Emphysema Disease Background

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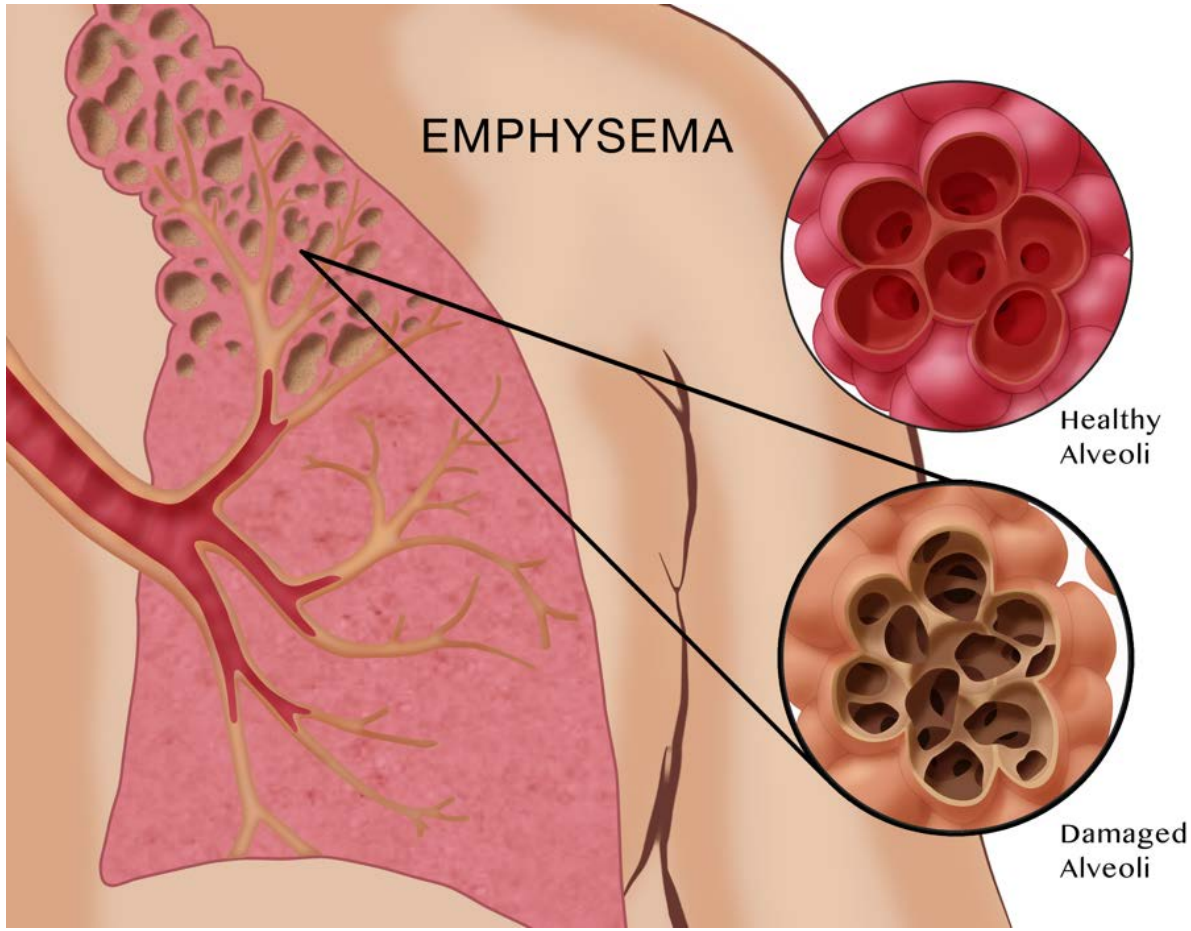
PneumRx

a BTG International group company

Emphysema Affects ~3.5 Million Americans[a]



- A subset of COPD
- Abnormal and permanent enlargement of lung air spaces distal to the terminal bronchiole
- Caused by irreversible destruction of alveolar walls
- Damaged alveoli lead to air trapping and hyperinflation

[a] CDC FastStats. https://www.cdc.gov/nchs/fastats/copd.htm.
Image reprinted from Monica Schroeder. Emphysema, Illustration C027/6604. Science Photo Library Web site. http://www.sciencephoto.com/media/703653/view/emphysema-illustration. Accessed June 4, 2018.

