



Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

A look across the border

Dr. Jim Bonham



Disclosure

I have no disclosures of commercial support.

Professionally, I am a member of the Executive Committee of ISNS

Why is screening different?



- The patients/families believe themselves to be well and are seeking reassurance and this gives us a particular burden of responsibility
- The initial test does not in itself give a definitive answer. It simply separates those who are more likely to have the condition (and require follow-up) from those who are less likely to have it

Why is screening different?



- “All screening programmes do harm; some do good as well, and, of these, some do more good than harm....” *Gray, BMJ (2008) 336:480*
- In the EU, as part of newborn screening, we conduct around 40 m tests per year, 35m for genetic disorders
- It is important that screening is considered as a programme and not just a test



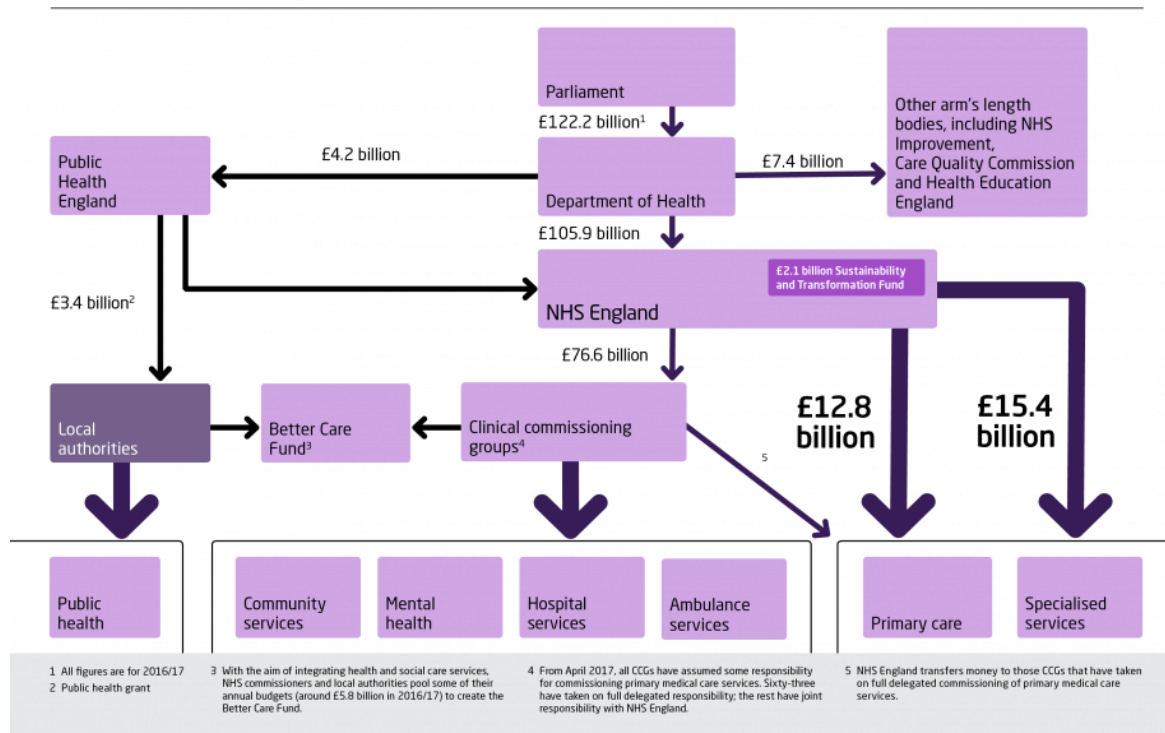
- The UK health system
- The UK screening system a brief overview
- Screening policy – how is it set?
- Some of our topical issues in newborn screening – the importance of small things
 - Patient pre-test information and declines
 - Sample transport and service availability
 - Failsafe
 - Blood spot quality
 - Assay performance
 - Supporting families
 - Natural history, outcomes and interferences
- A look to the future
 - SCID
 - DNA based screening

The UK health system



TheKingsFund > Ideas that change health care

The NHS: How the money flows



Screening policy – how is it set?



