Bloodspot programme delivery and expansion: Complexities from a Laboratory Perspective

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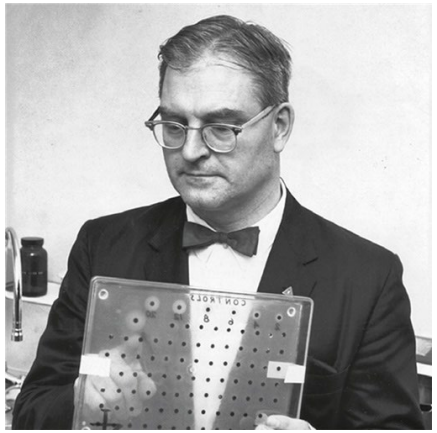
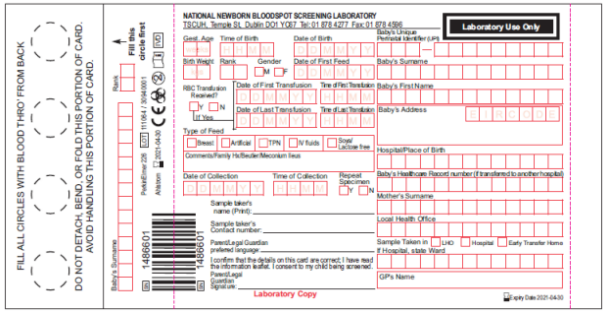
Role in the Newborn Screening Laboratory

- Ensure appropriate clinical pathways are followed for suspected cases
- Ensure QMS issues are resolved
- Planning and sign of new laboratory processes/methods

Newborn Bloodspot Screening

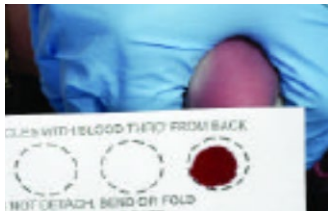
Aim: **Early detection** of rare inherited metabolic, hormonal or functional disorders before the onset of any clinical manifestations, enabling the **early introduction of treatment** which will lead to a better clinical outcome, avoid significant morbidity or premature mortality





Screening programme: pathway from sample to result & follow up

Pre-analytical



Analytical

Post analytical

- Not suspected
- Screen positive
  - Diagnostic testing
    - False positive
    - True positive → Clinical Pathway

KPIs

Conditions screened for in the Republic of Ireland

1966 - Phenylketonuria (PKU)
1971 - Homocystinuria (HCU)
1972 - Maple Syrup Urine Disease (MSUD)
- Classical Galactosaemia
1979 - Congenital Hypothyroidism (CHT)
2011 - Cystic Fibrosis (CF)
2018 - Medium Chain acyl CoA Dehydrogenase Deficiency (MCADD)
- Glutaric Aciduria Type 1 (GA1)
2022 - Adenosine Deaminase deficiency Severe Combined Immunodeficiency (ADA-SCID)

SMA and SCID approved for addition to the programme

Process for adding conditions to the programme

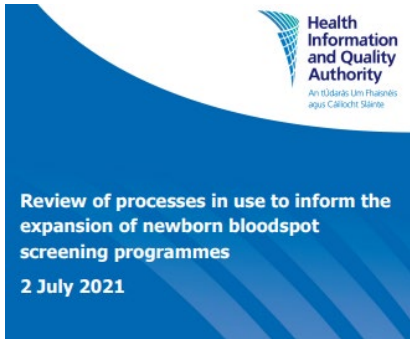
nsac
National Screening Advisory Committee