The Clinical Picture of Emphysema

- Breathlessness
- Cough
- Wheezing
- Loss of weight
- Barrel chest
- Sleep problems
- Lung infections

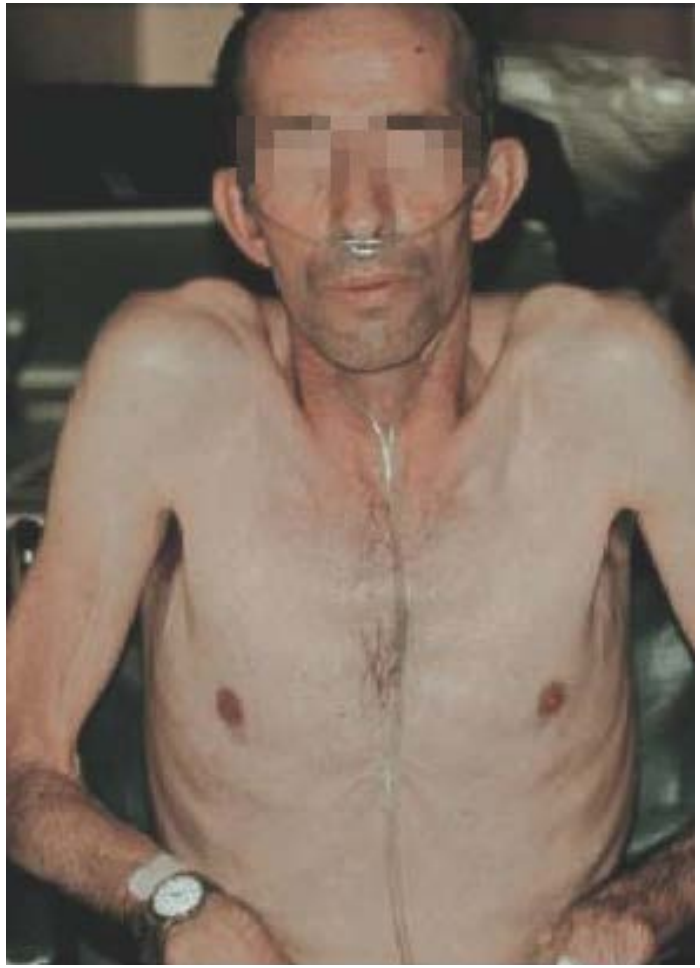


Image reprinted from http://what-when-how.com/acp-medicine/chronic-obstructive-diseases-of-the-lung-part-2/.

Emphysema and Lung Hyperinflation

- Hyperinflation is a devastating and common complication of emphysema

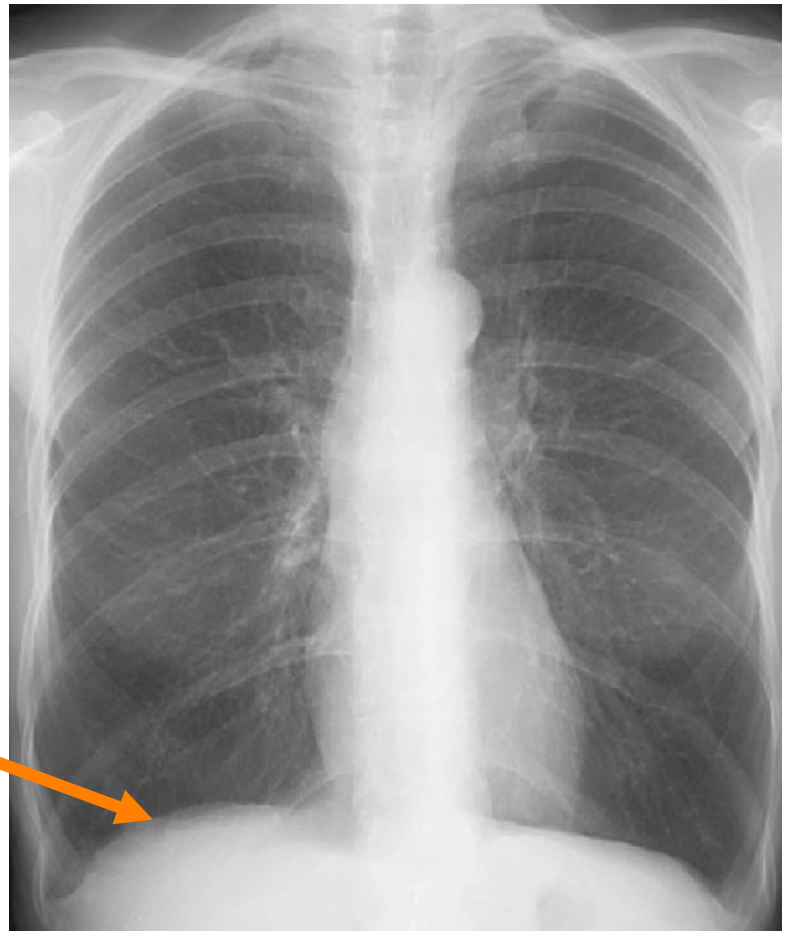
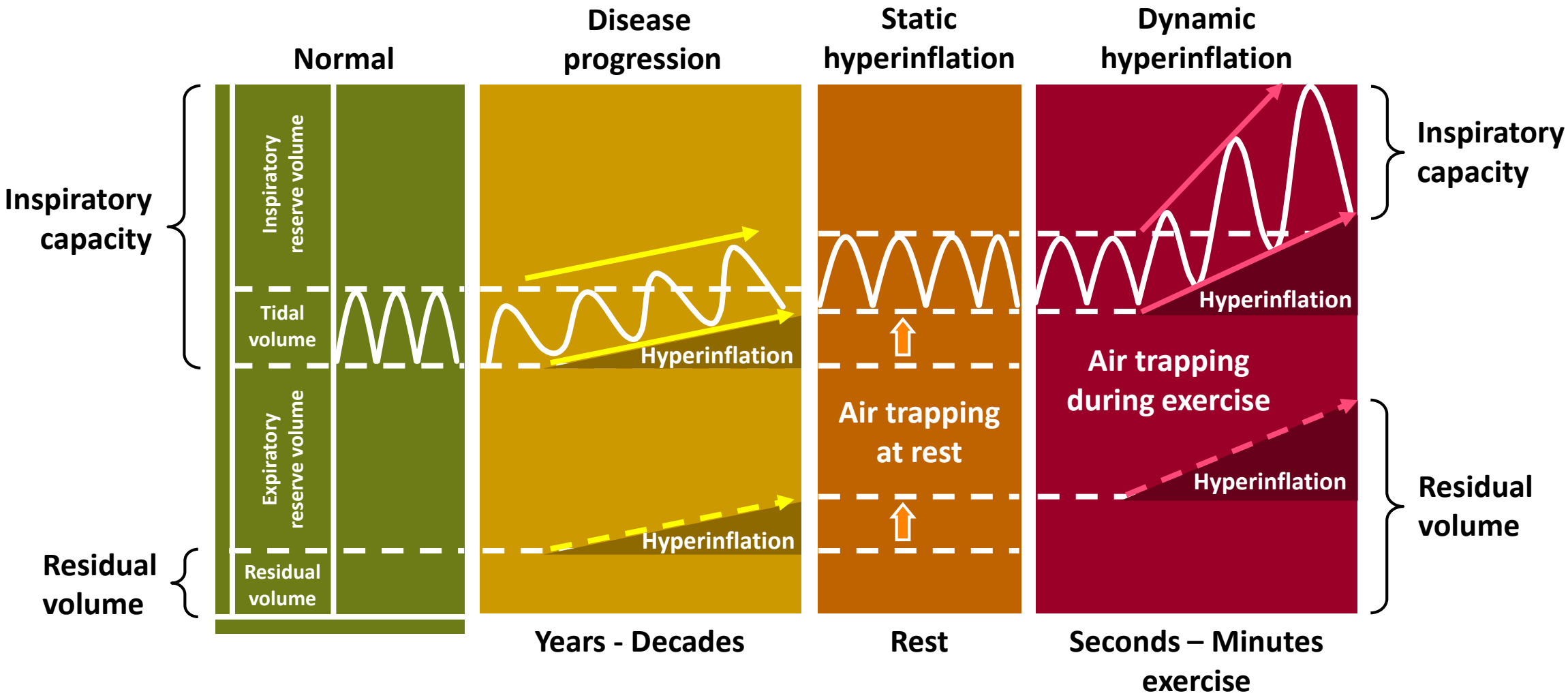


