

# **History of Newborn Screening for Cystic Fibrosis**

# The Dark Ages

Pre gene discovery (CFTR)

Immunoreactive serum trypsinogen (IRT)

Australia, Europe, Colorado, Wisconsin

# The Middle Ages

IRT + mutation analysis

1989 AAP Committee on Genetics – No screening until benefits proven to outweigh costs/risks

1997 NIH consensus conference – offer testing to all couples, pregnant or planning pregnancy

CDC Workshop – Pilot NB screening projects recommended

1998 Amer. College of Medical Genetics –  
no general screening until  
sensitive/specific tests for ethnic  
groups and genetic counseling  
available

ACOG – prenatal screening is not  
currently the standard of care

# The Renaissance

ACOG Recommends Prenatal Testing Panel

Nov 2003      CDC/CFF Workshop

CDC recommends that states  
consider magnitude of  
benefits/costs

# **Benefits**

Early nutritional intervention

Diagnosis median 1 year earlier

Improved growth

Improved cognitive development (1 study)

# Unclear

Respiratory outcome

Hospitalizations

Long term survival

# Risks

Psychosocial

Genetic counseling

Earlier exposure to infectious agents

# **States with Newborn Screening Programs for Cystic Fibrosis**

\*California

Colorado

Connecticut

Massachusetts

Mississippi

Montana

New Jersey

New York

Pennsylvania

South Carolina

Wisconsin

Wyoming

# **California Program**

Established Hispanic/Black cystic fibrosis  
gene profiles

# Problem Identification

IRT cut off level

DNA mutation panel

Genetic counseling

Diagnostic issues

Clinical practice

Educating providers

Evaluation

Program improvements

# Genetic Counseling

45% physician

28% nurse

23% genetic counselor

4% social worker

# Protocol Preferences

- CF Center arranges sweat test/DNA; no counseling until results available **3/14**
- CF Center provides preliminary counseling with + screen, arranges sweat test/DNA tests, and recounsels **5/14**
- + screen referred to state approved counseling resource then to CF Center for confirmation of diagnosis **6/14**

# Miscellaneous

42% of pregnant women have prenatal screening in California

Alaska = ?

IRT misses disproportionate number of cases with mild mutations

# **Benefits of Early Diagnosis**

- ★ Prevent deaths of undiagnosed patients
- ★ Improve access - avoid geographic & fiscal barriers
- ★ Avoid disparities related to gender, race, & ethnicity
- ★ Prevent protein energy malnutrition & stunted growth
- ★ Prevent prolonged micronutrient deficiencies (eg vit. ADEK)
- ★ Reduce risk for cognitive dysfunction
- ★ Preempt bronchopulmonary disease and Ps. a infection
- ★ Provide genetic risk information
- ★ Reduce costs for diagnosis & possibly treatment
- ★ Minimize certain psychosocial issues

# **Medical Consequences of Symptomatic Diagnosis in infants with Cystic Fibrosis**

Frank Accurso, MD

Marci Sontag, PhD

Scott Sagel, MD

Jeffrey Wagener, MD

University of Colorado

Children's Hospital

Denver, Colorado, USA

# Medical Consequences of Symptomatic Diagnosis in Infants with CF: Introduction

## Diagnosis of CF

Symptomatic (Conventional, Delayed)

Meconium Ileus

Family History

Prenatal Diagnosis

Newborn Screen

## Symptomatic Diagnosis

Short Term Consequences – FTT, micronutrient deficiency, etc.

Long Term Consequences – Impaired Growth,  
(Farrell et al., 2001)

# Medical Consequences of Symptomatic Diagnosis: Methods

What are the short term and long term rates of CF complications by mode of diagnosis?

What morbidity (hospitalization) occurs in the short term and in the long term by mode of diagnosis?

Methods:

CF Foundation patient registry 2000, 2001, 2002

# New Diagnoses Under a Year of Age

<u>Category</u>	<u>N</u>
SYMP	819
NBS	245
MI	444
Prenatal	66

Family History is excluded since it often appears in each category.

