Newborn screening: can lessons from history help us to avoid problems in the future?

Bridget Wilcken

The Sydney Children's Hospital at Westmead

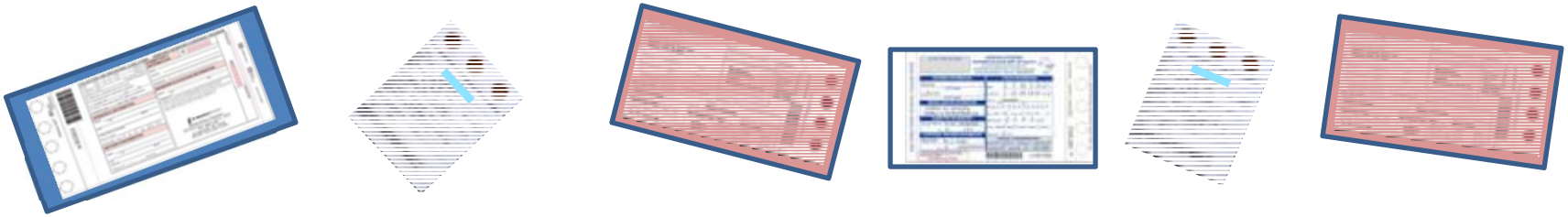
and University of Sydney

Australia

50 years of newborn screening

A huge public health success
Thousands of children spared lifelong disability or death
Screening will certainly expand its reach

BUT: problems remain, not yet addressed, and new problems are certainly to be expected



This talk

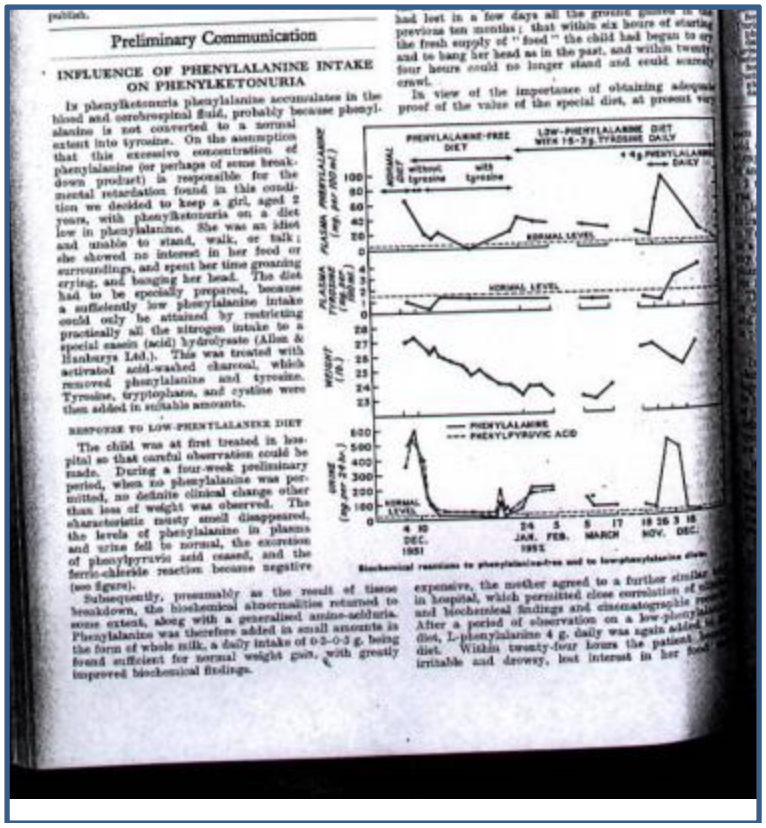
- History of the first newborn screening
- A very brief outline of progress so far
- Problems encountered, not yet completely solved
  - Long-term follow-up to assess outcomes
  - Cessation of programmes where benefit not shown
  - Mild phenotypes and the development of case-definition
  - Rational systems and criteria for inclusion of disorders
  - Development of national data-bases
  - Availability of confirmatory testing and treatment modalities
- A look to the future

First screening for PKU

- **The disorder was uncovered in 1934**
- **Stimulus for screening was the discovery of dietary treatment in the 50s**

First proof of efficacy of treatment of PKU

Bickel, Gerrard and Hickmans. Lancet, 1953



Preliminary Communication

INFLUENCE OF PHENYLALANINE INTAKE ON PHENYLKETONURIA

In phenylketonuria phenylalanine accumulates in the blood and cerebrospinal fluid, probably because phenylalanine is not converted to a normal extent into tyrosine. On the assumption that this excessive concentration of phenylalanine (or perhaps of some breakdown product) is responsible for the mental retardation found in this condition we decided to keep a girl, aged 2 years, with phenylketonuria on a diet low in phenylalanine. She was an idiot and unable to stand, walk, or talk; she showed no interest in her food or surroundings, and spent her time groaning, crying, and banging her head. The diet had to be specially prepared, because a sufficiently low phenylalanine intake could only be attained by restricting practically all the nitrogen intake to a special casein (acid) hydrolysate (Allen & Hanburys Ltd.). This was treated with activated acid-washed charcoal, which removed phenylalanine and tyrosine. Tyrosine, tryptophane, and cystine were then added in suitable amounts.

RESPONSE TO LOW-PHENYLALANINE DIET

The child was at first treated in hospital so that careful observation could be made. During a four-week preliminary period, when no phenylalanine was permitted, no definite clinical change other than loss of weight was observed. The characteristic musty smell disappeared, the levels of phenylalanine in plasma and urine fell to normal, the excretion of phenylpyruvic acid ceased, and the ferric-chloride reaction became negative (see figure).

Subsequently, presumably as the result of tissue breakdown, the biochemical abnormalities returned to some extent, along with a generalised amino-aciduria. Phenylalanine was therefore added in small amounts in the form of whole milk, a daily intake of 0·3–0·5 g. being found sufficient for normal weight gain, with greatly improved biochemical findings.

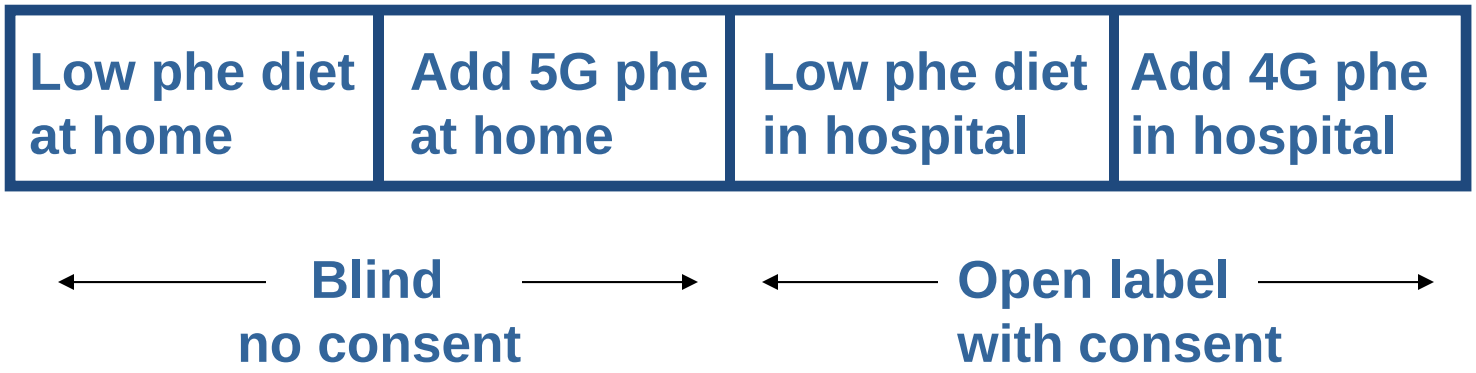
had lost in a few days all the gr... previous ten months; that within six hours of starting the fresh supply of "food" the child had begun to cry and to hang her head as in the past, and within twenty-four hours could no longer stand and could scarcely crawl.

In view of the importance of obtaining adequate proof of the value of the special diet, at present very expensive, the mother agreed to a further similar ... in hospital, which permitted close correlation of ... and biochemical findings and cinematographic ... After a period of observation on a low-phenylalanine diet, L-phenylalanine 4 g. daily was again added to the diet. Within twenty-four hours the patient became irritable and drowsy, lost interest in her food ...

