A look across the border

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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
Views and hot topics

- 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
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
Pre-test information

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

- 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\( \mu \)L vs 50\( \mu \)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 \( \mu \)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).
- 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 – 70µmol/L vs 1000µmol/L.
- With a growing range of disorders and less clear discrimination eg cystic fibrosis or homocystinuria it may be an important factor.
Assay recommendations

- **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
Diagnostic testing and supporting families

- **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*
      - 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 Adolesc 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 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.ehod-registry.org/)
- [https://www.eimd-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.
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
Increased use of DNA analysis as a first line or second tier

HICF-Welcome 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.