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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,*]

[a] *Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant, Paris, France*
[b] *Assistance publique-Hôpitaux de Paris, Hôpital Robert Debré, CF Center, Université Paris 7, Paris, France*
[c] *Alder Hey Children's NHS Foundation Trust, Liverpool, UK*
[d] *University of Liverpool, Liverpool, UK*
[e] *Charité Universitätsmedizin, Berlin, Germany*
[f] *Harvard Medical School, Boston, USA*
[g] *Brigham and Women's Hospital, Boston, USA*
[h] *Children's Hospital, St. Gallen, Switzerland*

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Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) results in the recognition of a number of infants with a positive NBS result, but an inconclusive diagnosis. Varied practice exists with respect to the management of these infants.
Methods: A Delphi consensus approach was used to determine agreement on statements generated by a core group of specialists. A designation (naming) exercise was required after Round 1 and further expert opinion was sought to guide that process. After Round 2, a sensitivity analysis was undertaken to assess the impact of attrition on subsequent agreement levels.
Results: Infants were divided into group A (normal sweat chloride and two CFTR mutations, at least one of which has unclear phenotypic consequences) and group B (intermediate sweat chloride and one or no CFTR mutations). 32 statements were produced for Round 1 and 24 achieved consensus. After Round 1, a designation exercise was undertaken and the term "CF Screen Positive, Inconclusive Diagnosis (CFSPID)" was suggested for Round 2. Agreement was achieved for this statement and for all other statements aside from the need for routine respiratory culture, on which there was divided opinion. The core group advocated local practice for this issue. A sensitivity analysis demonstrated that consensus for Round 2 was achieved by change in opinion rather than attrition.
Conclusion: We have generated a new designation and statements to guide the management of infants with CFSPID through a robust international Delphi process. These statements will be a valuable tool for CF teams and will improve the consistency of management of these infants.

Keywords: Cystic fibrosis; Newborn screening; CRMS; CFSPID

1. Introduction

Newborn screening (NBS) for cystic fibrosis (CF) is a valid public health strategy for a population with a high incidence of the condition [1]. There has been rapid and considerable global

* Corresponding author at: Institute of Child Health, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK. Tel.: +44 151 2525054; fax: +44 151 2525456.
E-mail address: kwsouth@liv.ac.uk (K.W. Southern).

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expansion of this strategy over the past ten years with a wide variety of protocols employed [2]. All programmes rely on measurement of immuno-reactive trypsinogen (IRT) from a dried blood sample taken during the first week of life [2]. This is a sensitive screening test for CF, but a second tier test is needed to improve the specificity of the protocol. Second tier tests vary from programme to programme, and often include DNA analysis [3]. The diagnosis is confirmed by clinical assessment, DNA testing and measurement of chloride concentration in sweat (the sweat test).

In some cases the sweat chloride result may be intermediate or CFTR gene changes may be recognised, the phenotypic consequences of which are unclear. Previous work by this group produced a consensus guideline for the evaluation and early management of infants with an inconclusive or equivocal diagnosis following screening [4]. This work provided an algorithm for the investigation of these infants with a particular focus on communication with the families.

At the same time a consensus group in the US also considered this issue and developed guidelines with similar themes to the European guidelines [5]. The US group proposed a term for designation of these infants, cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS). This designation reflects the nomenclature stream under which CF is categorised in the US and the need for a diagnostic designation to comply with the US funding arrangements. The European guidelines did not propose a designation, advocating clear communication of this interim situation to the family.

Despite these two guidelines, it has become apparent through published commentaries and surveys of European programmes that diverse practice exists with respect to the management of these infants, ranging from early discharge with little information to the family to full CF care in a CF centre [6,7]. There is limited data on the long-term outcomes, but it is clear from epidemiological studies that a significant number will have minimal or no phenotypic consequence [8,9]. We also know from case reports that a small number will develop significant CFTR related airway disease that has an impact on their well-being and potentially their survival [10].

In view of this lack of consensus and the limited evidence base on which to guide treatment, the ECFS Neonatal Screening Working Group (NSWG) organised a further Delphi process to determine consensus on the management of these infants. This paper describes the method employed and the recommendations.

