Journal of Cystic Fibrosis xxx (2019) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Short Communication

# Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition

K.W. Southern [a,*], J. Barben [b], S. Gartner [c], A. Munck [d], C. Castellani [e], S.J. Mayell [f], J.C. Davies [g], V. Winters [a], J. Murphy [a], D. Salinas [h], S.A. McColley [i], C.L. Ren [j], P.M. Farrell [k]

[a] Department of Women's and Children's Health, University of Liverpool, Liverpool, UK
[b] Division of Paediatric Pulmonology, Children's Hospital, St Gallen, Switzerland
[c] Paediatric Pneumonology and Cystic Fibrosis Unit, University Hospital Vall d'Hebron Barcelona, Spain
[d] Paediatric Cystic Fibrosis Centre, Hopital Robert Debré, Paris, France
[e] Cystic Fibrosis Centre, Gaslini Institute, Genoa, Italy
[f] Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, UK
[g] Imperial College, London, UK
[h] Children's Hospital Los Angeles, Pediatric Pulmonology Division, Department of Paediatrics, Keck School of Medicine, University of Southern California, Los Angeles, USA
[i] Division of Pulmonary Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, USA
[j] Division of Pediatric Pulmonology, Allergy and Sleep Medicine, Department of Pediatrics, Indiana University, Indianapolis, USA
[k] Department of Pediatrics and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

ARTICLE INFO

*Article history:*
Received 11 March 2019
Revised 10 April 2019
Accepted 10 April 2019
Available online xxxx

Newborn bloodspot screening (NBS) for cystic fibrosis (CF) is a successful public health strategy with a considerable impact on the well-being of young people with CF [1]. Most infants with a positive NBS result for CF will have either a clear diagnosis of CF (true positive NBS result) or CF excluded (false positive NBS result), however a small but significant number will have an inconclusive diagnosis. This is a challenging situation for families and for healthcare professionals [2].

There has been progress over the past ten years with respect to the evaluation, designation and management of these infants. This includes a global harmonisation process undertaken in 2016, with a publication in 2017, which provided a consistent international approach and definition [3,4]. A recent survey undertaken by the European CF Society (ECFS) with support from the Cystic Fibrosis Foundation (CFF) NBS Quality Improvement Group revealed significant confusion with respect to the designation of infants with inconclusive results after a positive NBS test (Online appendix for summary). The survey, which will be presented at the 2019 European CF Conference, demonstrated that doctors who classified themselves as CF specialists were as likely to be wrong with diagnostic options as those who classified themselves as respiratory pediatric consultants. In light of these results, we felt it important to highlight and clarify the published harmonised definition [3].

## 1. Background

Newborn bloodspot screening for CF results in the recognition of a small number of infants with a positive screening result but an inconclusive diagnosis, irrespective of the screening protocol used. The proportion of inconclusive diagnosis increases when NBS protocols use larger DNA panels and extended gene sequencing to identify cystic fibrosis transmembrane conductance regulator (*CFTR*) gene variants [5]. A number of bodies have considered the evaluation and management of infants with these findings. An expert group convened by the CFF produced the diagnostic designation CFTR-related metabolic syndrome (CRMS) to describe these infants [6]. This term is consistent with the World Health Organisation International Disease Classification system (aligned with CF) and is a designation that enables access to insurance funds for healthcare in the US. In Europe, a panel of experts embarked on a Delphi consensus exercise to determine guidance on the evaluation of infants in this situation [7]. At this time, the consensus group did not provide a designation for these infants as it was considered that a "name" might increase the risk of over medicalisation. A subsequent ECFS consensus determined agreement that a designation would be useful and, after wide stakeholder engagement, the term CF Screen Positive, Inconclusive Diagnosis (CFSPID) was adopted [8].

## 2. Global harmonisation exercise

There was cross Atlantic acknowledgement that having two terms to describe these infants was unsatisfactory and at a large international meeting supported by the CFF, there was consensus that the terms should be amalgamated to a joint CRMS/CFSPID designation with a consistent definition (Fig. 1) [3]. The harmonised definition reflected the increased capacity of the cftr2 website (https://www.cftr2.org/) to

* Corresponding author at: Institute in the Park, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK.
*E-mail address:* kwsouth@liv.ac.uk (K.W. Southern).

https://doi.org/10.1016/j.jcf.2019.04.010

Harmonised definition for Cystic Fibrosis Transmembrane Conductance Regulator- Related Metabolic Syndrome (CRMS)/Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) definition

***The designation CRMS/CFSPID should be applied to an infant with;***
***A positive NBS result for CF***
***AND EITHER***
***A sweat chloride value < 30 mmol/L and 2 CFTR variants* (mutations), at least one of which has unclear phenotypic consequences***
***OR***
***An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF causing variants** (mutations)***

