

# 2007 Diagnostics Update

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# TOPICS

- New Spirometry Guidelines
- Inhaled Insulin
- Exhaled Nitric Oxide

# 2005 ATS/ERS Guidelines for Interpretation of Lung Function



# Spirometry Reference Equations Recommended in the US

- Third National Health and Nutrition Examination Study (**NHANES III**) n=7,429
  - Large number of men, woman, and children including specific predictions for African Americans and Hispanic Americans ages 8 - 80



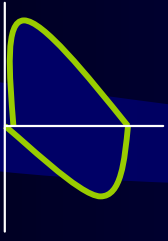
# Spirometry Reference Equations for Children < 8 yrs Recommended in the US

- Wang et al. 1993 *Pediatr Pulmonol* 15:75-88



# Repeatability

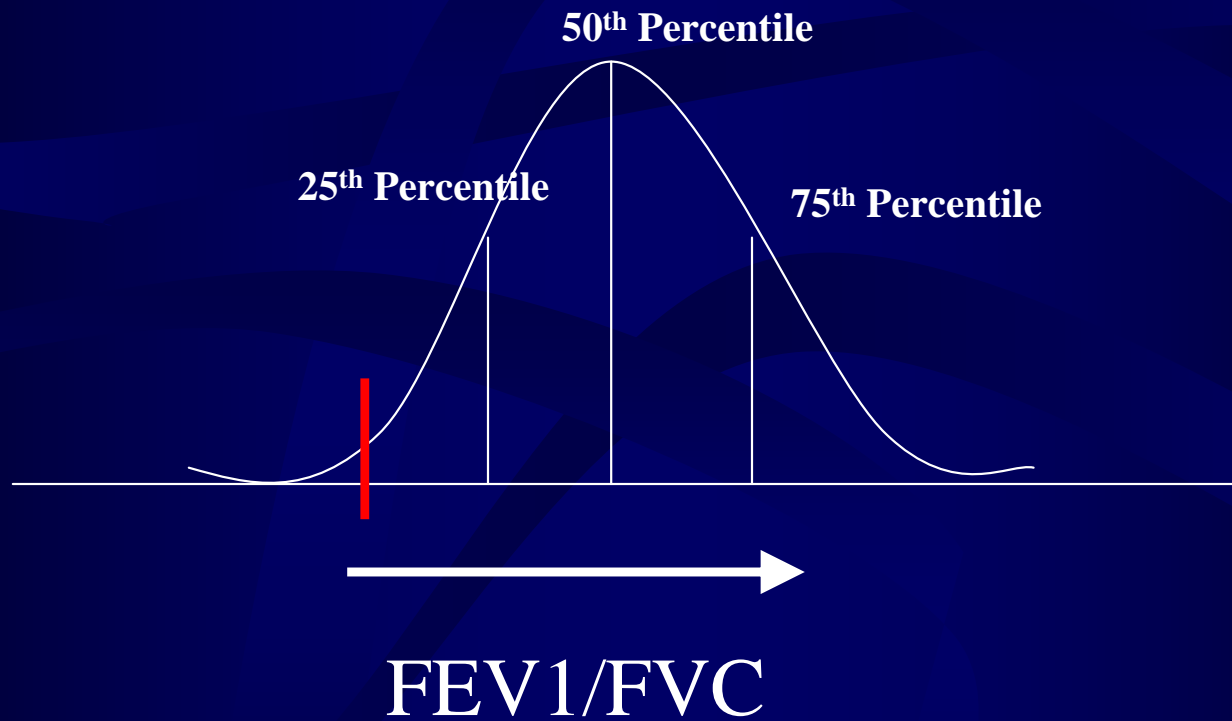
1. The term **reproducibility** should refer to visit to visit agreement
2. The term **repeatability** should be used for intratest agreement and replace the term reproducibility
3. New **repeatability criteria**: FEV1 & FVC must be within **.15 Liters** of each other



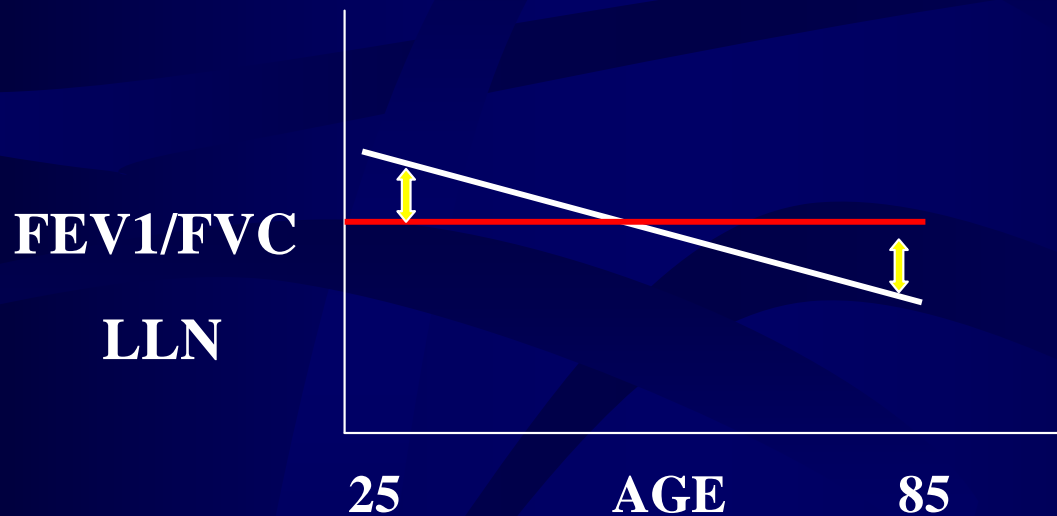
# Spirometry Interpretation

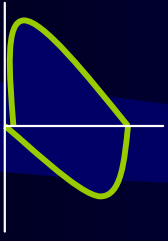
- Presence of Airflow Obstruction
  1.  $FEV_1/FVC < \text{Lower limit of Normal}$ 
    - LLN is the 5<sup>th</sup> Percentile

# FEV1/FVC in a Population



# FEV1/FVC LLN Accounts for Aging





# Spirometry Interpretation

- Degree of Airflow Obstruction
  - Use  $FEV_1$  % predicted

## FEV1

- |                     |                       |
|---------------------|-----------------------|
| • Mild              | $\geq 70\%$ predicted |
| • Moderate          | 60 – 69 % predicted   |
| • Moderately Severe | 50 – 59 % predicted   |
| • Severe            | 35 – 49 % predicted   |
| • Very Severe       | $\leq 35\%$ predicted |

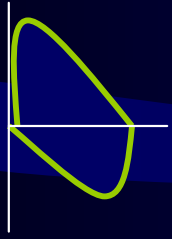


# Spirometry Interpretation

- **Non-Specific Decrease in Vital Capacity**
  - FVC < Lower limit of Normal
    - LLN is the 5<sup>th</sup> Percentile

*NOTE:*

- 1. The term restriction should not be used.*
- 2. There is no recommendation for degree of severity with a decreased Vital Capacity.*



# Top 5 Causes of Decreased Vital Capacity

- Poor Effort
- Obesity
- Obstruction
- Muscle Weakness
- Restrictive Lung Disease



# Bronchodilator Response

- 4 puffs of 100 $\mu$ g albuterol by spacer
- Significant change remains 12% and 200ml increase in FEV<sub>1</sub> & FVC



# The Great Disconnect

## Spirometry Utilization in COPD vs. 2-D Echo Utilization in CHF

CHF 78% 2-D Echo

COPD 30% Spirometry

Patients with both Dx's → 48% had a 2-D Echo  
→ 2% had Spirometry

# COPD in People >40

- 16% incidence in NHANES Study in US.
- 8% Mexico
- 20% Uruguay
- 11% Europe

**8% x people in world > 40yrs = 280 Million**

**3<sup>rd</sup> Leading Cause of Death in the World by 2020**

# Inhaled Insulin



  
**EXUBERA<sup>®</sup>**  
(insulin human [rDNA origin])  
Inhalation Powder



The **new look** of  
A1C control



The advertisement features a woman with short brown hair, smiling, wearing a light blue shirt. To her right, the text reads "The new look of A1C control". On the far right, there are two inhalation powder containers, one taller than the other, both with blue and white packaging. The background is a light green gradient.

