PFTs:

Updated Recommendations for Interpretation

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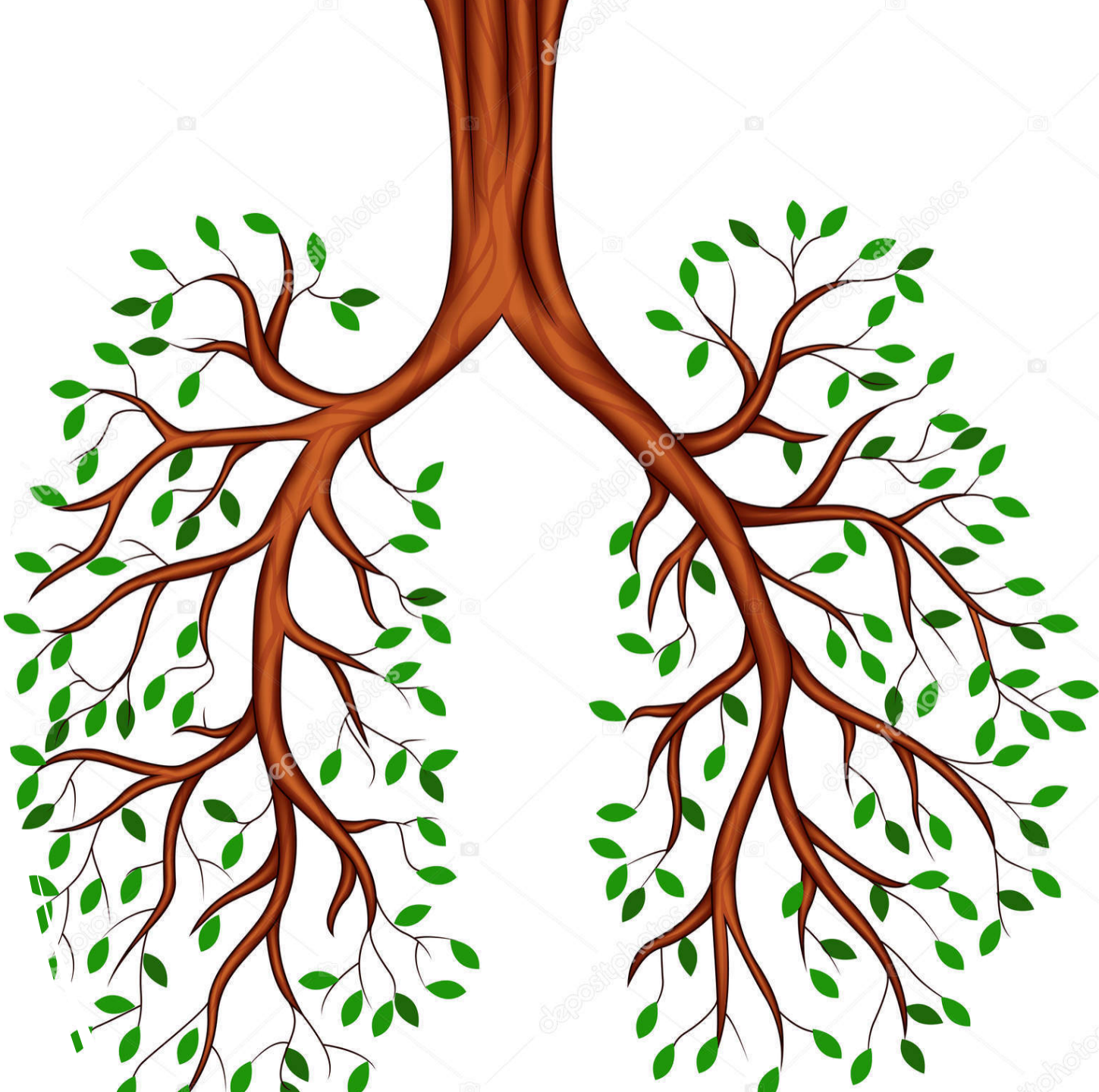
Update on Severe Asthma



Disclosures

- UpToDate author, chapters on asthma

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
S. STANOJEVIC ET AL.

ERS/ATS technical standard on interpretive strategies for routine lung function tests

Sanja Stanojevic[1], David A. Kaminsky[2], Martin R. Miller[3], Bruce Thompson[4], Andrea Aliverti[5], Igor Barjaktarevic[6], Brendan G. Cooper[7], Bruce Culver[8], Eric Derom[9], Graham L. Hall[10], Teal S. Hallstrand[8], Joerg D. Leuppi[11,12], Neil MacIntyre[13], Meredith McCormack[14], Margaret Rosenfeld[15] and Erik R. Swenson[8,16]

Stanojevic ERJ 2022

Outline

- Grading severity
- Bronchodilator response
- Interpretation algorithm
  - Defining obstruction
  - “Non-specific” pattern
- Reference population
  - Removal of race adjustment

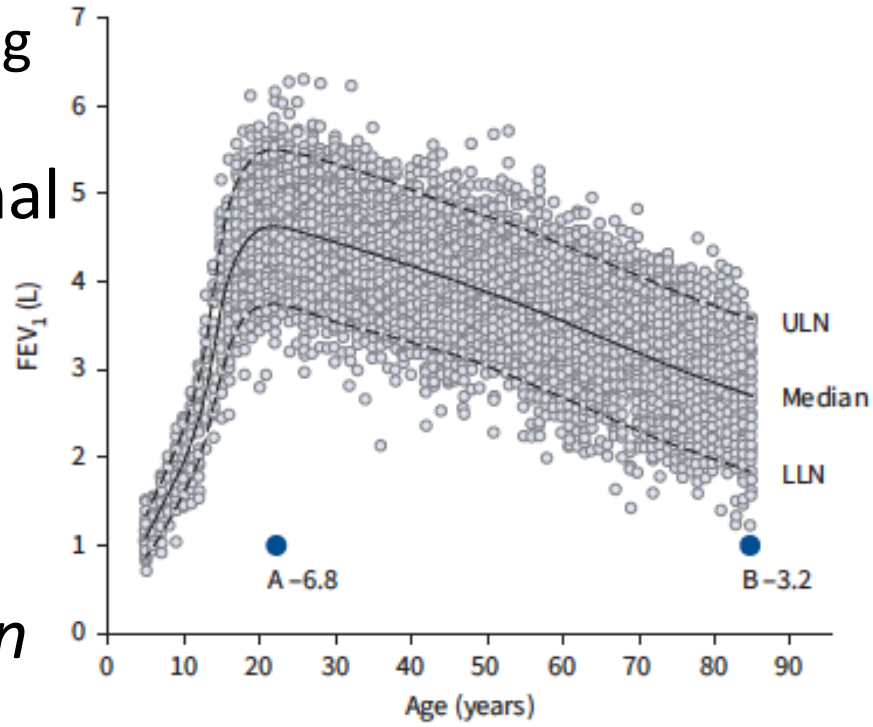
Purpose of PFTs

- Aid in diagnosis of lung disease
- Evaluation of dyspnea
- Monitor disease progression, treatment response, toxicity
- Estimation of risk

Grading Severity

Reminder: meaning of LLN

- Threshold, but not necessarily clinically meaningful
  - Does not necessarily define presence or absence of lung disease
- Low(er) chance (≦ 5%) this number is within normal range (based on the reference population)
  - Continuum



Also

- Changes in lung function *even if they remain within normal limits* can still be pathologic / clinically meaningful
  - Example: 95% predicted → 80% predicted

OLD: FEV_1 % predicted

TABLE 6 Severity of any spirometric abnormality based on the forced expiratory volume in one second (FEV_1)

Degree of severity	FEV_1 % pred
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

% pred: % predicted.

Pellegrino AJRCCM 2005

NEW: FEV_1 Z score

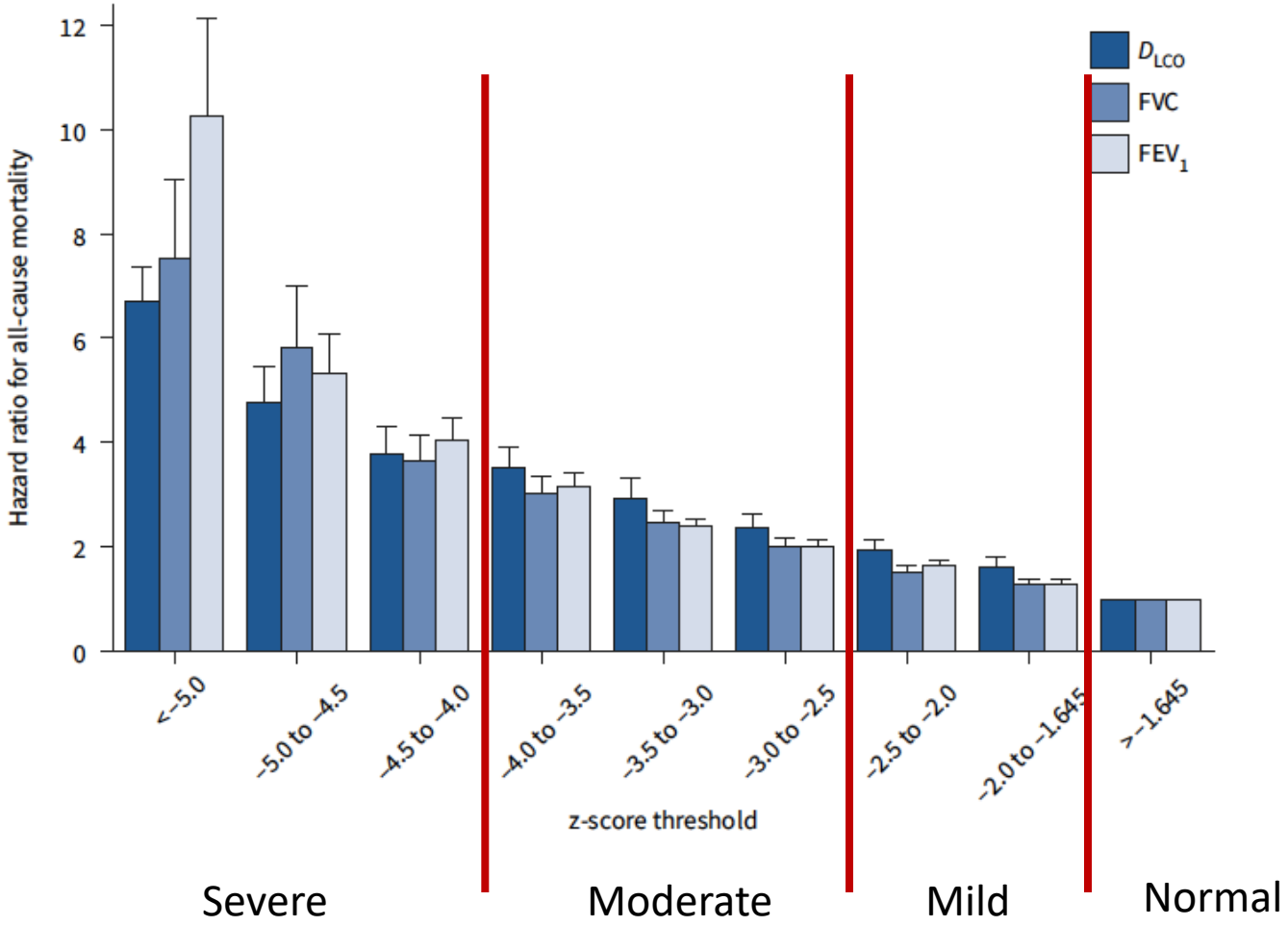
Z-score	Severity
> -1.645	Normal
-1.65 to -2.5	Mild
-2.5 to -4	Moderate
< -4	Severe

