Newborn Bloodspot Screening Wales

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Newborn screening in Wales, the past, present and future.

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Aims of talk

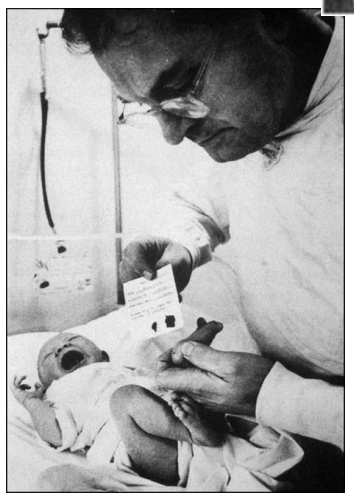
- The past - historical aspect of NBS in Wales.
- The present - review the conditions currently screened & numbers of babies screened and disorders detected.

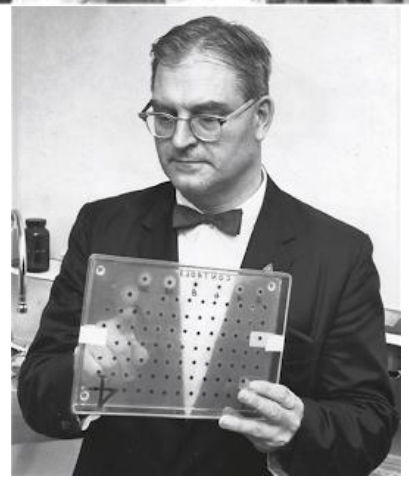
- The future – disorders to be added to NBS panel.
- Screening is more than a test!

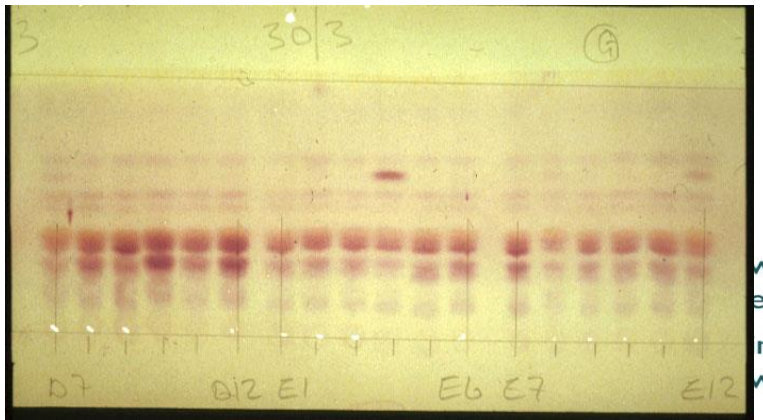
Historical aspects of NBS

- 1950s – Louis Woolf developed technique to remove phenylalanine from protein mixture

- 1960s -







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Wales – the 'cradle' of newborn screening!

TESTS FOR PHENYLKETONURIA

RESULTS OF A ONE-YEAR PROGRAMME FOR ITS DETECTION IN INFANCY AND AMONG MENTAL DEFECTIVES

BY

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The diagnosis of phenylketonuria is important for three different reasons: in young infants the detection of this metabolic error permits treatment with a low-phenylalanine diet in order to prevent or minimize mental deterioration; the ascertainment of all cases of phenylketonuria among mental defectives would permit an accurate estimate of the frequency in the population of the gene responsible; to the paediatrician the differentiation of phenylketonuria from other forms of mental deficiency is always important, not least because of the light it throws on the chances of later children in the family being affected. For these reasons any test which makes the diagnosis of phenylketonuria simpler or more reliable is to be welcomed.

Method

The mother of every child born in Cardiff was asked to bring a fresh specimen of her baby's urine to the infant-welfare clinic when the baby was 3 weeks old or as soon as possible after. A bottle containing a little chlorbutol as a preservative was provided by the health visitor. Ferric chloride solution (5%) was added drop by drop to the urine until a definite colour appeared.

