Newborn screening for cystic fibrosis

Thomas Ferkol, MD
Professor of Pediatrics, Cell Biology and Physiology
Washington University School of Medicine
St. Louis Children's Hospital

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Cystic fibrosis: objectives of the presentation

What is cystic fibrosis?

How is the diagnosis of cystic fibrosis made?

Does newborn screening impact on the course of disease?

Cystic fibrosis: objectives

What is cystic fibrosis?

Cystic fibrosis is a multisystem disease of exocrine gland function.

How is the diagnosis of cystic fibrosis made?

Does newborn screening impact on the course of disease?

Cystic fibrosis: clinical presentations

Respiratory

- recurrent sinopulmonary infections
- bronchiolitis/asthma
- nasal polyposis
- *Staphylococcus aureus* pneumonia
- *Pseudomonas aeruginosa* endobronchitis

Genitourinary

- male infertility

Sweat Gland Dysfunction

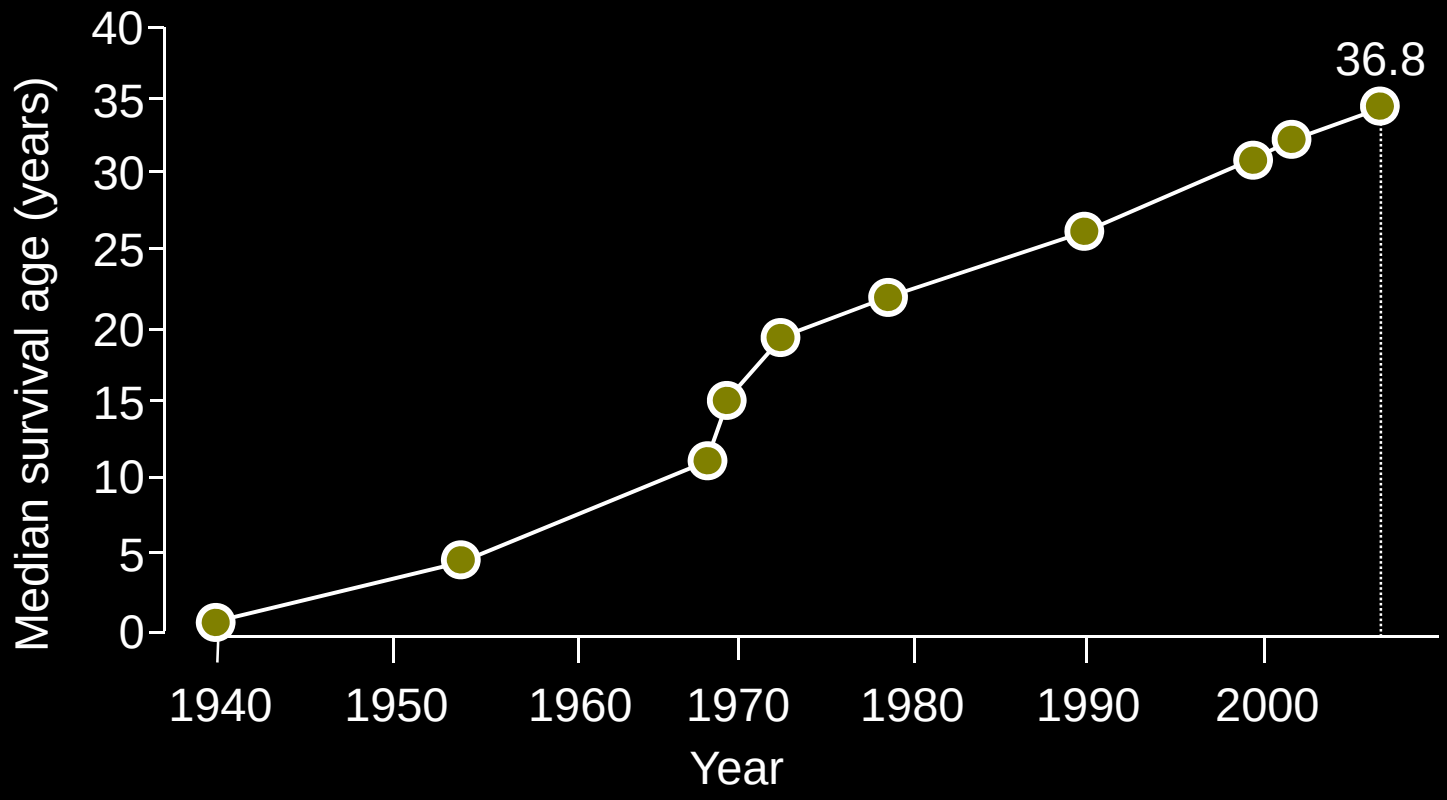
- hypochloremic, hyponatremic alkalosis

Cystic fibrosis: clinical presentations

Gastrointestinal

- meconium ileus
- meconium plug syndrome
- distal intestinal obstruction syndrome
- rectal prolapse
- neonatal hyperbilirubinemia
- failure to thrive
- hypoproteinemic edema
- hypovitaminosis
- recurrent pancreatitis
- biliary cirrhosis and portal hypertension

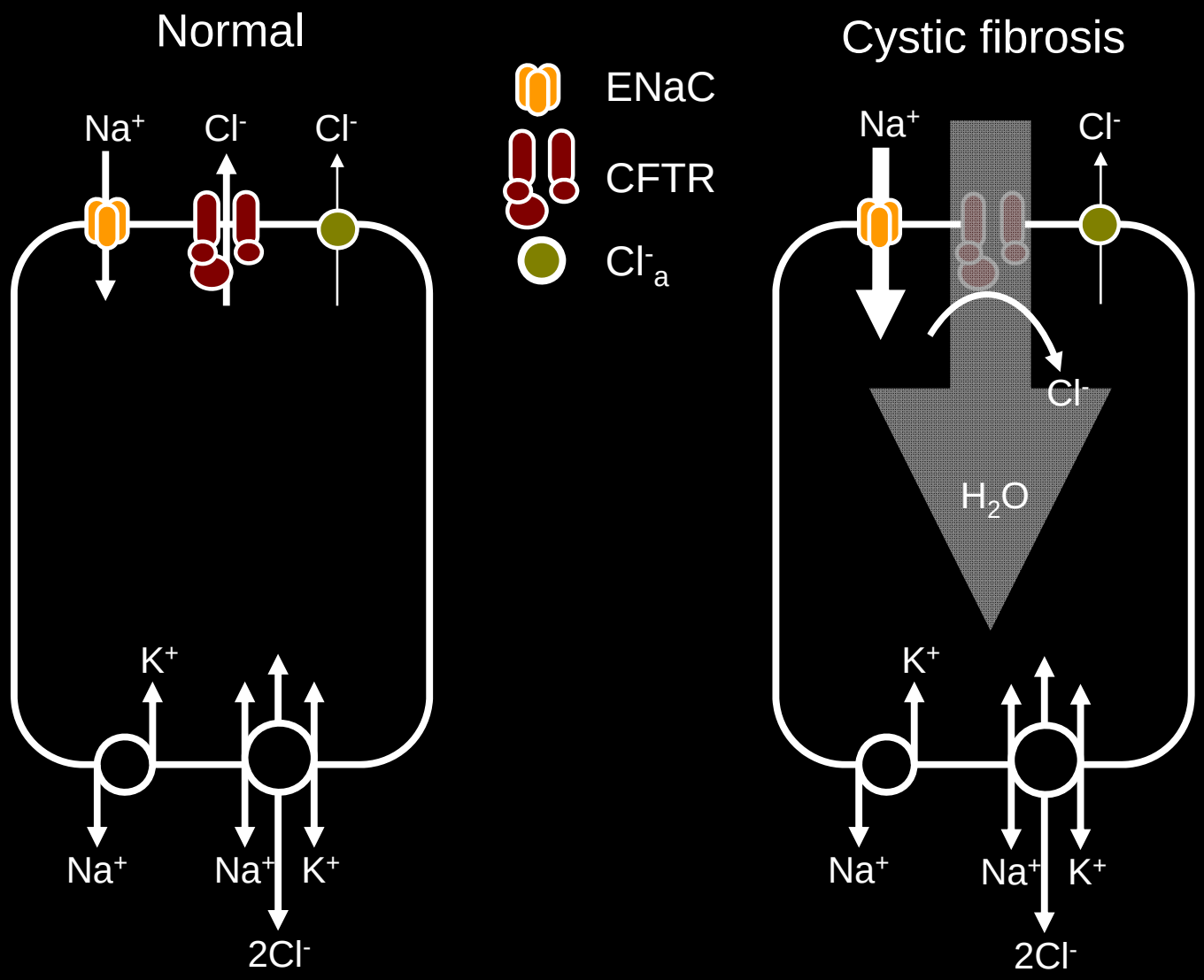
Cystic fibrosis: median survival age, 1940-2006



