CFTR Related Metabolic Syndrome (CRMS) Definition: Challenges in Application

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DISCLOSURES

I have no conflicts of interest to disclose regarding this presentation
Objective

Evaluate the accuracy and consistency with which CF Clinicians and Newborn Screeners apply the CFTR Related Metabolic Syndrome (CRMS) definition as stated by CF Foundation guidelines and the HRSA Pulmonary Workgroup CF case definition
BACKGROUND
EVOLUTION OF CYSTIC FIBROSIS (CF) DIAGNOSTIC TERMINOLOGY

Pre-2008

- Classic CF, Severe CF, PI CF
- Mild CF, Atypical CF, CF variant, PS CF
- Borderline
- CFTR related disorder
- CF spectrum
- CBAVD

Post -2009

- CF (PI/PS)
- CRMS
- CRD

CFF CONSENSUS STATEMENTS:
CF DIAGNOSIS GUIDELINES + CRMS GUIDELINES
CRMS Definition Development

• 2008: CFF sponsored workgroup of CF clinicians appointed to address gaps in CFF diagnosis statement on “diagnostic dilemmas” generated by NBS (particularly IRT/DNA based screening algorithms), and to propose standardized care protocols for newborns

• 2 rounds of Delphi method with 80% consensus -> J Peds Supplement
Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report

Philip M. Farrell, MD, PhD, Beryl J. Rosenstein, MD, Terry B. White, PhD, Frank J. Accurso, MD, Carlo Castellani, MD, Garry R. Cutting, MD, Peter R. Durie, MD, FRCP, Vicky A. LeGrys, DrA, CLS, John Massie, MBBS, FRACP, PhD, Richard B. Parad, MD, MPH, Michael J. Rock, MD, and Preston W. Campbell, III, MD

J Pediatr 2008;153:S4-S14

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

Druce 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

J Pediatr 2009;155:S106-16
Hypertrypsinogenemia with 1st sweat chloride (SC) = 30-59 mmol/L (Many NBS programs will also perform mutation testing)

- SC <30 mmol/L
  - 1 mutation
  - 0 mutations
  
  Resolve as Carrier
  CF NBS False Positive

- SC ≥60 mmol/L
  - 0 mutations
  - 1 Group A or D mutation
  - 2 mutations (with 1 Group B or D)
  - SC <30 mmol/L
  
  Repeat SC by 2 months of age
  SC ≥60 mmol/L
  - 0 mutations
  - 1 Group A or D mutation
  - 2 mutations (with 1 Group B or D)

  Resolve as Normal
  CF NBS False Positive

Possible CRMS
CF specialist evaluation

- SC <60 mmol/L
  - 0 mutations
  
  SC <40 mmol/L
  - 1 mutation

CFTR-Related Metabolic Syndrome (CRMS)
Follow at CF Center

<table>
<thead>
<tr>
<th>SC (mmol/L)</th>
<th>Number of CFTR Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A***</td>
</tr>
<tr>
<td>&lt; 60 ***</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 40-59</td>
<td>0</td>
</tr>
<tr>
<td>40-59</td>
<td>1 or 1</td>
</tr>
</tbody>
</table>

Unresolved: Possible CRMS

CF signs or symptoms develop

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* A= CF-causing, B= CFTR-related disorder, D= unknown or uncertain clinical relevance (3)
** Multimutation method, gene scanning or sequencing, duplication and deletion testing and evaluation for IVS-8 TG repeats; consider family evaluation for phasing to confirm mutations are trans (28).
*** A lower limit for sweat chloride has not been defined
CF case definition: Two Questions
How well is the CRMS definition functioning?

1. How accurately do expert CF clinicians (who may provide the case definition to the NBS program) apply the definition?
2. How is information gathered by NBS programs from CF clinicians used to close CF cases?
Timeline

• 2009
  – Publication of CRMS guidelines by CFF

• 2011
  – HRSA Pulmonary Workgroup begins NBS case definition project: Pulmonary workgroup: CF case definitions for CF, CRD and CRMS

• 2012
  – NACFC NBS SIG gathers CF expert clinician who test definitions
  – Definitions transformed to diagnosis grid

• 2013
  – HRSA/NewSteps project pilots test application of grid through test cases submitted by NBS programs
CF Clinician Test Group
Methods

- 38 CF physicians with newborn screening expertise
- Reviewed CRMS definitions and Cystic Fibrosis Foundation Guidelines for CF Diagnosis
- Presented with 15 clinical scenarios with CFNBS status, age, clinical history, genotype and sweat chloride data
- Clicker devices (Turning Point software) used to select one of 3 - 5 diagnostic choices for per scenario
- Given 30 seconds for response
DEFINITIONS PROVIDED

• **CF**
  – Sweat chloride concentration $\geq 60$ mmol/L, or
  – Two CF-causing mutations