- Who makes the decisions, countries vary:
 - Public Health/government eg UK - NSC
 - Health professionals eg US - ACMG
 - Commercial interests eg some developing countries
- Who influences the policy?
 - Patient/parent groups
 - Health professionals
 - Public Health doctors
 - Government
 - Industry
 - Is there a role for ISNS?
- How can new tests be considered?
 - Is there a defined route
 - Are good quality cost effectiveness studies available
- How can new programmes be introduced?
 - Pilot studies are needed but difficult to arrange and fund and there are ethical issues if it is perceived as research – even more difficult to stop!

UK newborn screening – a brief overview



- Began with PKU in 1969, CHT added in 1981, MCADD and Sickle in 2004, CF in 2007 and limited expanded screening in 2015 (GA1, HCU, MSUD, IVA)
- 16 screening labs all within hospitals, workload ranges from 30k pa – 130k pa, no set tariff but approx 25 euro/baby tested. All are accredited ISO 15189
- A unique NHS number is generated at birth and is mandatory
- Used by midwives who take a sample at day 5 of life in the family home
- Defined KPI's for transport, turn around time, time to treatment
- A national IT system logs and tracks progress using "status codes"
- The lab makes referral to specialist paediatrician for positives and to Child Health record Departments for all results to inform parents



- How much information is needed?
- How should it be given?
- Who should give it and when?
- What about other languages?
- What about declines?

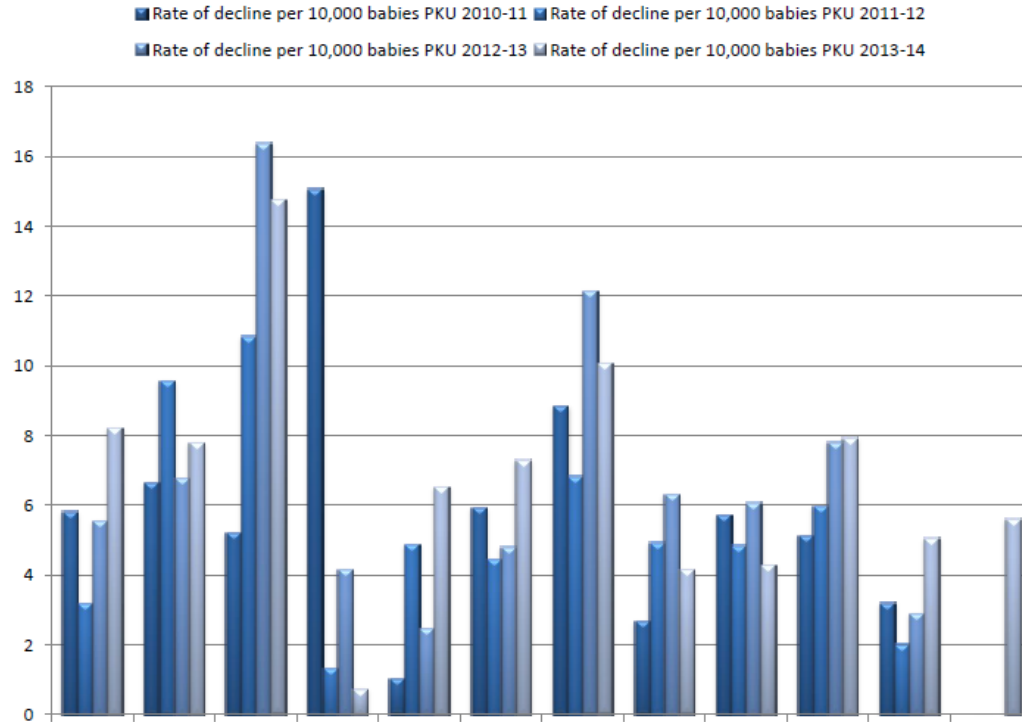


- Determining the pre-screening information to be given to parents.
- Focus groups and web survey :
- We asked parents what they wanted (Health Expect. 2011 Aug 12. 10.1111/j.1369 -7625):
 - They wanted to know what was happening and be asked
 - They did not want detailed information
 - They wanted to know where they could go for additional information if required
 - They did not want to sign for consent
 - They wanted to feel in control
- In the UK women are given written information during pregnancy and again 24h before the test – many do not read it.
- Uptake of translated versions is poor
- You tube video length clips may work



- Fiona Ulph et al Oct 2017 – a mixed method project
- Being informed is important
- Current UK practice with information delivered by midwives in first trimester and re-iterated if needed before sample collection may not be optimal and is expensive
- The best time may be last trimester
- Group sessions may be useful
- A range of materials and approaches would be welcomed

What about declines?