Cystic fibrosis: objectives

- What is cystic fibrosis?
  - An autosomal recessive disease, genetic mutations of the cystic fibrosis transmembrane conductance regulator result in abnormalities in chloride and sodium transport across an epithelium.
- How is the diagnosis of cystic fibrosis made?
- Does early diagnosis impact on the course of disease?

Cystic fibrosis transmembrane conductance regulator: ion transport



Cystic fibrosis: objectives

What is cystic fibrosis?

How is the diagnosis of cystic fibrosis made?

Does early diagnosis impact on the course of disease?

Cystic fibrosis: diagnosis

Requires:

Phenotypic clinical features

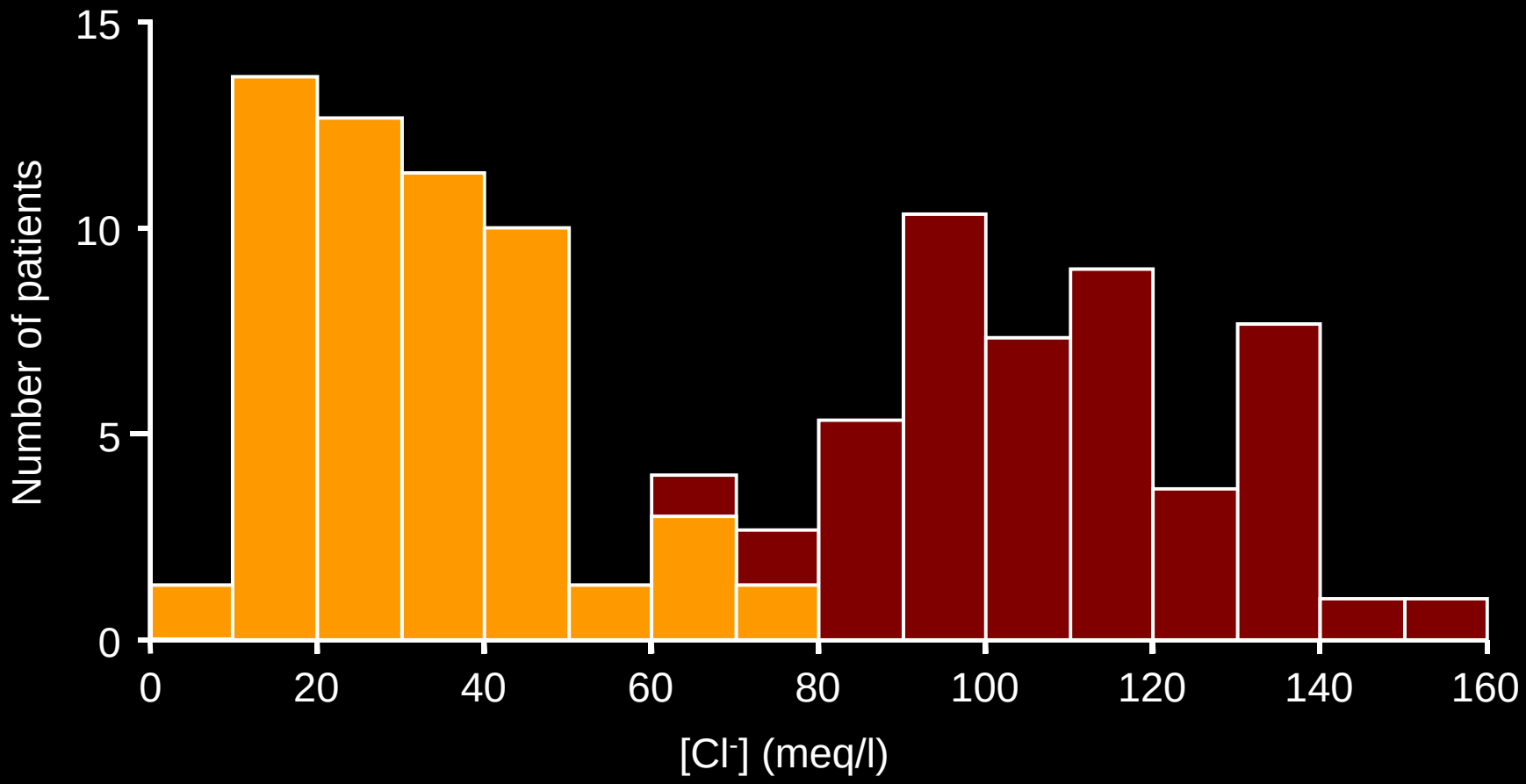
- chronic sinopulmonary disease (> 99 %), or
- gastrointestinal abnormalities, like pancreatic insufficiency (85 %), recurrent pancreatitis, meconium ileus, or focal biliary or multilobar cirrhosis
- obstructive azospermia in males
- history of cystic fibrosis in the immediate family
- Positive newborn screen

Laboratory evidence of CFTR dysfunction

- elevated sweat chloride measurements (>60 mmol/l)

Cystic fibrosis: pilocarpine iontophoresis

Di Sant'Agnese PA, *et al*. *Pediatrics*. 12:549;1953.



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Laboratory evidence of CFTR dysfunction

- elevated sweat chloride measurements (>60 mmol/l)
- mutation in CFTR gene on both alleles

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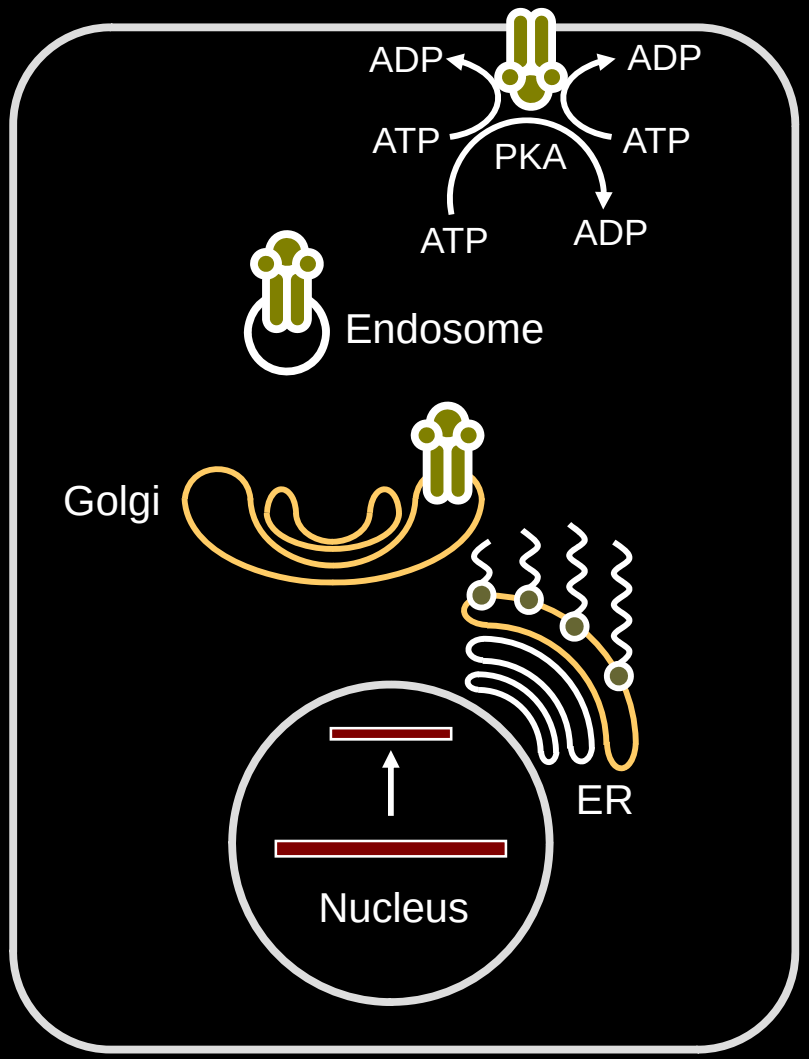
Cystic Fibrosis

