MDH Minnesota Department of Health

CF Screening in Minnesota

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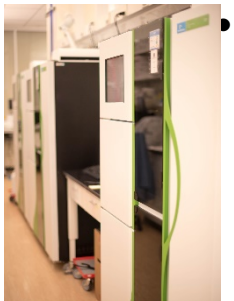
CF Screening

- Demographic entry
- Laboratory
  - Test <u>all</u> specimens regardless of quality
  - 1st tier = IRT by time-resolved FIA
    - Use Genetic Screening Processors (GSPs)
  - 2nd tier = Molecular
    - Use Luminex

CF Mutation Panel:

ΔF508	1717-1G>A	W1282X	2307insA
ΔI507	R560T	N1303K	Y1092X>
G542X	R553X	394delTT	M1101K
G85E	G551D	Y122X	S1255X
R117H	1898+1G>A	R347H	3876delA
621+1G>T	2184delA	V520F	3905insT
711+1G>T	2789+5G>A	A559T	
1078delT	3120+1G>A	S549N	*5T/7T/9T*
R334W	R1162X	S549R	*F508C*
R347P	3659delC	1898+5G>T	*I507V*
A455E	3849+10kbC>T	2183AA>G	*I506V*



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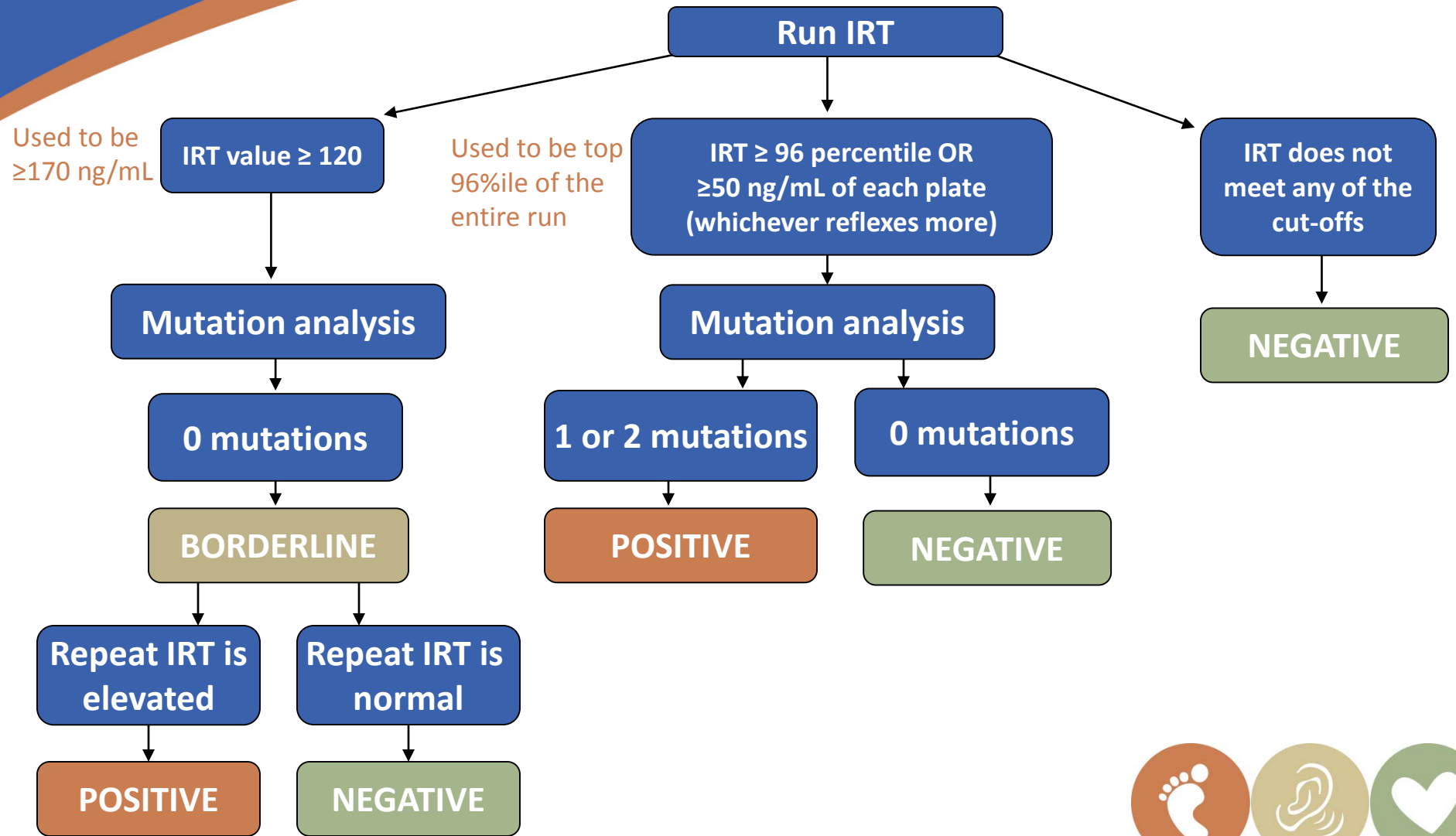
Laboratory Screening Algorithm



