DISCLAIMER:

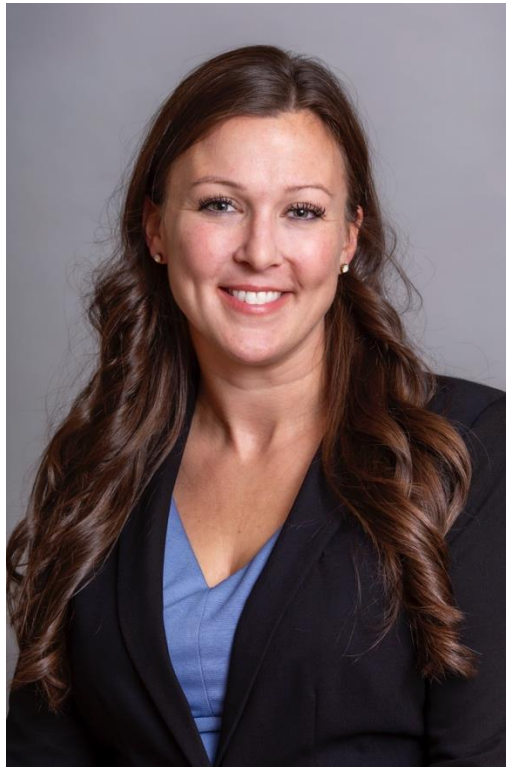
The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Ohio Department of Health.

# Cystic Fibrosis Newborn Screening in Ohio: Need to Know Information for the Primary Care Provider

January 21, 2025

# Who Are We?

**Silvia Cardenas MD, FAAP, FACCP**
Director, Cystic Fibrosis Newborn Screening Program
Associate Director, Pediatric Cystic Fibrosis Center
Cleveland Clinic Children's



**Jessica A. Roach APRN, CNP**
Nurse Practitioner, Pulmonary Medicine
Cystic Fibrosis Center Coordinator
Cincinnati Children's Hospital

**Julianne E Hartmann, MS, CGC**
Licensed, Certified Genetic Counselor
Coordinator, CF Newborn Screening Follow-Up Program
Division of Human Genetics
Cincinnati Children's Hospital

**Katelyn Krivchenia, MD**
Director of the Cystic Fibrosis
Newborn Screening Program
Associate Professor
Nationwide Children's Hospital

# Disclosures

Grant funding from Cystic Fibrosis Foundation (CFF)

*To improve process of sweat chloride testing and decrease late or missed diagnosis of cystic fibrosis.*

Educational outreach to primary care providers in Ohio regarding CF NBS

# Objectives

**Earlier diagnosis improves outcomes.**

- Explore changes in prognosis for babies with CF with early treatment

**The newborn screen is just a screening test.**

- Understand the limitations of the Ohio CF newborn screen

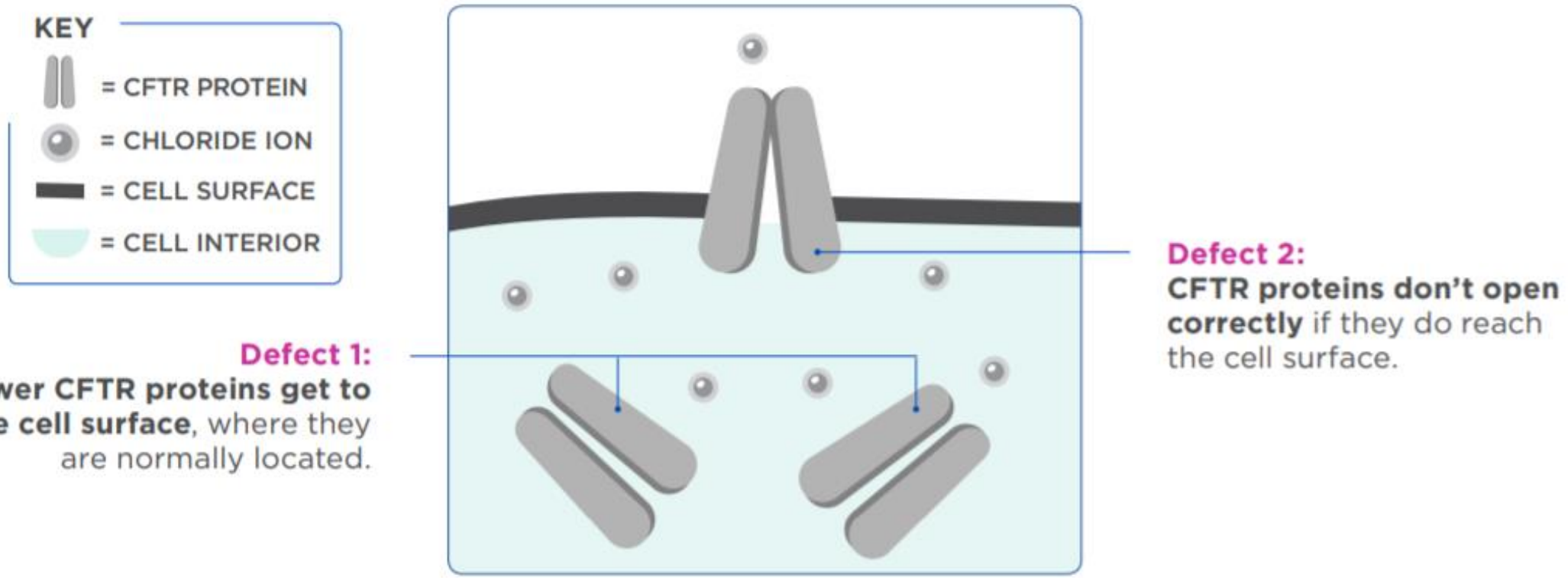
**Who needs a referral for more testing?**

- Review next steps for abnormal newborn screen results

## The underlying cause

CF is caused by mutations in the CF gene. These mutations lead to defects in a specific protein called the cystic fibrosis transmembrane conductance regulator (CFTR) protein. As a result of these defects, the CFTR proteins don't work the way they should. The most common mutation is the F508del mutation.

The F508del mutation causes both defects illustrated below:



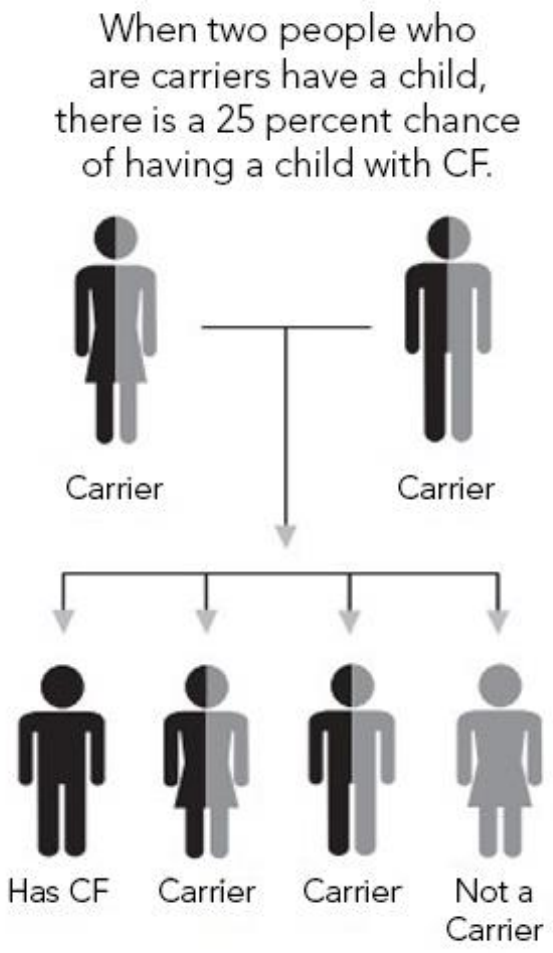

**Defect 1:**
**Fewer CFTR proteins get to the cell surface**, where they are normally located.

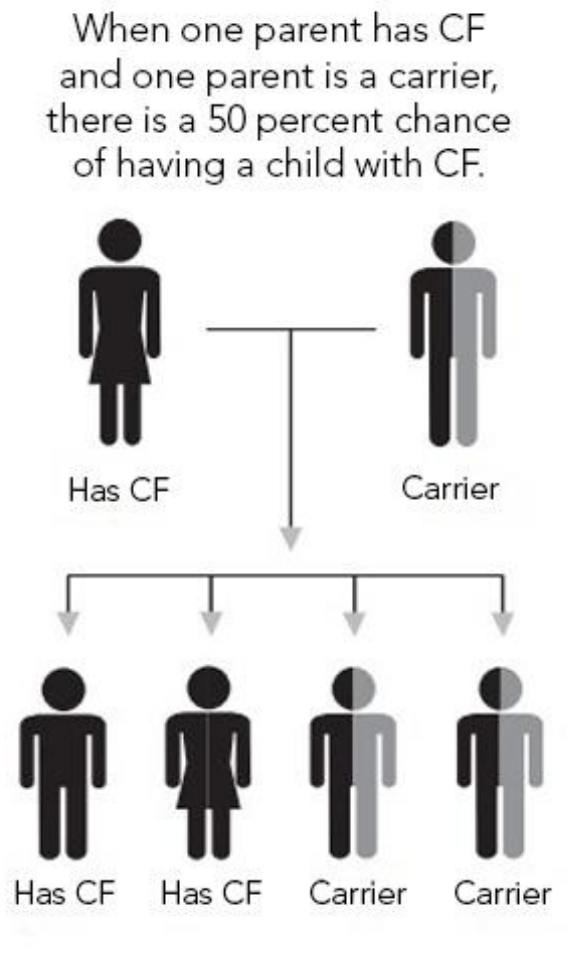
**Defect 2:**
**CFTR proteins don't open correctly** if they do reach the cell surface.

