TIMELINESS IN NEWBORN SCREENING: CONSIDERATIONS FOR CYSTIC FIBROSIS

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The primary goal of CF NBS is normal growth

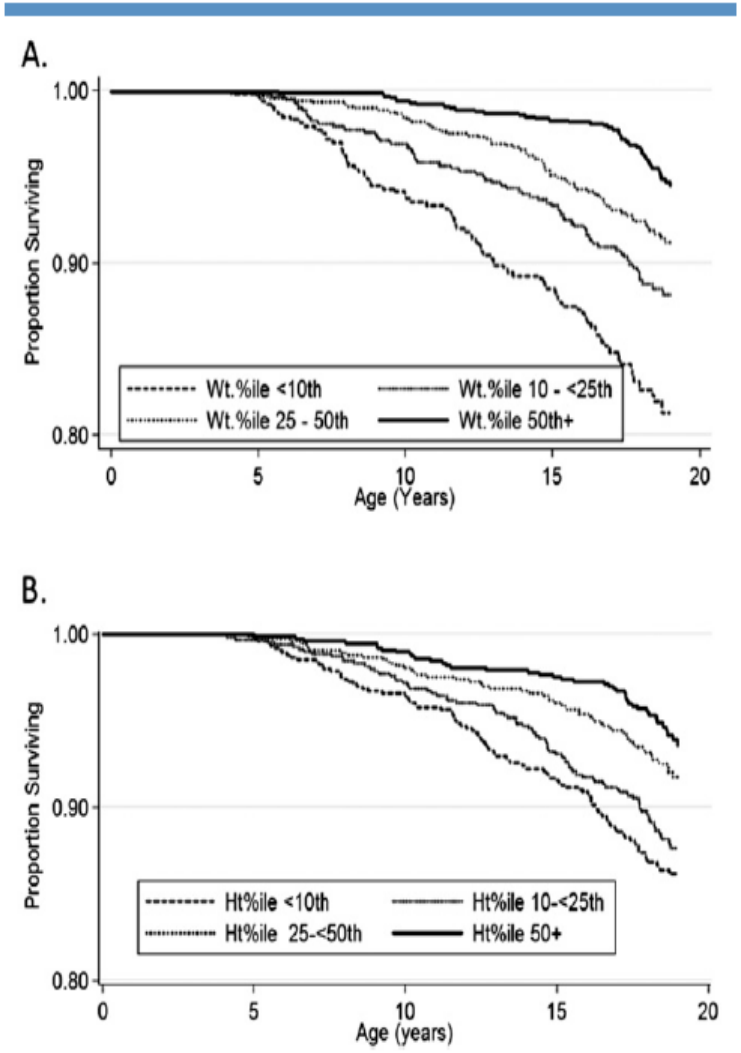
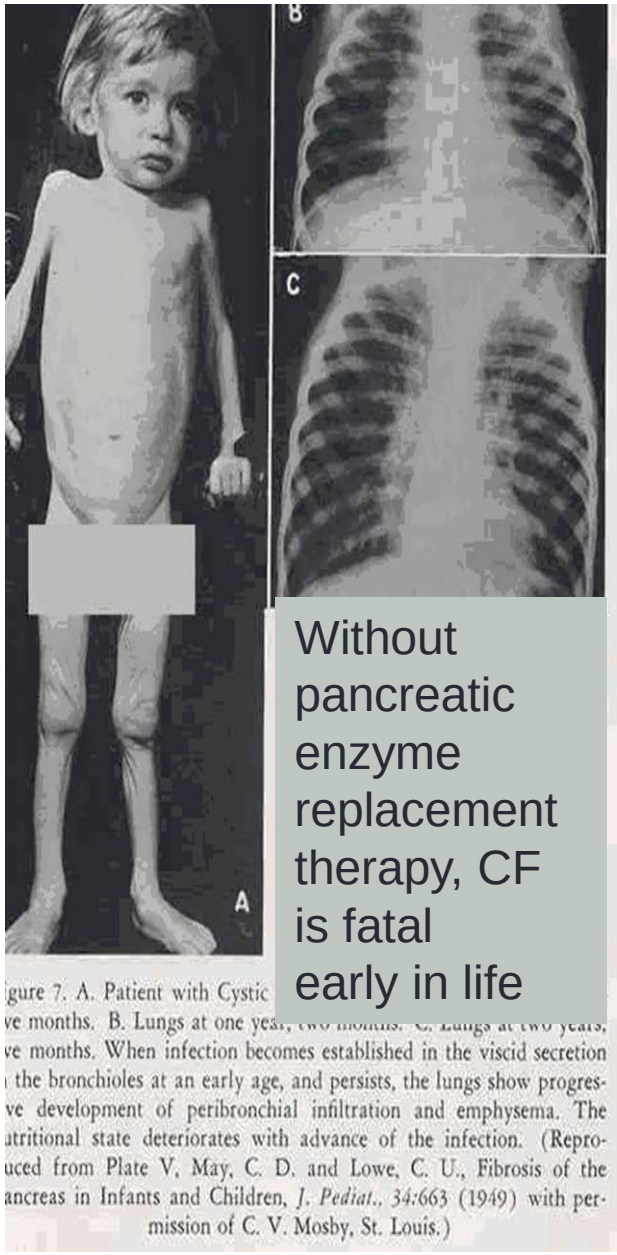