Sample transport and service availability



- National mail delivery services or courier – a nationally agreed envelope design allows mail to be prioritised
- Transit times vary - clear KPIs needed – in UK 3 working days
- Is a Monday – Friday laboratory service adequate, probably not for MSUD, IVA, MCADD – hence reporting on Saturday
- What about national holidays? – real problems around Christmas
- Six day working is becoming more common





- Following a transport incident some years ago an “alert” system was introduced based on NHS number
- At birth the midwife obtains an NHS number for the new baby – this is used in all newborn testing and babies are not tested without the NHS number
- At birth the baby is registered on the alert system known as “Failsafe”
- The midwife logs that a sample has been taken and the lab logs receipt – delayed samples show an alert
- Result codes are entered onto Failsafe once analysis is complete
- This is being considered as a means to deliver results to parents and to form part of the child health record.



Effect of Dried Bloodspot Quality on Newborn Screening Analyte Concentrations Roanna S. George and Stuart J. Moat Clin Chem 2016

- ($P < 0.001$). Smaller bloodspots produced significantly lower results (15%–24% for 10 μ L vs 50 μ L sample size) for all analytes at all concentrations measured ($P < 0.001$).
- Results obtained from peripheral punches were higher than those from a central punch although this did not reach statistical significance for all analytes
- Compression of bloodspots produced significantly lower results (14%–44%) for all analytes measured
- Insufficient and multispotted samples demonstrated heterogeneous results
- **CONCLUSIONS:** All bloodspots containing 20 μ L (bloodspot diameter 8 mm), those in which blood has not fully penetrated the filter paper, and all samples with evidence of compression should be rejected, since there is a risk of producing false-negative results.
- We have introduced a policy that we will only use a spot from which two punches can be made – around 8 mm diam. This caused an initial increase in rejection rate up to > 10% but with clear standards this has now reduced to around 2% (still too high but work in progress, a significant problem, 25,000pa)

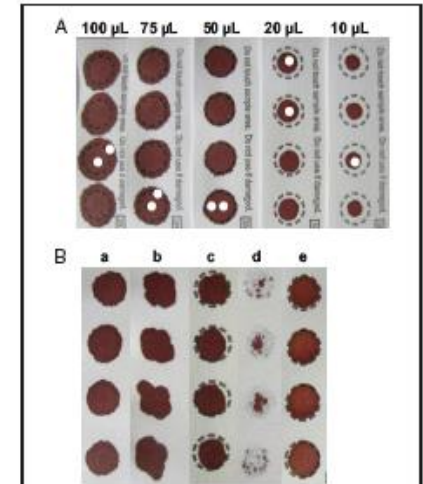
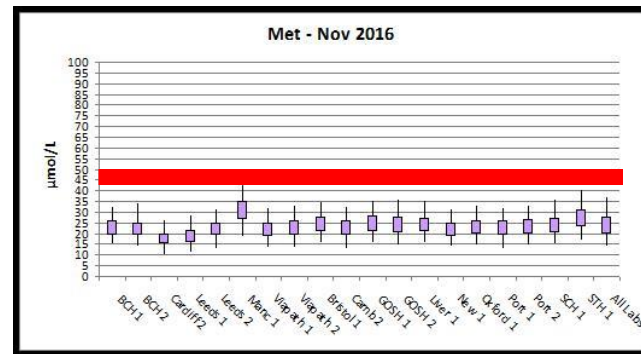
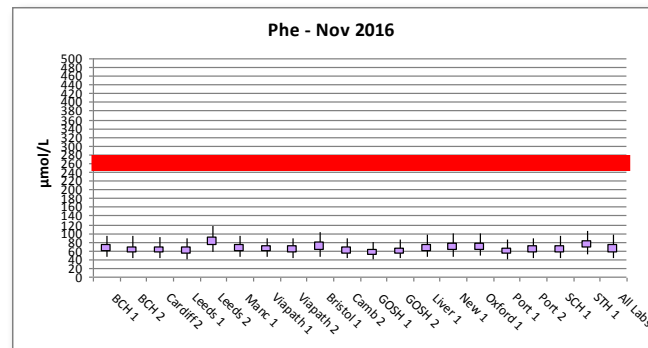