Image reprinted from https://www.med-ed.virginia.edu/courses/rad/cxr/pathology10chest.html.

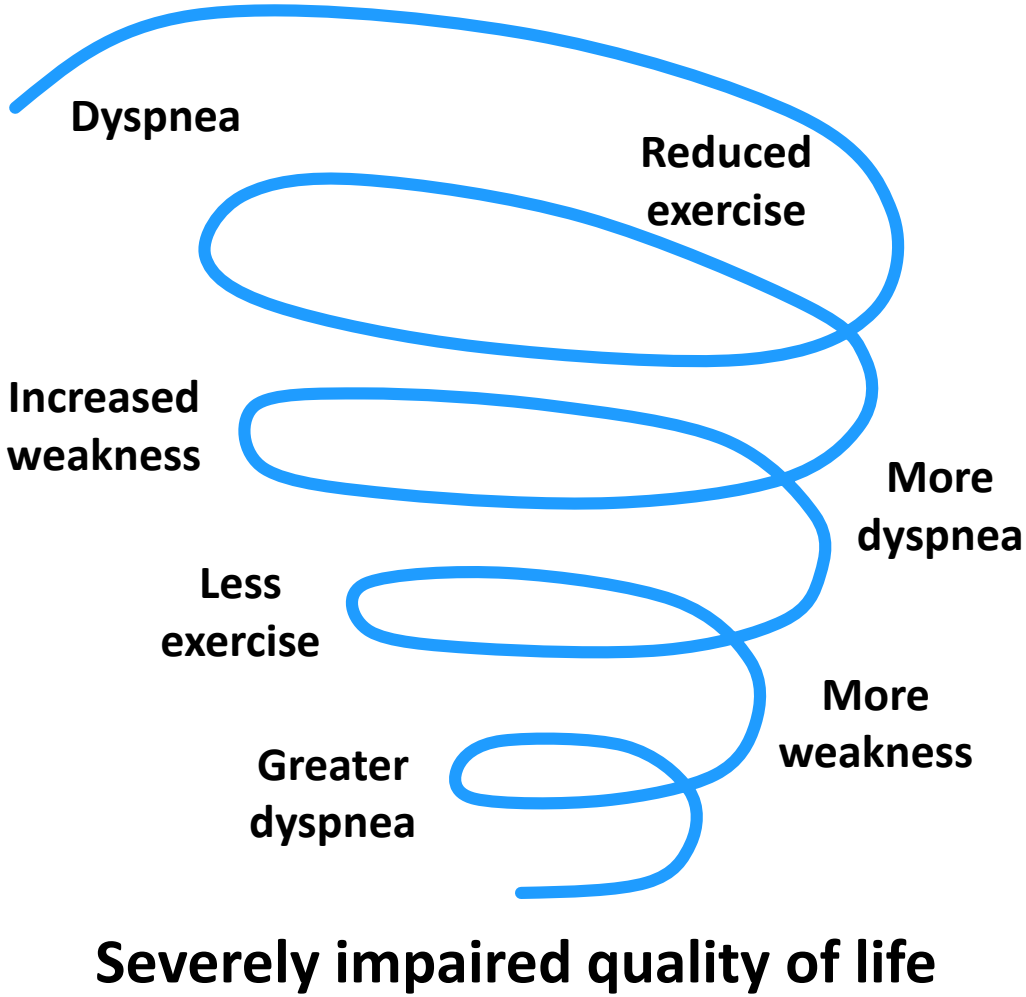
Progressive Air Trapping and Hyperinflation Leads to Decreased Inspiratory Capacity