Cloning and Genetics

Cystic fibrosis: molecular mechanisms of CFTR dysfunction

Class 3: regulatory mutants that fail to respond normally to activation signals, e.g., G551D

Class 1: premature termination of CFTR mRNA translation, e.g., S489X



Class 4: mutants that have altered channel properties, e.g., R117H

Class 2: CFTR protein degradation in the endoplasmic reticulum, e.g., ΔF508

Class 5: decreased functional CFTR synthesis or transport, e.g., A455E

Cystic fibrosis: molecular mechanisms of CFTR dysfunction

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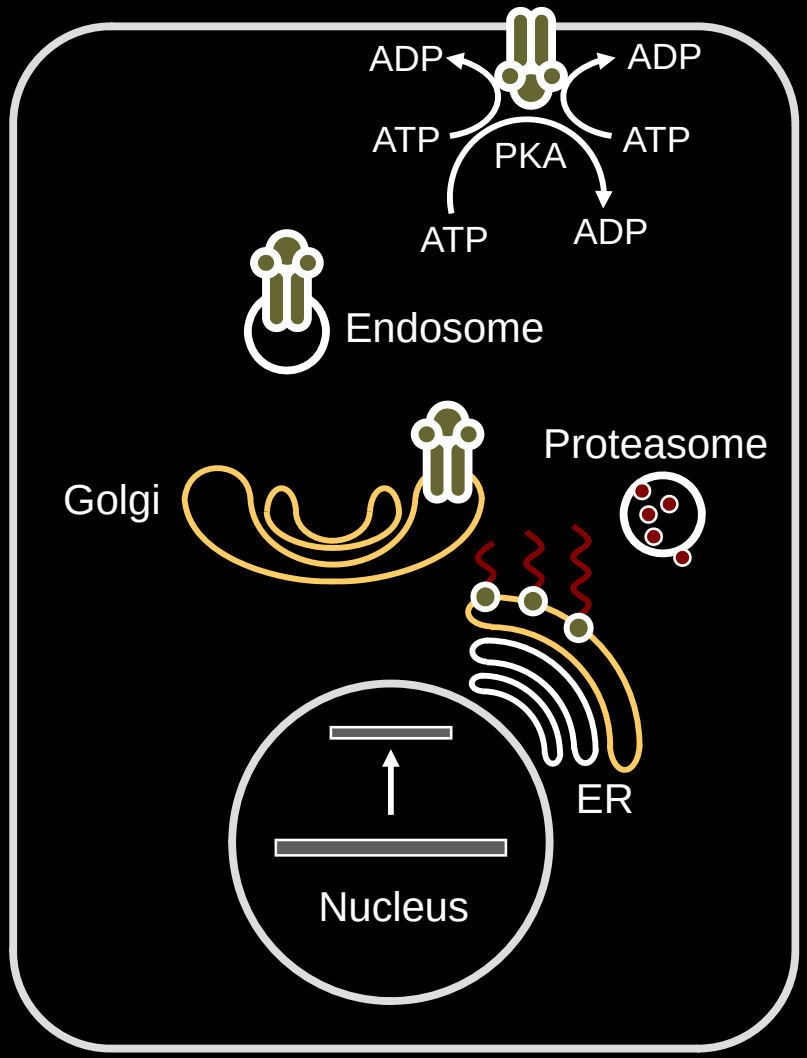

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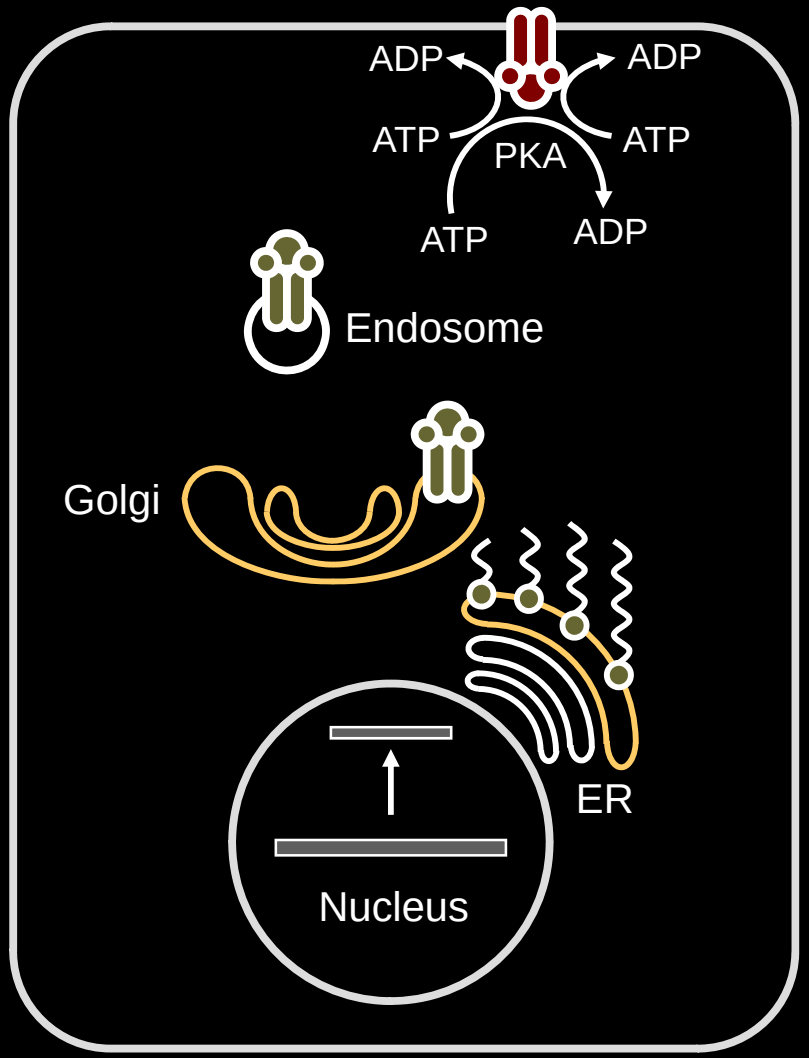