Results

Though there were 4,530 live births in Cardiff during the year, only 1,192 specimens of urine were collected and tested. The mothers of the 73.7% of babies that were not tested generally complained that it was

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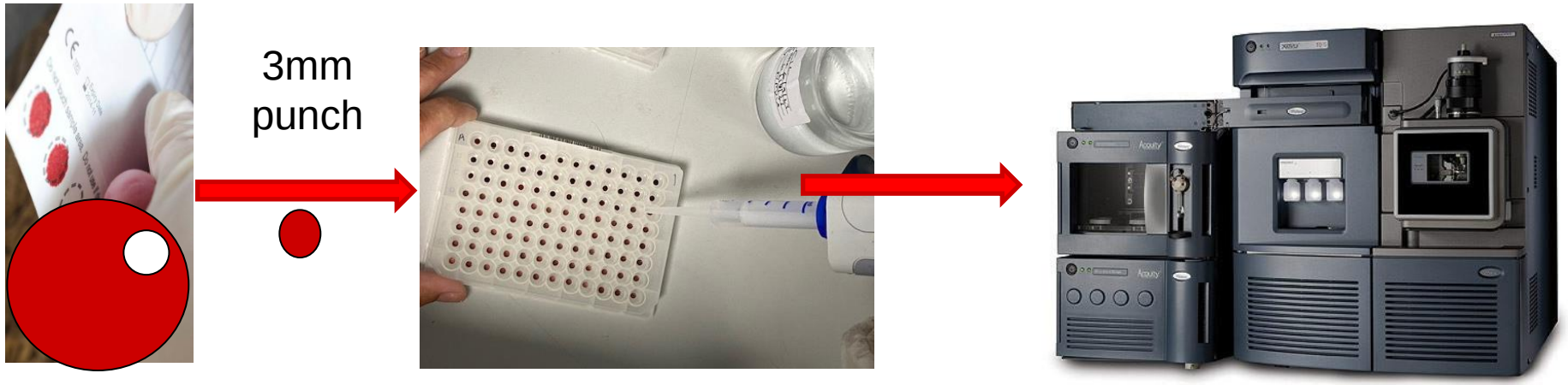
Historical aspects of NBS

- Early 2000s – Mass spectrometry facilitated expansion of NBS >50 IMDS could be screened



Phenylketonuria (PKU) (1970 -)

- Incidence 1:10,000 in UK
- AR condition – 3 cases per year in Wales.
- Deficiency of phenylalanine hydroxylase and v-rarely biopterin defects.
- Untreated - irreversible, learning disability
- Early treatment (by day 14) with Phenylalanine restricted diet prevents neuro-disability.
- Co-factor therapy (Sapopterin) – relaxed Phe diet & greater compliance.

Congenital Hypothyroidism (CHT) - 1980

- Affects 1 in 4,000 babies in UK (~185 / year in UK)
- Dysgenesis – 90% sporadic (2:1 girls:boys)
- Transient Hypothyroidism – appropriate follow up Ix TFTs, Tg & Imaging (TFTs in the Mother!)
- Early treatment (by day 14 of life) with thyroxine prevents neuro-disability.
- Clinical diagnosis – lethargy, poor feeding, constipation & jaundice (unconj bili).

Cystic fibrosis (CF) 1996-

Cystic fibrosis newborn screening: the importance of bloodspot sample quality

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ABSTRACT

Objective Wales has an immunoreactive trypsin (IRT)-DNA cystic fibrosis (CF) newborn screening (NBS) programme. Most CF NBS false negative cases are due to an IRT concentration below the screening threshold. The accuracy of IRT results is dependent on the quality of the dried bloodspot (DBS) sample. The aim of this study was to determine the cause of false negative cases in CF NBS and their relationship to DBS quality.

Design Longitudinal birth cohort.

Setting Wales 1996–2016.

Patients Children with CF.

Interventions Identification of all CF patients with triangulation of multiple data sources to detect false negative cases.

Main outcome measures False negative cases.

Results Over 20 years, 673 952 infants were screened and 239 were diagnosed with CF (incidence 1:2819). The sensitivity of the programme was 0.958, and positive predictive value was 0.476. Eighteen potential false negatives were identified, of whom eight were excluded: four screened outside Wales, two had complex comorbidities, no identified cystic fibrosis transmembrane

What is already known on this topic?