Adapted from O'Donnell DE. *Eur Respir Rev*. 2006;15(99):37-41.

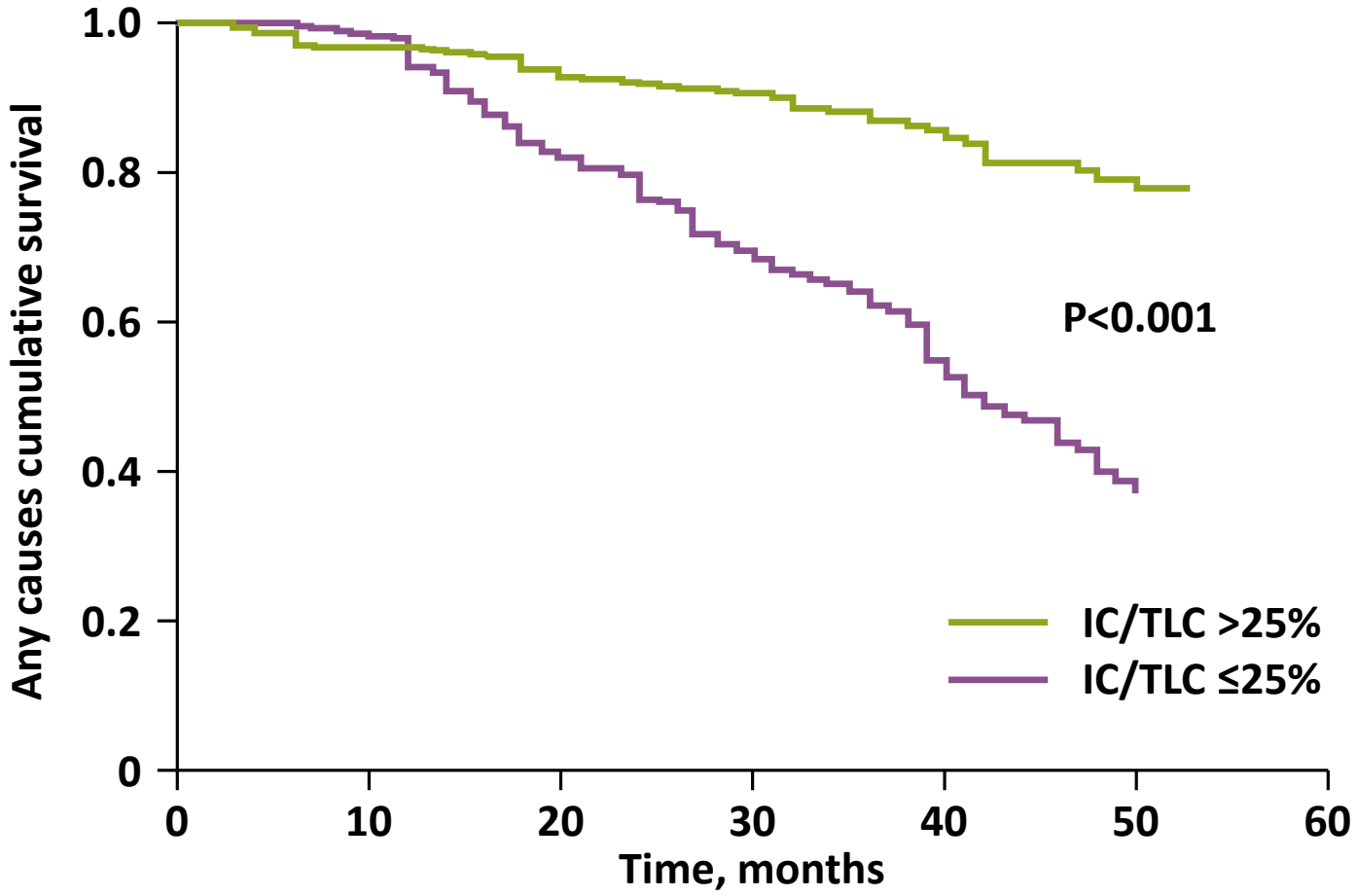
Breathlessness/Dyspnea Caused by Hyperinflation Leads to Significant Morbidity and Poor Survival