2. Methods

A core group (AM, AS, JB, KWS and SM) produced preliminary statements through a series of face-to-face meetings, teleconferences and email discussions. The level of evidence to support each statement was recorded. Once finalised by the core group, the statements were circulated by email to all members of two ECFS working groups (the Diagnostic Network and the Neonatal Screening Working Group). Additional invitations were made to increase multidisciplinary input. In total, 391 invitations were sent. It was determined, a priori, that an agreement level of 80% would constitute consensus, consistent with previous exercises by this group and work in other fields [4,11].

For Round 1, participants were asked to rate the statements by either agreeing or disagreeing. Participants in disagreement were asked to provide an alternative statement. Participants were encouraged to include comments, which were all assessed by the core group and influenced the altered statements for Round 2.

Following Round 1, the core group revised statements not achieving consensus taking into account comments and suggestions. When the meaning of a statement was changed these statements were called rewritten. Some statements that achieved consensus were modified, if the comments were felt to improve or clarify a statement. Modified and rewritten Round 2 statements were circulated to all respondents to Round 1, together with the original statements and comments.

During the consensus process it became apparent that most participants considered there was a requirement for a diagnostic label to classify infants with inconclusive diagnosis. A separate designation exercise (described more fully in Section 3) was therefore undertaken to determine consensus on a diagnostic term for these infants.

After Round 2, a sensitivity analysis was undertaken to determine if the result of Round 2 was a reflection of changing opinion or rather a consequence of attrition in the number of respondents. For participants that contributed to Round 2, we reassessed their responses to Round 1 to assess the impact on agreement. This analysis was to retrospectively assess the Delphi process and had no bearing on the final statements.

3. Results

The first outcome of the core group discussion was the decision that two sets of statements were necessary to reflect different degrees of clinical concern for infants with a normal sweat chloride value (<30 mmol L^{-1}) compared to infants with an intermediate sweat chloride value (30–59 mmol L^{-1}) [12].

- Group A, normal sweat chloride value (<30 mmol L^{-1})
- Group B, intermediate sweat chloride value (30–59 mmol L^{-1}).

Infants in Group A have two *CFTR* mutations, at least one of which has unclear phenotypic consequence. Infants in Group B have one or no *CFTR* mutations. Infants with two *CFTR* mutations and an intermediate sweat chloride should be referred to a CF clinic, as per previous consensus agreement [4].

Statements for Group B were associated with more active interventions. The decision to establish this grouping was subjective, after much discussion, and not based on any current evidence that infants in Group A have a better course than infants in Group B.

3.1. Round 1

32 statements were generated for Round 1 (Fig. 1).

Eighty-five responses from specialists in 25 countries (within and outside Europe) were received (22% response rate). Twenty-four of the 32 statements achieved a level of agreement over 80% (Fig. 1).

