Defining the aims of newborn screening

or Focus?

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Fifty years of newborn blood-spot screening

From this ➲

96- Channel gene sequencer

to this ➲

Bench-top tandem mass spectrometer

↔ and this
Improved analytical technology: Yet more diseases?


Orbitrap - A sensitive high-resolution Fourier transform ion cyclotron resonance mass spectrometer. Mass accuracy 1-2 parts per million. > 200 analytes simultaneously.

“Smaller, faster, more affordable”

“Guthrie card samples can be analyzed for both genetic and epigenetic differences together to view a more complete picture of the genome at birth.”

**US plan for $25M programme on genome sequencing in newborn screening**
AIMS

“Important health problems”

- To prevent the preventable
  
  Treatment, information

- Good > Harm
Elements of Newborn Screening Policy

What to screen for - the disease panel
Screening strategy
Information for parents
Consent
Sample collection
Analytical performance
Cut-offs and disease definition
Clinical provision
Documentation and oversight
Screening for Presymptomatic Disease

AIMS
“Important health problems”
  • To prevent the preventable
    * Treatment, information
    * Good > Harm

POLICY
  • What to screen for
  • How to do it
  • Subsequent actions

IMPLEMENTATION
  • Reality
  • ‘The devil is in the detail’
Policy: Fuzz or Focus?

Focus

*Detail* is sharply defined
*Object boundaries are clear*

Fuzz

*Objects are discernable*
*but* *detail* unclear and
*boundaries blurred*
1) The condition sought should be an important health problem.

2) There should be an accepted treatment for patients with recognised disease.

3) Facilities for diagnosis and treatment should be available.

4) There should be a recognised latent or early symptomatic stage.

5) There should be a suitable test or examination.

6) The test should be acceptable to the population.

7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8) There should be an agreed policy on whom to treat as patients.

9) The costs of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10) Case-finding should be a continuous process and not “a once and for all” project.

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The UK National Screening Committee

Replaced 10 W & J “principles” by 19 criteria

Requires 87 items of information under 35 general headings

• The health problem
  Incidence, prevalence, projected trends, morbidity, mortality, burden by age and sex, any primary preventive measures.

• The screening test
  Distribution of test values, cut-off points, agreement on normal/abnormal/borderline results, sensitivity, specificity, likelihood ratio, side-effects of test, acceptability to population tested.

• The diagnostic process
  Procedures, sequence of events, side-effects of diagnostic procedures, acceptability

• The treatment
  Evidence for effectiveness, side-effects/harm, acceptability, variability of treatment standards

• The screening programme
  Target population, beneficial effects (absolute risk reduction), adverse effects (physical, psychological), numbers needed to screen per treatable case, per person to benefit, made anxious, physically harmed (and ratios, with confidence intervals)

• Economic considerations
  Costs, savings, cost effectiveness, cost-benefit (cost per QALY), impact on other services

• Quality management, etc, etc …
“There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.”

Each disorder is regarded as a separate ‘programme’

After 15 years:
Screening for CF and Sickle Cell Disease (both decided at a political level)

Screening for MCADD

A pilot study of 5 additional disorders (Homocystinuria, MSUD, GA1, IVA, VLCHAD)
Policy based on quantitative evaluation: ACMG Scoring system (part)

<table>
<thead>
<tr>
<th>Criteria included in this Survey</th>
<th>Categories</th>
<th>Score</th>
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<tbody>
<tr>
<td>Incidence of condition</td>
<td>&gt;1:5,000</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>&gt;1:25,000</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>&gt;1:50,000</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&gt;1:75,000</td>
<td>25</td>
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<tr>
<td></td>
<td>&lt;1:100,000</td>
<td>0</td>
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<tr>
<td>Signs and symptoms clinically identifiable in the first 48 hours</td>
<td>Never</td>
<td>100</td>
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<tr>
<td></td>
<td>&lt;25% of cases</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>&lt;50% of cases</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&lt;75% of cases</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Always</td>
<td>0</td>
</tr>
<tr>
<td>Burden of disease (Natural Hx if untreated)</td>
<td>Profound</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>75</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>50</td>
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<tr>
<td></td>
<td>Mild</td>
<td>25</td>
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<tr>
<td></td>
<td>Minimal</td>
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Respondent Profiles

