Cystic Fibrosis Newborn Screening Update

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WA State Department of Health

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Seattle Children’s CF Clinic

For persons with disabilities, this document is available on request in other formats. To submit a request, please call 1-800-525-0127 (TDD/TTY call 711).
Cystic Fibrosis

- Autosomal recessive inherited disorder due to variants in the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial ion channel
- Characterized by
  - Exocrine pancreatic insufficiency resulting in digestive issues and risk for poor growth
  - Abnormal mucociliary clearance leading to chronic cough, chronic airway infection, progressive obstructive lung disease
- Very effective therapies now available
- Most common life-limiting disease among Caucasians though seen in all races/ethnicities
- ~30,000 diagnosed cases in US
- 10-15 infants per year diagnosed in WA State
CF Newborn Screening

• Started in WA State in 2006
• Universal in all 50 states by 2010
• Basis of all CF NBS algorithms is detection of elevated immunoreactive trypsinogen (IRT) in dried blood spot (marker of pancreatic stress)
• Most states use IRT-DNA algorithm
  • If IRT elevated on 1st DBS, genetic testing for CFTR variants conducted on that DBS
  • High sensitivity (~97-98%) but detects carriers in ~10:1 ratio compared to cases
• WA State originally chose IRT-IRT algorithm
  • We are one of several states that collect a routine 2nd DBS
  • Elevated IRT on 1st and 2nd DBS considered a + screen
  • Relatively high sensitivity (95-96%) while minimizing carrier detection
IRT-IRT-DNA algorithm

• We have now decided to change our algorithm to IRT-IRT-DNA
  • By adding genetic testing for CFTR variants, can lower IRT cut-off
  • Increases sensitivity from ~96% to 98% without huge increase in carrier detection
  • Originally developed in CO; also used in TX and several other states

• Start goal: May 15, 2019
Newborn Screening Algorithm Overview
Current Algorithm

• IRT-IRT: looking for persistent elevation ➔ refer for sweat chloride test

• IRT Cutoffs
  • 100 on 1st screen
  • 70 on 2nd screen

• Follow-up dependent on age, birth weight and clinical status
  • Limited DNA testing
    • Sick or too small for SwCl
    • Only DF508
New Algorithm

• IRT-IRT-DNA: looking for persistently elevated IRT → run DNA

• IRT cutoff lowered to 60 for both screens
  • If 1st screen elevated and 2nd screen not received by 16 days of life, lab will run DNA on 1st specimen
1st IRT (24 to 48 hours) > 60 ng/mL

2nd IRT (7 to 14 days) > 60 ng/mL

DNA mutation analysis (41 mutations)

Other Paths to DNA Testing:

Path 1:
- 1st IRT > 60 ng/mL
- 2nd IRT not received by DOH < 16 DOL

Path 2: "2nd Tier Protocol"
- 1st IRT 50-60 ng/mL
- 2nd IRT > 85 ng/mL (triggers 3rd IRT)
- 3rd IRT > 60 ng/mL

0 mutations identified

Normal

Report As Negative No Further Action

1 mutation identified

Likely CF Carrier but CF possible

Referral for sweat test at lab affiliated with accredited CF Center within 48-72 hours (newborn should be > 2 kg and 10 days of age to 4 weeks of age)

2 mutations identified

Presumed CF

Immediate referral to accredited CF Center within 48 hours for initiation of care and confirmatory tests

*unless clinical concerns arise*
CFTR Variant Panel

- 206 babies with CF born in WA since 2006
- Genotype analysis
- ACMG recommended panel

- Recommended panel by DOH of 41 disease-causing variants
- Approved by pulmonologists at SCH
<table>
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<td>Babies with (+) IRT results</td>
<td>46/week</td>
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<td>Babies with DNA run</td>
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<td>Babies with CF identified through NBS</td>
<td>11-16/year</td>
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<td>Babies who are carriers, but not affected</td>
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How do I interpret the results of the new CF NBS?