PHENYLALANINE-FREE DIET
LOW-PHENYLALANINE DIET WITH 10–12 g. TYROSINE DAILY
+ 4 g. PHENYLALANINE DAILY
without tyrosine
with tyrosine
NORMAL DIET
NORMAL LEVEL
PLASMA PHENYLALANINE (mg. per 100 ml.)
PLASMA TYROSINE (mg. per 100 ml.)
WEIGHT (lb.)
URINE (mg. per 24 hr.)
PHENYLALANINE
PHENYLPYRUVIC ACID
4 10 DEC. 1951
24 5 JAN. FEB. 1952
5 17 MARCH
19 26 3 10 NOV. DEC.

The experiment

- **“A girl aged 2 years…..was an idiot, unable to stand or talk … spent her time groaning, crying, banging her head”**
- **After near-removal of phenylalanine from the diet, she gradually improved, no longer cried, started to crawl, stand and climb**
- **Secret re-introduction of phenylalanine caused loss within days of all her developmental gains**



The first trial of treatment for PKU:
A cross-over design

How well did the treatment work?

- Babies and children needed a very low protein diet (vegetarian) with the special formula
- The treated children improved a lot, but were still intellectually retarded
- **Treatment needed to start at birth – it was very successful with siblings of known cases**
- The race was on to find a test for all newborns
- An early urine test led to some hospital based screening but was only partially successful in case-finding
  - Dr Willard Centerwell; several others

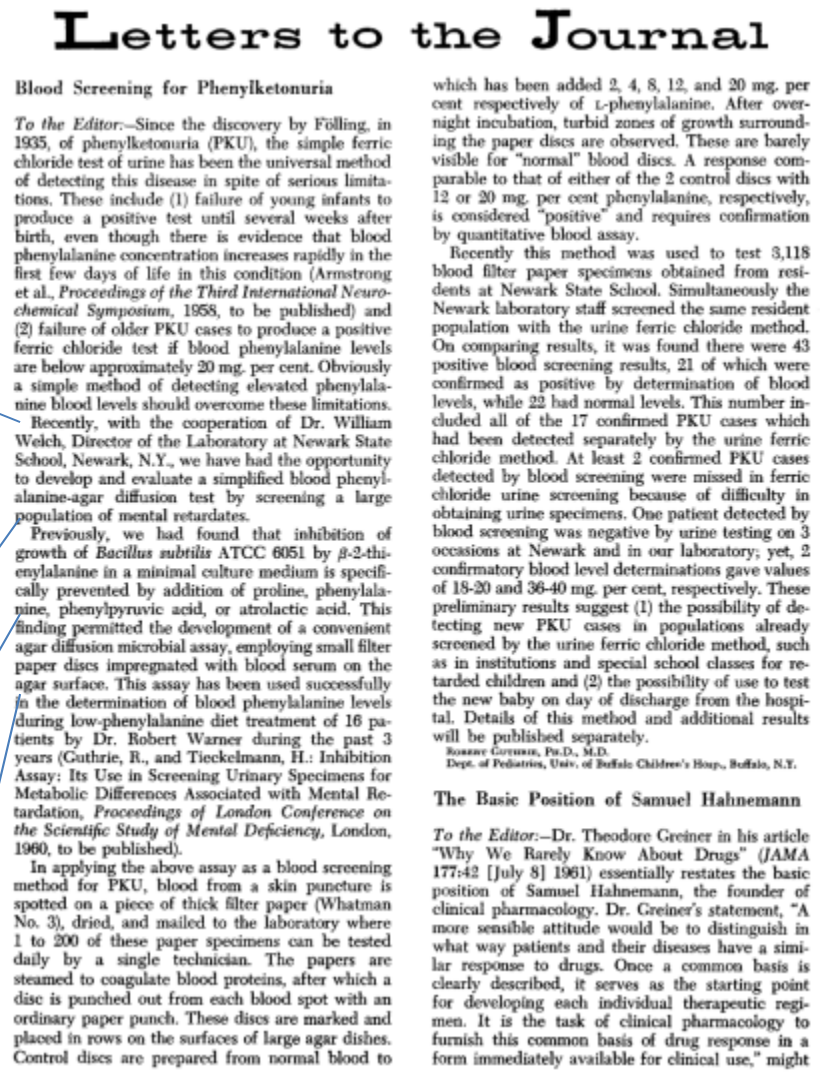
The first report of the new PKU test

JAMA Nov 25th 1961

Robert Guthrie PhD, MD

Recently, with the cooperation of Dr. William Welch, Director of the Laboratory at Newark State School, Newark, N.Y., we have had the opportunity to develop and evaluate a simplified blood phenyl-alanine-agar diffusion test by screening a large population of mental retardates.

finding permitted the development of a convenient agar diffusion microbial assay, employing small filter paper discs impregnated with blood serum on the agar surface. This assay has been used successfully in the determination of blood phenylalanine levels



Letters to the Journal

Blood Screening for Phenylketonuria

To the Editor:—Since the discovery by Fölling, in 1935, of phenylketonuria (PKU), the simple ferric chloride test of urine has been the universal method of detecting this disease in spite of serious limitations. These include (1) failure of young infants to produce a positive test until several weeks after birth, even though there is evidence that blood phenylalanine concentration increases rapidly in the first few days of life in this condition (Armstrong et al., *Proceedings of the Third International Neurochemical Symposium*, 1958, to be published) and (2) failure of older PKU cases to produce a positive ferric chloride test if blood phenylalanine levels are below approximately 20 mg. per cent. Obviously a simple method of detecting elevated phenylalanine blood levels should overcome these limitations.

Recently, with the cooperation of Dr. William Welch, Director of the Laboratory at Newark State School, Newark, N.Y., we have had the opportunity to develop and evaluate a simplified blood phenylalanine-agar diffusion test by screening a large population of mental retardates.

Previously, we had found that inhibition of growth of *Bacillus subtilis* ATCC 6051 by β-2-thienylalanine in a minimal culture medium is specifically prevented by addition of proline, phenylalanine, phenylpyruvic acid, or atrolactic acid. This finding permitted the development of a convenient agar diffusion microbial assay, employing small filter paper discs impregnated with blood serum on the agar surface. This assay has been used successfully in the determination of blood phenylalanine levels during low-phenylalanine diet treatment of 16 patients by Dr. Robert Warner during the past 3 years (Guthrie, R., and Tieckelmann, H.: Inhibition Assay: Its Use in Screening Urinary Specimens for Metabolic Differences Associated with Mental Retardation, *Proceedings of London Conference on the Scientific Study of Mental Deficiency*, London, 1960, to be published).

In applying the above assay as a blood screening method for PKU, blood from a skin puncture is spotted on a piece of thick filter paper (Whatman No. 3), dried, and mailed to the laboratory where 1 to 200 of these paper specimens can be tested daily by a single technician. The papers are steamed to coagulate blood proteins, after which a disc is punched out from each blood spot with an ordinary paper punch. These discs are marked and placed in rows on the surfaces of large agar dishes. Control discs are prepared from normal blood to which has been added 2, 4, 8, 12, and 20 mg. per cent respectively of L-phenylalanine. After overnight incubation, turbid zones of growth surrounding the paper discs are observed. These are barely visible for "normal" blood discs. A response comparable to that of either of the 2 control discs with 12 or 20 mg. per cent phenylalanine, respectively, is considered "positive" and requires confirmation by quantitative blood assay.

Recently this method was used to test 3,118 blood filter paper specimens obtained from residents at Newark State School. Simultaneously the Newark laboratory staff screened the same resident population with the urine ferric chloride method. On comparing results, it was found there were 43 positive blood screening results, 21 of which were confirmed as positive by determination of blood levels, while 22 had normal levels. This number included all of the 17 confirmed PKU cases which had been detected separately by the urine ferric chloride method. At least 2 confirmed PKU cases detected by blood screening were missed in ferric chloride urine screening because of difficulty in obtaining urine specimens. One patient detected by blood screening was negative by urine testing on 3 occasions at Newark and in our laboratory; yet, 2 confirmatory blood level determinations gave values of 18-20 and 36-40 mg. per cent, respectively. These preliminary results suggest (1) the possibility of detecting new PKU cases in populations already screened by the urine ferric chloride method, such as in institutions and special school classes for retarded children and (2) the possibility of use to test the new baby on day of discharge from the hospital. Details of this method and additional results will be published separately.

Robert Guthrie, Ph.D., M.D.
Dept. of Pediatrics, Univ. of Buffalo Children's Hosp., Buffalo, N.Y.