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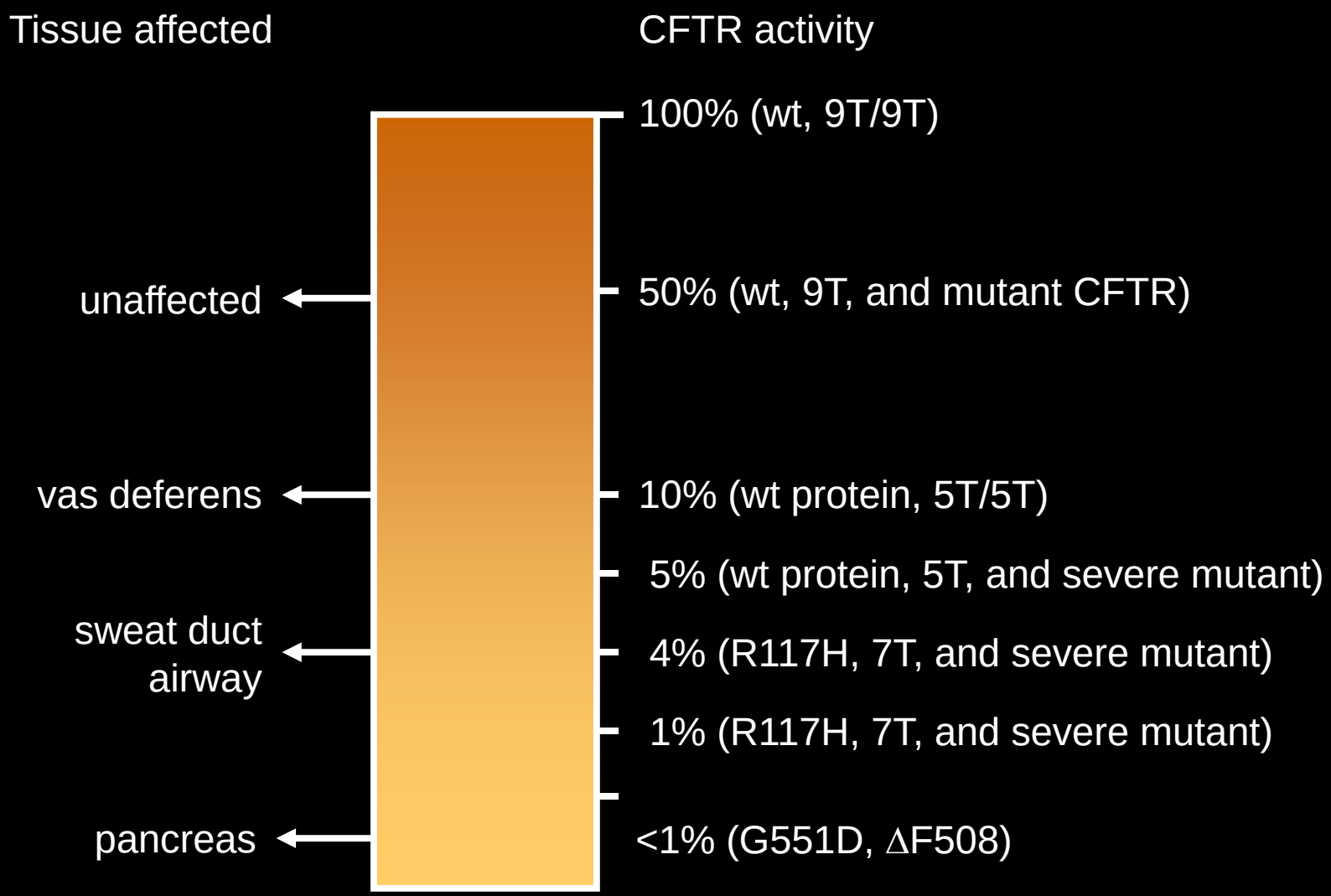
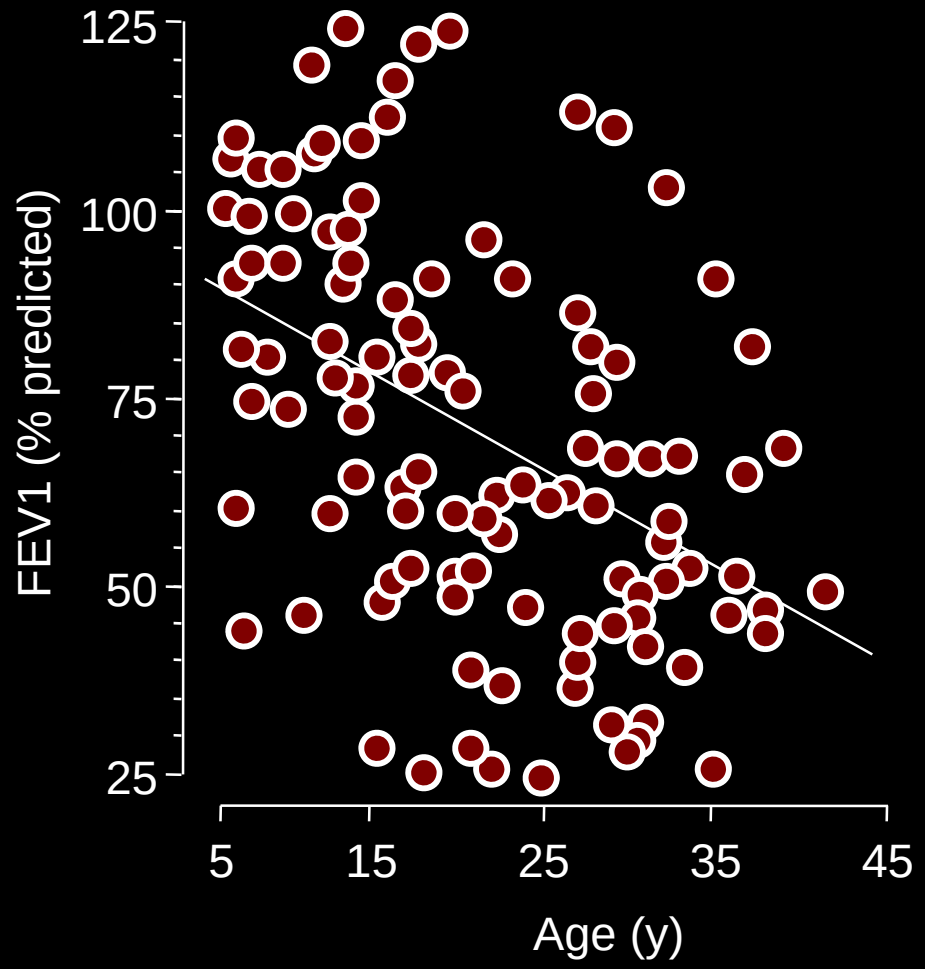
Cystic fibrosis: CFTR activity and tissue manifestations

Chillon M, *et al. New Eng J Med.* 332:1475;1995.



The relationship between ΔF508 genotype and pulmonary disease

Karem E, *et al. New Eng J Med*. 326:151;1990.



Cystic fibrosis: conclusions

- The diagnosis of cystic fibrosis is largely based on clinical presentation, but the clinical spectrum of cystic fibrosis is widening.
- Mutations of the CFTR gene can be associated different clinical phenotypes.
- The sweat chloride measurement is still the best diagnostic test for cystic fibrosis, but genetic analysis of CFTR alleles can be useful in the diagnosis of atypical or mild cases.

Cystic fibrosis: objectives

What is cystic fibrosis?

