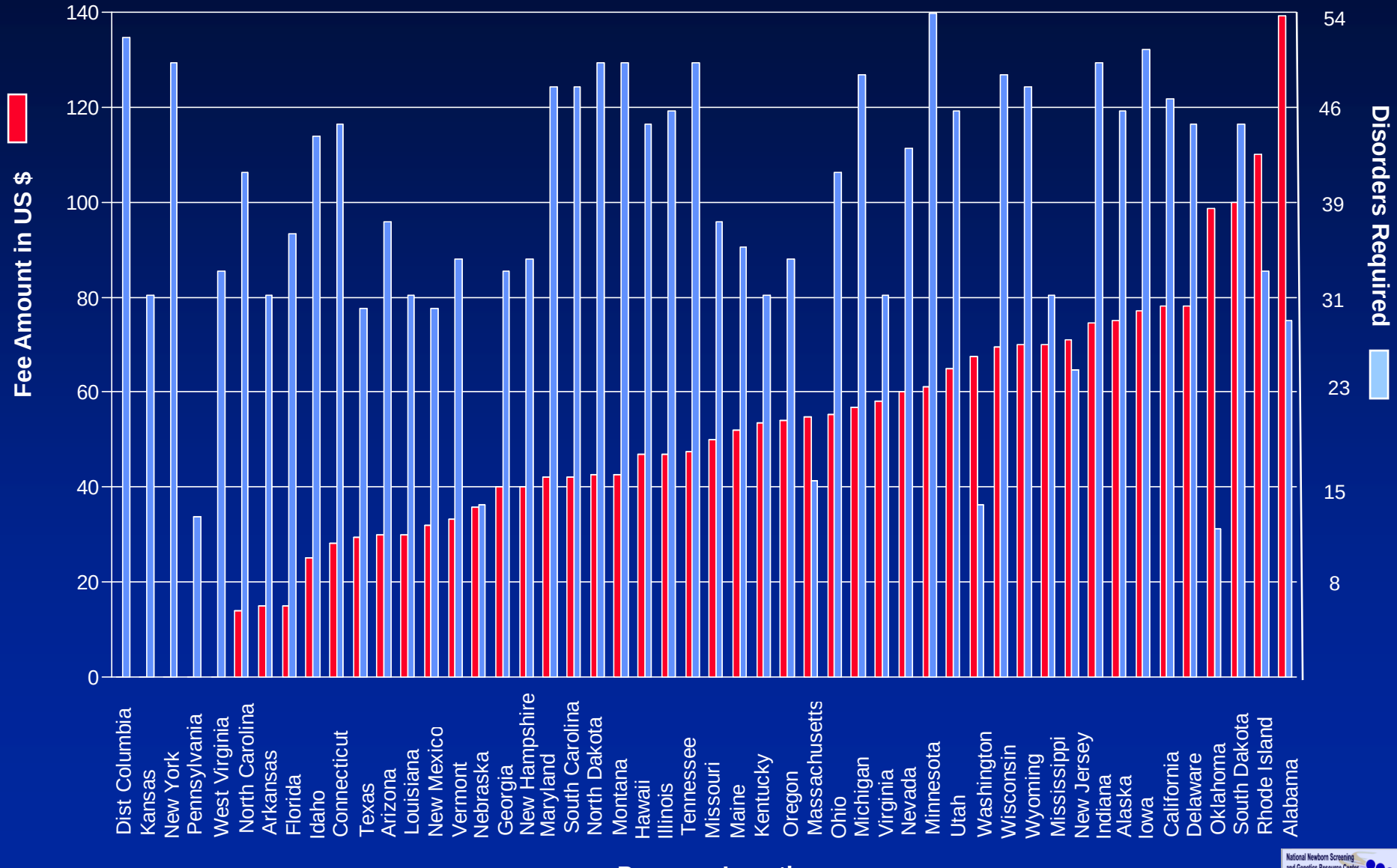
Conditions Required – August, 2008

(Conditions available as an option to a selected population are not counted – Must be universally required)