Z score vs Percent predicted

- How far from the predicted value (based on reference population) in standard deviations
- Z score more consistent across age and sex vs. % predicted
- Overall based on correlation with survival
- ***Severity of lung function impairment NOT disease severity***
  - Quality of life, functional impairment, symptoms etc.

Lung function and overall mortality

Improved fit to correlation with mortality compared to grading based on percent predicted



FEV_1 Z score

(NOT FEV_1/FVC, TLC or FVC!)

to grade severity

for any type of impairment

(obstruction, restriction, mixed, non-specific etc.)

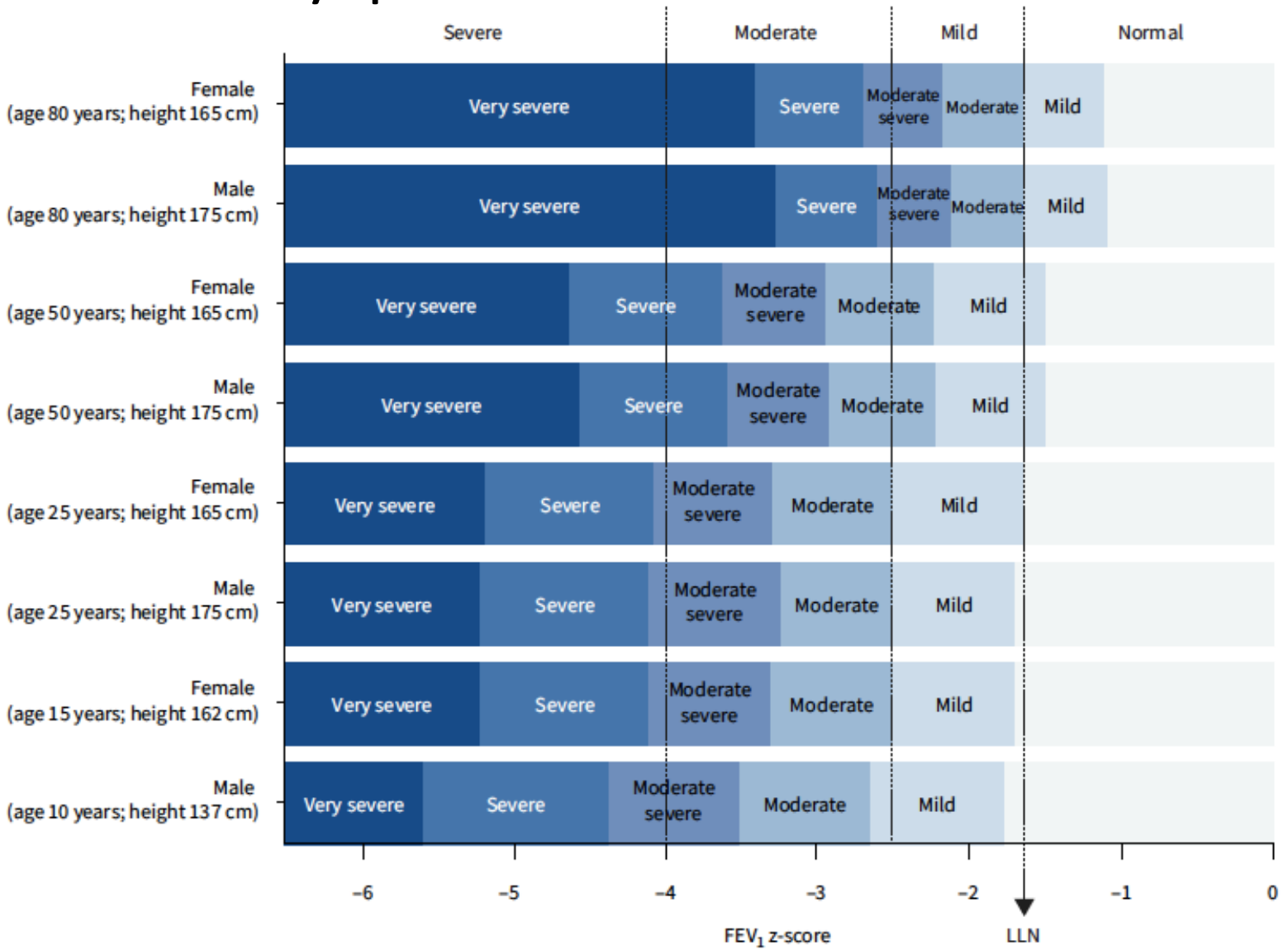
Most Important Take Home Point:

Recent updates may change the interpretation of your patients' results with ***NO ACTUAL CHANGE*** in the measurement of their lung function

When comparing to prior, always look at the absolute number (in liters)

How will this affect my patients?

- Older subjects
  - Former mod now mild
- Younger subjects
  - Grouping more stable
  - Mod and mod sev merged

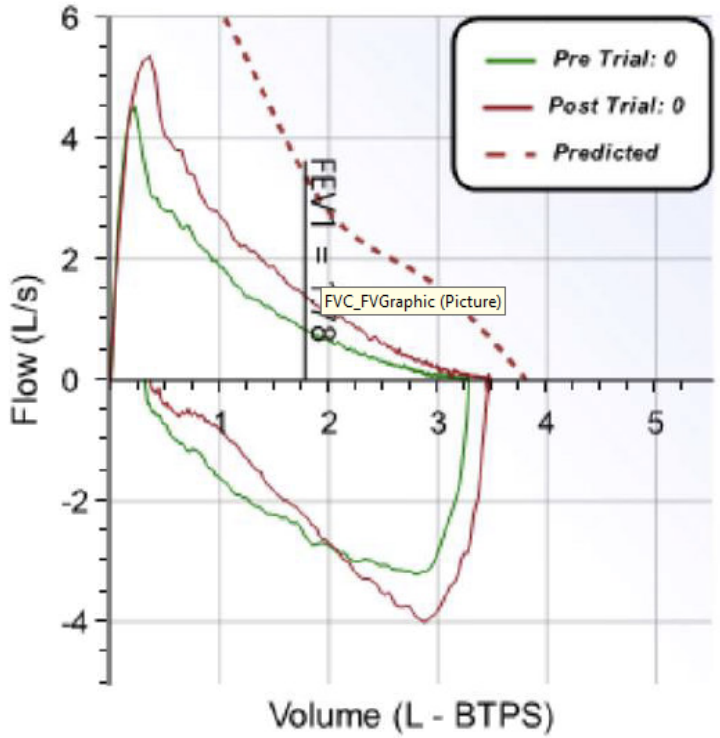


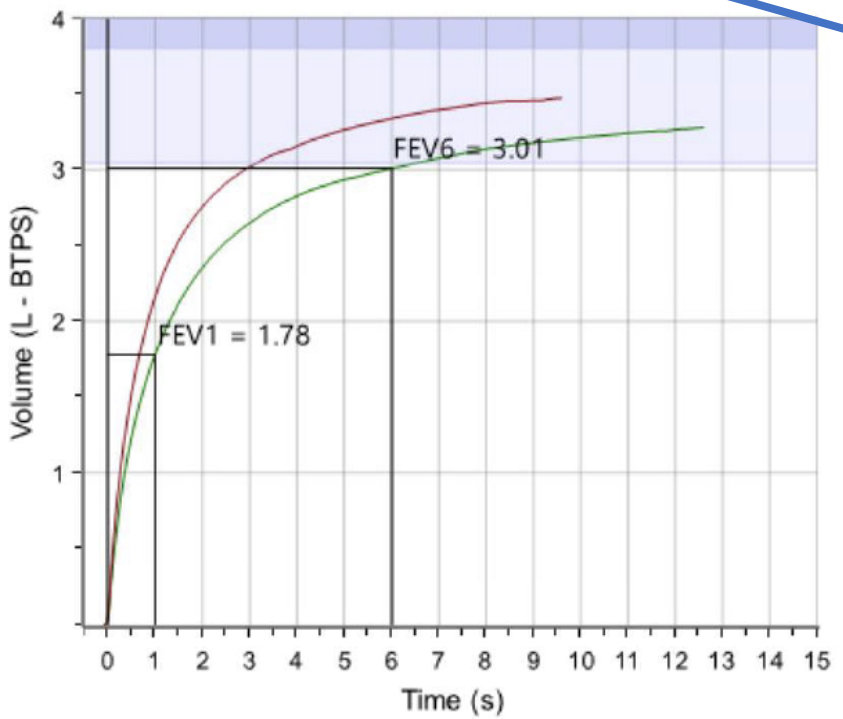
Spirometry

		Pre Bronchodilator								Post Bronchodilator				
		FVC B FEV1 A	Spirometry Grading							FVC B FEV1 B				
		Actual	Pred	% Pred	Lower	Upper	Z-Score			Actual	Z-Score	% Pred	% Chg	BDR
FEV_1	L	1.78	3.27	54	2.63	3.89	-3.72	A	M	2.16	-2.80	66	21	12
FVC	L	3.34	3.81	88	3.05	4.61	-1.00	N		3.48	-0.70	91	4	4
FEV_1 / FVC	%	53	86	62	75	95	-3.51	A	M	62	-2.80	72	17	--
FEF_{25-75} [ISO]	L/s	0.82	3.74	22	2.45	5.21	---			1.39	---	37	70	
PEFR	L/s	4.53	6.98	65	5.26	8.70	---			5.36	---	77	18	--
FET	s	13.80	0.00	----	6.00	0.00	---			9.61	---	----	-30	--

