UNIVERSITÄTS KLINIKUM FRANKFURT

Sinnvolle Grenzen des Neugeborenenscreenings

Martin Lindner
Zentrum für Kinder- und Jugendmedizin
Schwerpunkt Neurologie, Stoffwechsel, Endokrinologie, Prävention

DGNS – Jahrestagung
Nürnberg, 19. – 20.06.2015

PRINCIPLES AND PRACTICE OF SCREENING FOR DISEASE

J. M. G. WILSON

Principal Medical Officer, Ministry of Health, London, England

G. JUNGNER

Chief, Clinical Chemistry Department, Sahlgren's Hospital, Gothenburg, Sweden

Public Health Genomics 2011;14:9–16

PROGRAM MANAGEMENT LEVEL

Establish regulations

1. The overall benefits of screening should outweigh the potential harms, including psychological, physical and social harms
2. There should be promotion of human rights, including upholding the principles of equity, autonomy and confidentiality
3. Consumers should be included in screening policy-making and family members should be implicated in the screening process
4. Screening should be a continuing process and not a "once and for all" project
5. There should be an education program in place from the outset of the program and individual risk counselling should be available throughout the screening process
6. There should be a separate consent process for research that differs from the consent for clinical purposes

Manage resources

7. The need for screening, the goals and objectives, the roles and responsibilities, and the financing required should be defined from the outset
8. The infrastructure for screening, including education, testing, clinical services and program management, should be in place before the start of the program

Organize services

9. There should be an integrated screening program that incorporates the education, testing, clinical services and program management levels

Measure outcomes and assure quality control

10. There should be scientific evidence of screening program effectiveness
11. Economic evaluations should add to evidence favouring of screening, but should not be the sole criterion for deciding whether or not to offer screening
12. There should be quality assurance incorporated at all levels of the screening program and ongoing program evaluation should be planned from the outset

CLINICAL SERVICES LEVEL

Establish screening type, health problem of interest and target population

13. The condition sought should be a common and/or serious health problem
14. The natural history of the condition and of gene carriers should be adequately understood
15. There should be a recognizable early symptomatic stage, latent stage or increased level of genetic risk
16. There should be a defined target population

Establish proposed intervention

17. There should be an accepted intervention (ex. prevention, treatment, family planning) that forms part of a coherent management strategy
18. There should be an agreed policy on whom to categorize as "screen positive", "screen negative" and "screen indeterminate", and a defined process for each group following disclosure of screening results

LABORATORY TESTING LEVEL

Establish test parameters

19. There should be a suitable screening test
20. The screening test and the entire screening program should be acceptable to the target population and to society

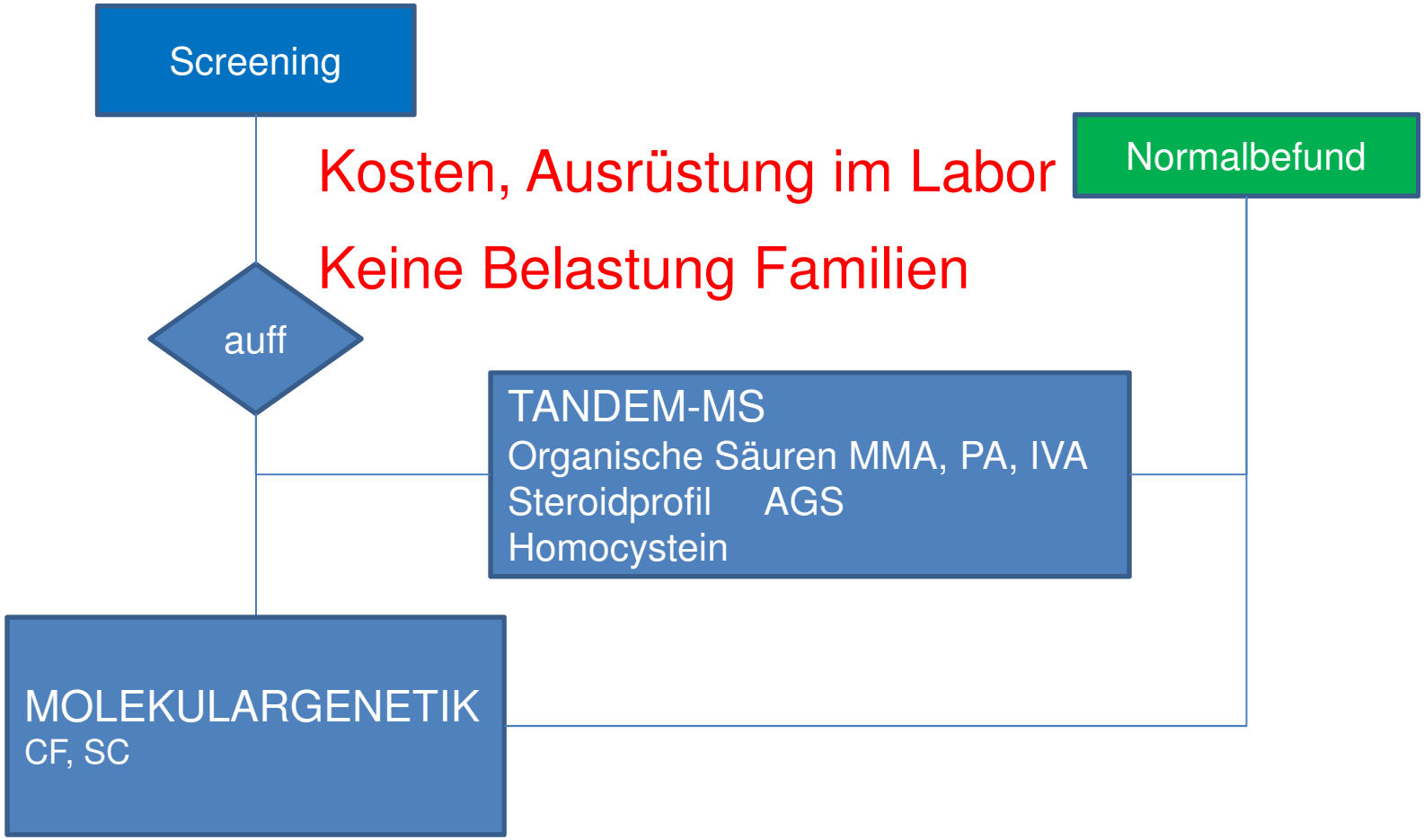
…benefits outweigh harms psychological, social