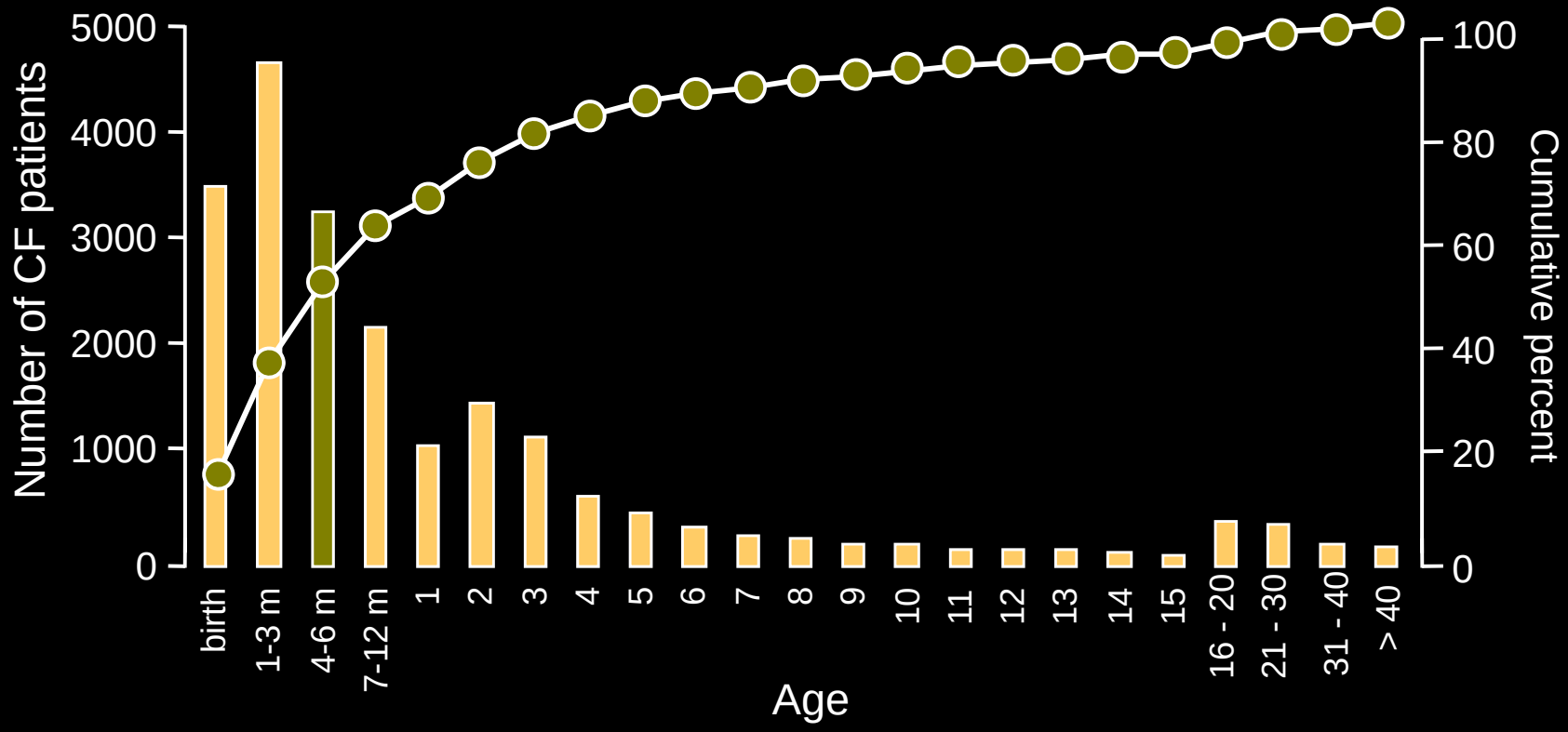
How is the diagnosis of cystic fibrosis made?

Does newborn screening impact on the course of disease?

Cystic fibrosis: epidemiology

Population	Epidemiologic	Newborn screening
Caucasian (US)	1 in 1,900-3,700	1 in 3,400-3,800
Caucasian (Great Britain)	1 in 2,400-3,000	1 in 2,200-3,200
Hispanic	1 in 8,000-9,000	--
African American	1 in 15,300	--
Native American	1 in 40,000	--
Asian (US, England)	1 in 10,000	--
Israel	1 in 5,000	--
Southern Europe	1 in 2,000-4,000	--

Age at diagnosis of cystic fibrosis patients



Fifty percent of patients are diagnosed by six months of age, and 68 percent by age one (2003 CFF Patient Registry)

Onset of cystic fibrosis disease

- Variable age, depending on genotype and clinical phenotype.
- At birth in 10-15% with meconium ileus (but may have negative screen.
- Malnutrition is often early (by 2 months)

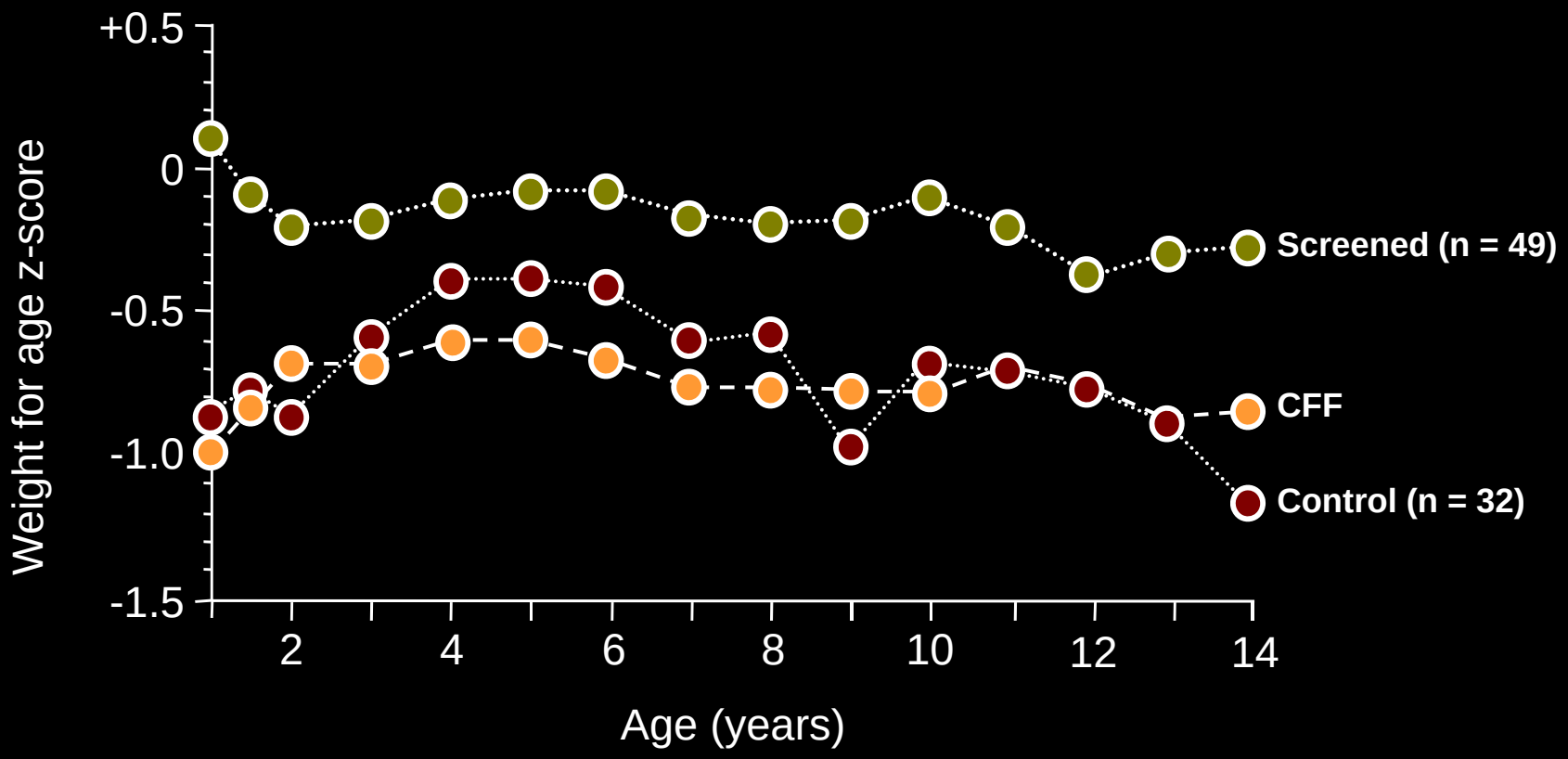
  Sokol RJ, *et al*, *Am J Clin Nutr*. **50**:1064;1989.
  Bronstein MN, et al, *J Pediatr.* **120**; 533;1992.

