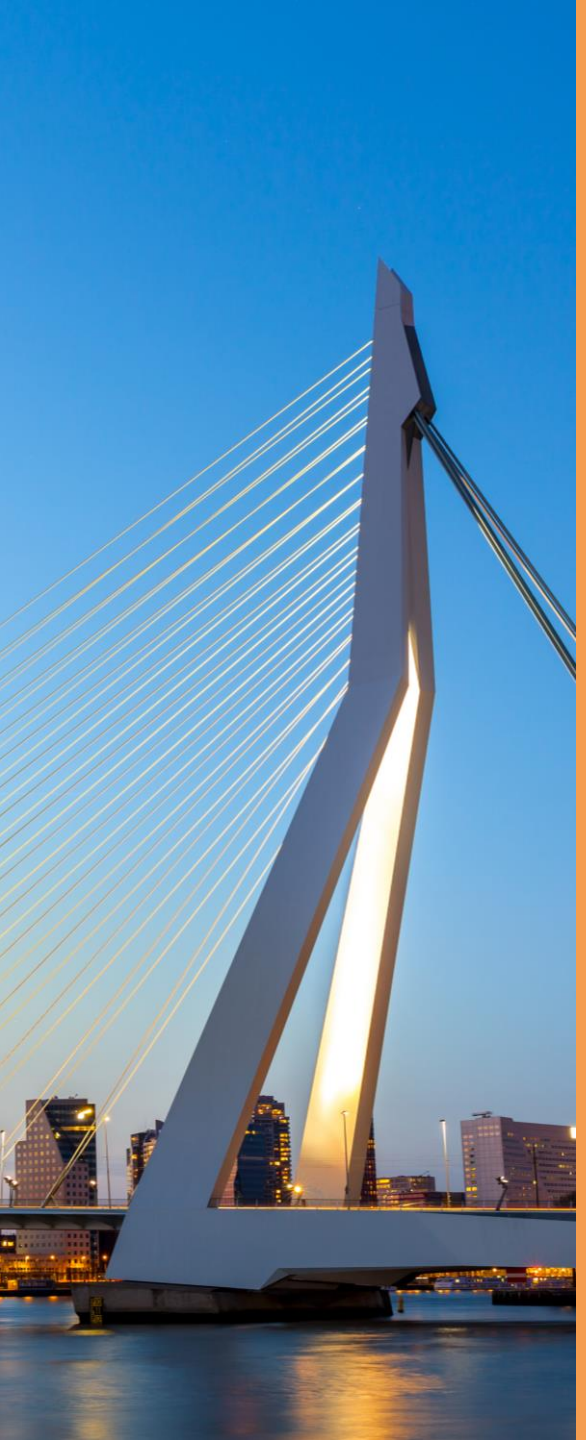

Newborn Screening as a system: from good practice to common practice

Prof James R Bonham

Newborn Screening for PIDs – now what?

November 8th 2023

We have much to celebrate !