…separate consent for research

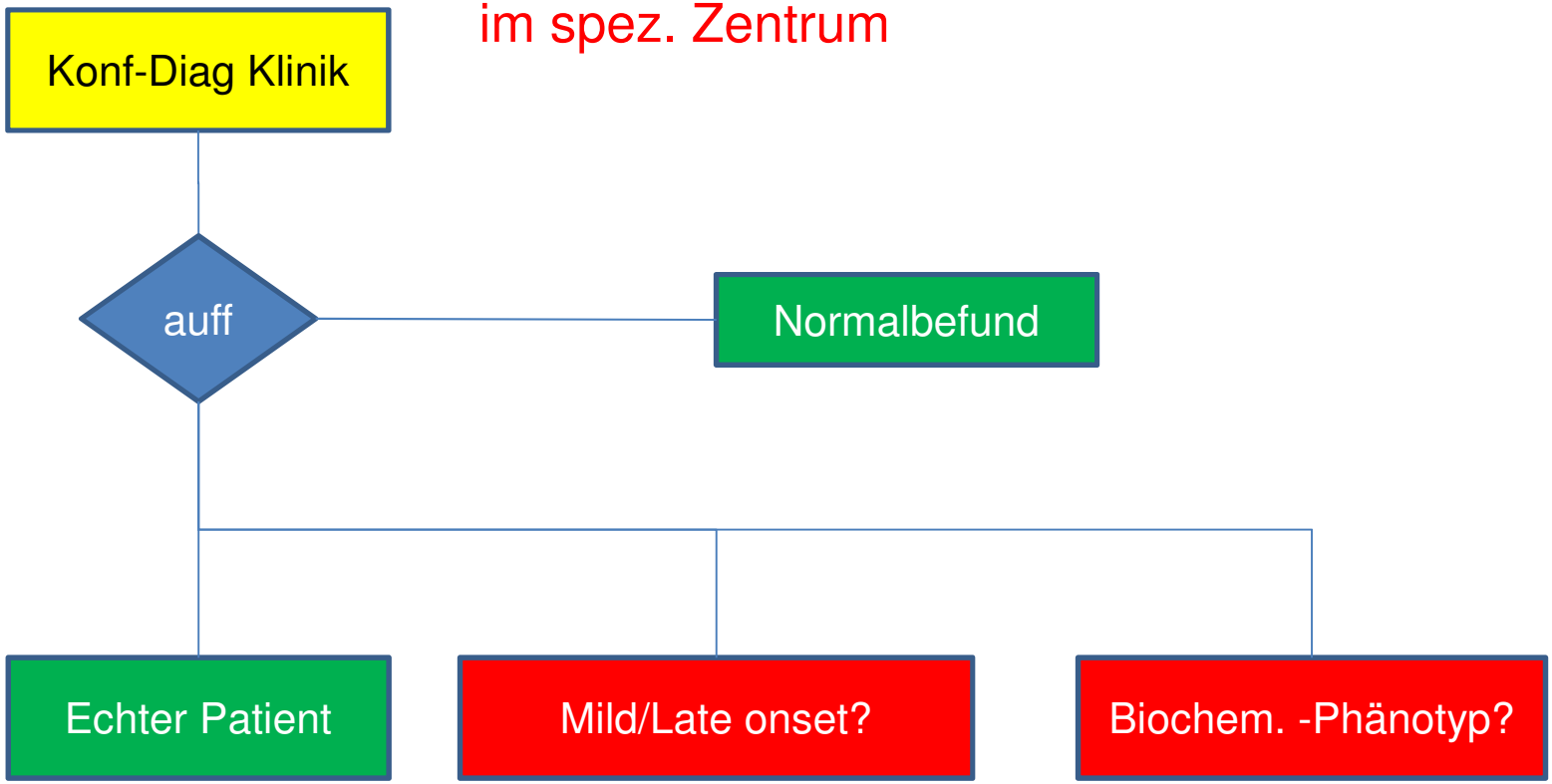
……accepted intervention prevention…family planning

…..acceptable to …society

Falsch positive – Reduktion durch Second tier Strategien



Geringere psychische Belastung bei Betreuung im spez. Zentrum



Evtl. hohe diagnost./Therapiekosten (Kasse)
Hohe psychische Belastung

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Clinical, Biochemical, and Genetic Heterogeneity in Short-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

B. Van Maldegem et al.

Conclusions SCADD is far more common than assumed previously, and clinical symptoms in SCADD are nonspecific, generally uncomplicated, often transient, and not correlated with specific *ACADS* genotypes. Because SCADD does not meet major newborn screening criteria, including a lack of clinical significance in many patients and that it is not possible to differentiate diseased and nondiseased individuals, it is not suited for inclusion in newborn screening programs at the present time.

the severe symptoms in children identified clinically, suggests the possibility that SCADD is usually a benign condition. If so, SCADD would be added to histidinemia [42] and Hartnup disease [43] as other examples of inborn errors believed to be clinically significant before newborn screening but, as a result of follow-up studies in children identified by newborn screening, was found to be usually benign. Individuals with SCADD who develop clinical disease

Molecular Genetics and Metabolism 95 (2008) 39–45

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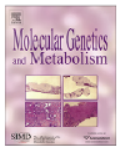
journal homepage: www.elsevier.com/locate/ymgme



Short-chain acyl-CoA dehydrogenase (SCAD) deficiency: An examination of the medical and neurodevelopmental characteristics of 14 cases identified through newborn screening or clinical symptoms

S.E. Waisbren [a,*], H.L. Levy [a], M. Noble [a], D. Matern [b], N. Gregersen [c], K. Pasley [a], D. Marsden [a]

[a] Department of Genetics, Children's Hospital Boston and Harvard Medical School, 1 Autumn Street, Room #525, Boston, MA 02215, USA
[b] Departments of Laboratory Medicine and Pathology, Medical Genetics, and Pediatric and Adolescent Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA
[c] Research Unit for Molecular Medicine, Institute of Clinical Medicine, Aarhus University Hospital, Skejby, DK-8200 Aarhus, Denmark

reflect ascertainment bias. The correct interpretation awaits further evidence. To obtain this evidence it may help if regions where SCADD is included in the newborn screening program compare long-term outcome data to those programs where SCADD was excluded from newborn screening. The following elements should be consid-

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 161, No. 3

was in Italy. Historically, removing conditions from mandatory newborn screening panels in the United States has been quite difficult, even when the condition is later determined to be a normal variant and not a disorder, such as histidinemia.[40]