U.S. Newborn Screening Fees – 2007

(Ascending Amount with Number of Mandated Disorders Overlayed)



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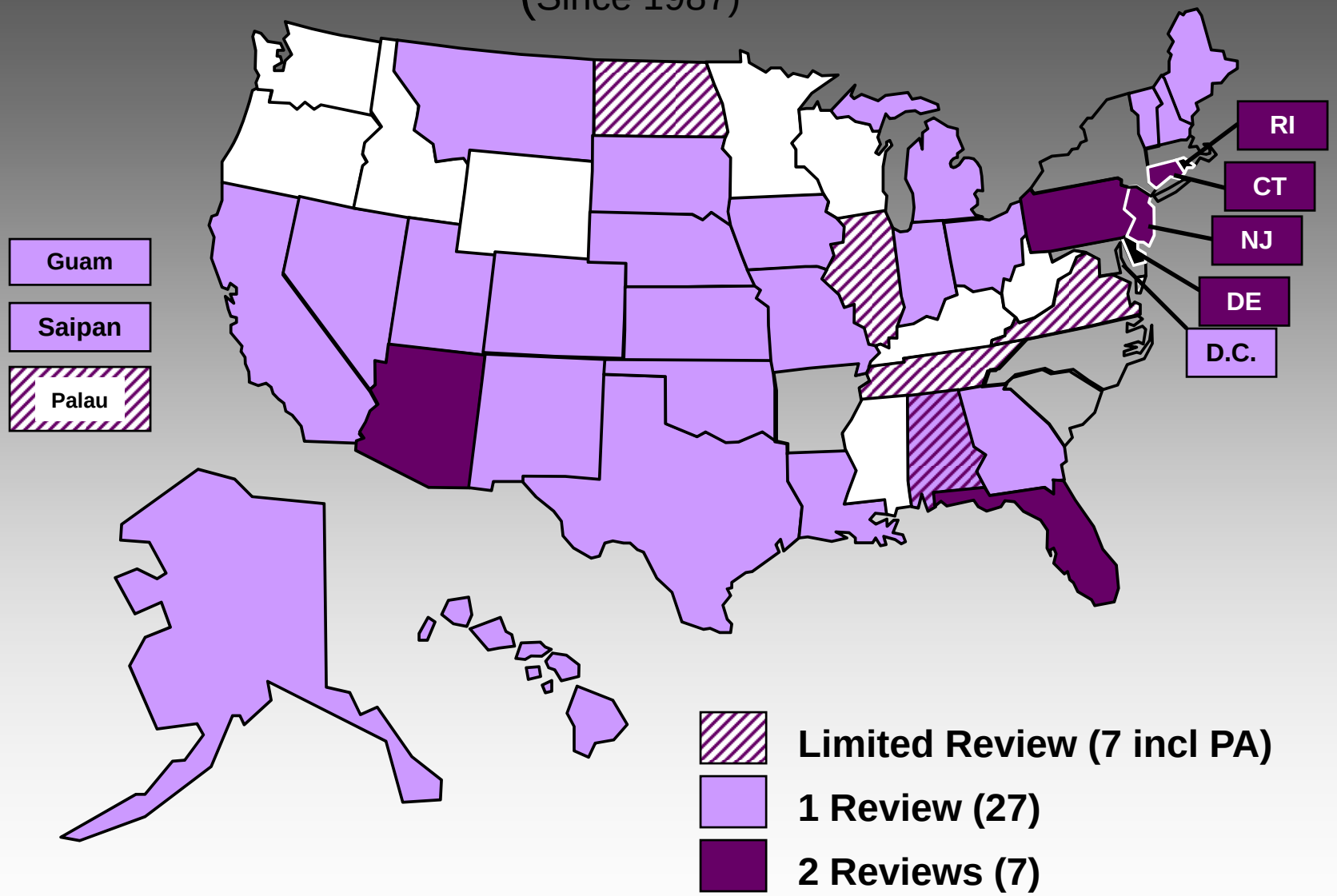
NNSGRC Consultative Reviews

‘Expert’ Assistance to state health departments to evaluate and improve the newborn screening program at the state level.