- Decreased exercise performance
- Impaired respiratory muscle and chest wall mechanics
- Decreased quality of life
- Prolonged respiratory failure requiring mechanical ventilation
- Increased mortality



Adapted from Global Initiative For Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. http://goldcopd.org

Hyperinflation Is Associated With Poor Prognosis



Reprinted from Casanova C, et al. *Am J Respir Crit Care Med*. 2005;171:591-597.

Emphysema Staging

GOLD Staging System[a]

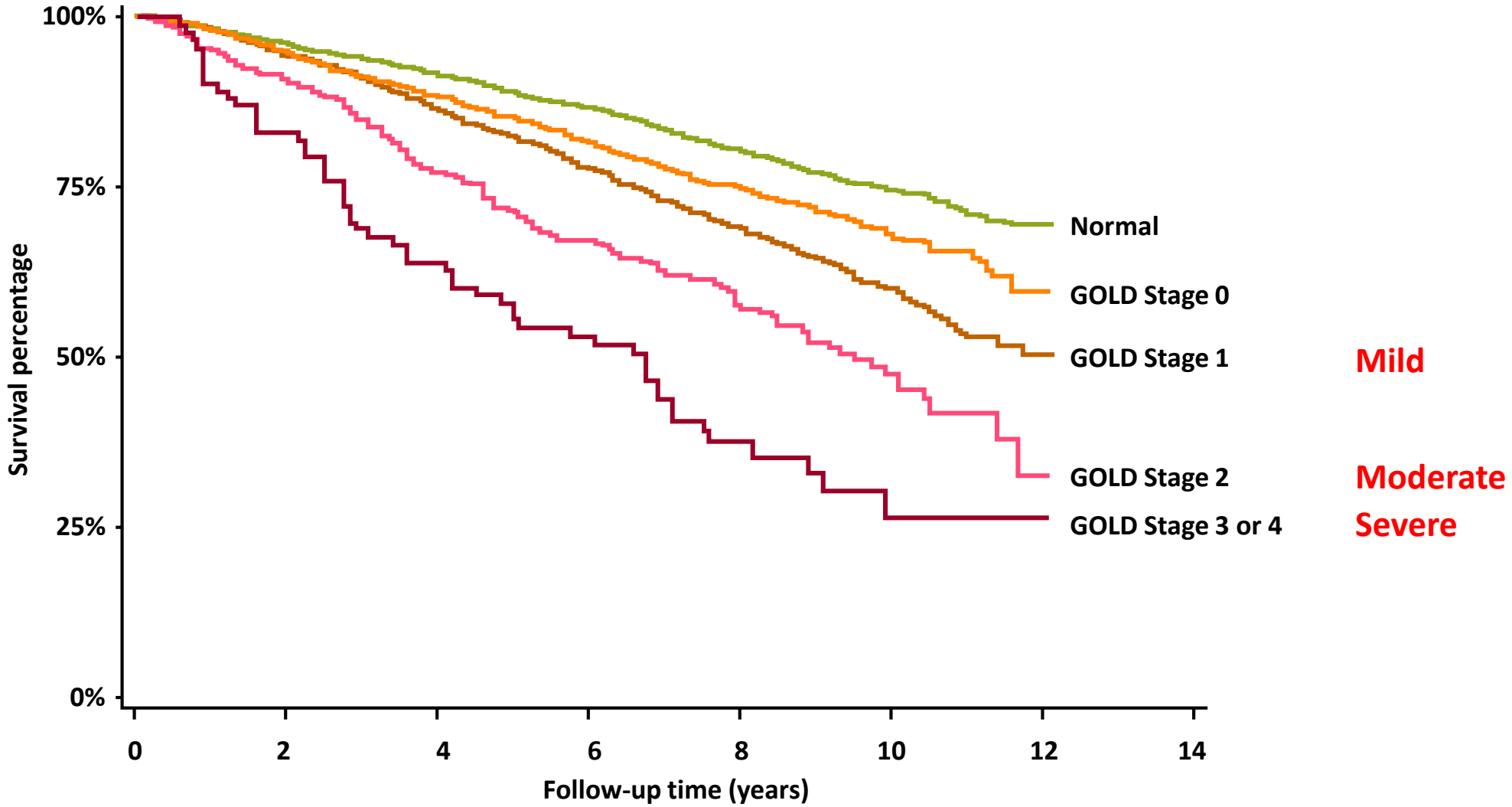
- **Stage 1:** Very mild emphysema with FEV_1 about 80% or more of normal
- **Stage 2:** Moderate emphysema with FEV_1 between 50% and 80% of normal
- **Stage 3:** Severe emphysema with FEV_1 between 30% and 50% of normal
- **Stage 4:** Very severe emphysema with FEV_1 < 30% of normal

~1.2 million[b]

[a] Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Pocket Guide to COPD Diagnosis, Management, and Prevention. 2017 Report.*

[b] Tilert T, et al. *Respir Res*. 2013;14:103; Murphy DE and Panos RJ. *Int J Chron Obstruct Pulmon Dis*. 2013;8:199-208; Mapel DW, et al. *Int J Chron Obstruct Pulmon Dis*. 2011;6:573-581; Hurst JR, et al. *N Engl J Med*. 2010;363(12):1128-1138.

