

Considerations in Choosing Screening Conditions: One (US) Approach

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Abstract

The lack of a national policy on newborn screening (NBS) in the United States has resulted in 51 state-specific NBS policies (including 50 states and the District of Columbia). In 2000, a working group of the American Academy of Pediatrics provided a national NBS blueprint for the future. Using this guidance, the Health Resources and Services Administration contracted with the American College of Medical Genetics to: (i) develop a decision-making algorithm for states to use in selecting conditions for screening panels, and (ii) recommend a panel of tests to guide states in their screening requirements. This report outlines and summarises the processes and outcomes leading to the current NBS recommendations in the United States.

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Introduction

Newborn screening (NBS) in the US is a state public health responsibility and a unifying national NBS policy does not currently exist. As a result, US NBS expansion has developed sporadically through the years, sometimes as a result of new scientific findings (i.e. testing and treatment advances), sometimes from financial incentives (i.e. federal grants), and sometimes as a result of consumer advocacy and accompanying political pressures. Consumer advocates directly influenced early screening efforts and they continue their influence today through advocacy organisations and individual lobbying efforts.¹

All states and the District of Columbia have legislation that results in required NBS.² In most states, NBS oversight is a responsibility of the state health department. Some state laws specify conditions that must be screened and may provide limited support funding. However, decisions about addition or deletion of NBS tests and other critical issues, including how financing will occur, are usually assigned to the state health officer or his/her designee. Many NBS programmes have an advisory committee (or in some cases subspecialty committees such as metabolic, haematology, endocrinology) that provides input into programme operations. In such cases, proposed programme changes are usually evaluated by this committee (in consultation with NBS programme personnel) and

recommendations are made to the appropriate policy maker(s). Despite recent changes (discussed later) most NBS programmes still lack formal procedures for adding or subtracting tests, and thus testing panels continue to vary. Funding issues play a major role in policy decisions and start-up funding for new processes is particularly problematic, often requiring specific legislative action. Once a screening change is initiated, it can usually be sustained by a screening fee. It is increasingly popular to add a surcharge to an existing fee rather than to increase an existing fee, which may require a rule or statute change.

Several reports have significantly impacted US NBS policies through the years. The World Health Organization's (WHO) first Scientific Group meeting on "Screening for Inborn Errors of Metabolism" suggested screening criteria that have formed the basis for screening policy through the years. In considering, "whether and how newborn screening programmes could improve the health of mankind," they suggested dividing screening conditions into 3 groups: "(i) conditions for which there is a well-defined screening test and a fairly uniform policy of management once the disease has been identified; (ii) conditions in which the abnormal gene can regularly be identified but in which the condition only becomes symptomatic in a specific environment; and (iii) a miscellaneous category which includes conditions for which more information is needed before they will fit

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easily into a routine screening programme.”³ The Wilson and Jungner companion report attempted to chart the public health course for “bringing to treatment those with previously undetected disease” while “avoiding harm to those persons not in need of treatment.” It recommended criteria for population screening and observed that early phenylketonuria (PKU) screeners had done a poor job of documenting successes.⁴ These population screening criteria were immediately embraced as useful for newborn screening, and programmes worldwide began to use them in deciding about screening panels.

Frankenburg revisited these screening principles in discussing how physicians might best decide on diseases for private practice screening programmes. He noted that, “...if the decision to screen is based only on the availability of a test or the apparent importance of a test, great harm can be done, both in the waste of valuable medical resources and in direct harm to the persons screened.” He concluded that, “The availability of a suitable screening test does not justify screening for a disease unless the disease is important, relatively prevalent, and amenable to early treatment. Screening... cannot be justified unless there is an acceptable, reliable, and valid test ... at a reasonable cost.”⁵

The US National Academy of Sciences also issued a report on genetic screening to, “... review current screening practices... identify the problems and difficulties and give some procedural guidance, in order to minimise the shortcomings and maximise the effectiveness of future genetic screening programmes.”⁶ While providing some useful national guidance with its 21 recommendations in 5 categories, it did little to change the use of Wilson and Jungner criteria in screening panel decisions.