SCAD noch immer im Screenigpanel

UNIVERSITÄTS KLINIKUM FRANKFURT

THE JOURNAL OF PEDIATRICS • www.jpeds.com COMMENTARY

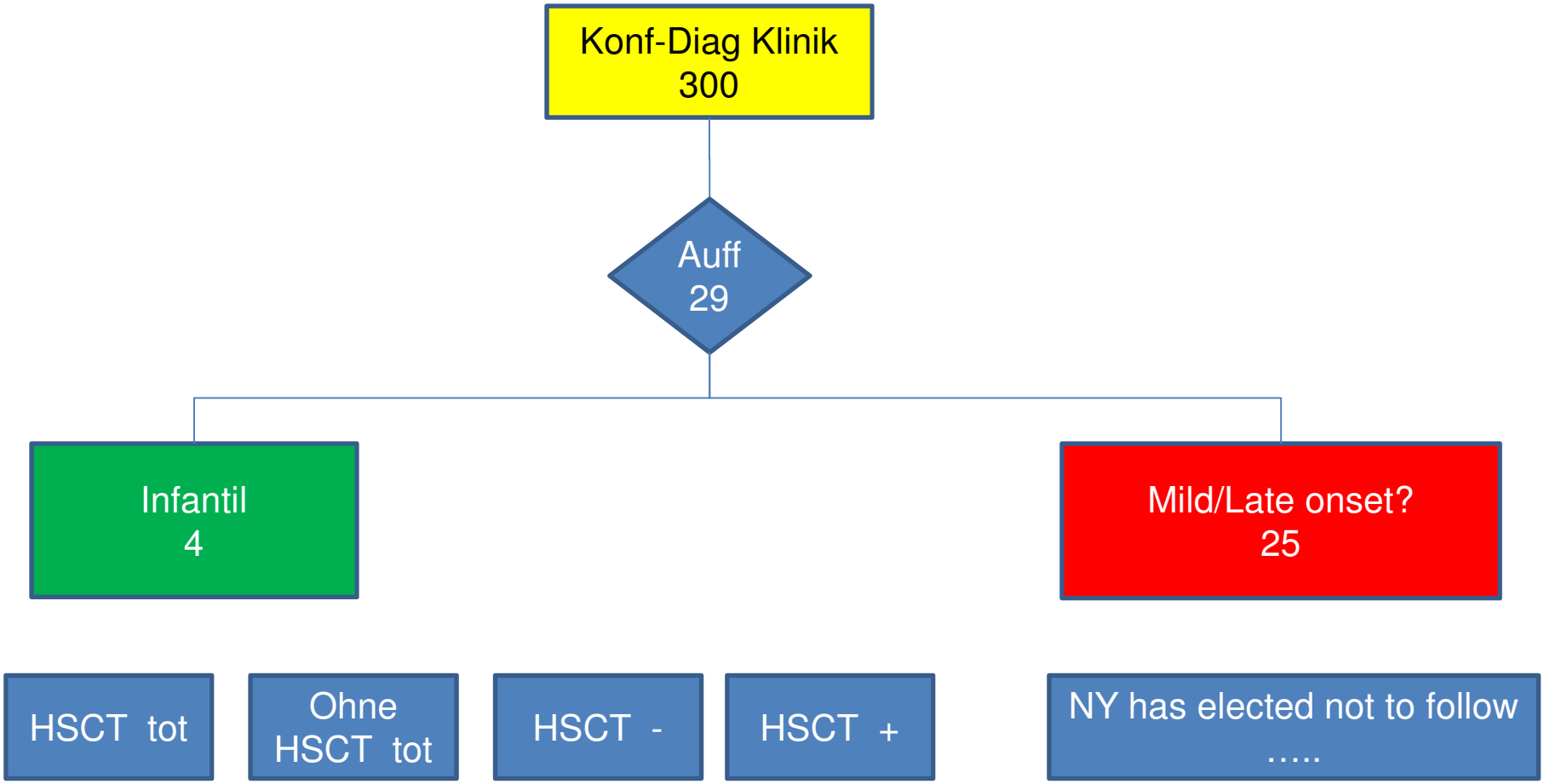
Parents: Critical Stakeholders in Expanding Newborn Screening

Lainie Friedman Ross, MD, PhD[1,2], and Darrel J. Waggoner, MD[1,3]

Lysosomal storage diseases (LSD) are rare genetic conditions that can affect individuals at different stages of life. Hunter Kelly (February 14, 1997 to August 5, 2005), the son of former Buffalo Bills quarterback Jim Kelly, died of complications from infantile Krabbe disease, one of the LSDs.[1] Bone marrow transplantation can sometimes slow down the progressive neurologic symptoms caused by Krabbe disease.[2] Mr Kelly advocated that the New York State Public Health Department screen for Krabbe disease to diagnose it early enough that bone marrow transplantation is an option. In August 2006, New York implemented Krabbe screening into its mandatory screening program.

In Illinois, in 2005, Bob and Sonya Evanosky successfully lobbied the Illinois legislature to mandate screening for 5 LSDs to be incorporated into its mandatory newborn screening program, including Krabbe disease, Pompe disease, and Fabry disease. This screening was to begin within 6 months identified would be of infantile-onset form.[9] In the first 4 years of newborn screening in New York, 300 children were called back for confirmatory studies.[10] Twenty-nine tested positive. Four (14%) were found to have the infantile form of the disease, and to date, one died without a transplantation, one died during the transplantation, one underwent transplantation but is doing poorly, and one is doing well. Another 25 children were classified as being at moderate-to-high risk of developing a form of Krabbe disease, but none have developed any symptoms, although they have become "patients in waiting."[11] Some may develop symptoms later in childhood, others in adulthood, and neither genetic testing nor biochemical assay can reliably predict when or if symptoms will develop. New York has elected not to follow the children identified by screening as moderate-to-high risk because of the psychological and emotional stress that the diagnosis and close monitoring may cause.[10]

M. Krabbe – Mandatory NBS New York 2006 - 2010



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BRIEF REPORT | Genetics inMedicine

Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Alex R. Kemper, MD, MPH[1], Nancy S. Green, MD[2], Ned Calonge, MD, MPH[3], Wendy K.K. Lam, PhD[1], Anne M. Comeau, PhD[4], Aaron J. Goldenberg, PhD, MPH[5], Jelili Ojodu, MPH[6], Lisa A. Prosser, PhD[7], Susan Tanksley, PhD[8] and Joseph A. Bocchini Jr, MD[9]

APPENDIX: PARTICIPANTS IN APRIL 2012 EXPERT MEETING, LISTED ALPHABETICALLY BY MAIN ORGANIZATION REPRESENTED

Agency for Healthcare Research and Quality
Christine Chang, MD, MPH
Denise Dougherty, PhD

Centers for Disease Control and Prevention
Carla Cuthbert, PhD
Randy Elder, MEd, PhD
Richard S. Olney, MD, MPH

Health Resources and Services Administration
Sara Copeland, MD
Sarah Linde-Feucht, MD
Michael C. Lu, MD, MS, MPH
Deboshree Sarkar, MPH
Bonnie Strickland, PhD
Lisa M. Vasquez, MPA

National Institutes of Health
Melissa Parisi, MD, PhD
Tiina Urv, PhD

Advisory Committee
Joseph A. Bocchini Jr, MD
Stephen McDonough, MD

Condition Review Workgroup
Anne M. Comeau, PhD
Alex R. Kemper, MD, MPH, MS
Aaron J. Goldenberg, PhD, MPH
Wendy K.K. Lam, PhD
Lisa A. Prosser, PhD
Jelili Ojodu, MPH

State Newborn Screening Programs
Janice Bach, MS, CGC (Michigan)
Julie Luedtke (Nebraska)
Sharmini V. Rogers, MBBS, MPH (Missouri)

Others
Cynthia Cameron, PhD (Michigan Public Health Institute)
Ned Calonge, MD, MPH (The Colorado Trust)
Christopher Kus, MD, MPH (Association of State and Territorial Health Officials)
Melissa McPheeters, PhD, MPH (Vanderbilt University Evidence-Based Practice Center)
Virginia A. Moyer, MD, MPH (US Preventive Services Taskforce)
Beth A. Tarini, MD, MS (University of Michigan)
Bradford L. Therrell Jr, PhD (National Newborn Screening and Global Resource Center, University of Texas Health Science Center at San Antonio)

Net benefit		Feasibility	Readiness		
			Ready	Developmental	Unprepared
Significant benefit	High certainty	High or moderate feasibility	A1	A2	A3
		Low feasibility	A4		
	Moderate certainty		B		
Zero to small benefit	High or moderate certainty		C		
Negative benefit			D		
	Low certainty		L		

Figure 1 The Advisory Committee decision matrix.