The Basic Position of Samuel Hahnemann

To the Editor:—Dr. Theodore Greiner in his article "Why We Rarely Know About Drugs" (*JAMA* 177:42 [July 8] 1961) essentially restates the basic position of Samuel Hahnemann, the founder of clinical pharmacology. Dr. Greiner's statement, "A more sensible attitude would be to distinguish in what way patients and their diseases have a similar response to drugs. Once a common basis is clearly described, it serves as the starting point for developing each individual therapeutic regimen. It is the task of clinical pharmacology to furnish this common basis of drug response in a form immediately available for clinical use," might

The first trial of PKU screening

- **Bob Guthrie had developed his test by 1961. He received a grant from the Children's Bureau in 1962 to mount a study of 400,000 infants, with 40 cases projected to be found**

- **On May 25th 1962 all states invited to participate. 29 states + Puerto Rico contributed data by Dec 31st 1963 (MA sent 125,000)**

- **14.1%infants from participating states tested – 404,568**
- **275 "presumptive positive" (0.067%). 37 had PKU.**
  - **One infant with PKU not tested (discharged before d 3). One had a result 4-6mg% and was picked up on a test at 4w. 100-fold variation among states for presumptive positive rate.**

Significant findings in the report

Guthrie and Whitney Children's bureau publication 419 1964

- At least 26 of 37 PKU cases (maybe more) were on diet by 1 month
- Birth incidence 1: 10,374
- Cases of "occult PKU" (mild or delayed Phe rise)
- Older PKU-affected siblings discovered
- Case of maternal PKU. "It is hoped all laboratories will test mothers" of non-PKU infants with elevated Phe levels
- Suggested protocols for intermediate Phe levels
- Early discharge seen as a problem – milk feed thought necessary
- "This procedure (screening for PKU) is recommended as a public health procedure"

- "Current investigation.....is directed towards a "multiple test" for a number of rare inherited conditions"

How well did things work for PKU screening?

- **Pretty well**
- **Very little adverse effect in reality (Brosco et al 2006)**
  - Early dietary struggles ; cases with phenylalanine deficiency symptoms; need for confirmation of diagnosis before instituting treatment
  - "Atypical" PKU due to pterin disorders not appreciated early
- **Factors aiding success:**
  - The natural history was well known
  - The surrogate effects of treatment (blood phe level) easy to measure
  - Mild cases thus fairly easy to identify and manage
- **Persisting problems:**
  - How long to treat?
  - What exact blood levels to aim for?
  - How to treat better – in a more acceptable way – or how to cure?

The time course of newborn screening

- **1963 – Guthrie's seminal paper; PKU screening starts**
  - **Other BIAs for MSUD, CBS deficiency, histidinaemia etc**
  - **Galactosaemia**
- **1975 – T4 assay for hypothyroidism**
  - **Soon overtaken by TSH as primary assay**
  - **Other disorders considered in the '70s included CF; DMD**
- **1980's – Cystic Fibrosis –blood-spot method; not well taken up**
  - **CAH; biotinidase; haemoglobinopathies;**
- **"In general, the new tests have been added casually, with little systematic assessment of their value and risks, and with little concern for obtaining informed consent". *Dianne B. Paul Task force on genetic testing***
- **Newborn screening was a quiet back-water for 30 years**

1990's NBS no longer a backwater but mainstream

- 1991Tandem mass spectrometry (MSMS):
  - Electrospray ionisation coming in; discussed at ISNS conference
- Mid 1990's Limited programmes: N Carolina, and Pennsylvania
  - Routine MSMS screening started in NSW 1998
  - Public pressure in US
- 2005 HHS Secretary's Advisory Committee on Heritable Disease recommends Uniform Screening Panel: 29 disorders (now 31)
- By 2006: MSMS screening widespread
  - ACMG. Newborn screening: toward a uniform screening panel and system. *Genet Med.* 2006;8 Suppl 1:1S-252S.
- Increasing consideration of other disorders to be included
- Analytical problems largely taken care of
  - Interpretation: Work on algorithms progressing

Facing the future with confidence needs solutions to current problems

- **Follow-up to assess benefit**
  - **Addressing definitions**
  - **National databases, perhaps international collaboration**
  - **Funding and long-term commitment**
- **Ceasing programmes where benefit not shown**
- **Mild phenotypes and who needs treatment**
  - **Lack of evidence about treatments**
- **Integrated systems: screening, diagnosis, clinical service**
- **Selecting disorders - must get a more rational approach**

Evidence of effectiveness in 2013

- **Effectiveness of newborn screening: Surprisingly little hard evidence**
  - **PKU and CH: No formal trials, but lots of evidence of benefit**
  - **CF: two RCTs**
  - **MS/MS:**
    - **only one formal assessment including adequate control populations**
    - **only 2 disorders with statistically significant benefit shown**
      - **MCADD, the commonest fatty acid oxidation defect**
      - **Glutaric aciduria type I**
    - **In several other disorders benefit is virtually certain**

Why is it difficult to assess benefit?

- **Randomised controlled trials usually not feasible**
  - ***Power*: rare diseases, would require huge numbers**
  - ***Recruitment* would take too long, (because of rarity)**
  - ***Follow-up* needed for many years – to adolescence or adulthood**
    - **Example of 3-methylglutaconyl-CoA hydratase deficiency**
  - **Preconceived idea of benefit introduces extra ethical problem**

Why is it difficult to assess benefit?

- More cases detected by screening than present clinically
- Cases detected by screening and those detected clinically are usually a different (overlapping) population
  - May be many times the expected number found by screening
  - “Unusual” cases
    - different mutation profile;
    - asymptomatic, but abnormal biochemistry persists
- Natural history not well known:
  - “Unusual” cases
  - Long-term evolution of early-treated classical cases

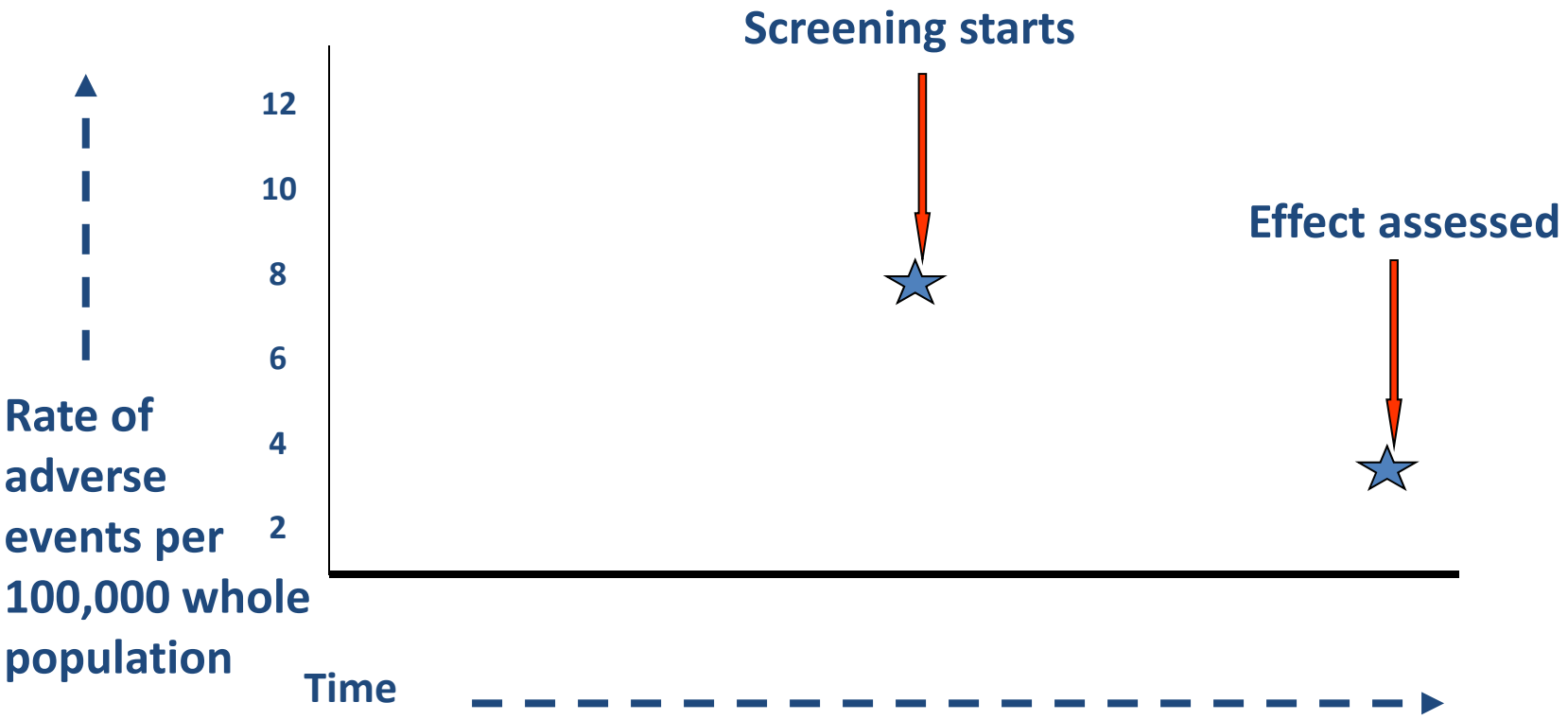
Why is it difficult to assess benefit?

