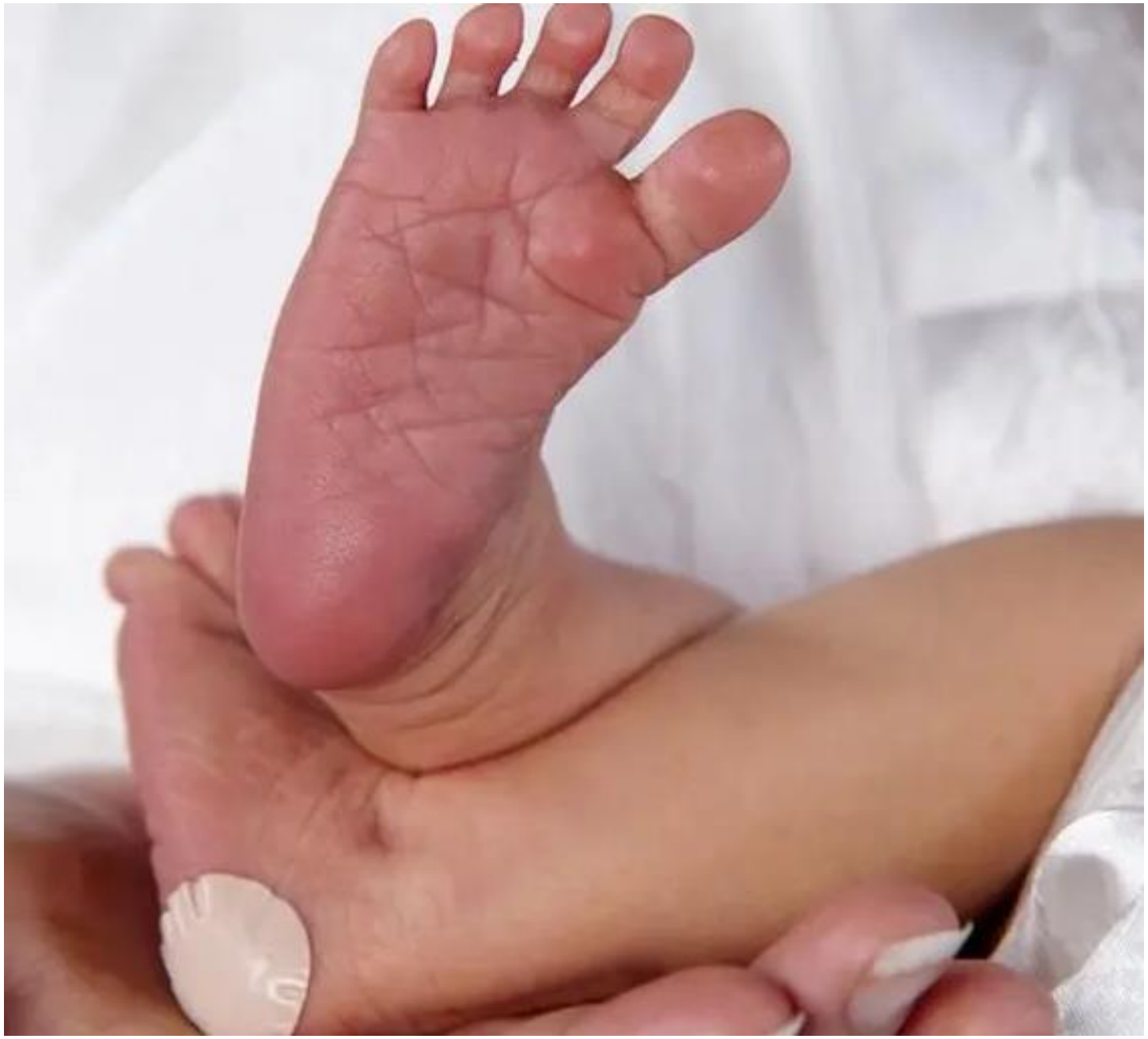
Noah's Ark
Children's Hospital for Wales
Ysbyty Plant Cymru

Cystic Fibrosis Newborn screening- what you need to know as a clinician



Autumn WPS Meeting 2024

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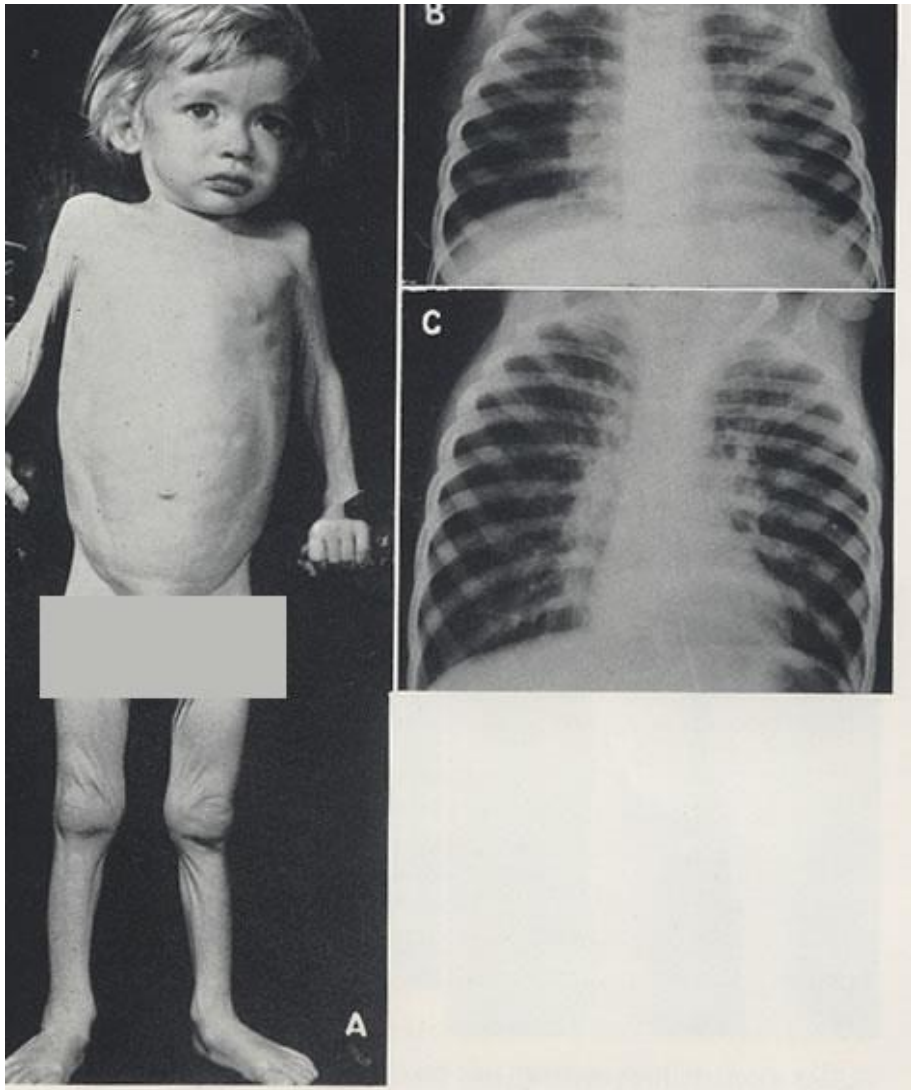
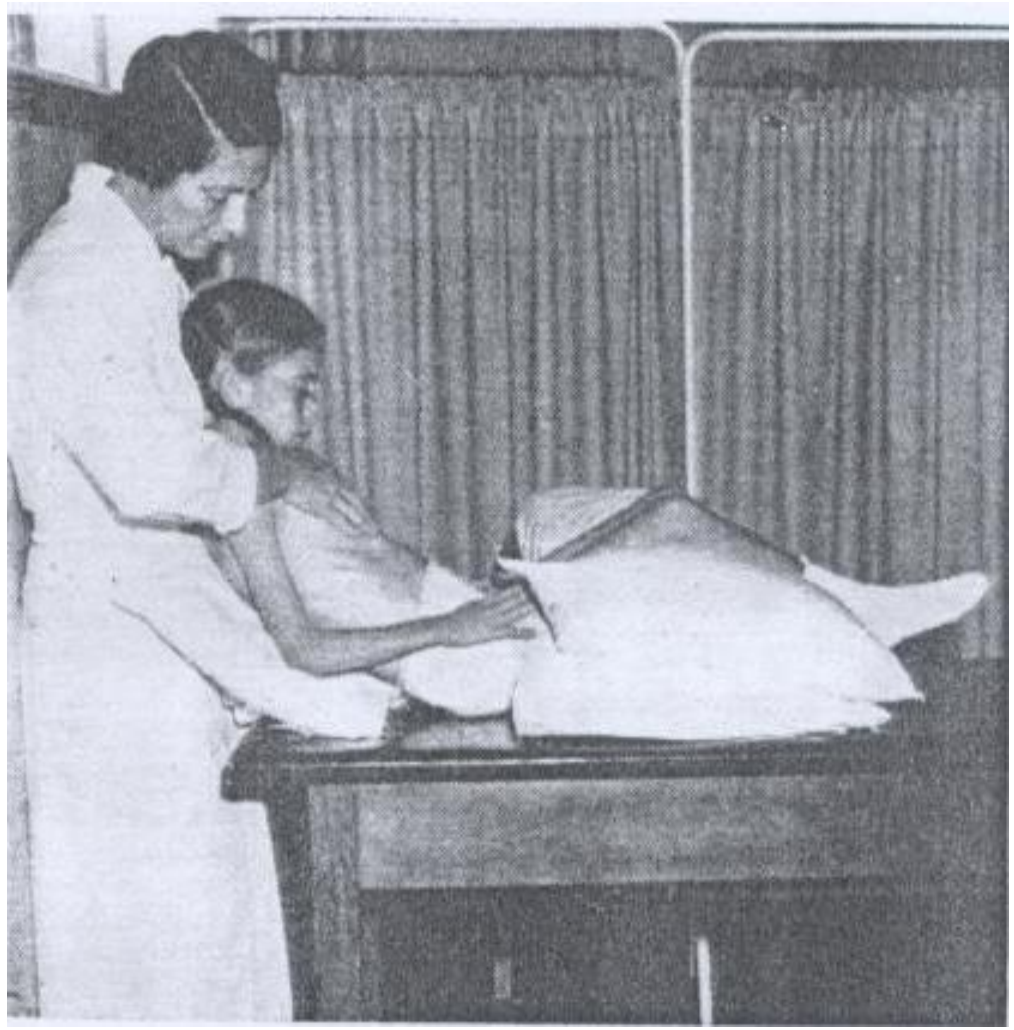