*the term "variant" is now preferred to "mutation", which was used in original paper. (3)
**Information on CFTR variant characterisation can be accessed at https://www.cftr2.org/

**Fig. 1.** Harmonised definition for Cystic Fibrosis Transmembrane Conductance Regulator- Related Metabolic Syndrome (CRMS)/Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) definition [3].

characterise *CFTR* variants as "CF causing", "non-CF causing", "varying clinical significance" or "unknown significance" [9]. The key difference between previous definitions of CFSPID and CRMS and the new harmonised definition was the inclusion of "CF causing variant" for the infants with an intermediate sweat chloride (30–59 mmol/L). Consequently an infant with two *CFTR* variants and an intermediate sweat chloride will now be designated as CRMS/CFSPID if only one variant is characterised as CF causing (Fig. 2). This is in contrast to the previous ECFS definition of CFSPID, in which infants with two *CFTR* variants and an intermediate sweat chloride would be referred for CF care.

## 3. What does this harmonised designation mean for healthcare professionals?

There is guidance for the early evaluation of infants with an inconclusive diagnosis after a positive NBS result for CF [6,7]. Key points include the organisation of a second sweat test to measure sweat chloride in a centre with a high level of experience. Infants with only one *CFTR* variant recognised and a normal repeat sweat chloride (<30 mmol/L) should be reported as carriers and no further testing undertaken. Infants with a CRMS/CFSPID designation are well and have no clinical features consistent with a diagnosis of CF. A positive outcome from the consensus exercises has been a move away from overmedicalising this situation and improved communication with families. It is important, however, that these infants continue to have regular clinical review by physicians with an interest in CF, as they have a risk to develop significant clinical features consistent with CF.

## 4. What does this mean for families?

This is an extremely unsettling situation for families; the traditional framework of health and disease is undermined [2]. Delivery of the

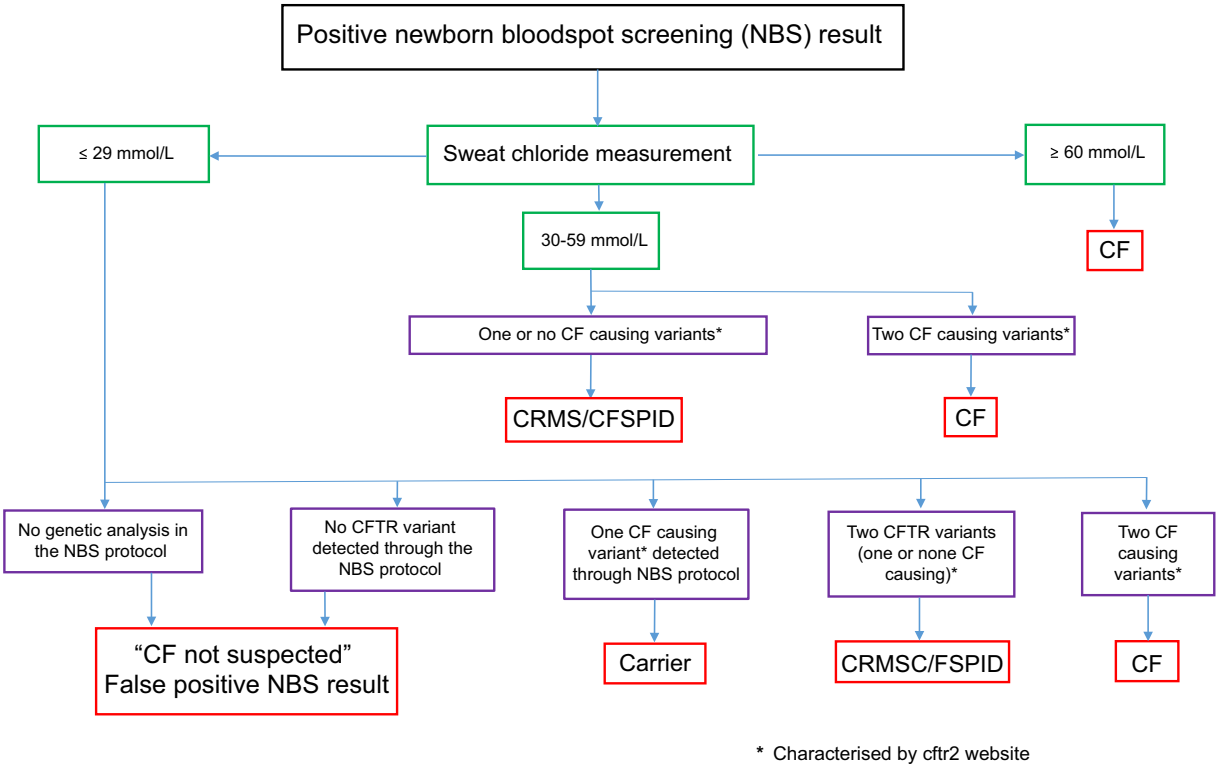


**Fig. 2.** An algorithm for the designation of infants following a positive newborn bloodspot screening (NBS) result. (CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator (gene); CRMS, CFTR-related metabolic syndrome; CFSPID, CF screen positive, inconclusive diagnosis; CRMS/CFSPID, harmonised definition)