Figure 3. Kaplan–Meier survival curves of patients with CF born between 1989 and 1992, stratified by **A,** weight and **B,** height categories at age 4 years.

Yen, Quinton and Borowitz *J Pediatrics*



igure 7. A. Patient with Cystic
ve months. B. Lungs at one yea
ve months. When infection becomes established in the viscid secretion
the bronchioles at an early age, and persists, the lungs show progres-
ve development of peribronchial infiltration and emphysema. The
atritional state deteriorates with advance of the infection. (Repro-
uced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the
ancreas in Infants and Children, *J. Pediat.*, 34:663 (1949) with per-
mission of C. V. Mosby, St. Louis.)

Without pancreatic enzyme replacement therapy, CF is fatal early in life

Historical perspectives

- Colorado started screening for CF in 1982
  - Benefit of NBS not fully recognized for many years
- Randomized, controlled trial in Wisconsin showed significant and sustained improved nutrition (key predictor of survival) in screened vs. non-screened children

TABLE 3. Demographic, Nutritional, and Clinical Characteristics at the Time of Diagnosis of CF in Patients Without MI

Characteristic	Screened Group (n = 56)	Control Group (n = 48)	P Value
Age at diagnosis, wk			<.001
Mean (SD)	13 (37)	107 (117)	
Median (range)	7 (4–281)	28 (3–372)	