Z -2.5 to -4
Moderate

50-59%
Moderately
severe





Bronchodilator Response Definition

BDR: bronchodilator response

- Old:
  - 12% ***AND*** 200cc
    - relative to measured baseline FEV_1 or FVC
- New
  - 10% change
    - relative to ***predicted*** value of FEV_1 or FVC

- Minimizes effect of baseline value in assessing BDR
- Based on studies of healthy subjects showing 10% to be ULN
- Better prediction / separation of subjects with asthma from normal or other lung diseases
- "Over-reliance on strict cut-offs for BDR should be avoided"
  - Not dichotomous trait
- NOTE: GINA guidelines 2025 still use older definition for BDR

Brand *Thorax* 1992
Quanjer *Chest* 2017
Tan *Thorax* 2012

BDR: bronchodilator response

- Absolute change expressed as a percentage of predicted value
- >10% considered significant

BOX 1 Determination of a bronchodilator response

$$\text{Bronchodilator response} = \frac{(\text{post-bronchodilator value (L)} - \text{pre-bronchodilator value (L)}) \times 100}{\text{predicted value (L)}^{\#}}$$

A change of >10% is considered a significant bronchodilator response.
#: predicted value should be determined using the appropriate Global Lung Function Initiative (GLI) spirometry equation.

For example, a 50-year-old male, height 170 cm, has a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of 2.0 L and a post-bronchodilator FEV_1 of 2.4 L. The predicted FEV_1 is 3.32 L (GLI 2012 "other" equation).

$$\text{Bronchodilator response} = \frac{(2.4 - 2.0) \times 100}{3.32} = 12.1\%$$

Therefore, their bronchodilator response is reported as an increase of 12.1% of their predicted FEV_1 and classified as a significant response.

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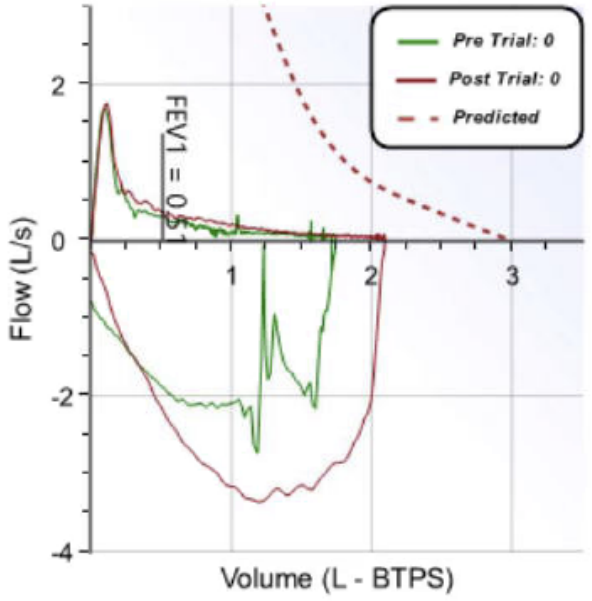
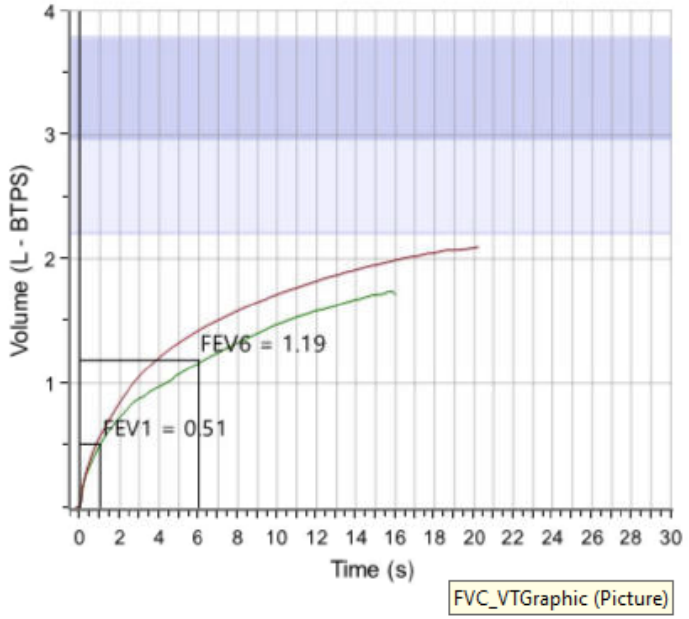
BDR: Old vs New Criteria

- OLD:
  - FEV_1 70cc and 14% ✗
  - FVC 360cc and 21% ✓
- NEW:
  - FEV_1
    - 0.7 / 2.33 *100 = 3% ✗
  - FVC
    - 0.36 / 2.98*100 = 12% ✓

Spirometry		Pre Bronchodilator								Post Bronchodilator				
		FVC A FEV1 B	Spirometry Grading							FVC C FEV1 A				
		Actual	Pred	% Pred	Lower	Upper	Z-Score			Actual	Z-Score	% Pred	% Chg	BDR
FEV₁	L	0.51	2.33	22	1.72	2.91	-4.63	A	S	0.58	-4.47	25	14	3
FVC	L	1.74	2.98	58	2.21	3.79	-2.70	A	M	2.10	-1.89	70	21	12
FEV₁ / FVC	%	29	79	37	66	90	-4.76	A	S	28	-4.81	35	-3	--
FEF_{25-75} [ISO]	L/s	0.13	2.02	6	0.98	3.48	---			0.21	---	10	62	--
PEFR	L/s	1.70	5.95	29	4.23	7.67	---			1.75	---	29	3	--
FET	s	15.98	0.00	----	6.00	0.00	---			20.20	---	----	26	--



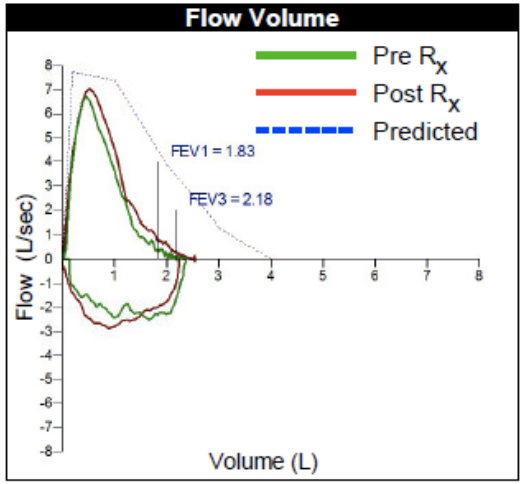


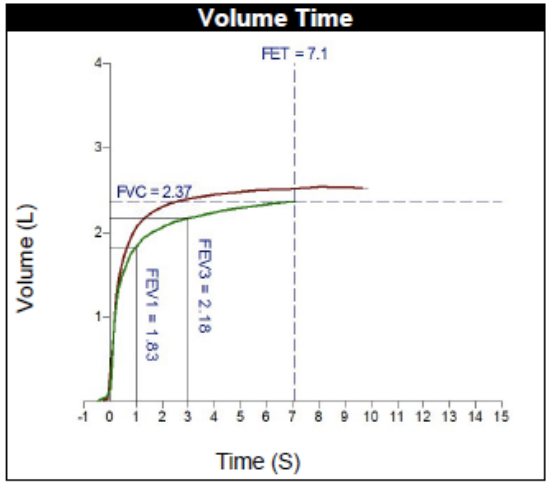
BDR: Old vs New Criteria

- OLD:
  - FEV_1 13% 230cc ✓
- NEW:
  - FEV_1 0.23 / 3.00 * 100 = 8% **X**

ATS compliant tests are indicated by a ✔ : FVC ✔ FRC DLCO VTG

Spirometry		Predicted Range Mean	Predicted Range 95%	Pre Bronchodilator Actual	Pre Bronchodilator % Pred	Post Bronchodilator Actual	Post Bronchodilator % Pred	Percent Change
FVC Effort Time		----	----	08:51		09:01		
FEV_1	L	3.00	2.11	1.83	61	2.06	69	13
FVC	L	4.02	2.93	2.37	59	2.55	63	8
FEV_1 / FVC	%	75	61	77	103	81	108	5
FEV_6	L	3.94	3.04	2.34	59	2.51	64	7
FEV_1 / FEV_6	%	77	68	78	101	82	106	5
FEF_{25-75}	L/s	2.17	0.88	1.56	72	1.97	91	26
PEFR	L/s	7.73	5.41	6.88	89	7.03	91	2
PIFR	L/s	5.16	----	3.11	60	2.85	55	-8