A valuable external review system using experts in laboratory, follow-up, administration, quality assurance and medicine to address specific program needs at the request and invitation of a public health screening program.

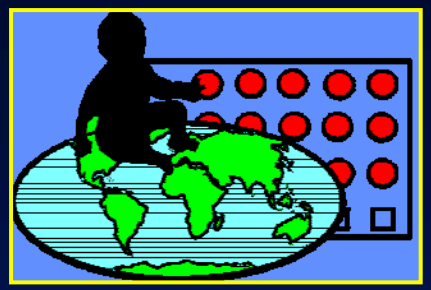
HRSA-Supported Quality Improvement Reviews

(Since 1987)



CLSI Standard LA04-A5 Package 2008 "Blood Collection on Filter Paper for Neonatal Screening Programs, Approved Standard"

- 3-Year shelf life for paper
- Better illustrations/descriptions
- 3-Month inventory of collection devices

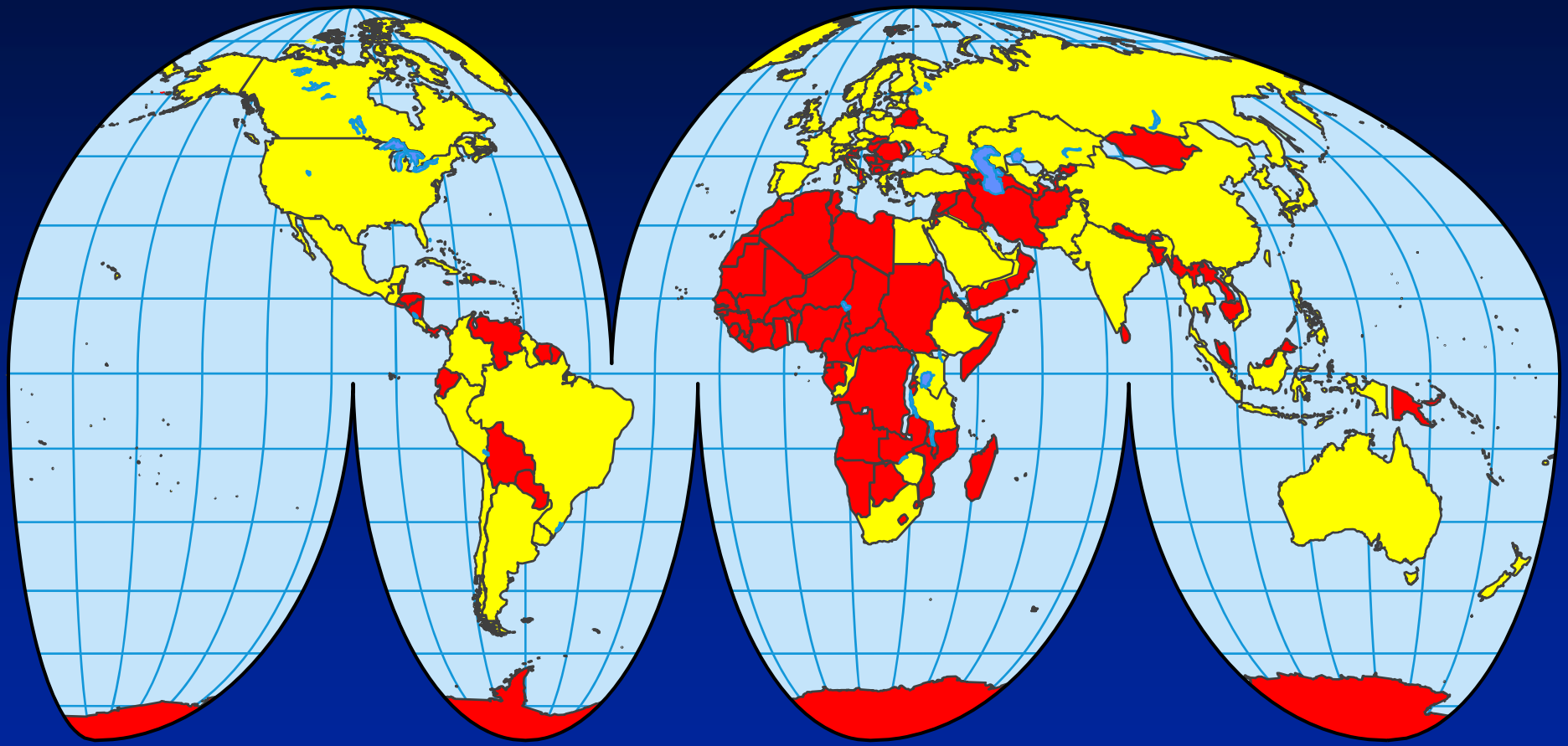


Newborn Screening
Quality Assurance Program

- Services provided:
  - Filter paper QC
  - Reference materials
  - QC materials
  - Proficiency testing
  - Consultation and network resource support
- Partners
  - Association of Public Health Laboratories
  - > 61 domestic screening laboratories
  - > 470 laboratories in > 72 countries