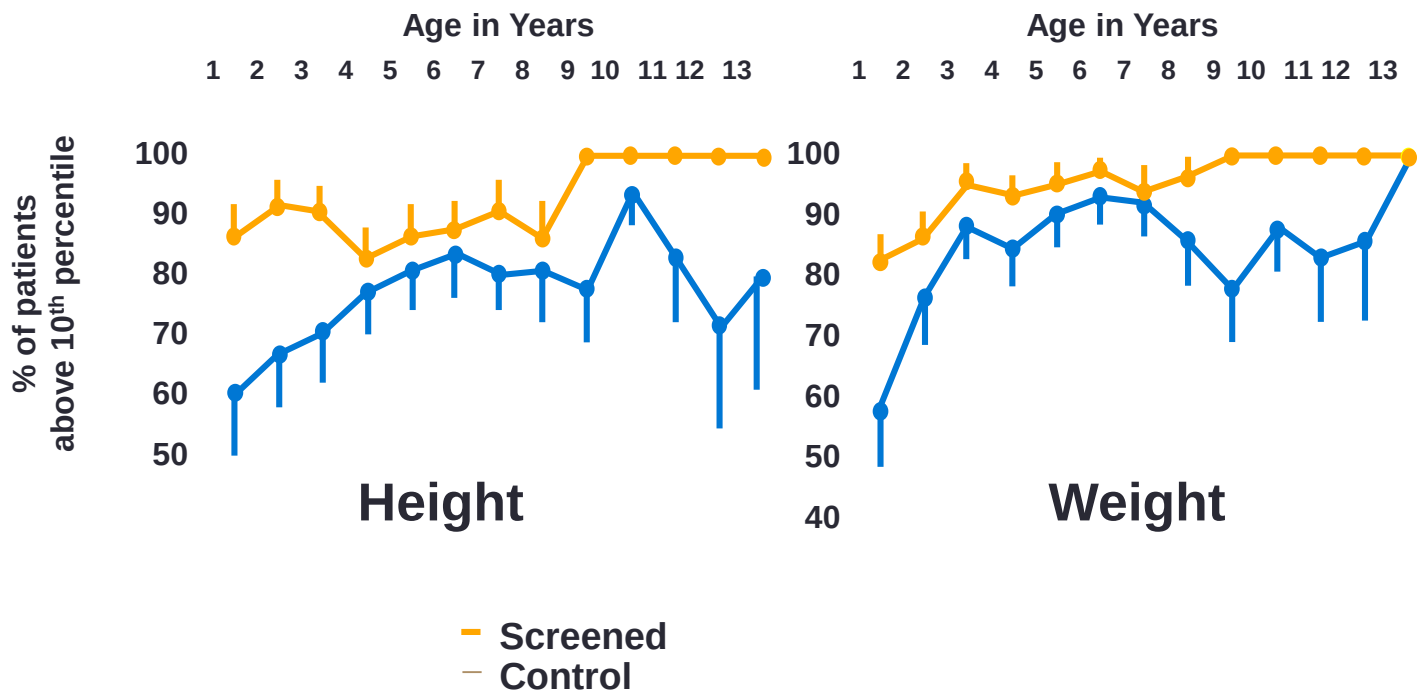
Early Diagnosis of Cystic Fibrosis Through Neonatal Screening Prevents Severe Malnutrition and Improves Long-Term Growth

Philip M. Farrell, Michael R. Kosorok, Michael J. Rock, Anita Laxova, Lan Zeng, Hui-Chuan Lai, Gary Hoffman, Ronald H. Laessig, Mark L. Splaingard and the Wisconsin Cystic Fibrosis Neonatal Screening Study Group

