Diagnostic challenges after NBS for CF

A greater degree of complexity than was anticipated

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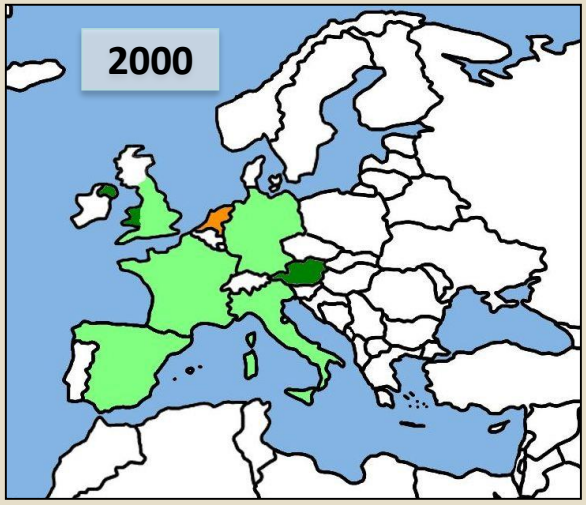
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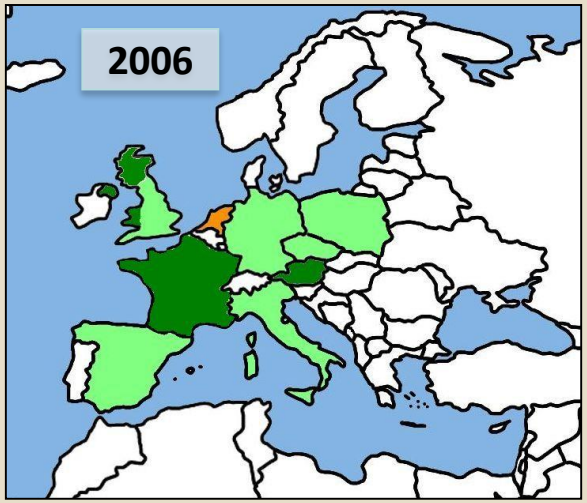
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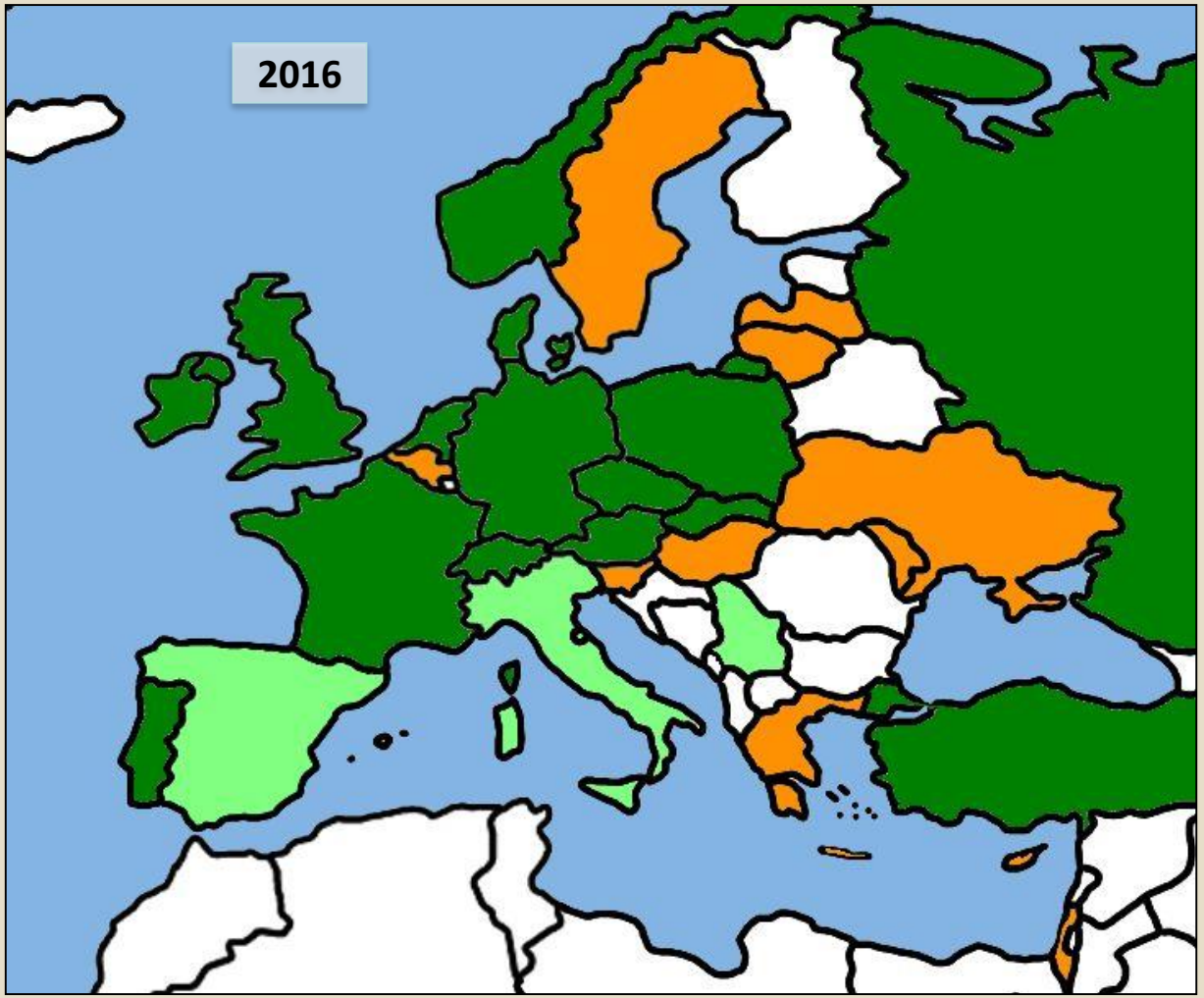
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Journal of Cystic Fibrosis