CDC
SAFER · HEALTHIER · PEOPLE

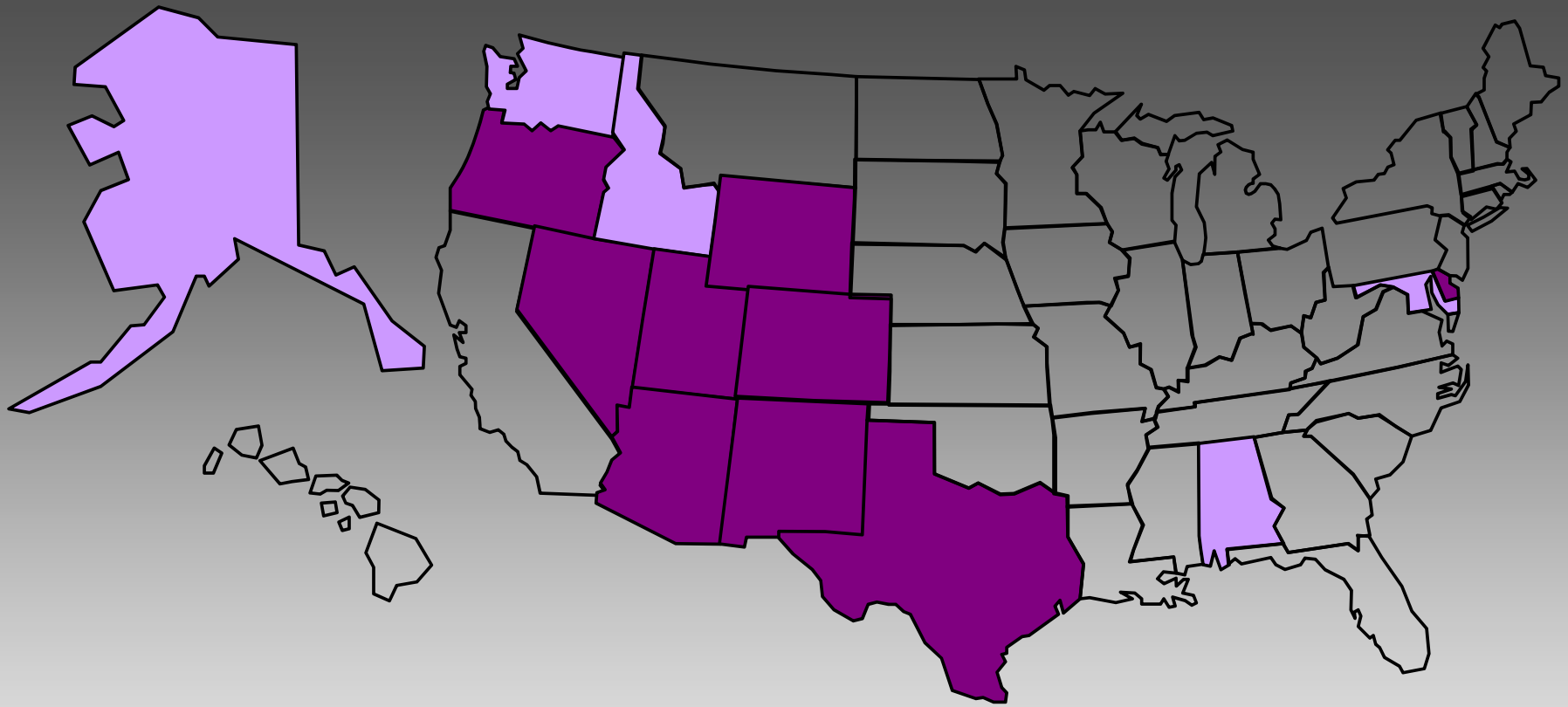
478 Laboratories in 72 Countries



PHL

Participants

CDC
SAFER · HEALTHIER · PEOPLE



U.S. Newborn Screening

2nd Screen Study

Status as of June 2008

Not Universally Required

Universally Required

Strongly Recommended (>85% compliance)

National Newborn Screening and Genetics Resource Center
Austin, Texas USA
NNSGRC

Challenges in newborn screening uniformity in U.S.

- National Mandate? – States left to decide
- Consent or Dissent? – All but 3 mandate screening without consent
- 1 screen or 2 screens – 8 States mandate 2 screens – may be important for CH, CAH, MS/MS
- Financing? – 5 States supported by gov't. while others have fee – fees vary from $10 - $139
- Treatment? – Smaller states lack local specialists

HRSA/ACMG UNIFORM PANEL (DRAFT 01/23/06)

NOMINATION OF CONDITION - Fact Sheet

Name of proponent		Date	
Condition			
Type of disorder			
Screening method			
Treatment strategy			

CONDITION	Comment	Gene		Locus		OMIM	
Incidence	(Reference required: By pilot screening or clinical identification?)						
Timing of clinical onset	(Relevance of the						
Severity of disease	(Morbidity, disability, mortality)						

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, size, preliminary results of past/ongoing pilot study for clinical validation)
Laboratory performance metrics	(Sensitivity, sp
Confirmatory testing	(Reliability av
Risks	(False positives, carrier detection, invasiveness of method, other)

Condition

Screening Test

National Newborn Screening and Genetics Resource Center
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NNSGRC