# A1C Control

- A1C is glycosylated hemoglobin (HgbA1C)
- A measure of the average blood glucose over three months

# Diabetes Statistics

- 20 million Americans (7%)
- 90% of these patients are diagnosed with type 2 diabetes
- Total Annual cost \$130 billion

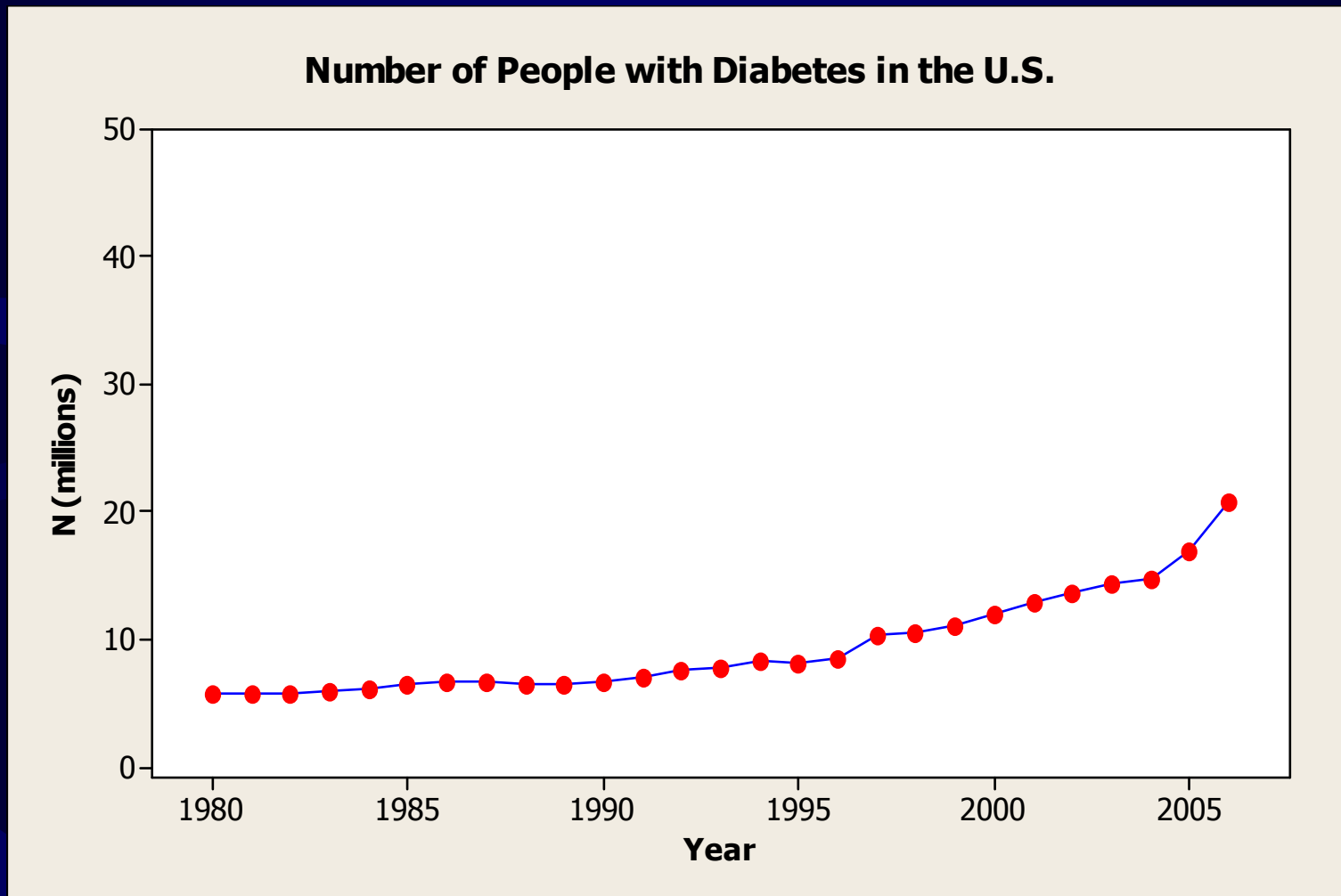
# Diabetes Mellitus

- Type 1
  - Insulin dependent
  - Juvenile onset (below age 30)
  - Autoimmune, pancreas destroyed
- Type 2 (90% of all patients)
  - Insulin *resistant*
  - Usually due to obesity (over-indulgence)
  - Now more common in children than type 1