**Because of these defects, chloride ions cannot move into or out of the cells like they should. This can cause thick, sticky mucus to build up in organs, such as the lungs.**

*(Vertex Pharmaceuticals, 2019)*

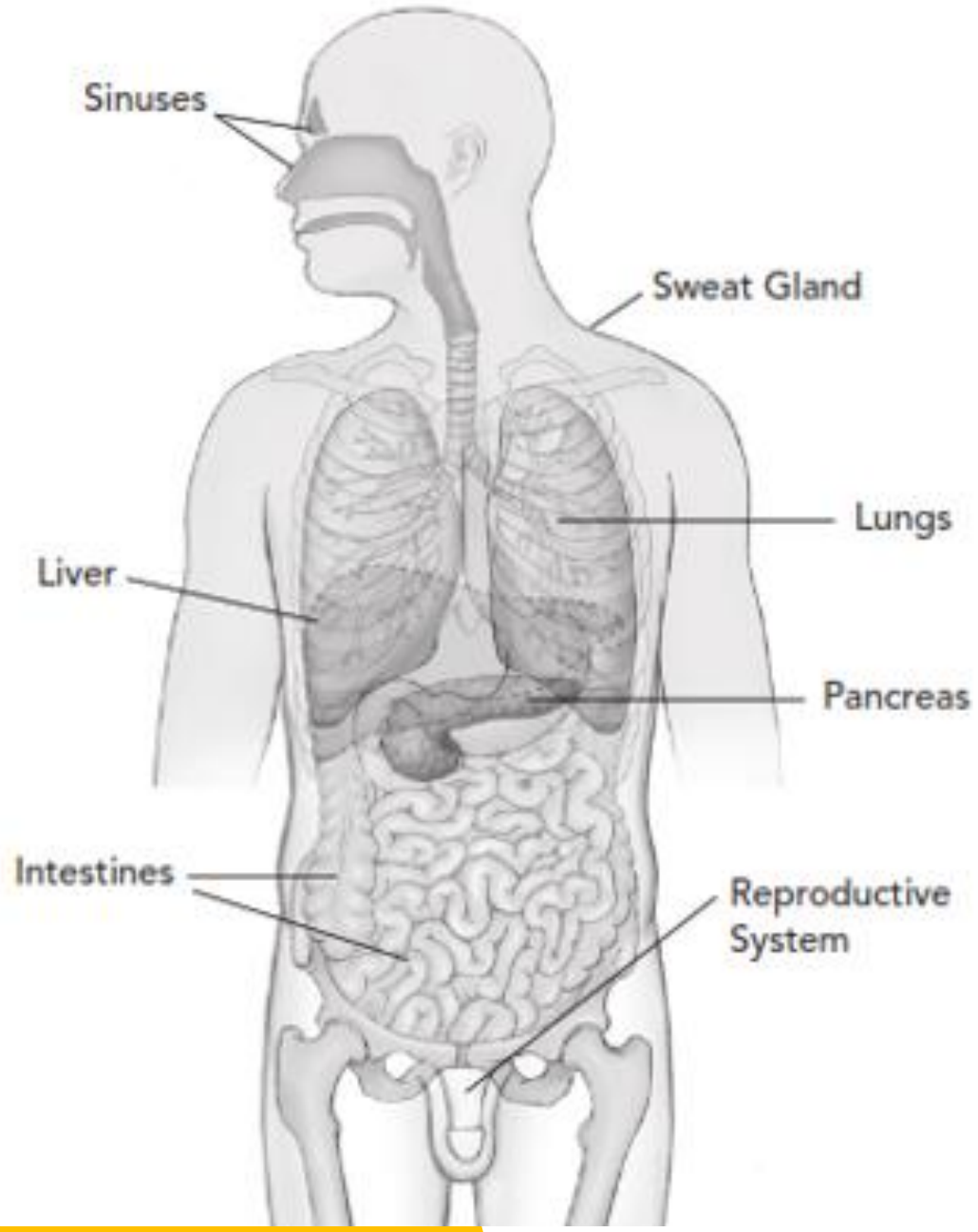
# Autosomal Recessive Inheritance




*(CFF.org)*

# Clinical Manifestations of CF




## Lungs

- Chronic cough, lung infections, bronchiectasis

## Sinuses

- Chronic sinusitis, nasal polyps

## Pancreas

- Pancreatic insufficiency, CF-related diabetes, pancreatitis

## Liver

- CF liver disease → cirrhosis

## GI tract

- Malabsorption, malnutrition, constipation, meconium ileus, intestinal obstruction

## Reproductive system

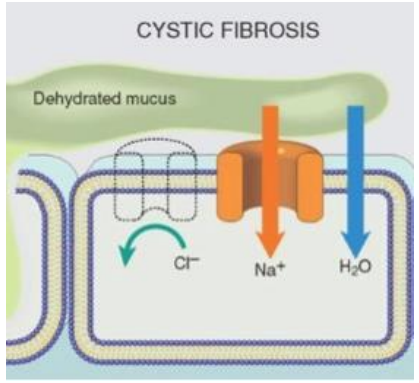
- Infertility for males, reduced fertility for females

## Sweat glands

- Excessive salt loss → dehydration, metabolic alkalosis

# Vicious cycle of CF

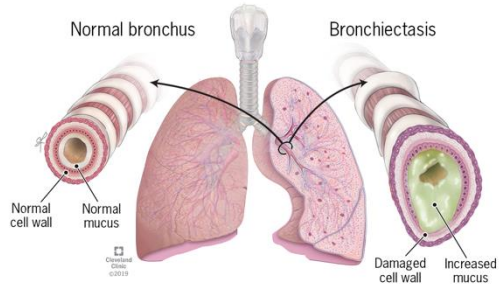
Airway clearance
Bronchodilators
Hypertonic saline
Pulmozyme

