

Newborn screening in the UK

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The PKU story

- PKU began in 1969, around 60 babies detected each year, would otherwise be severely mentally disabled, can develop normally on a low phenylalanine diet
- A total of approximately 2300 detected so far
- Cost of residential care would be £ 60m pa
- Cost of treatment + screening program = £8m pa

The neuroblastoma story

- Incidence of clinically detected disease 1:29,000
- When detected at <1y age at stage I,II or IVS the prognosis is much improved
- In 1985 it became possible to screen by measuring HVA and VMA in urine at 6 mo, taken up in Japan and Newcastle
- Survival in the screened population >90% compared with 50% in clinically detected cases
- However, after the introduction of screening the mortality rate due to neuroblastoma did not decline
- Two factors at work:
 - Poor sensitivity for cases that would go on to progress to clinically significant disease
 - Screening is differentially picking up the tumours that are least likely to progress and may spontaneously resolve.

How do we choose?

1. The condition being screened for should be an important health problem
2. The natural history of the condition should be well understood
3. There should be a detectable early stage
4. Treatment at an early stage should be of more benefit than at a later stage
5. A suitable test should be devised for the early stage
6. The test should be acceptable
7. Intervals for repeating the test should be determined
8. Adequate health service provision should be made for the extra clinical workload resulting from screening
9. The risks, both physical and psychological, should be less than the benefits
10. The costs should be balanced against the benefits

Wilson and Jungner, 1968

How do we choose?

1. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.
5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
15. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.
14. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

2003 update

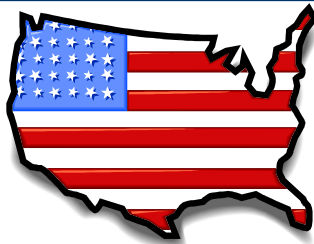
How is screening organised in the UK?

- Babies birth notified to regional child health system
- All babies tested at home on day 5-8 by midwife
- Sent to one of 13 Regional labs
- Positive cases referred to an appropriate paediatrician
- Results sent back to the child health system and the parent informed and given a hard copy letter to insert in the "baby book"

What have we chosen in the UK?

- Phenylketonuria, 1969 - 4 cases pa /70k births
- Congenital hypothyroidism, 1981 - 28 cases pa/70k births
- Cystic fibrosis, 1990 in Trent, 2007 in the rest of UK - 23 cases pa/70k births
- Sickle cell disease, 2007 - 17 cases pa/70k births + 550 carriers
- Medium chain acyl CoA dehydrogenase deficiency (MCAD), 2007 - 9 cases pa/70k births

Newborn blood-spot screening: National policies



USA: 29 conditions as a core panel
plus 25 conditions also be identified
when screening for the core panel



UK: 5 disorders

Comparable countries are responding to
changing technologies in very different ways

The International debate

- TMS (used for MCAD and PKU) is a gateway technology
- It allows the diagnosis of many other disorders

Phenylketonuria	D
Megaloblastic anemia	D
Homocystinuria	D
Tyrosinemia type 1	D
Galactosemia	D
Asymptomatic aciduria	S
Asparaginemia	S
HHLI syndrome	D
VALAD deficiency	D
UCHAD deficiency	D
MCAD deficiency	D
SCAD deficiency	S
Multiple acyl-CoA dehydrogenase defn.	S
CPT1 deficiency	S
CPT2 deficiency	S
CAC1 deficiency	S
Carnitine uptake deficiency	D
Propionic acidemia	D
Methylmalonic acidemia	D
Isovaleric acidemia	D
Glutaryl-CoA synthetase deficiency	D
Medium chain fatty acid deficiency	D
3-MHC-CoA lyase deficiency	D
Beta-ketothiolase (T2) deficiency	D
3-MHC carboxylase deficiency	D
Plus 17 other conditions	S
USA 2006†	S
Denmark 2005	D
Germany 2004	D
Netherlands 2005	D
England 2007	D

How do we resolve this?

- Unfortunately for a variety of reasons the overseas experience while helpful is not directly transferable:
 - Day of screening
 - Population differences
 - Differences in analytic approach
- We need carefully planned and conducted research using a conservative panel of conditions where clear clinical benefit is anticipated and the screening test can deliver a high positive predictive value.
- Careful assessment of possible dysbenefits eg impact on existing screening programmes, handling false positive results, informed choice/consent

Background to the project

- BSAG meeting 9th Jan 2007 reports on MCAD pilot, 7th Feb 2007, MCAD screening announcement
- Meeting (UKNSLN/MetBioNet) in Sheffield to discuss extended screening, 21st Sept 2007
 - A panel of possible disorders, IVA, MSUD, GA1, Hcys (subject to secondary testing), Tyr (subject to secondary testing), + others possible inc LCHAD, Cit, ASA, MMA, Ketothiolase
- Application to CLHRC bidding program in January 2008
- Agreement to offer matched funding for an extended screening study, approx £600k available, April 2008
- A meeting of International experts in London in June 2008
- Prepare "vignettes"

The practical difficulties

- Not enthusiasm or limited resources
- Concerns from public health that this is not technology creep
- Concerns from midwifery relating any increase in workload
- The need for truly informed consent would make the project very difficult to operate

The project

- The team: J Bonham, M Sharrard, A Chakrapani, A Morris, A Kent, M Henderson, A Raffle, H Burton, S Sanderson, L Moody, S Dixon, G Hoffmann
- Aim to test 500 k births in 2 years
- Disorder panel, MSUD, GA1, IVA, Hcys (non pyridixine responsive), LCHAD, Tyrosinaemia in one centre.

Timescales and planning

- | | |
|--|----------------|
| • Finalise disorder panel | December 2008 |
| • Agree project team | December 2008 |
| • Conduct work related to consent issues | April 2009 |
| • Work related to the potential impact of false positive results | July 2009 |
| • Careful literature background survey | September 2009 |
| • Agree research protocol | September 2009 |
| • Submission to ethics | September 2009 |
| • Obtain ethics approval | November 2009 |
| • Finalise screening and diagnostic protocols | December 2009 |
| • Midwife education etc | Jan-Mar 2010 |
| • Conduct initial lab work | Jan-Mar 2010 |
| • Begin screening | April 2010 |
| • End screening | March 2012 |
| • Analyse data and report | June 2012 |