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

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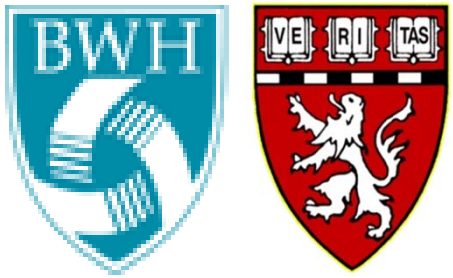
Colorado School of PUBLIC HEALTH



DISCLOSURES

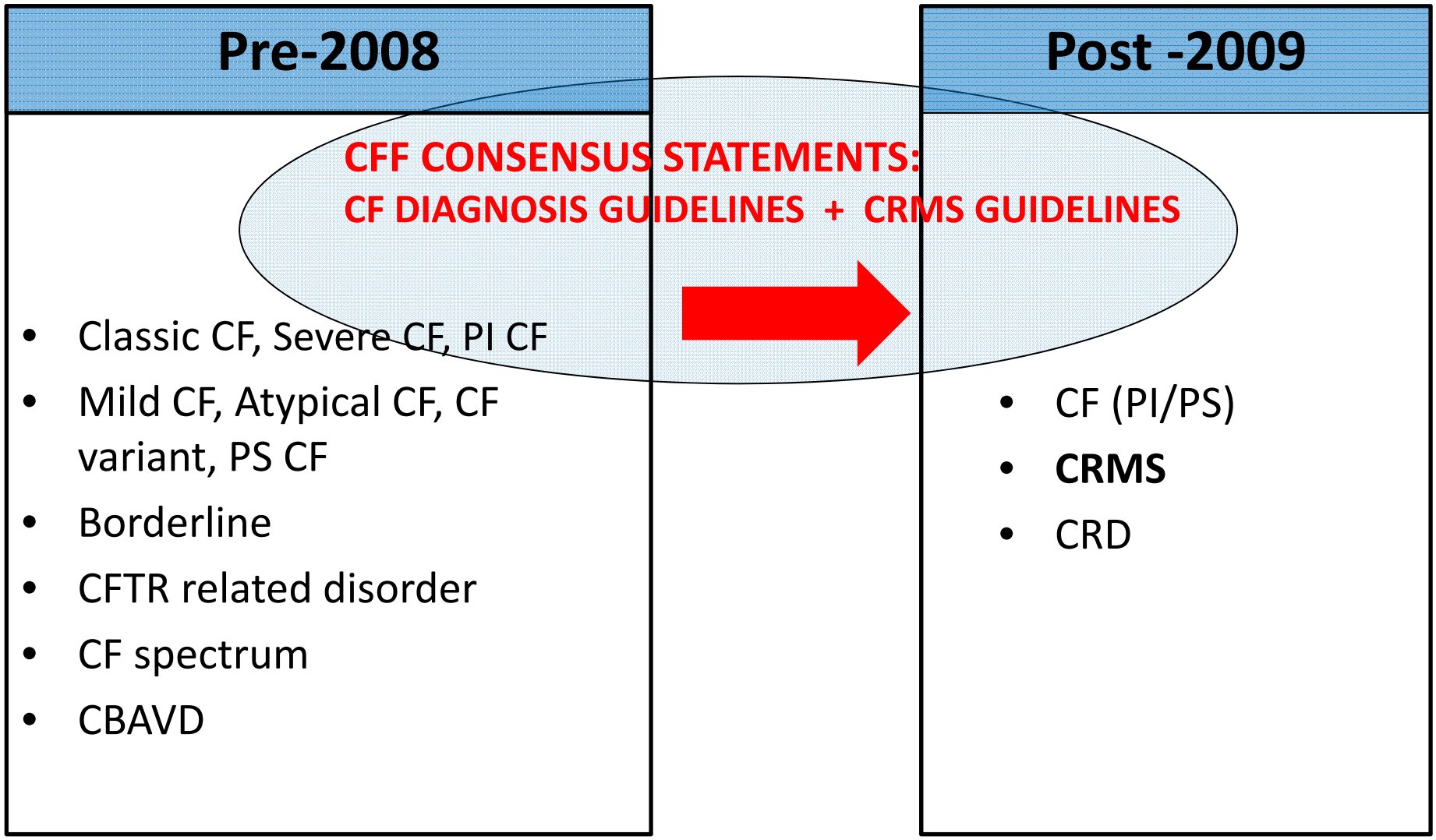
I have no conflicts of interest to disclose regarding this presentation