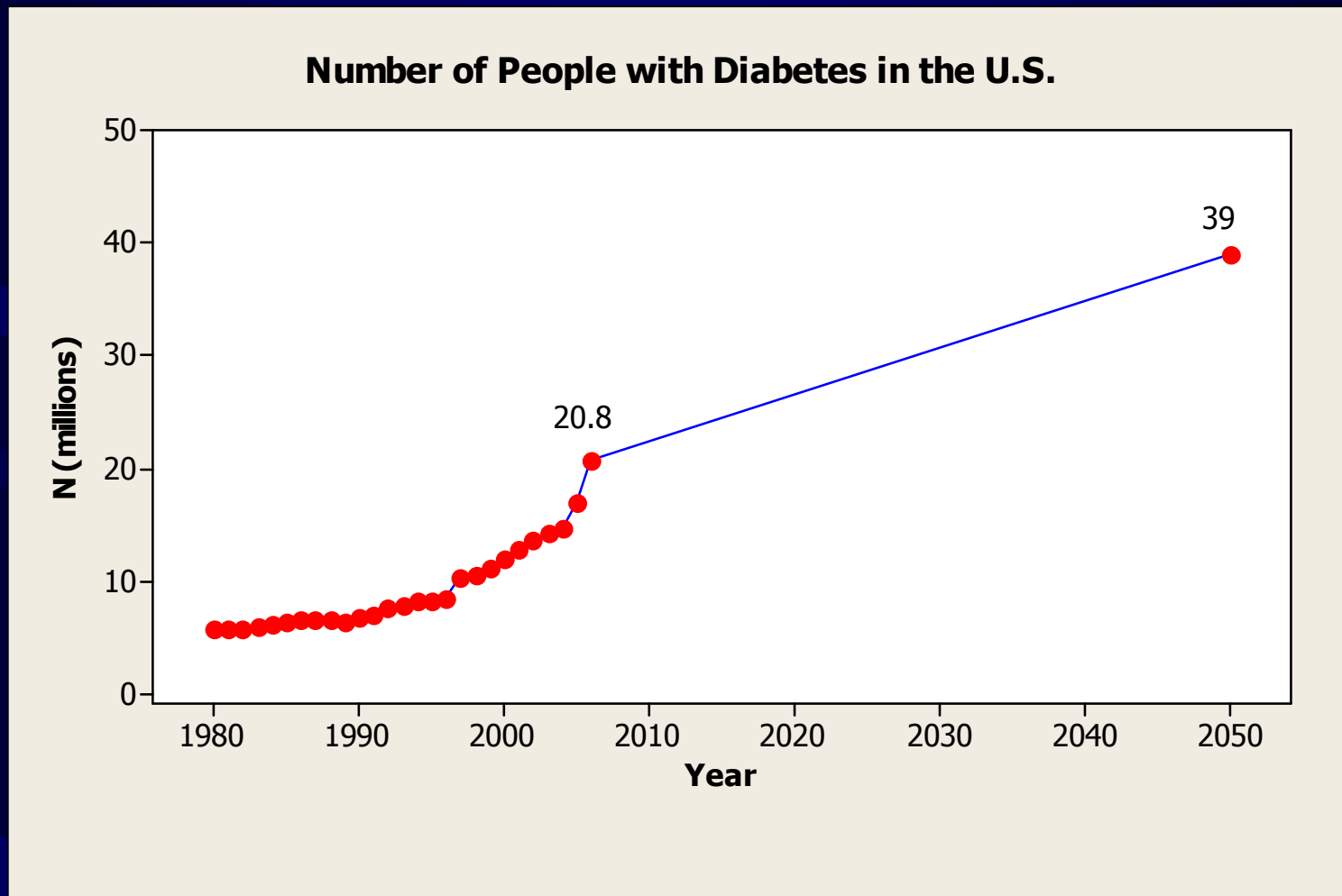
# Diabetes Statistics

- Projected to be 39 million people in the US by 2050
- If current trend continues, 1 in 3 Americans will develop Diabetes sometime in their lifetime
- On average, diabetics lose 10-15 years of life

# Diabetes Mellitus in the U.S.



# Diabetes Mellitus in the U.S.

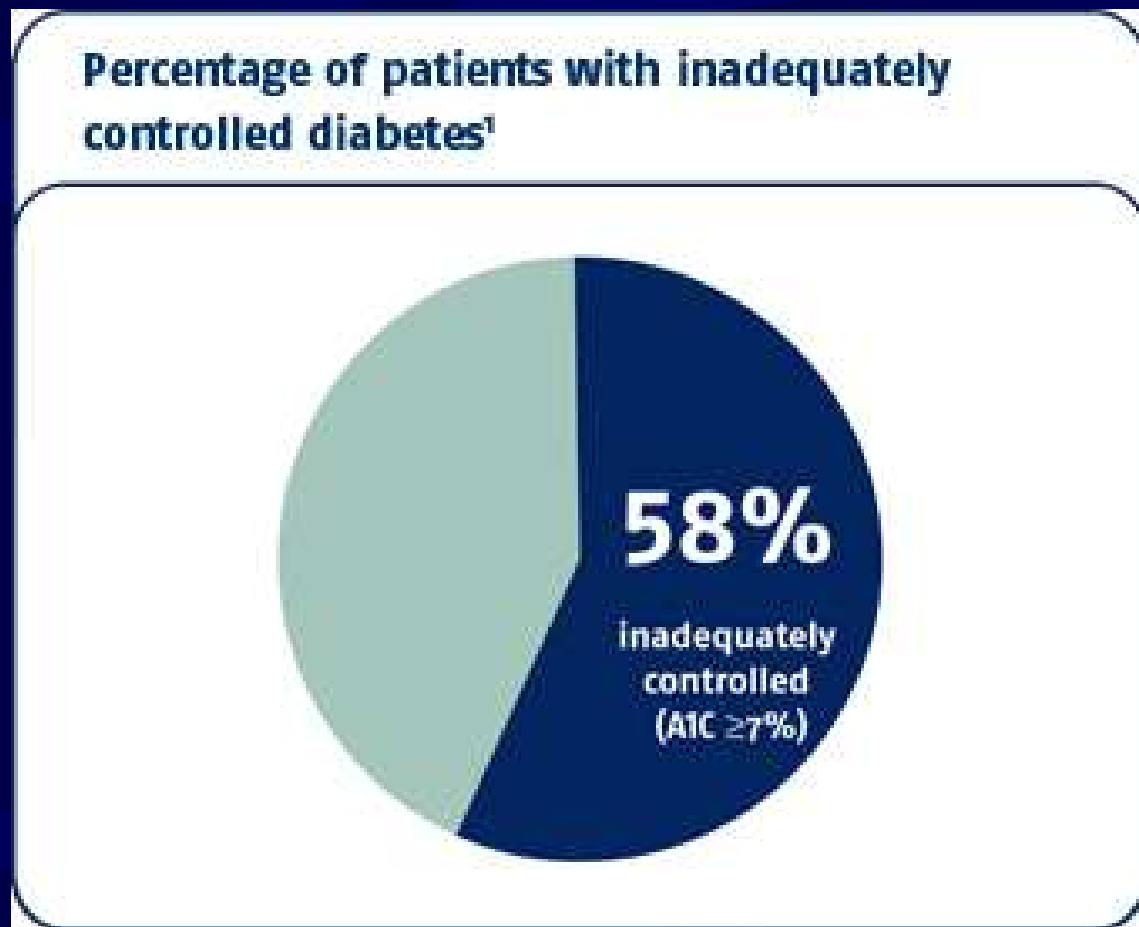


# *Why inhaled insulin ?*

- Injection phobia
- Injection site reactions
- Patient preference
  - Improved adherence ?
- Improved disease control ?

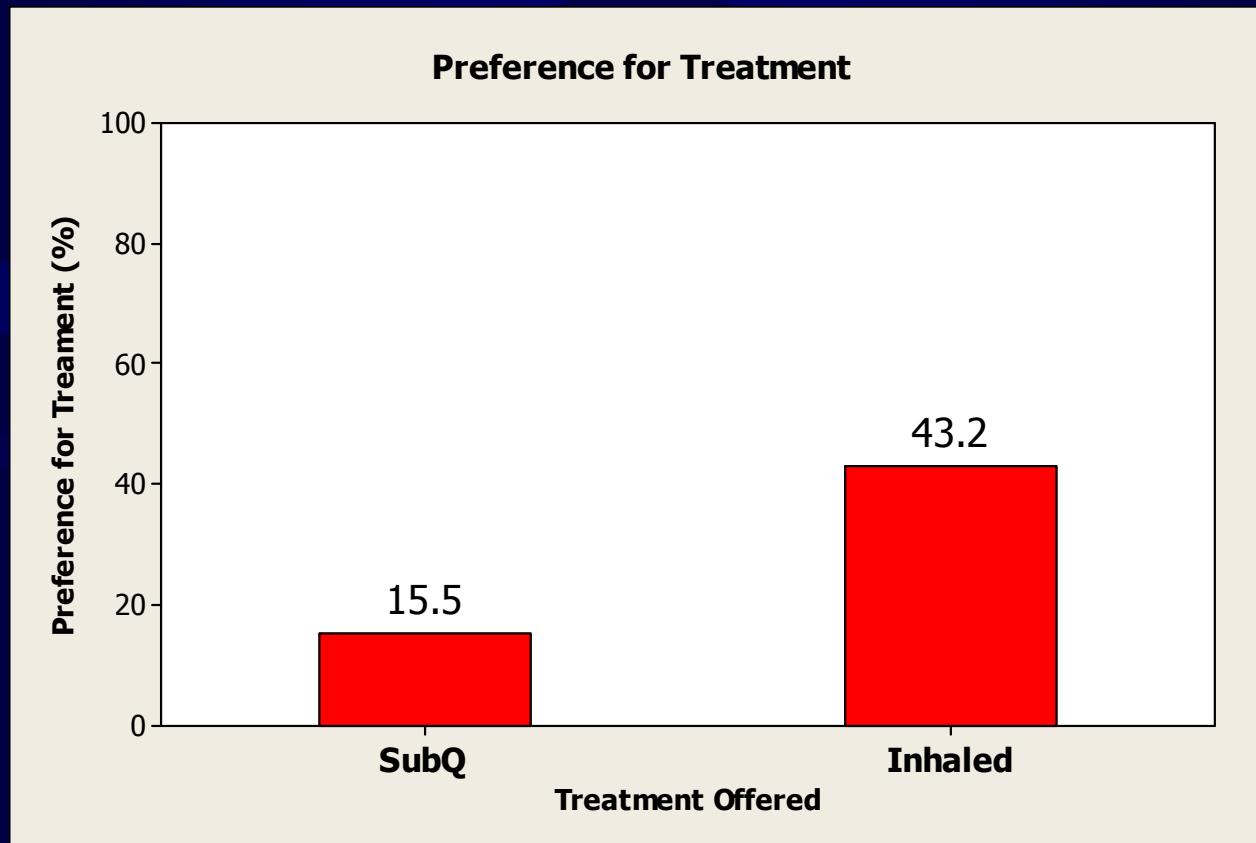
# Lack of Control

NHANES\* data show that 58% of patients had A1C levels  $\geq 7\%$



N=750 (NHANES III)