3.2. Designation exercise

In Round 1, specialists were asked to consider the statement,

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

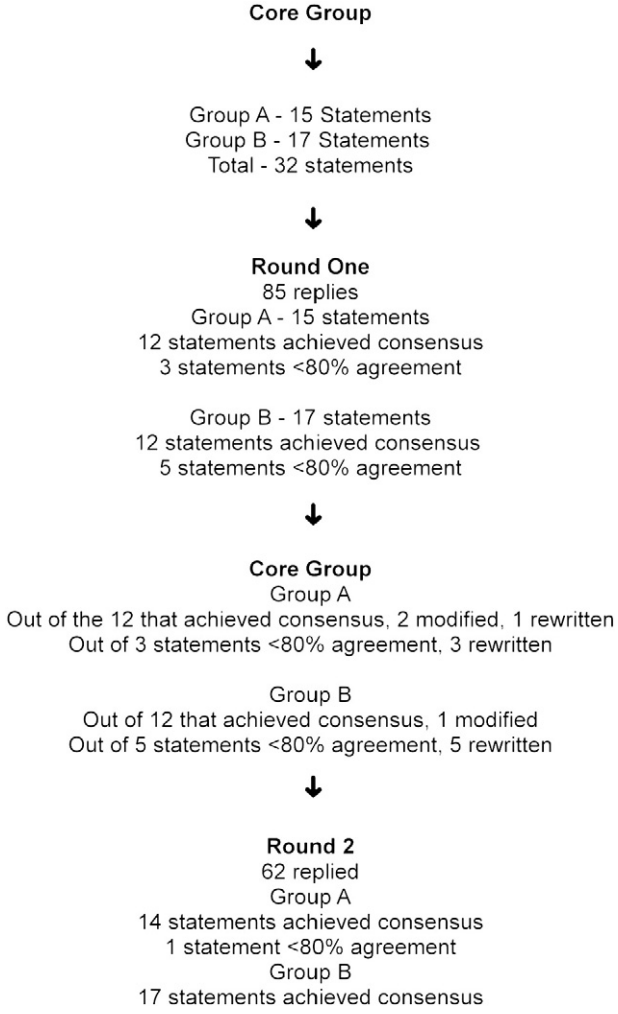

Fig. 1. An illustration of the phases of the Delphi process. The contributions at each phase are recorded. Statements that required a change in content were called rewritten. Some statements were modified (minor changes) to improve clarity, but with no change in meaning. Group A (normal sweat chloride value (<30 mmol L^{-1}) and two *CFTR* gene mutations, at least one of which has unclear phenotypic consequence) and Group B (intermediate sweat chloride value (30–59 mmol L^{-1}) and one or no *CFTR* mutations). Consensus was achieved if agreement was >80%.

This achieved an 80% agreement for Group A and 76% for Group B. It was clear from the comments that the majority of respondents considered that a consistent designation for these infants would be helpful for data collection and communication with families, but did not agree with the use of the term CRMS.

A list of 10 alternative designations (including "no label" option) was compiled by the core group from all the suggestions provided and circulated to the respondents from Round 1 as a separate designation exercise (Fig. 2). Sixty-three replies were received to the designation exercise. Fifty-eight respondents (92%) agreed with the use of a label, and it was clear from comments that including "screen positive" was an important part of the designation.

The results of this exercise were discussed by the core group and with representatives of the ECFS Diagnostic Network Working Group (ND) and the US Quality Improvement Consortium (RP). The designation exercise identified two clear favourites with respect to designation, "Screen Positive Equivocal Diagnosis of CF" and "Inconclusive CF Diagnosis" (Fig. 2). The core group and invited experts felt that a term that combined these statements would be ideal, as equivocal is a challenging word for some non-English speakers and it was felt important to include CF Screen Positive. The core group decided on the term Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) and a modified statement including this designation was circulated in Round 2. In Round 2, the statements (A7 and B7) advocating this term achieved 90% agreement for Group A and 92% for Group B.

3.3. Round 2

Eight statements did not achieve consensus in Round 1 and were all rewritten (3 from group A and 5 from Group B). Twenty-four statements (12 for each group) achieved agreement (>80%) in Round 1. Three of these (2 Group A, 1 Group B) were modified to improve clarity. One statement (on designation) was rewritten, despite achieving agreement for Group A. Three modified and nine rewritten statements were presented to the participants for Round 2 (Fig. 1).

Sixty-two responses were received for Round 2 (27% attrition rate). A consensus of greater than 80% was achieved on all six statements relating to Group B, and 5 of the six statements for Group A, therefore following Round 2 consensus was achieved on 31 out of 32 statements (Table 1). The statement on respiratory cultures is discussed below.

4. Specific issues and comments

4.1. Follow-up arrangements and cross infection

The Round 1 statement suggested that children should be followed up in a specialist CF clinic "unless local circumstances enable reliable long-term follow-up". Although this statement achieved consensus for Group A, it did not for Group B. Comments revealed that participants felt strongly that the care of these infants should be led by a CF specialist physician whether or not this was in a CF clinic because of the difficulty