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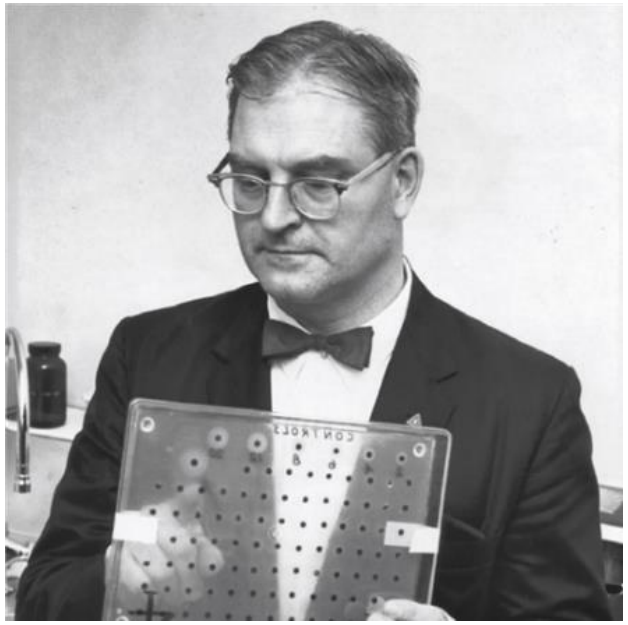
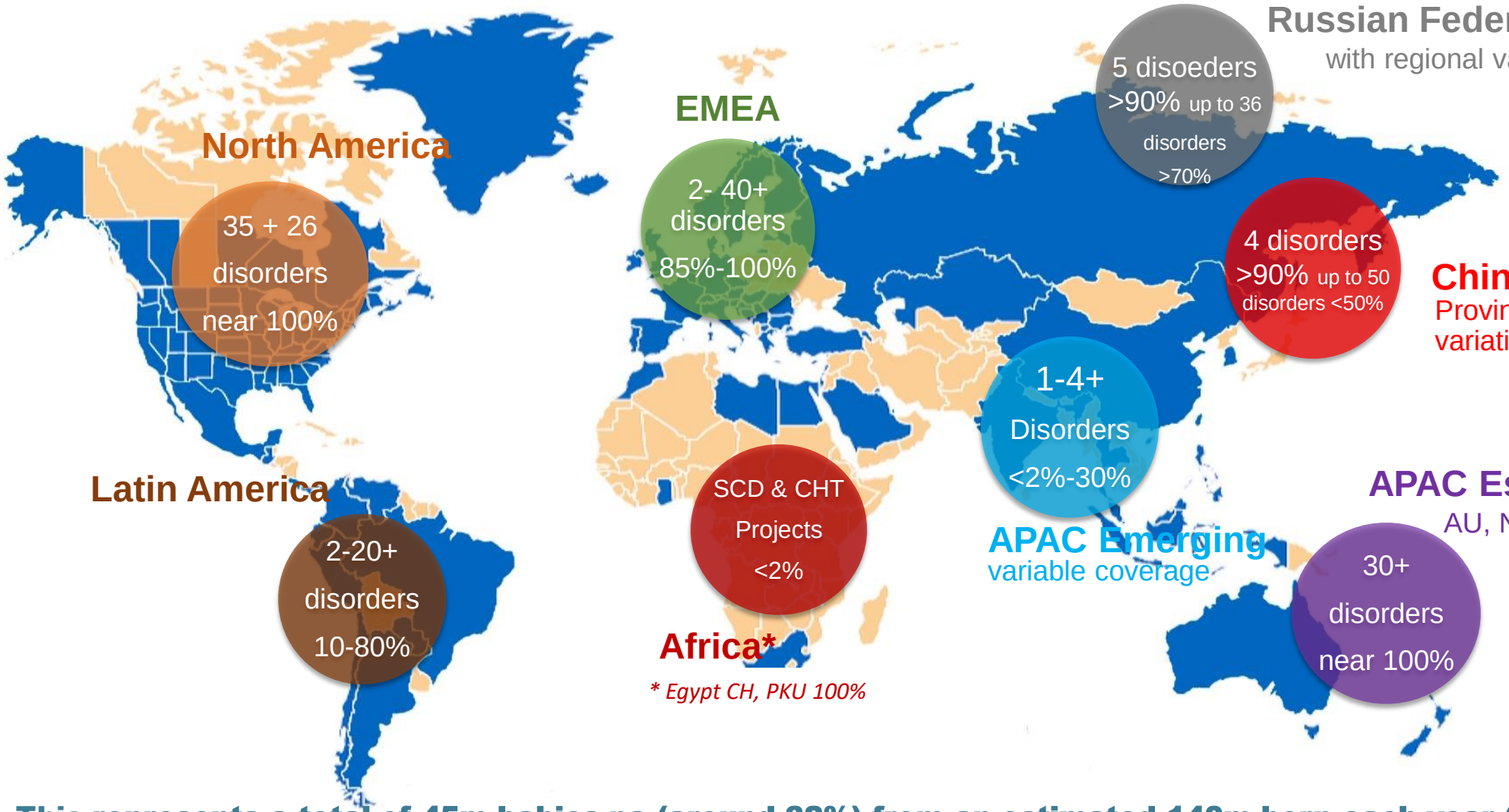
- It is now 60 years since Dr Robert Guthrie described a test to detect phenylketonuria (PKU) shortly after birth
- Perhaps even more importantly he also described a simple and effective means of blood collection using a ‘dried blood spot card’ to allow this to be carried easily to a testing laboratory
- Since then it is estimated that worldwide approximately 750 million babies have been screened we have detected more than 60,000 children with PKU who have benefited from this life changing intervention
- Of course this did not stop there, and in the intervening years disorders have been added progressively to the growing list of conditions that could be detected by newborn screening. Starting with congenital hypothyroidism (CHT) but progressing to other disorders where this would significantly benefit the child.
- This led many around the world to describe newborn screening as: **‘One of the major Public Health Advances of the 20th Century’**