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Original Article

The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe

Jürg Barben [a,*], Carlo Castellani [b], Jeannette Dankert-Roelse [c], Silvia Gartner [d], Nataliya Kashirskaya [e], Barry Linnane [f], Sarah Mayell [g], Anne Munck [h], Dorota Sands [i], Olaf Sommerburg [j,k], Simon Pybus [l], Victoria Winters [l], Kevin W Southern [l]

Recent ECFS exercise

- 16 national programmes provided data
- 13 with performance data for 2014
  - Including false negatives and CFSPID
  - Sensitivity adequate for most
  - PPV less good
  - Timeliness an issue
- Considerable variability
- Enormous potential to drive forward CF care
  - Not always realised

Mean Number of Infants
IRT
Healthy
CF
2500
2000
1500
1000
500
300
200
60
30
10
0
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
270
285
300
315
330
345
360
375
390

Mean Number of Infants
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345
360
375
390
IRT

Processing a positive result

- Multi-agency working is key to performance
  - Especially if DNA analysis used
- Timeliness is important
  - But this is not a medical emergency
- Interface with family is vulnerable point
  - Clear information
  - Preparedness (reduce the acute anxiety of false+ results)
  - Sweat test and clinical assessment

The need for a sweat test

- CFTR gene characterisation
- The CFTR-2 project
  - Baltimore, Cutting and Sosnay
  - >200 mutations characterised
    - CF causing (272)
    - Mutations of varying clinical consequence (19)
    - Non CF causing (12)
    - Mutations of unknown significance (3)
- Bergougnoux et al. (27117206)