# Length and Weight < 1 yr of age

Complication	SYMP	NBS	MI	Pre
Stunting (length <3 <sup>rd</sup> percentile)	213/810 <b>26%*</b> (23-29)	21/239 <b>9%*</b> (6-13)	84/429 <b>19%</b> (16-23)	6/65 <b>9%</b> (4-19)
Wasting (weight<3 <sup>rd</sup> percentile)	265/813 <b>33%*</b> (29-36)	26/240 <b>11%*</b> (8-16)	123/433 <b>28%</b> (24-32)	7/65 <b>11%</b> (5-21)

\*, \* p<0.0001

# *Pseudomonas* colonization < 1 yr of age

Complication		SYMP	NBS	MI	Pre
Pseudomonas					
	Any <i>PsA</i>	228/774 <b>29%*</b> (26–33)	32/211 <b>15%*</b> (11–20)	99/387 <b>26%</b> (22–30)	11/48 <b>26%</b> (14–37)
	Mucoid <i>PsA</i>	21/774 <b>3%**</b> (2–4)	1/218 <b>&lt;1%**</b> (0–2)	8/387 <b>2%</b> (1–4)	2/48 <b>4%</b> (1–14)

\*, \* p<0.0001

\*\*, \*\* p<0.06

# Hospitalizations under a year of age

Complication	SYMP	NBS	MI	Pre
Hospitalized (in year of diagnosis)	523/819 <b>64%*</b> (60–67)	55/245 <b>22%*</b> (18 –28)	340/444 <b>76%</b> (73–80)	17/66 <b>26%</b> (17-38)
Days Hospitalized (per patient hospitalized)	<b>18± 1**</b>	<b>18± 4**</b>	<b>33± 2</b>	<b>18± 4</b>

\*,\* p<0.0001

\*\*,\*\* p NS

# Complications under a year of age

Complication	SYMP	NBS	MI	Pre
Edema or hypoproteinemia	39/819 <b>5%*</b> (4–7)	0/245 <b>0%*</b> (0–1)	1/444 <b>&lt;1%</b> (0–1)	0/66 <b>0%</b> (0–5)
Electrolyte Imbalance	44/819 5% ** (4–6)	8/245 3% ** (2–6)	3/444 1% (0–2)	1/66 1% (0–8)
Patients with one or more complications and hospitalizations	570/819 <b>70%***</b> (66–72)	71/245 <b>29%***</b> (23–34)	322/444 <b>58%</b> (54–62)	21/66 <b>31%</b> (17–38)