# Inhaled Insulin may Increase Acceptance of Treatment



N=779 Type 2 diabetics with poor control (A1C >8) from seven countries  
Freemantle: Diabetes Care, Volume 28(2).February 2005.427-428

# Companies developing inhaled insulin

Why: 5 billion dollar market by 2010

## Trademarks

- |                        |              |         |
|------------------------|--------------|---------|
| • Pfizer & Nektar      | Exubera*     | DPI     |
| • Eli Lilly & Alkermes | HIIP         | DPI     |
| • Novo Nordisk         | AERx         | aerosol |
| • MannKind             | Technosphere | DPI     |
| • CoreMed              | Alveair      | aerosol |

\* FDA approved

# Inhaled insulin delivery devices







**In one breath, slowly and deeply breathe the EXUBERA cloud in through your mouth.**

**Take the mouthpiece out of your mouth.**

**Close your mouth and hold your breath for 5 seconds.**

**Then breathe out normally.**

# EXUBERA Cautions

- Contra-indications
  - Current smokers
  - Poorly controlled lung disease
  - Rapid decline in lung function
- “Not recommended”
  - Asthma or COPD
  - FEV1 below 70% predicted
  - DLCO below 70% predicted

# FDA Cautions

- **The following should be considered prior to initiating EXUBERA:**
  - Patients should be informed that in clinical studies, treatment with **EXUBERA** was associated with small, nonprogressive mean declines in pulmonary function relative to comparator treatments
  - Because of the effect of **EXUBERA** on pulmonary function, all patients should have lung function assessed

# Changes in FEV1 and DLCO with Exubera in type 1 DM

Mean change	<u>SC*</u>	<u>Exubera</u>
FEV1	-2mL	-65 mL
DLCO	-0.03	-1.7 units

Cough was more frequent in the Exubera group (27% vs 5%), but was not associated with changes in lung function.

- 41 centers, international, 6 months
- 335 diabetics, mean age 34
- Normal baseline lung function
- Excluded smokers, asthma, COPD
- PFT machines not standardized

\* SC = subcutaneous insulin

Qualtrin T 2004

# Changes in FEV1 and DLCO with Exubera in *type 2 DM*

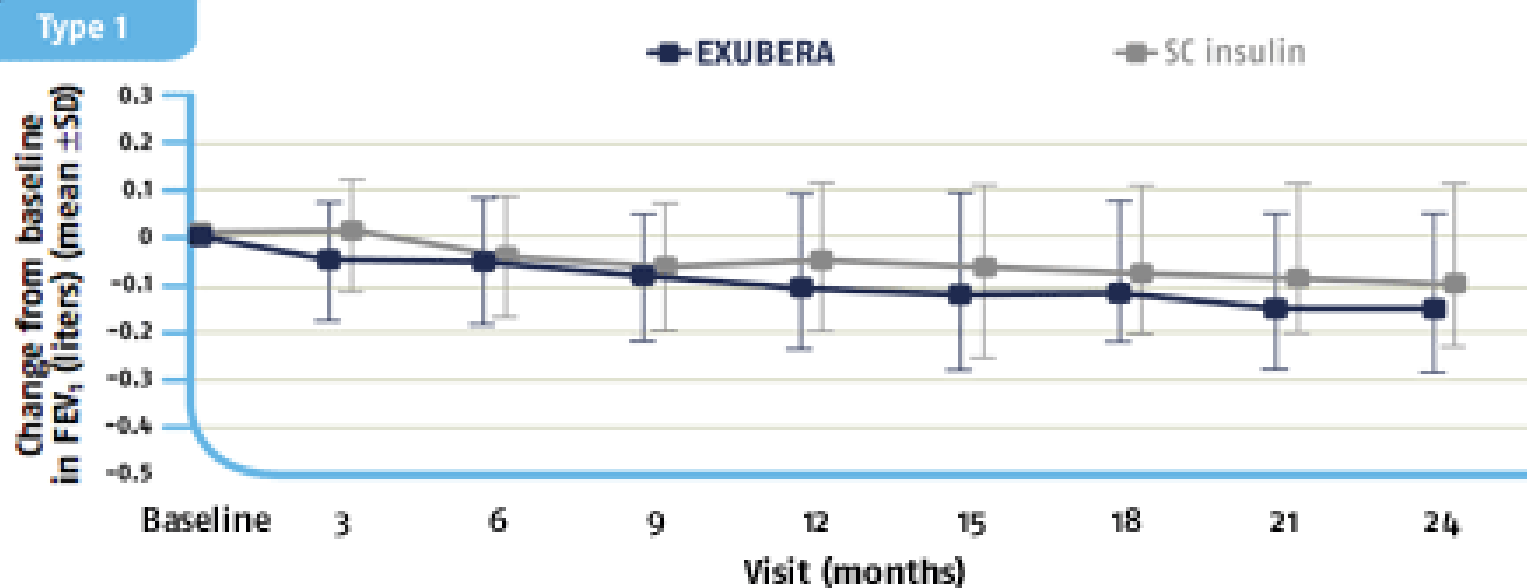
Mean change	<u>SC</u>	<u>Exubera</u>
FEV1	-1mL	-16 mL
DLCO	-0.83	-0.97 units

These differences were not statistically significant,  
nor were those from a separate 6 month study.

- 40 centers, international, *3 months*
- 143 type 2 diabetics, mean age 53
- Normal baseline lung function
- Excluded smokers, asthma, COPD
- PFT machines not standardized