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



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

SUPPLEMENT www.jpeds.com • The Journal of Pediatrics

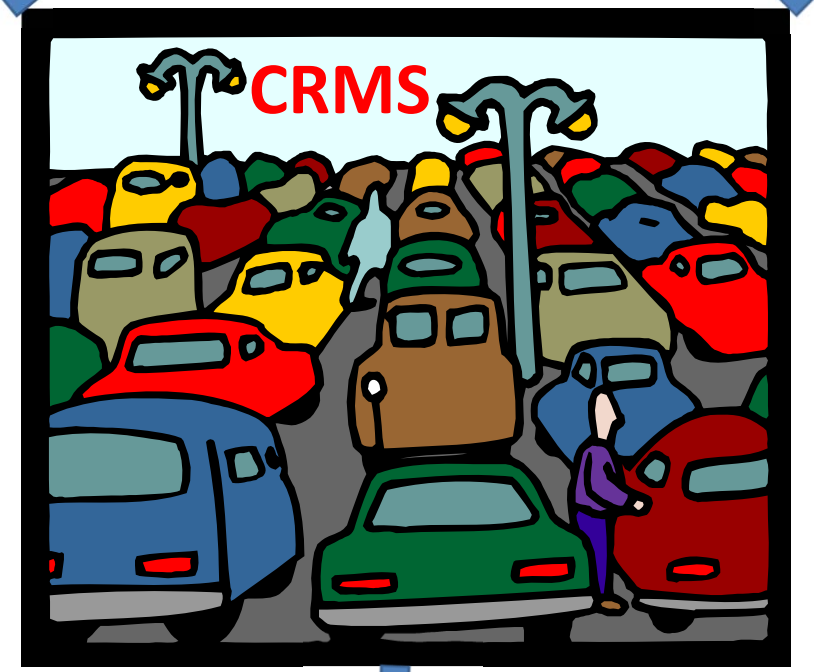
Cystic Fibrosis Foundation Practice Guidelines for the Management of Infants with Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome during the First Two Years of Life and Beyond