\*, \* p<0.0005

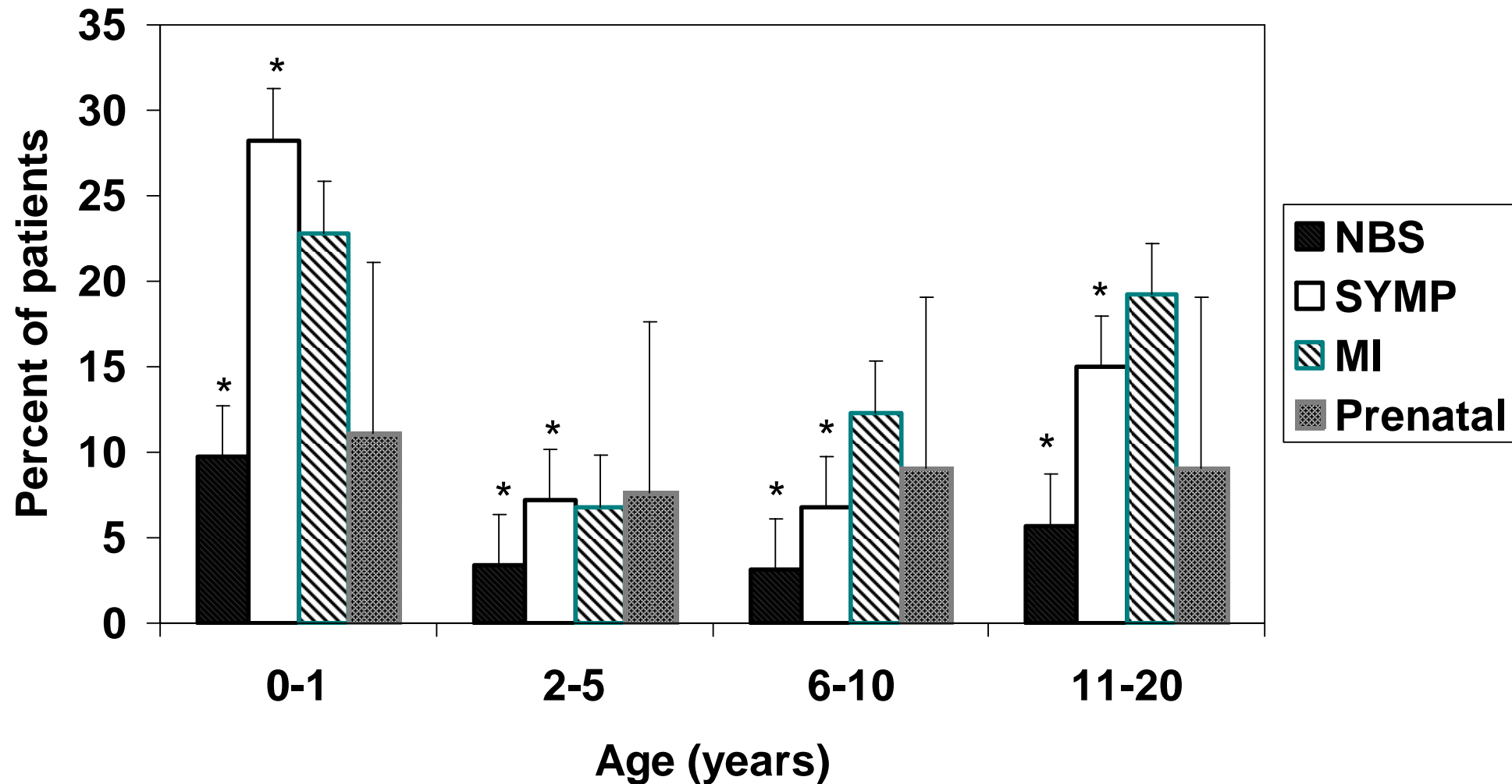
\*\*, p NS

\*\*\*, \*\*\* p<0001

# Long Term Complication and Morbidity Rates: 2002 