- If 1st IRT is elevated and 2nd is normal, screen is considered normal and nothing needs to be done.
- If 1\textsuperscript{st} and 2\textsuperscript{nd} IRTs are elevated, DNA analysis will be performed by state.
  - If no variants identified, nothing more needs to be done unless baby is symptomatic.
  - If 1 variant identified, baby has about a 10% chance of having CF (90% chance of being a carrier).
  - If 2 variants identified, baby very likely has CF.
- If 1\textsuperscript{st} IRT elevated and 2\textsuperscript{nd} DBS not collected in a timely fashion, DNA analysis will be performed on 1\textsuperscript{st} DBS.
What do I do when I get the results?

• If the newborn screen is normal, nothing needs to be done unless the baby is symptomatic

• If 1 variant identified (10% chance of CF),
  • Refer baby for a sweat test within 2 to 3 business days at a CF Foundation-accredited lab
    • If normal, baby most likely a carrier
      • Consider genetic counseling
    • If sweat test positive (>60) or in intermediate range (30-59), refer immediately to CF center
    • If QNS and baby without symptoms, repeat in 6 weeks

• If 2 variants identified (baby very likely has CF),
  • Refer to CF center for visit within 2 to 3 business days
PCP Materials
Changes

- Variant-specific packets
  - Sweat test lab requisition form only for 1 variant
  - Referral to CF care center for 2 variants
- Incorporated feedback from:
  - Pulmonology specialists
  - Genetic counselors
  - Parent advisory group
  - Survey of local primary care practices
  - DOH team
1 Variant Identified

PCP Actions:
- Within 24 hours: Notify and discuss results with parent(s)
- Within 2-3 business days: Refer for SwCl test and provide parents with scheduling number
- Complete and return Referral Notification Form
Referral Packet: 1 Variant Identified

NEWBORN SCREENING RESULTS & NEXT STEPS
Cystic Fibrosis (CF) – 1 Variant

BABY NAME | DOB 1/1/2018 | MOTHER: MOM NAME

Two dried bloodspot samples were submitted to the State Newborn Screening lab for the infant above. The levels of immunoreactive trypsinogen (IRT) were found to be elevated for both specimens. In addition, one variant in the CF gene was detected on the newborn screening CF variant panel. These results indicate that this child may have CF. See below for result details.

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<th>State Laboratory #</th>
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<th>Normal IRT range for Age</th>
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NEXT STEPS

☐ Notify parents of results within 24 hours and discuss the following key points:

- Results: Newborn screening identified one change (variant) in this baby’s CF gene, which indicates this baby may have CF (about a 1 in 10 chance).
- Disease: CF is a genetic disease that primarily impacts breathing and digestion. It is a chronic disease that requires life-long treatment. In order to have CF, a baby must have two variants in their CF gene, but the newborn screening CF variant panel does not screen for all known variants. A sweat test is needed to evaluate whether the baby has CF.
- Diagnostic test: Babies with CF have better outcomes if diagnosed and treated as early as possible. The baby should have a sweat test done ASAP to confirm or rule out CF. The sweat test is a simple, painless test that measures the amount of salt in the sweat. Results of the sweat test are usually available the same day. Babies with normal sweat tests are likely to be CF “carriers” and no further action is needed unless there are clinical concerns. Babies with sweat chloride ≤50 mEq/L have CF and need to be referred to a CF Foundation-accredited care center within 2 to 3 business days to initiate appropriate therapies. Babies with intermediate sweat chloride values (50-59 mEq/L) may have CF and need to be referred to a CF Foundation-accredited care center within 2 weeks for further testing.
- Care plan: No special care (such as dietary changes) is needed for this baby at this time.

☐ Refer and facilitate scheduling diagnostic sweat chloride test at an accredited Cystic Fibrosis Foundation care center/collection site (see attached list) within 2 to 3 business days.
- Complete the attached lab requisition form and fax form to the appropriate laboratory.
- Provide the associated sweat test scheduling number as well as the attached informational materials to the family and have them call to schedule the test in the next 1-2 days.
- Include a copy of this informational packet in the patient’s electronic medical record.
- Complete and send Referral Notification Form back to the Newborn Screening Program.

QUESTIONS?