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

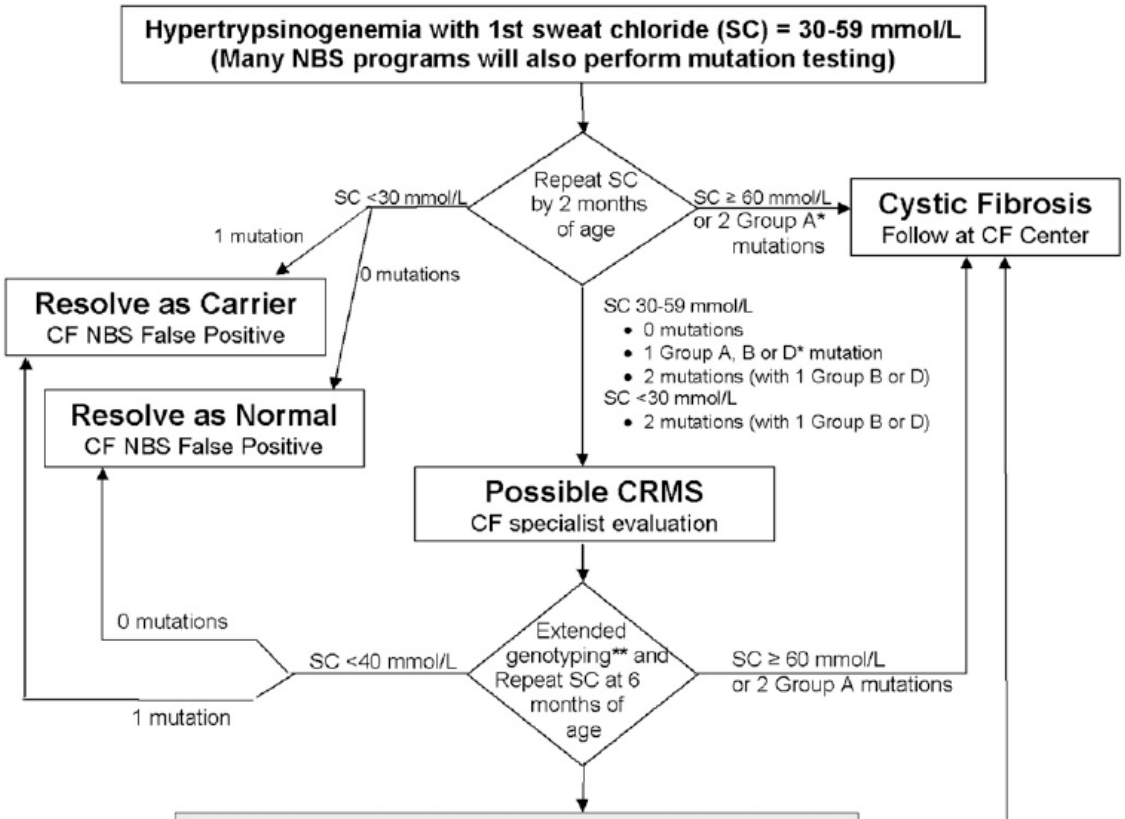
J Pediatr 2009;155:S106-16

CF

CRD



NOT CF



CFTR-Related Metabolic Syndrome (CRMS) Follow at CF Center		
SC (mmol/L)	Number of CFTR Mutations	
	Group A**	Group B or D**
< 60 ***	1	1
< 60 ***	0	2
40-59	1 or	1
Unresolved: Possible CRMS		
40-59	0	0

* 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 ≥ 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 ≥ 6 months) and fewer than two CF causing mutations
  - Or, sweat chloride concentration <30 mmol/L (< 40 mmol/L if age ≥ 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 ≥ 6 months) and fewer than two CF causing mutations
  - Or, sweat chloride concentration <30 mmol/L (< 40 mmol/L if age ≥ 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:

	Responses	
	Percent	Count
CF	0%	0
CRMS	47%	17
CF Carrier	53%	19
Totals	100%	36

QUESTIONS REQUESTING AN INFANT'S DIAGNOSIS GIVEN THE FOLLOWING INFORMATION:								
CFNBS	Age	Clinical History Provided	Genotype	Sweat Chloride			Correct Answer	% correct
Positive								
	6 months	None						
			DF508 / R117H (no additional genetic information available)*					
				<30 meq/L			CRMS	70
				50 meq/L			CRMS	73
				70 meq/L			CF	97
			Two CFTR sequence variants that are considered benign (e.g. F508C)					
				<30 meq/L			Not CRMS	86
				50 meq/L			CRMS	92
				60 meq/L			CF	74
	12 months	None						
			One CF causing mutation detected on NBS. Extended genetic analysis reveals a second mutation which is not included in CFTR2 but has rare case reports associated with a CF phenotype.					
				100 meq/L			CF	86
				50 meq/L			CRMS	56
			CF causing mutation / CF causing mutation of variable consequence					
				<60 mmol/L			CRMS	100
			Two CFTR mutations of which no more than one is known to be CF causing					
				<30 mmol/L			CRMS	47
Negative								
	12 months	Developed symptoms that make CF a clinical consideration prompting sweat testing						
			Two CFTR mutations of which no more than one is known to be CF causing					
				40 -59 mmol/L			CRD	39