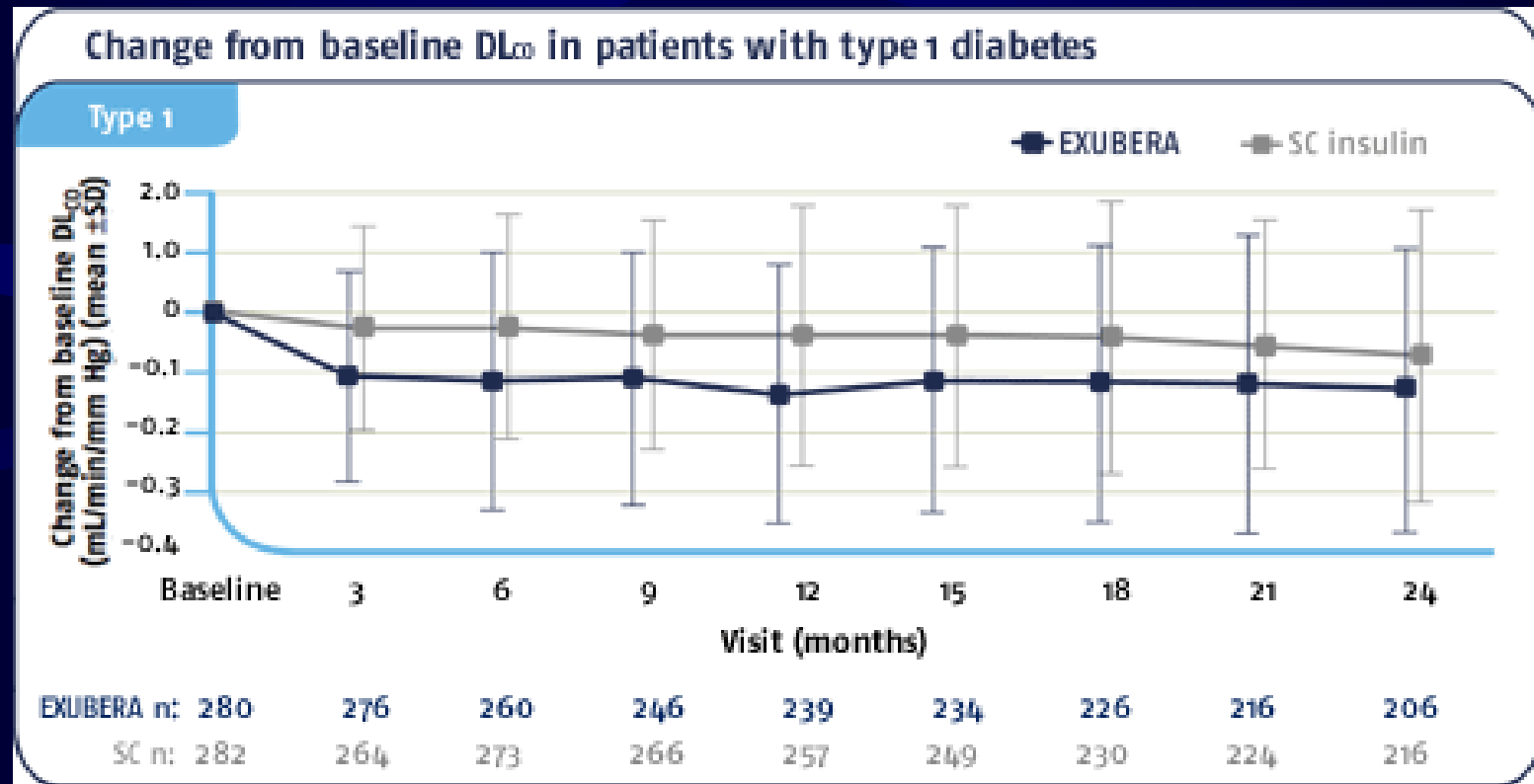
# Type 1

Change from baseline in FEV<sub>1</sub> in patients with type 1 diabetes over 24 months



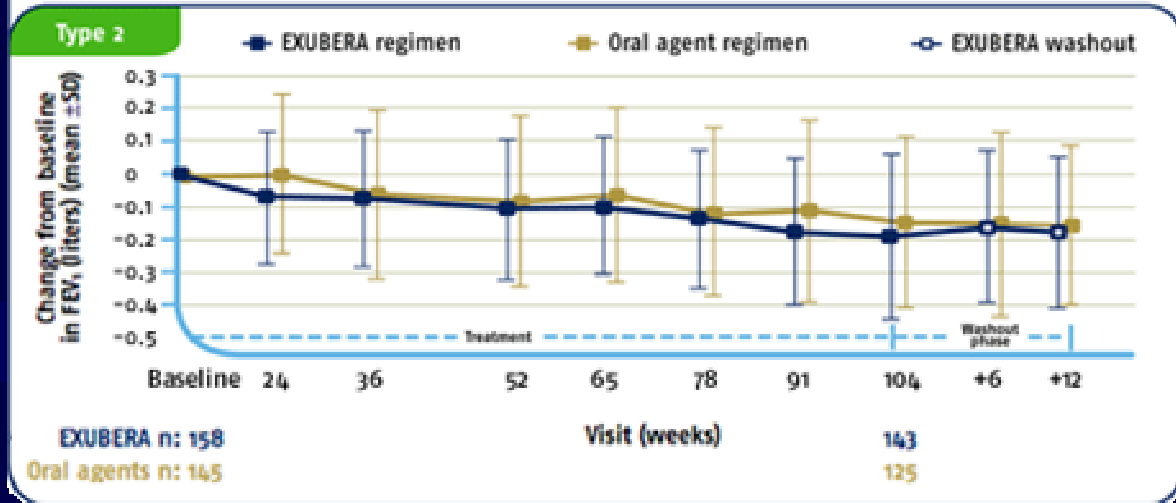
EXUBERA n:	282	277	260	247	240	235	226	217	208
SC n:	280	263	273	264	259	250	230	224	216

# Type 1

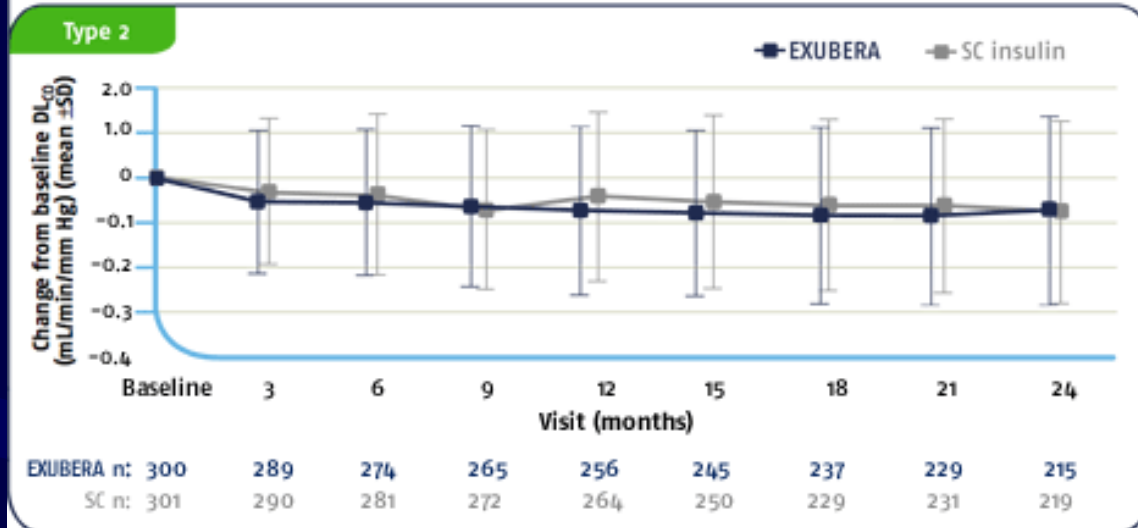


# Type 2

Spirometry results (FEV<sub>1</sub>) over 2 years



Change from baseline DL<sub>CO</sub> in patients with type 2 diabetes



# Pulmonary Function Monitoring

- Spirometry
  - Prior to initiating Exubera
  - After 6 months of therapy
  - Annually thereafter
  - Repeat if FEV1 declines by 20%
- If the >20% decline is confirmed, EXUBERA should be discontinued
- Assessment of DLCO should be considered



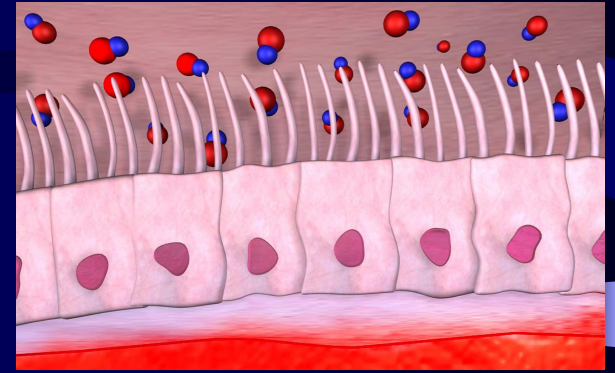
# Analysis of Exhaled Nitric Oxide for Patients with Asthma