- **Control groups from unscreened population(s) are needed to assess the effect of screening**

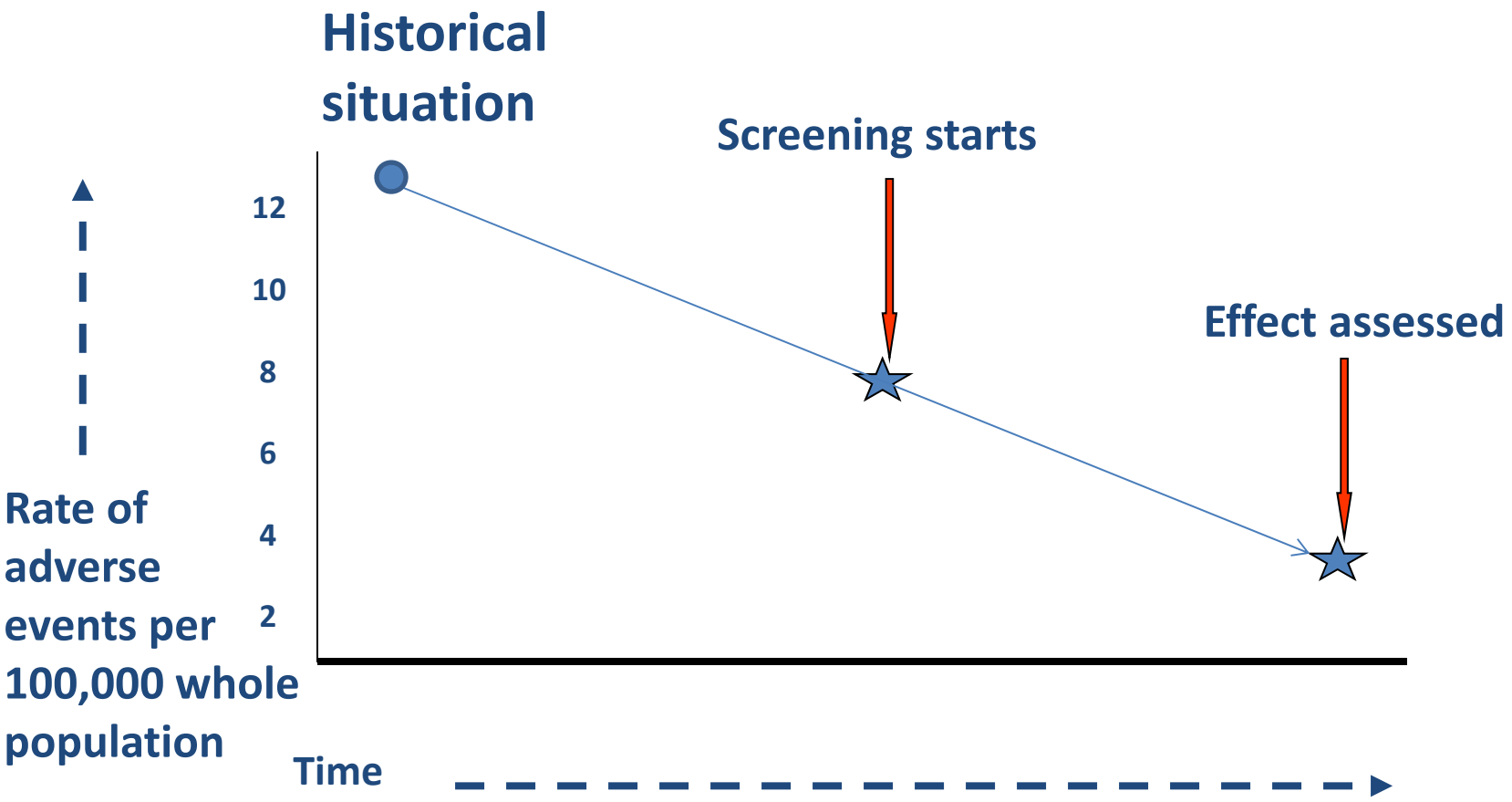
- **Comparability of treatment needed**
- **Complete ascertainment, (or a good estimate of missing cases)**
- **Possible bias using historical controls**
- **Need for case definitions (ability to compare like with like)**

- **Without an RCT, clinical endpoints must be assessed on a whole population basis (because screen-detected cases differ)**

Historical control groups: Possible scenario



Control groups: Possible scenario



Ceasing to screen for disorders if no benefit shown

Programmes with unclear or no benefit, that ceased

- **Histidinaemia:**
  - Screening in several regions for up to 17 years
  - Most patients had restrictive diets; a few had liver biopsies
  - Even by 1974 the benign nature was evident (Levy et al NEJM)
  - No current screening
  - 2013 Dietary product Histidon: **"Histidon can be used in infants, children and adults for the dietary management of Histidinaemia. "**

- **Compare this with Isobutyryl CoA dehydrogenase and SCAD deficiency**

  "Isobutyryl-CoA dehydrogenase deficiency - IBCD can cause heart problems and anemia. Treatment includes a special diet, special formula and regular feedings". NYMAC 2013

  But most clinicians feel sure these are conditions benign, and do not treat. We no longer screen

Programmes with unclear or no benefit, that ceased

- **Histidinaemia:**
  - Screening in several regions for up to 17 years
  - Most patients had restrictive diets; a few, liver biopsies
  - Even by 1974 the benign nature was evident (Levy et al NEJM)
  - No current screening
- **Toxoplasmosis:**
  - No evidence that early detection and treatment alters outcome
  - Denmark ceased screening in 2007 after evaluation
  - [Screening, since 1986, continues in Massachusetts]
- **Neuroblastoma:**
  - Screening test detected cases that were destined to regress and usually remain undetected: no alteration in morbidity or mortality
  - A trial in US/Canada demonstrated no benefit

Evaluating outcomes: programmes continuing with unclear benefit

- **G-6-PD deficiency:**
  - Screening in areas where the deficiency is common but clinically rather benign
  - May be useful – no evidence presented so far
  - Huge follow-up needs may compromise existing screening for other disorders

Mild phenotypes
Lack of evidence about treatments

- **Not a new problem, but more obvious now**
  - Congenital hypothyroid screening: probable over-diagnosis
  - MCAD, VLCAD, citrullinemia: unclear natural history of the mild phenotype
- **MCAD**
  - Unusual genotypes, not recorded in clinically presenting cases
    - eg199C>T 985A>G/199C>T cases mild as far as NBS data goes
    - All neonates are subject to catabolic stress in first 72hrs
    - 199C>T is temperature sensitive, so unclear if a stress with fever would cause metabolic decompensation where other stress would not
- **VLCAD**
  - Detection of many more cases than ever present clinically
  - Probably needs enzyme analysis to identify those prone to decompensation who need close management. Other markers may be helpful

VLCAD – NSW experience

- Screening since 1998; mild-case problem evident
- 2011-12: We studied all patients with a positive screening result (cut-off and region 4 tool results) over a two year period.
  - Plasma acylcarnitines, enzyme analysis, a repeat DBS and mutation analysis requested on all
- We also collected data on all patients diagnosed previously who had had symptoms attributable to VLCAD (diagnosed initially either because of symptoms or by NBS)
- Patients were classified as having classical VLCAD if they had had
  - Symptoms clearly attributable to VLCAD AND either
  - Enzyme analysis in skin fibroblasts in our established VLCAD range or persistently abnormal biochemistry specifically indicating VLCAD
- 20 classified as VLCAD (8 born elsewhere or before screening)
- 22 screen-detected classified as non-VLCAD/non-classical VLCAD