Fig. 1. Sample volume and quality factors.
(A), Effect of sample volume on bloodspot diameter. The white circles represent central and peripheral punch locations taken from each bloodspot during this study. (B), Examples of poor-quality bloodspots: a, double layered/applied to both sides of card; b, multispotted samples; c, insufficient sample applied (view of front of card); d, insufficient sample applied (view of back of card); e, 20- μ L spots compressed.

Assay performance ?



- We have a responsibility to limit false positives and false negatives and ensure robust assay performance
- With a limited range of tests and a clear separation between affected patients and normals, uncertainty may be less problematic eg PKU – 70 $\mu\text{mol/L}$ vs 1000 $\mu\text{mol/L}$
- With a growing range of disorders and less clear discrimination eg cystic fibrosis or homocystinuria it may be an important factor





- Analytic
 - Understand test performance and consider ways that this can be improved eg use of common Int Stds or kits, regular national meetings to discuss performance issues, systems to gather and collate population data, best practice guidelines for instrument set-up
 - Ensure traceability – ISO 15189, reference materials
 - Define MU by use of independent IQC material
 - Consider second tier testing where appropriate
 - Explore the use of R4S and CLIR
 - Be aware of the effects of reagent batch changes, pool data and bring pressure on manufacturers to improve performance
 - Be vigilant to identify known issues and spot new ones, sharing experience – ISNS bulletin Board



- False positive results and how patients find it:
 - **Parents tell us that false positives are not a huge problem in theory** - *Dixon S JIMD 2012*
 - **In practice the evidence is somewhat contradictory**
 - > *Tu WJ PLoS One 2012*
39% of mothers with a false +ve result describe concerns about child's future development vs 10% in the normal screened group
 - > *Waisbren SE et al JAMA 2003*
Children with FP result twice as likely to experience hospitalisation 21% vs 10% and mothers report increased PSI score $p < 0.001$
 - Vs**
 - > *Lipstein EA Genet Med 2009*
200 children with FP and 137 normal showed no difference in healthcare utilisation
 - > *Prosser LA Arch Pediatr Adol Med 2008*
91 parents with FP result vs 50 with a normal. Demonstrated a high tolerance in a WTP study
 - **Why is this and what do the parents want?**
 - > Many studies tell us that better communication reduces stress
 - > Generally studies do not compare how the family was given the news or supported in the time to confirmation

Diagnostic testing and supporting families



- Recent Publication in BMC paediatrics – 2017 – looked at semi structured interviews with 10 parents and 11 health professionals following a newborn screening diagnosis for IMDs
- The key issues that emerged were:
 - A rapid and defined turn around time for confirmatory tests
 - Authoritative and informed advice
 - Support for family relationships
 - An adaptable means of providing information
 - Understanding the workload implications for Health Professionals
 - A consistency of approach
- We have used research funding to develop a patient centered App
 - It was developed at Coventry University by Fine Art and design students
 - It has been co-produced by CLIMB (the patient group) and the research team
 - It will be formally evaluated by psychologists from Coventry by the summer
 - It will be owned by CLIMB with support from BIMDG




- When we begin to screen we change the spectrum of disease of disease identified – screen identified cases may differ from clinically identified cases
- An initiative to be launched in the UK in summer 2018 for metabolic disorders
- There is a need to look systematically and longitudinally at outcomes when new conditions are introduced. While national initiatives are important the scale offered by international collaboration is essential.
 - <https://www.ehod-registry.org/>
 - <https://www.eimd-registry.org/>
- New interferences need to be identified and reported – a recent survey among nine European countries indicated that pivalate results in false positive results for IVA. In 3 this was predominantly from antibiotics, in 3 from moisturising creams and in one it was mixed. This may change screening algorithms