# Background

- 1991 – eNO first measured by Gustafsson
- 1993 – eNO found elevated in asthmatics
  - Kjell Alving – Karolinska Institute
- Guidelines
  - 1997 ERS
  - 1999 ATS
  - 2005 ATS+ERS
- >1200 eNO publications
- 2006 - CPT code

# Exhaled NO

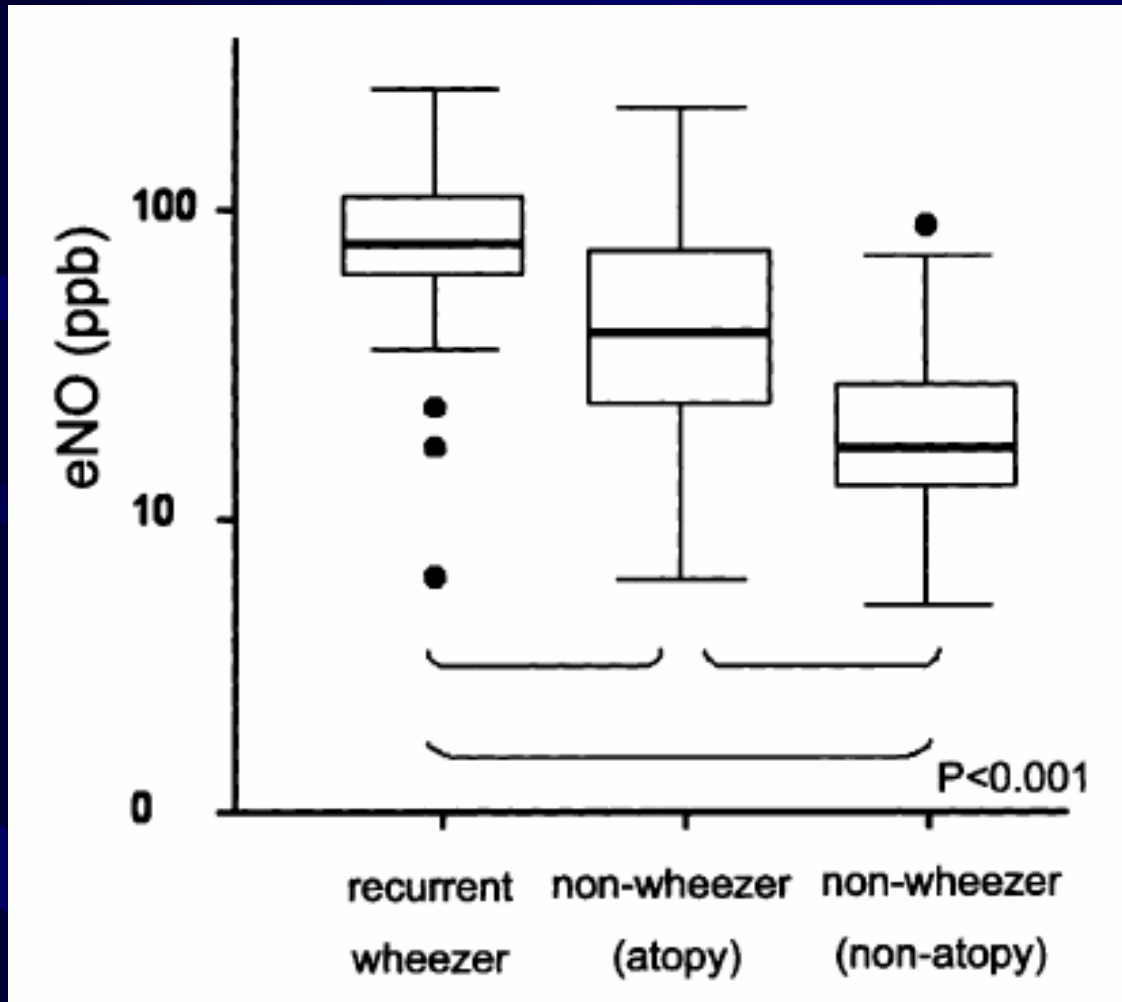


- Index of eosinophilic airway inflammation
- Not increased with bronchospasm
- $FE_{NO\ 0.05}$  Fraction of exhaled nitric oxide at a flow of 50mL/sec

# Indications

- Confirm asthma
- Differentiate asthma from COPD
- Guide inhaled corticosteroid therapy
  - Predict ICS response (& non-response)
  - Monitor ICS compliance
  - Titrate ICS daily dose (step-up, step-down)