In 1999, the Maternal and Child Health Bureau of the US Health Resources and Services Administration (MCHB/HRSA), in response to increasing congressional NBS interest fuelled by consumer advocacy, contracted with the American Academy of Pediatrics (AAP) for a NBS Task Force to: (i) review the issues facing state NBS systems, and (ii) to make recommendations. The collective report of its 5 multi-disciplinary work groups provided national guidance for US NBS in the 21st century. The Task Force’s foremost concerns were of unequal availability of state screening services, lack of national policy defining the parameters for state-required NBS, and programme finances. Their “agenda for action” identified a need for partnerships between the public health system(s), health professionals and consumers to: define federal and state responsibilities, model NBS regulations, define minimum system standards, model guidelines and protocols for professionals, model systems of care from infancy to adulthood, design strategies for informing and involving families and the public, and fund demonstration projects to

evaluate technology, quality assurance, and health outcomes.⁷

The AAP NBS report provided a publication to which various agencies could turn for guidance and documentation of improvement needs. Shortly after its publication, an Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC – now called the Advisory Committee on Heritable Disorders in Newborns and Children) was created to advise the Secretary of Health and Human Services (HHS) on NBS issues (among others). In response to the AAP report, MCHB/HRSA contracted with the American College of Medical Genetics (ACMG) “to undertake the scientific and medical analysis of conditions being considered for newborn screening and develop the criteria for assessing and evaluating conditions.” Specifically to: “(i) recommend a uniform screening panel for all US NBS programmes, and (ii) develop a model decision-matrix for use in state NBS programme considering expansion.”⁸

Method

Expanded details of the methodology employed by ACMG have been reported.⁹ A “NBS Steering Committee” of stakeholder partners was first assembled for project planning and oversight. Next, a multi-disciplinary “NBS Expert Group” was chosen and 2 work groups were created: “NBS Conditions and Criteria” and “Diagnosis and Follow-up.” All participants were selected to bring strong scientific and clinical perspectives to discussions of the issues with attention paid to professional, cultural, ethnic, and geographic diversity. To vet various ideas and potential project outputs, a limited number of experts (outside reviewers) were selected for input throughout the project deliberations.⁹

Input into the project included expert reviews of the scientific literature, invited presentations from national and international experts, comments from the public and professional organisations, and meetings of both the NBS Expert Group and the various working groups. Eighty-four conditions amenable to NBS were selected for review. Infectious diseases were deferred for consideration in another forum leaving 81 conditions for final consideration. To guide the process, a group of basic principles about newborn screening was developed by the NBS Expert Group. The NBS Conditions and Criteria Working Group developed evaluation criteria for a quantitative assessment tool (Table 1). This tool was used to evaluate the known information about each condition by polling interested individuals and recognised experts. The data obtained were statistically evaluated and the poll responses were compared to the scientific literature. A core panel of required and secondary conditions was developed

Table 1. Quantitative Instrument used to Gather Information on Current Knowledge about Conditions under Consideration by the ACMG Expert Group⁹

Criteria	Categories	Score	Criteria	Categories		Score
Incidence of condition	>1:5,000	100	Availability of treatment	Treatment exists and is widely available in most communities.		50
	>1:25,000	75		Treatment exists but availability limited.		25
	>1:50,000	50		No treatment available or necessary.		0
	>1:75,000	25				
	<1:100,000	0				
Signs and symptoms clinically identifiable in the first 48 hours	Never	100	Potential efficacy of existing treatment	Prevents all negative consequences.		200
	<25% of cases	75		Prevents most negative consequences.		100
	<50% of cases	50		Prevents some negative consequences.		50
	<75% of cases	25		Treatment efficacy not proven.		0
	Always	0	Benefits of early intervention (INDIVIDUAL OUTCOME)	Clear	Scientific evidence that early intervention from screening optimises outcome	200
				Some		100
			No		0	
Burden of disease (Natural history if left untreated)	Profound	100	Benefits of early identification (FAMILY AND SOCIETY)	Clear	Evidence that early identification provides clear benefits to family and society	100
	Severe	75		Some		50
	Moderate	50		No		0
	Mild	25	Early diagnosis and treatment prevent mortality	Yes		100
	Minimal	0		No		0
Does a sensitive AND specific screening test exist?	Yes No	200 0	Availability of diagnostic confirmation	Providers are widely available.		100
Test characteristics (Yes = apply score; No = zero)	Doable in neonatal blood spots OR by a single in-nursery physical method.	100		Limited availability of providers.		50
	High throughput (>200/employee).	50		Available only in a few centres.		0
	Acute management	Analytical cost <\$1/test / condition.	50			
		Multiple analytes relevant to one condition are detected in same run.	50	Providers are widely available.		100
		Other conditions identified by same analytes.	50	Limited availability of providers.		50
		Multiple conditions detected by same test (multiplex platform).	200	Available only in a few centres.		0
Cost of treatment	Inexpensive	50	Simplicity of therapy	Managed at primary care or family level.		200
	Expensive (>\$50,000/patient/year)	0		Requires periodic specialist involvement.		100
				Requires regular specialist involvement		0
			Total	Maximum score available		2100

as a recommendation for implementation by all US NBS programmes.⁹ The completed report was provided to MCHG/HRSA and subsequently to the ACHDGDNC.