SCID – the NSC view in Dec 2017



- There are approximately 17 SCID cases in the UK each year. 30% (5-6) of whom would be detected through cascade testing (ie would be found without the need for a screening programme)
- The main benefit of screening is to find and treat babies before they become infected. The model estimates that without screening eight babies would die from infections and with screening that would be reduced to two.
- Approximately 260 families would receive false positive results which would be confirmed by flow cytometry within two
- A PCR based screening strategy was estimated to cost £3.2 million / year and to have a high likelihood of being cost effective. Some uncertainties were identified such as the cost of the test.
- In relation to the test, the main findings of the reviews were that more information on the test cut off, incidental findings and the false positive rate in a UK population was required.
- In relation to the treatment, although good outcomes were reported from transplantation in a number of studies the long term outcomes were difficult to interpret because of small sample sizes, inter study variation in outcomes and variation in length of follow up.

phescreening.blog.gov.uk
ePHE_Screening
August 2017

 NSC UK National Screening Committee

UK NSC on newborn screening for Severe Combined Immune Deficiency (SCID)

Following a review of the evidence against strict criteria, the UK NSC will consult publicly on the proposal for an evaluation of SCID.

Severe Combined Immune Deficiency (SCID) refers to some rare inherited conditions. These affect the development of the baby's immune system. SCID makes it more difficult for babies to fight off infections from about 3 months of age. Infections that are not serious in most babies can be life threatening in those with SCID. The damaged immune system can be repaired with a stem cell transplant.

Newborn screening would look for babies with low numbers of white blood cells. Early detection by newborn screening can improve the success of the stem cell transplants. This is because doctors can help the baby to avoid infections before the transplant if they know the baby has SCID.

Key findings supporting the UK NSC recommendation

The UK NSC found that screening for this purpose is likely to be effective at a reasonable cost. But the evidence in some areas is uncertain. For example:

- the number of healthy babies found to have low numbers of white cells (that is, a 'false positive' result) is not known
- what care and treatment is best for babies who are found to have low numbers of white cells for reasons other than SCID
- what proportion of babies are found by screening rather than as siblings

The UK NSC is recommending that screening for SCID should be tried in a practical evaluation in the NHS. This will help the Committee decide whether screening for SCID should be part of the newborn blood spot screening programme.

The UK NSC regularly reviews its recommendations on screening for different conditions in the light of new research evidence becoming available.

To find out more about the UK NSC's SCID recommendation, please visit:

legacy.screening.phe.org.uk/scid

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of screening and supports implementation of screening programmes.

Find out more about the UK National Screening Committee at www.gov.uk/uknsc. The UK NSC evidence review process is described at www.gov.uk/government/publications/uk-nsc-evidence-review-process and a list of all UK NSC recommendations can be found at legacy.screening.phe.org.uk/recommendations.

The UK NSC secretariat is hosted by Public Health England (www.gov.uk/ukphel).

SCID – the plans



- A national pilot in England in 2019
- No decision yet on the method
- Likely to test all babies for one year
- Issues to consider:
 - Pre-test information
 - All labs or some
 - Linking to Child Health Record Departments for results
 - Information to gather
 - What happens at the end of the pilot?
- A workshop planned at ISNS Oct 2018

phescreening.blog.gov.uk
@PHE_Screening

August 2017

UK NSC on newborn screening for Severe Combined Immune Deficiency (SCID)

Following a review of the evidence against strict criteria, the UK NSC will consult publicly on the proposal for an evaluation of SCID.

Severe Combined Immune Deficiency (SCID) refers to some rare inherited conditions. These affect the development of the baby's immune system. SCID makes it more difficult for babies to fight off infections from about 3 months of age. Infections that are not serious in most babies can be life threatening in those with SCID. The damaged immune system can be repaired with a stem cell transplant.

Newborn screening would look for babies with low numbers of white blood cells. Early detection by newborn screening can improve the success of the stem cell transplants. This is because doctors can help the baby to avoid infections before the transplant if they know the baby has SCID.

