

# Current Landscape of COPD Treatment

**Nicola A. Hanania, MD, MS, FCCP**  
**Associate Professor of Medicine**  
**Pulmonary and Critical Care Medicine**  
**Director, ALA Airway Clinical Research Center**

**Baylor**  
College of  
Medicine®



**ACRC NETWORK**  
Airways Clinical Research Centers



# Disclosures

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- Grant support: NIH, ALA, GSK, BI, Sunovion, Roche, Cheisi, Astra Zeneca, Mylan
- Consultant: GSK, Sunovion, Novartis, Forest, Genentech/Roche, Astra Zeneca



# GOLD: Global Initiative for Chronic Obstructive Lung Disease

## GOLD definition of COPD<sup>1</sup>

- Common, preventable, **treatable—partially reversible**
- Characterized by persistent airflow limitation
- Usually **progressive and disabling**
- Associated with enhanced **chronic inflammatory response** in airways/lung to noxious particles or gases

## COPD is heterogeneous<sup>2</sup>

- Multiple risk factors, phenotypes, comorbidities
- **Exacerbations and comorbidities contribute to severity**

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. [www.goldcopd.org](http://www.goldcopd.org).

2. Goh F et al. Expert Rev RespirMed. 2013;7(6):593-605.

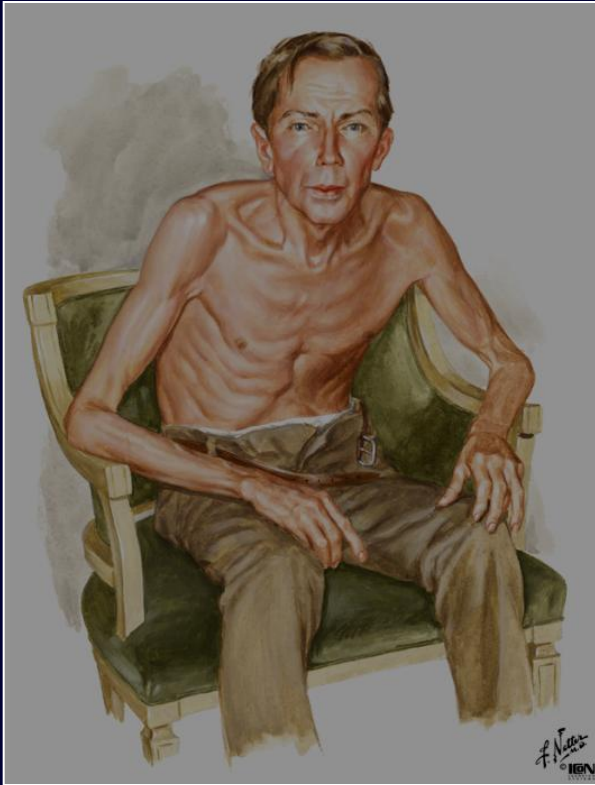
# The Impact of COPD in the United States

- COPD prevalence in U.S.
  - estimates range from 5.1% to 6.2%
  - Gender: Adult women > men (6.1% vs. 4.1)
- In 2010, COPD accounted for
  - 10.3 million physician office visits/y
  - 1.5 million ED visits
  - 699,000 hospital discharges
- Costly
  - Direct COPD (2010): \$29.5 billion/y
  - Indirect (2010): \$20.4 billion/y
- Third leading cause of death
- Fourth leading cause of hospital readmissions

1. Akinbami LJ, Liu X. *NCHS Data Brief, No. 63, June 2011*; 2. American Lung Association. <http://www.lung.org/finding-cures/our-research/trend-reports/copd-trend-report.pdd>; 3. Hooper R et al. *Eur Respir J*. 2012;39:1343–1453; 4. Ford ES, et al. *Chest*. 2013;144(1):284-305; 5. Am. Lung. Association. 2014. <http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html>; 6. Heron M. *Natl Vital Stat Rep*. 2012;60(6):1-94; 7. Jencks SF, et al. *N Engl J Med*. 2009; 360:1418-1428.

# COPD: The Old Look

## Perception<sup>3,4,5</sup>



COPD is a disease of the elderly<sup>1</sup>

COPD is a disease of men<sup>2</sup>

<sup>1</sup>Tinkelman, et al. *Am J Manag Care*. 2003;9:767-771. <sup>5</sup>Chapman KR. *Clin Chest Med*. 2004;25:331-334.. <sup>3</sup>Rennard SI. *New Engl J Med*. 2004;350:965-966. <sup>4</sup>Kleinschmidt P. Chronic obstructive pulmonary disease and emphysema. Available at <http://www.emedicine.com>. <sup>5</sup>Rennard SI. *New Engl J Med*. 2004;305:965-966.

