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

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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
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

Blood Screening for Phenylketonuria

To the Editor—Since the discovery by Willi, in 1933, of phenylketonuria (PKU), the simple ferric chloride test of urine has been the universal method of detecting this disease is despite 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, 1959, 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 beta-phenylalanine in a minimal culture medium is specifically associated with the addition of proline, phenylalanine, piperazine, or l-alanine. This finding permitted the development of a convenient agar diffusion microtest 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 W. S. G. during the past three years (Guthrie, R., and Tiedekemmi, 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 filter paper (Whatman No. 3), dried, and mailed to the laboratory, where 1 to 300 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 clearly visible for "normal" blood discs. A response comparable to that of either of the 3 control discs with 12 or 26 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 36-48 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.

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The Basic Position of Samuel Hahne mann

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 doctors 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

- **1991** Tandem 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

<table>
<thead>
<tr>
<th>Time</th>
<th>Rate of adverse events per 100,000 whole population</th>
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- **Screening starts**
- **Effect assessed**
Control groups: Possible scenario

- **Rate of adverse events per 100,000 whole population**
- **Time**
- **Historical situation**
- **Screening starts**
- **Effect assessed**
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

1 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?
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
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)*

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<thead>
<tr>
<th>COHORT</th>
<th>MEAN HOSPITAL DAYS</th>
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<tr>
<td>UNSCREENED, no MI, born 1978-1979 n=24</td>
<td>27.5 (range 0-112)</td>
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<tr>
<td>UNSCREENED, no MI, born 1979-1981 n=24</td>
<td>27.0 (range 0-240)</td>
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<tr>
<td>SCREENED, no MI, born 1981-1982 n=17</td>
<td>3.4 (range 0-20)</td>
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<tr>
<td>SCREENED, no MI, born 1982-1983 n=17</td>
<td>4.4 (range 0-31)</td>
</tr>
<tr>
<td>MECONIUM ILEUS, Screened and unscreened, born 1978 to 1983 n=16</td>
<td>16</td>
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No admissions:  Unscreeneed 15/48 (31%) screened 24/34 (71%)  p < 0.0005

Admission > 21d: Unscreeneed 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

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<tr>
<th>AGE years</th>
<th>5</th>
<th>10</th>
<th>15</th>
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<tr>
<td>N=57 US, 60 S</td>
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<tr>
<td>FEV₁ % predicted</td>
<td>9.0%</td>
<td>9.4%</td>
<td>12.3% (2.9-21.7)</td>
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<tr>
<td>Difference (95% CI)</td>
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<tr>
<td>FVC % predicted</td>
<td>8.5%</td>
<td>8.4%</td>
<td>12.6% (3.7-21.7)</td>
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<tr>
<td>Difference (95% CI)</td>
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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

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

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?”
Public pressure: Screening for X-ALD

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.................