Key findings supporting the UK NSC recommendation

The UK NSC found that screening for this purpose is likely to be effective at a reasonable cost. But the evidence in some areas is uncertain. For example:

- the number of healthy babies found to have low numbers of white cells (that is, a 'false positive' result) is not known
- what care and treatment is best for babies who are found to have low numbers of white cells for reasons other than SCID
- what proportion of babies are found by screening rather than as siblings

The UK NSC is recommending that screening for SCID should be tried in a practical evaluation in the NHS. This will help the Committee decide whether screening for SCID should be part of the newborn blood spot screening programme.

The UK NSC regularly reviews its recommendations on screening for different conditions in the light of new research evidence becoming available.

To find out more about the UK NSC's SCID recommendation, please visit:

legacyscreening.phe.org.uk/scid

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of screening and supports implementation of screening programmes.

Find out more about the UK National Screening Committee at www.gov.uk/uknsc. The UK NSC evidence review process is described at www.gov.uk/government/publications/uk-nsc-evidence-review-process and a list of all UK NSC recommendations can be found at legacyscreening.nhs.uk/recommendations

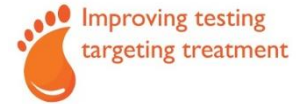
The UK NSC secretariat is hosted by Public Health England (www.gov.uk/phe).

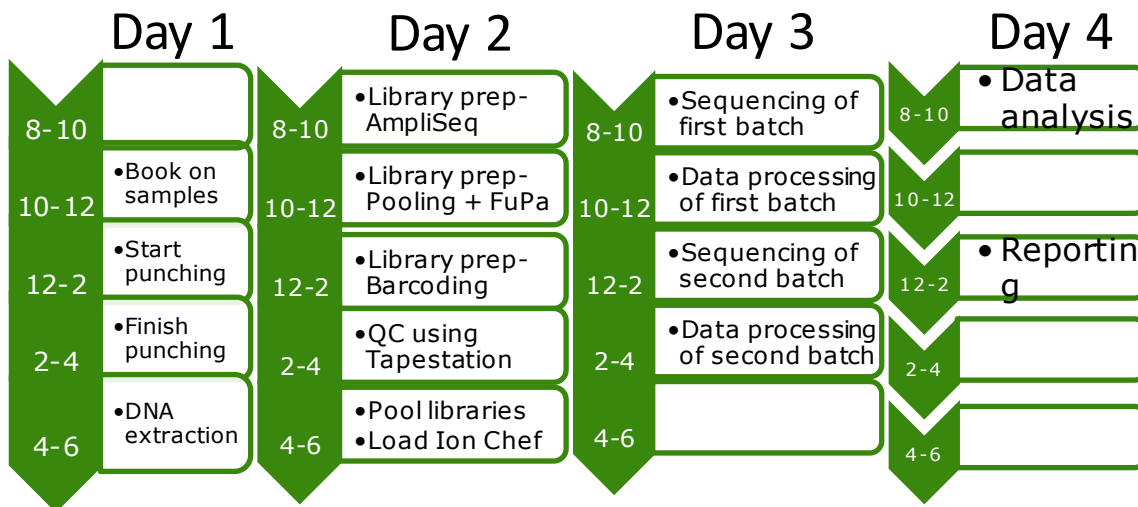
Increased use of DNA analysis as a first line or second tier



HICF-Wellcome funded project

- Aim 1
 - > Development of a genotype-phenotype database
 - > Important clinical resource
 - > Enhance disease understanding
 - > For 6 inherited metabolic diseases: MSUD, HCU, IVA, GA1, PKU & MCADD
- Aim 2
 - > Optimisation of High-Throughput NGS for NBS
 - > Utilise healthy control individuals' DNA
 - > Compare DNA extracted from Venous Blood (VB) with DNA extracted from Dried Blood Spots (DBS)
 - > Aim to obtain same sequence quality from DBS DNA as from VB DNA using NGS
 - > Use current screened disorders to trial the analysis





- 2 x 96 samples would be punched per day meaning that ~ 1000 samples could be sequenced per week.
- Doubling up on automation equipment would increase sample high-throughput capability.