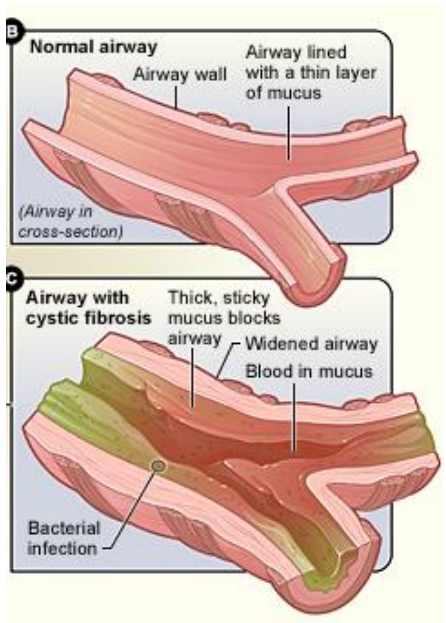



impaired airway clearance

VEST, Acapella, manual percussion

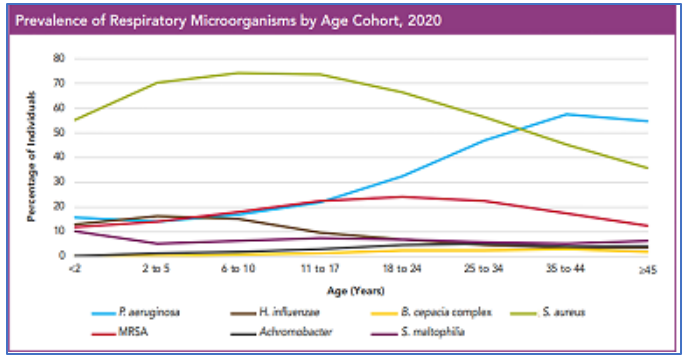
mucus plugging, airway obstruction




Antibiotics:
IV, inhaled

chronic infection




increased inflammation, increased mucus production

lung damage, bronchiectasis

Anti-inflammatory therapy:
macrolides, ibuprofen

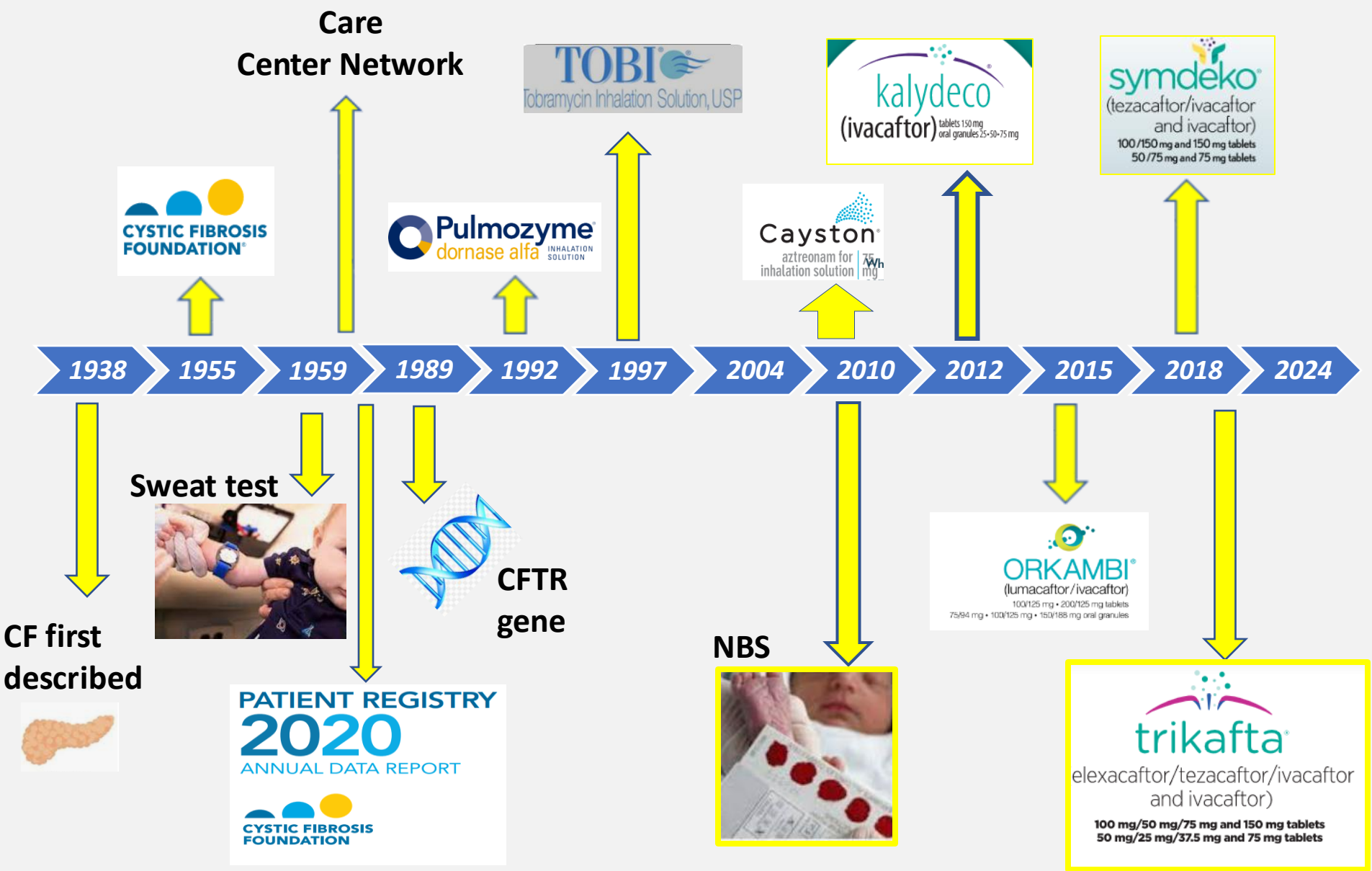
# Goals of CF Care

- Maintain lung function → FEV1 remains the best predictor of mortality
- Reduce pulmonary exacerbations[1] → Lung damage → End-stage lung disease

- Improve nutritional status → Improved survival :
  - ➢ lower BMI related to reduced lung function and increased morbidity

*Waters et al . European Respiratory Journal 2012*

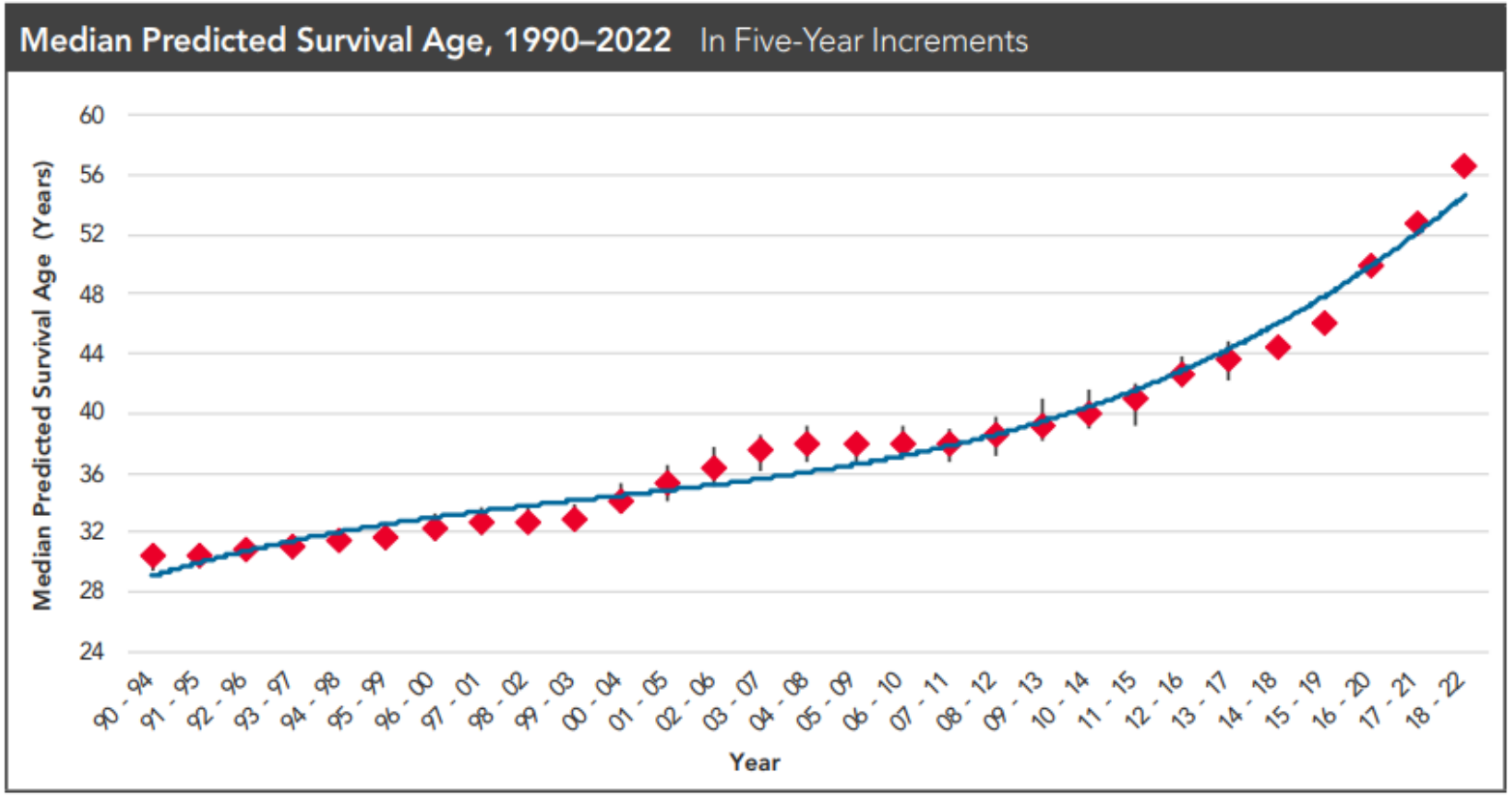
# History of Cystic Fibrosis



# The CF Landscape Has Changed

## Highly Effective Modulator Therapy

- Kalydeco, Orkambi, Symdeko, Trikafta
- New medicines correct the CFTR protein
- Anybody with ***F508del*** mutation is eligible for Trikafta
- Lungs function more like CF carriers
- Medications and treatments (for lung disease) may be weaned