VLCAD – NSW experience

- **Not all patients had every test:**
- **Symptomatic VLCAD patients n=12 (4 NBS, 2 adult onset)**
  - **8/8 diagnostic enzyme results and fibroblast profile**
  - **9/9 elevated plasma C14, C14:1 after the neonatal period**
  - **7/7 two known severe mutations**
- **Asymptomatic VLCAD n=8**
  - **8/8 diagnostic enzyme results and fibroblast profile**
  - **8/8 elevated plasma C14, C14:1 on confirmatory test**
  - **4/5 two severe mutations; 1/5 one severe mutation only (+abn enzymology)**
- **Non-VLCAD, positive newborn screen n=22**
  - **10/10 normal enzymology and fibroblast profile**
  - **19/22 normal plasma C14, C14:1 on confirmatory test**
  - **2/22 borderline plasma results; 1/22 borderline results ? misclassification**

VLCAD – NSW experience

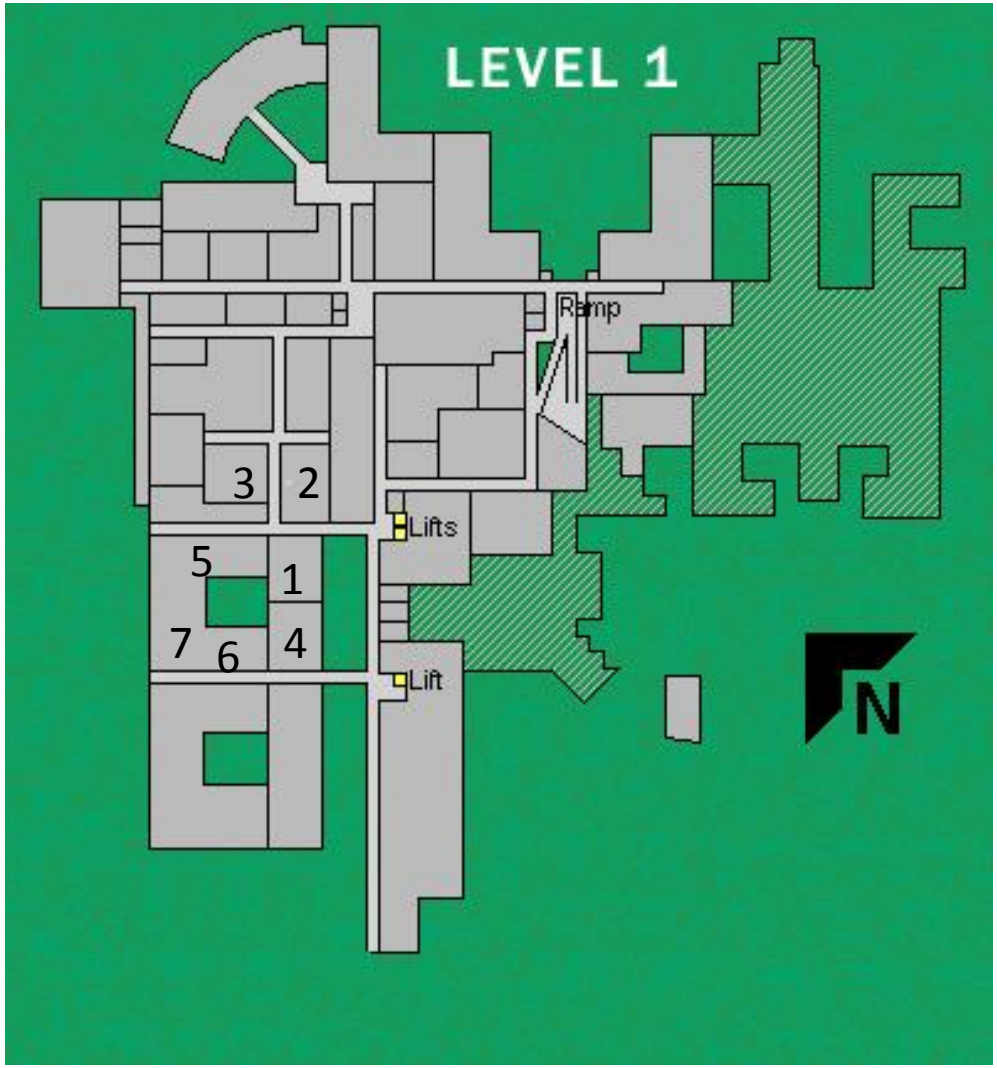
- **The study is ongoing**

- **Newborn screening results have been problematic**
  - **but C14 & C14:1 very well correlated with enzymatic results**
- **Enzymatic studies seem likely to indicate best those at risk for childhood symptoms (Spiekerkoetter 2012)**
- **Elevated Plasma C14 and C14:1 levels at confirmation (ie within the first 2 weeks) may provide very good differentiation**
- **Mutation analysis not (yet) as discriminatory**

Facing the future with confidence needs solutions to current problems

- Follow-up to assess benefit
  - Addressing definitions
  - National databases, perhaps international collaboration
  - Funding and long-term commitment
- Ceasing programmes where benefit not shown
- Mild phenotypes and who needs treatment
  - Lack of evidence about treatments
- **Integrated systems: screening, diagnosis, clinical service**
- **Selecting disorders - must get a more rational approach**

Integrated system: laboratory and clinical services in Australasia are mainly co-located



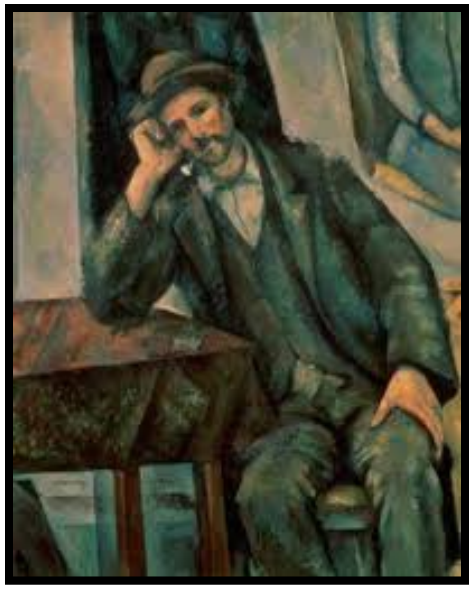
Children's Hospital at Westmead, Sydney, New South Wales
Level 1

1. **Newborn Screening Lab**
2. **Biochemical Genetics Lab**
3. **Metabolic Physicians**
4. **Nutrition and dietetics**
5. **Cytogenetics Lab**
6. **Molecular Genetics Lab**
7. **Clinical genetics**

I and 2 are statewide services. 3 largely so.

More integration: development of national (or international) databases

- Privacy issues and lack of funding make the development of cross-border databases very difficult
- Some problems could be solved for rare diseases if we had these in place
- A pipe-dream?



Cezanne

A summary of what is needed to underpin the screening of new disorders

- Definition of disorders: for guidance, dealing with mild cases, assessment of outcomes
- Better data storage
- Work on aspects of treatment: evidence, availablility
- Support for long-term outcome assessment
  - funding
  - expertise (clinical, economic, public health)
  - the will to do it
- A move towards integration of services would almost certainly be helpful for management – and would pave the way for:
- Disease-specific databases (enhanced by definitions)

Assessment of disorders for inclusion in a screening program

- Not too good in the past

How much evidence is needed for a decision?

model of cystic fibrosis – 30 years of screening

- 1979 – description from New Zealand of applicable method

  - Crossley , Elliott and Smith Dried blood-spot screening for cystic fibrosis in the newborn 1979 Lancet , i: 472-4

  - Dried blood-spot IRT was two to 14 times higher in CF neonates than in controls, even in stored samples

MEAN TRYPSIN CONCENTRATION (μg/l)*

Year of sample collection	C.F.	Control 1	Control 2	Ratio†
1974	100	7	27	5·8
	100	17	0	10·0
1975	195	5	25	13·0
1976	187	27	53	4·7
	110	17	0	14·0
	168	0	100	3·4
1977	145	35	105	2·1
	140	50	37	3·2
1978	355	27	70	7·3
	225	47	36	5·4
	325	75	47	5·3

	Non-C.F. babies with low stool-trypsin	Control 1	Control 2	Ratio*
1978	75	77	85	0·92
	62	45	120	0·75
	40	70	110	0·44
	77	72	85	0·98
	42	70	37	0·79

* As measured in a 150 μl volume of two 12 mm discs eluted in 0·5 ml buffer.

† Value for C.F. or babies with low stool-trypsin, divided by means of controls.

How much evidence is needed?