Newborn Screening Program: Reesha Recnal, Disorder Follow-up Consultant; 206-418-5421
Clinical Consultations Dr. Margaret Rosenfeld, Seattle Children’s Hospital, 206-587-5644

More Information about CF: see attached materials or visit the Cystic Fibrosis Foundation website at www.cff.org/What-is-CF/Testing
NEWBORN SCREENING DISORDER—FACT SHEET
Cystic Fibrosis (CF) – 1 Gene Variant Identified

NEWBORN SCREENING FINDINGS
The state laboratory performs newborn screening on tiny samples of blood taken from a baby’s heel after birth. The screening test for CF measures the amount of an enzyme in a baby’s blood called immunoreactive trypsinogen (IRT). If a baby’s IRT level is higher than expected, the lab looks for changes (called variants) in the CF gene. This baby had a positive newborn screen for CF because one variant was found. Additional testing with a test called a sweat test is needed to determine if this baby has CF. This baby has about a 1 in 10 chance of having CF.

ABOUT THE CONDITION
CF is a treatable disorder that affects the body’s control of salt levels. It causes thick, sticky mucus to build up in the lungs, digestive system and other organs. In order to have CF, a baby must have two variants in the CF gene, one from each parent. Babies with only one variant are called “carriers” and do not have symptoms of CF. The newborn screening genetic panel can miss some variants, so we do not yet know whether this baby has one or two variants. About one in every 3,500 babies in the United States is born with CF.

SIGNS/SYMPTOMS
Signs of CF may include difficulty gaining weight, frequent/bulky stools, cough and respiratory infections. CF causes thick, sticky mucus to build up in the lungs and digestive system, leading to respiratory and digestive problems that can be very serious. Early detection and treatment is important to improve the digestive problems, growth and breathing difficulties. CF cannot be cured at the present time, but special medicines can control many of the effects.

TREATMENT
Treatments will vary depending on the baby, but will typically include medicine to help the baby’s digestion, a high-calorie diet and special chest therapy. People with CF receive their CF care at specialized CF centers.

NEXT STEPS
Babies with one CF variant detected need a sweat test to determine if they have CF. The sweat test is a simple, painless test that measures the amount of salt in the sweat. Babies with CF have a high level of salt in their sweat. This test is performed only at Cystic Fibrosis Foundation accredited care centers. Results are usually available the same day. If a baby doesn’t make enough sweat to give a result, the test will be repeated when the baby is a little older.

Babies with normal sweat tests are likely to be CF carriers. Their families can see a genetic counselor to talk about the CF carrier result, but the baby does not need any more CF testing unless the baby shows symptoms of CF later. Babies with abnormal sweat tests most likely have CF and should be referred immediately to an accredited CF care center for medical care. Some babies will have intermediate sweat test results and also need to be referred to an accredited CF care center for more testing. No special treatment or diet is necessary for the baby at this time based on the positive newborn screen.
NEWBORN SCREENING DISORDER CLINICAL RESOURCES

Cystic Fibrosis (CF)

ACCREDITED CF CARE CENTERS

**Seattle**
Seattle Children’s Hospital Cystic Fibrosis Center
4800 Sand Point Way NE
Seattle, WA 98105-5371
Phone: (206) 987-2024
Fax: (206) 985-3124

*Sweat test scheduling:* (206) 987-3860

**Tacoma**
Mary Bridge Children’s Health Center
Cystic Fibrosis Center
311 S. “L” St.
Tacoma, WA 98405
Phone: (253) 792-6630

*Sweat test scheduling (Tacoma or Olympia):*
(253) 403-1187

**Military Families**
Madigan Army Medical Center
Cystic Fibrosis Center
9040 Jackson Ave
Joint Base Lewis-McChord, WA 98431
Phone: (253) 968-2310
Fax: (253) 968-5294

*Sweat test scheduling:* (253) 968-2310

**Spokane**
Providence Physician’s Group at Sacred Heart
Cystic Fibrosis Clinic
105 W. 8th Ave, Suite 660E
Spokane, WA 99204
Phone: (509) 474-6960
Fax: (509) 474-6961

*Sweat test scheduling:* (509) 474-4403

**Yakima (sweat collection ONLY)**
Virginia Mason Memorial Hospital
Seattle Children’s Affiliate Sweat Collection Site
2811 Tieton Dr
Yakima, WA 98902
Phone: 509-575-8445
Fax: 509-577-5000