Registry

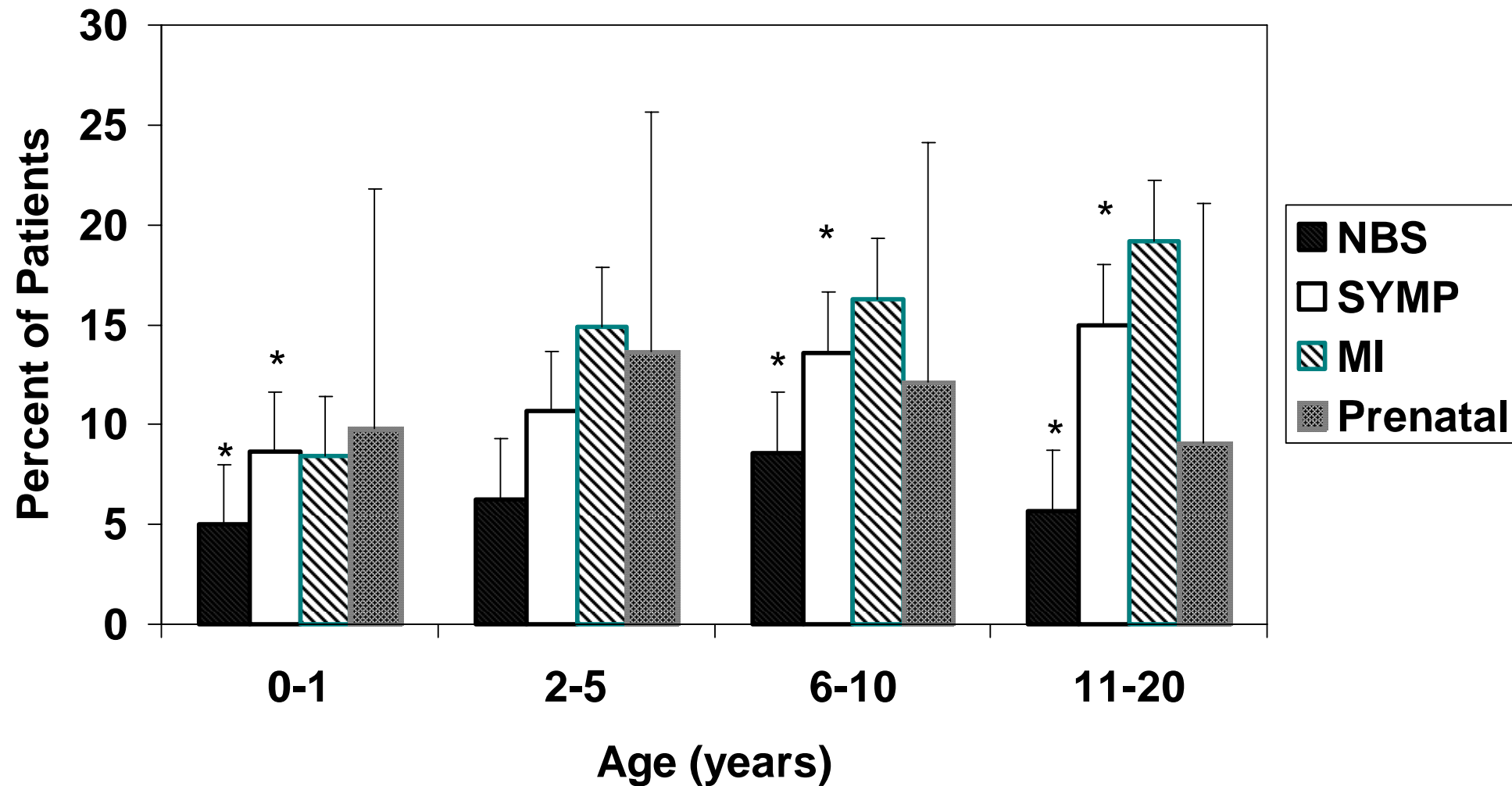
<u>Age (yrs)</u>	<u>N</u>
0-1	1,028
2-5	2,732
6-10	3,895
<u>11-20</u>	<u>6,992</u>
total	14,647