Pediatrics 2001;107;1-13
DOI: 10.1542/peds.107.1.1

NBS: The Wisconsin Study

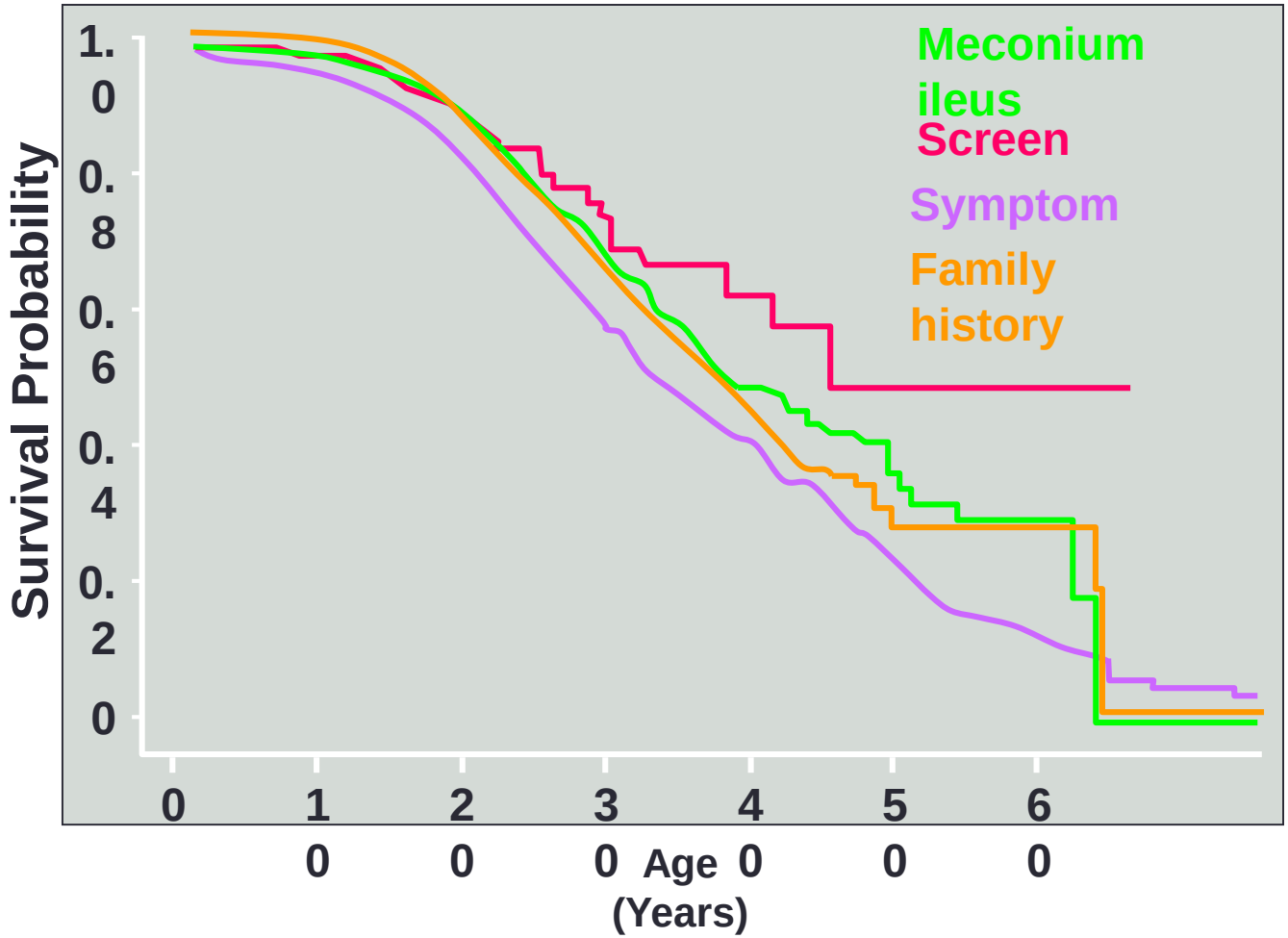
Height and Weight Are Higher for Infants with CF Identified by NBS



Farrell PM, et al. *Pediatrics*. 2001.

NBS: The Wisconsin Study

Early Diagnosis by NBS May Improve Survival



Lai HJ, et al. *Am J Epidemiol*. 2004.

Early treatment is essential

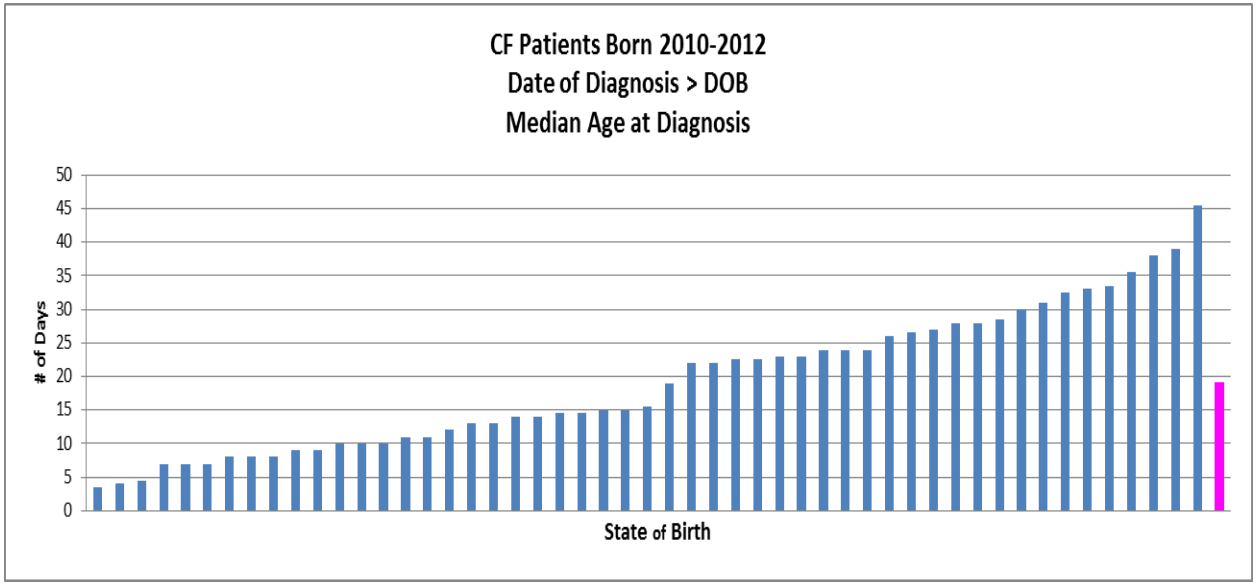
Table I. Treatment Recommendations for Infants with Cystic Fibrosis