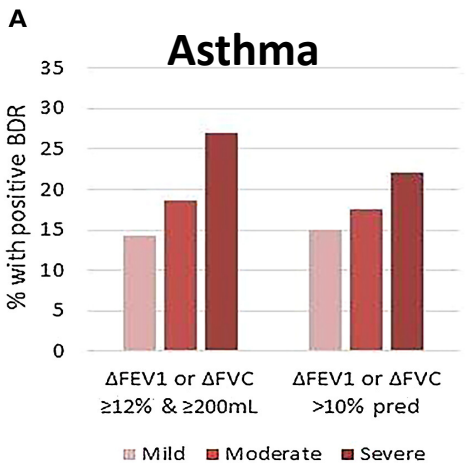


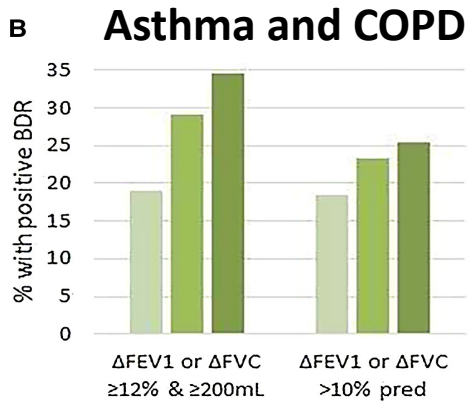


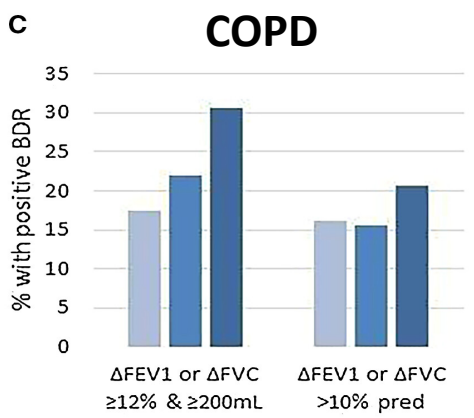
Spirometer Calibration to ATS
By: Philip Gorman
Same Day - 06:48 AM

Old vs new in obstructive lung disease

- ~7000 patients from 18 different countries
- MD diagnosed
  - Asthma 3500 individuals
  - Asthma and COPD 800 individuals
  - COPD 2500 individuals
- Overall <u>decrease</u> in prevalence using 2021 criteria





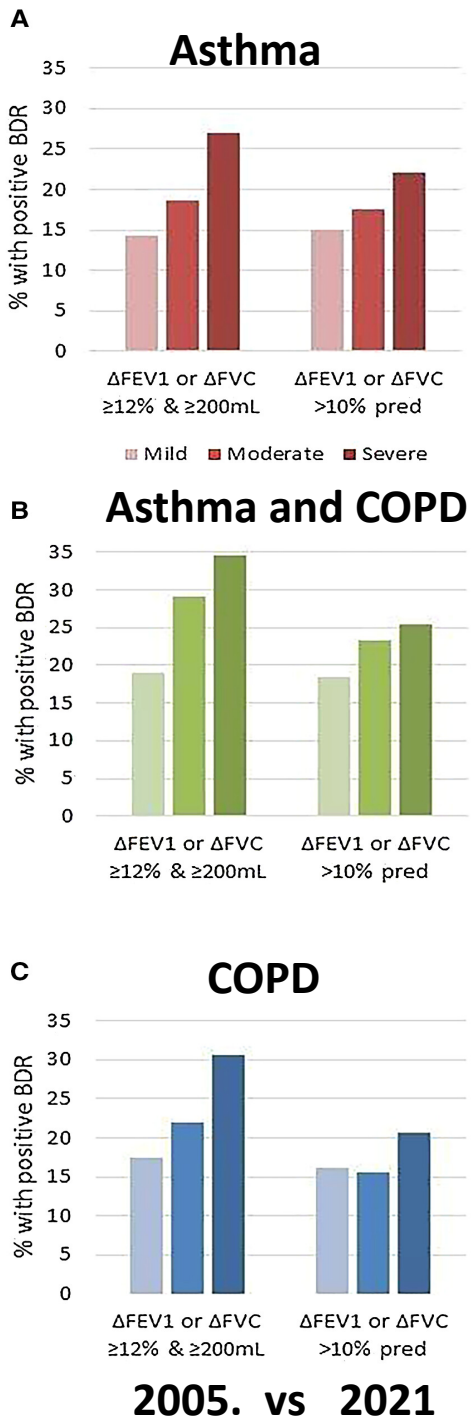


2005. vs 2021

Beasley AJRCCM 2024

Old vs new in obstructive lung disease

- Similar prevalence among these diagnoses
  - →Not very good at differentiating asthma from COPD
- Distinguishing asthma from COPD
  - 2005 definition
    - Moderate sensitivity 55%, low specificity 30%
  - 2021 definition
    - Low sensitivity 18%, high specificity 82%



Beasley AJRCCM 2024

+BDR as “treatable trait” vs diagnostic criterion

- Asthma patients +BDR 2021
  - Lower lung function
  - Higher FeNO
  - Worse respiratory symptoms
  - Higher likelihood of hospitalization for exacerbation in prior 12m
  - Higher proportion on:
    - triple therapy, maintenance oral steroids, biologics
  - +BDR 2005 definition predicted exacerbations in the following year but NOT 2021 definition
- Authors propose:
  - NOT use to diagnose or differentiate asthma vs. COPD
  - DO use this is a marker of an individual with more severe or symptomatic disease, in need of treatment / monitoring

Beasley AJRCCM 2024

Interpretation

Defining obstruction

FEV_1/FVC Ratio and Obstruction

ATS/ERS: LLN

- Depends on reference population (esp age)
- Normal ratio is LOWER as we age
- Use of fixed cutoff risk of:
  - Overdiagnosis in older
  - Underdiagnosis in younger

GOLD: 70%

- Simplicity
- Does NOT depend on reference population chosen
- Used in trials of treatment
- Correlation with clinical outcomes*

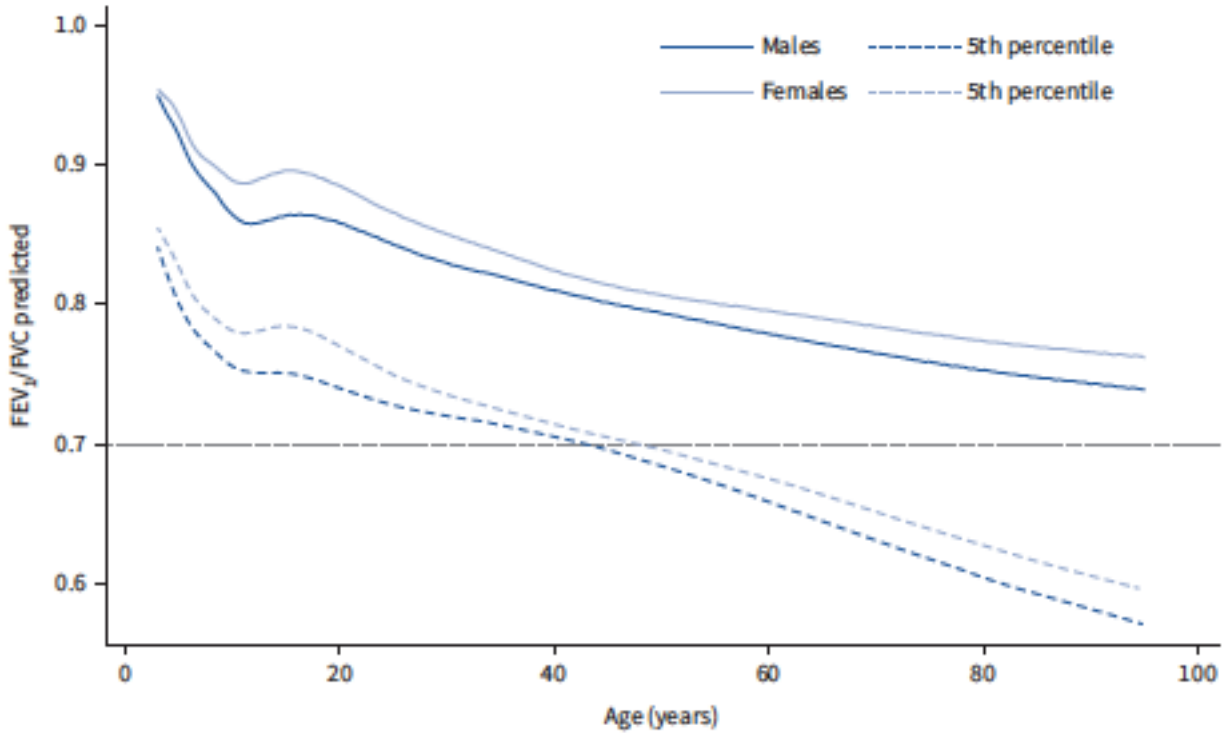


FIGURE 4 Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) predicted and lower limits of normal (5th percentile) compared with the fixed cut-off of 0.7.

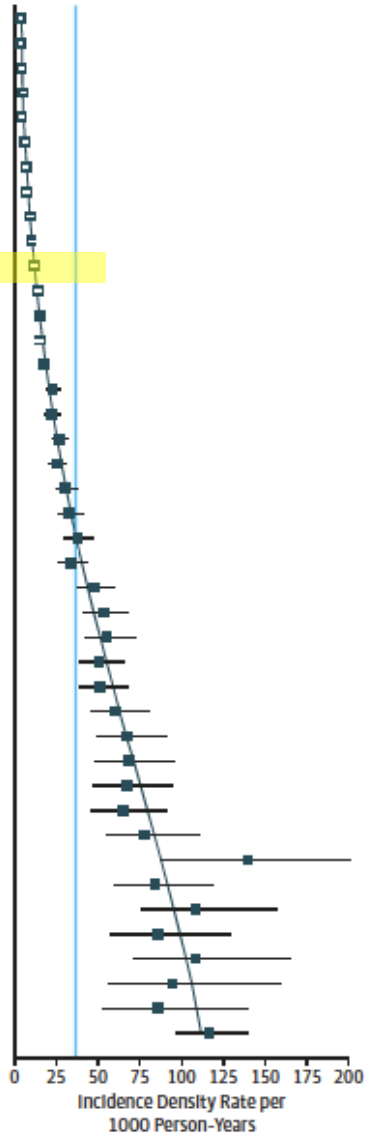
*Bhatt JAMA 2019

Obstruction: LLN vs 70%

- 4 population-based studies
  - Spirometry
  - COPD-related outcomes
- 24,000 participants
  - Mean age 63
  - 37% never smokers
- Prevalence of obstruction:
  - LLN: 15%
  - 70%: 26%

Figure 1. Incidence Density Rates for COPD-Related Hospitalization and Mortality According to Initial FEV_1:FVC