igure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, ve months. B. Lungs at one year, two months. C. Lungs at two years, ve months. When infection becomes established in the viscid secretion the bronchioles at an early age, and persists, the lungs show progres- ve development of peribronchial infiltration and emphysema. The atritional state deteriorates with advance of the infection. (Repro- uced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the ancreas in Infants and Children, *J. Pediat., 34:*663 (1949) with per- mission of C. V. Mosby, St. Louis.)



Benefits of Newborn Bloodspot Screening (NBS) for CF

What is CF NBS?

All Wales CF NBS program

UK CF NBS program

Incidence of CF in Europe

Sweat test is the diagnostic test for CF

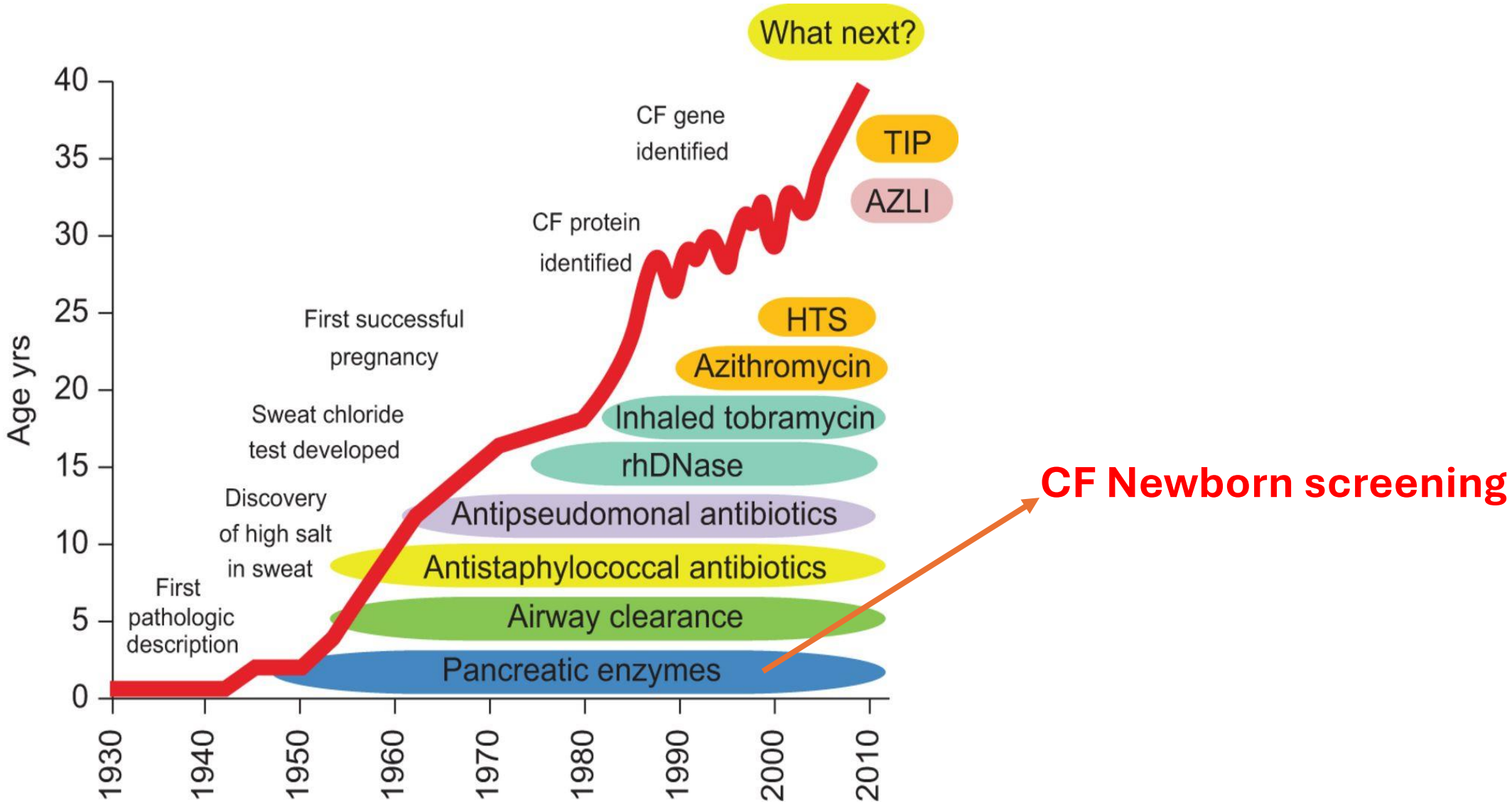
CF NBS is not a diagnostic test

Case history & Parent experience

Key take home messages

In the era of CF modulators

Schematic illustration of how the introduction of novel cystic fibrosis (CF) therapies influenced patient survival over the decades.