Strength of evidence graded using the USPSTF grading system (2):				
	Estimate of Net Benefit (Benefit minus Harms)			
Certainty of Net Benefit	**Substantial**	**Moderate**	**Small**	**Zero/negative**
High	A	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

Question #	Recommendation	Strength of Evidence
Initial Diagnosis:		
1	The CF Foundation recommends that treatment for infants diagnosed with CF by NBS should be done at an accredited CF care center, with the goal of an initial visit within 24-72 hours of diagnosis (1-3 working days in absence of overt symptoms).	Consensus recommendation

diagnosed with CF and are intended to help guide families, primary care providers, and specialty care centers in the care of infants with CF. *(J Pediatr 2009;155:S73-93)*.

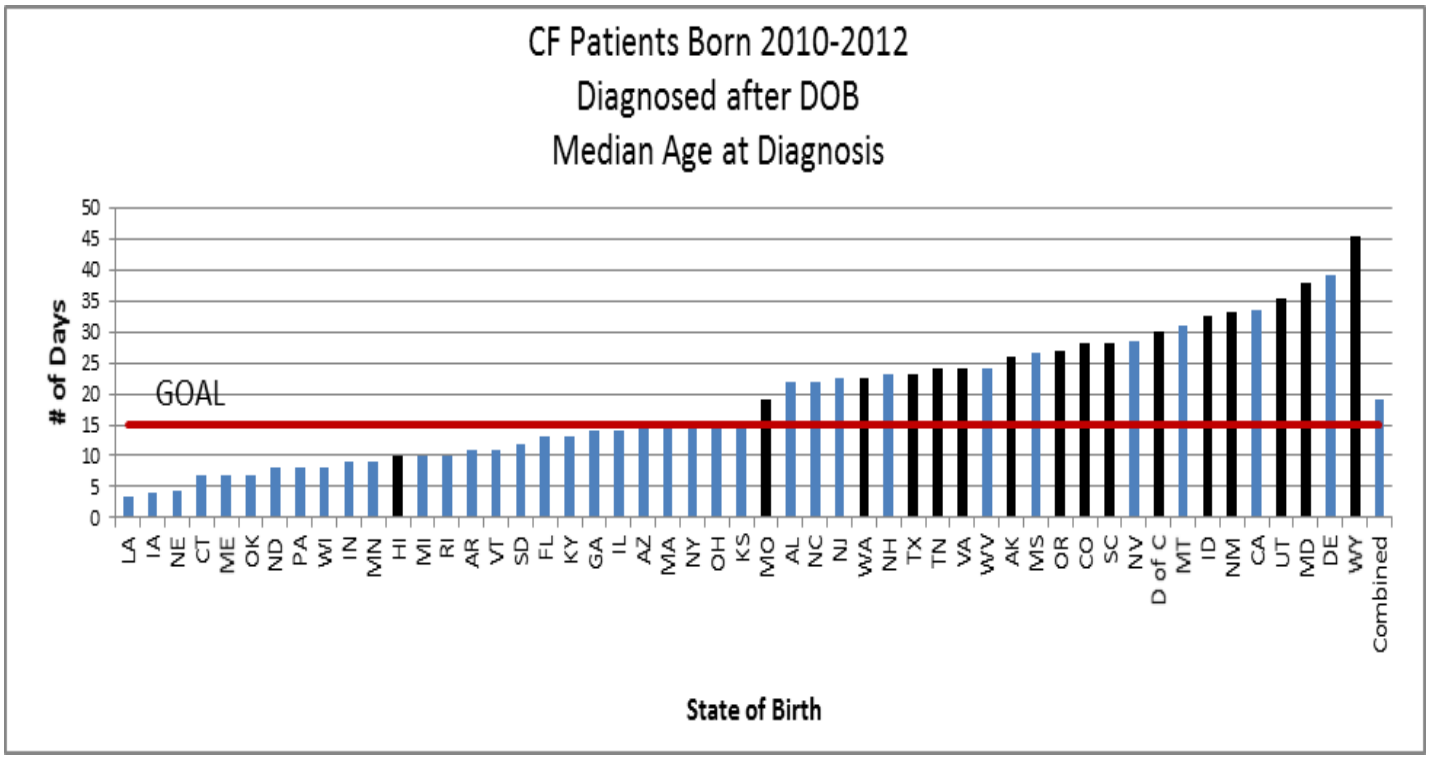
Median age at CF diagnosis is variable



Each blue bar represents one state. The average median, 19.1 days, is shown in pink. Median age at diagnosis ranged from 4 to 45.5 days.

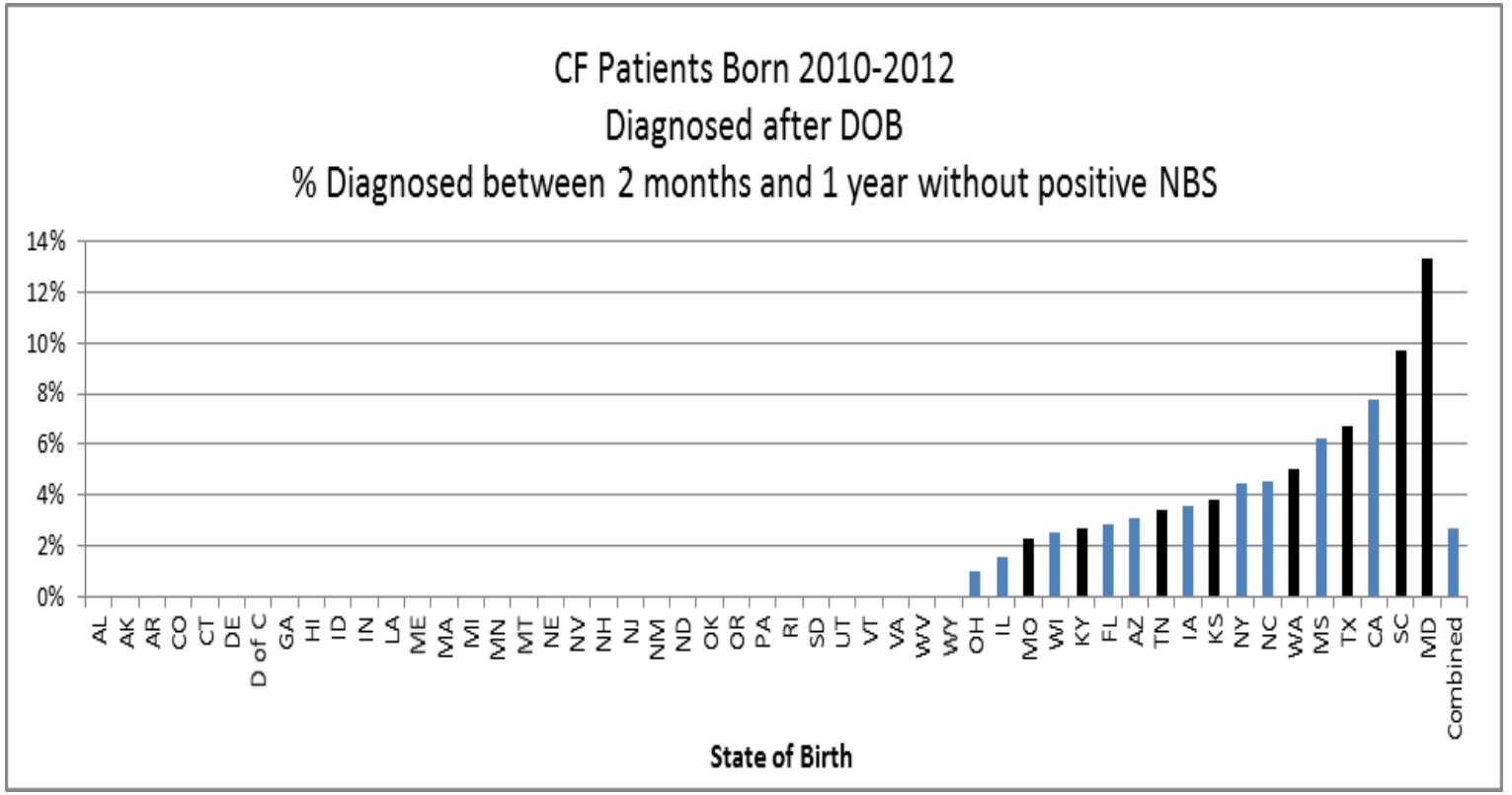
Caveats: multiple methods of diagnosis, including prenatal; data censored to make date of birth first possible date of diagnosis.