FEV_1:FVC Stratum	COPD-Related Hospitalization and Mortality	
	No. of Events	No. at Risk
>0.80	387	6079
0.79- 0.80	82	1298
0.78-0.79	93	1345
0.77-0.78	115	1438
0.76-0.77	105	1404
0.75-0.76	130	1362
0.74-0.75	146	1333
0.73-0.74	145	1297
0.72-0.73	164	1157
0.71-0.72	157	1062
0.70-0.71	165	974
0.69-0.70	167	833
0.68-0.69	153	742
0.67-0.68	143	711
0.66-0.67	130	557
0.65-0.66	143	477
0.64-0.65	124	422
0.63-0.64	126	374
0.62-0.63	98	312
0.61-0.62	87	246
0.60-0.61	79	212
0.59-0.60	75	181
0.58-0.59	67	168
0.57-0.58	72	139
0.56-0.57	65	133
0.55-0.56	54	105
0.54-0.55	54	104
0.53-0.54	49	88
0.52-0.53	49	82
0.51-0.52	43	71
0.50-0.51	34	62
0.49-0.50	32	54
0.48-0.49	34	50
0.47-0.48	31	50
0.46-0.47	29	39
0.45-0.46	33	52
0.44-0.45	29	44
0.43-0.44	23	35
0.42-0.43	22	29
0.41-0.42	14	23
0.40-0.41	16	23
<0.40	114	165



Bhatt JAMA 2019

Obstruction: LLN vs 70%

- Best C statistic: 71%
  - Better than LLN threshold
- Sensitivity vs Specificity

Figure 2. Discriminative Accuracy of Various Fixed FEV_1:FVC Thresholds for Airflow Obstruction With Respect to COPD-Related Hospitalization and Mortality

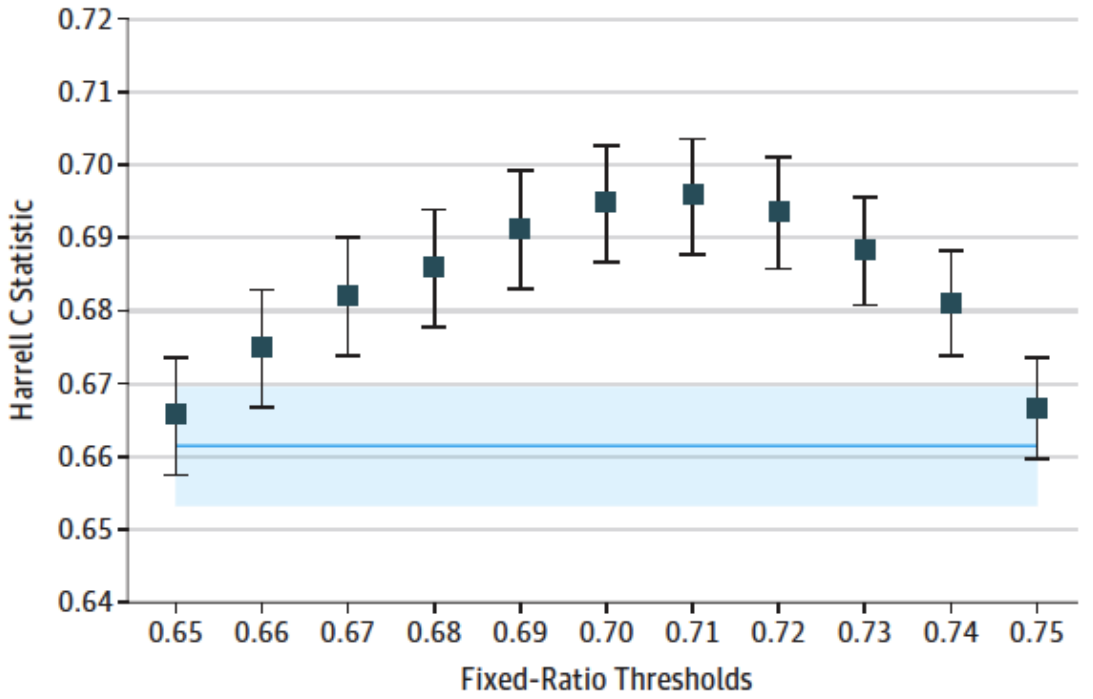
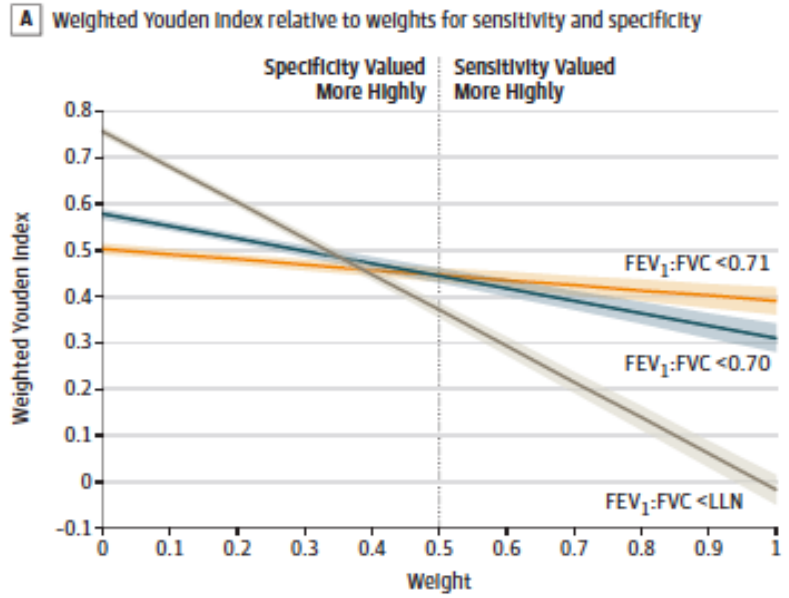


Figure 3. Weighted Youden Index for Various FEV_1:FVC Thresholds Across a Range of Relative Weights for Sensitivity and Specificity