→

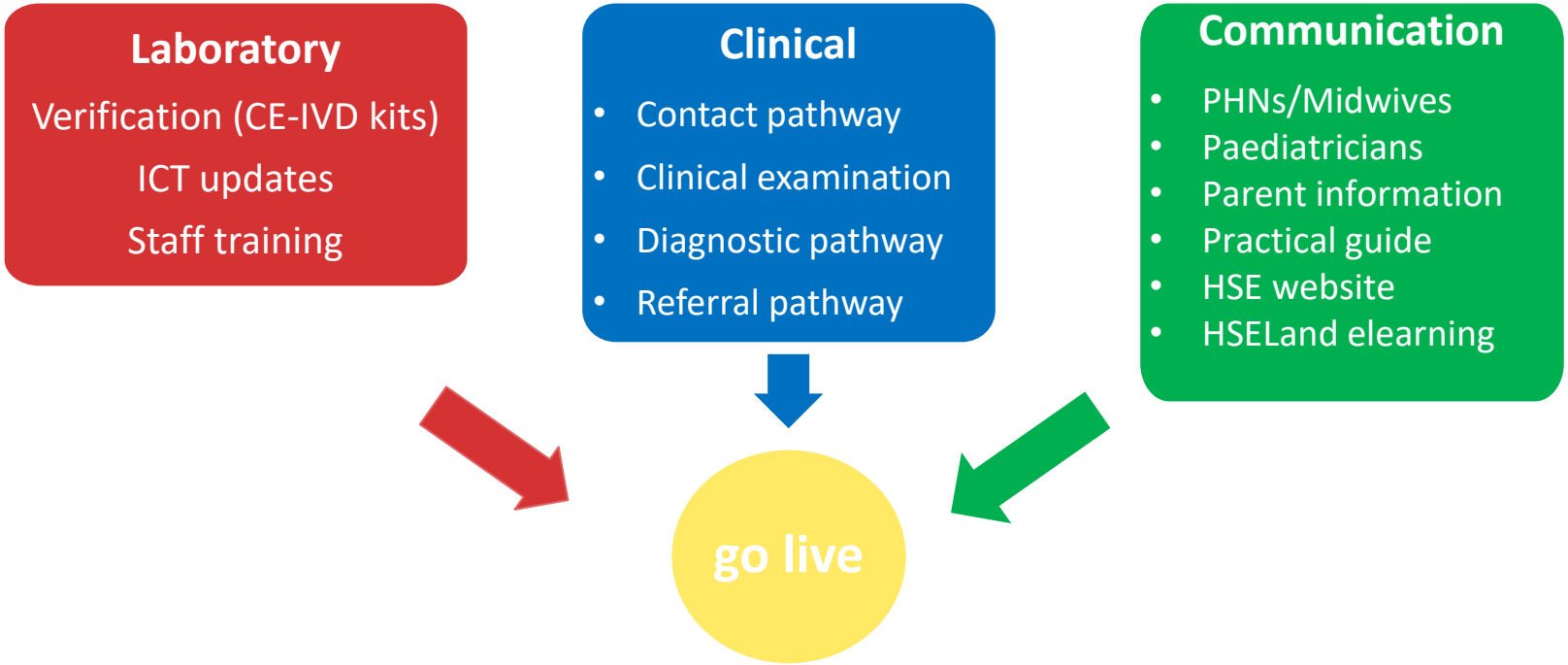
Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