Cystic Fibrosis NBS QI Consortium goal for age at diagnosis is 15 days



IRT/DNA during study time period IRT/IRT during study time period

False negative NBS are variable between states



CFTR multi-mutation panels are less predictive in minority populations

Table 2 Comparison of *CFTR* mutation detection between ethnic/racial groups through Illinois newborn screen

	Patients Diagnosed	Patients with 2 defined mutations by NBS (%)	Patients with 0 or 1 defined mutations by NBS (%)	p value*
Total	104	88 (84.6%)	16 (15.4%)	
Ethnicity/Race				
Non- Hispanic Caucasian	74	67 (90.5%)	7 (9.5%)	
Hispanic Caucasian	15	9 (60%)	6 (40%)	0.002
African American	3	3 (100%)	0 (0%)	0.567
Information not provided	12	9 (75%)	3 (25%)	0.119

* Compared with Caucasian non-Hispanic reference group

J Genet Counsel (2012) 21:671–675
DOI 10.1007/s10897-012-9481-2

CFF PDR 2010-2014: diagnosis after false negative NBS

All cases in registry (n=28,674)		False negative NBS (n=74)	
White, non-Hispanic	85%	White, non-Hispanic	77%
Hispanic	8%	Hispanic	11%
Black	5%	Black	7%
Other/ more than one	3%	Other/ more than one	5%

Why early diagnosis?

- Clear benefits of newborn screening shown in population diagnosed at median age of 7 weeks

.....BUT

There is evidence of a growth deficit in infants with CF, even with NBS diagnosis

Studies on CF infant growth show deficits during the first year of life

- From NACFC 2015---only abstracts published
- FIRST study (Lai et al)
  - Prospective study of feeding, growth EFA status and inflammatory biomarkers in infants with CF diagnosed through NBS
  - Weight at 41st , height at 61st percentile at birth, declined to 19th/20th percentile by age 2 months. EFA deficiency noted.
  - Weight, but not length recovered by 12 months of age
- BONUS study (Gelfond et al)
  - Prospective study of growth in infants diagnosed with CF through NBS; careful evaluation of PERT dosing
  - Similar findings; length not recovered by 12 months of age

Studies on CF infant growth show deficits during the first year of life

- Comparative registry analysis (Schechter et al)
  - CFF registry evaluating growth in infants seen for first visit at a median age of 1 month of age
  - Years 2010-2013
    - 2010 was first year **all** US states included CF in NBS protocol
  - Compared infants on PERT to infants not on PERT (proxy for pancreatic insufficieny)
  - PERT infants had lower weight and length at birth and were significantly smaller in weight, weight for length, and length percentiles at 1 month of age.
  - All deficits except weight for length percentile continued at 12 months.

Hypothesis

- Given that growth is sustainably increased by NBS diagnosis, and that there are growth deficits in the **SCREENED** population at 12 months of age, earlier intervention is needed to improve growth
  - Other than earlier PERT therapy, specific interventions are not yet described

Quality improvement case

- Variability in median age of diagnosis by State suggests improvements in the NBS system can improve quality and outcomes
- Targets for improvement
  - Earlier completion of CF algorithm
  - Earlier visits for evaluation and confirmatory testing
  - Reducing QNS sweat tests
  - Treating infants with presumptive CF