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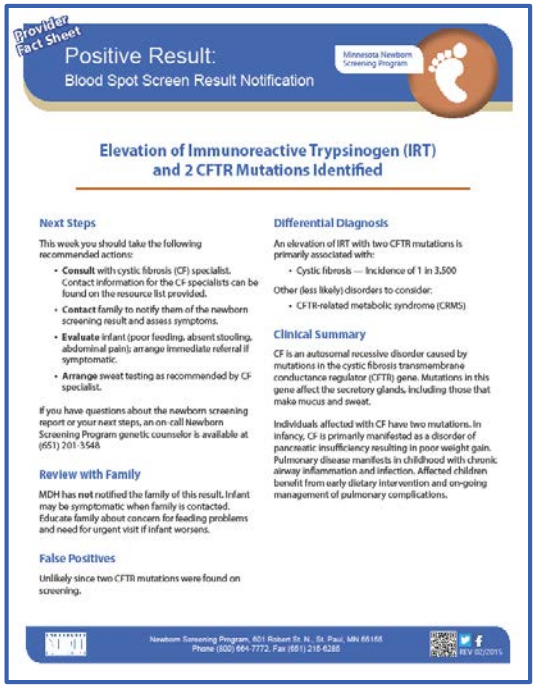
CF Notification

- MDH Genetic Counselors
  - Primary care clinic/provider notification
    - Borderline = repeat screen
    - Positive = sweat test at CF Center
  - CF Centers notification (positives only)



Provider Fact Sheet

Positive Result:
Blood Spot Screen Result Notification

Minnesota Newborn Screening Program

Elevation of Immunoreactive Trypsinogen (IRT) and 2 CFTR Mutations Identified

Next Steps

This week you should take the following recommended actions:

- **Consult** with cystic fibrosis (CF) specialist. Contact information for the CF specialists can be found on the resource list provided.
- **Contact** family to notify them of the newborn screening result and assess symptoms.
- **Evaluate** infant (poor feeding, absent stooling, abdominal pain); arrange immediate referral if symptomatic.
- **Arrange** sweat testing as recommended by CF specialist.

If you have questions about the newborn screening report or your next steps, an on-call Newborn Screening Program genetic counselor is available at (651) 201-5548.

Review with Family

MDH has **not** notified the family of this result. Infant may be symptomatic when family is contacted. Educate family about concern for feeding problems and need for urgent visit if infant worsens.

False Positives

Unlikely since two CFTR mutations were found on screening.

Differential Diagnosis

An elevation of IRT with two CFTR mutations is primarily associated with:

- Cystic fibrosis — Incidence of 1 in 3,500

Other (less likely) disorders to consider:

- CFTR-related metabolic syndrome (CRMS)

Clinical Summary

CF is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Mutations in this gene affect the secretory glands, including those that make mucus and sweat.

Individuals affected with CF have two mutations. In infancy, CF is primarily manifested as a disorder of pancreatic insufficiency resulting in poor weight gain. Pulmonary disease manifests in childhood with chronic airway inflammation and infection. Affected children benefit from early dietary intervention and on-going management of pulmonary complications.

Newborn Screening Program, 601 Robert St. N., St. Paul, MN 55155
Phone (800) 664-7772, Fax (651) 215-6285

REV 02/2015

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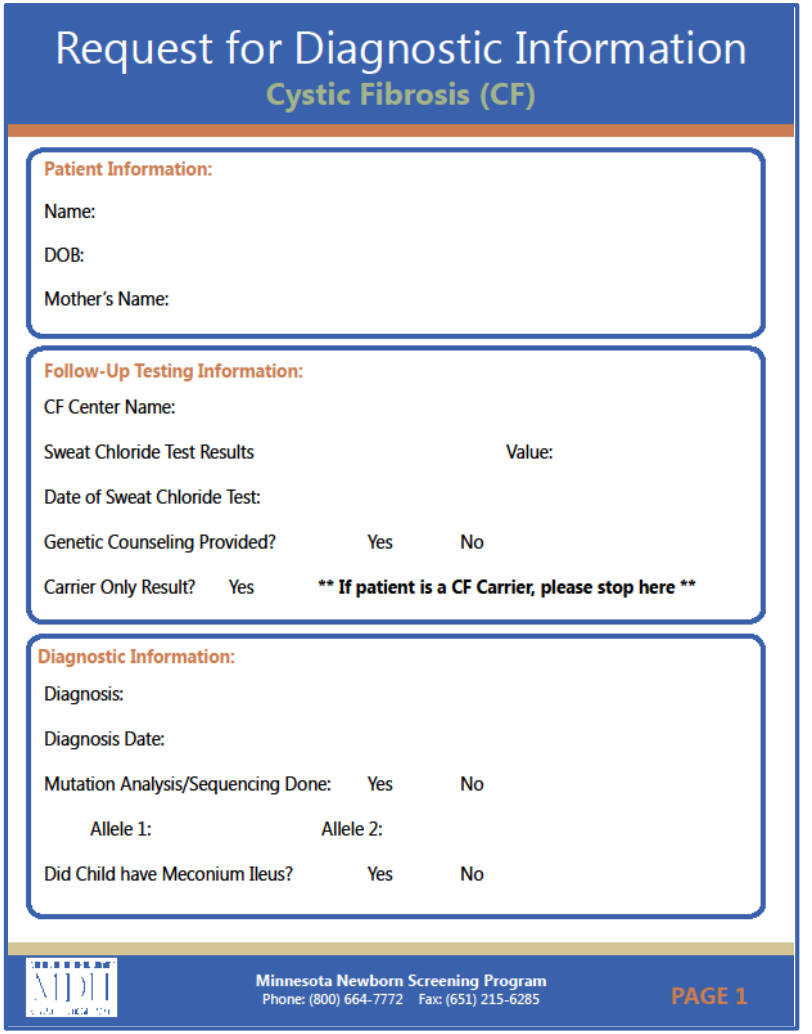
CF Follow-up