*CFTR2 lists R117H as a CF causing mutation with variable clinical consequences

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				70 meq/L			CF	97
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			One CF causing mutation detected on NBS. Extended genetic analysis reveals a second mutation which is not included in CFTR2 but has rare case reports associated with a CF phenotype.					
				100 meq/L			CF	86
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Negative								
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				40 -59 mmol/L			CRD	39

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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

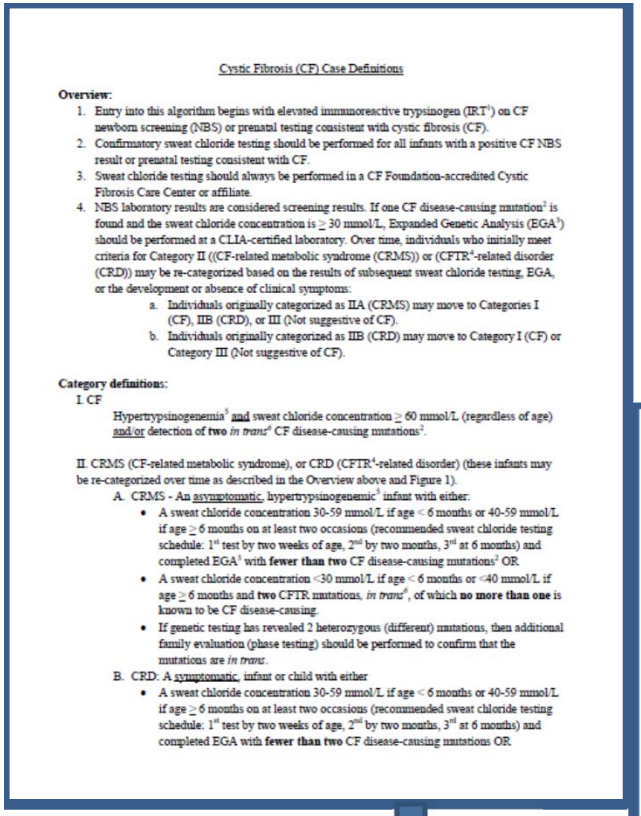
- In one case, while 56% correctly identified CRMS, 33% preferred the options “possible” or “probable” CF, suggesting that CRMS has not yet been accepted by the CF clinical community.
- CFF guidelines for **CF diagnosis** through NBS were not adhered to by **1/3** of respondents, suggesting that new 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



Cystic Fibrosis (CF) Case Definitions

Overview:

1. Entry into this algorithm begins with elevated immunoreactive trypsinogen (IRT[1]) on CF newborn screening (NBS) or prenatal testing consistent with cystic fibrosis (CF).
2. Confirmatory sweat chloride testing should be performed for all infants with a positive CF NBS result or prenatal testing consistent with CF.
3. Sweat chloride testing should always be performed in a CF Foundation-accredited Cystic Fibrosis Care Center or affiliate.
4. NBS laboratory results are considered screening results. If one CF disease-causing mutation[2] is found and the sweat chloride concentration is ≥ 30 mmol/L, Expanded Genetic Analysis (EGA[3]) should be performed at a CLIA-certified laboratory. Over time, individuals who initially meet criteria for Category II ((CF-related metabolic syndrome (CRMS)) or (CFTR[4]-related disorder (CRD)) may be re-categorized based on the results of subsequent sweat chloride testing, EGA, or the development or absence of clinical symptoms:
    a. Individuals originally categorized as IIA (CRMS) may move to Categories I (CF), IIB (CRD), or III (Not suggestive of CF).
    b. Individuals originally categorized as IIB (CRD) may move to Category I (CF) or Category III (Not suggestive of CF).

Category definitions:

I. CF

Hypertrypsinogenemia[5] and sweat chloride concentration ≥ 60 mmol/L (regardless of age) and/or detection of **two** *in trans*[6] CF disease-causing mutations[2].