J. Stuart Elborn Eur Respir Rev 2013;22:3-5

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Impact of CF NBS in the UK

Advantages

- **Improved nutritional outcomes**: help prevent malnutrition and improve growth.
- **Improved pulmonary outcomes**: have better lung function and delayed onset of PA infection. Fewer chest morbidity.
- **Improved child survival**
- **Better quality of life and longer life span**
- **Less expensive than traditional diagnosis**: Screening seems less expensive than traditional diagnosis.
- **Prenatal counselling for parents in future pregnancies**

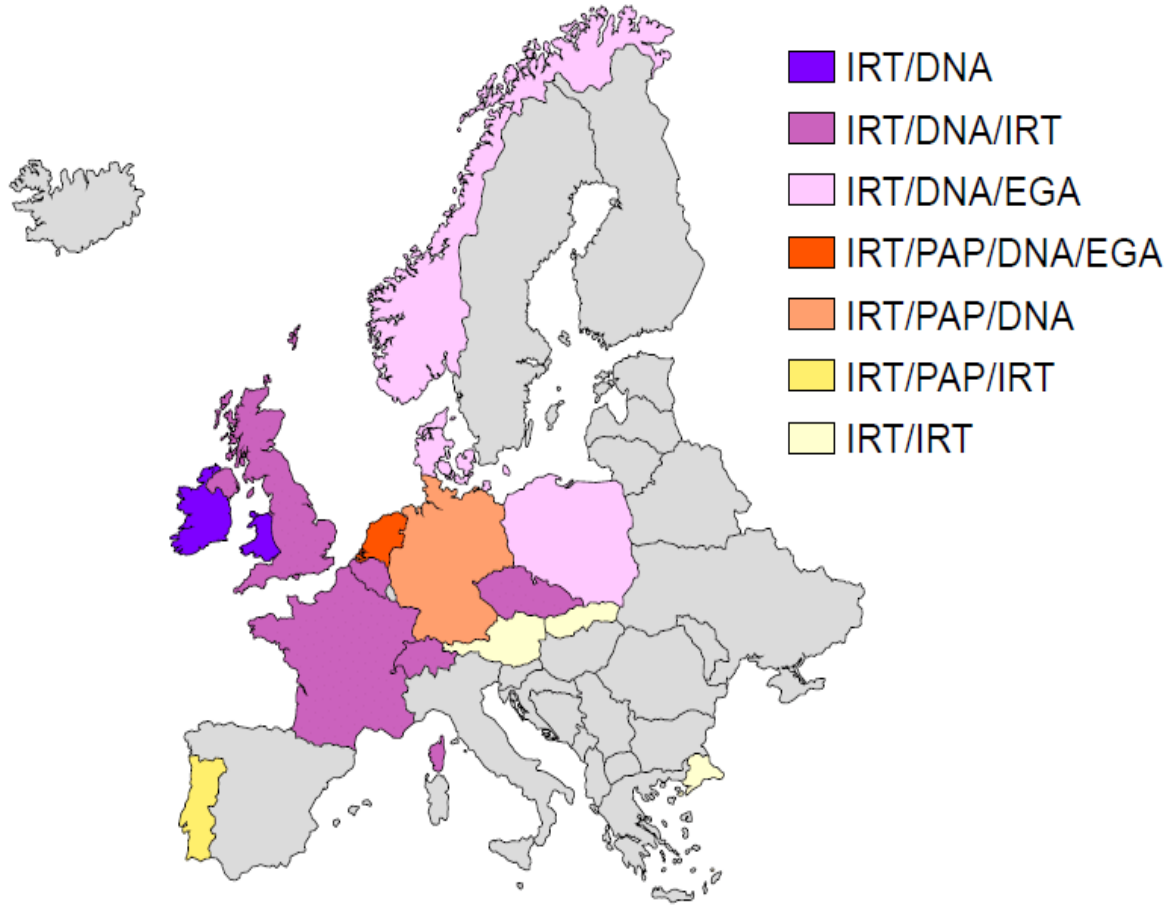
Disadvantages

- **Carriers identified**
- **False negatives and false positives**
- **Medicalisation of infants with equivocal results:** detection of CF screen positive indeterminate diagnosis (CFSPID)

KW Southern, MM Merelle, JE Dankert-Roelse *et al.* Cochrane Database Syst Rev. 2009;CD001402

CF blood-spot newborn screening

- Combination of biochemical and genetic tests.
- All protocols consist of multiple tiers of testing but all test dried blood spot immunoreactive trypsinogen level (IRT) as the first biochemical assay which when significantly raised will trigger further testing for CF mutation analysis.
- The sequence of tests after IRT is diverse, depending on local geographic, ethnic, legal and economic situation.