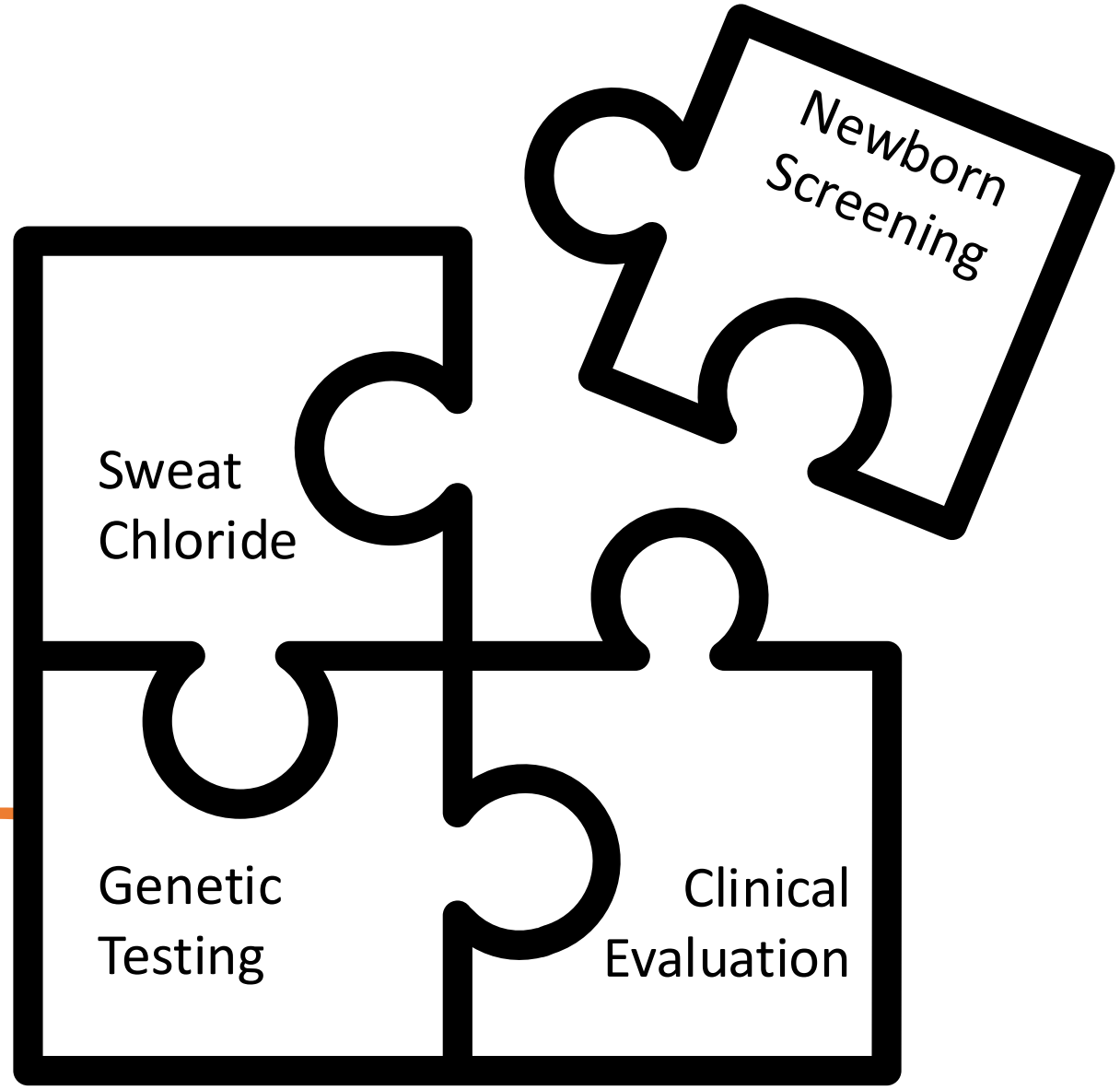

*Median survival has increased from mid-20s to mid 50s and* ***<u>continues to climb!</u>***

# Take-home Point

**CF outcomes have drastically improved**
***Not a death sentence with treatment***

***Early diagnosis improves prognosis***

# Diagnosing CF



# Diagnostic Criteria for CF

**At least one of the following:**

- Clinical symptoms consistent with CF in at least one organ system

**or**

- Positive newborn screen

**or**

- Having a sibling with CF

**PLUS:**

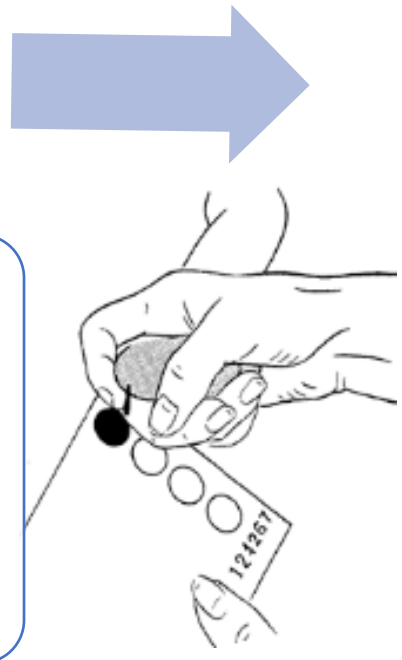
- Evidence of CF transmembrane conductance regulator (CFTR) dysfunction:
  - Elevated sweat chloride ≥60 mmol/L
  - Presence of two disease-causing mutations in the *CFTR* gene, one from each parental allele

# Newborn Screening for CF

- Started in Ohio in 2006 – IRT/DNA (process differs by state)

## Immunoreactive trypsinogen (IRT)

- Most infants with CF have elevated IRT levels
- Floating cut off >96%ile
- If IRT elevated, then sent for DNA



## DNA analysis for CFTR mutations

- Currently only tests for **39 most common CFTR mutations** (over 2000 identified to date)
- Assay run from same bloodspot
- Only run if IRT flags – so important to know when IRT is reliable

# When IRT is not reliable

| | |
|---|---|
| **Falsely High IRT** | • prematurity/low birth weight<br>• low APGARs, neonatal stress, respiratory distress<br>• pancreatic injury<br>• hypoglycemia<br>• serious congenital anomalies |
| **Falsely Low IRT** | • meconium ileus<br>• gastroschisis<br>• bowel atresia<br>• pancreatic sufficient CF<br>• in utero exposure to CFTR modulators |

# Newborn Screen

**RESULTS**

| *Test* | *Value* | *Reference Range* | *Risk Level* | *Action* |
|---|---|---|---|---|
| Amino Acid Profile | | Profile | | |
| Thyroid Stimulating Hormone (TSH) | | < 34 µU/mL S | | |
| Fatty Acid Profile | | Profile | | |
| Organic Acid Profile | | Profile | | |
| Biotinidase | | > 17 MRU | | |
| Galactose-1-PO4-Uridyl Transferase | | > 2.0 U/gHb | | |
| Hemoglobin | | FA | | |
| **Immunoreactive Trypsinogen (IRT)** | **162.9 ng/mL** | **< 96 Percentile** | **Elevated** | **1** |
| **CFTR Mutations** | **3659delC** | | | |
| 17-OH Progesterone (17-OHP) | | < 35 ng/mL | | |
| Severe Combined Immunodeficiency (TREC) | | Normal TREC Detection | | |
| Lysosomal Storage Disorder | | LSD Profile | | |
| Spinal Muscular Atrophy (SMN1) | | Normal SMN1 Detection | | |
| X-Linked Adrenoleukodystrophy (C26:0LPC) | | <0.18 µM | | |

**RECOMMENDED ACTIONS**

1. Elevated risk for Cystic Fibrosis (CF). Seek consultation with pediatric cystic fibrosis center and diagnostic testing.

# Diagnostic testing - Genetic testing

## CF common mutation panel

- Various assays, but only test for a small number of CFTR variants
- Part of NBS (but only run if IRT is flagged as abnormal)
- Quicker results

## CFTR sequencing with deletion/duplication

- Looks through the entire CFTR gene for all possible CFTR mutations
- NOT currently part of NBS – must be ordered separately
- Takes 3-4 weeks for results

# Diagnostic testing – Sweat Chloride

Measures the amount of chloride in the sweat

Objective measure of how CFTR protein is functioning

The most reliable test to diagnose CF

Still need genetic testing and clinical picture

Patient education

Painless, may feel tingly
Lasts ~1 hour
Same day results
Dress warm

# Sweat Chloride Results

| Sweat Chloride Concentration | Result | Interpretation |
|---|---|---|
| ≤ 29 mmol/L | Normal | CF unlikely |
| 30-59 mmol/L | Intermediate | Possible CF, additional testing recommended |
| ≥ 60 mmol/L | Abnormal | Diagnosis of CF, if confirmed by a second test and if clinical symptoms of CF present |
| QNS | Quantity Not Sufficient | Testing needs repeated |

# NBS showing presumed CF (2 CFTR variants)

**RESULTS**

| *Test* | *Value* | *Reference Range* | *Risk Level* | *Action* |
|---|---|---|---|---|
| Amino Acid Profile | | | | |
| Thyroid Stimulating Hormone (TSH) | | | | |
| Fatty Acid Profile | | | | |
| Organic Acid Profile | | | | |
| Biotinidase | | | | |
| Galactose-1-PO4-Uridyl Transferase | | | | |
| Hemoglobin | | | | |
| **Immunoreactive Trypsinogen (IRT)** | **115.5 ng/mL** | **< 96 Percentile** | **Elevated** | **1** |
| **CFTR Mutations** | **dF508/dF508** | | | |
| 17-OH Progesterone (17-OHP) | | | | |
| Severe Combined Immunodeficiency (TREC) | | | | |
| Lysosomal Storage Disorder | | | | |

F508del/F508del
Sweats 91/91

**RECOMMENDED ACTIONS**

1. Elevated risk for Cystic Fibrosis (CF). Seek consultation with pediatric cystic fibrosis center and diagnostic testing.