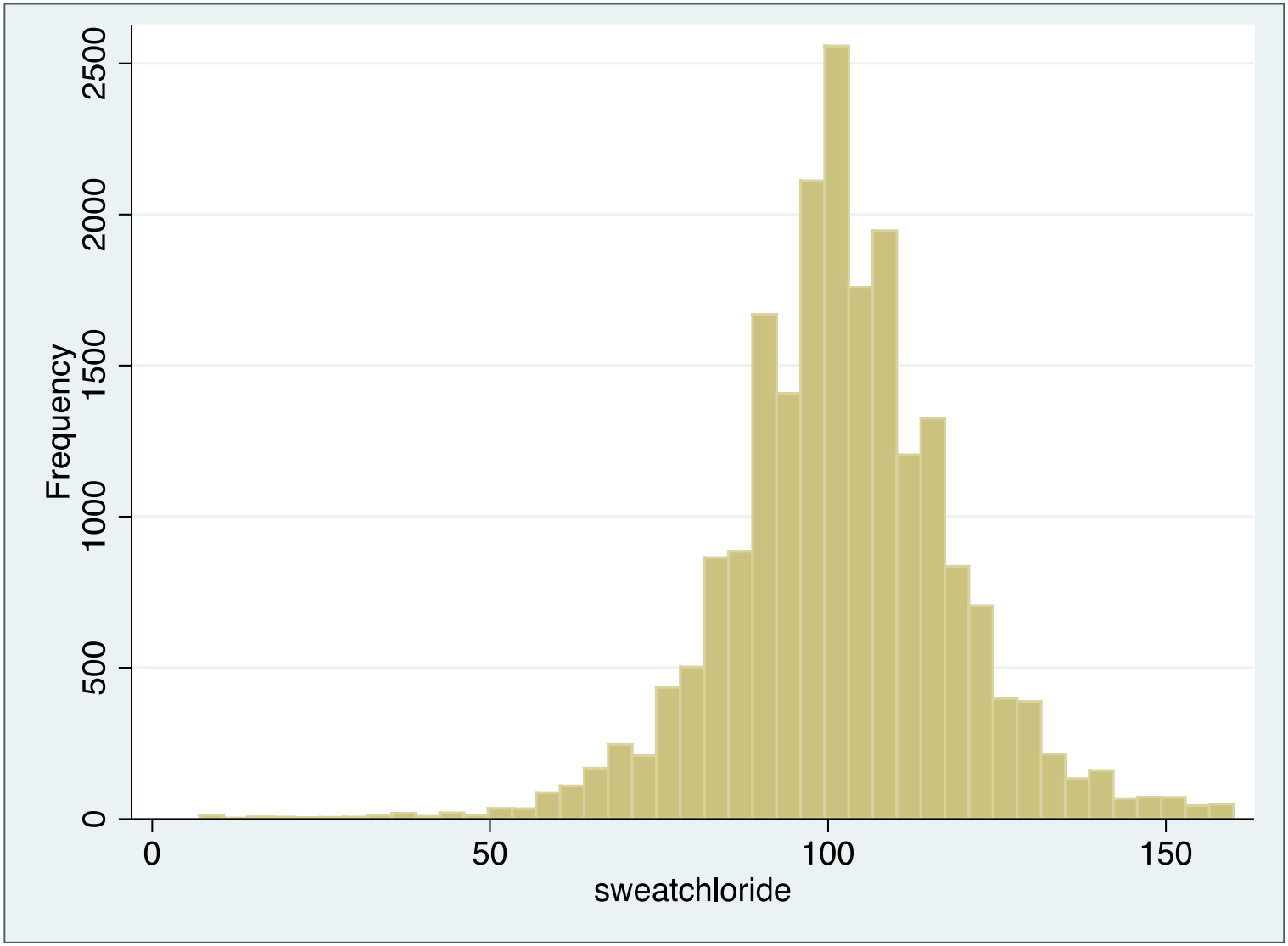
The challenge of sweat testing

- Smaller and younger population
  - Increased QNS rates
  - Obsolete equipment
  - Centralisation of laboratory services (increasingly undertaken by clinical staff)
  - Sweat conductivity
- ECFS survey, Cirilli and colleagues
- Grimaldi et al (26074372)
  - A concern, recommending less sweat testing!