II. CRMS (CF-related metabolic syndrome), or CRD (CFTR[4]-related disorder) (these infants may be re-categorized over time as described in the Overview above and Figure 1).

A. CRMS - An asymptomatic, hypertrypsinogenemic[5] infant with either:
- A sweat chloride concentration 30-59 mmol/L if age < 6 months or 40-59 mmol/L if age ≥ 6 months on at least two occasions (recommended sweat chloride testing schedule: 1st test by two weeks of age, 2nd by two months, 3rd at 6 months) and completed EGA[3] with **fewer than two** CF disease-causing mutations[2] OR
- A sweat chloride concentration <30 mmol/L if age < 6 months or <40 mmol/L if age ≥ 6 months and **two** CFTR mutations, *in trans*[6], of which **no more than one** is known to be CF disease-causing.
- If genetic testing has revealed 2 heterozygous (different) mutations, then additional family evaluation (phase testing) should be performed to confirm that the mutations are *in trans*.

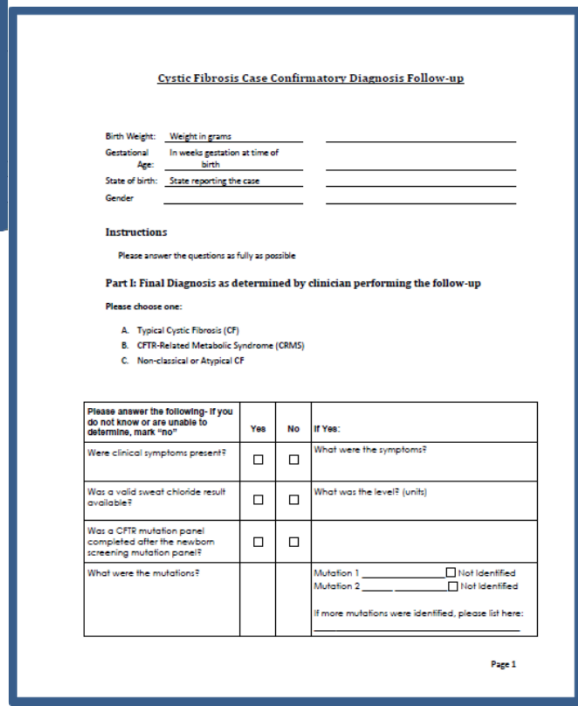
B. CRD: A symptomatic, infant or child with either
- A sweat chloride concentration 30-59 mmol/L if age < 6 months or 40-59 mmol/L if age ≥ 6 months on at least two occasions (recommended sweat chloride testing schedule: 1st test by two weeks of age, 2nd by two months, 3rd at 6 months) and completed EGA with **fewer than two** CF disease-causing mutations OR

PULMONARY WORKGROUP

Category	Classification	Clinical	Sweat Chloride	Non Newborn Screen Molecular	Newborn Screen Molecular	NBS Result
Typical CF	Definite		>=60 mmol/L (regardless of age)		2 CF disease-causing mutations	
	Definite		No valid sweat chloride result available	2 CF disease-causing mutations *in trans* –	2 CF disease-causing mutations *in trans*	
	Definite		<60 mmol/L	2 CF disease-causing mutations *in trans* ***and*** 1 or both have been previously shown to have lower chlorides,(e.g., L206W or 3849+10kbC>T)	2 CF disease-causing mutations *in trans* ***and*** 1 or both have been previously shown to have lower chlorides,(e.g., L206W or 3849+10kbC>T)	
	Definite	No known medical condition associated with false positive sweat chloride	>=60 mmol/L x 2 (regardless of age, two independent results from separate days)			
	Classification	Clinical	Sweat Chloride	Non Newborn Screen Molecular	Newborn Screen Molecular	
	Probable		No valid sweat chloride result available		2 CF-causing mutations in trans	