GENETICS in MEDICINE | Volume 16 | Number 2 | February 2014

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Discretionary Advisory Committee on
Heritable Disorders in Newborns and Children
5600 Fishers Lane, Room 18A19
Rockville, Maryland 20857
(301) 443-1080 – Phone
(301) 480-1312 – Fax
www.hrsa.gov/heritabledisorderscommittee

June 3, 2013

The Honorable Kathleen Sebelius
Secretary of Health and Human Services

The Committee feels strongly that there are significant benefits in screening for Pompe disease. Data shows that screening for Pompe, as opposed to clinical identification alone, results in earlier diagnosis and treatment of the infantile form of the disease. Enzyme replacement therapy has been shown to significantly modify the course of the infantile form of Pompe disease and earlier treatments with enzyme replacement therapy result in better outcomes for affected infants. The screening tests have a high sensitivity and specificity in detecting infants with Pompe disease. The addition of Pompe disease to the RUSP will also allow for more research to occur to examine the impact of early treatment for late onset cases thus helping to minimize the prolonged and often painful search for a diagnosis faced by adults with late onset of Pompe disease.

Mandatory screening in den meisten US Staaten

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 0 2 2015

Joseph A. Bocchini, Jr., MD
Committee Chairperson
Discretionary Advisory Committee on Heritable Disorders
in Newborns and Children

Screening Panel (RUSP) were forwarded to the Interagency Coordinating Committee on Screening in Newborns and Children (ICC) for additional input regarding implementation.

implementation of state newborn screening for Pompe disease including resource limitations for laboratory testing, management of late-onset cases, and increased burden on treatment and follow-up systems. However, the ICC emphasized that over time, adoption of this recommendation will help increase the number of newborns screened and decrease the morbidity and mortality of babies born with this disease.

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 0 2 2015

Joseph A. Bocchini, Jr., MD
Committee Chairperson
Discretionary Advisory Committee on Heritable Disorders
in Newborns and Children

Taking into consideration the information presente[d] [...]rts, I accept the DACHDNC recommendation to add Pompe disease to the RU[SP]. [...]rdable Care Act requires that most health plans cover the evidence-informe[d] [...]are and screenings provided for in the comprehensive guidelines supported by [...]rces and Service Administration (HRSA). Because the RUSP is a compr[ehensive] guidelines, a condition added to the RUSP must be covered. It should be underst[ood] [...]on of Pompe disease to the RUSP does not constitute a requirement for states t[o] [...]reening, only a recommendation. I recognize

Erhebliche Kosten für Screening, Konfirmationsdiagnostik, Therapie

Folgekosten infolge Phänotypen

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Neurology. 2011 Aug 9;77(6):522-3. doi: 10.1212/WNL.0b013e318228c15f. Epub 2011 Jul 13.

"I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients.

Kwon JM, Steiner RD.

Comment on

- Making diagnosis of Pompe disease at a presymptomatic stage: to treat or not to treat? [Neurology. 2011]

J Inherit Metab Dis (2010) 33 (Suppl 2):S205–S210
DOI 10.1007/s10545-010-9106-6

NEWBORN SCREENING

Expanded newborn screening: reducing harm, assessing benefit

Bridget Wilcken

Table 1 Some of the problems common to newborn screening programmes

Problem	Possible effect	Example(s)	References
Over-diagnosis of mild cases	Unnecessary treatment; worry. Outcome seems more beneficial	? congenital hypothyroidism Neuroblastoma	La Franchi 2010 Woods et al. 2002
Newly discovered mild forms of disorders	Uncertainty about management	Citrullinaemia	Discussed in this article
Including disorders of little/no clinical significance	Unnecessary treatment; harmful treatment; worry	Histidinaemia SCADD	Popkin et al. 1974
Late effects of a disorder previously unrecognised	Effective management not in place	Maternal PKU MGC type I	Lenke and Levy 1980 Wortmann et al. 2010
New phenocopies not previously recognised	Wrong treatment instituted at first	Pterin disorders in PKU screening	Danks et al. 1978
Lack of evidence for treatment modalities	Guidelines based on practice (practice might be wrong)	VLCADD	Arnold et al. 2009 Spiekerkoetter et al. 2009

SCADD Short-chain acylCoA dehydrogenase deficiency, *PKU* phenylketonuria, *MGC* methylglutaconyl CoA hydratase deficiency, *VLCADD* very-long-chain acylCoA dehydrogenase deficiency

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BMJ

BMJ 2014;348:g3267 doi: 10.1136/bmj.g3267 (Published 13 May 2014)

NEWS

Newborn babies will be tested for four more disorders, committee decides

Nigel Hawkes

Four new genetic disorders will be added to those already screened for in newborn babies, the UK National Screening Committee has announced.

The decision followed a 12 month pilot study at six centres in England, which found 12 confirmed cases of these four rare conditions in just under 440 000 births, using blood samples taken from the "heel prick" blood test given to all newborns at 5 to 8 days of age.

Recommended Uniform Screening Panel[1]
Core[2] Conditions[3]
(as of April 2013)

ACMG Code	Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
		Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders			
PROP	Propionic acidemia	X					
MUT	Methylmalonic acidemia (methylmalonyl-CoA mutase)	X					
Cbl A,B	Methylmalonic acidemia (cobalamin disorders)	X					
IVA	Isovaleric acidemia	X					
3-MCC	3-Methylcrotonyl-CoA carboxylase deficiency	X					
HMG	3-Hydroxy-3-methylglutaric aciduria	X					
MCD	Holocarboxylase synthase deficiency	X					
BKT	B-Ketothiolase deficiency	X					
GA1	Glutaric acidemia type I	X					
CUD	Carnitine uptake defect/carnitine transport defect		X				
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency		X				
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency		X				
LCHAD	Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency		X				
TFP	Trifunctional protein deficiency		X				
ASA	Argininosuccinic aciduria			X			
CIT	Citrullinemia, type I			X			
MSUD	Maple syrup urine disease			X			
HCY	Homocystinuria			X			
PKU	Classic phenylketonuria			X			
TYR I	Tyrosinemia, type I			X			
CH	Primary congenital hypothyroidism				X		
CAH	Congenital adrenal hyperplasia				X		
Hb SS	S,S disease (Sickle cell anemia)					X	
Hb S/BTh	S, Beta-thalassemia					X	
Hb S/C	S,C disease					X	
BIOT	Biotinidase deficiency						X
CCHD	Critical congenital heart disease						X
CF	Cystic fibrosis						X
GALT	Classic galactosemia						X
HEAR	Hearing loss						X
SCID	Severe combined						X