Do we still need to sweat test?

- YES
- ECFS/CTN SOPs
- NBS guidance
- Recent international exercise
- Provides a physiological phenotype


NANODUCT
WESCOR



Thanks to Patrick Sosnay and the CFTR-2 team

Carrier recognition

- Presented as a “useful result”
- Is carrier recognition a false positive result?
- Acute anxiety around the result
  - Need for timeliness and efficient processing
- UK “second-IRT” approach
  - Anxiety still extreme
- Longer term issues
  - Disclosure, when or if ever?

Unclear diagnosis after NBS

- An infant with a positive newborn screening result and,
  - One or no mutations and a repeatedly intermediate sweat chloride value (30-59)
  - Two CFTR mutations, one of which has unclear phenotypic consequences and a normal sweat chloride

- Please note “Atypical CF” and “CFTR-related disease” are not appropriate terms for these infants as in both these scenarios patients have presented clinically

Journal of Cystic Fibrosis 8 (2009)71-78

A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis

Mayell S [a], Castellani C [b], Munck A [c], Craig J [a] , Southern KW [a]
on behalf of the ECFS Screening Working Party

[a] *University of Liverpool, Liverpool, United Kingdom*

[b] *Cystic Fibrosis Center Azienda Ospedaliera, Verona, Italy*

[c] *AFDPHE, Paris, France*

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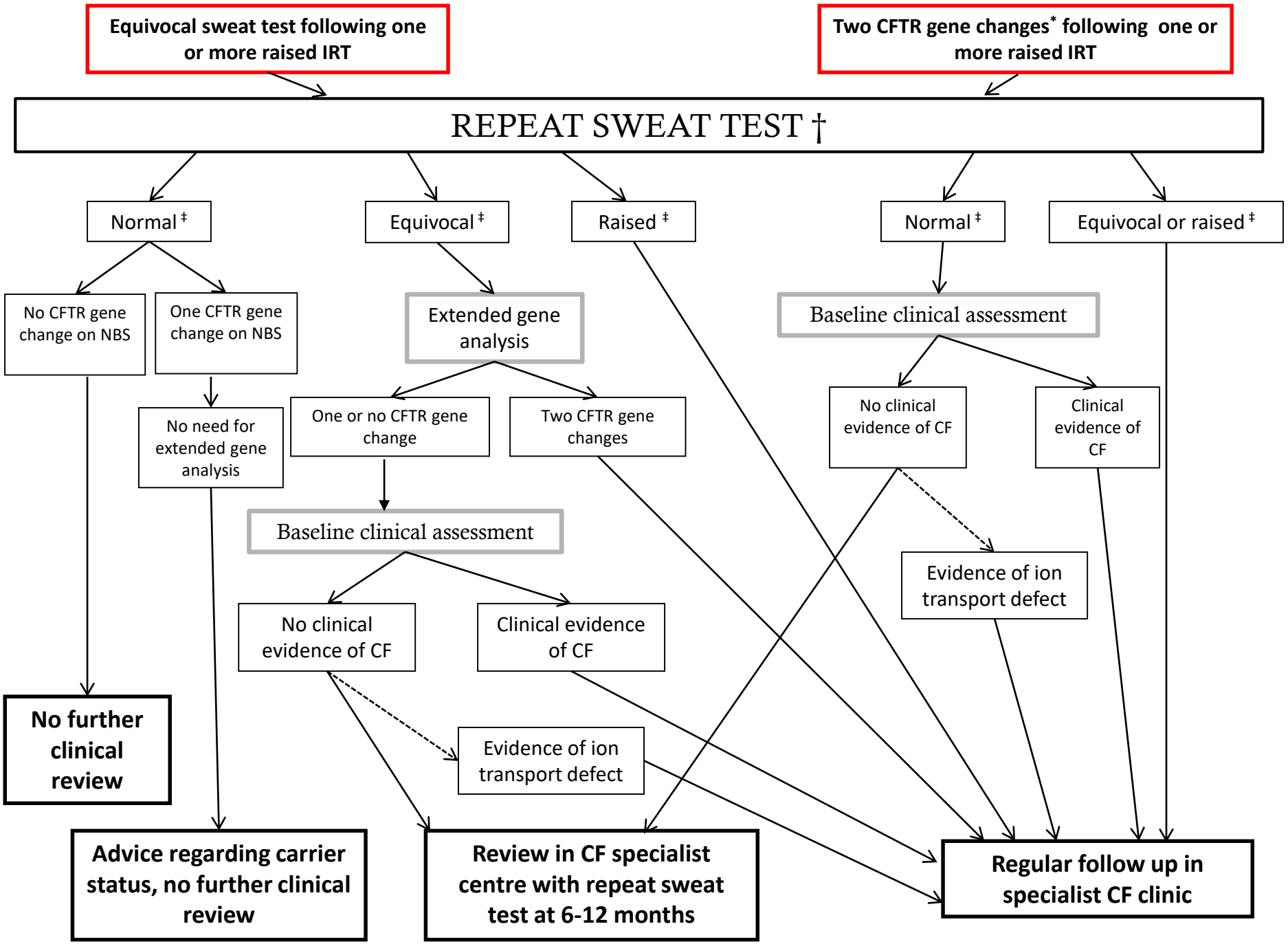
Equivocal sweat test following one or more raised IRT
Two CFTR gene changes* following one or more raised IRT
REPEAT SWEAT TEST †
Normal ‡
Equivocal ‡
Raised ‡
Normal ‡
Equivocal or raised ‡
No CFTR gene change on NBS
One CFTR gene change on NBS
Extended gene analysis
Baseline clinical assessment
No need for extended gene analysis
One or no CFTR gene change
Two CFTR gene changes
No clinical evidence of CF
Clinical evidence of CF
Baseline clinical assessment
Evidence of ion transport defect
No clinical evidence of CF
Clinical evidence of CF
No further clinical review
Evidence of ion transport defect
Advice regarding carrier status, no further clinical review
Review in CF specialist centre with repeat sweat test at 6-12 months
Regular follow up in specialist CF clinic