- Lung disease can also begin early (1-3 months)

  Abman SH, *et al*, *J Pediatr*. **119**: 211;1991.
  Farrell PM *et al*, *Pediatr Pulmonol*. **36**: 230-240;2003.

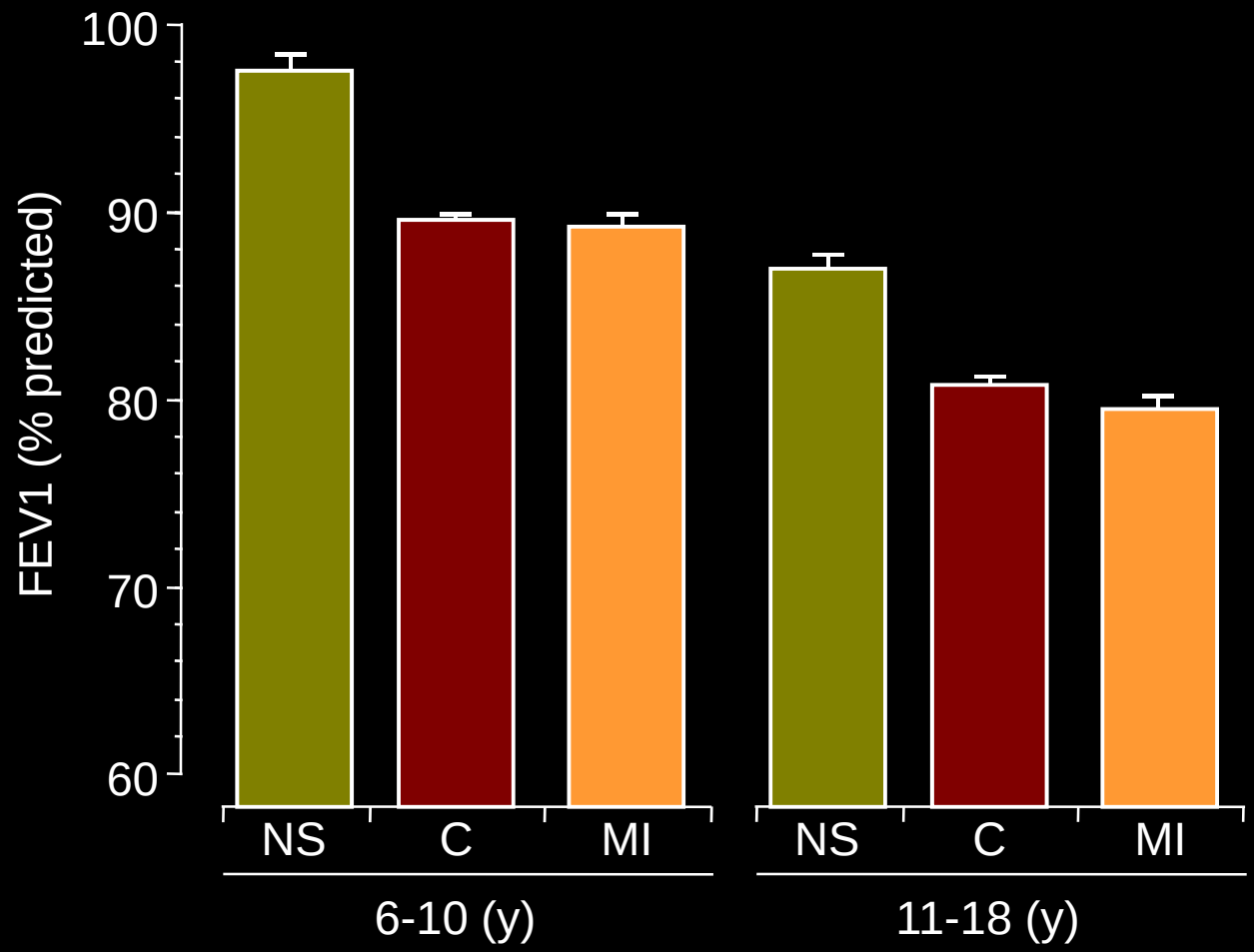
Cystic fibrosis: effect of neonatal screening on growth

Farrell PM, *et al. J Pediatr*. 147:S30:2005.



Pulmonary function in cystic fibrosis patients by diagnostic category

Accurso FJ, *et al. J Pediatr*. 147:S37;2005.



CDC

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports | October 15, 2004 / Vol. 53 / No. RR-13

Newborn Screening for Cystic Fibrosis

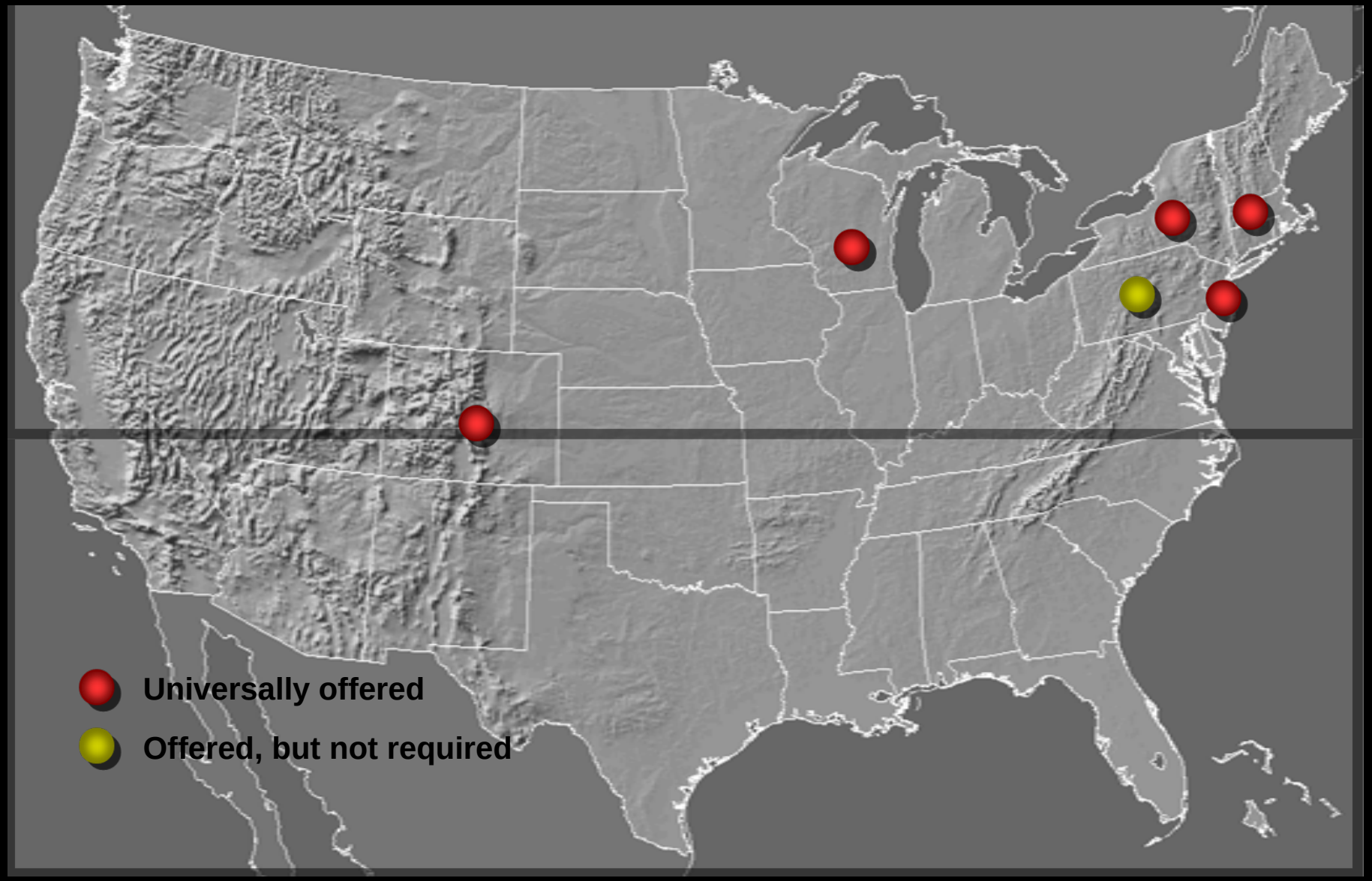
Evaluation of Benefits and Risks and Recommendations for State Newborn Screening Programs