# NBS with elevated IRT and 0 CFTR variants

**RESULTS**

| *Test* | *Value* | *Reference Range* | *Risk Level* | *Action* |
|---|---|---|---|---|
| Amino Acid Profile | | | | |
| Thyroid Stimulating Hormone (TSH) | | | | |
| Fatty Acid Profile | | | | |
| Organic Acid Profile | | | | |
| Biotinidase | | | | |
| Galactose-1-PO4-Uridyl Transferase | | | | |
| Hemoglobin | | | | |
| Immunoreactive Trypsinogen (IRT) | 126.9 ng/mL | < 96 Percentile | Low | |
| CFTR Mutations | 0 Mutations | | | |
| 17-OH Progesterone (17-OHP) | | | | |
| TREC | | | | |
| Lysosomal Storage Disorder | | | | |

**RECOMMENDED ACTIONS**

Is this NBS normal?

What test is needed?

Sweats 107/107
406-1G>A, W1089X

Parents are CF carriers
Echogenic Bowel on US
Hispanic ethnicity

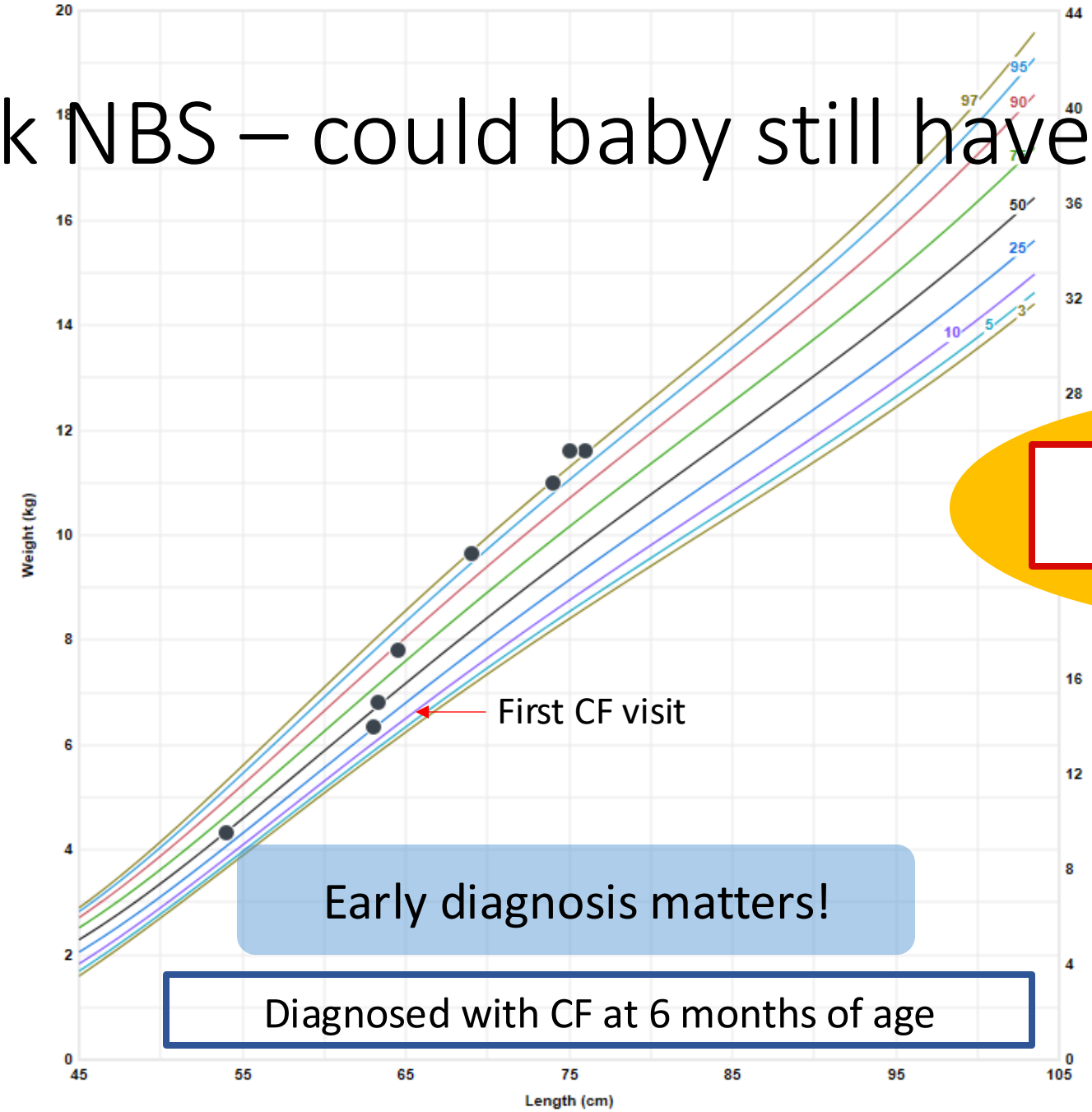
Diagnosed with CF at 3 years of age during hospitalization for respiratory failure
Hispanic ethnicity – rare mutations that were missed by NBS

# Low Risk NBS – could baby still have CF?

**RESULTS**

| *Test* | *Action* |
|---|---|
| Amino Acid Profil | |
| Thyroid Stimulatir | |
| Fatty Acid Profile | |
| Organic Acid Prof | |
| Biotinidase | |
| Galactose-1-PO4 | |
| Hemoglobin | |
| Immunoreactive T | |
| 17-OH Progesterc | |
| Severe Combinec (TREC) | |
| Lysosomal Storag | |
| Spinal Muscular A | |
| X-Linked Adrenol | |

**RECOMMENDE**




Source: Centers for Disease Control and Prevention (CDC), 2000

Sweats 84/89
F508del/L558S

Early diagnosis matters!