Overall Survival in NHANES III Stratified by Lung Function Impairment (6,261 Participants Age ≥50 yr)



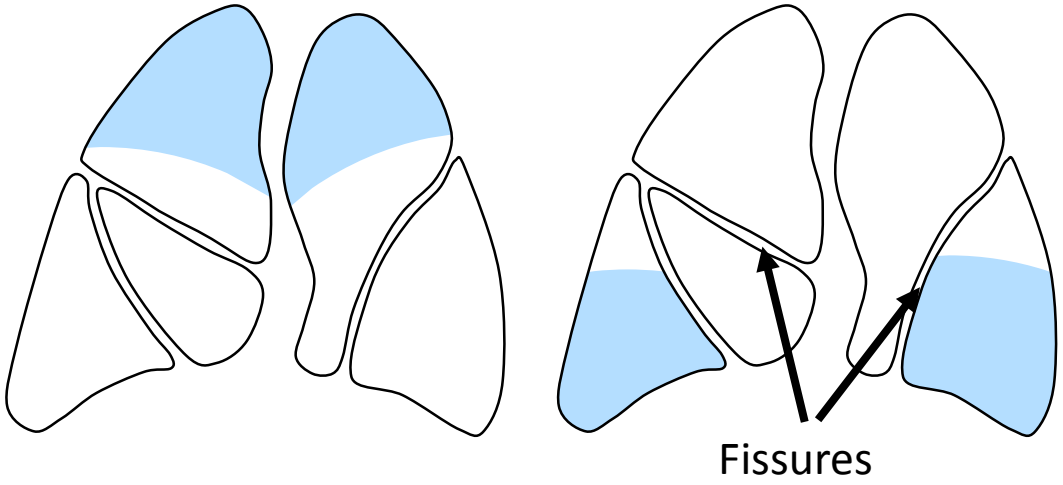
Reprinted from Shavelle RM, et al. *Int J COPD*. 2009;4:137-148.

Disease Characteristics of Emphysema

Heterogeneous

Upper lobe

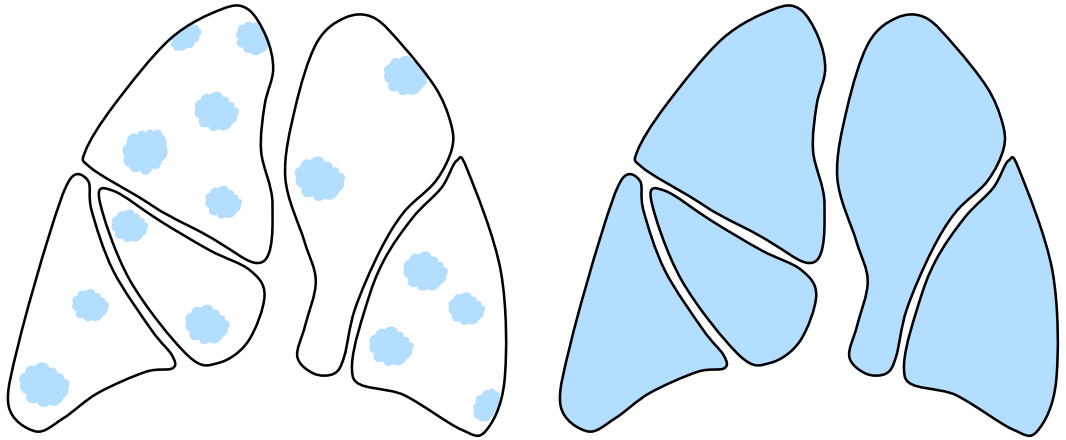
Lower lobe (basal segment)



Homogeneous

With patchy areas

Completely homogeneous



Reprinted from Cederlund K, et al. *Chest*. 2002;122(2):590-596.