+ SCID + Pompe +

ACMG Code	Secondary Condition	Metabolic Disorder			Hemoglobin Disorder	Other Disorder
		Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders		
Cbl C,D	Methylmalonic acidemia with homocystinuria	X				
MAL	Malonic acidemia	X				
IBG	Isobutyrylglycinuria	X				
2MBG	2-Methylbutyrylglycinuria	X				
3MGA	3-Methylglutaconic aciduria	X				
2M3HBA	2-Methyl-3-hydroxybutyric aciduria	X				
SCAD	Short-chain acyl-CoA dehydrogenase deficiency		X			
M/SCHAD	Medium/short-chain L-3-hydroxyacl-CoA dehydrogenase deficiency		X			
GA2	Glutaric acidemia type II		X			
MCAT	Medium-chain ketoacyl-CoA thiolase deficiency		X			
DE RED	2,4 Dienoyl-CoA reductase deficiency		X			
CPT IA	Carnitine palmitoyltransferase type I deficiency		X			
CPT II	Carnitine palmitoyltransferase type II deficiency		X			
CACT	Carnitine acylcarnitine translocase deficiency		X			
ARG	Argininemia			X		
CIT II	Citrullinemia, type II			X		
MET	Hypermethioninemia			X		
H-PHE	Benign hyperphenylalaninemia			X		
BIOPT (BS)	Biopterin defect in cofactor biosynthesis			X		
BIOPT (REG)	Biopterin defect in cofactor regeneration			X		
TYR II	Tyrosinemia, type II			X		
TYR III	Tyrosinemia, type III			X		
Var Hb	Various other hemoglobinopathies				X	
GALE	Galactowpimerase deficiency					X
GALK	Galactokinase deficiency					X
	T-cell related lymphocyte deficiencies					X

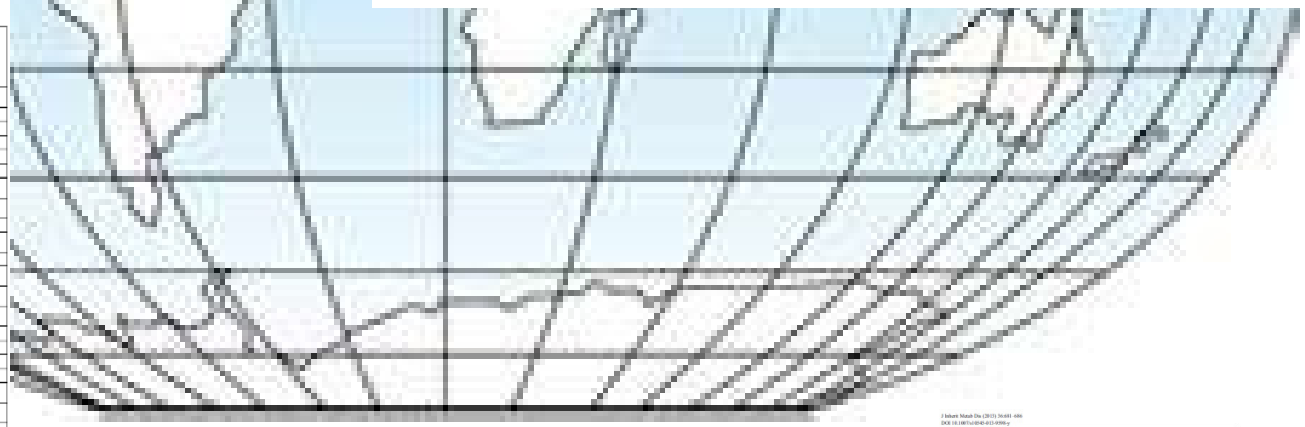
J Inherit Metab Dis (2013) 36:681–686 683

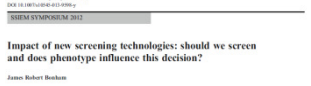
Table 1 Disorders included within newborn screening programmes in European countries (adapted from Loeber et al 2012)

	PKU	MCAD	MSUD	GA1	IVA	LCHAD	Hcys	VLCAD	Tyr1	PA	MMA	CPT1	CPT2
Austria	+	+	+	+	+	+	+	+	+	+	+	+	+
Belgium	+	+	+	+	+	–	+	–	+	+	+	–	–
Denmark	+	+	+	+	–	+	–	+	+	+	+	–	–
Czech Republic	+	+	+	+	+	+	–	+	–	–	–	–	–
France	+	$	–	–	–	–	–	–	–	–	–	–	–
Germany	+	+	+	+	+	+	–	+	–	–	–	+	+
Hungary	+	+	+	+	+	+	+	+	+	+	+	+	+
Iceland	+	+	+	+	+	+	–	+	–	+	+	+	+
Ireland	+	–	+	–	–	–	+	–	–	–	–	–	–
Netherlands	+	+	+	+	+	+	+	+	+	–	–	–	–
Portugal	+	+	+	+	+	+	+	+	+	+	+	+	+
Spain	+	+	+	+	+	–	+	+	+	+	+	+	+
Switzerland	+	+	–	–	–	–	–	–	–	–	–	–	–
United Kingdom	+	+	(+)	(+)	(+)	(+)	(+)	–	–	–	–	–	–
TOTAL	14	12	12	11	10	9	9	9	7	7	7	6	6

+ included in programme, – not included in programme, (+) included in pilot study, *PKU* phenylketonuria, *MCAD* medium chain acyl CoA dehydrogenase deficiency, *MSUD* maple syrup urine disease, *GA1* glutaric aciduria type 1, *IVA* isovaleric acidaemias, *LCHAD* long chain hydroxyl acyl CoA dehydrogenase deficiency, *Hcys* homocystinuria, *VLCAD* very long chain acyl CoA dehydrogenase deficiency, *Tyr 1* tyrosinaemia type 1, *PA* propionic acidaemia, *MMA* methylmaolinic acidaemia, *CPT1* carnitine palmitoyl transferase 1 deficiency, *CPT2* carnitine palmitoyl transferase 2 deficiency

$: The French National Authority is now recommending screening for MCAD



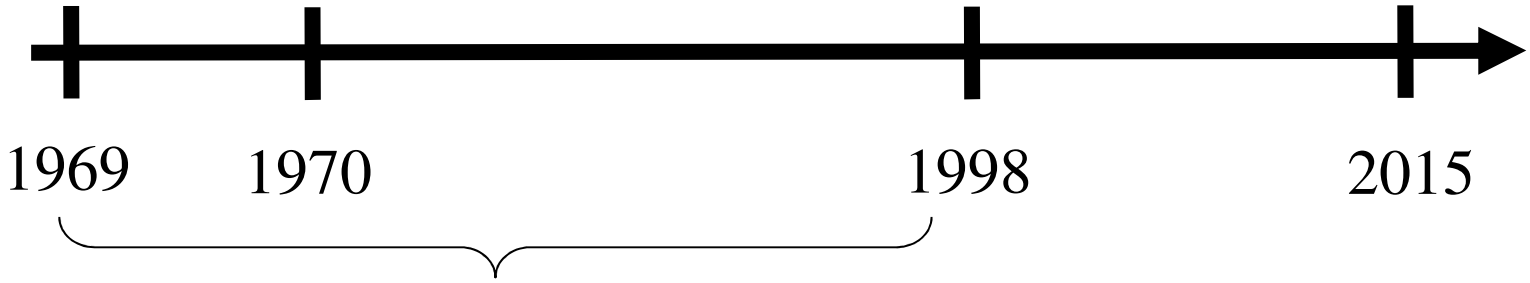


SSIEM SYMPOSIUM 2012

Impact of new screening technologies: should we screen and does phenotype influence this decision?