Image courtesy of Natus Medical Incorporated

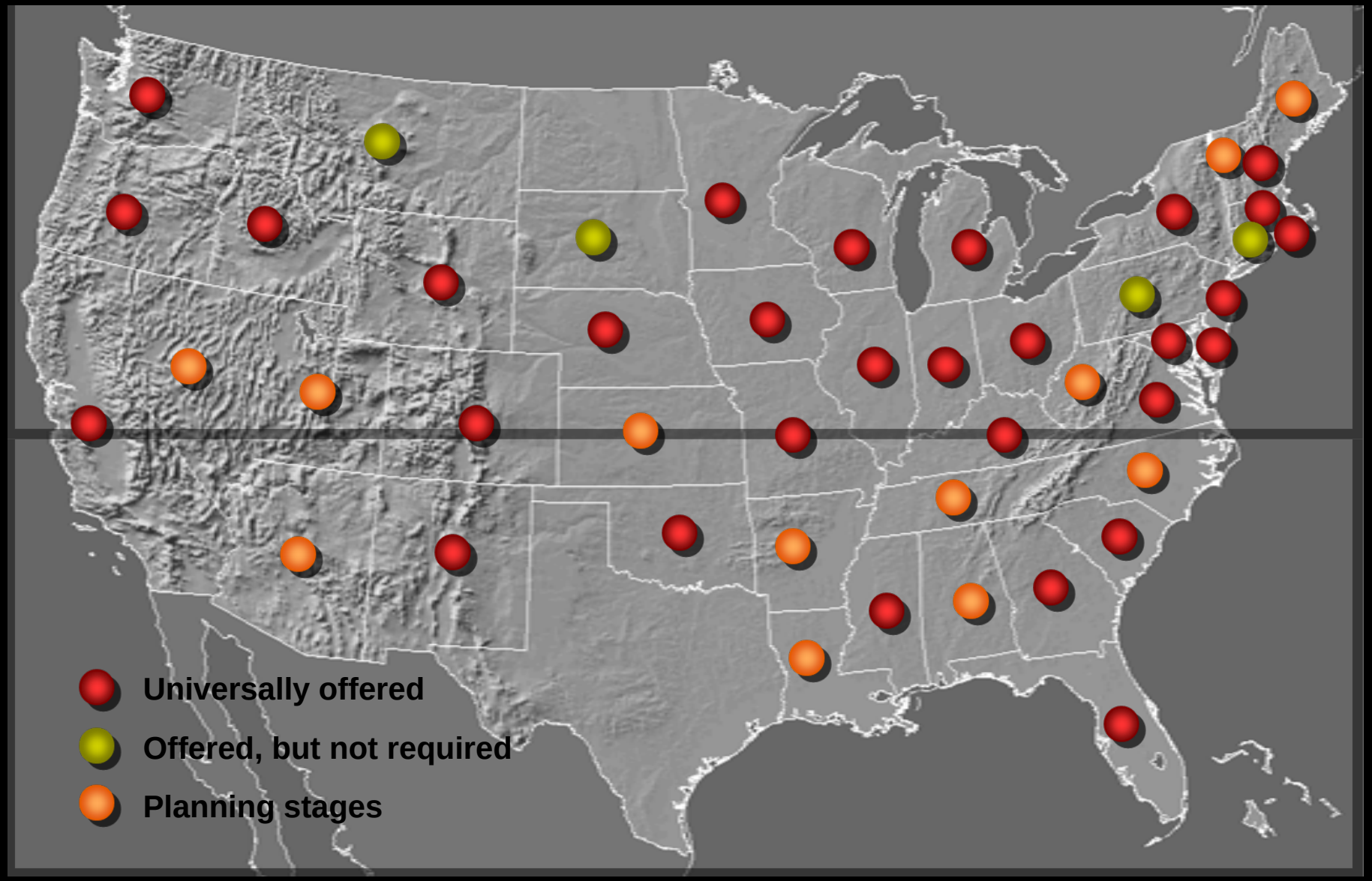
INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Cystic fibrosis newborn screening in the United States (2004)



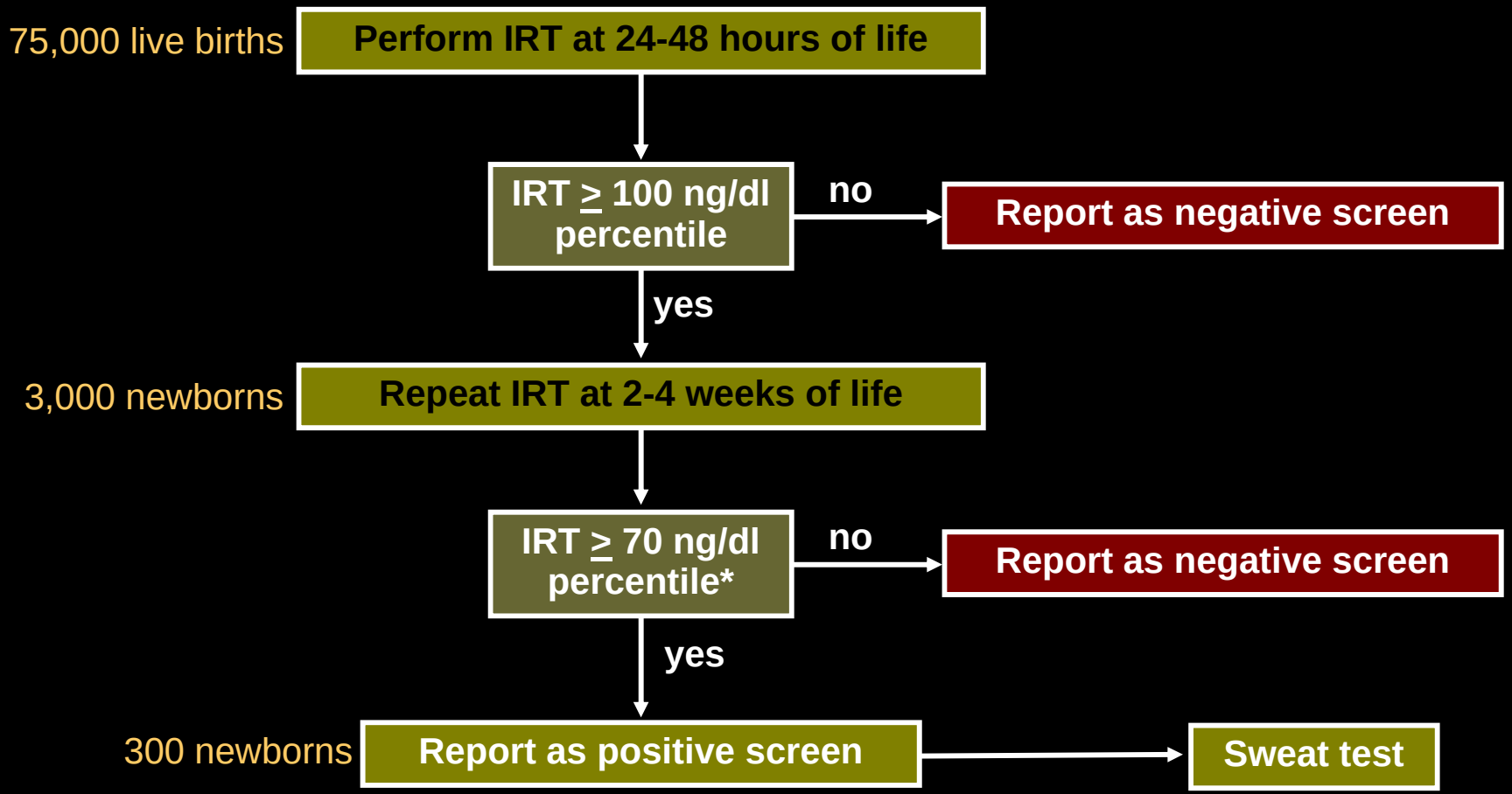
Cystic fibrosis newborn screening in the United States (2007)