- All cystic fibrosis (CF) newborn screening (NBS) programmes are predicated on the analysis of immunoreactive trypsin (IRT) in newborn dried bloodspot (DBS) samples.
- The vast majority of false negatives cases are due to IRT concentration below the screening threshold.
- The accuracy of IRT screening results is dependent on the quality of the DBS sample received for analysis.

What this study adds?

- The majority of false negatives had a low bloodspot IRT and were associated with poor quality samples.
- Improving the quality of DBS will improve the sensitivity of CF NBS programmes.

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Duchenne Muscular Dystrophy (1990-2011)

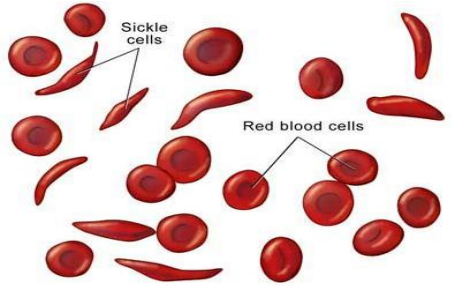
- Fatal X-linked neuromuscular disorder
- Incidence 1:5000 males
- Serum CK / genetics / muscle Biopsy
- Mean age of diagnosis ~5 years of age
- Treatment – steroids, physio, new molecular drugs
- Screened 343,170 boys
  - 145 screen positives, 66 confirmed CK (56 DMD)
  - 17 False negative cases
- Wales NBS Programme terminated in 2011

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

- Screening commenced in 2008 in England (2012 Wales)
- Incidence 1:10,000 in UK (80 cases / year in UK)
- AR - Fatty acid oxidation disorder
- Non-ketotic hypoglycaemia
- Mean age at first presentation is 14 months - 25% mortality rate
- Treatment to prevent metabolic crisis
- Emergency regime: glucose polymer (maxijul) and IV dextrose

Sickle cell disorders - 2013

- Affects millions worldwide, esp. those of African, Mediterranean, Middle Eastern, and South Asian descent
- HbSS, S/C, S/D^{Punjab}, S/E, S/β thalassaemia (β+, β0, δβ, Lepore), S/O^{Arab},S/HPFH.
- AR - UK incidence 1:2,500 (Wales – 3-4 cases / year)
- Sickle crisis → vaso-oclusion → hypoxia & ischaemic infarcts.
- Treatment - Immunisations, antibiotics, education
- Wales NBS identifies Disease states only



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Maple syrup urine disease (MSUD)

- Disorder of branch chain keto acid metabolism
- AR - Incidence ~1:200,000 (3-4 cases per year in UK)
- **Typical neonatal presentation**
  - Day 2-3 non-specific symptoms
    - Lethargy, poor feeding, irritability, ketonuria, lactic acidosis
  - Day 4-7 first clear symptoms - encephalopathy
  - Day 7-10 hospitalised - seizures, coma
  - Day 10-16 – diagnosed
  - **Treatment** – leucine restricted diet

Homocystinuria (HCU)

- Cystathionine ß-synthase (CBS) – B6 non-responsive
- AR - Incidence ~1:200,000
- **Clinical**
  - Occular
  - Skeletal system
  - CNS
  - Vascular system
- **Treatment** – methionine restricted diet and betaine

Isovaleric acidaemia (IVA)

- Isovaleryl-CoA dehydrogenase deficiency
- AR - Incidence ~1:115,000
- Clinical
  - Lethargy, feeding problems, vomiting, acidosis, unusual odour, metabolic encephalopathy, coma, & MOF
- Therapy - carnitine, low protein diet – prognosis good
- False positives due to pivalate containing antibiotics

Glutaric aciduria type 1 (GA1)

- Glutaryl CoA dehydrogenase deficiency
- AR - Incidence ~1:110,000
- Clinical
  - Macrocephaly, acute encephalopathic crisis (6-18 months), dystonic-dyskinetic movement disorder
  - Emergency protocol, carnitine, Lysine restricted diet
- Excretors vs non-excretors
- Non-accidental injury cases

Timeline & numbers screened

- PKU – 1970 (1.837M, 181 PKU cases)
- CHT – 1980 (1.41M, 816 cases)
- DMD – 1990-2011 (343K screened, 56 cases)
- CF – 1996 (0.871M screened, 273 cases)
- MCADD – 2012 (367K screened, 33 cases)
- SCD – 2013 (329K screened, 34 cases)
- IMD's – 2015 (279K screened - HCU x3, GA1 x3, MSUD x1, IVA x1)

Where do we want to go with newborn bloodspot screening?