Unclear diagnosis after NBS

- IRT is a sensitive test
  - Castellani et al. Am J Med Genet A. 2005 (15832355)
- European guidance
  - Mayell et al. JCF 2009 (PMID 20605539)
- CFF guidance
  - Borowitz et al. J Pediatr 2009;155:106-16 (19914443)
  - CFTR-related metabolic syndrome (CRMS)
    - ~1 in 10 infants registered on the US Registry

SUPPLEMENT www.jpeds.com • THE JOURNAL OF PEDIATRICS

Cystic Fibrosis Foundation Practice Guidelines for the Management of Infants with Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome during the First Two Years of Life and Beyond

Drucy Borowitz, MD, Richard B. Parad, MD, MPH, Jack K. Sharp, MD, CM, Kathryn A. Sabadosa, MPH, Karen A. Robinson, PhD, Michael J. Rock, MD, Philip M. Farrell, MD, PhD, Marci K. Sontag, PhD, Margaret Rosenfeld, MD, MPH, Stephanie D. Davis, MD, Bruce C. Marshall, MD, and Frank J. Accurso, MD

Through early detection, newborn screening (NBS)[1] for cystic fibrosis (CF) offers the opportunity for early intervention and improved outcomes. NBS programs screen for hypertrypsinogenemia, and most also identify mutations in the CF transmembrane conductance regulator (CFTR) gene. Individuals identified by NBS are diagnosed with CF if they have an elevated sweat chloride level or if they have inherited 2 disease-causing mutations in the CFTR gene. Mutations in the CFTR gene can cause CF, but not all CFTR mutations are disease-causing. The term *CFTR-related metabolic syndrome* (CRMS) is proposed to describe infants identified by hypertrypsinogenemia on NBS who have sweat chloride values <60 mmol/L and up to 2 CFTR mutations, at least 1 of which is not clearly categorized as a "CF-causing mutation," thus they do not meet CF Foundation guidelines for the diagnosis of CF. With what is now near-universal CF NBS in the United States, an increasing number of infants with CRMS are being identified. Given our inadequate knowledge of the natural history of CRMS, standards for diagnosis, monitoring, and treatment are absent. This document aims to help guide the monitoring and care of individuals with CRMS while our knowledge base on appropriate management evolves. *(J Pediatr 2009;155:S106-16)*.

Second European Project

Mayell, Munck, Shawcross, Barben, Derichs and Southern

- Management of infants with an equivocal diagnosis
- Variable across Europe
  - Within regions
  - Within clinics!
- Delphi exercise
  - Core group statements

Designation of infants

Round 1:

"Physicians should avoid using terms such as CFTR-related metabolic syndrome (CRMS) to designate these infants as this may lead to unnecessary medicalisation"

80% group A
76% group B

Designation of infants

- Majority did not agree with use of term CRMS

BUT

- Majority suggested need for a label

  communication (family & professional)

  justify follow up

  healthcare funding

Designation exercise

Infants with an unclear diagnosis following NBS,

- Should not be labeled
- Should be called "Screen-positive not CF" (SPCF)
- Should be called "Screen Positive Equivocal Diagnosis of CF" (SPEDCF)
- Should be called "CFTR related metabolic syndrome" (CRMS)
- Should be called "Equivocal CF Diagnosis" (EDCF)
- Should be called "Pre-CF"
- Should be called "Risk of CF"
- Should be called "non-classical CF"
- Should be called "Inconclusive CF Diagnosis" (IDCF)
- Should be called "Unclear CF Diagnosis" (UDCF)
- Any other suggestion, please write below

Please note CFTR-related disorder and Atypical CF are not appropriate designations as these terms refer to specific clinical presentations outlined by the ECFS Diagnostic Network statements.

Designation exercise

Infants with an unclear diagnosis following NBS,

- Should not be labeled
- Should be called "Screen-positive not CF" (SPCF)
- Should be called **"Screen Positive Equivocal Diagnosis of CF" (SPEDCF)** (33%)
- Should be called **"CFTR related metabolic syndrome" (CRMS)**
- Should be called "Equivocal CF Diagnosis" (EDCF)
- Should be called "Pre-CF"
- Should be called "Risk of CF"
- Should be called "non-classical CF"
- Should be called **"Inconclusive CF Diagnosis" (IDCF)** (27%)
- Should be called "Unclear CF Diagnosis" (UDCF)
- Any other suggestion, please write below

Please note CFTR-related disorder and Atypical CF are not appropriate designations as these terms refer to specific clinical presentations outlined by the ECFS Diagnostic Network statements.

Designation exercise

- Options emailed to NSWG and DNWG
- 63 replies
- 92% agreed with use of label
- Importance of “screen positive”
- Core group review + DNWG + US QIC
- New term, CFSPID, offered for Round 2

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Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening

A. Munck [a,b], S.J. Mayell [c], V. Winters [d], A. Shawcross [c], N. Derichs [e], R. Parad [f,g], J. Barben [h], K.W. Southern [c,d,]