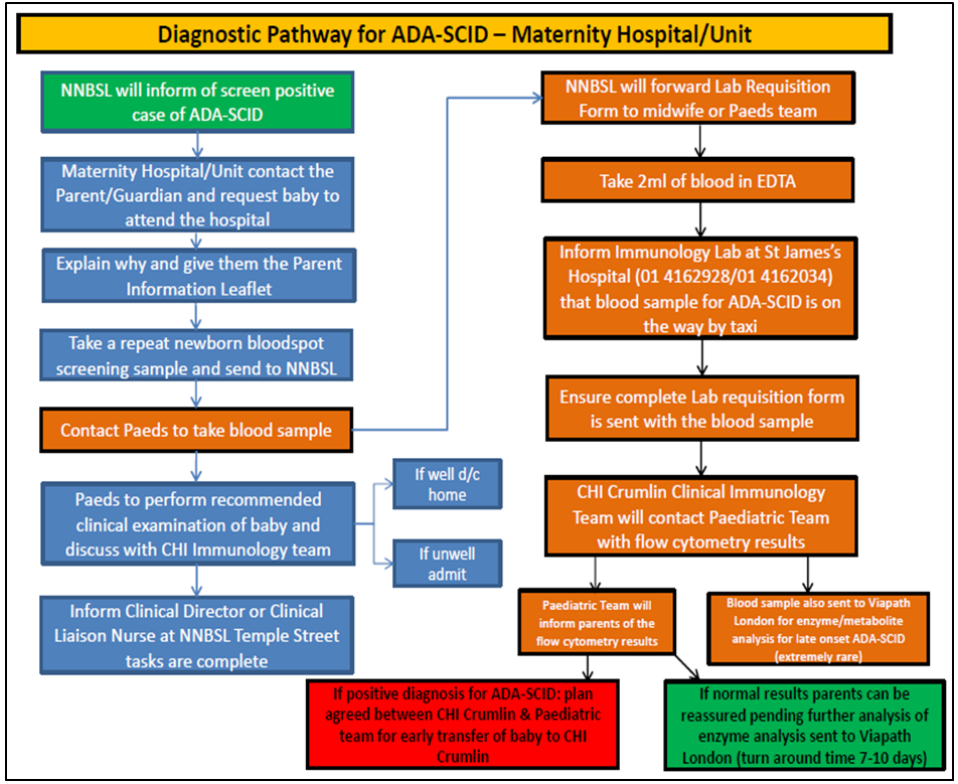
→

NSAC make recommendation to Minister for Health



Programme expansion workstreams




Diagnostic Pathway for ADA-SCID – Maternity Hospital/Unit
NNBSL will inform of screen positive case of ADA-SCID
Maternity Hospital/Unit contact the Parent/Guardian and request baby to attend the hospital
Explain why and give them the Parent Information Leaflet
Take a repeat newborn bloodspot screening sample and send to NNBSL
Contact Paeds to take blood sample
Paeds to perform recommended clinical examination of baby and discuss with CHI Immunology team
If well d/c home
If unwell admit
Inform Clinical Director or Clinical Liaison Nurse at NNBSL Temple Street tasks are complete
NNBSL will forward Lab Requisition Form to midwife or Paeds team
Take 2ml of blood in EDTA
Inform Immunology Lab at St James's Hospital (01 4162928/01 4162034) that blood sample for ADA-SCID is on the way by taxi
Ensure complete Lab requisition form is sent with the blood sample
CHI Crumlin Clinical Immunology Team will contact Paediatric Team with flow cytometry results
Paediatric Team will inform parents of the flow cytometry results
Blood sample also sent to Viapath London for enzyme/metabolite analysis for late onset ADA-SCID (extremely rare)
If positive diagnosis for ADA-SCID: plan agreed between CHI Crumlin & Paediatric team for early transfer of baby to CHI Crumlin
If normal results parents can be reassured pending further analysis of enzyme analysis sent to Viapath London (turn around time 7-10 days)

Laboratory aspects of expansion

- Precision
- Accuracy
- Carryover
- Limit of quantitation

Determination of cut-off value

  - Analysis of 5000 ‘not affected’ cards (good quality)
  - Verification of preliminary cut-off with known positive cases
  - Review of cut-offs of other laboratories, literature and international databases
  - Consider factors such as gestational age, birth weight
- Further analysis to estimate false positive rate

Compliance with ISO15189:2022 Medical laboratories – requirements for quality and competence

Ongoing Quality Assurance

- KPIs agreed with NNBSP governance group
  - Time to clinical pathway
  - False positive rates