# Percent of patients less than the 3rd percentile for weight: 2002 Registry



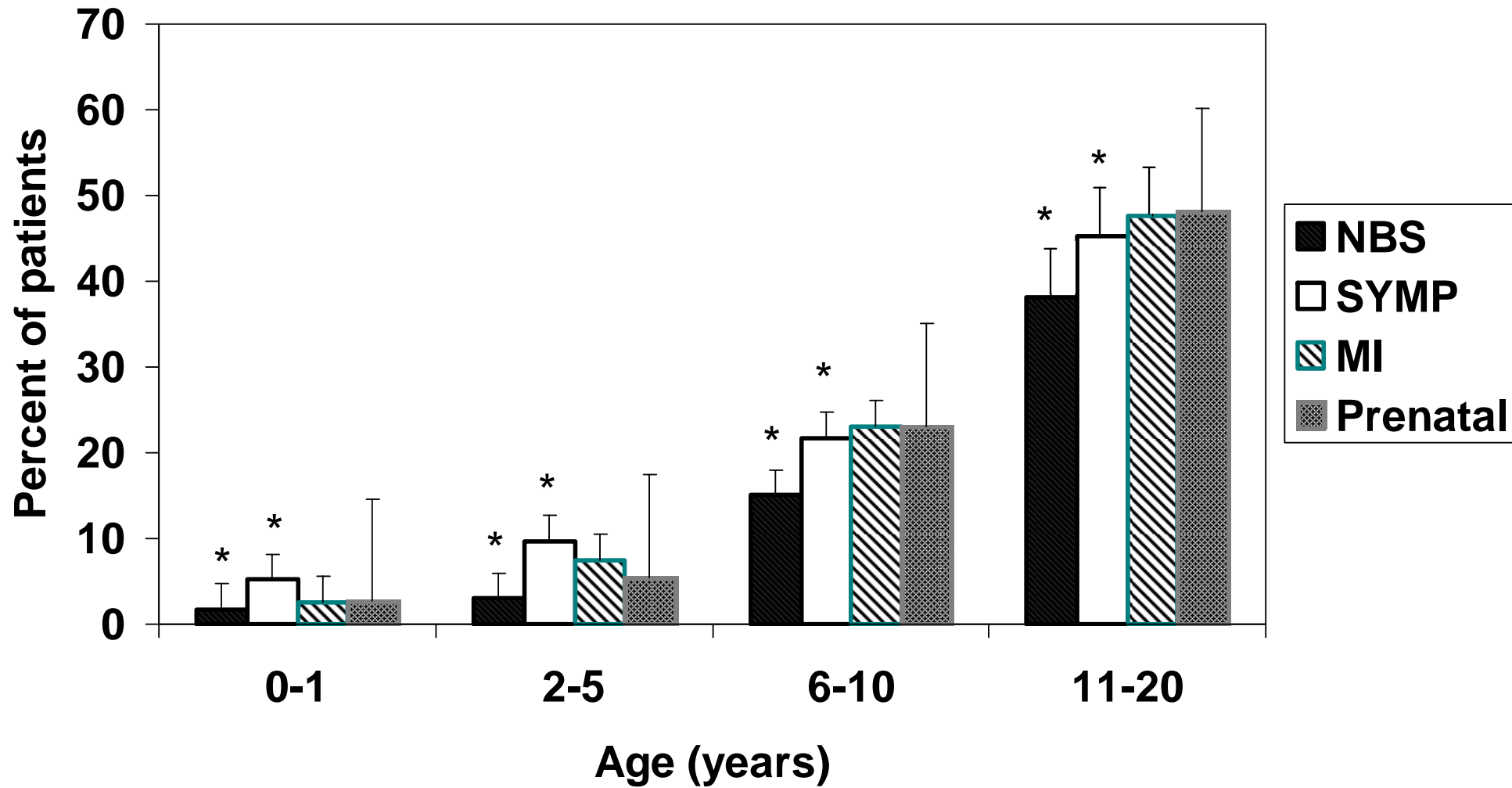
\*, \* p < 0.05 SYMP vs NBS each age range

