Towards a consensus on the investigation and management of infants with an equivocal diagnosis following newborn screening for Cystic Fibrosis.

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Introduction

Newborn screening (NBS) for Cystic Fibrosis (CF) may result in recognition of infants with an equivocal diagnosis (reflecting the heterogeneous nature of the condition). Gene changes are sometimes recognised, the phenotypic consequence of which are unclear (most notably R117H on a 7/9T background). In addition, some babies with only one mutation recognised may have an equivocal sweat test result.

The Delphi process is a consensus method using a qualitative approach to decision making in areas where there is a lack of published information. The process utilises expert opinion and occurs in rounds. Round one assesses the extent of agreement between experts and subsequent rounds of consensus development aim to resolve disagreement and ultimately to achieve consensus.

We have employed the Delphi process to form an international consensus as to how to investigate and manage infants with an equivocal diagnosis following NBS.

Methods

Twenty-one statements were composed by a core group (CC, AM and KWS). These were circulated by email to all members to the ECFDN and EFCS Screening Working Group. Additional invitations were made to increase multidisciplinary input.

In round one, for each statement, the specialist was asked to tick one of three options: agree; could agree if reworded or disagree. In the case of disagreement, comments and suggestions were requested. The level of agreement constituting consensus was determined *a priori* to be 80%.

After round one, statements not achieving consensus were modified by the core group, taking into account comments made by respondents. In round two, the initial statements, degree of agreement from round one, a summary of respondents' comments, and a second set of proposed statements were circulated to all respondents. The process is ongoing in order to achieve consensus for all statements.

Results

Round one: Forty-one responses from specialists in 11 European countries were received for round one. A consensus was achieved on twelve statements. A further five statements were approaching consensus (>60%). Four statements had poor level of agreement.

Round two: The nine statements not achieving consensus were modified by the core group, following analysis of respondents' comments. Statements (numbers 1, 13,14) were modified despite attaining consensus in view of respondents' comments.

Thirty-seven responses were obtained following round two. A consensus was achieved on a further ten statements (including modified numbers 1,13,14). Two statements remain to achieve consensus and work is ongoing on these.

Conclusion

The Delphi process is a rigorous technique to achieve a valid consensus. We received a good response and have achieved an international consensus on nineteen statements on the investigation and management of infants with equivocal diagnosis following NBS. Two statements are yet to achieve consensus and we hope to attain this by August 2007.

The consensus statements should provide a valuable resource for CF teams with emerging and established NBS programmes.

	Statement	First round	Second round	Current status
1*	An infant with one or more raised IRT measurements and an equivocal sweat test (sweat Cl⁻ =30 and <60 mmol l⁻¹) requires assessment and review in a specialist CF clinic (with >50 patients).	Consensus (clinic size modified) (80%)	Consensus (89%)	Consensus
2*	An infant with two *CFTR* gene changes and a normal sweat test requires assessment and review in a specialist CF clinic (>50 patients).	Approaching consensus (78%)	Consensus (89%)	Consensus
3	In these cases a repeat sweat test should be undertaken in a centre with suitable experience (>150 sweat tests pa) of a validated technique for measuring sweat chloride (Appendix A).	Consensus (85%)	Consensus	Consensus
4	Infants from statement 1, who have a normal repeat sweat test in an accredited centre (sweat Cl⁻ <30 mmol l⁻¹), do not require further clinical review (negative CF screening test).	Consensus (84%)	Consensus	Consensus
5	Extended gene analysis must be undertaken in infants with two equivocal sweat tests and one or no *CFTR* mutations recognised (Appendix B).	Consensus (85%)	Consensus	Consensus
6	Infants with one or more raised IRT measurements, one *CFTR* mutation and a normal sweat test (Cl <30) do not require extended gene analysis.	Consensus (80%)	Consensus	Consensus
7*	Infants with one or more raised IRT measurements, one *CFTR* mutation and a normal sweat test (Cl <30) do not require review in a specialist CF clinic (negative CF screening test). Appropriate advice regarding carrier status should be given.	Approaching consensus (71%)	Consensus (92%)	Consensus
8*	Infants with two equivocal sweat tests require baseline assessment for respiratory disease (airways culture and chest radiograph). Further investigations may be indicated as determined by the clinical situation (for example, chest CT scan and bronchoscopy).	Poor agreement (41%)	Consensus (89%)	Consensus
9*	Infants with two equivocal sweat tests require baseline assessment for non-respiratory disease (fecal analysis for elastase and abdominal USS). Other investigations as clinically indicated.	Poor agreement (54%)	Consensus (92%)	Consensus
10	Infants with two equivocal sweat tests and any clinical evidence supportive of a CF diagnosis should have regular follow up in a CF specialist clinic (Appendix C).	Consensus (90%)	Consensus	Consensus
11*	Infants with two equivocal sweat tests, one or no CF causing mutations and no clinical evidence of CF should be *considered* for further investigation of a physiological defect (Appendix D).	Poor agreement (56%)	Consensus (83%)	Consensus
12a*	Infants with two equivocal sweat tests, one CF causing mutation (after 5) and no evidence of ion transport defect on further testing, if done, should be reviewed in a specialist CF clinic at regular but infrequent intervals (yearly).	Poor agreement (58%) Two statements generated for second round	Approaching consensus (71%)	Approaching consensus
12b*	Infants with two equivocal sweat tests, no CF causing mutation (after 5) and no evidence of ion transport defect on further testing, if done, should be reviewed in a Paediatric clinic (with formal links to a specialist CF Centre) at regular but infrequent intervals (yearly).	Poor agreement (58%) Two statements generated for second round	Approaching consensus (71%)	Approaching consensus
13*	Infants with two equivocal sweat tests, one or no CF causing mutation and evidence of ion transport defect on further testing should have regular follow up in a specialist CF clinic.	Consensus (modified to fit 12) (88%)	Consensus (97%)	Consensus
14*	All infants with two equivocal sweat tests should have the test repeated between 6-12 months of age in a centre with suitable experience (as 3).	Consensus (age modified) (80%)	Consensus (89%)	Consensus
15*	Infants with two *CFTR* gene changes but a normal sweat test (at least one performed in a centre with adequate experience, as per statement 3) should have detailed clinical assessment (as 8&9).	Approaching consensus (73%)	Consensus (100%)	Consensus
16	Infants with two *CFTR* gene changes, a normal sweat test and any clinical evidence of CF should have regular follow up in a CF specialist clinic.	Consensus (85%)	Consensus	Consensus
17*	Infants with two *CFTR* gene changes, a normal sweat test and no clinical evidence of CF should be *considered* for further investigation of a physiological defect (Appendix D).	Approaching consensus (74%)	Consensus (97%)	Consensus
18	Infants with two *CFTR* gene changes, a normal sweat test, no clinical evidence of CF but evidence of abnormal ion transport should have regular follow up in a specialist CF clinic.	Consensus (83%)	Consensus	Consensus
19*	Infants with two *CFTR* gene changes, a normal sweat test, no clinical evidence of CF and no evidence of abnormal ion transport should be reviewed in a paediatric clinic (with links to a specialist CF centre) at regular but infrequent intervals (yearly).	Approaching consensus (73%)	Approaching consensus (77%)	Approaching consensus
20	All infants with two CFTR gene changes and a normal sweat test, should have the sweat test repeated at 9-12 months.	Consensus (87%)	Consensus	Consensus
21	Clinical and demographic information on all infants with an equivocal diagnosis should be entered onto a database or registry (pending consent from legal guardian).	Consensus (88%)	Consensus	Consensus

* revised statement for second round

The following contributed to this project:

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