Case Definitions

Joint meeting of the
Newborn Screening and
Genetic Testing Symposium
and the
International Society for
Neonatal Screening
May 5-10, 2013
Atlanta, GA

Anne Marie Comeau, PhD, Deputy Director
New England Newborn Screening Program
Associate Professor, Pediatrics
Pulmonologist report of a missed CF case

<1 yr old
Lung disease, bowel resection, liver transplant
Sweat Cl: 105 mEq/l
Sweat Cl: 92 mEq/l
One copy of 5t
Pulmonologist report of a missed CF case

IRT percentiles: 41, 24, 58

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One copy of 5t

NOT CF
Even the best case definitions (two independent sweat tests) can fail.

When things don’t add up.....
Pulmonologist report of a missed CF case

4 month old
Failure to thrive
Sweat Cl: 60 mEq/l
Pulmonologist report of a missed CF case

IRT percentile: 61.4

5 month old

Failure to thrive

Sweat Cl: 60 mEq/l

Full seq: 711+1G>T; 7t7t
Pulmonologist report of a missed CF case

IRT percentile: 61.4

>6 month old

Failure to thrive

Sweat Cl: 60 mEq/l

Sweat Cl: 35 mEq/l

Full seq: 711+1G>T;7t7t
Pulmonologist report of a missed CF case

IRT percentile: 61.4

>6 month old

Failure to thrive

Sweat Cl: 60 mEq/l

Sweat Cl: 35 mEq/l

Full seq: 711+1G>T;7t7t
In this case, Specialist continues to follow the child in clinic…

It’s not a missed case of CF.

How to characterize this child?

Should newborn screening be trying to find infants with these characteristics?
Newborn Screening May Miss Adrenal-Gland Disorder

TUESDAY, June 12 (HealthDay News) -- Routine newborn screening failed to identify about one-fifth of infants with an adrenal gland disorder called congenital adrenal hyperplasia, a new study has found.

This genetic disorder is characterized by a
Who are these 20% CAH infants not found by newborn screening?

What do they have – and should we be trying to identify those with these conditions?
Babies' blood tests can end in false-positive screening scares

Newborn panels can save lives, but about 200,000 a year aren't accurate.

By JoNel Aleccia
Health writer

After seven years of unexplained infertility, Ann Najdek-Andrada finally had a son, a baby boy who seemed as perfect as she'd always imagined.

But that fantasy was shattered when Gianni was two weeks old. That's when the call came saying the child had tested positive for cystic fibrosis — and that it would take nearly four months to find out for sure.
of the babies we do identify…..some will not have the condition…but do they have something related to it?

Where does “it” end and “related” begin?

What are the characteristics of infants with RUSP and related disorders…
Additional Acknowledgements

Melissa A Parisi, NICHD
Jelili A Ojodu, APHL
Cindy Hinton, CDC
Marci K Sontag, Newsteps, CO SPH
Inderneel Sahai, UMass
Surveillance Case Definitions
for newborn screening

Decision-making
To screen or not to screen
Choice of algorithm

Quality assurance
Quality monitoring of screening

Evaluation and Research
Clinical utility of screening
Defining Surveillance Case Definitions

1. To be developed for each RUSP condition,
2. To be used primarily by newborn screening programs,
3. To be based on clinical and laboratory information available by one year of age,
4. To be assigned based on the fit with pre-determined criteria,
5. To encompass a measure of certainty.

6. NOT to determine whether an infant is treated or followed at a clinic.
Minimum Criteria

Simple format
Outline each set that meet minimum criteria
Clarity relative to ands and ors
Intuitive search…

When NBS receives a STFU diagnosis, where does it fit and how certain is it?
Process

Convene clinical working groups for draft definitions

Standardize formats

Incorporate in a REDCap system at NewSTEPs

Pilot preliminary evaluations in state NBS programs
Case Definition Development

• Clinical Experts –

• Federal and National Partners – CDC, NICHD, NLM, NHLBI, NIH/ORD, ACMG, APHL, NNSGRC
2012 Case Definition Meeting

Swapna Abhyankar
Cindy Ashley
Becky Bailey
Lou Bartoshesky
Linda Beischel
Stan Berberich
Natasha Bonhomme
Bob Bowman
Amy Brower
Michele Caggana
Colleen Clarke
Anne Comeau
Sara Copeland
William Cramer
Hank Dorkin
Roger Eaton
Lisa Feuchtbaum
Bryant Fortner
Lucy Fossen
Debra Freedenberg
Michael Glass
Aaron Goldenberg
Art Hagar
Alaina Harris
Kathryn Hassel
Cindy Hinton
Amy Hoffman
Philis Hoggatt
Patrick Hopkins
Cindy Ingham
Ward Jacox
Carol Johnson
Jamey Kendall
Janice Kong
Michelle Lewis
Sharon Linard
Jennifer Macdonald
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Susan Oliver
Richard Parad
Melissa Parisi
Julie Raburn-Miller
Deborah Rodriguez
Inderneel Sahai
Scott Shone
Susan Tanksley
Laura Taylor
Lois Taylor
Patricia Terry
Tiina Urv
Sheila Weiss
Kupper Wintergerst
Alan Zuckerman
## Pilot Study Participants