- By 1981, limited programs in NZ, France, Belgium, UK, Australia, USA
- 1983 – influential US paper condemns screening - theoretical objections – mainly not borne out
- By 1985
  - Good evidence related to nutritional benefits from screening programme in Colorado
  - Good evidence of significant short-term benefits – morbidity, hospitalisations

NSW Cystic fibrosis screening

Admissions to hospital in first 2 years of life (excluding birth episode) for CF related illness (Wilcken & Chalmers Lancet 1985)

COHORT	MEAN HOSPITAL DAYS
UNSCREENED, no MI, born 1978-1979 n=24	27.5 (range 0-112)
UNSCREENED, no MI, born 1979-1981 n=24	27.0 (range 0-240)
SCREENED, no MI, born 1981-1982 n= 17	3.4 (range 0-20)
SCREENED, no MI, born 1982-1983 n=17	4.4 (range 0-31)
MECONIUM ILEUS, Screened and unscreened, born 1978 to 1983 n=16	16

No admissions: Unscreened 15/48 (31%) screened 24/34 (71%) $p < 0.0005$

Admission > 21d: Unscreened 20/48 (42%) screened 1/34 (3%) $p < 0.0005$

Unscreened (48) and screened (52)cohorts Differences in lung function: All scores favour the screened group

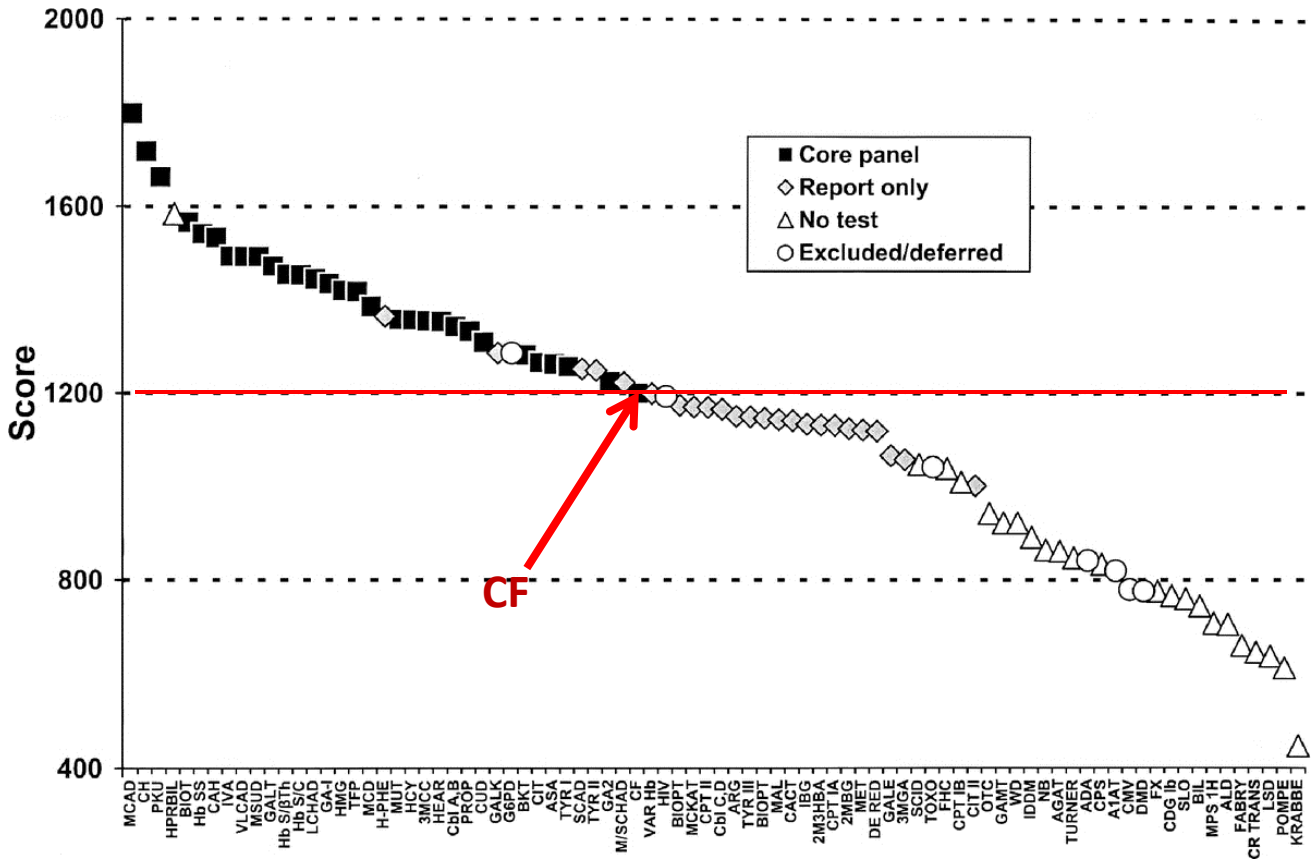
AGE years N= 57 US, 60 S	5	10	15 N=48 US, 52 S *
FEV_1 % predicted Difference (95% CI)	9.0%	9.4%	12.3% (2.9-21.7)
FVC % predicted Difference (95% CI)	8.5%	8.4%	12.6% (3.7-21.7)

McKay KO, Waters DL, Gaskin KJ. The influence of newborn screening for cystic fibrosis on pulmonary outcomes in New South Wales. J Pediatr. 2005 Sep;147(3 Suppl):S47-50.

How much evidence is needed

- 1985 – two randomised controlled trials start
  - Wisconsin trial – splendid design overall, but far more pancreatic sufficient patients in the unscreened group, creating a bias
    Additional problem with early pseudomonas infection in clinics
- By 1989 –better growth and nutrition, little if any harm
- Early 1990's – pulmonary benefits, cognitive benefits likely
- Studies showing cost benefit
- 2004 CDC recommends screening "The magnitude of the health benefits from screening for CF is sufficient that states should consider including routine newborn screening for CF in conjunction with systems to ensure access to high-quality care".
- 2006 – early survival benefits clearly shown (Grosse)
  but screening in less than half US states, none in Canada, not implemented throughout UK

2006 ACMG uniform panel – CF just scraped in



2010: After 30 years of screening in New Zealand, New South Wales, and a few US states, newborn screening for CF finally became universal in US, UK, and many European countries

Assessing disorders for possible inclusion in a newborn screening panel

- US approach structured and working well
  - Nominating a condition: structured nomination process
  - Advisory committee reviews proposal and may send it for:
  - Systematic evidence review
  - Report to a Decision Process Workgroup
  - Possible recommendations:
    - Inclusion; further questions; needs broader evidence; or recommendation not to include at this time
- Key questions:
  - Direct evidence of benefit?
  - Definition of disorder
- Two new disorders approved so far: SCID & CCHD
- Parental pressure advocating screening for some non-approved disorders

Australasia's criteria (Human Genetics Society of Australasia)

- **Four simple criteria;**
  - **benefit from early diagnosis (likely benefit accepted);**
  - **suitable test;**
  - **available treatment and follow-up systems;**
  - **balance of harms and benefits appears positive**
- **Tool for assessment similar to US model**

- **http://www.hgsa.org.au/2011/08/newborn-blood-spot-screening/**

The situation in Europe

- **Wide divergence**
  - **MSMS screening: 0-27 disorders in 27 different countries**
  - **UK: PKU and MCAD, plus 5 disorders in a controlled trial**
    - **Very conservative approach**
- **Outcome studies few; no good controls**
  - **Germany has produced the best data so far**
- **Some patients treated in non-specialised centres**
- **No centralised method of disorder selection**

Ethical problems with both approaches

- **The conservative: screen for few disorders**
  - **Eg: an estimated 80 UK babies with GA I will have died or suffered devastating disability since 2000**
- **The inclusive approach – do everything?**
  - **How many US babies have been medicalised, having unneeded diets, tests, etc**
- **Need for a middle way**
  - **Screening as research**
  - **With consent**

Newborn screening – the future

- **The need for screening performed explicitly as research, with IRB approval and consent, is pressing**

- **The example of Krabbe disease should underline this**

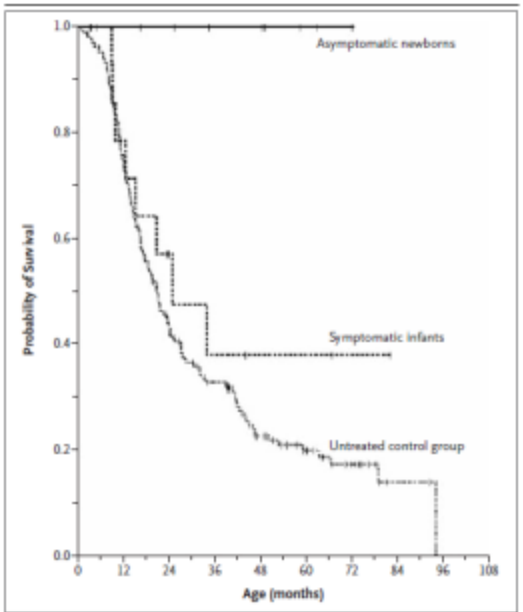


Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with Krabbe's Disease.