# Percent of patients less than the 3rd Percentile for Length: 2002 Registry



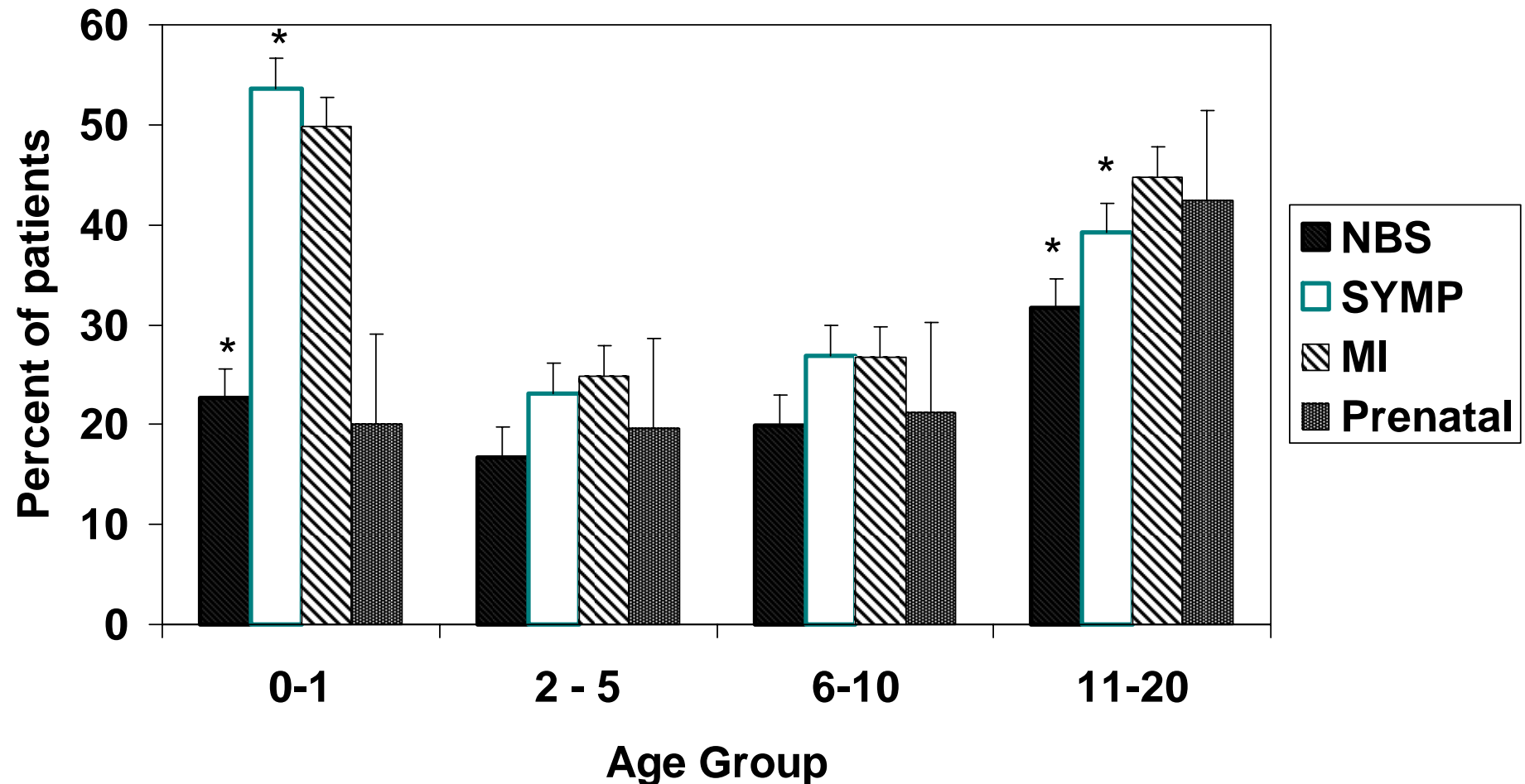
\*, \* p < 0.05 SYMP vs NBS

# Percent of Patients with mucoïd *Pseudomonas* by age Group



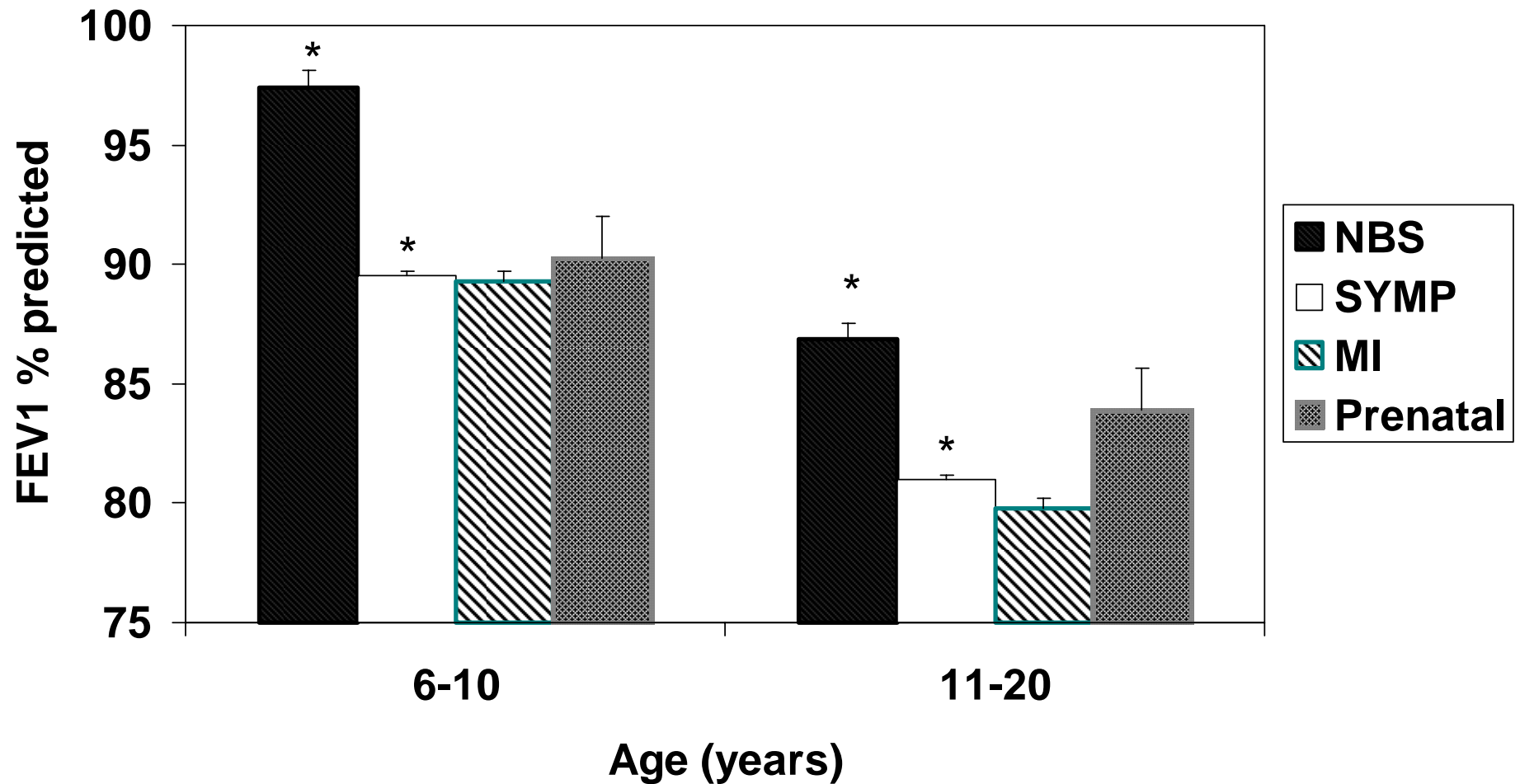
\*,\* p < 0.05 SYMP vs NBS each age range