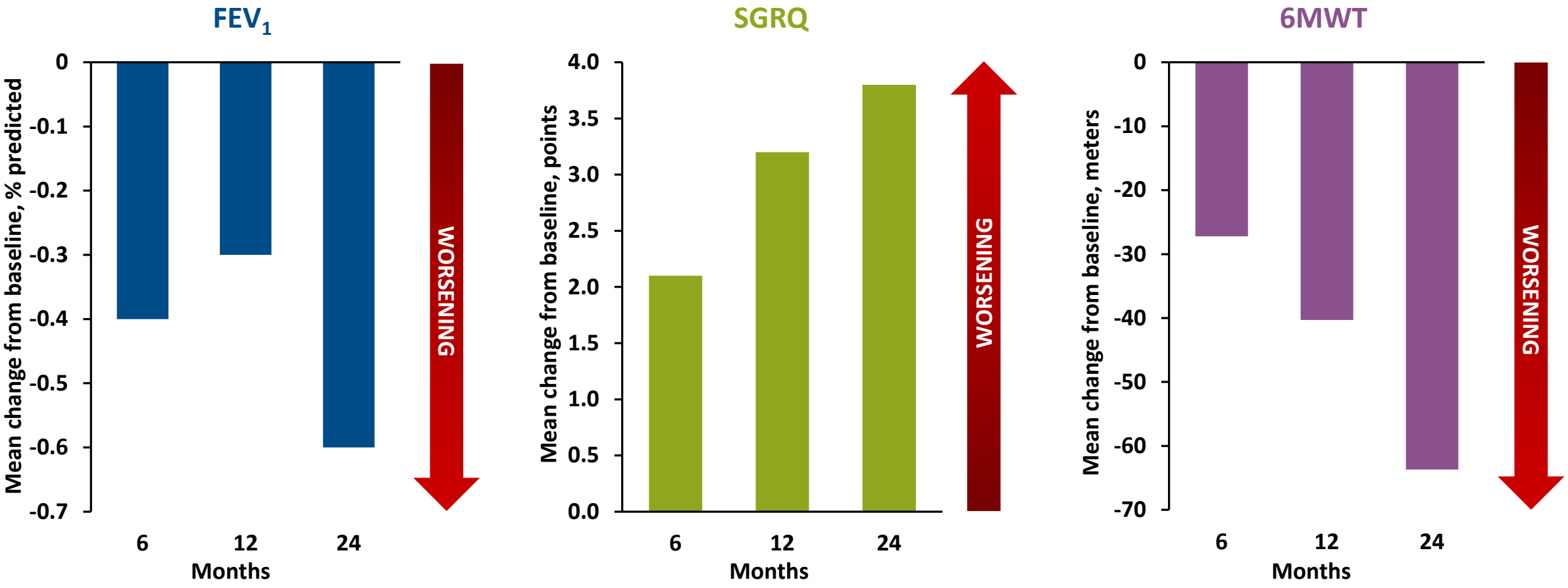
Key Clinical Parameters in the Assessment of Emphysema

Measure/Endpoint	Definition
Lung Function	
FEV_1	Forced Expiratory Volume in 1 Second
RV	Residual Volume
Quality of Life	
SGRQ	St. George's Respiratory Questionnaire
Exercise Capacity	
6MWT	6-Minute Walk Test

Natural History of Severe Emphysema

Data From NETT Control Group Over 2 Years

Worsening of all clinical outcomes over time

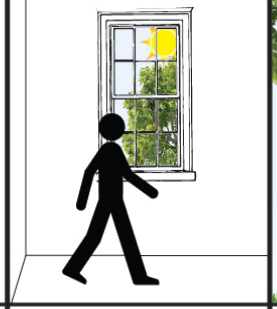


NETT=National Emphysema Treatment Trial.

Fishman A, et al. *N Engl J Med*. 2003;348(21):2059-2073.

St. George Respiratory Questionnaire Assesses Breathlessness With Activity (Question 11)

Breathlessness adversely impacts quality of life and limits activities of daily living