• **CRMS (CFTR related metabolic disorder)**:
  – Sweat chloride concentration 30-59 mmol/L (40-59 mmol/L if age $\geq 6$ months) and fewer than two CF causing mutations
  – Or, sweat chloride concentration $<30$ mmol/L ($<40$ mmol/L if age $\geq 6$ months) and two CFTR mutations of which no more than one is known to be CF causing
  – Sweat chloride confirmed on at least two occasions

• **CRD (CFTR Related Disorder)**:
  – A negative CFNBS or CFNBS not performed
  – A symptomatic infant or child
  – Sweat chloride concentration 30-59 mmol/L (40-59 mmol/L if age $\geq 6$ months) and fewer than two CF causing mutations
  – Or, sweat chloride concentration $<30$ mmol/L ($<40$ mmol/L if age $\geq 6$ months) and two CFTR mutations of which no more than one is known to be CF causing
  – Sweat chloride confirmed on at least two occasions
CRMS
(CFTR Related Metabolic Disorder)

• Sweat chloride concentration 30-59 mmol/L* and fewer than two CF causing mutations (0,1)
- or -

• Sweat chloride concentration <30 mmol/L and two CFTR mutations of which no more than one is known to be CF causing (0,1)

*40-59 mmol/L if age ≥ 6 months
Example of Question

17) In an infant with a positive CFNBS who at 12 months of age has 2 or more sweat chlorides sweat chloride concentration <30 mmol/L and two CFTR mutations of which no more than one is known to be CF causing, the case definition should be:

<table>
<thead>
<tr>
<th></th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent</td>
</tr>
<tr>
<td>CF</td>
<td>0%</td>
</tr>
<tr>
<td>CRMS</td>
<td>47%</td>
</tr>
<tr>
<td>CF Carrier</td>
<td>53%</td>
</tr>
<tr>
<td>Totals</td>
<td>100%</td>
</tr>
</tbody>
</table>
*CFTR2 lists R117H as a CF causing mutation with variable clinical consequences*
*CFTR2 lists R117H as a CF causing mutation with variable clinical consequences*
Results

- 33% (2/6) CRMS scenarios responded with >80% consensus for the correct diagnosis.
- 66% (2/3) CF scenarios responded with >80% consensus for the correct diagnosis.
Results

• In one case, while 56% correctly identified CRMS, 33% preferred the options “possible” or “probable” CF, suggesting that CRMS has not yet been accepted by the CF clinical community.

• CFF guidelines for CF diagnosis through NBS were not adhered to by 1/3 of respondents, suggesting that new diagnostic criteria for CF and CRD are also not well understood by CF clinicians.

• Correct response rate improved in later questions, indicating better guideline comprehension with repetition.
HRSA+
NBS Case Definition Initiative

An attempt to standardize the definitions used to close cases by US NBS Programs
Case Definition Development

• Pulmonary Workgroup and contributors to CF case definitions
  Hank Dorkin
  Mike Rock
  Drucy Borowitz
  Richard Parad
  Laurie Varlotta
  Michelle Howenstine
  Phil Farrell
  Frank Accurso
  Sara Copeland
  Anne Comeau

• Federal and National Partners – CDC, NICHD, NLM, NHLBI, NIH/ORD, ACMG, APHL, NNSGRC, HRSA
**PULMONARY WORKGROUP**

**HRSA MODIFICATION**

**TOOL**
CF Case Definition Tool

Cystic Fibrosis Case Confirmatory Diagnosis Follow-up

Birth Weight: Weight in grams
Gestational Age: In weeks gestation at time of birth
State of birth: State reporting the case
Gender

Instructions
Please answer the questions as fully as possible

Part I: Final Diagnosis as determined by clinician performing the follow-up
Please choose one:
A. Typical Cystic Fibrosis (CF)
B. CFTR-Related Metabolic Syndrome (CRMS)
C. Non-classical or Atypical CF

Based on the information above- please categorize your level of certainty for this case:
A. Definite
B. Probable
C. Possible
D. Unable to assess/incomplete

Were CFTR mutations detected on the newborn screening mutation panel?

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Identified</th>
<th>Not Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Did the HBS result indicate an elevated IRT?