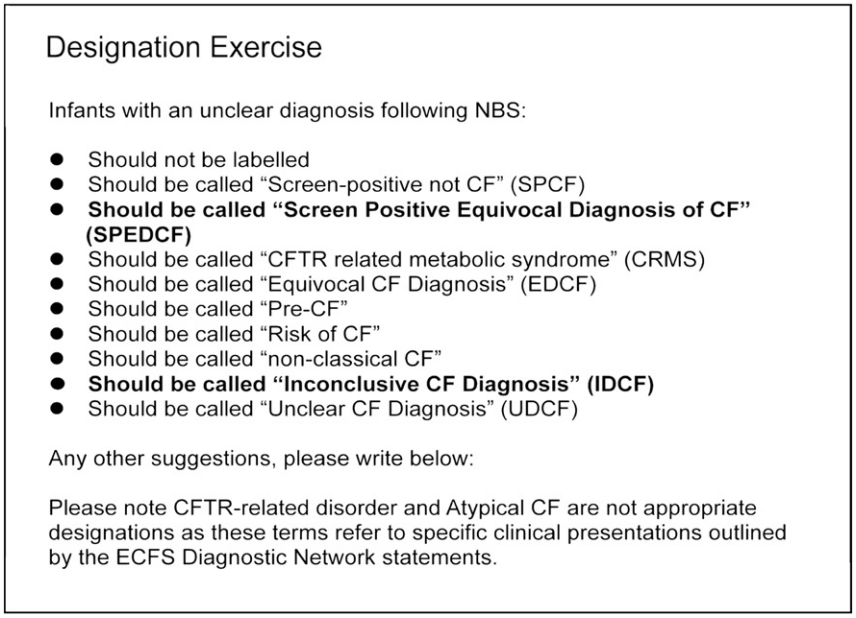

Fig. 2. From the responses to Round 1, the core group produced these 10 options, which were circulated for the designation exercise. Respondents were asked to select their preferred option. The two most popular options were "Screen Positive Equivocal Diagnosis of CF" (33%) and "Inconclusive CF Diagnosis" (27%).

in determining outcomes for these infants. The statement was therefore rewritten for Round 2.

A statement relating to cross-infection achieved consensus in Round 1, but was modified for Round 2, because the core group felt that comments improved the clarity of the statement.

4.2. The CFTR-2 website (www.cftr2.org)

The majority of respondents felt that CFTR-2 was an important source of information but that responsibility for reviewing this website should be with clinicians, not the parents. Whilst the website may be helpful for families, respondents commented that a number of rarer mutations are not currently included in the website and the resource is only available in English. The statement was therefore rewritten to state that clinicians should regularly review the website and discuss the findings with families. This achieved consensus for both Groups A and B.

4.3. Influenza vaccine

The Round 1 statement suggested routine annual influenza vaccination and there were varied responses to this, reflecting the lack of evidence in this area. Agreement was achieved for Group B (intermediate sweat chloride), but not Group A. Many respondents felt this recommendation excessive for children who are likely to be healthy. A rewritten statement for Group A was circulated in round 2, removing routine influenza vaccination from the recommendations for this group and this achieved agreement.

4.4. Respiratory cultures

Agreement was not achieved on statement 12 for Group A. This reflects divided opinion on this matter, ranging from respondents who felt that undertaking a respiratory culture was an unnecessary and distressing investigation for an infant to those who felt strongly that cultures should be obtained at every patient encounter with the CF service. It was not possible to achieve consensus regardless of the direction of the statement. We have recommended that local practice should be adopted for routine respiratory culture.

4.5. Dietary salt intake

In Round 1, it was suggested that children in Group B (intermediate sweat chloride) should be advised not to restrict their dietary salt intake, in contrast to the usual public health advice. This was felt to be excessive, as in the absence of confirmed CF the risk of salt loss was felt to be minimal under normal circumstances. The statement was rewritten to advise non-restriction of dietary salt intake only in periods of increased sweat loss and consensus was achieved.

4.6. Sensitivity analysis

Sixty two participants responded to Round 2. When the Round 1 responses of these participants were analysed retrospectively, there were some different outcomes compared to the results for all the respondents. One statement that did not reach consensus in Round 1 did when only respondents to Round 2 were considered, but 8 statements that did reach consensus in Round 1 had a level of agreement below 80%.

Table 1
The 31 statements that achieved consensus. These recommendations guide management of infants in Group A (normal sweat chloride value (<30 mmol L^{-1}) and two *CFTR* gene mutations, at least one of which has unclear phenotypic consequence) and Group B (intermediate sweat chloride value (30–59 mmol L^{-1}) and one or no *CFTR* mutations). One statement (A12) did not achieve satisfactory agreement.