*Sweat test scheduling:* 509-575-8445

**Portland**
Oregon Health & Science University
Cystic Fibrosis Center
707 SW Gaines
Portland, OR 97239-2998
Phone: (503) 494-8023

*Sweat test scheduling:* (503) 494-7882

ONLINE RESOURCES

Cystic Fibrosis Foundation
[www.cff.org](http://www.cff.org)
[https://www.cff.org/What-is-CF/Testing](https://www.cff.org/What-is-CF/Testing)
PCP & PARENTS – COMPLETE THIS SECTION TO AVOID DELAY OF TEST RESULTS

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<th>Baby’s Last Name</th>
<th>Baby’s First Name</th>
<th>Baby’s Middle Name</th>
<th>Baby’s Birth Date</th>
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<tr>
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<td>Mother’s First Name</td>
<td>Mother’s Middle Name</td>
<td>Diagnosis Code</td>
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Ordering Provider: Send Report to

Address, City, State, Zip

Phone, Fax

Results will also be forwarded to the WA State Newborn Screening Lab.

BILLING INFORMATION

*All tests will be billed to the referring institution unless complete billing and diagnosis information is provided when appropriate.

BILL TO: ☐ Referring institution (provide billing address if different from report address) ☐ Insurance (attach copy of card)

☐ DHSH (attach coupon) Seattle Children’s is able to bill Medicaid from Alaska, Idaho, Montana & Washington only

Guarantor/Insurance Subscriber: Subscriber DOB: Relationship to Patient

Address, City, State, Zip

Phone

Insurance Company: Group Number: Policy Number

Claims Address, City, State, Zip

IMPORTANT INFORMATION REGARDING MEDICAL NECESSITY

PHYSICIAN NOTIFICATION: Only tests that you believe are appropriate for patient care should be ordered. Medicare/Medicaid will pay only for tests that are medically necessary for the diagnosis and treatment of the patient, rather than for screening purposes.

NEWBORN SCREENING FOLLOW-UP TESTING FOR: CYSTIC FIBROSIS

DIAGNOSTIC TEST AND INSTRUCTIONS

• Sweat Chloride Test (Pilocarpine Iontophoresis Sweat Chloride Determination)
  o Infant should weigh > 2 Kg (4.4 lbs) with corrected gestational age at least 36 weeks

PLEASE SCHEDULE SWEAT TEST AND FAX THIS REQUISITION FORM TO THE APPROPRIATE LABORATORY:

<table>
<thead>
<tr>
<th>Lab Name</th>
<th>Scheduling #</th>
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<tbody>
<tr>
<td>Seattle Children’s Hospital, Seattle</td>
<td>(206) 987-3860</td>
<td>(206) 985-3124</td>
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<tr>
<td>Mary Bridge Children’s Hospital, Tacoma or Olympia</td>
<td>(253) 403-1187</td>
<td>(253) 403-4339</td>
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<tr>
<td>Virginia Mason Memorial Hospital, Yakima</td>
<td>(509) 575-8445</td>
<td>(509) 452-5000</td>
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<tr>
<td>Sacred Heart Medical Center, Spokane</td>
<td>(509) 474-4403</td>
<td>(509) 474-6961</td>
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<tr>
<td>Oregon Health Sciences University, Portland</td>
<td>(503) 494-7682</td>
<td>(503) 494-8898</td>
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<tr>
<td>Medigan Army Medical Center, Tacoma</td>
<td>(253) 568-2310</td>
<td>(253) 568-5294</td>
</tr>
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* Please note: Some infants may not produce an adequate volume of sweat to perform a valid sweat chloride test. If the volume of sweat collected is insufficient, we generally recommend attempting a repeat sweat test at six weeks of age. If you wish to discuss this result further, please contact the CF clinic associated with the laboratory where the sweat testing was performed.*

**FOR LABORATORY SITE: Please fax copy of results to Newborn Screening Program at (206) 363-1610**
2 Variants Identified

PCP Actions:

- Within 24 hours: Notify and discuss results with parent(s)
- Within 2-3 business days: Refer to accredited CF care center and schedule initial appointment
- Complete and return Referral Notification Form
Referral Packet: 2 Variants Identified

NEWBORN SCREENING RESULTS & NEXT STEPS
Cystic Fibrosis (CF) – 2 Variants

BABY NAME | DOB 1/1/2018 | MOTHER: Mom Name

Two dried bloodspot samples were submitted to the State Newborn Screening lab for the infant above. The levels of Immunoreactive trypsinogen (IRT) were found to be elevated for both specimens. In addition, two variants in the CF gene were detected on the newborn screening CF variant panel. These results indicate that this child very likely has CF. See below for result details.

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<th>Normal IRT range for Age</th>
<th>Status</th>
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<td>75</td>
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</table>

NEXT STEPS

- Notify parents of results within 24 hours and discuss the following key points:
  - **Results:** Newborn screening identified two changes [variants] in this baby’s CF gene. The result indicates it is very likely that this baby has CF.
  - **Disease:** CF is a genetic disease that primarily impacts breathing and digestion. It is a chronic disease that requires lifelong treatment.
  - **Clinical evaluation:** Babies with CF have better outcomes if diagnosed and treated as early as possible. The baby should be seen at a CF center ASAP where the specialist can discuss the diagnosis, begin necessary treatments and arrange any additional testing.
  - **Care plan:** No special care (such as dietary changes, respiratory treatments) is needed for this baby while they wait to be seen in CF clinic. If there is a delay in being seen, the CF care team will call the family to discuss initiating appropriate therapies (such as pancreatic enzyme replacement therapy).
  - Refer and call to schedule clinic visit at an accredited Cystic Fibrosis Foundation care center (see attached list) within 2 to 3 business days.
  - Provide parent(s) a copy of the informational materials attached – Disorder Fact Sheet and Clinical Resources.
  - Include a copy of this informational packet in the patient’s electronic medical record.
  - Complete and send Referral Notification Form back to the Newborn Screening Program.

QUESTIONS?

Newborn Screening Program: Reesa Reonal, Disorder Follow-up Consultant, 206-418-5421

MORE INFORMATION ABOUT CF: see attached materials or visit the Cystic Fibrosis Foundation website at www.cff.org/What-is-CF/Testing

Clinical Consultation:
Dr. Margaret Rosenfeld,
Seattle Children’s Hospital
206-987-5544
Cystic Fibrosis (CF) – 2 Gene Variants Identified

NEWBORN SCREENING FINDINGS
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ABOUT THE CONDITION
CF is a treatable disorder that affects the body's control of salt levels. It causes thick, sticky mucus to build up in the lungs, digestive system and other organs. In order to have CF, the baby must have two variants in the CF gene, one from each parent. About one in every 3,500 babies in the United States is born with CF.

SIGNS/SYMPTOMS
Signs of CF may include difficulty gaining weight, frequent/bulky stools, cough and respiratory infections. CF causes thick, sticky mucus to build up in the lungs and digestive system, leading to respiratory and digestive problems that can be very serious. Early detection and treatment is important to improve the digestive problems, growth and breathing difficulties. CF cannot be cured at the present time, but special medicines can control many of the effects.

TREATMENT
Treatments will vary depending on the baby, but will typically include medicine to help the baby’s digestion, a high-calorie diet and special chest therapy. People with CF receive their CF care at specialized CF centers.

NEXT STEPS
Babies with two variants detected most likely have CF and should be referred immediately to an accredited CF care center for clinical evaluation. There are centers in Seattle, Tacoma, Spokane, and Portland, Oregon. The specialists at the CF care center will be able to discuss the diagnosis, start necessary treatments and order additional testing if needed. The baby does not need any special diet or treatments while waiting to be seen at the CF Clinic unless there is an unexpected delay. Then the specialists at the CF clinic will call you to discuss what to do while waiting.
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Cystic Fibrosis (CF)

ACCREDITED CF CARE CENTERS

**Seattle**
Seattle Children’s Hospital Cystic Fibrosis Center
4800 Sand Point Way NE
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Questions?
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* Category refers to the QuantStudio classification of variants available for the custom CFTR panel.