Results

The ACMG NBS Expert Group produced a list of 29 core conditions that should be included in all required NBS panels. Additionally, 25 “secondary” conditions (potentially identified incidental to screening for the core panel) were listed as optionally required (see Table 2). These secondary conditions lacked sufficiently high scores for inclusion in the core group, usually because of a lack of efficacious treatment, and represent a de facto research agenda. Included

in the report was the recommendation for full optimisation of screening technologies (i.e. full scan interpretations for tandem mass spectrometry) and reporting of all significant findings. Also included in the secondary conditions were screening for kinase- and epimerase-deficient forms of galactosemia and other significant haemoglobinopathies, all currently detectable with current testing procedures. Arguments supporting these decisions are documented in the full ACMG report. Details of supporting studies and findings were also reported in a companion special issue of the journal, *Pediatrics* (see supplement to *Pediatrics*, vol. 117, 2006). The final report was approved by the ACHDGDNC and sent to the Secretary of HHS for review and further action.

Table 2. Conditions Recommended for Inclusion in US Newborn Screening Programmes

29 core conditions	25 secondary conditions
MS/MS Detectable Organic Acid Disorders	
Isovaleric Acidemia	Methylmalonic Acidemia
Glutaric Acidemia Type I	Malonic Acidemia
3-Hydroxy 3-Methyl Glutaric Aciduria	Isobutyryl-CoA Dehydrogenase Deficiency
Multiple Carboxylase Deficiency	2-Methyl 3-Hydroxy Butyric Aciduria
Methylmalonic Acidemia (Mutase Deficiency)	2-Methylbutyryl-CoA Dehydrogenase Deficiency
3-Methylcrotonyl-CoA Carboxylase Deficiency	3-Methylglutaconic Aciduria
Methylmalonic Acidemia (Cbl A,B)	
Propionic Acidemia	
Beta-Ketothiolase Deficiency	
MS/MS Detectable Fatty Acid Oxidation Disorders	
Medium-Chain Acyl-CoA Dehydrogenase Deficiency	Short-Chain Acyl-CoA Dehydrogenase Deficiency
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency	Glutaric Acidemia Type II
Long-Chain L-3-Hydroxy Acyl-CoA Dehydrogenase Deficiency	Medium/Short Chain L-3-Hydroxy Acyl-CoA Dehydrogenase Deficiency
Trifunctional Protein Deficiency	Medium-Chain Ketoacyl-CoA Thiolase Deficiency
Carnitine Uptake Defect	Carnitine Palmitoyltransferase II Deficiency
	Carnitine Acylcarnitine Translocase Deficiency
	Carnitine Palmitoyltransferase I Deficiency (liver)
	Dienolyl-CoA Reductase Deficiency
MS/MS Detectable Amino Acid Disorders	
Phenylketonuria	Benign Hyperphenylalaninemia
Maple Syrup Urine Disease	Tyrosinemia Type II
Homocystinuria	Tyrosinemia Type III
Citrullinemia	Defects of Biopterin Cofactor Biosynthesis
Argininosuccinic Acidemia	Defects of Biopterin Cofactor Regeneration
Tyrosinemia Type I	Argininemia
	Hypermethioninemia
	Citrullinemia Type II
Hemoglobinopathies	
Sickle Cell Anemia (SS-Disease)	Variant Hemoglobinopathies
Sickle-C Disease (SC-Disease)	
S-Beta Thalassemia	
Other	
Transferase Deficient Galactosemia (Classical)	Galactokinase Deficiency
Primary Congenital Hypothyroidism	Galactoepimerase Deficiency
21-Hydroxylase Deficient Congenital Adrenal Hyperplasia	
Biotinidase Deficiency	
Hearing Screening	
Cystic Fibrosis	