Where are we now around the world with screening - conditions and coverage?



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!

Not just about geography, but also new conditions that can be detected early

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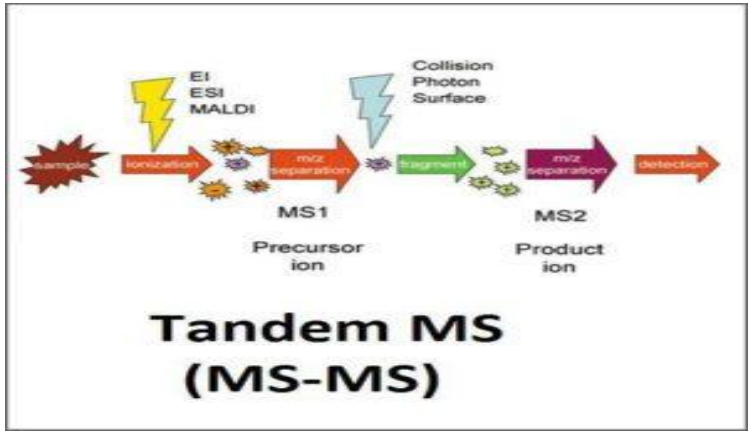
- In the early 1990's along came: ESI linked with MS/MS allowed many pathogenic metabolites, typically acylcarnitines and aminoacids, to be detected simultaneously from a single punched disk in around 1-2min/sample. *Millington and Chase 1993*
- The number of conditions rose progressively to evolve into a RUSP panel, in the US, of 35 core conditions + 26 secondary conditions



And now genomics

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- **Genomics**
  - 30 years on from Millington and Chase and there is now an opportunity to consider the use of genomics
  - As an adjunct – as in the use of NGS when screening for cystic fibrosis as a second line test
  - As a specific marker, as in the measurement of TRECs when screening for SCID or a homozygous deletion of SMN1 when screening for SMA
  - As a first line test using sequencing:
    - In custom designed panels
    - As WES
    - Most ambitiously as WGS
- **Several extended evaluations are happening around the world**
  - In the US, in the UK, in Europe, in Australasia and elsewhere
  - One example – 'The Generation Study' in the UK seeks to offer WGS to 100,000 newborn in the next 2 – 3 years and on 2nd October listed 223 conditions including 500 genes.
  - https://www.genomicsengland.co.uk/news/genomics-england-announces-list-of-rare-conditions-to-be-included-in-world-leading-research-study

Despite this success we need to be careful

- Of course as in most of medicine, there is a balance and sometimes difficult choices to make
- The patients/families believe themselves to be well and this gives us a particular burden of responsibility
- “All screening programmes do harm; some do good as well, and, of these, some do more good than harm….” *Gray, BMJ (2008) 336:480*
- More screening does not automatically mean better screening

So how can we ensure the best for our families and for our children?

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- Understand the conditions and the impact of screening on what we detect – increased phenotypic heterogeneity
- Recognise and understand the harms – uncertainty and false positive clinical referrals
- Recognise that screening is only part of the story
- The need for planning and co-ordination
- The need to engage families and the public and really listen
- We need to learn from others and share our experience
- Learn from incidents
- Assess long term outcomes

How does screening change what we detect?