	Group A, normal sweat chloride value (<30 mmol L^{-1}) and two *CFTR* mutations, at least one of which has unclear phenotypic consequences
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.
	Group B, intermediate sweat chloride value (30–59 mmol L^{-1}) and one or no *CFTR* mutations
B1	Infants should be followed up in a 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).
B2	For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection.
B3	Infants should undergo a repeat sweat test aged 6–12 months.
B4	Clinic follow-up may be 3-monthly, or less frequently depending on clinical assessment. The frequency of follow-up appointments may lessen with time, but children should be followed up annually as a minimum standard.
B5	Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated.
B6	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.
B7	Reflecting the absence of a clear diagnosis, the term "Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)" should be used to describe these infants.
B8	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.
B9	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).
B10	Oral antibiotics should be provided when the infant has a cough (lower threshold than for the general population). The Primary care physician should be provided with clear guidance to this effect. If the cough persists for more than 2 weeks, the infant should be reviewed by the CF team, respiratory cultures taken and further investigation considered.
B11	Children should receive annual influenza vaccine in addition to all routine childhood immunisations.
B12	Children should not be exposed to cigarette smoke.
B13	Respiratory cultures should be taken routinely at annual review and when clinically indicated.
B14	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.
B15	Parents should be informed of the sweat test result and advised that during periods of high sweat loss*, dietary salt intake should not be restricted. (* hot weather, increased physical activity, fever etc.).
B16	Families should be offered a referral for genetic counselling.
B17	Details of all children in this group should be kept on an appropriate database.

Overall this exercise demonstrates that the consensus achieved in round 2 was a result of changing opinion as opposed to attrition with only previously positive participants responding to Round 2.

The final statements are listed in Table 1. Consensus was not achieved for statement A12 concerning respiratory cultures, and we recommend that clinics continue to use local protocols, until more evidence is available to guide practice.

5. Discussion

The management of children with an inconclusive diagnosis following NBS for CF has been extremely variable between different countries, regions and even within the same clinic. Clear guidance to CF teams on this topic is required. We hope the production of these recommendations will lead to a more consistent experience for families in this position.

The recommendations have been developed through a robust and inclusive process, adopting a Delphi approach. The consensus statements reflect a general reluctance to engage these healthy infants in unnecessary medicalisation but also anxiety that some of these infants will eventually develop significant disease. Communication and education of the families have been a consistent theme and developments in the field, such as the CFTR-2 website, have been incorporated in this process.

The use of the new term Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) is aimed at aiding

communication between professionals and with families. It is a descriptive term rather than a diagnostic label, as these infants do not have a disease but have a number of risk factors for developing CF related issues in the future. Two other benefits of designation are 1) providing a "diagnostic" label, which is important in some healthcare systems to activate appropriate support and 2) providing a clear classification to support reliable data entry to facilitate long term analysis of outcomes. At present, data from these infants is either inappropriately stored on CF registries or not at all.

Another key outcome of this process was the division of these infants into those with a normal sweat chloride (Group A) and those with an intermediate sweat chloride (Group B). Statements for Group B reflected a higher level of clinical concern for these infants.

Thirty two statements were produced to guide CF physicians and multi-disciplinary teams in managing these infants consistently. The nature of follow-up and investigations was one of the most debated issues by participants but we have managed to attain consensus from a wide range of experts and views. It was considered important that these children are managed by a clinician with experience in CF, though not necessarily in a CF clinic since they do not have CF and do not require input from the multidisciplinary team. One of the key themes in the consensus is that these children should not be "over-medicalised". Other than a repeat sweat test at 6–12 months of age, no routine investigations are advised at diagnosis for these children.

At annual review, no routine investigations are advised. We could not achieve a consensus on the matter of routine respiratory cultures in asymptomatic children, reflecting the strength of feeling on this issue. Overall, it was agreed that investigations should be guided by clinical symptoms and signs. Clear information should be provided to both families and the primary care physician regarding recognising and acting on significant symptoms.

The importance of communication with families is highlighted throughout the guideline and participants felt very strongly that this was one of the main issues, although at the moment it was felt that accessing the CFTR-2 website should be the primary responsibility of the physician rather than the parents.

Duration of follow-up has not been discussed, as this will be dependent on individual progress. Infants may move from a designation of CFSPID to CF if clinical features of CF become apparent or if the sweat test moves from an intermediate to a CF-confirmatory result. Infants with CFSPID have a positive newborn screen for cystic fibrosis representing some degree of lifetime risk for the development of CFTR-related disorder which families should be aware of. [13] Infants in Group B who have one or no mutations whose sweat test subsequently returns to normal range could be considered as having a significantly lower lifetime risk. Future work will determine more clear recommendations on the length of follow-up.