HRSA MODIFICATION

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

Please answer the following- if you do not know or are unable to determine, mark "no"	Yes	No	If Yes:
Were clinical symptoms present?	☐	☐	What were the symptoms?
Was a valid sweat chloride result available?	☐	☐	What was the level? (units)
Was a CFTR mutation panel completed after the newborn screening mutation panel?	☐	☐	
What were the mutations?			Mutation 1 _____ ☐ Not Identified Mutation 2 _____ ☐ Not Identified If more mutations were identified, please list here: _____

Page 1

CF Case Definition Tool

Cystic Fibrosis Case Confirmatory Diagnosis Follow-up

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Gestational Age: In weeks gestation at time of birth

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Part I: Final Diagnosis as determined by clinician performing the follow-up

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Please answer the following- if you do not know or are unable to determine, mark "no"	Yes	No	If Yes:
Were clinical symptoms present?	☐	☐	What were the symptoms?
Was a valid sweat chloride result available?	☐	☐	What was the level? (units)
Was a CFTR mutation panel completed after the newborn screening mutation panel?	☐	☐	
What were the mutations?			Mutation 1 _____ ☐ Not Identified Mutation 2 _____ _____ ☐ Not Identified If more mutations were identified, please list here: _____

Were CFTR mutations detected on the newborn screening mutation panel?	☐	☐	
What were the mutations?			Mutation 1 _____ ☐ Not Identified Mutation 2 _____ _____ ☐ Not Identified
Did the NBS result indicate an elevated IRT?	☐	☐	

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

Pilot Study Participants

Alabama	Cindy Ashley
Arizona	Sondi Aponte
Delaware	Lou Bartoshesky
Florida	Lois Taylor
Hawaii	Janice Kong
Illinois	Claudia Nash
Iowa	Carol Johnson
Kansas	Jamey Kendall
Louisiana	Colleen Clarke
Maryland	Johnna L. Watson
Massachusetts	Anne Comeau
	Neela Sahai
Missouri	Jami Kiesling
Nebraska	Julie Luedtke
	Krystal Baumert
	Karen Eveans
New York	Beth Vogel
	Michele Caggana
	Deborah A. Rodriguez
South Dakota	Lucy Fossen
Utah	Kim Hart
Vermont	Cynthia Ingham
Virginia	Jennifer MacDonald