Within laboratory

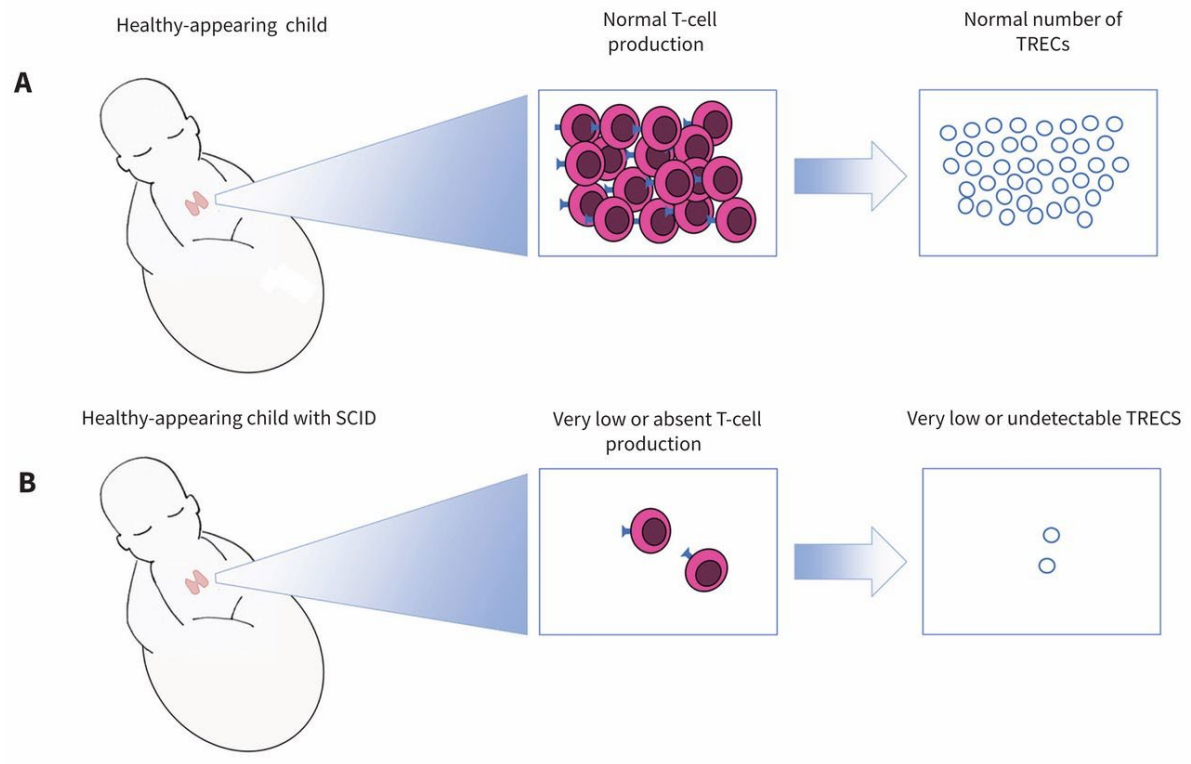
- Ongoing review of cut-offs
- Internal QC
- Participation in external quality assessment schemes/inter-laboratory comparisons

Addition of SMA and SCID to NBS programme

- Spinal Muscular Atrophy (SMA) is a rare neuromuscular condition associated with irreversible neuron loss
- Caused by homozygous deletions in the SMN1 gene (95% of cases)
- NBS is based on detection of this homozygous deletion in the DBS
- The number of SMN2 copy number determines disease severity (2nd line testing)
- Estimated incidence of childhood presentations (types 1-3) in Ireland 1:14,653[1]
- The availability of disease modifying treatments has improved the prognosis especially when instituted early

1. Health technology assessment of the addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme. HIQA. Nov 2023

NBS for SCID using TREC (T cell receptor excision circle) assay



Multiplex RT-PCR for SCID/SMA NBS

EONIS™ assay consists of four easy steps; punching, extraction, amplification and data analysis.

Dedicated analysis software enables quantification of TREC and KREC, while SMN1 results are reported qualitatively. SMA carrier status will not be detected or reported. RPP30 is used as an internal amplification control as well as basis for the quantification. Software analysis includes automated run acceptance criteria from kit controls to ensure that the quality of measured data is not compromised.

Punching of DBS samples and controls

Extraction with manual or automated workflow

Amplification of TREC, KREC, SMN1 & RPP30

Result interpretation in the EONIS™ analysis software

Amplification curves

PUNCHING → EXTRACTION → AMPLIFICATION → DATA ANALYSIS

Molecular Technology: Change Management

- New equipment
- Staff expertise and training on new equipment
- Dedicated laboratory space
- Processes to avoid risk of contamination
  - new workflows
  - separate workspaces for bloodspot punching and PCR analysis
  - new ‘culture’ for staff working in this area

Timelines of Expansion

ADA-SCID (technology already in place)

Approval
14th Aug 2020

Go live
22nd May 2022

21 months
(Cyberattack/pandemic)

SCID/SMA

Approval
SCID: Jan 2023
SMA: Nov 2023

Funding

Equipment
tender

Laboratory
reburbishment

Staff
recruitment

Laboratory
Clinical
Communications
workstreams

Questions

Sláinte Leanaí Éireann

Children's Health Ireland