Asymptomatic Newborns, HSCT

Symptomatic infants HSCT

Untreated controls

Considerable improvement in mortality
NEJM 2005 Escolar et al

Krabbe Disease
(Globoid-cell leukodystrophy)

- 2005 HSCT improves mortality and morbidity (Escolar et al NEJM)
- 2006 New York State started screening
  - Expert advisory consortium advised against this
  - Family pressure; political decision (Hunter's Hope Foundation)
- Problems encountered:
  - 3X to 10X more than expected potentially "affected", (two mutations and/or low enzyme activity)
  - Differentiation of early onset cases problematic
- 2010: >1,000,000 screened; 4 early onset detected (only 1 clearly had some benefit); 24 others with low enzyme activity and 1-2 mutations, and uncertain diagnosis
- Cost: For screening, $750,000 annually (Salveson PhD thesis Columbia 2011)

Krabbe Disease
(Globoid-cell leukodystrophy)

- **Duffner, Caviness et al., 2009 review of 25 children pre-symptomatically transplanted (two after NBS diagnosis)**
  - The transplant procedure carries a 15 % mortality rate;
  - All had progressive neurologic deterioration, (developmental delay, spasticity, loss of motor milestones, language deficits)
  - All had height and weight below the third percentile for sex and age
  - Some had acquired microcephaly
  - None have died of progressive Krabbe disease: longest follow-up is 13 years

- **[Animal models: All transplanted animals to date have ultimately died of Krabbe disease. At death, evidence of severe myelin destruction is universal]**

- **Majority of cases found by NBS have unclear phenotype**
  - For each infantile onset case about 7 more have reduced enzyme activity and 2 identified mutations
  - Only 30% of classical have a common predictive mutation (a 30kb deletion)

Is screening for Krabbe disease justifiable?

- **“I believe these children need to be evaluated in a program that has the expertise to address the question. .....The question of survival has been answered but at least 10 years are needed to understand if the improvements in neurological function are maintained long term”. Maria Escolar (CHOP) – a metab-L reply**

- **Is it a benefit to convert a lethal infantile disorder to a chronic progressive one?**
  - **Different groups would answer differently**
  - **Current screening in NY state, and legislated in 2 other states in USA**
  - **Not approved by the Secretary's Advisory Committee**
  - **Many states being pressured by parent groups (ie, outside the approval system)**

Newborn screening – the future

- The future is already here with LSDs, SCID
- Under consideration:
  - Disorders that can take advantage of new molecular-based treatments (read-through, chemical chaperones etc) eg Duchenne muscular dystrophy
  - Rett Syndrome
  - Fragile X
  - Long QT
  - Diabetes mellitus
  - Next generation sequencing
  - Etc, etc

Three main drivers for including new disorders

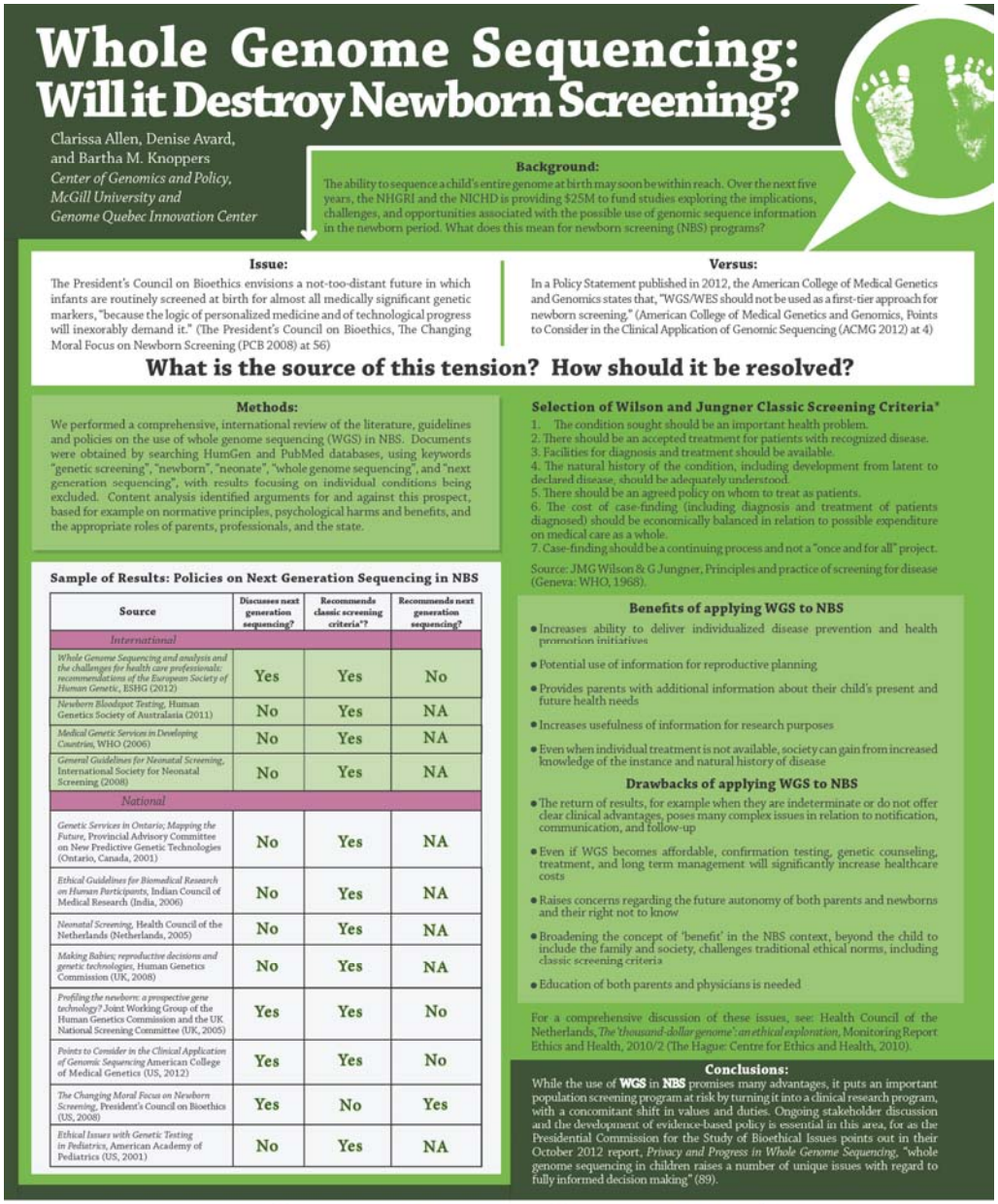
- **New treatments for previously untreatable disorders**
  - Mutation specific therapies eg for DMD
  - Many others
- **Advances in technology that make screening feasible**
  - MSMS was the prime example
  - Many others now: (bead-based immunoassays, microfluidics, etc)
  - Genomic technologies will be affordable in the future (soon?)
    - Huge practical and ethical problems with this
- **Public pressure**
  - Frequent in the US
  - Seems very infrequent elsewhere

Next generation sequencing

- Whole genome, exome, or targeted sequencing
- Enormous problems:
  - Variations of unknown significance
  - All babies will be carriers of several serious disorders
  - Risk factors: An average person after genome sequencing might need information about 100 genetic risks discovered in the genome
  - The public would find such information alarming – not to speak of overburdened genetic counsellors!
  - What about the large issue of epigenetic factors?
  - Can automation provide meaningful information?
  - Will panels of specific groups of disorders be one answer?
- Almost certain to be the way of the future
- May need to re-think the aims of newborn screening
  - Pressure to screen for adult-onset disease and risk prediction: do we want this as part of newborn screening?

Clarissa Allen, Denise Avard
Bartha Knoppers
Centre for genomics and policy
McGill University

"Whole genome Sequencing:
Will it destroy newborn screening?"



Whole Genome Sequencing: Will it Destroy Newborn Screening?

Clarissa Allen, Denise Avard, and Bartha M. Knoppers
Center of Genomics and Policy, McGill University and Genome Quebec Innovation Center

Background:
The ability to sequence a child's entire genome at birth may soon be within reach. Over the next five years, the NHGRI and the NICHD is providing $25M to fund studies exploring the implications, challenges, and opportunities associated with the possible use of genomic sequence information in the newborn period. What does this mean for newborn screening (NBS) programs?