Pubmed ID number 25630966

- A1 Infants should be followed up in specialist CF clinic. If they are seen in a non-CF clinic they should be reviewed by a CF physician (or a physician with an interest in CF).
- A2 For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection.
- A3 Infants should undergo a repeat sweat test aged 6-12 months. Depending on genotype, a further sweat test may be considered in the second year of life.
- A4 Infants should be reviewed in clinic between 6 and 12 months of age, and thereafter annually (or more frequently, as indicated by clinical concerns or family anxieties).
- A5 Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated.
- A6 Families should be fully informed regarding their child's genetic and biochemical results. They should understand that their child does not have a definitive diagnosis of cystic fibrosis and that this will be reviewed annually.
- A7 Reflecting the absence of a clear diagnosis, the term "Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)" should be used to describe these infants.
- A8 Clinicians should review the CFTR-2 website at the annual review for new information regarding the infant's genotype and discuss these findings with the family.
- A9 Families and the primary care physician should be given clear information as to how to contact the CF team in the following situations; failure to gain weight adequately, persistent loose stools or persistent respiratory symptoms (more than 2 weeks).
- A10 Children should receive routine childhood immunizations.
- A11 Children should not be exposed to cigarette smoke.
- A13 Children and their families should be encouraged to adopt a healthy
- lifestyle consistent with national guidance on exercise, nutrition and other
- aspects of public health policy.
- A14 Families should be offered a referral for genetic counselling.
- A15 Details of infants in this group should be kept on an appropriate national database.
- *A12 Did not reach consensus (79% agreement). Respiratory cultures should be taken routinely at annual review and when clinically indicated.*

Management themes

- More active approach for infants with an intermediate sweat chloride value
- Management based on clear information and referral pathways
  - A “hands off” approach
- Some marked difference of opinion with respect to the need for regular respiratory culture
  - Local practice recommended

Long-term outcomes for children with CFSPID

- Canadian/Italian experience
  - Ooi et al. (25963003)
- Sidney experience
  - Groves et al. (25812778)
- US experience (registry trial)
  - Ren et al. (21538969)
- Limited conversion to CF
  - Depends on the programme and population screened
  - Age 2 years is optimal time for repeat sweat test

CFSPID graduation

Should CFSPID graduate to CFTR-RD?

- Children with CFSPID are at increased risk of developing a CFTR-RD (Bombieri et al. 2011)
- CFTR related disorder is a condition which is not cystic fibrosis but likely relates to CFTR dysfunction (CBAVD is the clearest example)
- If children with CFSPID develop clinical characteristics of CF, is it appropriate to call them CFTR-RD
  - Probably not

What about graduation to normality?

- When should these children be discharged from follow-up, if at all
- No consensus as yet
- In reality most families "vote with their feet"
- If the child is going to school (age 5-6 years) and has not had any clinical features characteristic of CF, it seems unlikely that they will develop CF
- Increased risk of CFTR-RD needs outlining

International exercise

- Move towards “harmonisation”
- The following term will be recommended
  - CRMS/CFSPID

SUPPLEMENT www.jpeds.com • THE JOURNAL OF PEDIATRICS

Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation

Philip M. Farrell, MD, PhD[1], Terry B. White, PhD[2], Clement L. Ren, MD[3], Sarah E. Hempstead, MS[2], Frank Accurso, MD[4], Nico Derichs, MD[5], Michelle Howenstine, MD[3], Susanna A. McColley, MD[6], Michael Rock, MD[1], Margaret Rosenfeld, MD, MPH[7], Isabelle Sermet-Gaudelus, MD, PhD[8], Kevin W. Southern, MBChB, PhD[9], Bruce C. Marshall, MD[2], and Patrick R. Sosnay, MD[10]

Objective Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis criteria.

Study design To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with *CFTR* mutations. An a priori threshold of ≥80% affirmative votes was required for acceptance of each recommendation statement.

Results After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and a second round of voting.