COLLECTED CASES

Please choose one:	Were clinical symptoms present?	What were the symptoms?	Was a valid sweat chloride result available?	How many levels were reported?	What was the first level?	What was the second level?	What was the third level?	What were the units?	Was a CFTR mutation panel completed after the newborn screening mutation panel?	How many NBS mutations were identified?	What was Mutation 1?	What was Mutation 2?	If more than 2 mutations were identified, please list additional mutations here:	Were CFTR mutations detected on the newborn screening mutation panel?	How many CFTR mutations were detected on the newborn screening mutation panel?	What was Mutation 1?	What was Mutation 2?	If more than 2 mutations were identified, please list additional mutations here:	Did the NBS result indicate an elevated IRT?	Based on the inf
C. Non-classical or Atypical CF	No		Yes		36			MOL/L	Yes		2 delta F508	R347H		Yes		1 delta F508			Yes	B. Probable
B. CFTR-Related Metabolic Syndrome (CRMS)	No		Yes		39			MMOL/L	Yes	More than 2	delta F508	R1174	7T/9T	Yes		2 delta F508	R1174H		Yes	B. Probable
B. CFTR-Related Metabolic Syndrome (CRMS)	No		Yes		18, 17			mmol/L	No					Yes		2 deltaF508	R117H without 5T		Yes	A. Definite
B. CFTR-Related Metabolic Syndrome (CRMS)	No		Yes		34, 30			mmol/L	No					Yes		2 deltaF508	R117H (host)		Yes	A. Definite
B. CFTR-Related Metabolic Syndrome (CRMS)	No		Yes		18, 25			mmol/L	No					Yes		2 deltaF508	D1152H		Yes	A. Definite
B. CFTR-Related Metabolic Syndrome (CRMS)	No		Yes	1	31			mmol/L	No	None identified				Yes		2 delF508	R117H + 7T		Yes	B. Probable
A. Typical Cystic Fibrosis (CF)	No		Yes		95				Yes		1 3120+1G>A			Yes		1 same			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		No						No	None identified				Yes		2 F508	2789+5G>A		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		104				No	None identified				Yes		2 F508	F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		100			unknown	No	None identified				Yes		2 F508	F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		111				No	None identified				Yes		2 G551D	F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		unknown			unknown	No	None identified				Yes		2 F508	F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		unknown			unknown	No	None identified				Yes		2 F508	F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	bowel obst	No						No	None identified				No					No	B. Probable
A. Typical Cystic Fibrosis (CF)	No		No						No	None identified				Yes		2 F508	F508		No	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Malabsorb	No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		48			MMOL/L	Yes		2 delta F508	P5J		Yes		1 delta F508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	early onset	Yes		109			MMOL/L	Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Neonatal ill	Yes		94			MMOL/L	Yes		1 delta F508			Yes		1 delta F508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Wheezing	Yes		95			MMOL/L	No	None identified				No					Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	loose stool	No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	upper airw	No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	No						Yes		2 delta F508	delta F508		Yes		2 delta F508	delta F508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		95,99			mmol/L	Yes		2 deltaF508	G542X		Yes		2 deltaF508	G542X with 9T/9T		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	Yes		79, 95			mmol/L	No					Yes		1 deltaF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		96,86			mmol/L	No	None identified				Yes		2 deltaF508	deltaF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		66, 89			mmol/L	No	None identified				Yes		2 deltaF508	deltaF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		95,79			mmol/L	No	None identified				Yes		2 deltaF508	deltaF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	No						No					No					No	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		81, 85			mmol/L	Yes		2 deltaF508	p.I336K		Yes		1 deltaF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Meconium	No						No	None identified				Yes		2 deltaF508	711+1G>t		No	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		132			ng/L	No	None identified				Yes		1 DeltaF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		81			MMOL/L	No	None identified				Yes		1 DeltaF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		93			MMOL/L	No	None identified				Yes		2 deltaF508	deltaF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		116				No	None identified				Yes		2 deltaF508	deltaF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		93			MMOL/L	No	None identified				Yes		2 deltaF508	G542X		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes		62				No	None identified				Yes		2 deltaF508	R117H, 5T /9T		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes	2	106	109		mmol/l	No		1 deltaF508			Yes		1 deltaF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	Yes	2	68	92		mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	Yes		68 and 92			mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Steatorrhe	Yes	2	91	92		mmol/L	Yes		2 delF508	c.2061delG		Yes		1 delF508			Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	Yes	2	77	84		mmol/L	No	None identified				Yes		2 delF508	delF508		No	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes	2	87	93		mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	Steatorrhe	Yes	2	91	92		mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	No		Yes	2	101	98		mmol/L	No	None identified				Yes		2 delF508	3659delC		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	steatorrhe	Yes	2	88	95		mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite
A. Typical Cystic Fibrosis (CF)	Yes	meconium	Yes	2	106	97		mmol/L	No	None identified				Yes		2 delF508	delF508		Yes	A. Definite

SUMMARY OF CASE CATEGORIZATION

		Data				
		CF	CRMS	CRD	UNK	
Tool	CF	43	1		3	
	CRMS		7			
	CRD		1	0		
	UNK	1			1	
Incomplete 2						

% CASES CORRECTLY CHARACTERIZED:

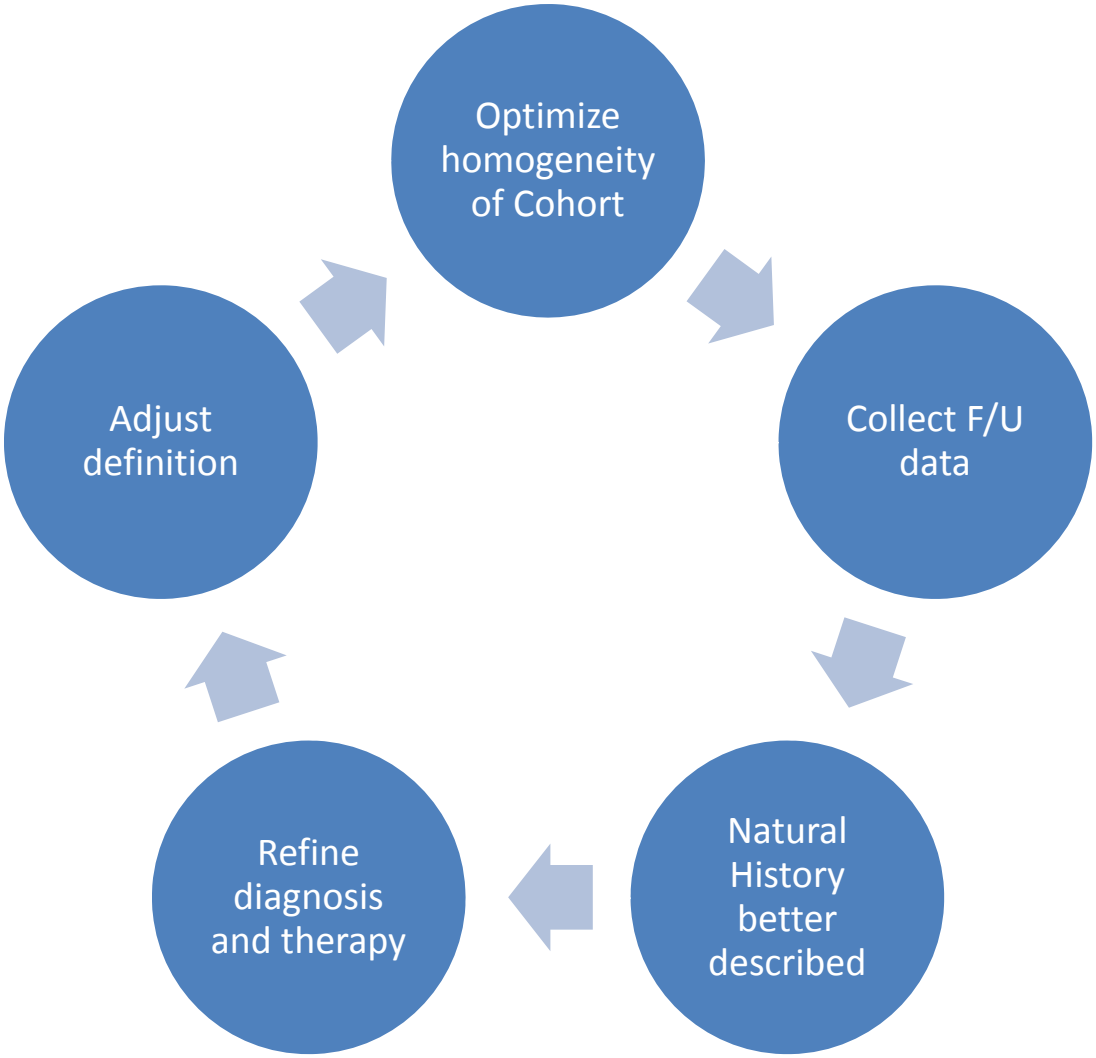
CF 98%

CRMS 77%

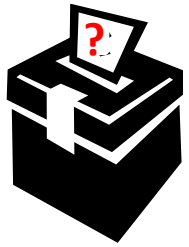
PROBLEMS

- 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

POTENTIAL


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**

CF Clinician → **TOOL** → **Diagnosis**

Defined Clinical Data → **?=**

NBS PROGRAM → **TOOL** → **Diagnosis**

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.