<p>| | |</p>
<table>
<thead>
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<th></th>
<th></th>
</tr>
</thead>
</table>

Please answer the following- if you do not know or are unable to determine, mark “no”

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were clinical symptoms present?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What were the symptoms?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a valid sweat chloride result available?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What was the level? (units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a CFTR mutation panel completed after the newborn screening mutation panel?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What were the mutations?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If more mutations were identified, please list here:

Mutation 1
Mutation 2

Page 1
## Pilot Study Participants

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<thead>
<tr>
<th>State</th>
<th>Name</th>
<th>State</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>Cindy Ashley</td>
<td>Missouri</td>
<td>Jami Kiesling</td>
</tr>
<tr>
<td>Arizona</td>
<td>Sondi Aponte</td>
<td>Nebraska</td>
<td>Julie Luedtke</td>
</tr>
<tr>
<td>Delaware</td>
<td>Lou Bartoshesky</td>
<td>New York</td>
<td>Beth Vogel</td>
</tr>
<tr>
<td>Florida</td>
<td>Lois Taylor</td>
<td>South Dakota</td>
<td>Lucy Fossen</td>
</tr>
<tr>
<td>Hawaii</td>
<td>Janice Kong</td>
<td>Utah</td>
<td>Kim Hart</td>
</tr>
<tr>
<td>Illinois</td>
<td>Claudia Nash</td>
<td>Vermont</td>
<td>Cynthia Ingham</td>
</tr>
<tr>
<td>Iowa</td>
<td>Carol Johnson</td>
<td>Virginia</td>
<td>Jennifer MacDonald</td>
</tr>
<tr>
<td>Kansas</td>
<td>Jamey Kendall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louisiana</td>
<td>Colleen Clarke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maryland</td>
<td>Johnna L. Watson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massachusetts</td>
<td>Anne Comeau Neela Sahai</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
### COLLECTED CASES

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Diagnosis</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Mutation 1</th>
<th>Mutation 2</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>Cystic Fibrosis</td>
<td>30</td>
<td>M</td>
<td>Fever</td>
<td>Delta F508</td>
<td>81</td>
<td>2 Delta F508, 81</td>
</tr>
<tr>
<td>002</td>
<td>Cystic Fibrosis</td>
<td>25</td>
<td>F</td>
<td>Wheeze</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>003</td>
<td>Cystic Fibrosis</td>
<td>40</td>
<td>M</td>
<td>Shortness of breath</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>004</td>
<td>Cystic Fibrosis</td>
<td>35</td>
<td>F</td>
<td>Fatigue</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>005</td>
<td>Cystic Fibrosis</td>
<td>30</td>
<td>M</td>
<td>Cough</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>006</td>
<td>Cystic Fibrosis</td>
<td>35</td>
<td>F</td>
<td>Chest pain</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>007</td>
<td>Cystic Fibrosis</td>
<td>40</td>
<td>M</td>
<td>Headache</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
<tr>
<td>008</td>
<td>Cystic Fibrosis</td>
<td>45</td>
<td>F</td>
<td>Diarrhea</td>
<td>80</td>
<td>81</td>
<td>2 Delta F508, 80</td>
</tr>
</tbody>
</table>

**Note:** The table above represents a summary of collected cases with various symptoms and genetic mutations. Further analysis is necessary for a detailed understanding.
## SUMMARY OF CASE CATEGORIZATION

<table>
<thead>
<tr>
<th>Tool</th>
<th>CF</th>
<th>CRMS</th>
<th>CRD</th>
<th>UNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>43</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CRMS</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRD</td>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>UNK</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Incomplete 2

% CASES CORRECTLY CHARACTERIZED:
- CF 98%
- CRMS 77%
PROBLEMS

• Grid is incomplete (missing scenarios)
• Grid is not conform with terminology in CFF Guidelines (e.g. Atypical CF)
• Definition likely to change when more data on natural history is available
• Judging a level of certainty (“possible, probable, etc”) adds a subjective layer of complexity
Optimize homogeneity of Cohort
Collect F/U data
Natural History better described
Refine diagnosis and therapy
Adjust definition
IMPLICATIONS

CURRENT: CF CLINICIAN DIAGNOSIS → NBS PROGRAM CASE DESIGNATION

PROPOSED: CF Clinician → Defined Clinical Data → NBS PROGRAM

TOOL

Definition Clinical Data

Diagnosis

?= =

Diagnosis

OPTIMAL DIAGNOSTIC ASSIGNMENT
Conclusions

• As with all NBS disorders, CF is a complex disease which is difficult to define by both clinician and newborn screening stakeholders
• NBS can’t consistently depend on CF clinician’s individual interpretation
• A standardized algorithm for CF case definition, based on consensus, should be used both by newborn screening programs for case closure and CF clinicians for determination of appropriate care and monitoring
Conclusions

• CRMS diagnostic criteria are neither clearly understood nor consistently applied in clinical practice.

• Given the inconsistent manner with which our CF experts follow diagnostic guidelines, significant concerns are raised regarding the accuracy of incidence reported to central databases such as PORTCF.
Conclusions

Tools to either educate clinicians and data entry staff or diagnostic aids to help generate consistent categorization will:

1) improve accuracy of CRMS incidence estimates by CFF and NBS programs
2) better inform initiation of appropriate follow-up and care protocols
3) minimize the impact of diagnostic odyssey on parents.