Missouri birth rates and expected numbers of cystic fibrosis patients

Race/ethnicity	Missouri birth rate	CF frequency	Anticipated CF newborns
Caucasian	62,375	1 in 1,900-3,700	19-32
African-American	11,028	1 in 15,300	0.7
Hispanic	3267	1 in 8,000	0.4
Asian-American	1496	1 in 10,000	0.1
Native American	353	1 in 40,000	0.0

Newborn screening for cystic fibrosis (IRT/IRT)



Requires second specimen
Recalls more African-American low APGAR babies

Rock MJ, *et al*. *Pediatr Pulmonol*. **6**:42;1989.

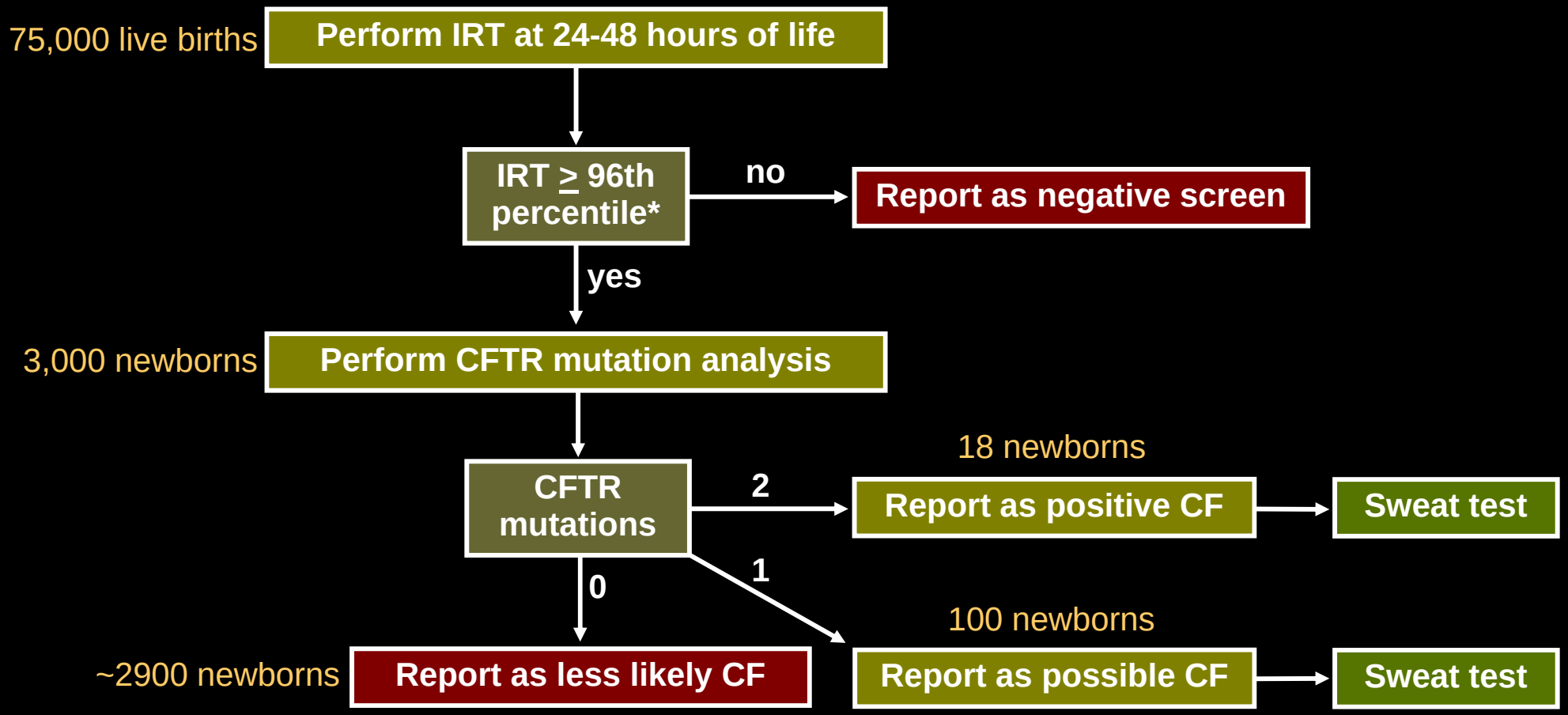
Cystic fibrosis: frequency of common CFTR mutations worldwide

Mutation	% of mutant CFTR alleles
ΔF508	66.0
G542X	2.4
G551D	1.8
W1282X	1.5
N1303K	1.2
R553X	0.9
3849 + 10 kB C-to-T	0.6
621 +1 G-to-T	0.6
1717 +1 G-to-A	0.5
1078 del T	0.5

Cystic fibrosis: ΔF508 frequency in different ethnic groups

Population	% of mutant CFTR alleles
Caucasian (worldwide)	66
Caucasian (northern Europe)	70-80
Caucasian (southern Europe)	50-55
Hispanic (US)	46
Jews (Ashkenazi)	30
African American	48
Native American	<5

Newborn screening for cystic fibrosis (IRT/DNA)



One sample
More specific
Ultrahigh IRT levels trigger sweat chloride measurement in some states

Newborn screening for cystic fibrosis: year one results

Missouri (IRT-IRT)

Initial newborn screening specimens: 81,100
Total requested repeat screens: 421
Total referred to CF Centers: 107
Total confirmed CF: 23 (12 from central and southwest Missouri)
False Positives: 84
False Negatives: 0

Illinois (IRT-DNA)

Initial newborn screening specimens: 79,506
Positive screens: 320
Total confirmed CF: 22 (11 patients from central and southern Illinois)
False Positives: 84
False Negatives: 0

Requirements for successful cystic fibrosis newborn screening

Farrell MH and Farrell PM. *J Pediatr.* 143:707;2003.

- Organize a collaborative program involving cystic fibrosis centers and the state screening lab.
- Establish follow-up mechanisms and communication between center, referring physicians, and the state screening lab.
- High quality sweat testing.
- Multidisciplinary, center-based care.
- Optimize nutritional management using proven methods for both evaluation and treatment.
- Improve respiratory management aimed at early treatment and prevention of chronic infections (especially *Pseudomonas aeruginosa* acquisition).

Benefits of early diagnosis through cystic fibrosis neonatal screening

- Prevent malnutrition and stunted growth
- Prevent micronutrient deficiencies (fat-soluble vitamins)
- Delay progression of lung disease
- Reduce risk for cognitive dysfunction due to malnutrition
- Enhance quality of care and quality of life
- Reduce costs for diagnosis and possibly treatment
- Improve access and avoid geographic and fiscal barriers
- Avoid disparities related to gender, race and ethnicity
- Provide genetic counseling for parents