Management of infants with an inconclusive diagnosis after NBS for CF is challenging. The production of these recommendations will hopefully result in a more consistent approach for families in this situation and a firmer foundation on which to assess the outlook for these infants. These recommendations will be reviewed as more evidence on the outcome of infants with CFSPID becomes available.

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Appendix A

Contributors	Affiliation
Balfour-Lynn Ian M	Royal Brompton Hospital, London, UK
Beckers Michael	Association Luxembourgeoise de Lutte contre la Mucoviscidose a.s.b.l., Luxembourg
Barben Jürg	Children's Hospital, St. Gallen, Switzerland
Berrocal Castañeda, Montserrat	Complexo Hospitalario Universitario de Ourense, Spain
Bhatt Jayesh	Nottingham Children's Hospital, Nottingham, UK
Blau Hannah	Schneider Children's Medical Center of Israel, Petah Tikva, Israel
Boga Alfonso Solar	Teresa Herrera Hospital, A Coruña, Spain
Brouard Jacques	Centre Hospitalier Universitaire de Caen, Caen, France
Burrows Elinor	Alder Hey Children's NHS Foundation Trust, Liverpool, UK
Bush Andrew	Imperial College and Royal Brompton Hospital, London, UK
Caballero Graciela	Instituto de Previsiòn Social BPS, Montevideo, Uruguay
Carr Siobhán B	Royal Brompton Hospital, London, UK
Castellani Carlo	Cystic Fibrosis Centre, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
Chivers Mark A	BC Childrens's Hospital, Vancouver, British Columbia, Canada
Cirilli Natalia	Cystic Fibrosis Centre, United Hospitals — Salesi Children's Hospital, Italy
Colon Cristobal	Hospital Clínico Universitario de Santiago de Compostela, Spain
Corbetta Carlo	Ospedale dei Bambini "V. Buzzi", Milan, Italy
Cowlard Jacqui	Barts Health NHS Trust, London, UK
Dankert-Roelse Jeannette	Dutch Society of Paediatrics, Netherlands
Davies Jane C	Imperial College London & the Royal Brompton & Harefield NHS Foundation Trust, UK
De Boeck Kris	University Hospital of Leuven, Leuven, Belgium
Derichs Nico	Charité Universitätsmedizin Berlin, Germany
Desai Maya	Birmingham Children's Hospital, Birmingham, UK
Dluholucký Svetozar	Children Faculty Hospital, Banská Bystrica, Slovakia
Doull Iolo	Children's Hospital for Wales, Cardiff, Wales
Elborn Stuart	Queens University, Belfast, Northern Ireland, UK
Escribano-Montaner Amparo	University Clinic Hospital of Valencia, Valencia. Spain
Fall Andrew	Royal Hospital for Sick Children, Edinburgh, Scotland, UK
Farriaux Jean Pierre	International Society of Neonatal Screening, France
Felix Miguel	Hospital Pediátrico, Centro Hospitalar Universitário de Coimbra, Portugal
Gartner Silvia	Hospital Universitari Vall d'Hebron, Barcelona, Spain