Conclusions It is recommended that diagnoses associated with *CFTR* mutations in all individuals, from newborn to adult, be established by evaluation of CFTR function with a sweat chloride test. The latest mutation classifications annotated in the Clinical and Functional Translation of CFTR project (http://www.cftr2.org/index.php) should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis; these terms are now merged and equivalent, and CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis may be used. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes for use in diagnoses associated with *CFTR* mutations are included. *(J Pediatr 2017;181S:S4-15).*

PMID number; 28129811

Concluding statements

- What we know and what we don't know

Processing a positive result

- What we know
  - Varied practice
  - Timeliness is a factor
  - Sweat testing is critical
  - Evaluation of performance requires large datasets over long time periods
- What we don't know
  - The holistic impact of CF diagnosis
    - A bio-ethical approach
  - The impact of timeliness on longer term outcomes

Carriers

- What we know
  - DNA analysis increases carrier recognition
  - Larger panels increase carrier recognition
  - Carrier recognition continues to cause short term anxiety and misunderstanding
- What we don't know
  - The longer term implications for the family and the child
  - The ethical judgement on not disclosing carrier status (masking techniques)

CRMS/CFSPID

- What we know
  - Difficult time for families
  - Most will be well
  - Small number develop clinical features consistent with CF
- What we don't know
  - When can we release these children from a medical diagnosis
  - What is the *a priori* risk of developing a CFTR-related disorder?

Summary

- Processing a positive NBS result is complex
  - A job for a CF specialist team
- How we screen has a direct impact on outcomes
  - Carrier recognition
  - CFSPID
  - Bio-ethical implications are not clear
- Data is needed
  - Clear recording of infants with CFSPID/Carriers
  - Focus on outcome

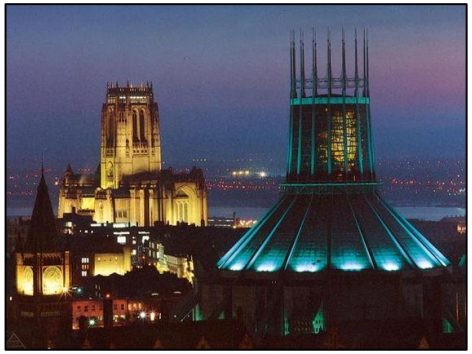
Thanks

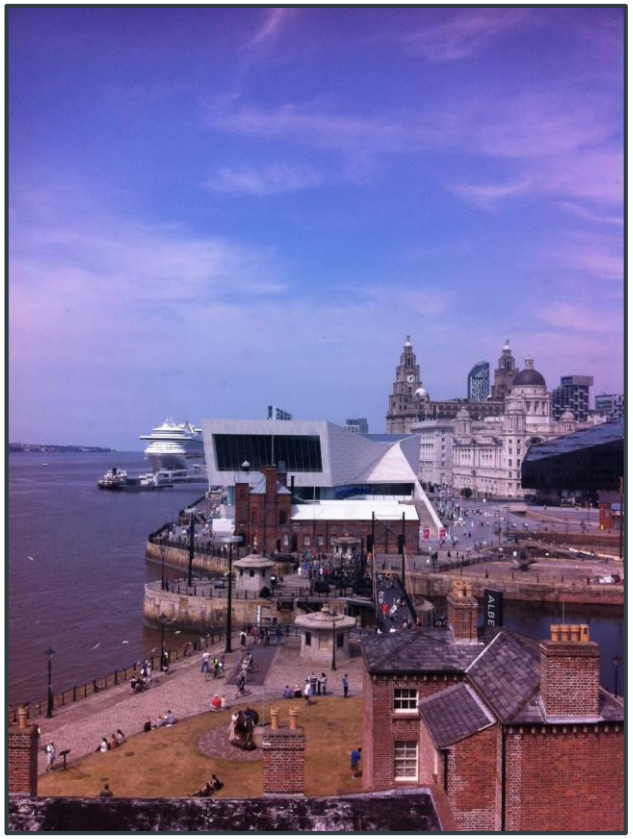
- Vicki Winters, Jurg Barben and Anne Munck
- Natalia Cirilli
- Core Committee of the NSWG
- Carlo Castellani
- Harmonisation committee
  - Clement Ren

- kwsouth@liverpool.ac.uk

Liverpool 2019

European CF conference





Istanbul 2005