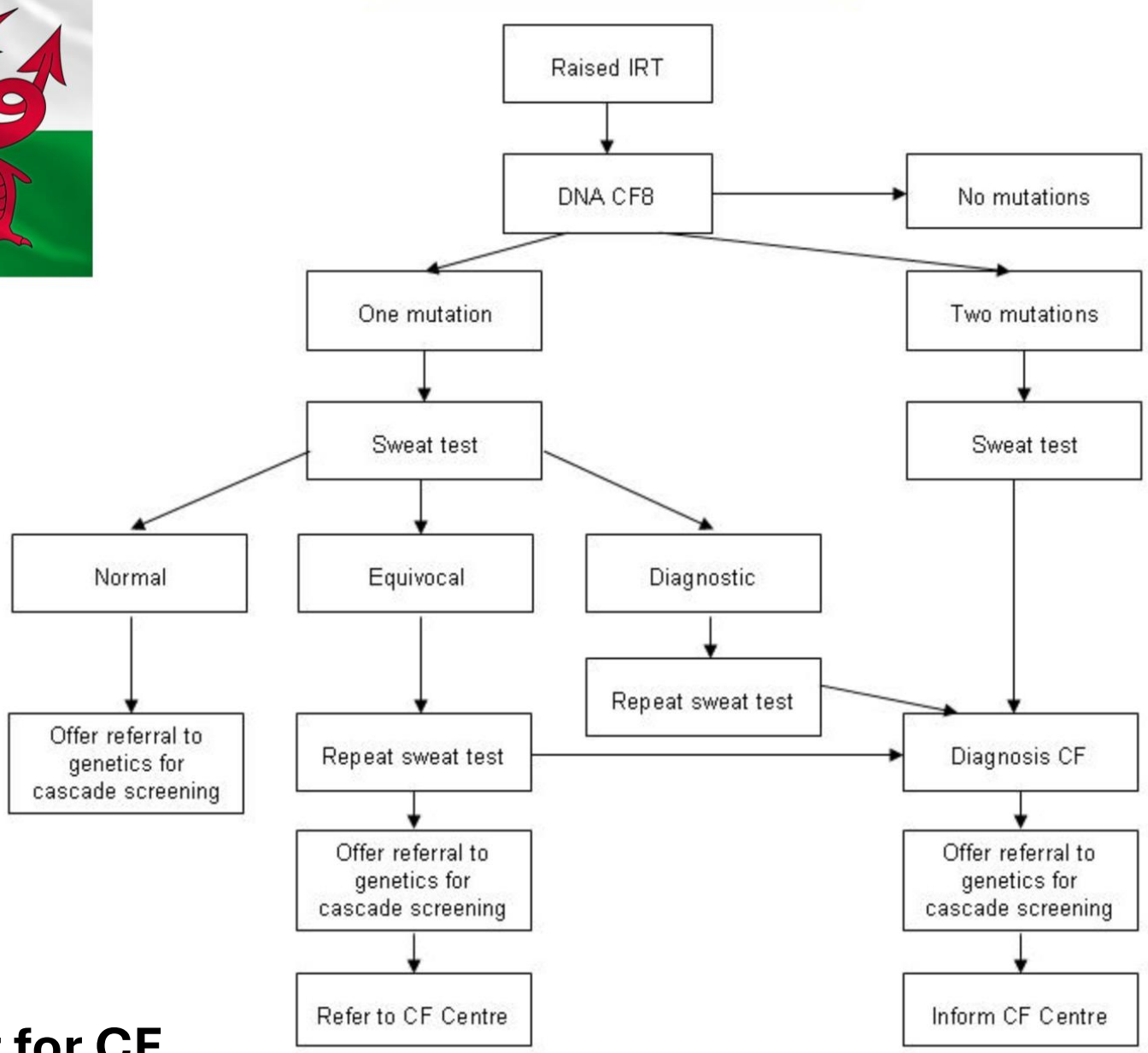


All Wales CF NBS programme

Screen positive NBS:

- Dried blood spot IRT raised to >99.5th centile (57mcg/l) with one or more of CF 8 variants identified referred to clinical team.
- **Safety netting:** IRT > 170mcg/l with no mutations, referred to clinical team

Sweat test is the main diagnostic test for CF



All Wales CF NBS algorithm

All Wales CF NBS programme

- Started in Dec 1996 based on IRT-DNA protocol. DNA analysis consist of the CF8 panel.
- 871, 000 babies were screened.
- 4758 with high IRT on blood spot were referred for CF8 mutation analysis.
- 22 babies per year are referred to clinical teams for diagnostic sweat testing which they received by 21-28 days old.
- 273 babies have been diagnosed with CF through newborn screening
- All diagnosis were made in CF NBS babies by 28 days old.

Cystic fibrosis newborn screening: the importance of bloodspot sample quality

Iolo Doull ,[1] Christopher William Course ,[1] Ruth E Hanks,[1] Kevin W Southern,[2] Julian T Forton,[1] Lena P Thia,[1] Stuart J Moat[3,4]

Archives Dis Child 2021;106:253-257.

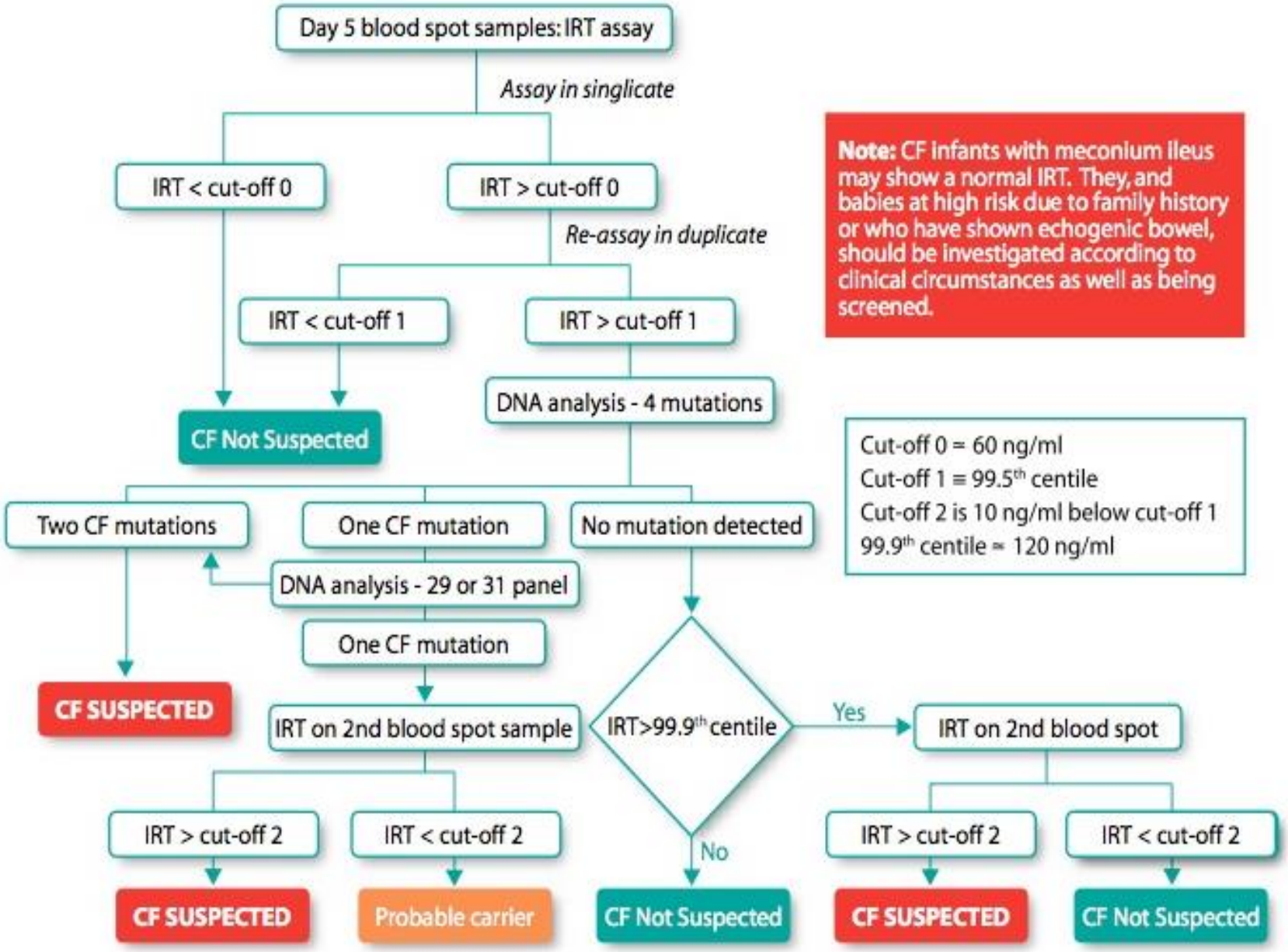
- IRT/ DNA analysis in Wales has high sensitivity (97%) and positive predictive value (0.476)
- False negative results were due to poor sampling on Guthrie card for NBS prick test.
- Education and teaching to improve the quality of sampling for Guthrie test ; improve the sensitivity of the CF NBS programme.

UK CF NBS programme

Started in 2007.
IRT-DNA-IRT protocol.

Pro: minimize detection of unaffected carriers. Reduce the number who require sweat testing

Con: cost of complexity in the screening pathway. Increase uncertainty and anxiety for families needing a second IRT. Later diagnosis in those positive needing second IRT.