- CF Centers
  - Notify us of follow-up outcomes
  - Inform us of false negatives
- MDH Health Program Representatives
  - Tracks diagnostic outcomes



Request for Diagnostic Information
Cystic Fibrosis (CF)

Patient Information:

Name:

DOB:

Mother's Name:

Follow-Up Testing Information:

CF Center Name:

Sweat Chloride Test Results Value:

Date of Sweat Chloride Test:

Genetic Counseling Provided? Yes No

Carrier Only Result? Yes ** If patient is a CF Carrier, please stop here **

Diagnostic Information:

Diagnosis:

Diagnosis Date:

Mutation Analysis/Sequencing Done: Yes No

Allele 1: Allele 2:

Did Child have Meconium Ileus? Yes No

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Special Circumstances

- Clinical Concern or At-risk Individuals
  - E.g., newborn with meconium ileus, known family history, etc
  - Providers notify MDH GC's, GC's notify the lab to pursue molecular without regard to the IRT level, GC's notify the initiating provider of the result

Special Circumstances

- "Border Babies"
  - Work well with other states and the border state CF Centers
    - Have had two newborns recently where one moved to Michigan and another to Washington
    - Both infants were still able to have a sweat test performed in <30 days

Challenges

- Missed Cases
  - IRT not high enough to flag 2nd tier
    - Had a false negative in 2015 because IRT was 51.3 ng/mL
    - Added fixed cut-off of ≥50 ng/mL
  - Floating cut-off varies from day to day
    - Added fixed cut-off of ≥50 ng/mL
  - Off-panel mutations (esp. for nonwhite ethnic groups)
    - Case scenario

Case Scenario

- July 7, 2015
  - Newborn screen with IRT of 391.5 and delta F508 mutation
  - GC call to primary care clinic; find out baby has Hispanic heritage. Recommend consultation this week (usually it is at one month).
- First WCC – doctor asked mom if Dept of Health has called her because her son screened positive for CF; arranges sweat test.
- August 27, 2015 - Follow-up staff reach out to CF Centers – not in system
- October 2015 – Follow-up staff reach out to PCP and get normal sweat test results from a medical group that is not on our list of CF Centers; sweat test was done on 8/3/15 and were 27 and 25 with a cut-off of 29. Case closed as false positive.
- January 11, 2016 – learn that child is at a hospital with failure to thrive and is about to get a feeding tube; sweat test results positive at 103 and 114.

Take-aways/Solutions from Case Scenario

- Good reminder to state with each notification that family is not aware of the result and that they need to tell them
- Earlier short-term follow-up for cases where there are two mutations or an IRT of >100 with one mutation (currently 45 days→2 weeks)
- Results were normal but from a non-accredited center, follow-up staff now have to consult with a GC
- Created a document that will go out with each notification that will describe why a CFF-accredited center is important

- Expand panel or do next generation sequencing?

Challenges

- Timeliness
  - Sweat test recommended around 1 month of age (consult earlier for positives with 2 mutations)
    - MN specialists have expressed that sweating too early can result in QNS results → negative impacts for families (time, lost wages, additional costs to come back, winter travel conditions, etc)
  - Do not perform 2nd tier molecular on weekends/holidays
    - Would require additional staff, increase costs, etc
  - One disorder category where it is not unusual for families to decline follow-up (e.g., had prenatal testing or known family history and mutations are on our panel)
    - Education? Expand panel?
  - Travel to accredited centers; made more complicated by MN winters
    - Encourage non-accredited centers to seek accreditation?

Challenges

- Variable Factors
  - NICU newborns
  - IRT is not perfect as a first tier
  - CRMS/CF-SPID
  - Meconium ileus masking IRT
- Psychosocial
  - False positive heterozygotes and parental anxiety

Long-Term Follow-up

- Typically track long-term data/outcomes
- Due to historical and program reasons, MDH doesn't track LTFU for CF. LTFU meets with CF Centers periodically to share family/financial resources.
- LTFU seeks to better partner with CF centers to better understand system gaps and maximize patient outcomes.