Diagnosed with CF at 6 months of age

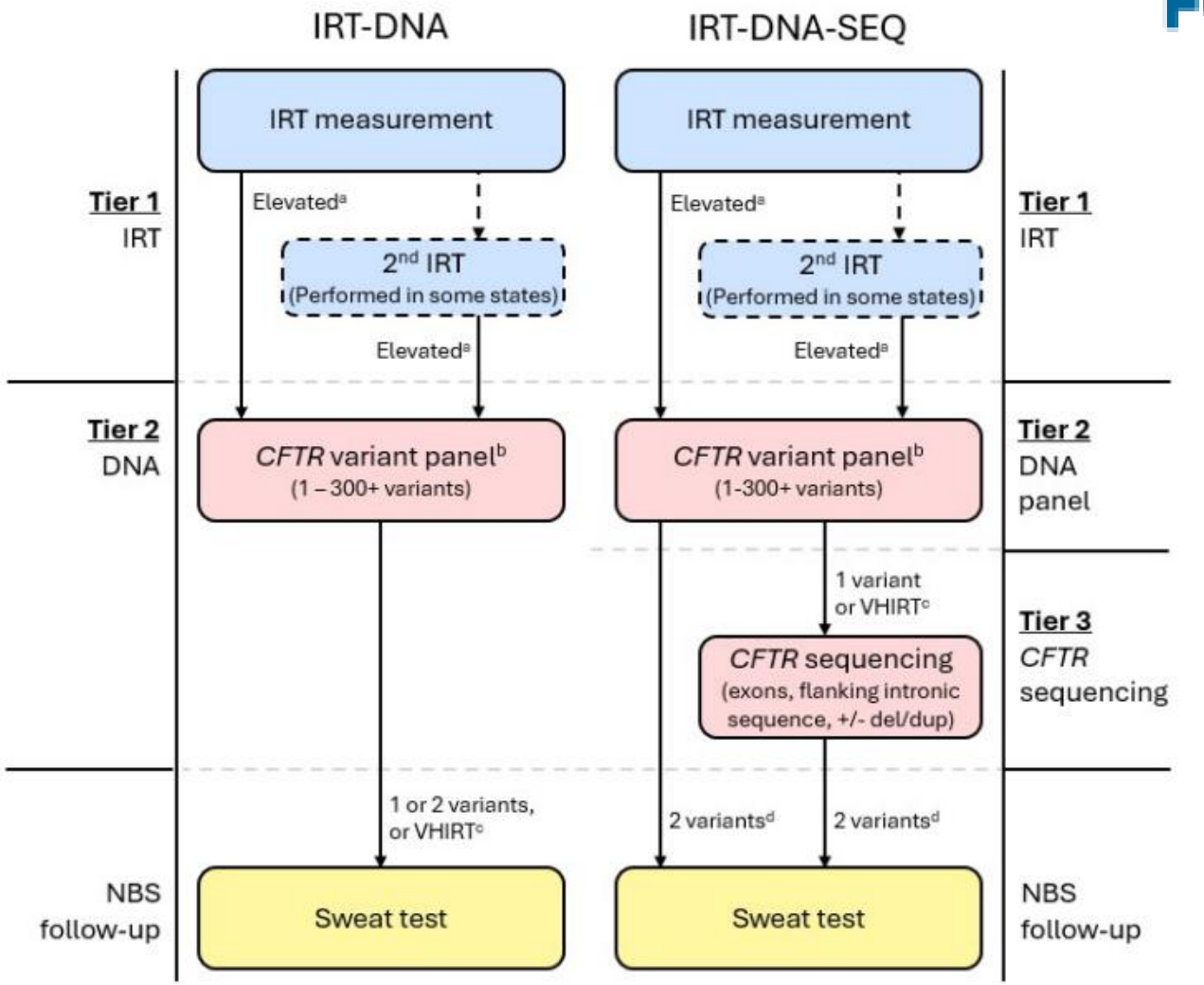
# Take-home Point

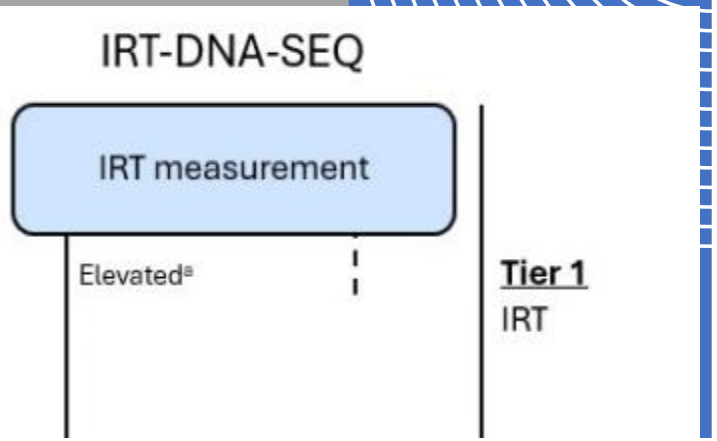
**The newborn screen is a screening test**

***There are limitations***

***Babies with CF get missed***

# CFF Updated Consensus guidelines






# Planned process for Ohio

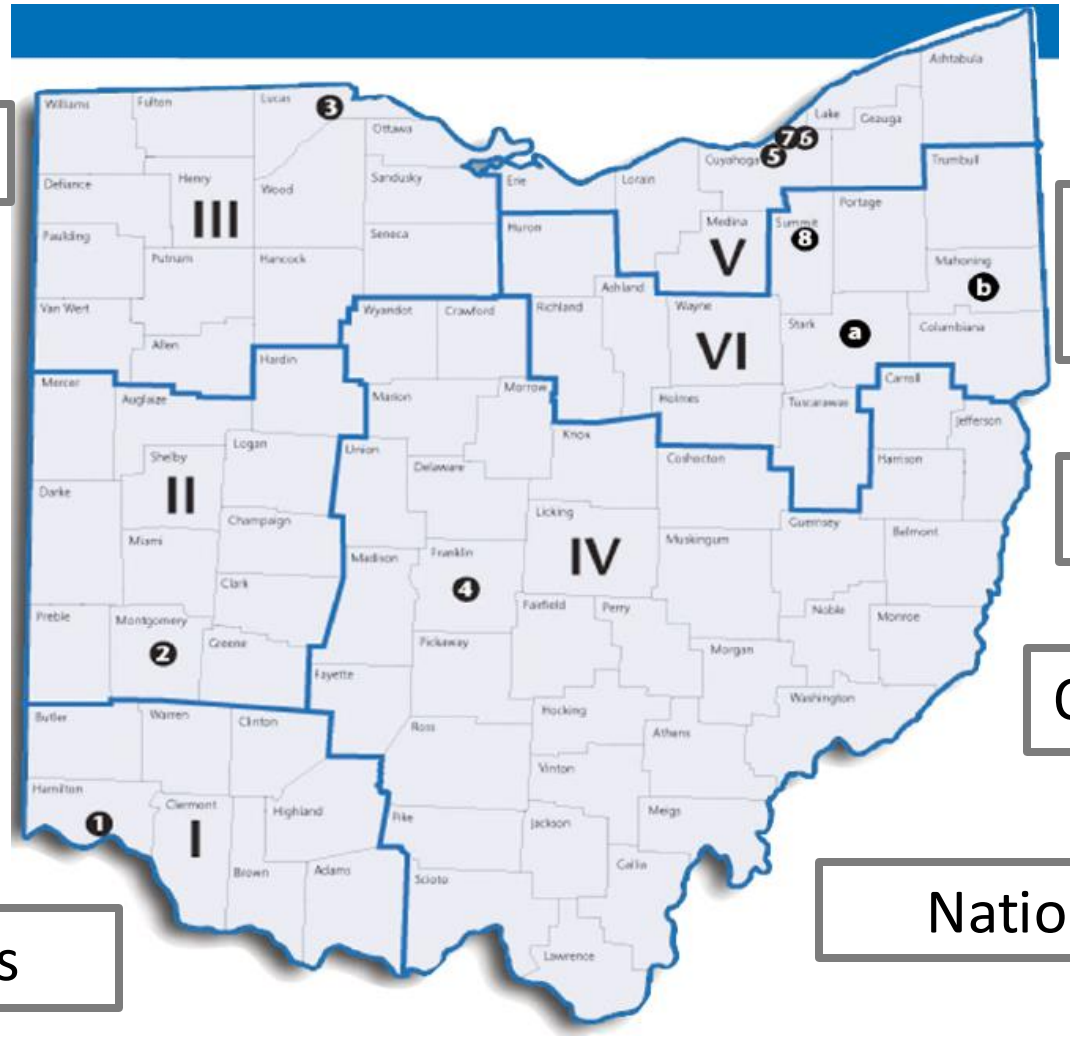
- IRT measured as before – 96%-tile floating cut-off
  - If elevated, blood sent to University of Wisconsin lab

# State-wide collaboration

Toledo Children’s

Dayton Children’s

Cincinnati Children’s




Cleveland Clinic Children's

Rainbow Babies and Children

Akron Children’s Hospital

Ohio Department of Health

Nationwide Children’s

# Take-home Point

**What to do with abnormal NBS results?**

***Follow ODH Guidance on Reports***

# Language on Abnormal Screens

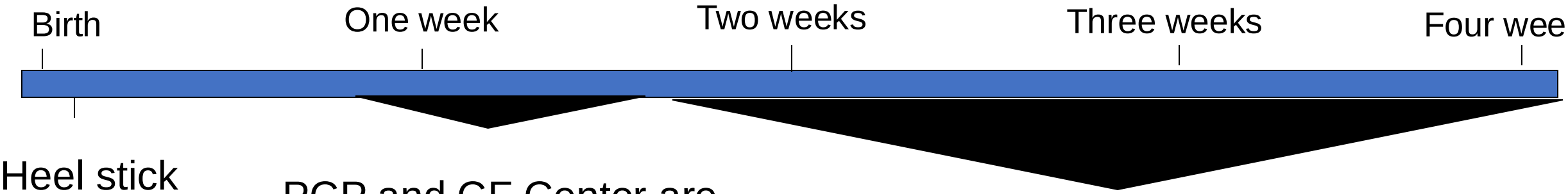
As the provider of record for this infant (as indicated on the newborn screening card), you should take the following actions.

1. Communicate screening results to infant's parents or legal guardian
2. If infant has an elevated IRT and no (0) identified CFTR mutations:
    a. Redraw a newborn screen at 4 weeks of age to monitor IRT level
3. If infant has an elevated IRT and at least 1 identified CFTR mutation:
    a. Refer infants within 2 weeks to an Ohio Cystic Fibrosis Clinic for follow-up. Enclosed is a list of the Cystic Fibrosis Service Teams in Ohio for referral purposes.
    b. Recommend genetic counseling for all families for whom CFTR mutations have been identified through newborn screening. Enclosed is a list of Regional Genetic Centers in Ohio for referral purposes.
4. Report diagnostic information (including copies of all diagnostic tests, consults, and treatment information) to the Ohio Department of Health Newborn Screening Laboratory (address listed above) as required by OAC.