Causes of false negative and false positive CF NBS

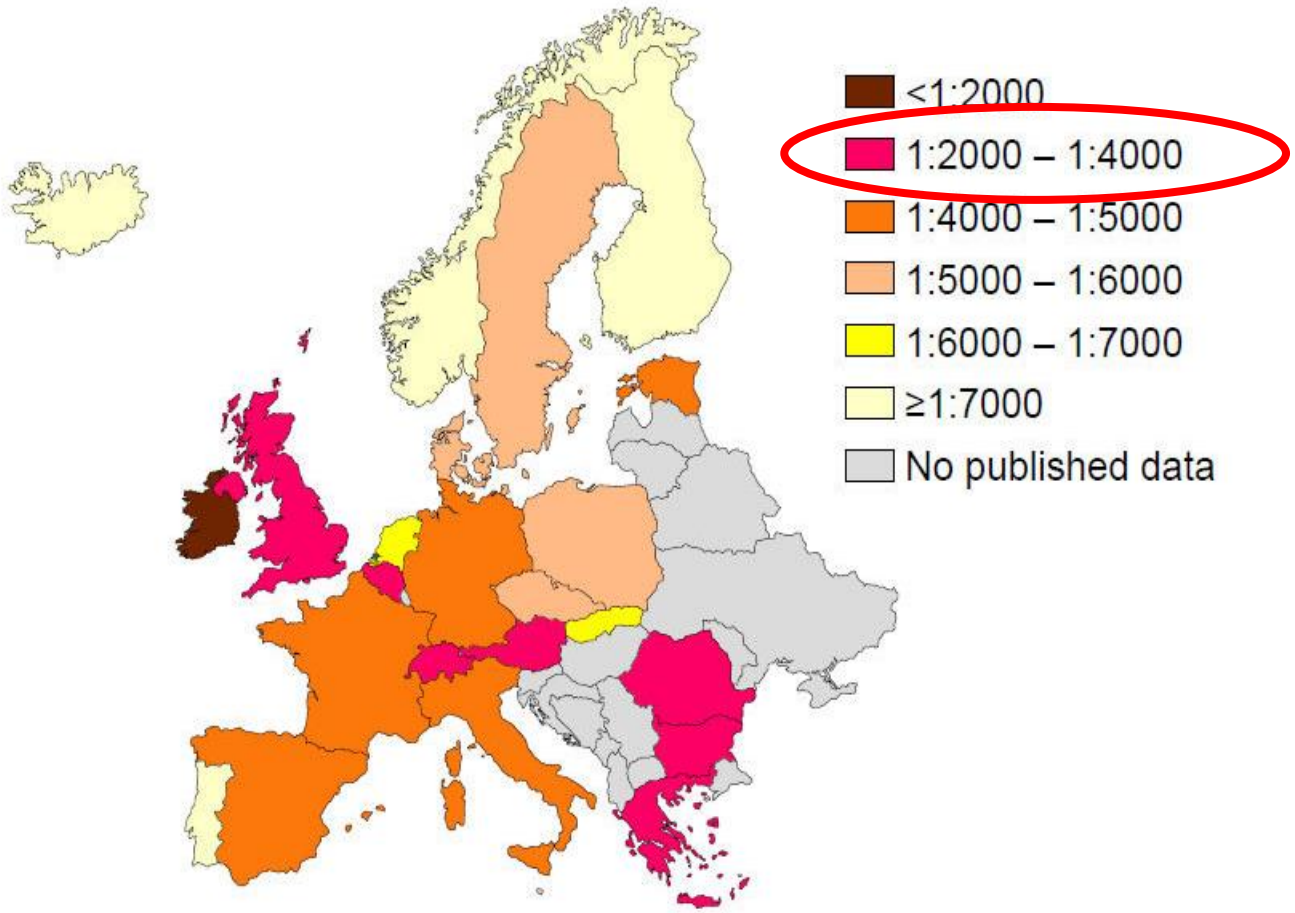
False Negative

- Meconium ileus/ echogenic bowel
- Viral acute gastroenteritis or respiratory illness
- Premature or small-for-dates babies
- Congenital heart disease
- Gastroschisis
- Galactoasemia
- Taken too late (cannot rely in blood spot IRT if heel prick is >8 weeks)
- Poor sampling of dried blood spot
- Blood transfusion
- Infants of CF mothers on Kaftrio/ Kalydeco

False Positive

- Clinically very ill or malnourished infants/ preterm infants
- Test is taken too early
- Laboratory error

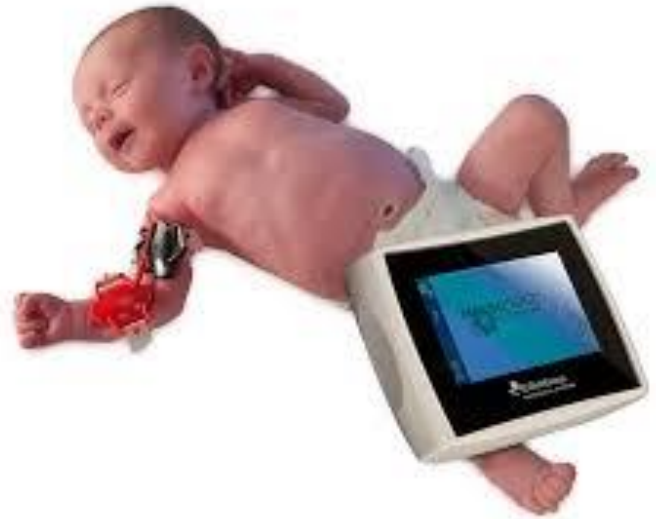
Incidence of CF in Europe



Incidence of CF in Wales (since newborn screening)