James Robert Botham

Neugeborenenscreening – Entwicklung Methoden



Ein Test/KH

Metabolite, enzymatisch
Enzymaktivitäten
Immunologische Hormone

Tandem-MS

Metabolite

Enzyme (LSD)

Molekulargenetik

Mutationen CF, SC

TREC (SCID)

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NEWS IN F

BIOPHARMACY Protocol will stop exploitation — and create red tape p.14 | BOTANY Forensic chemistry to stop South Africa's plant thieves p.17 | ASTRONOMY Telescope bounty sparks acce debate p.18

The genomes of ill newborns can be sequenced in less than 24 hours to give clinicians a rapid diagnosis.

GENOMICS

Fast sequencing saves newborns

Rapid analysis of infant genomes is aiding diagnosis and treatment of inexplicably ill babies.

NIH – Projekt

Diagnose in 28/44 kritisch kranken NG

500/5 Jahren

240 gesunde NG - 240 NICU

randomisiert

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JAMA April 21, 2015 Volume 313, Number 15

VIEWPOINT

Newborn Screening
Evolving Challenges in an Era of Rapid Discovery

Donald B. Bailey Jr, PhD
RTI International, Research Triangle Park, North Carolina.

Lisa Gehtland, MD
RTI International, Research Triangle Park, North Carolina.

Changes in Screening Technology

A fourth disrupter is the inevitability of new, more accurate, and cost-effective ways of screening. Genetic testing in newborn screening could identify hundreds of significant genetic variants, only a few of which meet criteria for the RUSP.[4] This would force a complete reconceptualization of screening because decisions will be required about the types of information that should be disclosed and whether parent choice for return of results should become part of newborn screening.

These emerging disrupters are real. They challenge the current state of newborn screening, and advocates are shifting the question from why screen to why not screen. A volun-

TITLE: **Non-invasive Prenatal Testing: A Review of the Cost Effectiveness and Guidelines**

DATE: 10 February 2014

CONTEXT AND POLICY ISSUES

Review

CellPress

Special Issue: Nurturing the Next Generation

Noninvasive fetal genomic, methylomic, and transcriptomic analyses using maternal plasma and clinical implications

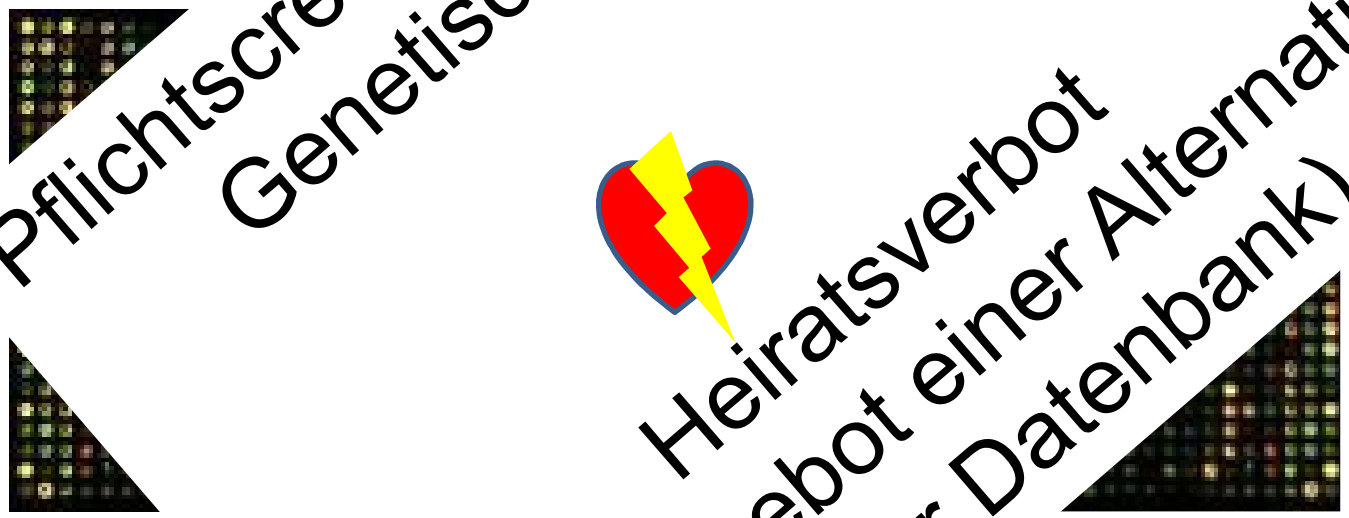
Ada I.C. Wong and Y.M. Dennis Lo

Li Ka Shing Institute of Health Sciences and Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China

Noninvasive prenatal fetal genome sequencing

From whole-chromosome aneuploidy detection to subchromosomal aberration detection, the resolution of looking at

- **Carrier Testing for Severe … e Diseases by Next-Generation Sequ…**
- *Sci Transl Med 12 Ja…*
- 450 Gene autosc…



Pflichtscreening bei Verlobung
Genetische Beratung
Heiratsverbot
(Evtl. Angebot einer Alternative aus der Datenbank)

DNS-Chip

Table 1 Classification system used by the Advisory Committee

Net benefit to the population of newborns screened		States' capability to offer comprehensive newborn screening	
Rating	**Description**	**Rating**	**Description**
A	High certainty that screening for the targeted condition would lead to a significant net benefit	1	Screening has high to moderate feasibility[a] and most newborn screening programs are ready for comprehensive screening
B	Moderate certainty[b] that screening for the targeted condition would lead to a significant benefit	2	Screening has high to moderate feasibility and most newborn screening programs have developmental readiness for comprehensive screening
C	High or moderate certainty that screening for the targeted condition would lead to a small to zero net benefit	3	Screening has high to moderate feasibility and most newborn screening programs are unprepared for comprehensive screening
D	High or moderate certainty that screening for the targeted condition would lead to a negative net benefit	4	Screening has low feasibility
L	Low certainty regarding the net benefit of screening		

[a]High to moderate feasibility is based on the Advisory Committee's determination that there is an established and available screening test that can be adopted, a clear approach to diagnostic confirmation, and a treatment plan that is acceptable to clinicians and affected individuals and their families, and plans for long-term follow-up can be established.[b]Moderate certainty indicates that the Advisory Committee believes that further research could change the magnitude or direction of findings within any of the key questions such that the assessment of net benefit would be small to zero or even negative.

Sinnvolle Grenzen des Neugeborenenscreenings
Achtung Meinung!

- Klare Zieldefinition
  - Indivdueller Patientennutzen
  - Familie
  - Gesellschaft
- Klare Zuständigkeiten S… …terien zur Bewertung potenziell… …eiten
  - Labormethodik, C… …Spezifität
  - Konfirmations… …ientendefinition
  - Behandlu…
  - Ökonomi…
- Forschungsp… …kte nur mit Informed consent

NBS = Gesellschaftspolitik

H.-C. Liao et al. / Clinica Chimica Acta 431 (2014) 80–86

Table 2
The screening algorithm for the Fabry, Pompe, and Gaucher studies.