# A high eNO confirms asthma in children with recurrent wheeze



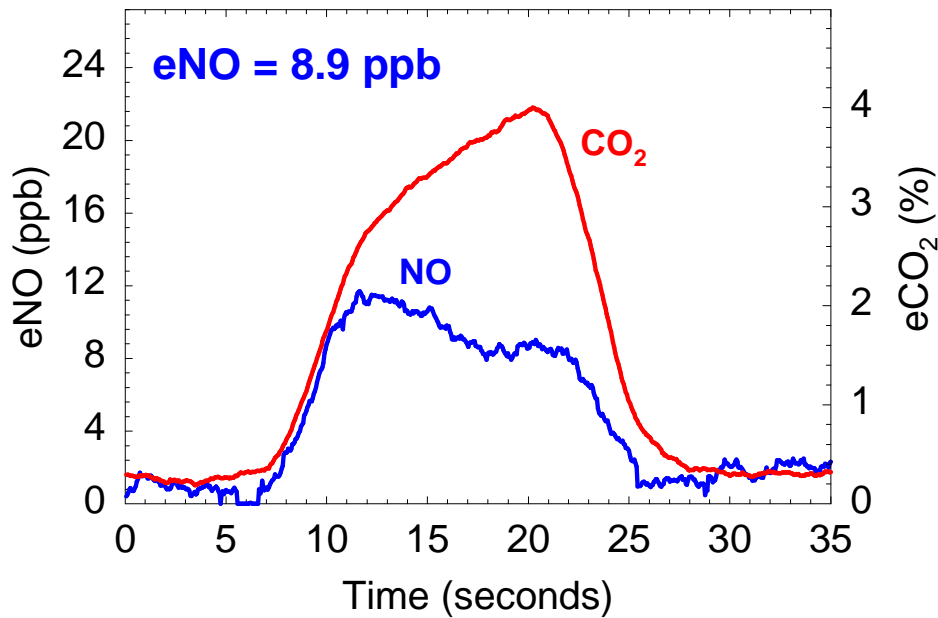
Normal range  
5-30 ppb



# Asthmatic Examples

## Age 5, Female, Mild-Persistent Corticosteriod Treated

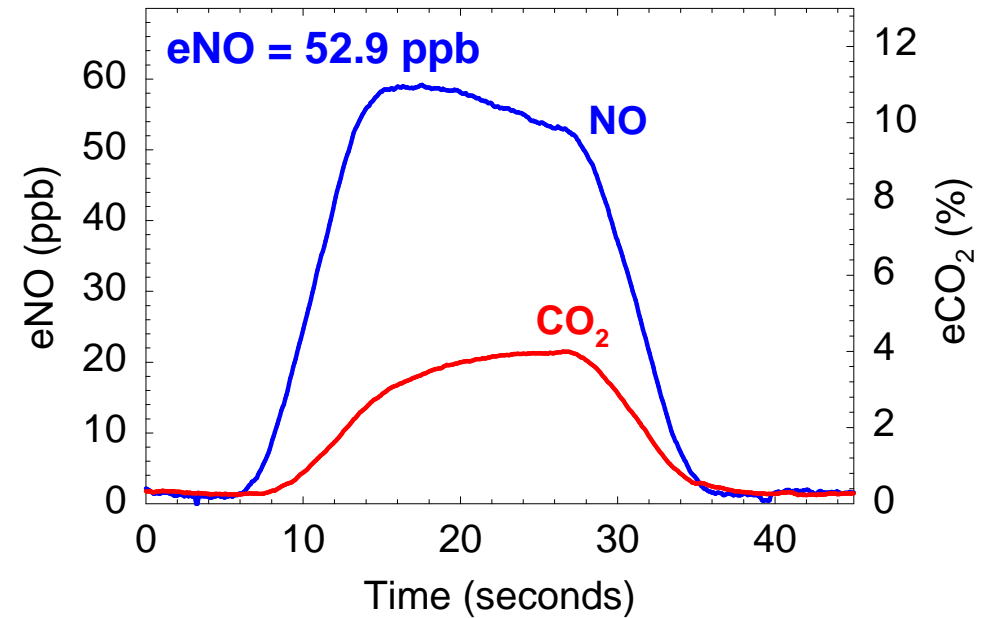
*Normal Airway*



## Age 14, Male, Mild-Persistent Non-Treated

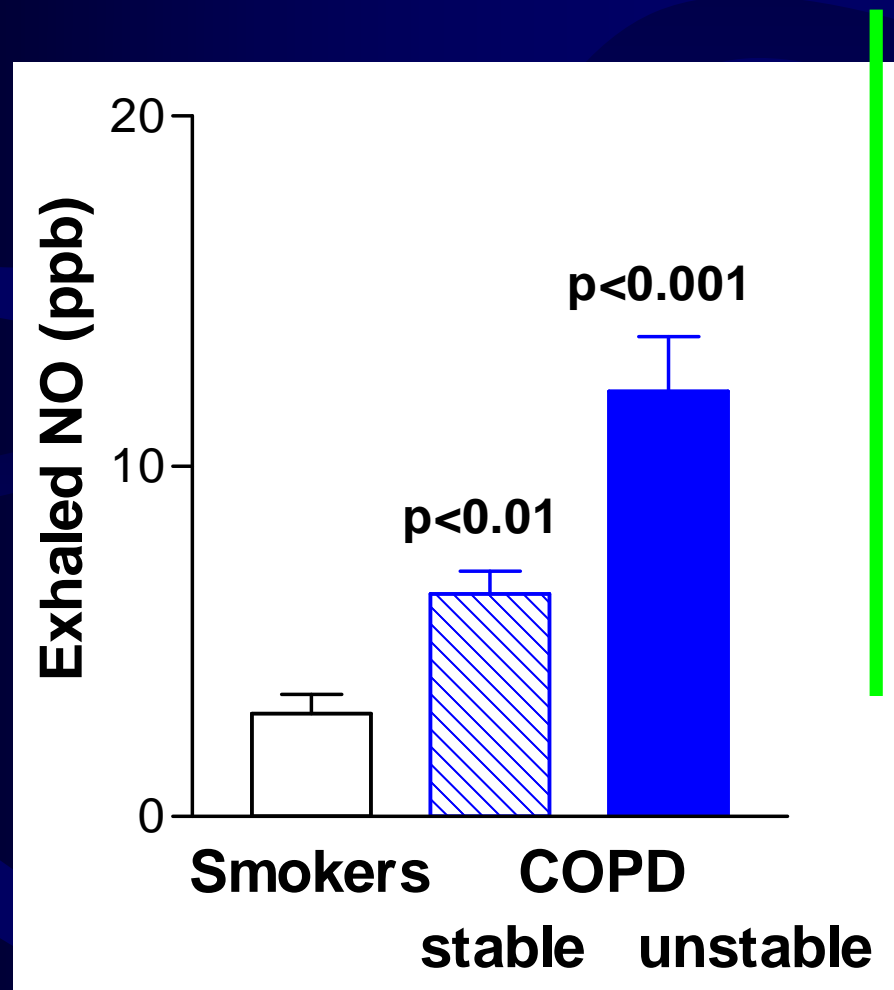


*Inflamed Airway*





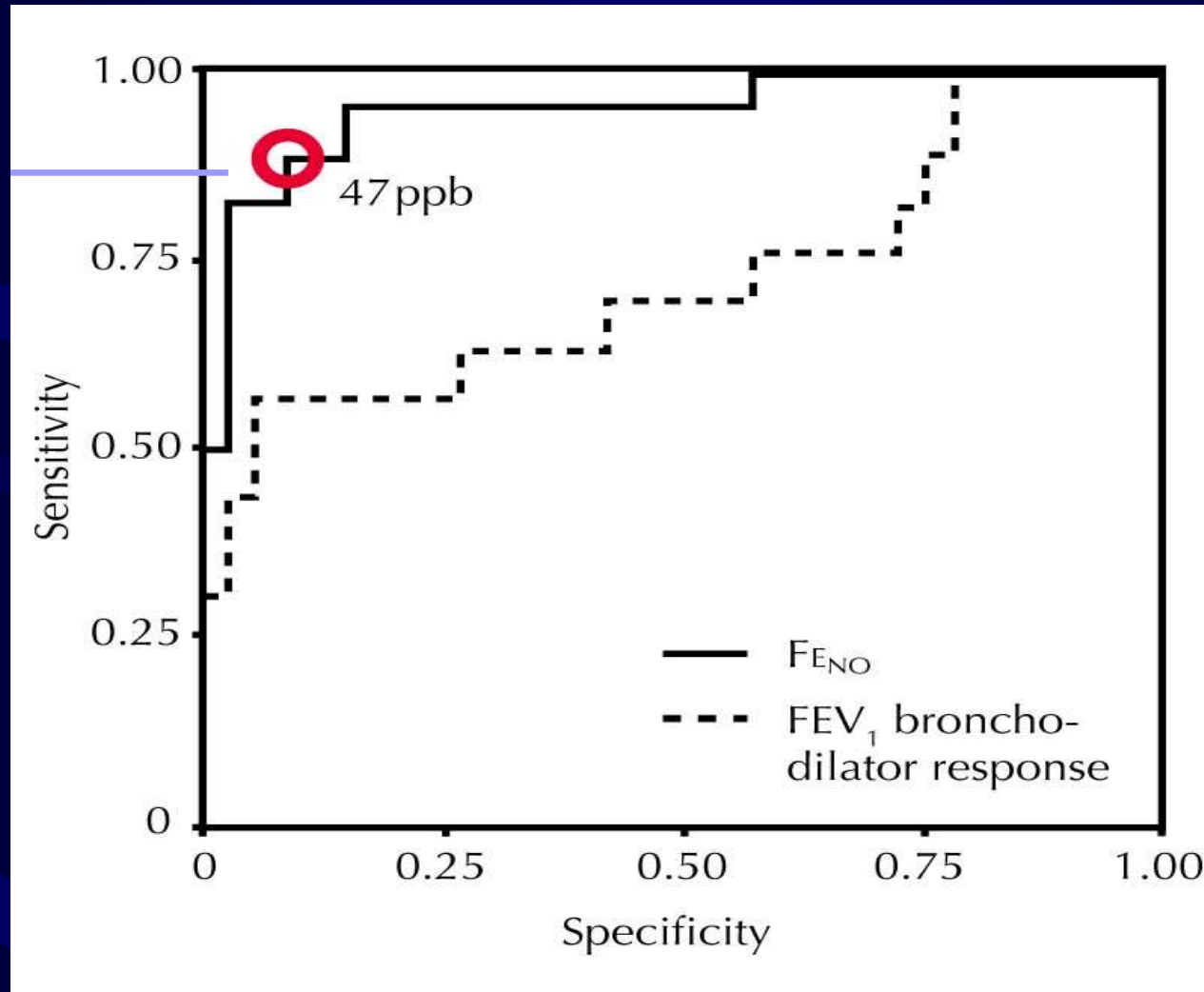
# eNO remains normal during COPD exacerbations