Issue:
The President's Council on Bioethics envisions a not-too-distant future in which infants are routinely screened at birth for almost all medically significant genetic markers, "because the logic of personalized medicine and of technological progress will inexorably demand it." (The President's Council on Bioethics, The Changing Moral Focus on Newborn Screening (PCB 2008) at 56)

Versus:
In a Policy Statement published in 2012, the American College of Medical Genetics and Genomics states that, "WGS/WES should not be used as a first-tier approach for newborn screening." (American College of Medical Genetics and Genomics, Points to Consider in the Clinical Application of Genomic Sequencing (ACMG 2012) at 4)

What is the source of this tension? How should it be resolved?

Methods:
We performed a comprehensive, international review of the literature, guidelines and policies on the use of whole genome sequencing (WGS) in NBS. Documents were obtained by searching HumGen and PubMed databases, using keywords "genetic screening", "newborn", "neonate", "whole genome sequencing", and "next generation sequencing", with results focusing on individual conditions being excluded. Content analysis identified arguments for and against this prospect, based for example on normative principles, psychological harms and benefits, and the appropriate roles of parents, professionals, and the state.

Sample of Results: Policies on Next Generation Sequencing in NBS

Source	Discusses next generation sequencing?	Recommends classic screening criteria*?	Recommends next generation sequencing?
International			
Whole Genome Sequencing and analysis and the challenges for health care professionals: recommendations of the European Society of Human Genetic, ESHG (2012)	Yes	Yes	No
Newborn Bloodspot Testing, Human Genetics Society of Australasia (2011)	No	Yes	NA
Medical Genetic Services in Developing Countries, WHO (2006)	No	Yes	NA
General Guidelines for Neonatal Screening, International Society for Neonatal Screening (2008)	No	Yes	NA
National			
Genetic Services in Ontario; Mapping the Future, Provincial Advisory Committee on New Predictive Genetic Technologies (Ontario, Canada, 2001)	No	Yes	NA
Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research (India, 2006)	No	Yes	NA
Neonatal Screening, Health Council of the Netherlands (Netherlands, 2005)	No	Yes	NA
Making Babies; reproductive decisions and genetic technologies, Human Genetics Commission (UK, 2008)	No	Yes	NA
Profiling the newborn: a prospective gene technology? Joint Working Group of the Human Genetics Commission and the UK National Screening Committee (UK, 2005)	Yes	Yes	No
Points to Consider in the Clinical Application of Genomic Sequencing American College of Medical Genetics (US, 2012)	Yes	Yes	No
The Changing Moral Focus on Newborn Screening, President's Council on Bioethics (US, 2008)	Yes	No	Yes
Ethical Issues with Genetic Testing in Pediatrics, American Academy of Pediatrics (US, 2001)	No	Yes	NA

Selection of Wilson and Jungner Classic Screening Criteria*
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. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
5. There should be an agreed policy on whom to treat as patients.
6. 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.
7. Case-finding should be a continuing process and not a "once and for all" project.

Source: JMG Wilson & G Jungner, Principles and practice of screening for disease (Geneva: WHO, 1968).

Benefits of applying WGS to NBS
- Increases ability to deliver individualized disease prevention and health promotion initiatives
- Potential use of information for reproductive planning
- Provides parents with additional information about their child's present and future health needs
- Increases usefulness of information for research purposes
- Even when individual treatment is not available, society can gain from increased knowledge of the instance and natural history of disease

Drawbacks of applying WGS to NBS
- The return of results, for example when they are indeterminate or do not offer clear clinical advantages, poses many complex issues in relation to notification, communication, and follow-up
- Even if WGS becomes affordable, confirmation testing, genetic counseling, treatment, and long term management will significantly increase healthcare costs
- Raises concerns regarding the future autonomy of both parents and newborns and their right not to know
- Broadening the concept of 'benefit' in the NBS context, beyond the child to include the family and society, challenges traditional ethical norms, including classic screening criteria
- Education of both parents and physicians is needed

For a comprehensive discussion of these issues, see: Health Council of the Netherlands, *The 'thousand-dollar genome': an ethical exploration*, Monitoring Report Ethics and Health, 2010/2 (The Hague: Centre for Ethics and Health, 2010).

Conclusions:
While the use of **WGS** in **NBS** promises many advantages, it puts an important population screening program at risk by turning it into a clinical research program, with a concomitant shift in values and duties. Ongoing stakeholder discussion and the development of evidence-based policy is essential in this area, for as the Presidential Commission for the Study of Bioethical Issues points out in their October 2012 report, *Privacy and Progress in Whole Genome Sequencing*, "whole genome sequencing in children raises a number of unique issues with regard to fully informed decision making" (89).

Acknowledgements

Public pressure: Screening for X-ALD

Molecular Genetics and Metabolism 105 (2012) 416–420

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

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

Combined extraction of acyl carnitines and 26:0 lysophosphatidylcholine from dried blood spots: Prospective newborn screening for X-linked adrenoleukodystrophy

Yana Sandlers [a,d,*], Ann B. Moser [b,d], Walter C. Hubbard [c], Lisa E. Kratz [a,d], Richard O. Jones [b,d], Gerald V. Raymond [a,b,d]

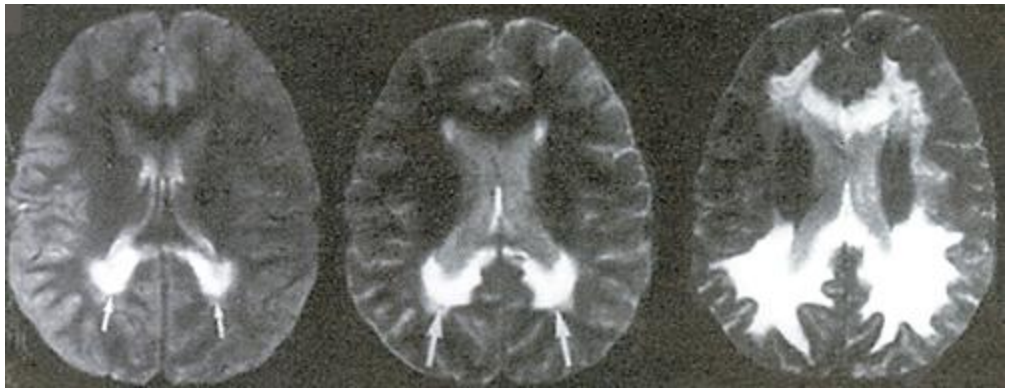
[a] Department of Pediatrics at Johns Hopkins University, 707 N. Broadway, Baltimore, MD 21205, USA
[b] Department of Neurology at Johns Hopkins University, 707 N. Broadway, Baltimore, MD 21205, USA
[c] Division of Clinical Pharmacology, Johns Hopkins University, 600 N. Wolfe St, Baltimore, MD 21287, USA
[d] Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, USA

A211-2013: Enacts Aidan's law to require adrenoleukodystrophy screening of newborns

Budget signed off for screening in NYS – March 30th 2013

X-ALD

- Progressive disorder that mainly involves the nervous system and adrenal cortex
- Associated with the accumulation of VLCFA
- Incidence of males with X-ALD 1:20,000 – 1:50,000
- 35%-40% of boys under 10 years with biochemical diagnosis of ALD will develop a fatal childhood cerebral phenotype (“Lorenzo’s oil” movie)



NBS for X-ALD

- **Some of the same problems as for Krabbe:**
  - **Difficulty of telling who will develop childhood cerebral disease**
  - **Treatment is BMT/HSCT, with a significant mortality and morbidity**
- **Early diagnosis clearly mitigates problems; screening would save lives**
  - **But might also cost lives unnecessarily**
  - **Associated with considerable parental anxiety**
    - **Serial MRI every 6-12 months, into adulthood**
- **Certain to be more generally adopted soon, if screening test has suitable performance**

Summary

- Newborn screening started well with PKU, and has evolved, recently with increasing speed
- Problems that have been apparent for some time are not yet fully addressed
  - Integrating systems of screening, diagnosis, management
  - Defining disorders and gathering evidence about who needs treatment
  - Demonstrating benefit (proper outcome studies)
  - Modifying programs where no benefit shown
  - Including new disorders on an explicit research basis
- Inclusion of new disorders: need for more thought
  - Managing pressure from parent groups
  - Redefining the aims of newborn screening if this seems needed

If you want to keep up with newborn screening, there are less than 1,400 or so papers to read each year, so it's not impossible.....