European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

7th ERN EURO-NMD

# ANNUAL MEETING

## Current and future perspectives on Newborn Screening

*Prof James R Bonham*

Funded by the European Union

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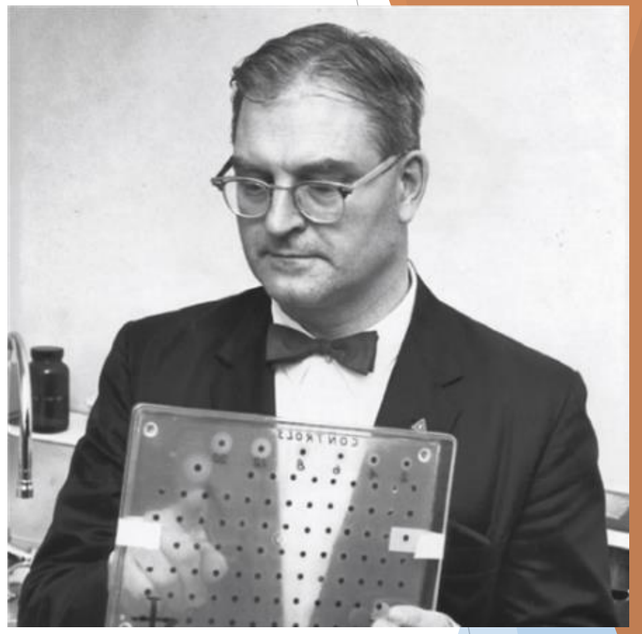
# We have much to celebrate !

- 2023 marked 60 years since Dr Robert Guthrie described a test to detect phenylketonuria (PKU) shortly after birth
- Since then it is estimated that worldwide approximately 750 million babies have been screened and more than 60,000 children with PKU have benefited from this life changing intervention
- It did not stop with PKU, first conditions one by one and then MS/MS in the 1990's
- Today almost 70,000 babies are identified and treated each year as a result of NBS
- This led many around the world to describe newborn screening as: **'One of the major Public Health Advances of the 20th Century'**
- So where are we now?



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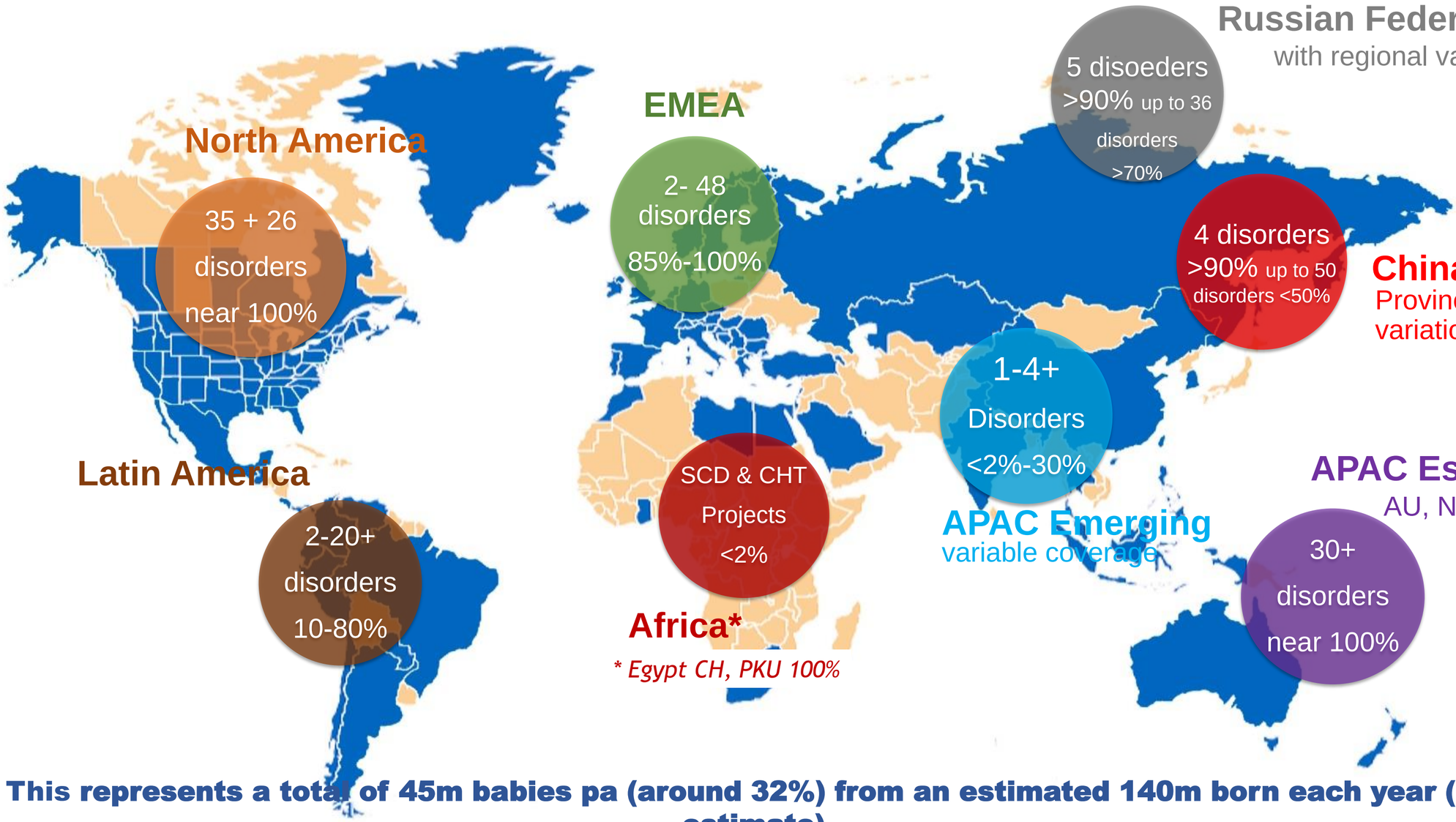
# Where are we now around the world with screening ?