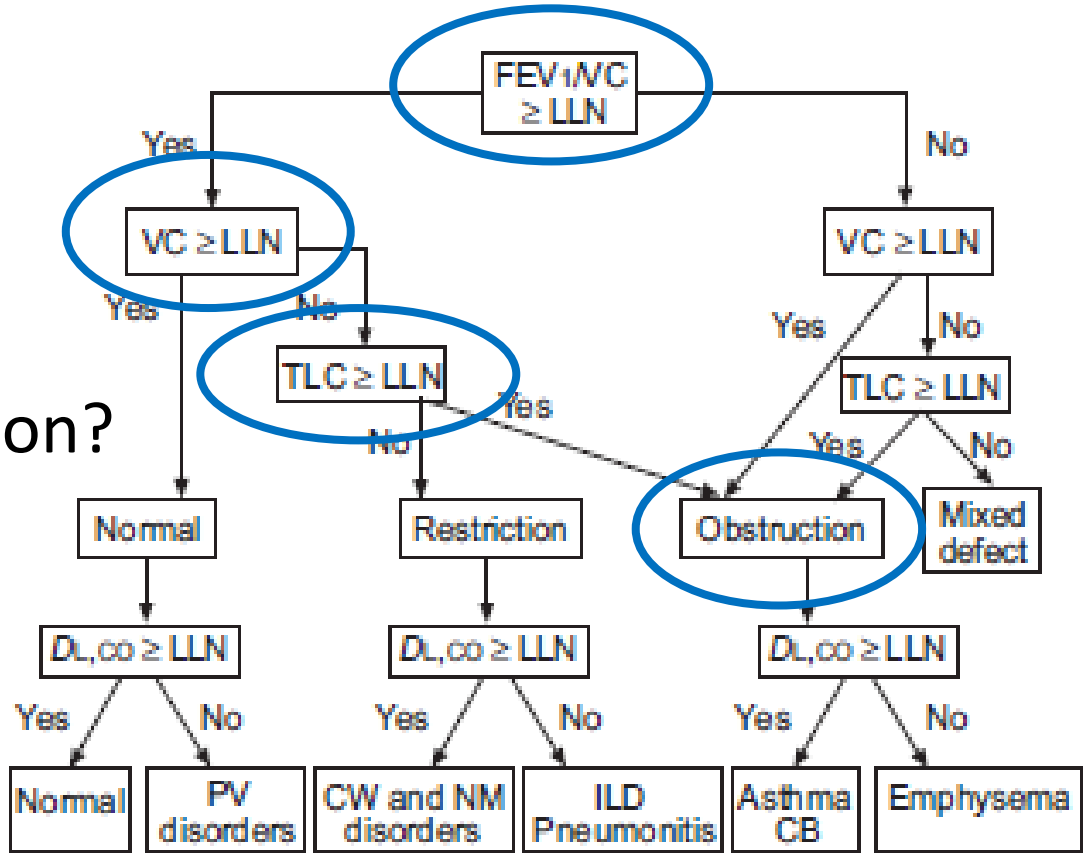


Interpretation

“Non-specific” pattern

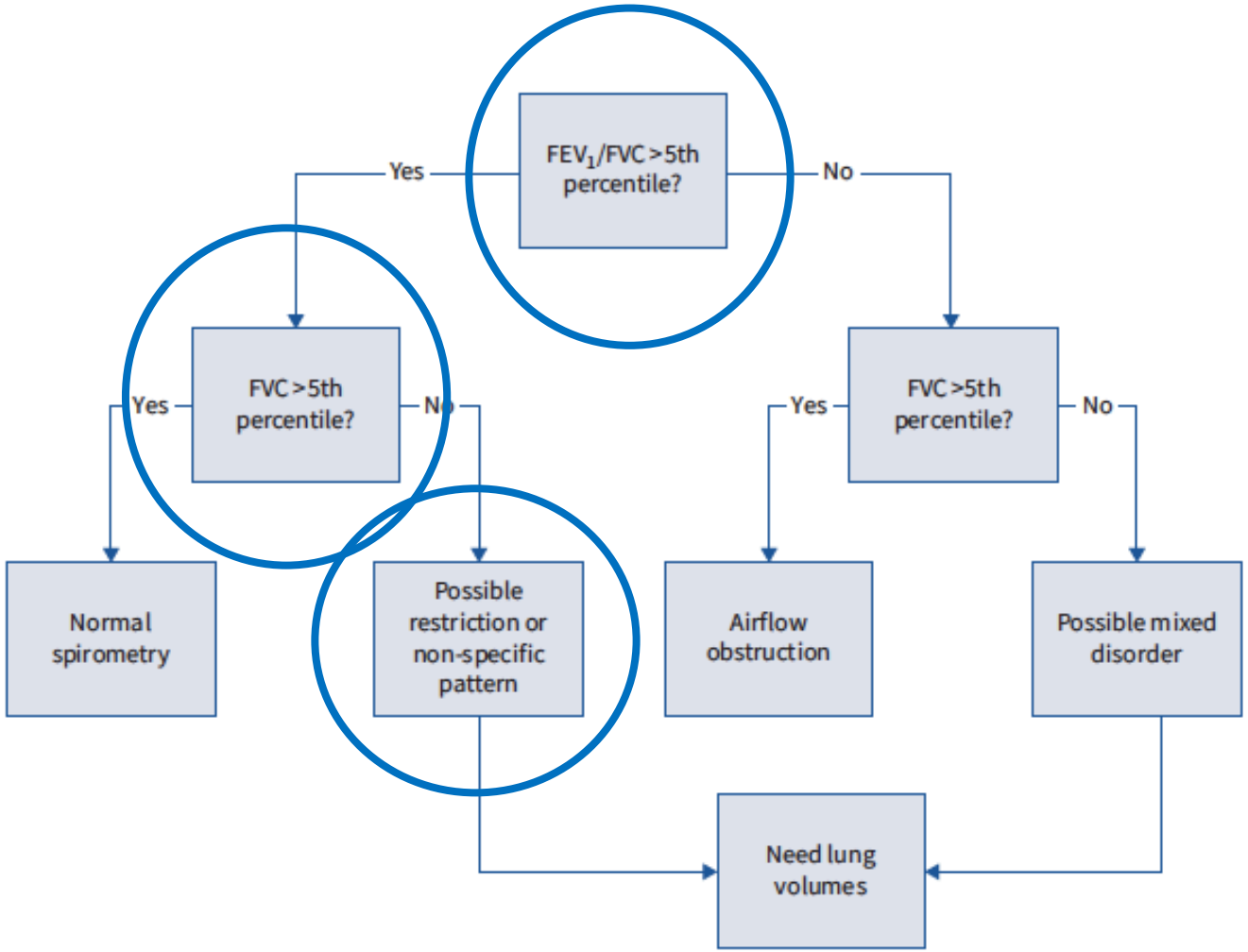
Old algorithm

- normal ratio = obstruction?



Pellegrino ERJ 2005

New algorithm : Spirometry



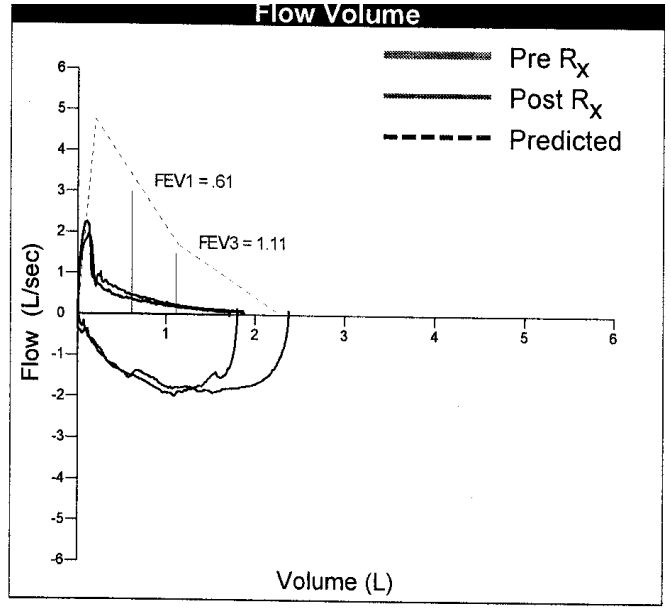
“non-specific” impairment

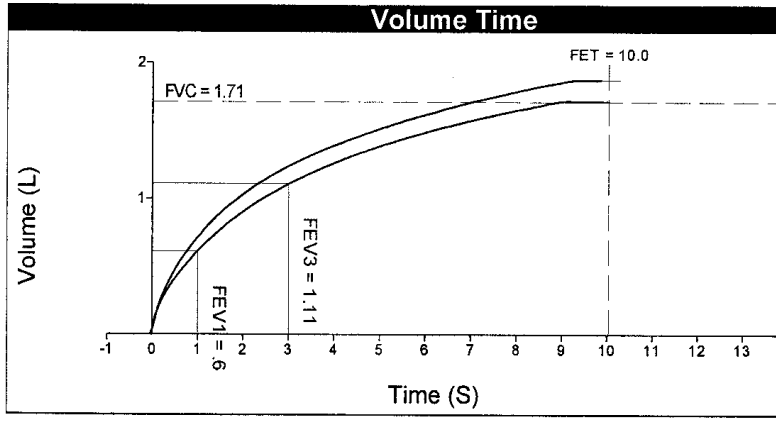
Reduced FEV_1 and FVC, normal FEV_1/FVC, <u>normal TLC</u>

- Reduced effort
  - Failure to inhale or exhale completely ”falsely low” FEV_1 and FVC
- Severe Obstruction
  - Flow reduced cannot exhale long enough to get to RV, should appear concave
- Early obstruction
  - Small airway collapse →reduced FVC, increased RV but ratio still normal
- Early restrictive pattern
  - FVC reduction not yet RV reduction
- In current or former smokers
  - Preserved Ratio Impaired Spirometry or PRISm
- 3 year follow up of non-specific pattern
  - 1/3 develop overt obstruction or restriction
  - 2/3 remain with this pattern

Non-specific pattern

- Obtain lung volumes→ if reduced then restriction
- Look at FV loop, VT curve, FEF_{25-75}
  - Concave, failure to reach plateau suggestive of obstruction
  - Air trapping or hyperinflation?
    - RV, RV/TLC, or TLC > ULN
- Compare FVC to SVC
  - △ >100cc : airway collapse during forced exhalation
- Assess BD response
  - If + suggestive of airways disease





Reference Equations

Reference equations

- Age
  - Growth during childhood, decline during adulthood
- Height
  - Proxy for chest size / torso length
- Sex
  - Recommended to use biological sex not gender identity, though to be determined on case-by-case basis
    - Timing of hormonal therapy, if given, may affect lung growth (if during adolescence)
- Race…

The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms

Darshali A. Vyas, M.D., Leo G. Eisenstein, M.D., and David S. Jones, M.D., Ph.D.

Vyas NEJM 2020

Problems with race-based adjustment

- Historically based on racist concepts, including justification of slavery
- Supports false idea of biological differences
  - Race is a social construct
- Adjusting for differences contributes to harm
  - Delay/missing disease diagnoses
  - Mask differential exposures → reinforce health disparities
- Race-neutral equations
  - Correlate better with clinical outcomes including
    - Disease-specific hospitalization
    - Mortality

Bhakta AJRCCM 2023

AMERICAN THORACIC SOCIETY DOCUMENTS

Race and Ethnicity in Pulmonary Function Test Interpretation

An Official American Thoracic Society Statement

Nirav R. Bhakta, Christian Bime, David A. Kaminsky, Meredith C. McCormack, Neeta Thakur, Sanja Stanojevic, Aaron D. Baugh, Lundy Braun, Stephanie Lovinsky-Desir, Rosemary Adamson, Jonathan Witonsky, Robert A. Wise, Sean D. Levy, Robert Brown, Erick Forno, Robyn T. Cohen, Meshell Johnson, John Balmes, Yolanda Mageto, Cathryn T. Lee, Refiloe Masekela, Daniel J. Weiner, Charlie G. Irvin, Erik R. Swenson, Margaret Rosenfeld, Richard M. Schwartzstein, Anurag Agrawal, Enid Neptune, Juan P. Wisnivesky, Victor E. Ortega, and Peter Burney; on behalf of the American Thoracic Society Committees on Pulmonary Function Testing and on Health Equity and Diversity

This Official Statement of the American Thoracic Society was Approved February 2023

The ATS Statement was endorsed by the European Respiratory Society on March 1, 2023