96/97 to 05/06	1:2941
06/07 to 15/16	1:3728
16/16 to 23/24	1:4317

Sweat testing

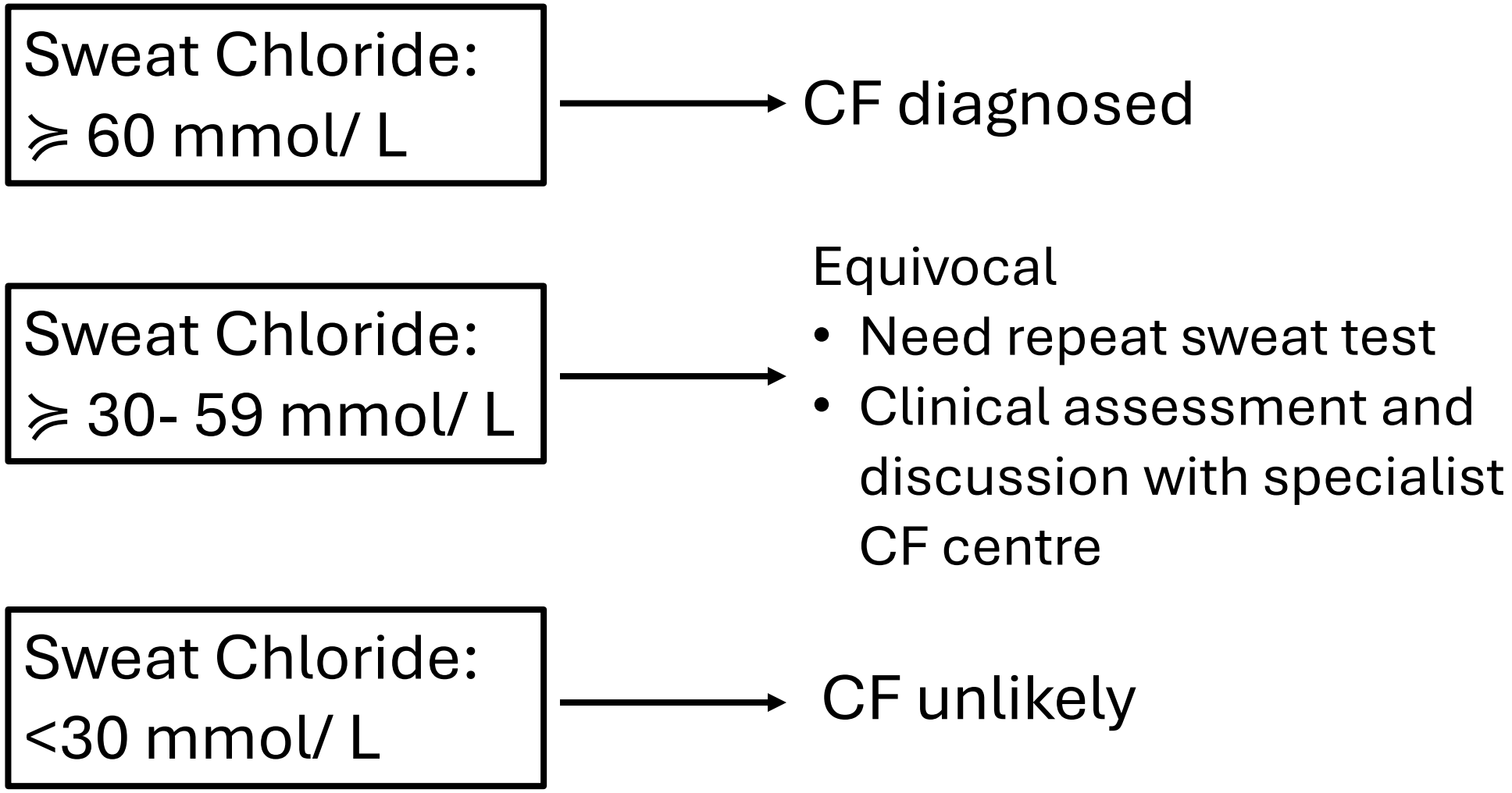


- Two staged test: sweat induction and collection
- Timing of test:

✓ At least > two weeks old or corrected gestation at least 36 weeks. Do not perform if <48h after birth

✓ Weighs more than 2-3 kg

Outcomes of sweat test



JV Pagaduan, M Ali, M Dowlin *et al*. Revisiting sweat chloride tests results based on recent guidelines for diagnosis of cystic fibrosis. Practical Laboratory Medicine 10 (2018) 34-37

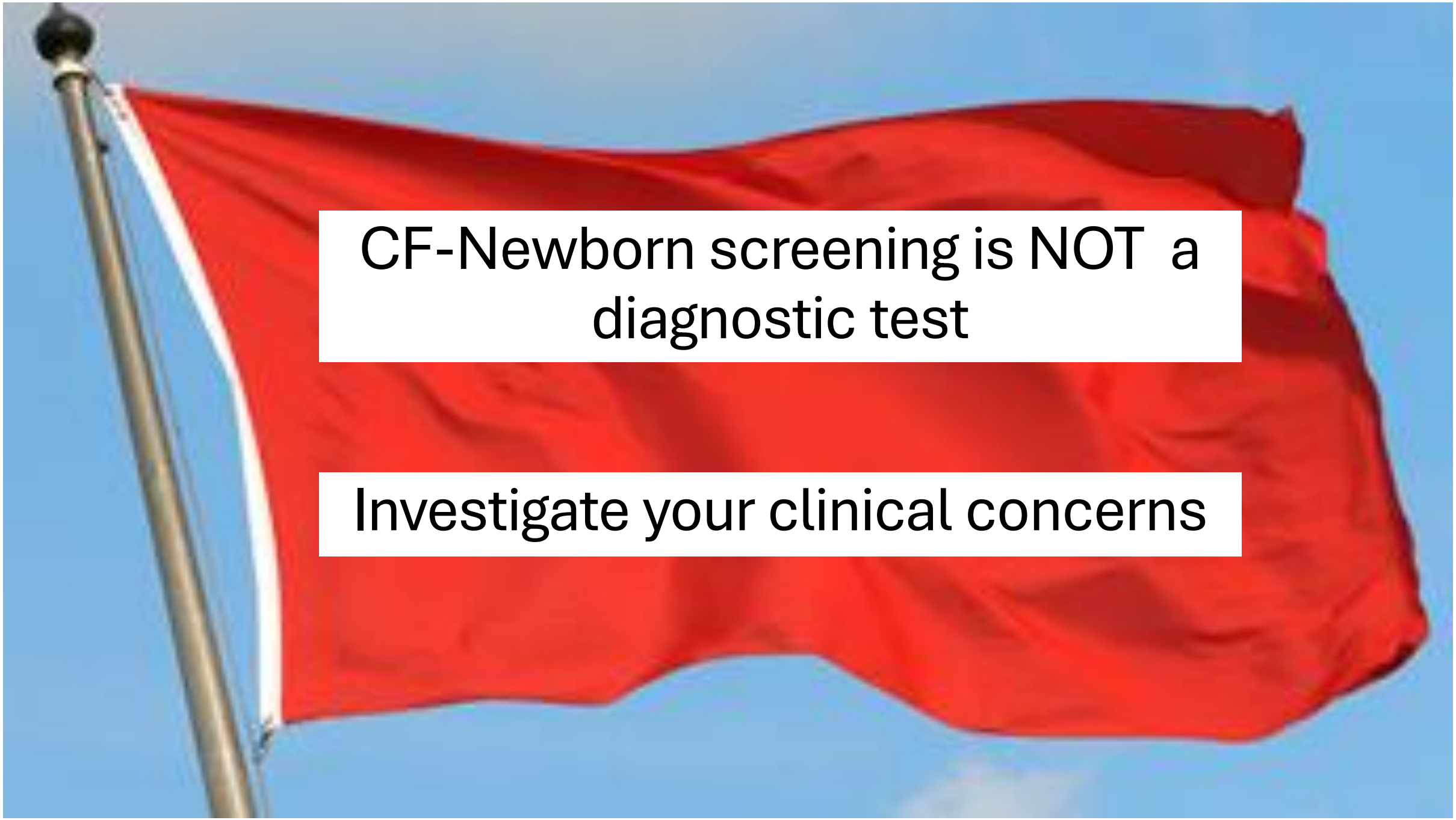
Causes of false negative and false positive sweat tests

False Negative

- Improper testing technique
- Inadequate sweat collected and analysed
- Oedematous patient

False Positive

- Improper testing technique
- Atopic dermatitis/ Ectodermal dysplasia
- Untreated adrenal insufficiency
- Glycogen storage disease
- Hypothyroidism
- Pancreatitis
- Panhypopituitarism
- Hereditary nephrogenic diabetes insipidus
- Medications: topiramate