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Contributors	Affiliation
Gilchrist Francis J	Royal Stoke University Hospital, Stoke-on-Trent, UK
Gonska Tanja	University of Toronto and Hospital for Sick Children, Toronto, Ontario, Canada
Goyens Philippe	Université Libre de Bruxelles, Brussels, Belgium
Hull Jeremy	Children's Hospital, Oxford, UK
Hanssens Laurence	Université Libre de Bruxelles, Brussels, Belgium
Holubova Andrea	University Hospital Motol, Prague, Czech Republic
Javadpour Sheila	Our Lady's Children's Hospital Crumlin, Dublin, Ireland
Kashirskaya Nataliya	Research Centre for Medical Genetics RAMS, Moscow, Russia
Kavanagh Caroline	Norfolk and Norwich University Hospital Foundation Trust, Norwich, UK
Kerem Eitan	Hadassah Hebree University Medical Center, Jerusalem, Israel
Krivec Uroš	University Children's Hospital, Ljubljana, Slovenia
Krulisova Veronika	Charles University and University Hospital Motol, Prague, Czech Republic
Lebecque Patrick	Cliniques Universitaires St Luc, Université de Louvain, Belgium
Hjelte Lena	Stockholm CF Centre, Karolinska University Hospital, Stockholm, Sweden
Lentini Eduardo R	Hospital de Niños de Mendoza, Argentina
Lindblad Anders	Queen Silvia Children's Hospital, Göteborg, Sweden
Linnane Barry	University Hospital Limerick, Dooradoyle, Limerick, Ireland
Loughrey Clodagh	Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland, UK
Lucidi Vincenzina	Bambino Gesù Children's Hospital, Rome, Italy
Marshall Tom	Royal Hospital for Sick Children, Edinburgh, Scotland, UK
Mayell Sarah J	Alder Hey Children's NHS Foundation Trust, Liverpool, UK
McCormick Jonathan	Tayside Children's Hospital, Ninewells Hospital, Dundee, UK
McShane Donna	Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
Melotti Paola	Cystic Fibrosis Centre, Azienda Ospedaliera Universitaria Integrata Verona, Italy
Minicucci Laura	G. Gaslini Children Hospital, Genova, Italy
Moeller Alexander	Children's Hospital, Zurich, Switzerland
Mondejar Pedro	Clinic University Virgen de la Arrixaca Hospital, Murcia, Spain.
Montgomery Mark	University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada
Moure-González José Domingo	Hospital Clínico Universitario de Santiago, Spain
Munck Anne	Assistance Publique-Hôpitaux de Paris, Université Paris 7, Paris, France
Nährlich Lutz	Justus-Liebig-University Giessen, Giessen, Germany
Padoan Rita	Cystic Fibrosis Regional Support Centre, Children's Hospital, Brescia, Italy
Petrocheilou Argyri	Aghia Sophia Children's Hospital, Athens, Greece
Piekuse Linda	Scientific Laboratory of Molecular Genetics, Riga Stradinš University, Riga, Latvia
Proesmans Marijke	University Hospital Leuven, Leuven, Belgium
Ratjen Felix	Hospital for Sick Children, University of Toronto, Toronto
Reid Alastair	Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland, UK
Repetto Teresa	Cystic Fibrosis Centre, Meyer Hospital, Florence, Italy
Robberecht Eddy	Universitair Ziekenhuis, Gent, Belgium
Rock Michael	University of Wisconsin, Madison, USA
Cols Roig, Maria	Hospital Sant Joan de Déu, Barcelona, Spain
Schellenberg Amy	BC Childrens's Hospital, Vancouver, British Columbia, Canada
Schmidt Sebastian	Universitäts-Kinderklinik, Greifwald, Germany
Sermet Isabelle	Hôpital Necker-Enfants Malades, Paris, France
Skalická Veronika	Charles University and University Hospital Motol, Prague, Czech Republic
Sommerburg Olaf	University Children's Hospital III, Heidelberg, Germany
Storrøsten Olav Trond	Oslo University Hospital, Oslo, Norway
Southern Kevin W	Alder Hey Children's NHS Foundation Trust & University of Liverpool, Liverpool, UK
Suri Ranjan	Great Ormond Street Hospital, London, UK
Taccetti Giovanni	Cystic Fibrosis Centre, Meyer Hospital, Florence, Italy
Takáč Branko	Children Faculty Hospital, Banská Bystrica, Slovakia
Timothy Adams	NHS Ayrshire & Arran, Kilmarnock, Scotland
Tümmler Burkhard	Medizinische Hochschule Hannover, Germany
Ujhelyi Rita	Heim Pál Hospital for Children, Budapest, Hungary
Uyan Zeynep Seda	Kocaeli University, Kocaeli, Turkey
Vazquez Carlos	Hospital Universitario de Cruces, Barakaldo, Bizkaia, Spain
Villares Porto-Dominguez, Ana	Complexo Hospitalario Universitario de Ourense, Spain
Vilotijevic Dautovic Gordana	Institute for child and youth health care of Vojvodina, Province of Vojvodina, Serbia
West Noreen	Sheffield Children's NHS Foundation Trust, Sheffield, UK
Wilschanski Michael	Hadassah Hebrew University Hospital, Jerusalem, Israel
Wyatt Hilary	King's College Hospital, London, UK

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