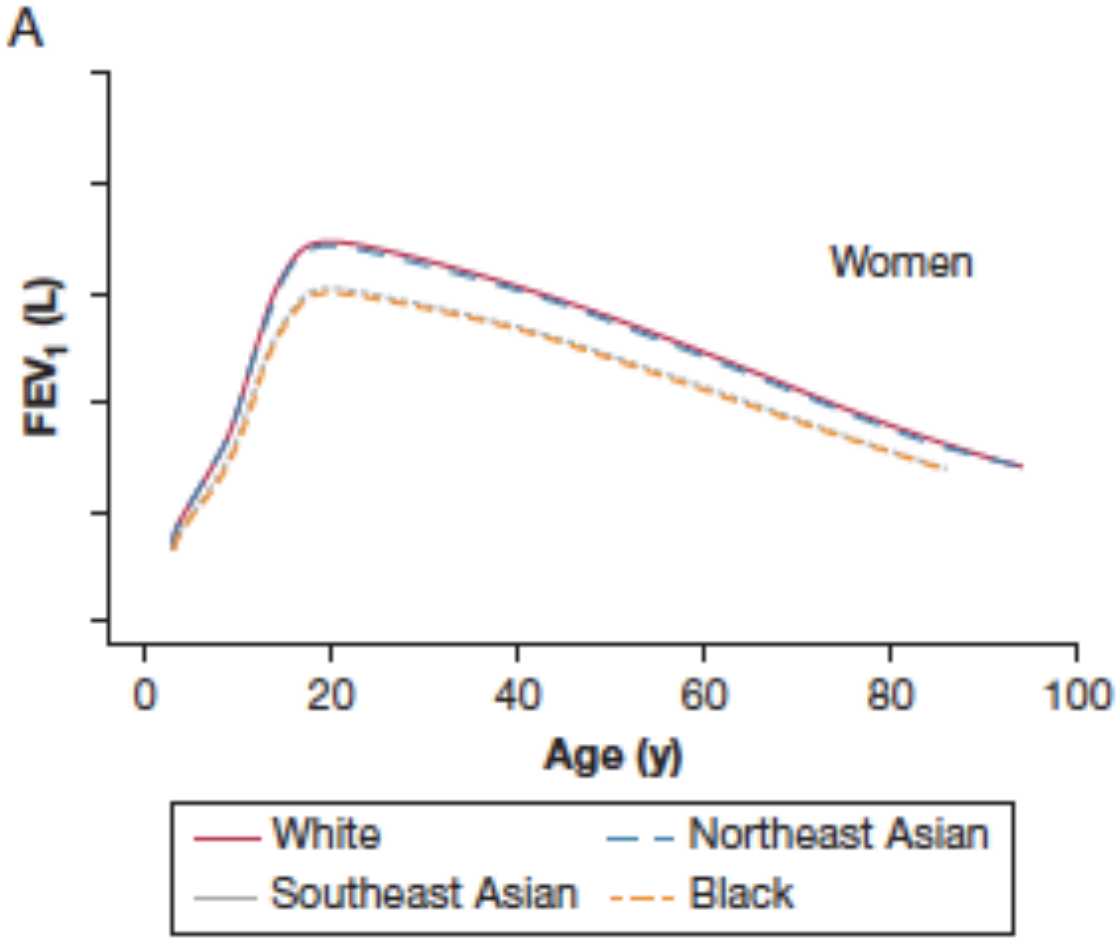
Bhakta AJRCCM 2023

Observed differences

- Falsely attributed to biological differences between races

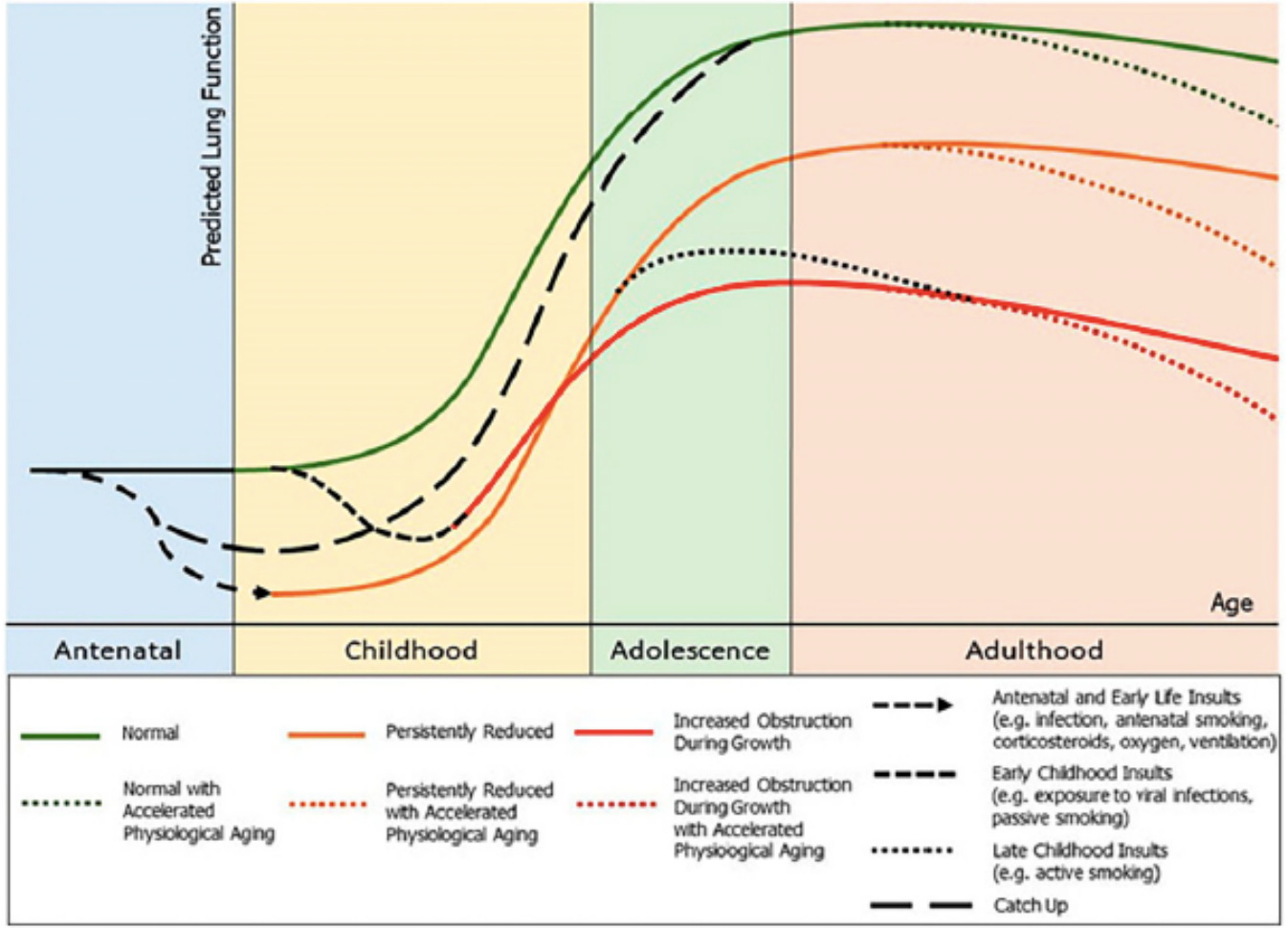
vs.

- Disproportionately experienced exposures



Factors affecting lung growth

- Maternal smoking
- Prematurity
- Early life infections
- Poor nutrition
- Second-hand smoke
- Exposure to pollutants
- Indoor air exposures
- Allergens
- Systemic Racism



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How will use of race-neutral equations affect interpretation for my patients?:

Whites:

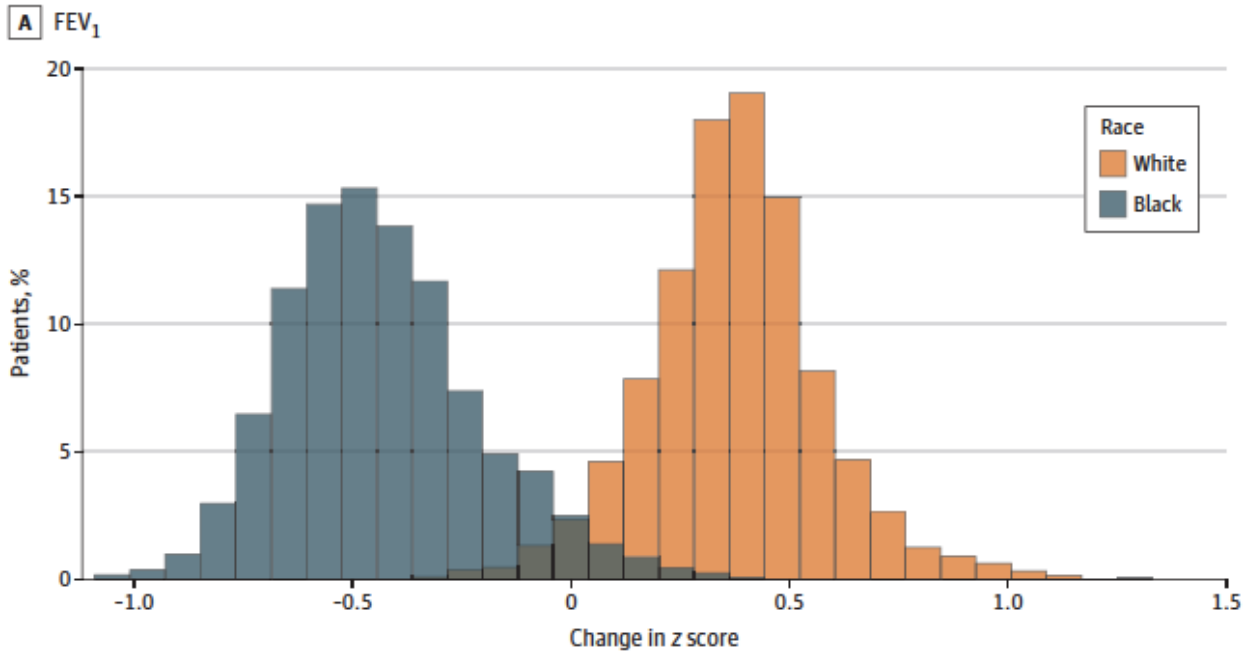
- Predicted numbers will be LOWER than using race-specific equations
  - MORE results will be found to be NORMAL / above LLN than with race-specific equations

AA, Asian, other racial and ethnic groups :

- Predicted numbers will be HIGHER than using race-specific equations
  - MORE results will be found to be ABNORMAL / below LLN than with race- specific equations