CF-Newborn screening is NOT a diagnostic test
Investigate your clinical concerns

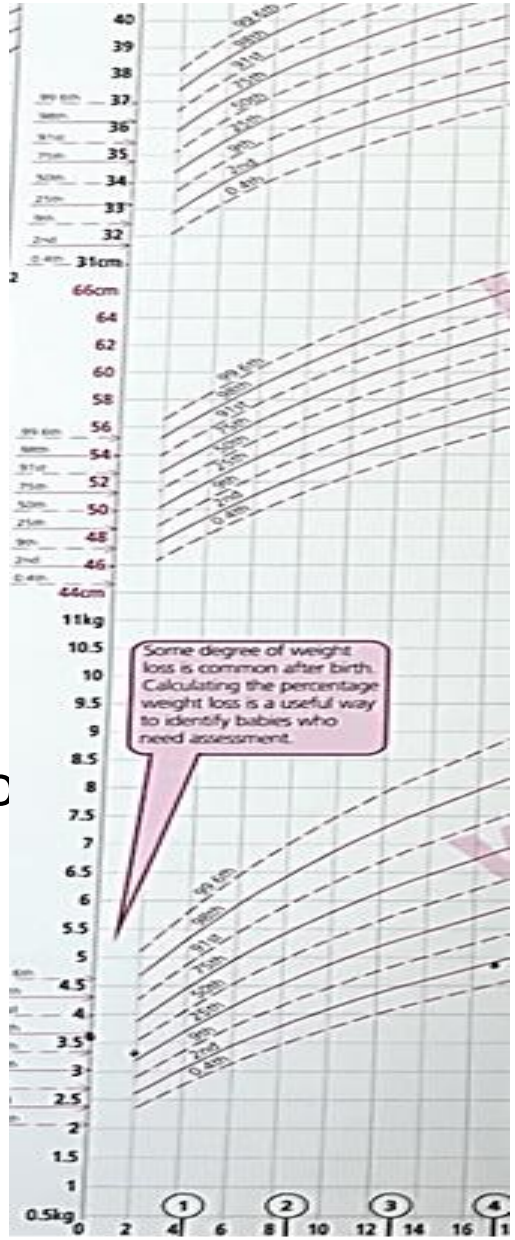
Case Study

- Born at term by breech delivery. No antenatal concerns.
- Frequently unsettled with vomiting and possets.
- Frequent loose stools.
- Suboptimal weight (Birth weight on 75th centile dropped to 25th centile at 2 months)

- Saw medical professionals; diagnosed as having cow's milk protein intolerance and was put on cow's milk protein free milk.

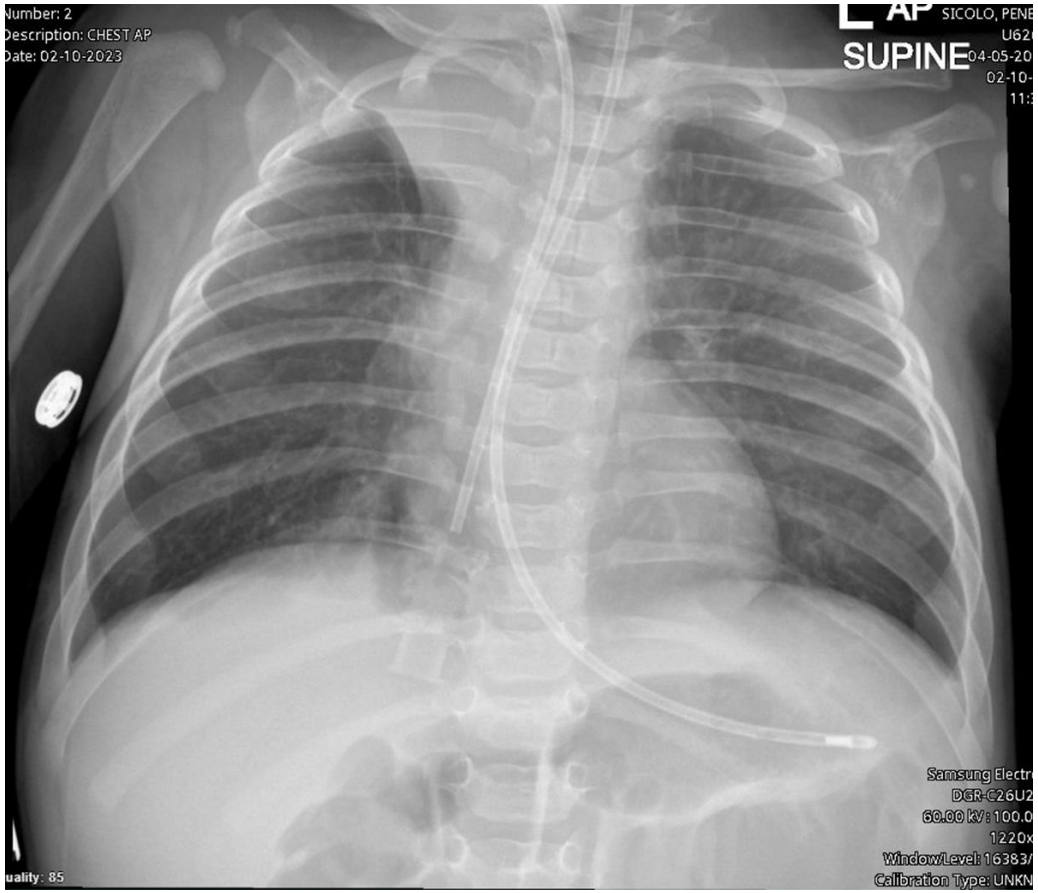
Case Study

- At 4 month old, she presented to the local hospital acutely with worsening cough, breathlessness and poor feeding.
- From early days, she has fast breathing and frequent cough.
- Weight has dropped across three centiles to the 2nd centile from birth; faltering growth.
- Shiny loose stools



Investigations

- **Chest Xray**: right upper lobe consolidation
- **Sweat test**: 95 mmol/l
- **Faecal elastase** <15mcg/gm: confirming pancreatic insufficiency
- **Cough swab**: staph aureus and pseudomonas aeruginosa
- **Guthrie card**: good sample collected at Day 6. Normal IRT 49 (well below the level for genetic analysis)
- **Genetics**: F508del/ 489+1 G→T