# Percent of Patients Hospitalized by mode of diagnosis: 2002 Registry



\*,\* p < 0.05 SYMP vs NBS

# Percent Predicted FEV1 by Mode of Diagnosis: 2002 Registry



\*, \* p < 0.05 SYMP vs NBS each age range

# Medical Consequences of Symptomatic Diagnosis: Conclusions

1. Symptomatic Diagnosis of CF is associated with increased complication rates and morbidity compared to Diagnosis by Newborn Screening in both the short and long term.
2. No deleterious effect on Pulmonary Function or Mucoicid *Pseudomonas* colonization could be detected in patients Diagnosed through Newborn Screening compared to the Symptomatic Diagnosis group.
3. The data suggest an advantage for the Newborn Screened group in pulmonary function and Mucoicid *Pseudomonas* colonization compared to Symptomatic Diagnosis group.

# TYPES OF SCREENING

- IRT
- IRT / IRT
- IRT +  $\Delta F508$
- IRT + Multimutation panel

# IRT – Rate of Decline in CF

- In neonatal period IRT is very high in most CF patients (200 – 300).
- IRT of CF babies with pancreatic sufficiency at birth declines at a slower rate than in pancreatic insufficient babies. May be elevated for years.
- Babies with meconium ileus have a lower newborn peak IRT & may be in normal range.

# IRT / IRT

- 1<sup>st</sup> before nursery discharge
- 2<sup>nd</sup> at 2 weeks of age

# IRT / mutation testing

- IRT +  $\Delta F508$
- IRT + mutation panel

# Sensitivity of various protocols

	IRT cutoff 1 <sup>st</sup> specimen	DNA testing used	Direct referral for ultrahigh IRT	Sensitivity
Colorado	140 mg/ml	NO	NA	93%
Colorado	105 mg/ml	NO	NA	95%
Wisconsin	180 mg/ml	NO	NA	87%
Wisconsin	110 mg/ml	$\Delta$ F508	NO	94%
Wisconsin	96% of daily average	$\Delta$ F508	NO	94%
Wisconsin	96% of daily average	25 mutations	NO	95%
Massachusetts	95% of monthly average	$\Delta$ F508	NO	86%
Massachusetts	95% of monthly average	16-27 mutations	IRT > 99.8%	99%

# Oregon CF Screening Estimates (annual)

# Alaska System

1<sup>st</sup> IRT + ⇒ notification of physician

2<sup>nd</sup> IRT + ⇒ notification of physician and CF Center



preliminary counseling and sweat chloride

Negative sweat test



Counseling

Positive sweat test



Counseling

CF Care