Change in Z score with race-neutral equations

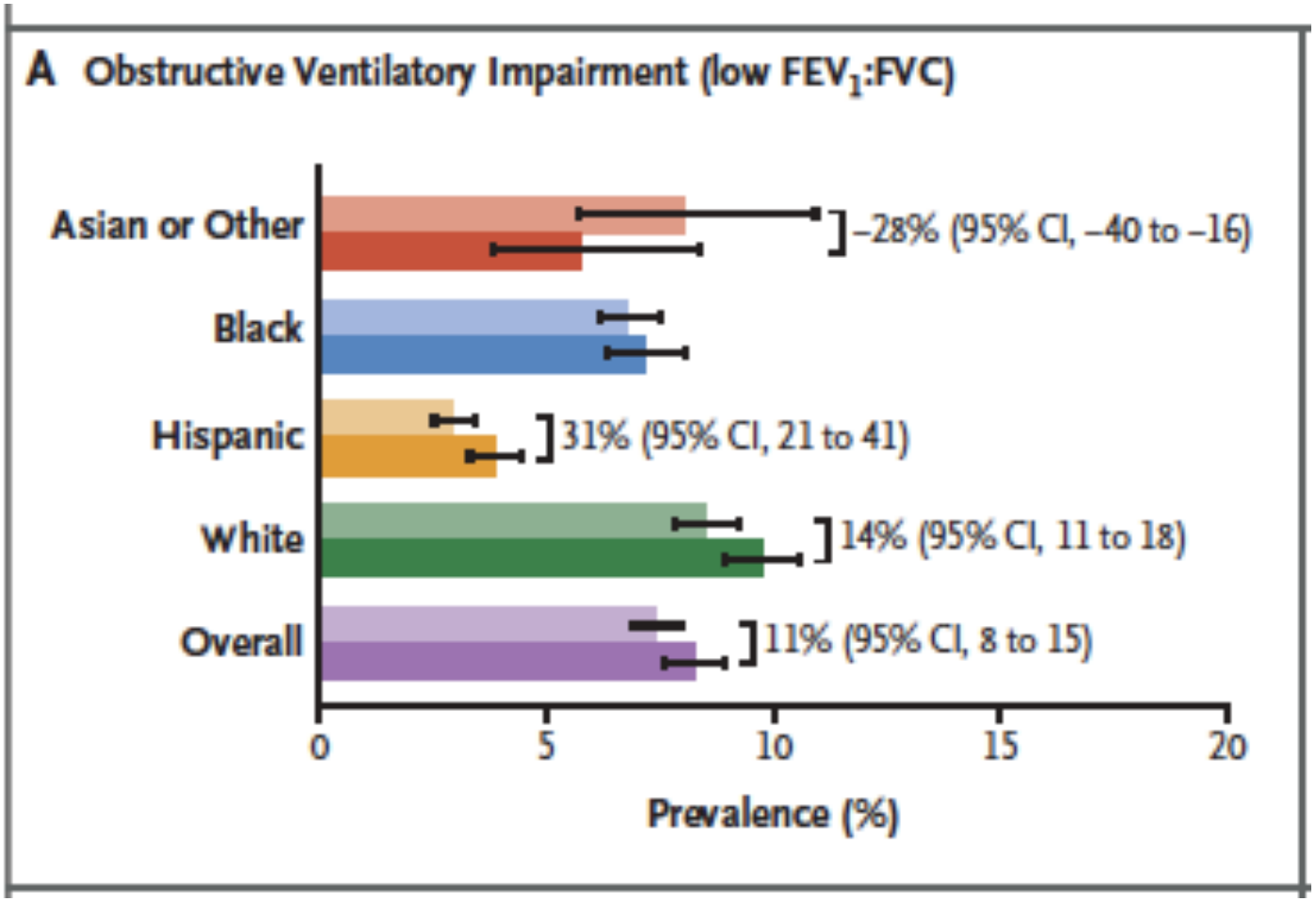
Figure 2. Association of Race-Neutral Reference Equations With Forced Expiratory Volume in First Second of Expiration (FEV_1), Forced Vital Capacity (FVC), and Percent FVC Exhaled in the First Second (FEV_1/FVC) *z* Scores in Black and White Individuals



Moffett JAMA Network Open 2023

New vs Old

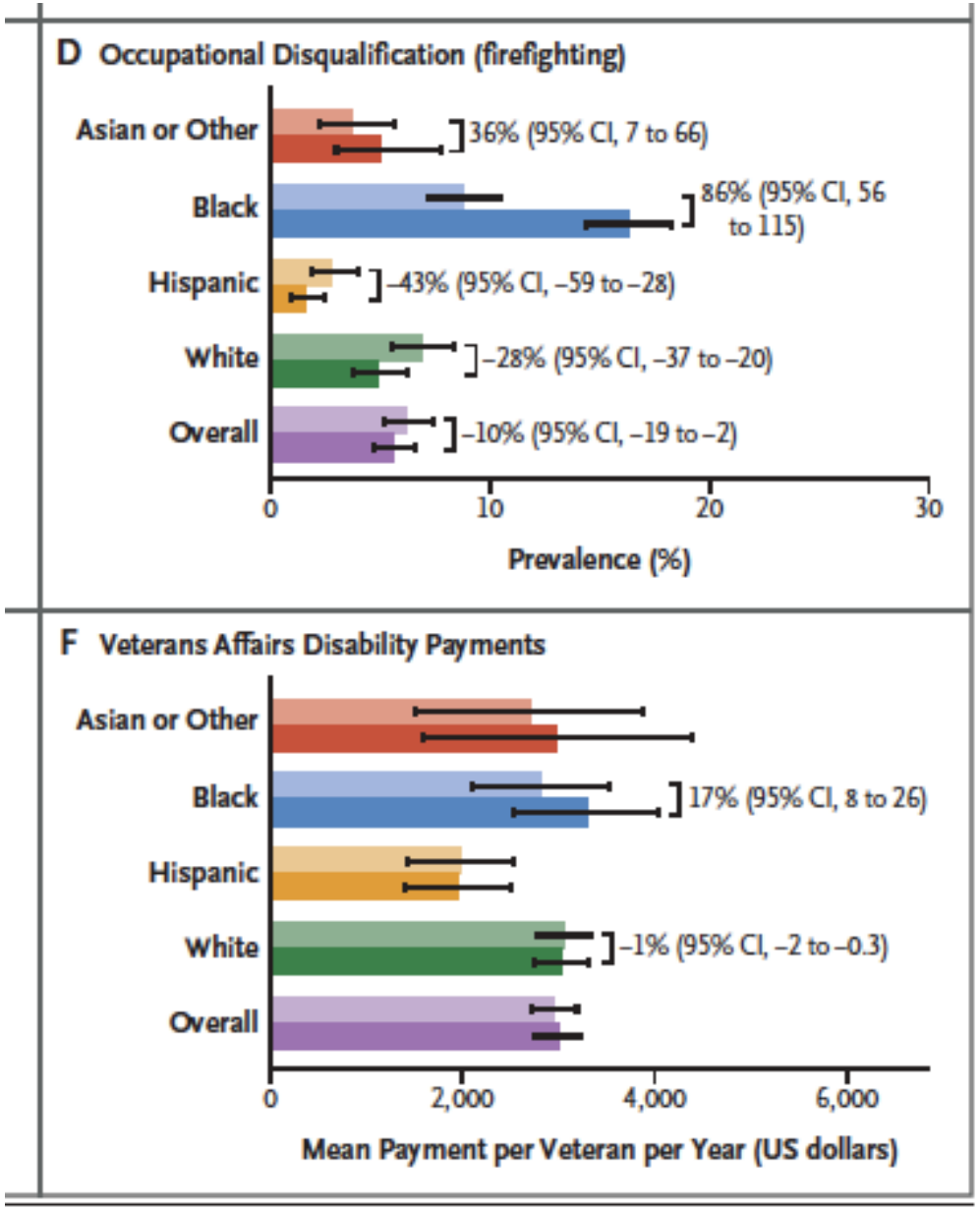
- Obstruction
  - ↑Overall
    - Black, Hispanic, White
  - ↓ Asian / Other



Diao NEJM 2024

New vs Old

- Occupational disqualification
  - ↓Overall
    - Hispanic, White
  - ↑ Asian/Other, Black
- VA Disability Payment
  - ↔ Overall
    - Hispanic
  - ↑ Asian/Other, Black
  - ↓White
- Other effects
  - Treatment / Clinical trial eligibility
  - Lung transplant referral



Diao NEJM 2024

JAMA Surgery | Original Investigation

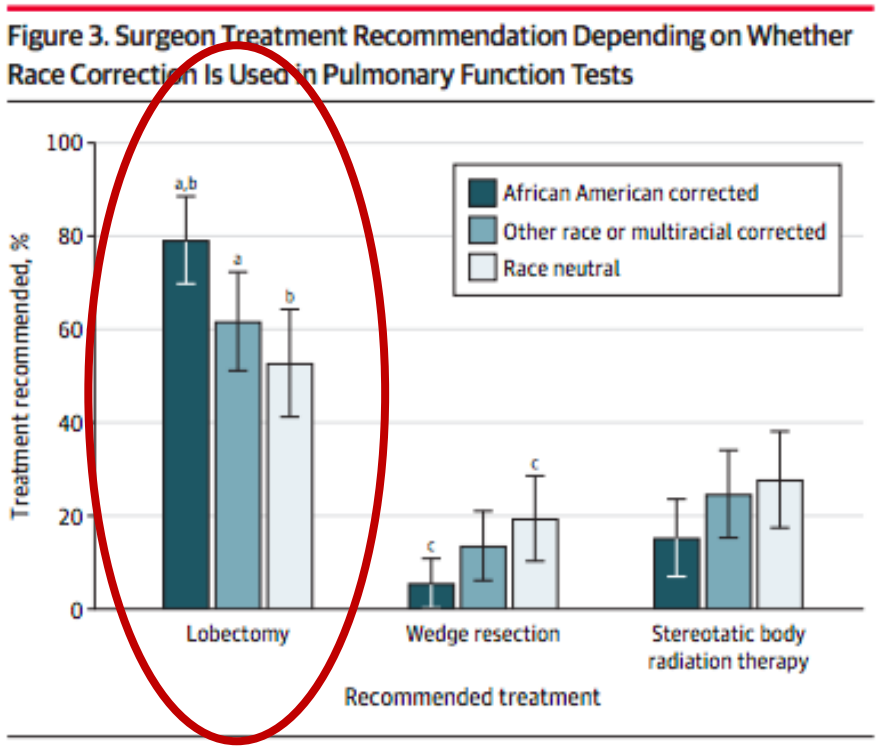
Clinical Implications of Removing Race-Corrected Pulmonary Function Tests for African American Patients Requiring Surgery for Lung Cancer

Sidra N. Bonner, MD, MPH, MSc; Kiran Lagisetty, MD; Rishindra M. Reddy, MD, MBA; Yadonay Engeda, BA; Jennifer J. Griggs, MD, MPH; Thomas S. Valley, MD, MSc

- Case Vignette
  - 71 AA woman, 3.6cm mass
  - FEV_1 1.2L
  - Evaluate for RUL lobectomy
- 200 thoracic surgeons:

  Randomized to 3 values for % pred post-op FEV_1
  - AA Race-adj 49% predicted
  - GLI-other 45% predicted
  - "neutral" 42% predicted

Use additional information such as 6MWD, CPETs etc



Bonner JAMA Surgery 2023
Medlock JAMA Surgery 2023

Summary

- Severity grading using Z scores
  - Fewer categories, more correlated with mortality
  - May have a change in severity without change in lung function, esp older patients
- Bronchodilator response
  - More specific, less sensitive
- Defining obstruction
- “Non-specific” pattern
  - Possible meaning
  - Look for other clues
- Switch to race-neutral equations
  - effects on patients, clinical decision-making

Thank you!