# When does NBS need to be repeated?

1. Inconclusive results
   - Drawn before 24 hours of life
     → Repeat NBS as soon as possible
   - Within 30 days of blood transfusion
     → Repeat 30 days post transfusion

# General Timeline for Testing




Heel stick (24-72 hrs of age)

PCP and CF Center are notified of abnormal screen

Communication between CF center and PCP office may vary across the state

PCP alerts family that results show **increased** risk, further testing required

Babies with 2 CFTR variants are seen ASAP to **start treatment**

Babies with 1 CFTR variant, seen by 4 weeks if possible **to complete evaluation**

# What to tell families

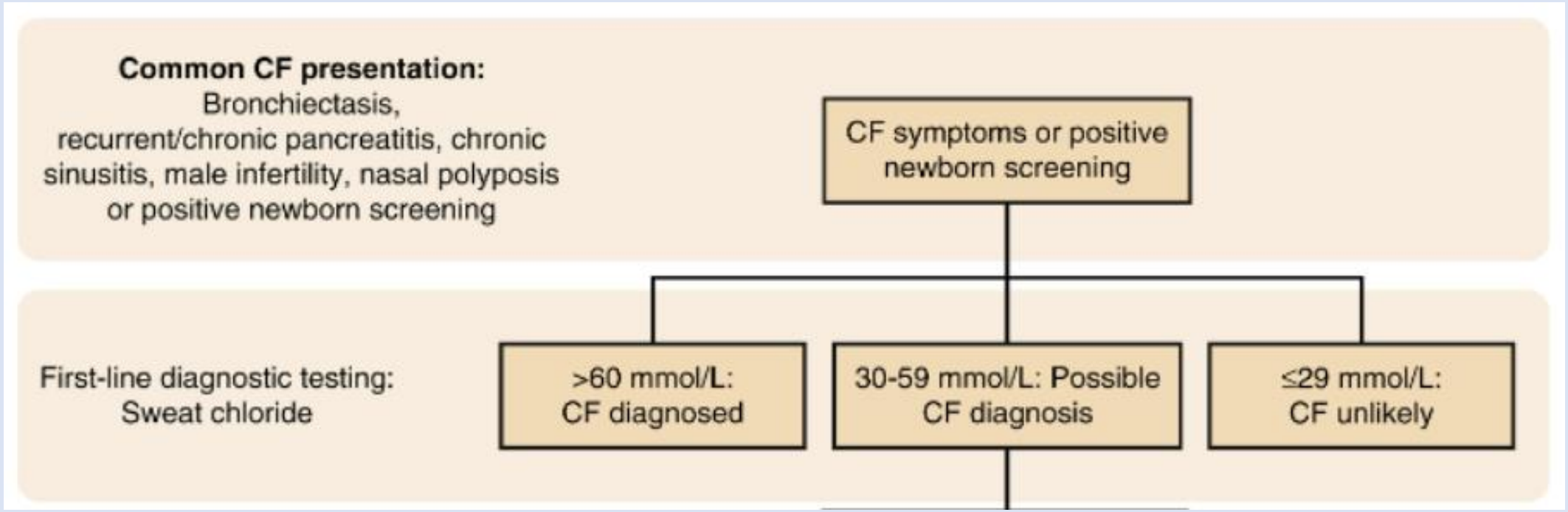
- All abnormal NBS require further testing.
- The CF team will be contacting you to talk more.

*If CF diagnosed/suspected:*

- CF is a very different disease than in the past.
- The CF team is the best place to go for information.
- The CF team will be contacting you to talk more.

*If unsure about how to interpret results* – contact your CF center!

# Cystic Fibrosis – Diagnosis without NBS



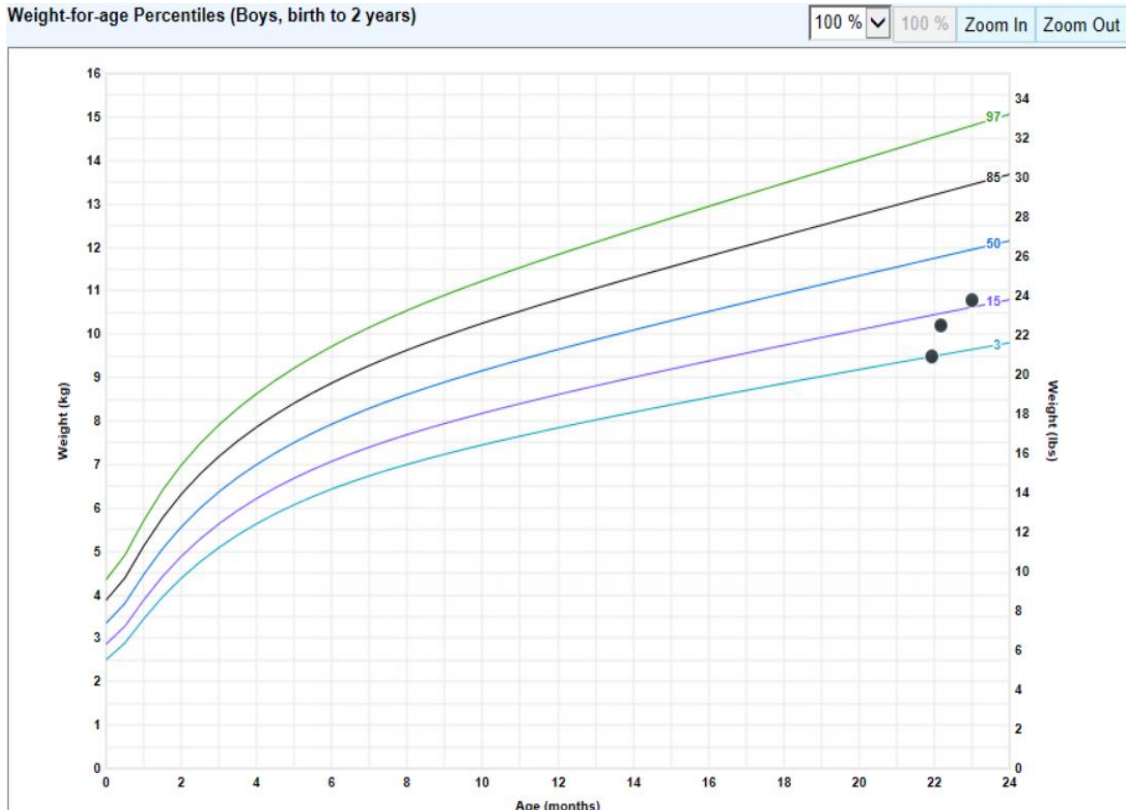

*(Murray and Nadel's Textbook of Respiratory Medicine 2022)*

# Late Diagnosis – Case 1

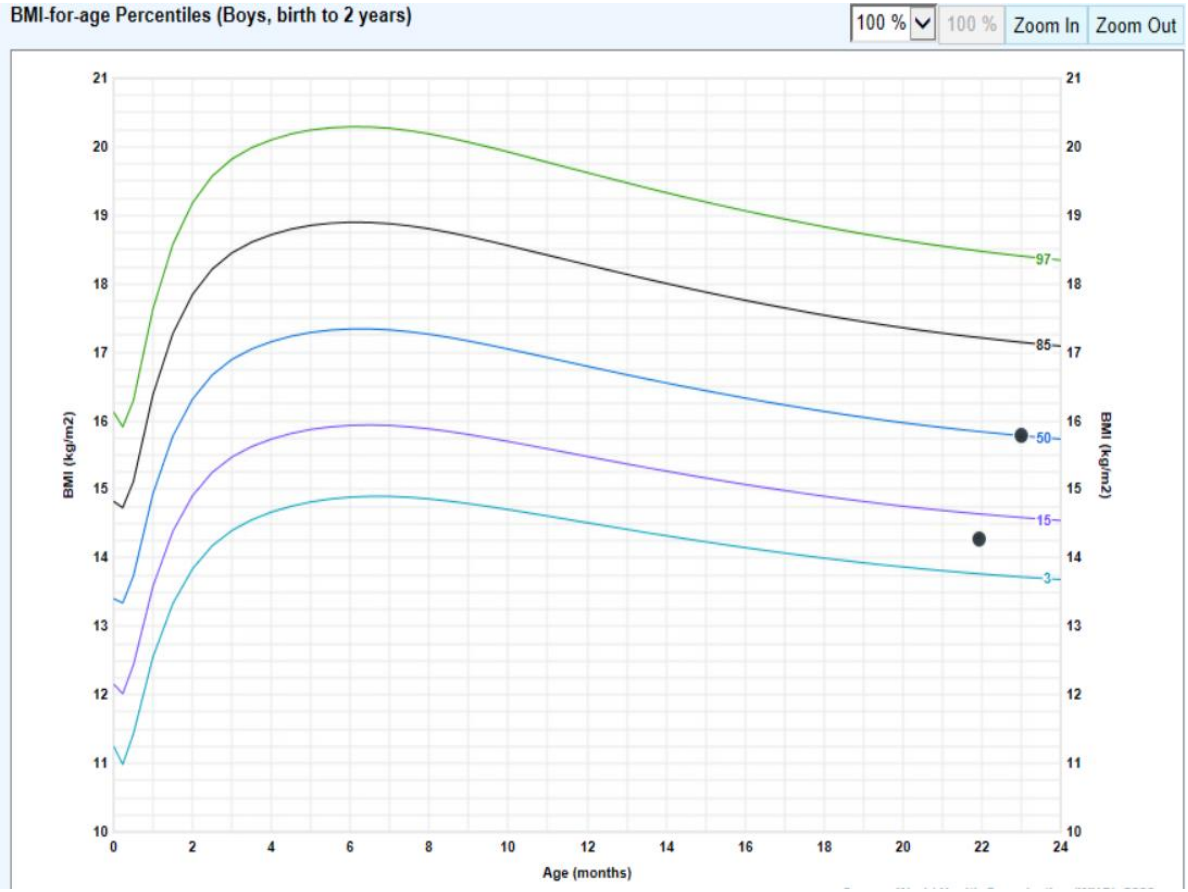
- Background:
  - 21-month-old, Caucasian, Amish family
  - Significant PMH: home birth
  - Newborn screening by midwife “negative”, later confirmed not to have included CF.
- Clinical presentation:
  - Admitted for progressive weight loss, abdominal distension, pale stools and chronic cough.
  - On exam:
    - weight: 9.48kg (3rd percentile, Z-Score: -1.89)
    - length: 81.5 cm (6th percentile, Z-Score: -1.53)
    - W/L : (Z-Score -1.5)