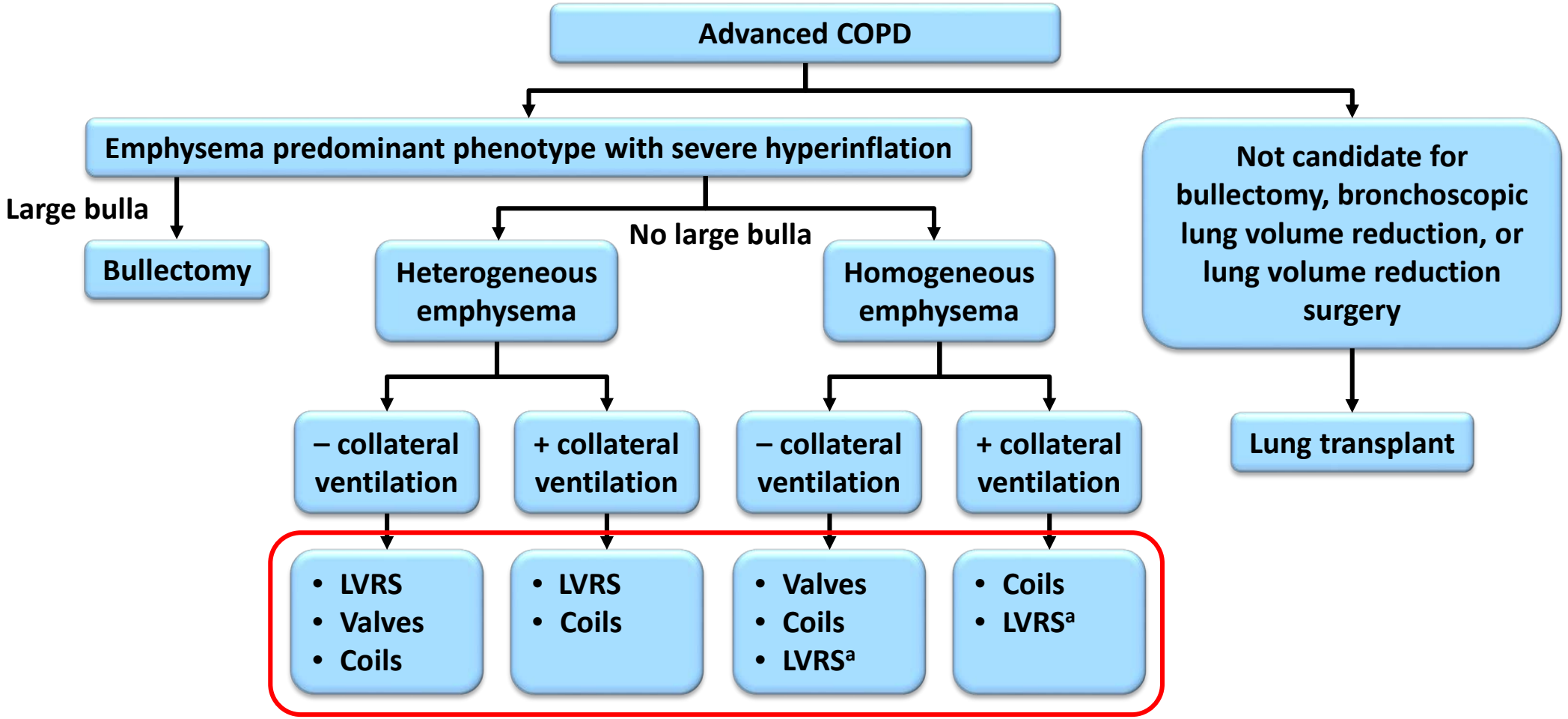
I don't feel out of breath doing these activities	I do feel out of breath doing these activities					
						
Sitting or lying still	Washing or dressing yourself	Walking around the house	Walking outside on level ground	Walking up a flight of stairs	Walking up hills	Playing sports or other physical activities

Available Treatment Options Have Limitations in Severe Emphysema

	Pharmacotherapy (SAMA, SABA, LAMA, LABA, ICS PDE-4 inhibitors)	Lung volume reduction surgery (LVRS)	Lung transplantation
Patient population	All emphysema patients	GOLD 3 and 4 Severe hyperinflation No large bulla Upper lobe emphysema	Selected patients with GOLD 4
Level of evidence[a]	Level A	Level A	Level C
Benefits	Limited benefit in severe emphysema	Improves survival, QoL, and functional capacity	Improved QoL and functional capacity
Risks	Minimal	Significant morbidity and mortality	Significant morbidity and mortality
Limitations	**Limited clinical benefit**	**High risk of mortality**	**Very few patients qualify**
		~200 procedures/year[b]	<1000 transplants/year[c,d]

[a] Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://goldcopd.org; [b] Decker MR, et al. *J Thorac Cardiovasc Surg.* 2014;148(6):2651-2658-e1; Agency for Healthcare Research and Quality. HCUPnet - Hospital Inpatient National Statistics; [c] Valapour M, et al. *Am J Transplant*. 2018;18:363-433; [d] Whitson BA, Hayes B. *J Thorac Dis*. 2014;6(8):1018-1023.

Bronchoscopic Lung Volume Reduction Represents an Option for Severe Emphysema Patients



Adapted from Global Initiative for Chronic Obstructive Lung Disease: Pocket Guide to COPD Diagnosis, Management, and Prevention. 2018 Report.

[a] At some but not all centers.

Severe Emphysema Represents a Substantial Unmet Need

- Severe emphysema affects an estimated 1.2 million people in the United States[a]
- Lung hyperinflation is strongly associated with patient-centered outcomes: dyspnea, exercise capacity, and daily physical activity[b]
- Reducing hyperinflation improves clinical outcomes and quality of life
- Current treatment options for severe emphysema patients are limited
  - Surgical options (LVRS and lung transplant) are limited by patient eligibility, high procedural risks and complications, and increased morbidity and mortality
  - Current pharmacologic options have limited benefit in severe emphysema patients
- ***A nonsurgical lung reduction therapy is needed that is effective in* reducing hyperinflation in patients *with heterogeneous and homogeneous emphysema* and severe hyperinflation**

[a] Tilert T, et al. *Respir Res*. 2013;14:103; Murphy DE and Panos RJ. *Int J Chron Obstruct Pulmon Dis*. 2013;8:199-208; Mapel DW, et al. *Int J Chron Obstruct Pulmon Dis*. 2011;6:573-581; Hurst JR, et al. *N Engl J Med*. 2010;363(12):1128-1138.

[b] Garcia-Rio F, et al. *Am J Respir Crit Care Med*. 2009;180:506-512.