Please cite this article as: K.W. Southern, J. Barben, S. Gartner, et al., Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clar..., Journal of Cystic Fibrosis, https://doi.org/10.1016/j.jcf.2019.04.010

initial positive NBS result and the subsequent inconclusive result places the family in a psychologically vulnerable position with oscillating emotions. It is essential that families have clear and precise information at all stages of this process, including the longer term risks that a child with CRMS/CFSPID faces, especially the development of a CFTR related disorder (CFTR-RD); a monosymptomatic clinical entity (for example, CBAVD/pancreatitis/bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF [3,10].

## 5. The outlook for these children

A number of infants with CRMS/CFSPID will develop clinical features consistent with a diagnosis of CF, and will be transitioned to a CF diagnosis (albeit a less typical form in most cases). This is more likely to occur for infants with an initial intermediate sweat chloride value [4]. In other CRMS/CFSPID infants, a diagnosis of CF may be established because of a subsequent positive sweat test result or from new knowledge reclassifying a *CFTR* variant as CF causing (https://www.cftr2.org/mutations_history). All infants with CRMS/CFSPID have a risk of developing a CFTR-RD, but the extent of this is not currently quantifiable and likely relates to individual *CFTR* variants [11–14]. The accurate designation of infants with CRMS/CFSPID is vital and facilitates the establishment of appropriate databases to monitor longterm outcomes. This information will provide a clearer assessment of risk for children with CRMS/CFSPID as they grow into adults.

## Conflicts of interest

There are no conflicts of interest.

## Acknowledgements

We would like to acknowledge Bruce Marshall and Judith Szypa, whose support was invaluable for the international harmonisation exercise, funded by the CFF.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.04.010.

## References

[1] Hoch H, Sontag MK, Scarbro S, Juarez-Colunga E, McLean C, Kempe A, et al. Clinical outcomes in U.S. infants with cystic fibrosis from 2001 to 2012. Pediatr Pulmonol 2018;53(11):1492–7.
[2] Hayeems RZ, Miller FA, Barg CJ, Bombard Y, Carroll JC, Tam K, et al. Psychosocial response to uncertain newborn screening results for cystic fibrosis. J Pediatr 2017;184:165–71 e1.
[3] Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017;181S:S4–S15 e1.
[4] Ren CL, Borowitz DS, Gonska T, Howenstine MS, Levy H, Massie J, et al. Cystic fibrosis Transmembrane conductance regulator-related metabolic syndrome and cystic fibrosis screen positive, inconclusive diagnosis. J Pediatr 2017 181S:S45-S51 e1.
[5] Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, et al. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe. J Cyst Fibros 2017;16(2):207–13.
[6] Borowitz D, Parad RB, Sharp JK, Sabadosa KA, Robinson KA, Rock MJ, et al. 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. J Pediatr 2009;155(6):S106–16 Suppl.
[7] Mayell SJ, Munck A, Craig JV, Sermet I, Brownlee KG, Schwarz MJ, et al. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. J Cyst Fibros 2009;8(1):71–8.
[8] Munck A, Mayell SJ, Winters V, Shawcross A, Derichs N, Parad R, et al. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): a new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. J Cyst Fibros 2015;14:706–13.
[9] Sosnay PR, Salinas DB, White TB, Ren CL, Farrell PM, Raraigh KS, et al. Applying cystic fibrosis Transmembrane conductance regulator genetics and CFTR2 data to facilitate diagnoses. J Pediatr 2017 181S:S27-S32 e1.
[10] Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros 2011;10(Suppl. 2):S86–102.
[11] Thauvin-Robinet C, Munck A, Huet F, Genin E, Bellis G, Gautier E, et al. The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening. J Med Genet 2009;46(11):752–8.
[12] Terlizzi V, Carnovale V, Castaldo G, Castellani C, Cirilli N, Colombo C, et al. Clinical expression of patients with the D1152H CFTR mutation. J Cyst Fibros 2015;14(4):447–52.
[13] Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology 2011;140(1):153–61.
[14] Salinas DB, Azen C, Young S, Keens TG, Kharrazi M, Parad RB. Phenotypes of California CF Newborn screen-positive children with CFTR 5T allele by TG repeat length. Genet Test Mole Bioma 2016;20(9):496–503.

Please cite this article as: K.W. Southern, J. Barben, S. Gartner, et al., Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clar..., Journal of Cystic Fibrosis, https://doi.org/10.1016/j.jcf.2019.04.010