# Late Diagnosis – Case 1

- Diagnostic Test Results:
  - Sweat Chloride: 98mmol/L / 101mmol/L
  - Stool elastase  <10
  - Genetic testing : homozygous F508del




Weight for age




Body Mass Index

# Late Diagnosis - Case 2

- Background:
  - Abnormal newborn screen

| | | | |
|---|---|---|---|
| Immunoreactive Trypsinogen (IRT) | 72.2 ng/mL | < 96 Percentile * | Moderate |
| CFTR Mutations | deltaF508 | | |

  - Parents are both CF carriers, but their results are unavailable
  - **Sweat chloride results: 23/23** (29 and under is normal)
- Clinical Presentation:
  - 11 months, urgent care for bronchiolitis
  - 16 months & 19 months, urgent care for URI and otitis media
  - 24 months, urgent care for URI
  - 3.5 years, admitted for abdominal pain
    - Echogenicity in pancreas, elevated lipase → acute pancreatitis

# Late Diagnosis - Case 2

CFTR2 DATABASE

Results for D1152H and F508del

Variant D1152H

- The drug ivacaftor (Kalydeco), the drug combination of tezacaftor and ivacaftor (Symdeko or Symkevi), and the drug combination of elexacaftor, tezacaftor, and ivacaftor (Trikafta or Kaftrio) have been approved in some countries for individuals with this variant.

Variant F508del

- The drug combination of lumacaftor and ivacaftor (Orkambi), the drug combination of tezacaftor and ivacaftor (Symdeko or Symkevi), and the drug combination of elexacaftor tezacaftor, and ivacaftor (Trikafta or Kaftrio) have been approved in some countries for individuals with this varia

- This variant combination has varying consequences.
- Some patients with this variant combination have CF.
- Other patients with this variant combination do not have CF.
- Because of this variability, it is very important that CLINICAL CRITERIA ALONE be used to determine whether a person with this variant has CF.
- Because the clinical manifestations of CF can vary over the course of a person's lifetime, people who have this variant plus a variant that is known to cause CF should have periodic check-ups with their doctor even if they have no clinical signs or symptoms of CF at the present time.
- **Patients with CF who have this variant are likely to be pancreatic sufficient.**
- There are 715 patients with this variant combination in the CFTR2 database.

# Low Risk NBS but Clinical Symptoms?

The NBS for CF is NOT perfect.

Individuals with milder CF or CFTR-related disorder often have symptoms that develop over time.

If there is ever concern for CF – get a sweat test! Regardless of age or NBS results.

# Wrapping Up

**Earlier diagnosis improves outcomes.**

- Explore changes in prognosis for babies with CF with early treatment

**The newborn screen is just a screening test.**

- Understand the limitations of the Ohio CF newborn screen

**Who needs a referral for more testing?**

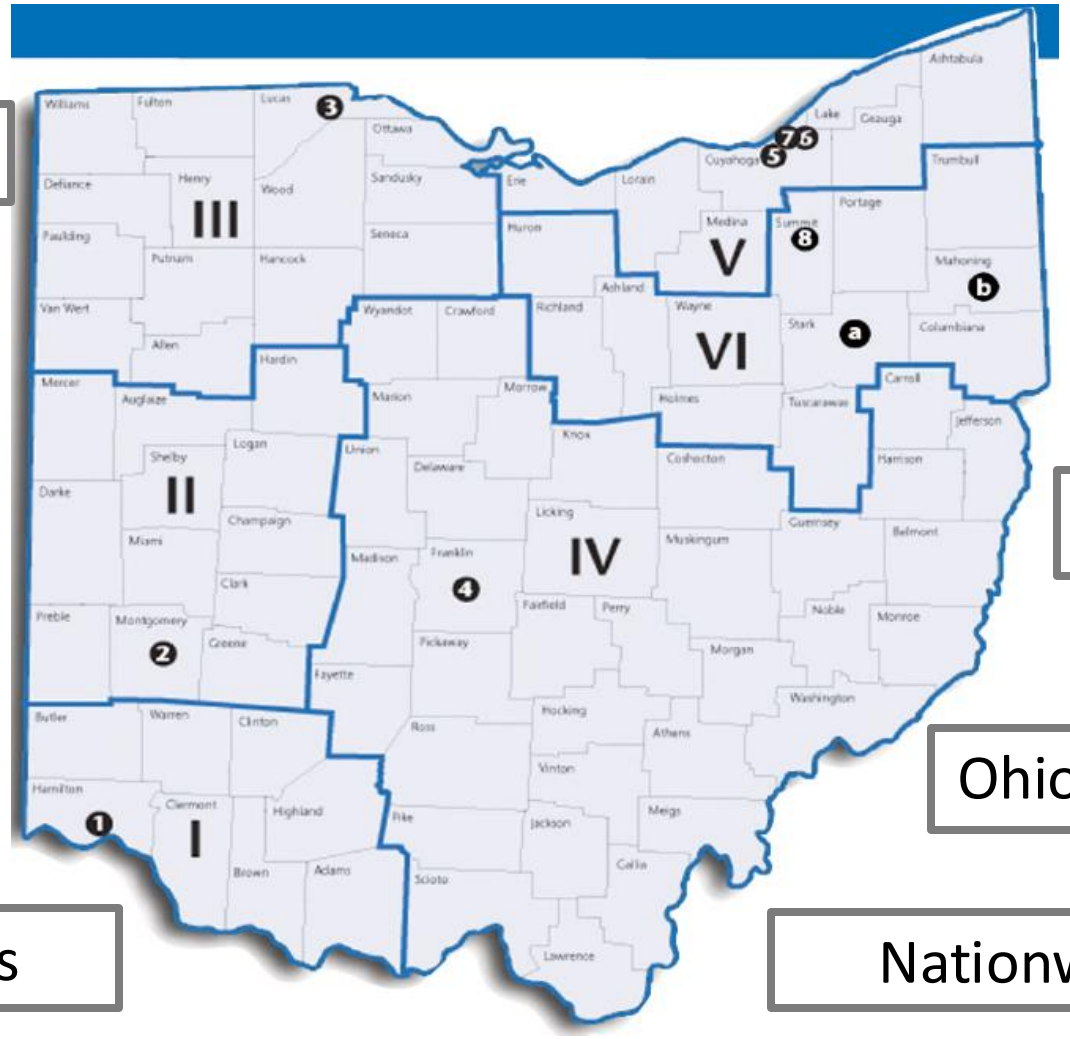
- Review next steps for abnormal newborn screen results

# Contact your CF Center or the ODH for Help

Toledo Children’s

Dayton Children’s

Cincinnati Children’s




Cleveland Clinic Children's

Rainbow Babies and Children

Akron Children’s Hospital

Ohio Department of Health

Nationwide Children’s

# Questions?

**Earlier diagnosis improves outcomes.**

- Explore changes in prognosis for babies with CF with early treatment

**The newborn screen is just a screening test.**

- Understand the limitations of the Ohio CF newborn screen

**Who needs a referral for more testing?**

- Review next steps for abnormal newborn screen results

@aapohio

@OHPediatricians

@ohioaap

Ohio AAP

Ohio Chapter,
American Academy
of Pediatrics

@ohioaap

Ohio Chapter

INCORPORATED IN OHIO

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

## Visit our website!

www.ohioaap.org