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- **Phenotypic heterogeneity**
  - **Biotinidase deficiency**
    - Clinically identified biotinidase deficiency <1:100,000
    - Early screening reports identified biotinidase deficiency 1: 41,000
    - More recent screening reports identified biotinidase deficiency 1:1,897
  - **Congenital hypothyroidism**
    - Pre-screening 2:1 female:male 1:6,000
    - Post screening 1:1 female:male 1:1,500
  - **Cystic Fibrosis**
    - Around 20 babies each year are given a designation of CF-SPID
  - **Isovaleric acidaemia**
    - An example about uncertainty in the 'Intention to Treat'
    - From 24 'Positives' over then years
      - 7 were symptomatic and required treatment with diet and carnitine – all had an initial C5> 7.6 µmol/L
      - 17 remained asymptomatic and were simply given advice on emergency regimen with 2 on mild protein restriction – all had an initial C5 < 7.2
  - A wide spectrum in many disorders can result in uncertainty but there are a variety of ways that we can understand the significance of a positive result for the baby and the family – including further biochemistry and genetics

Planning and co-ordination: Screening is more than a test, it is a pathway

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- The offer of a test – with a proper understanding
- Taking the sample – good quality at the right time
- Effective transport – even at Christmas!
- A good turn around time – even when machines breakdown or staff are sick
- Effective and timely referral into appropriate clinical care
- Agreed national confirmatory testing and case definition
- Agreed national treatment guidelines
- Assessment of long term outcome

Care Pathway

Talk to families and the public

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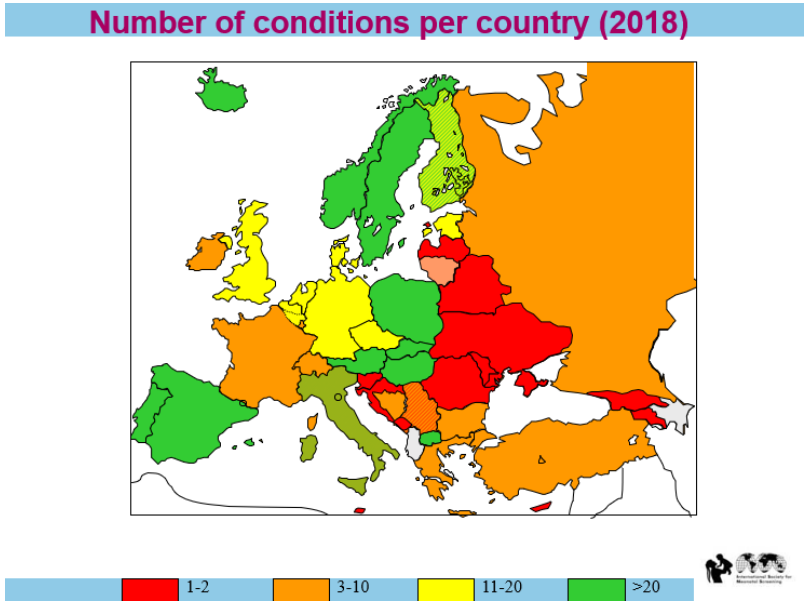
- The public, the families and the patients are the experts about what will work in Public Health
- We wanted to use extended genomic when screening for cystic fibrosis
- But what should we report?
  - All mutations so that no conditions would be missed or only those that we were sure were pathogenic
  - Over a year we asked the public, patients/families and the doctors
  - The public prized certainty of outcome above detecting every baby
  - The professionals and the families wanted no baby to be missed
- This is still work in progress but it illustrates that views can vary

Learn from others

- Difference provides the opportunity to learn, a 2021 study of screening practice in Europe revealed significant differences in the way that we tackle screening:
  - Which conditions are screened
  - The day of sampling
  - The turn around time of results
  - Whether parents are notified of normal results
- What about ‘pilot studies’ – can we share a framework and learn from one another?
- Several initiatives are underway eg Screen4Rare to improve equity and deliver key work streams
- And of course Conferences!



How should we then respond?

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- Recognise that screening can bring life changing and sometimes life saving benefit to many
- Recognise that screening can also seriously worry families without cause, particularly if poorly planned or poorly researched
- Work actively to maintain public confidence and not take this for granted
- Exploit new opportunities and new technologies as the become available
- Undertake screening only when we are sure that we can directly benefit the baby detected
- Learn from one another