Normal range  
5-30 ppb

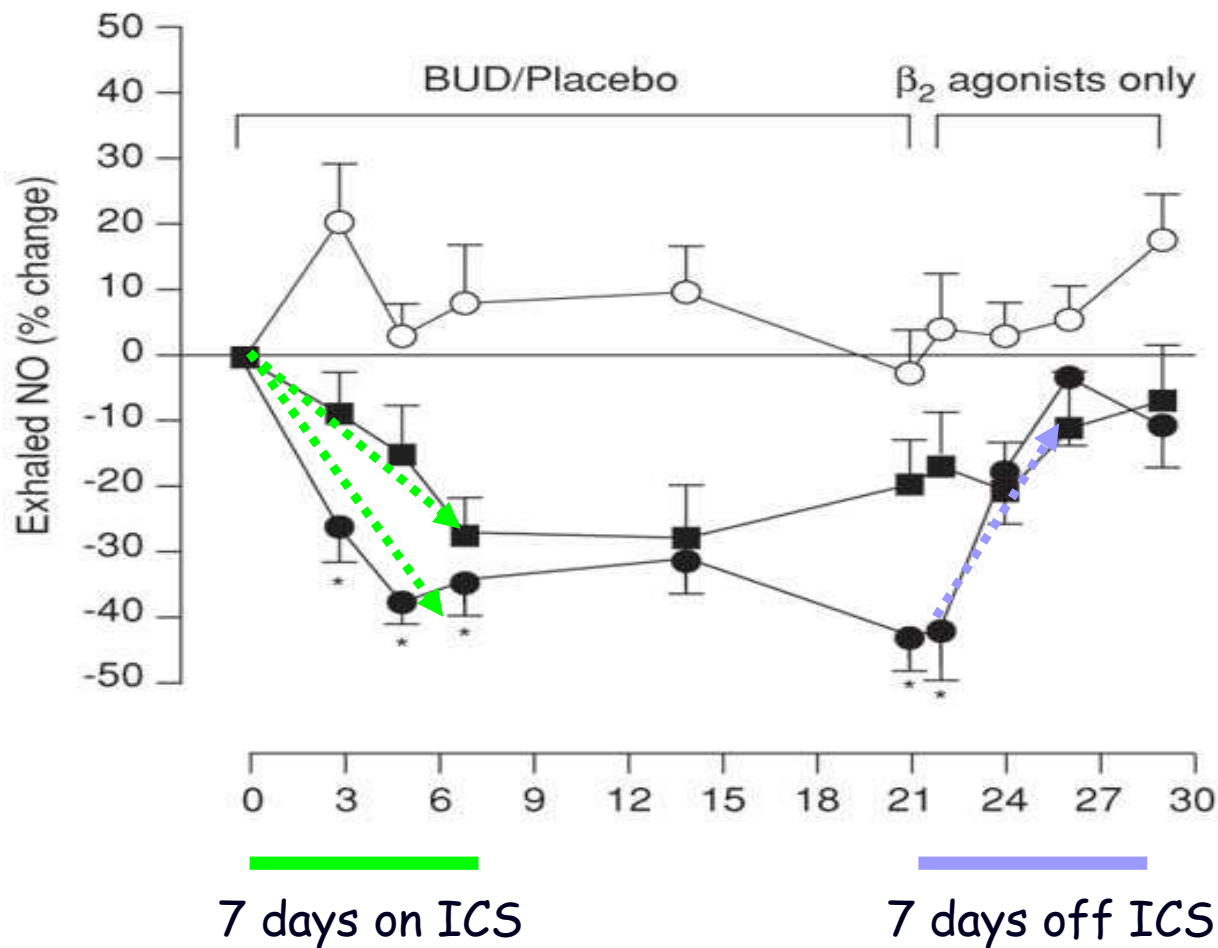
# eNO >50ppb predicts ICS response much better than does spirometry

Optimal  
eNO  
cut-point



ROC curve from Smith, AJRCCM 2005

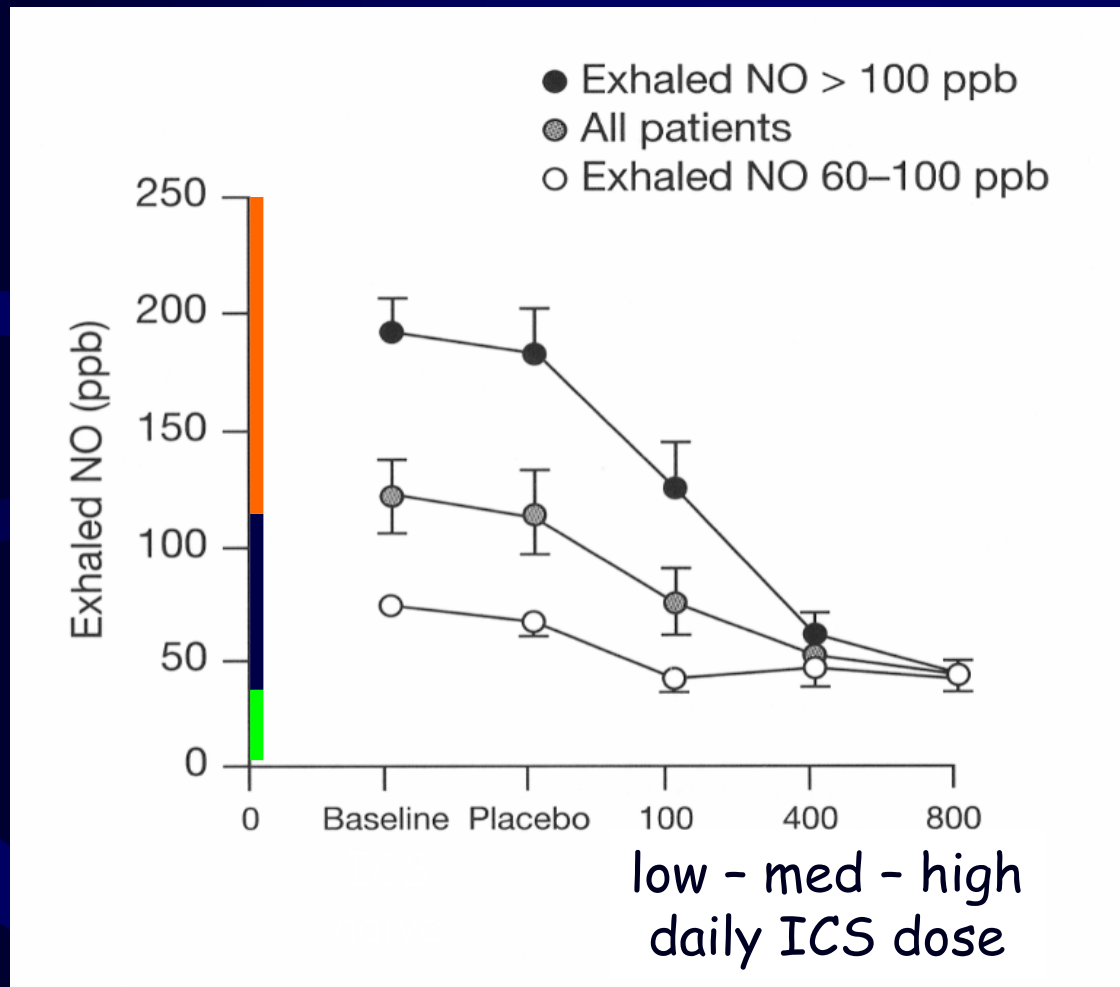
ICSs suppress airway inflammation,  
so eNO falls rapidly with ICS therapy.



Poor asthma control  
Yellow-orange zone

Good asthma control  
Green zone

# ICS dose : eNO response



# Exhaled NO

- Equipment Expensive
- Advantages over spirometry
- Reimbursable