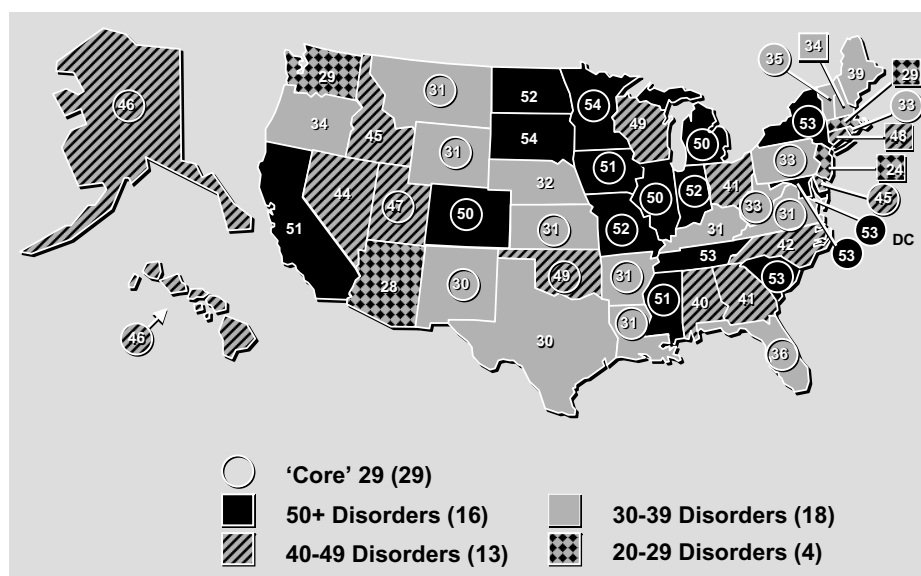


Fig. 1. Conditions required to be screened in various US jurisdictions – 12 January 2009. Some conditions may be required but not yet implemented pending funding or other issues. Available at: <http://genes-r-us.uthscsa.edu/nbsdisorders.doc>. Accessed 12 January 2009).

Discussion

In response to public pressure from consumer advocates, improved screening technologies, evolving medical information, the national guidance provided by the ACMG report, and the subsequent ACHDGDNC actions, almost all US NBS programmes have recently undergone some form of expansion.¹⁰ Figure 1 provides a summary of the current status of NBS in the various states. The numbers listed refer only to state required screening conditions. In some cases, a requirement may exist but may not yet have been implemented, usually because of financial or training/technology issues. For example, Massachusetts, with 29 conditions on the map, actually provides optional screening for 11 other conditions and lists 21 others as likely to be identified due to the screening methods used. When a number is circled on the map, it indicates that screening for the “core 29” conditions is currently required on all newborns. In cases where there is no circle, it is usually the result of technical wording in the state requirement for hearing screening, which sometimes fails to require screening on all newborns. A few states have not yet implemented screening for cystic fibrosis and some do not yet require screening for tyrosinemia type I.

During the coming year, it is anticipated that all programmes will require screening for essentially all of the “core 29” conditions. Some controversies still exist regarding the secondary 25 conditions and some programmes include conditions outside of the 54 core/secondary list. For example, 2 programmes screen for toxoplasmosis, 1 programme screens for G6PD deficiency, etc. One programme includes screening for Krabbe disease and one has just completed its first year-long trial of screening for severe combined immunodeficiency disorder.¹⁰ The ACHDGDNC has recently published its

process for considering other conditions for addition to the core group of recommended screening conditions and has now begun to accept nominations.¹¹ Reports on the outcome of nominations are available at: <http://www.hrsa.gov/heritabledisorderscommittee/reports/default.htm>.

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REFERENCES

1. Therrell BL. U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab* 2001;74:64-74.
2. Therrell BL, Johnson A, Williams D. Status of newborn screening programs in the United States. *Pediatrics* 2006;117:S212-52.
3. World Health Organization Scientific Group on Screening for Inborn Errors of Metabolism. Screening for inborn errors of metabolism. *World Health Organ Techn Rep Ser* 1968;401:1-57.
4. Wilson JMG, Jungner F. Principles and practice of Screening for disease (Public Health Papers No. 34). Geneva: World Health Organization, 1968.
5. Frankenburg WK. Selection of diseases and tests in pediatric screening. *Pediatrics* 1974;54:612-6.
6. National Research Council. Genetic screening: Programs, principles, and research. Washington, D.C: National Academy of Science, 1975.
7. American Academy of Pediatrics, Newborn Screening Task Force. Serving the family from birth to the medical home – newborn screening: a blueprint for the future. *Pediatrics* 2000;106(suppl):383-427.
8. American College of Medical Genetics Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system – Executive Summary. *Pediatrics* 2006;117:S296-S307.
9. American College of Medical Genetics, Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system. *Genet Med* 2006;8 Suppl1:1S-252S.
10. Therrell BL, Buechner C, Lloyd-Puryear MA, van Dyck PC, Mann MY. What's new in newborn screening? *Pediatr Health* 2008;2:411-29.
11. Green NS, Rinaldo P, Brower A, Boyle C, Dougherty D, Lloyd-Puryear M, et al. Committee report: advancing the current recommended panel of conditions for newborn screening. *Genet Med* 2007;9:792-6.