LUNCH TIME!

Expansion of NBS in UK

- International approach 20 - 50+ disorders!!
- UK (n=9) approach conservative…
- Genomics – generation study (England) 200 conditions ~500 variants (sensitivity ~30%).
- PHE disbanded – Screening now under NHSE
- Additional disorders:
  - Tyrosinaemia Type 1, SCID & SMA
- UK NSC Blood spot task group – in service evaluations

Tyrosinaemia type 1 (HT1)

- AR - 1:50-60,000 – fumarylacetoacetate hydrolase def.
- Hepatic failure, renal & neuro involvement, long term risk of hepatocellular carcinoma
- Majority cases present <6 months with acute liver failure & renal dysfunction
- Treatment (NTBC) first described in 1992 – particularly effective when initiated early in life
- Widely accepted that HT1 meets criteria for NBS
- Implementation ?July 2025

Severe combined immune deficiency (SCID)

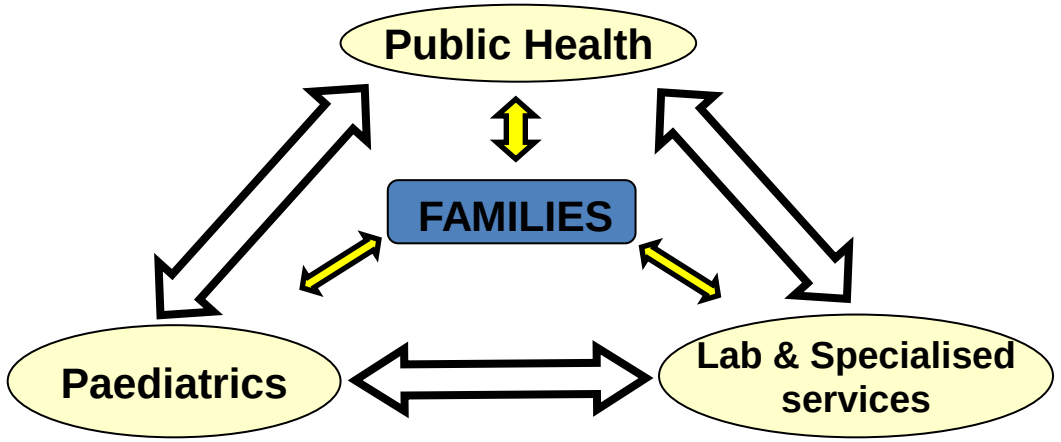
- Incidence 1:50-60,000
- T cell deficiency - Susceptible to life threatening infections
- If diagnosed before overwhelming infection can treat with stem cell transplant
- Health economics
- UK NSC – evaluation
  - Pilot 6 sites in England April 2019
- Awaiting decision by UKNSC

Spinal muscular atrophy (SMA)

- AR - Incidence 1:10,000
- SMN1 gene – crucial for survival of α-motor neurons in spinal cord – progressive neurodegeneration.
- Wide phenotypic spectrum – SMN2 copy number
- Treatment – Gene therapy & antisense oligo-NT therapy
- Early treatment within first 2 weeks of life
- Research pilot – Oxford 2022
- UK NSC / ISE - 2025

Screening is more than a test…

- No benefits without harms.
- NBS tests are NOT totally accurate (with 100% sensitivity and specificity).
- NBS is not the same as diagnostic testing.
- Screening is a PROGRAMME and not just a TEST!



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Summary

- NBS – major public health success of the 21st century
- Technological advances allow additional disorders to be added to the programme
- NBS is a PROGRAMME and not just a TEST
- NBS tests are NOT totally accurate (FNs and FPs cause harms).
- Careful communication of positive screening results to minimise harms / anxieties.
- No benefits with harms!

Thank you!