<table>
<thead>
<tr>
<th>State</th>
<th>Name</th>
<th>State</th>
<th>Name</th>
</tr>
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<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>
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<tr>
<td>Delaware</td>
<td>Lou Bartoshesky</td>
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<td>Krystal Baumert</td>
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<td>Karen Eveans</td>
</tr>
<tr>
<td>Hawaii</td>
<td>Janice Kong</td>
<td>New York</td>
<td>Beth Vogel</td>
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<tr>
<td>Illinois</td>
<td>Claudia Nash</td>
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<td>Kansas</td>
<td>Jamey Kendall</td>
<td>Utah</td>
<td>Kim Hart</td>
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<td>Louisiana</td>
<td>Colleen Clarke</td>
<td>Vermont</td>
<td>Cynthia Ingham</td>
</tr>
<tr>
<td>Maryland</td>
<td>Johnna L. Watson</td>
<td>Virginia</td>
<td>Jennifer MacDonald</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>Anne Comeau</td>
<td></td>
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<tr>
<td></td>
<td>Neela Sahai</td>
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<tr>
<td>RUSP CONDITION</td>
<td># STATES PILOTING</td>
<td># CASES CONTRIBUTED</td>
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<tr>
<td>CAH</td>
<td>8</td>
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<tr>
<td>CONGENITAL HYPOTHYROIDISM</td>
<td>6</td>
<td>68</td>
<td></td>
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<tr>
<td>CYSTIC FIBROSIS</td>
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# Congenital hypothyroidism

<table>
<thead>
<tr>
<th>Primary Congenital Hypothyroidism</th>
<th>Category</th>
<th>Serum TSH mU/L*</th>
<th>Serum Total or Free T4*</th>
<th>Other studies</th>
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<tbody>
<tr>
<td></td>
<td>Definite</td>
<td>TSH &gt; 10</td>
<td>&lt; age established reference range</td>
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<tr>
<td></td>
<td>Probable</td>
<td>TSH &gt; 10</td>
<td>normal T4/total T4</td>
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<td>Possible**</td>
<td>TSH 6-10</td>
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<td>Possible**</td>
<td>TSH 6-10</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Incomplete</td>
<td>Untested or unknown</td>
<td>Untested or unknown</td>
<td></td>
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<td></td>
<td>Definite</td>
<td>TSH &lt; 10</td>
<td>&lt; age established reference range</td>
<td>documentation of other pituitary hormone deficiencies or midline defects</td>
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<td>Probable**</td>
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</table>
## Congenital Hypothyroidism

Please Choose One:

<table>
<thead>
<tr>
<th>Hypothyroidism type</th>
<th>Frequency Reported</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>A. Primary Congenital Hypothyroidism</td>
<td>66</td>
<td>97.06</td>
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<tr>
<td>B. Secondary Congenital Hypothyroidism</td>
<td>1</td>
<td>1.47</td>
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<tr>
<td>Does not match A or B</td>
<td>1</td>
<td>1.47</td>
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</table>
68 RECORDS

66 listed as Definite Primary Congenital Hypothyroidism
  28  Definite (TSH > 10 and fT4 < age adj ref range)
  28  Probable (TSH > 10)
  3   Possible (TSH 6-10)
  7   Incomplete – no data

1 listed as Secondary Congenital Hypothyroidism
  1   Incomplete (TSH < 10)

1 no diagnosis available.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical</th>
<th>Sweat Chloride</th>
<th>Non Newborn Screen Molecular</th>
<th>Newborn Screen Molecular</th>
<th>NBS Result</th>
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<tbody>
<tr>
<td>Definite</td>
<td>&gt;=60 mmol/L (regardless of age)</td>
<td></td>
<td>2 CF disease-causing mutations</td>
<td>2 CF disease-causing mutations in trans –</td>
<td></td>
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<tr>
<td>Definite</td>
<td>No valid sweat chloride result available</td>
<td></td>
<td></td>
<td>2 CF disease-causing mutations in trans</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>&lt;60 mmol/L</td>
<td></td>
<td>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&gt;T)</td>
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<td></td>
</tr>
<tr>
<td>Definite</td>
<td>No known medical condition associated with false</td>
<td>&gt;=60 mmol/L x 2 (regardless of age, two independent results)</td>
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</table>
## Discordant certainties

**listed as type: CF definite**

<table>
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<tr>
<th>Complete?</th>
<th>Field25</th>
<th>annes determination</th>
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<tr>
<td>A. Definite</td>
<td>2 nbs mut, 1 96</td>
<td>definite</td>
</tr>
<tr>
<td>A. Definite</td>
<td>2 nbs, 1 101, 1 98</td>
<td>definite</td>
</tr>
<tr>
<td>A. Definite</td>
<td>2 nbs, 1 93, 1 92</td>
<td>definite</td>
</tr>
<tr>
<td>A. Definite</td>
<td>2 nbs mut, 1 68 and 1 92</td>
<td>definite</td>
</tr>
<tr>
<td>A. Definite</td>
<td>1 mut 1 95</td>
<td><strong>incomplete</strong></td>
</tr>
<tr>
<td>A. Definite</td>
<td>1 nbs mut, 1 99</td>
<td>incomplete</td>
</tr>
<tr>
<td>A. Definite</td>
<td>1 nbs mut, 1 dx mut, 1 94</td>
<td>no fit</td>
</tr>
<tr>
<td>A. Definite</td>
<td>1 nbs, 1.5 dx, 1 92</td>
<td><strong>no fit</strong></td>
</tr>
<tr>
<td>A. Definite</td>
<td>1 nbs mut, 1 81</td>
<td>no fit</td>
</tr>
</tbody>
</table>
Cystic fibrosis

• 45 Listed as typical CF definite
  – 28 met criteria
  – 5 better fit is probable
  – 3 better fit is incomplete
  – 1 better fit is CRMS
  – 8 no good fit- want to avoid judgment calls
Status

Still have some work to do. Data elements may need more clarity. All permutations need to be available. Training of Programs and Clinicians to ensure quality data.

Thank-you
Looking forward to your comments!
Thank-you