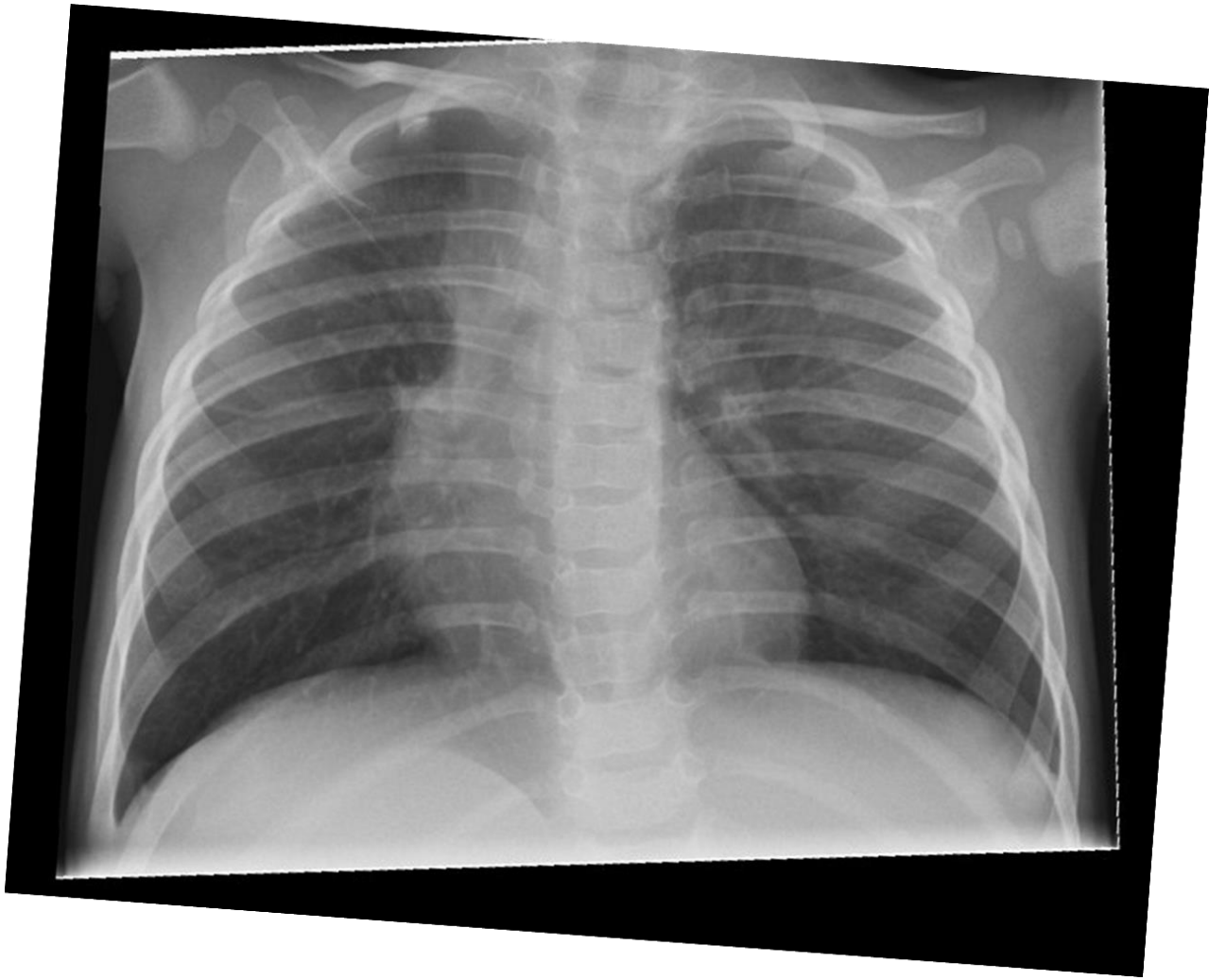


Management

- Commenced on IV antibiotics locally and transferred to UHW for further treatment under the care of the CF team
- Commenced on nebulized mucolytics and chest physiotherapy
- Bronchoscopy and bronchoalveolar fluid: Pseudomonas aeruginosa (non mucoid), staph aureus, achromobacter xylosidans
- Commenced on creon
- One month hospital stay:
  - Intensive nebulized mucolytics (DNAse and hypertonic saline) and chest physiotherapy.
  - Nutritional supplements via nasogastric tube feeding and creon
  - Lots of education and psychological support for parents

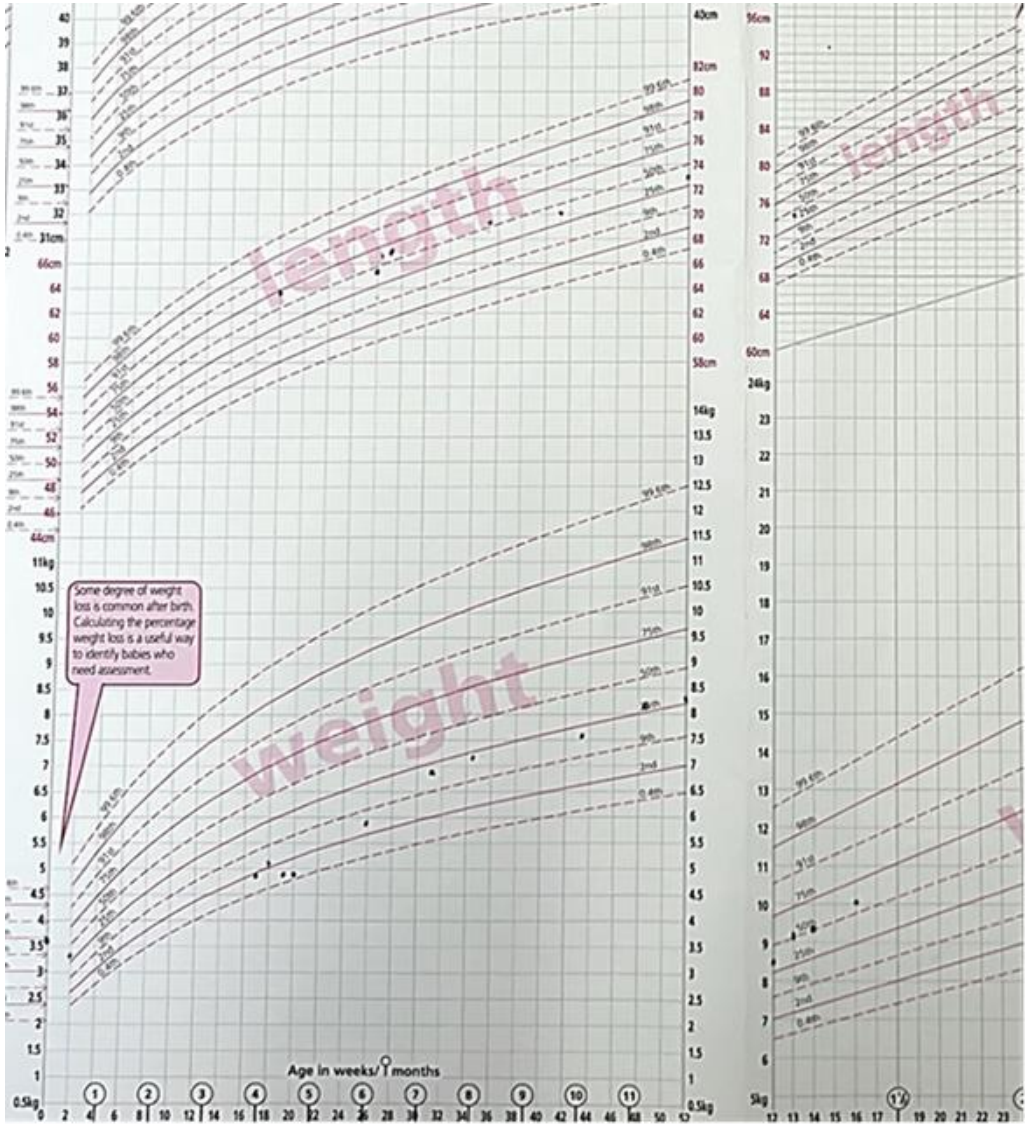
Progress in the last 12 months

- She has re-isolated Pseudomonas aeruginosa and is currently on second cycle of nebulized antibiotics eradication therapy.
- Chest Xray still has evidence of partial right upper lobe collapse/ atelectasis although much improved from first Xray at presentation.

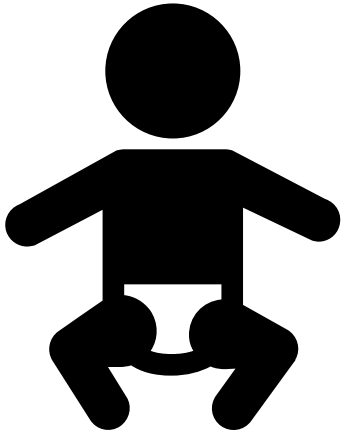


- No steatorrhoea
- Weight increased from 2nd centile at diagnosis (4 months old) to 50-75th centile (16 months)

- Parents has split up although she sees dad frequently
- Mum suffers from anxiety and can be disorganized with her care.
- Receives lots of support from the CF MDT regularly with home visits



Parent experience: “I thought I had a perfectly healthy baby”



Penelope mp3.mp3

Key take home messages

Timely and accurate diagnosis will lead to early treatment which has a great impact on health outcomes for CF

CF newborn screening is NOT a diagnostic test. Always investigate your clinical concern with a sweat test

Clear communication can reduce misconceptions and improve understanding of CF and improve outcomes

Many thanks to the multi-disciplinary teams of South, West Mid and North Wales Paediatric CF Network

Thank you for listening. Happy to take questions.

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