	Fabry study	Pompe study	Gaucher study
Period	2010.2–2013.1	2010.2–2013.1	2013.9–2013.1
Total newborns	200,904	200,904	108,658
First DBS			
Participated LSD study	191,767 (95.45%)[a]	191,786 (95.46%)	101,134 (94.91%)
Cutoff (μmol/L/h)	1.5	1.6	7.5
Recall DBS	379 (0.20%)	874 (0.46%)	141 (0.14%)
Referred newborns	–	9[b]	–
Recall DBS			
Cutoff (μmol/L/h)	1.0	1.0	7.5
Referred newborns	79 (0.041%)	225 (0.117%)	5 (0.005%)
Confirmation center			
Rejected newborns[c]	12	9	1
Normal newborns	3	209	1
Newborns with mutation	Classic/novel: 8 IVS4+919G>A: 56	Infantile: 5 Late-onset: 11	Classic: 1 Heterozygote: 2

[a] The cutoff value of each study, number and percentage of newborns detected under each category are indicated.
[b] Nine newborns were referred to hospitals directly after the first DBS screening due to GAA values lower than the critical cutoff value.
[c] Newborns who rejected to have further confirmation.

x 280 mm

Beginn Enzymersatztherapie bei Late onset Patienten?

Langzeiterfolg bei infantilen Formen?

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This assessment will include:

- authority laboratory testing
- Interpretation reporting tracking
- assurance of diagnostic evaluation evaluation of outcomes.

- to ensure quality implementation of the screening test
  - adequate training programs for new technologies
  - the assured availability of quality reagents and quality
  - availability of quality-control and proficiency-testing samples
  - a centralized quality-assurance program

- data-reporting systems
- established approach for diagnostic confirmation

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BRIEF REPORT | Genetics inMedicine

Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Alex R. Kemper, MD, MPH[1], Nancy S. Green, MD[2], Ned Calonge, MD, MPH[3], Wendy K.K. Lam, PhD[1], Anne M. Comeau, PhD[4], Aaron J. Goldenberg, PhD, MPH[5], Jelili Ojodu, MPH[6], Lisa A. Prosser, PhD[7], Susan Tanksley, PhD[8] and Joseph A. Bocchini Jr, MD[9]

APPENDIX: PARTICIPANTS IN APRIL 2012 EXPERT MEETING, LISTED ALPHABETICALLY BY MAIN ORGANIZATION REPRESENTED

Agency for Healthcare Research and Quality
Christine Chang, MD, MPH
Denise Dougherty, PhD

Centers for Disease Control and Prevention
Carla Cuthbert, PhD
Randy Elder, MEd, PhD
Richard S. Olney, MD, MPH

Health Resources and Services Administration
Sara Copeland, MD
Sarah Linde-Feucht, MD
Michael C. Lu, MD, MS, MPH
Deboshree Sarkar, MPH
Bonnie Strickland, PhD
Lisa M. Vasquez, MPA

National Institutes of Health
Melissa Parisi, MD, PhD
Tiina Urv, PhD

Advisory Committee
Joseph A. Bocchini Jr, MD
Stephen McDonough, MD

Condition Review Workgroup
Anne M. Comeau, PhD
Alex R. Kemper, MD, MPH, MS
Aaron J. Goldenberg, PhD, MPH
Wendy K.K. Lam, PhD
Lisa A. Prosser, PhD
Jelili Ojodu, MPH

State Newborn Screening Programs
Janice Bach, MS, CGC (Michigan)
Julie Luedtke (Nebraska)
Sharmini V. Rogers, MBBS, MPH (Missouri)

Others
Cynthia Cameron, PhD (Michigan Public Health Institute)
Ned Calonge, MD, MPH (The Colorado Trust)
Christopher Kus, MD, MPH (Association of State and Territorial Health Officials)
Melissa McPheeters, PhD, MPH (Vanderbilt University Evidence-Based Practice Center)
Virginia A. Moyer, MD, MPH (US Preventive Services Taskforce)
Beth A. Tarini, MD, MS (University of Michigan)
Bradford L. Therrell Jr, PhD (National Newborn Screening and Global Resource Center, University of Texas Health Science Center at San Antonio)

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PRINCIPLES AND PRACTICE OF SCREENING FOR DISEASE

J. M. G. WILSON
Principal Medical Officer, Ministry of Health, London, England

G. JUNGNER
Chief, Clinical Chemistry Department, Serafimer's Hospital, Stockholm, Sweden

(2) Familienplanung als Benefit auch bei nicht-behandelbaren KH

(7) Und (8) als Voraussetzung

(1) The condition sought should be an important health problem.

(2) There should be an accepted treatment for patients with recognized disease.

(3) Facilities for diagnosis and treatment should be available.

(4) There should be a recognizable latent or early symptomatic stage.

Schriftliches Einverständnis bei Pilotprojekten/Forschungsvorhaben

(5) There should be a suitable test or examination.

(6) The test should be acceptable to the population.

(7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

(8) There should be an agreed policy on whom to treat as patients.

(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

(10) Case-finding should be a continuing process and not a "once and for all" project.

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Sinn des Neugeborenenscreenings

Frühzeitige Therapie verbessert die Situation des Patienten

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VIEWPOINT

Newborn Screening Controversy
Past, Present, and Future

Michelle Huckaby Lewis, MD, JD
Berman Institute of Bioethics, Johns Hopkins University, Baltimore, Maryland.

screening criteria.[4] Discussions about the appropriateness of adding new conditions to state newborn screening panels are ongoing, particularly when a state legislature requires the addition of a condition based on political pressure from child advocates rather than with the full support of the scientific community as was the case when Krabbe disease was added to the New York newborn screening panel.[5]

and that newborn screening programs will continue to face new challenges and generate new controversy as they continue their evolution in response to technological advances. It is imperative that care providers understand these controversies so that they can have meaningful conversations with concerned parents and educate parents about the potential value of newborn screening for their children. The following examples il-

Wilson & Jungner 1968

Evaluation of screening procedures

The Conference on Preventive Aspects of Chronic Disease considered the evaluation of case-finding tests and programmes in 1951 and the

Compare outcome after NBS vs. w/o NBS

(2) Reliability
(3) Yield
(4) Cost
(5) Acceptance
(6) Follow-up services

(7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

(8) There should be an agreed policy on whom to treat as patients.

(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

(10) Case-finding should be a continuing process and not a "once and for all" project.

Neugeborenenscreening – Leitlinien – Richtlinien - Gesetze

NGS Länder-Laborsache

Organoazidurien (-ämien)

Isovalerianazidämie
Propionazidämie
Methylmalonazidurie
Glutarazidurie Typ I
3-MCC M.
HMG-CoA-Lyase M.
Multipler Carboxylase M.
Biotinidase Mangel
Beta-Ketothiolase M.

Fettsäuren Oxidationsdefekte

Short-chain acyl-CoA DH M.

Medium-chain acyl-CoA DH M.

Very long-chain acyl-CoA DH M.

Long-chain 3-OH acyl-CoA DH M.
2,4-Dienoyl-CoA Reduktase M.
Multipler Acyl-CoA DH M.
Primärer Carnitin M.
Carnitin-Acylcarnitin Translokase M.
Carnitin Palmitoyl Transferase I + II M.
Medium-chain 3-ketoacyl-CoA thiolase M.