**This represents a total of 45m babies pa (around 32%) from an estimated 140m born each year (UN estimate)**

**Much to celebrate - Much to achieve!**

# The achievements

- More than 500,000 children have received early, cost effective and life changing treatment
- Remarkable acceptance by the parents – decline rates are <1:1,000 (> 99.9% uptake) - contrasting sharply with vaccine wariness in many of our societies, highlighted by COVID-19
- Popularity with doctors, politicians, health policy makers and NGOs
- The WHO has recently endorsed ‘newborn screening’ in LMICs to help reduce the under 5 mortality rate
- A clear set and widely accepted set of criteria (Wilson & Jungner) to guide selection of conditions – this has been in place since 1968 and has formed our thinking and safeguarded an ethical approach to whole population screening
- Incorporation of technological advances from ‘agar gels’ to mass spectrometry and radiometric techniques to enzyme linked immunoassay
- The development of automation and IT to track babies and help manage the screening pathway
- Novel and improved treatments to improve outcome

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# Alongside this – an even greater potential

- Genomic screening brings the potential to move newborn screening from 10 – 50 conditions to 200 or more
- It can link those genetics changes to specific and possibly very effective targeted genomic therapies
- It can shorten the time to diagnosis and significantly improve outcome for conditions that we cannot detect now
- It can complement metabolomic information
- It can provide important information to families to inform future reproductive choices
- It may bring health economic benefit

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# What could possibly go wrong?

- **False positive results** – the positive predictive value of screening tests are typically around 50 – 60% - alongside the 500,000 true positives we have alarmed 400,000 families unnecessarily.
- The effect upon families is difficult to study but can be profound – with some conflicting evidence
  - *Tu WJ  PLoS One 2012* - 39% of mothers with a false +ve result describe concerns about the 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 $p<0.001$

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# What could possibly go wrong?

- **Uncertainty - p**erhaps even more significantly the uncertainty of the significance of the outcome and the difficulties for physicians and families
- When we begin to screen we identify the target ‘clinically presenting’ form but also many less well defined cases that may be unclear eg CF-SPID, increase in incidence of biotinidase deficiency from <1:100,000 to >1:10,000, mild forms of hypothyroidism etc
- An example from isovaleric acidaemia - a 10 year look back in the UK, 108 screen positive cases: 84 were false positives – largely due to pivalate containing antibiotics; 24 were ‘true positives’, of these: 7 were symptomatic and required treatment; 17 remained asymptomatic and were simply given advice on emergency regimen with 2 on mild protein restriction
- To treat or not to treat?

# What could possibly go wrong?

- A label that can increase anxiety and uncertainty within families without any clear benefit
- Civil liberties issues in times of political uncertainty if DNA profiles and samples are stored on all children born
- The cost of treatment – there are 5,000 rare disorders, 4,000 are genetic – prevalence of each may be around 1:50,000, this means 320k patients pa – if genomic treatments were developed for 10% at an average cost of 1m Euro – that would mean 32 bn Euro pa

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# In the midst of this opportunity and risk - what should we do?

- Protect what we have:
  - Public confidence in existing screening – accepted by 99.9% of families contrasting sharply with vaccine wariness – in Europe, a 10% drop, to 90% uptake would mean 280 children with CHT missed, 140 with CF missed, 35 with PKU missed etc each year
  - Meaningful consent is difficult - even for 9 conditions (UK NBS panel) but virtually impossible for 200+
  - We rely on the 'unwritten contract' that if you are doing a test on my baby that I cannot understand (or spell), and I get an unexpected phone call after screening, you will have an effective treatment if my baby has the condition
- Reduce false positive results by the increased use of second tier testing
- Agree clear case definitions and undertake outcome studies to reduce uncertainty and modify screening when needed
- Work across genomics/metabolomics/ enzyme assay where possible
- Use risk based analysis of results eg CLIR

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# In the midst of this opportunity and risk - what should we do?

- Work to secure legal protection to limit access to stored data and samples
- Remember that screening is a pathway and not just a test – it needs to be carefully planned and monitored
- Work together to share practice and learn from one another so that ‘good practice’ becomes ‘common practice’
- Co-design and share pilot scheme data
- Dialogue with, but do not be led by Pharma
- Recognise that the patient voice is not the public voice but include both

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# Where do we begin?

- We need thoughtful, unbiased debate and advice based on evidence
- We may need to gather the evidence – outcome studies
- We will need to share the evidence – publication and a forum to discuss and liaise
- We need to put the patients, families and physicians at the centre – not just the technology
- Can we begin in the ERNs with those already involved in newborn screening eg Euro-NMD, MetabERN, ERN RITA (PIDs)
- Form an ‘ERN - Rare disease newborn screening liaison group’ – links to S4R

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