<table>
<thead>
<tr>
<th>Respondents</th>
<th>No. of Profiles</th>
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<tr>
<td>TESTING</td>
<td>41</td>
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<tr>
<td>FOLLOW UP</td>
<td>95</td>
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<td>ADMINISTR</td>
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<td>POLICY</td>
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<td>Primary Care PROVIDER</td>
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<tr>
<td>CONSUMER</td>
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<tr>
<td>Specialty Care PROVIDER</td>
<td>159</td>
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</tbody>
</table>
MCADD
PKU
IVA
VLCAD
MSUD
LCHAD
GA-1
HMG
Propionic acidaemia
Benign hyperphenylalaninaemia
SCADD
Propionic acidaemia: a heterogeneous disorder

~50% present before 10 days of age

**Classical form**

- severe
- early onset
- often fatal
- poor outcome

Do not screen?

Propionic acidaemia is a typical Fuzzy condition
Which Diseases: Clinical reality

Propionic acidaemia
Methylmalonic acidaemia (mutase)
Isovaleric acidaemia
Beta-ketothiolase deficiency
3-Methylcrotonyl-CoA carboxylase deficiency

The range of severity within a disorder overlaps with that of adjacent disorders
Elements of Newborn Screening Policy

What to screen for - the disease panel
- Screening strategy
- Information for parents
- Consent
- Sample collection
- Analytical performance
- Cut-offs and disease definition
- Clinical provision
- Documentation and oversight
Screening Strategy
Which Biological Level to Start from?

Blood spot

Gene level:
• Specific mutation
• Gene scanning, etc

Protein level:
Enzyme, hormone, structural, etc

Metabolite level:
• Specific metabolites
• Ratios / profiles

Metabolite level
Gene level

Blood spot

Which Biological Level to Start from?
UK Pilot Study of Screening for MCADD Deficiency: The Initial Screen

Routine Newborn Screening Dried Blood Spot Samples:
Underivatised MRM
Octanoylcarnitine (C8)

Yes

C8 ≥ 0.40 µmol/L
[A]

No

C8 ≥ 0.50 µmol/L
Mean [A, B, C]

Yes

Presumptive Positive MCADD
Referral to designated clinician

↓

Bloodspot C8, urine hexanoylglycine, genotyping
UK Pilot Study of Screening for MCADD Deficiency: ‘Clinical Decision Tree’

EMS: Extended Mutation Screening

MCADD - Definite Phenotype

- Yes
  - c.985A>G homozygous (2 copies)
    - No
      - c.985A>G heterozygous (1 copy)
        - Yes
          - Biochemically abnormal
            - Yes
              - EMS 2 mutations
                - No
                  - EMS 1 mutation only
                    - No
                      - CARRIER
            - No
              - EMS Other mutation identified with c.985A>G
                - Yes
                  - CARRIER
          - No
            - Biochemically abnormal
              - Yes
                - EMS (Likely)
            - No
              - NOT MCADD

MCADD-Definite or Uncertain phenotype

NOT MCADD (?Other IEM)

CARRIER
UK Pilot Study of Screening for MCADD Deficiency
Samples taken at first (‘diagnostic’) clinical consultation

UK Pilot Study of Screening for MCADD Deficiency
Samples taken at first ('diagnostic') clinical consultation
UK Pilot Study of Screening for MCADD Deficiency
Reducing the number of carriers detected

Routine newborn screening dried blood spot samples:
- Underivatised MRM
- Octanoylcarnitine (C8)

1. If $C_8 \geq 0.40 \mu\text{mol/L}$, go to step 2. Otherwise, go to step 5.

2. Re-test $C_8$ in duplicate [B, C] and test for $C_{10}$.

3. If $C_8 \geq 0.50 \mu\text{mol/L}$ and $\text{Mean } [A, B, C]$, go to step 4. Otherwise, go to step 5.

4. Obtain $C_{10}$ results and calculate the $C_8:C_{10}$ ratio.

5. If $C_8:C_{10} \geq 1.0$, go to step 6. Otherwise, go to step 7.

6. MCADD suspected; referral to designated clinician.

7. MCADD not suspected; no further action.
Carriers can be detected at the protein level too!

Sickle Cell screening in Trent: ~59,000 babies

HPLC then isoelectric focusing

- **10** sickle cell disease (SS or SC)
- **1** thalassaemia
- **209** sickle carriers
- **151** other carriers (C, D,E)
- **14** variants - not significant or unknown significance
- **313** repeat samples because of transfusion

All 10 cases of sickle cell disease were already diagnosed! 😞

Offered counselling 😊?