Aminoazidopathien und Harnstoffzyklusdefekte

PKU
nonPKU-HPA
nichtketotische Hyperglyzinämie
Ahornsirup Krankheit
Tyrosinämie I
Zitrullinämie
Argininosukzinat Lyase Mangel
Homozystinurie
HHH-Syndrom

Screeningkommission der DGKJ - Empfehlung

Kinderrichtlinie des G-BA – Bundesweit gültig

Phenylketonurie

MCAD Defekt

VLCAD Defekt

LCHAD Defekt

CPT1, CPT2, CACT

Ahornsirup-KH

Glutarazidurie Typ 1

Isovalerianazidämie

Galaktosämie, Biotinidasemangel

Kongenitale primäre Hypothyreose

AGS

Gendiagnostikgesetz

G-BA – Richtlinie angepasst 3/2011

1969 1970 1998 1999 2003 2005 2010

The vision

http://www.climatesciencewatch.org/wp-content/uploads/2011/05/nsa_aerial.jpg

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Alles wurde schon einmal gesagt …..

- **Neugeborenen-Screening für Schweren**
- **Kombinierten Immundefekt (SCID)**
- Prof. Janine Reichenbach

- **Vorsorgeuntersuchungen & Screeningprogramme aus der Public Health Sicht: Versprechungen, Fallstricke und Gefahren**
- Prof. Marcel Zwahlen

- **Mit Sicherheit ins Ungewisse**
- Prof. Adalbert Roscher

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commentary

Long-term follow-up after diagnosis resulting from newborn screening: Statement of the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Alex R. Kemper, MD, MPH[1], Coleen A. Boyle, PhD[2], Javier Aceves, MD[3], Denise Dougherty, PhD[4], James Figge, MD, MBA[5], Jill L. Fisch[6], Alan R. Hinman, MD, MPH[7], Carol L. Greene, MD[8], Christopher A. Kus, MD, MPH[9], Julie Miller, BS[10], Derek Robertson, MBA, JD[11], Brad Therrell, PhD[12], Michele Lloyd-Puryear, MD, PhD[13], Peter C. van Dyck, MD, MPH[13], and R. Rodney Howell, MD[14]

***Genet Med* 2008:10(4):259–261.**

GOAL OF LONG-TERM FOLLOW-UP

The principal goal of long-term term follow-up is to assure the best possible outcome for individuals with disorders identified through newborn screening. The time frame for long-term follow-up is the lifespan of the affected individual; however, the responsibility of the ACHDGDNC as set by its authorizing legislation is from birth to age 21 years.

DEFINITION OF LONG-TERM FOLLOW-UP

Fundamentally, long-term follow-up comprises the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of individuals identified with a condition included in newborn screening. Integral to assuring appropriate long-term follow-up are activities related to improving care delivery, including engagement of affected individuals and their families as effective partners in care management, continuous quality improvement through the medical home, research into pathophysiology and treatment options, and active surveillance and evaluation of data related to care and outcomes.

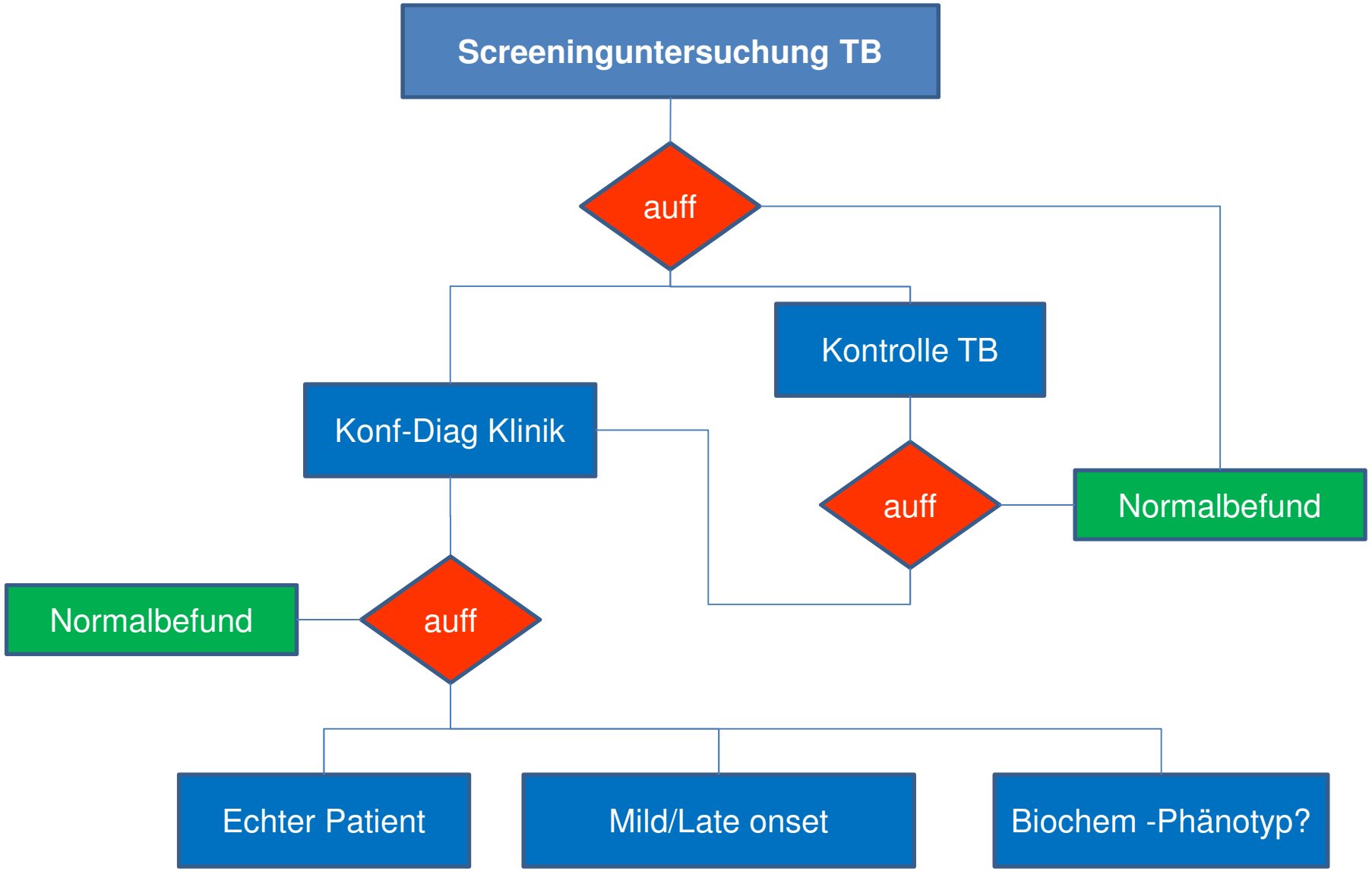
COMPONENTS OF LONG-TERM FOLLOW-UP CARE

Care coordination through a medical home

Evidence-based treatment

Continuous quality improvement

New knowledge discovery


Screeninguntersuchung TB
auff
Kontrolle TB
Konf-Diag Klinik
auff
Normalbefund
Normalbefund
auff
Echter Patient
Mild/Late onset
Biochem -Phänotyp?