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	(Extent of preve
Availability	(Any limits of availability)
Risks	(Potential medical or other ill effects from treatment)

Treatment

KEY REFERENCES (Specific citations - limit to 15)	
1	
2	
3	
4	
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7	
8	
9	
10	
11	

Submit nomination to:

Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetic Services Branch
Division of Services for Children with Special Health Needs
Maternal and Child Health Bureau
5600 Fishers Lane, Rm 18-A-19
Rockville, MD 20857
301-443-8604-fax
301-443-1080-phone

Submission check list	
	Cover letter by proponent
	Nomination form
	Copy of references listed on this form

Contact information (proponent)

REFERENCES (continued)	
12	
15	

References

Examples of Candidate Conditions for Expansion of Uniform Panel (in alphabetical order)

- CDG type Ib
- CMV
- DMD
- G6PD
- Fabry disease
- FHC
- HIV
- Krabbe disease
- Pompe disease
- SCID
- SMA
- Toxoplasmosis
- Wilson disease
- Many (?) others……

National Newborn Screening and Genetics Resource Center Austin, Texas USA NNSGRC

2nd Conference on Strengthening Newborn Screening in the Middle East and North Africa
Cairo, Egypt – April 11-14, 2008

National Newborn Screening and Genetics Resource Center
Austin, Texas USA
NNSGRC

1st Conference of Asia Pacific Regional Newborn Screening Network for Developing Programs
Cebu, Philippines – April 5 -7, 2008

International NBS Listserv Available

http://genes-r-us.uthscsa.edu

http://www2.uthscsa.edu/nnsis/

http://www.marchofdimes.com/peristats/

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NNSGRC