Now avoided by testing at the DNA level 😊

Disagreement on reporting variants of no or unknown clinical significance

Anglia and Oxford

North Thames

West

Trent

West Midlands

South

South and West

Northern and Yorkshire
Elements of Newborn Screening Policy

❖ What to screen for - the disease panel
❖ Screening strategy
  Information for parents
  Consent
  Sample collection
  Analytical performance
  Cut-offs and disease definition
  Clinical provision
  Documentation and oversight
Written information prior to screening

- Reduces stress for parents of positive cases (0.1%)
- *May* increase anxiety in the other 99.9%
- ‘Terms and Conditions’ disclaimers, hopefully to reduce:
  Hysteria over secrecy (government DNA stores etc)
  Medico-legal claims for true false-negative results
- Be internet-aware – recommend reliable sites

Parental consent

- Parental choice *versus* mandatory screening
  - Should parents’ religious views be respected?
  - Should there be options to refuse specific tests?
- The right of the child to standard medical care
Elements of Newborn Screening Policy

😊 What to screen for - the disease panel
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😊 Information for parents
❓ Consent
  - Sample collection
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Use of ‘surrogate’ internal standards where Isotopically-labelled analyte is not available

<table>
<thead>
<tr>
<th>Internal Standard</th>
<th>Analytes Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_3$C8</td>
<td>C5-DC, C10:1</td>
</tr>
<tr>
<td>$d_3$C18</td>
<td>C18:1, C18:2, C18:1OH, C18OH</td>
</tr>
<tr>
<td>$d_3$C10</td>
<td>C12, C10:1</td>
</tr>
<tr>
<td>$d_9$C5</td>
<td>C5-OH, C5:1</td>
</tr>
<tr>
<td>$d_9$C14</td>
<td>C14:1, C14:2, C14OH</td>
</tr>
<tr>
<td>$d_3$C16</td>
<td>C16:1OH, C16:1, C16-OH</td>
</tr>
<tr>
<td>$d_3$C3</td>
<td>C3-DC</td>
</tr>
</tbody>
</table>

Clinical and Laboratory Standards Institute (USA). July 2010
*Newborn Screening by Tandem Mass Spectrometry: Approved Guideline*
Internal standards counts with individual DBS samples

\[ y = 0.9934x + 0.0066 \]
Internal standards counts with individual DBS samples

\[ y = 0.5485x + 0.4515 \]
Elements of Newborn Screening Policy

😊 What to screen for - the disease panel
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❓ Consent
✔ Sample collection
❗ Analytical performance
‼ Cut-offs and disease definition
   Clinical provision
   Documentation and oversight
Congenital Hypothyroidism

Estimated UK incidence prior to screening
15 per 100,000 births

Clinical referral rate after screening (Trent):
1980-85  32 per 100,000
2008-10  52 per 100,000
A 62% increase!

Re-evaluating the 1980-85 data using the 2008 UK protocol (cut-off for immediate referral 20 mU/L instead of 40 mU/L) gives a 51% increase.
‘Trent’ cases referred 1990 -2009
(only those with TSH in initial sample ≥20 mU/L)
The clinical referral rate (Trent):

Immediate referral with TSH >40 mU/L *
   32 per 100,000

Immediate referral with TSH > 20 mU/L *
   52 per 100,000

* If the initial sample TSH >10 mU/L a second sample is requested
  Cut-off for the second sample is 10 mU/L

Several UK labs are using second-sample cut-offs of 6 mU/L or less
Many of the additional cases receive T4 treatment.
Elements of Newborn Screening Policy

- Sad What to screen for - the disease panel
- Grinning Screening strategy
- Happy Information for parents
- Confused Consent
- Green Sample collection
- Exclamation Analytical performance
- Exclamation Exclamation Cut-offs and disease definition
  - Clinical provision
  - Documentation and oversight