# COPD in Younger Patients and Women Is on the Rise

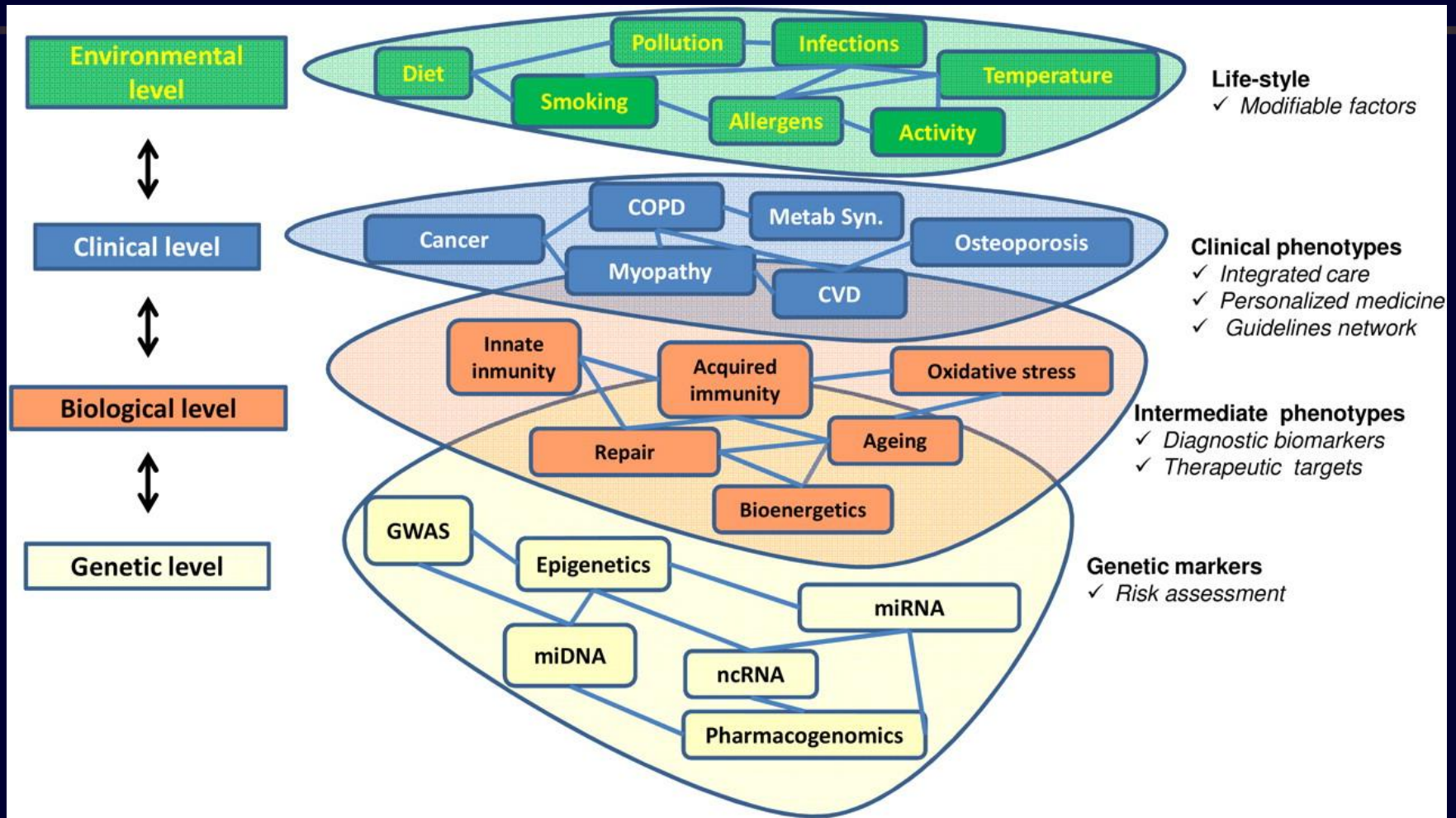
## Reality



Reality: COPD afflicts the working-age population.

Reality: COPD is also a disease of women.

# COPD: The New Look



# Risk Factors for COPD

## Smoking<sup>1,2</sup>

(~80% of cases)

- Current or former smoker



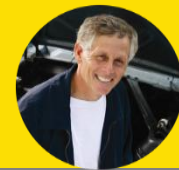
## Genetic factors<sup>1,2</sup>

- Alpha-1 antitrypsin deficiency  
(~2-3% of emphysema cases in US)
  - Can cause COPD even without smoking history/environmental exposure

## Key Risk Factors for COPD

## Age<sup>2</sup>

- >40 years of age



## Environmental exposure<sup>2</sup> (10% - 20% of cases)

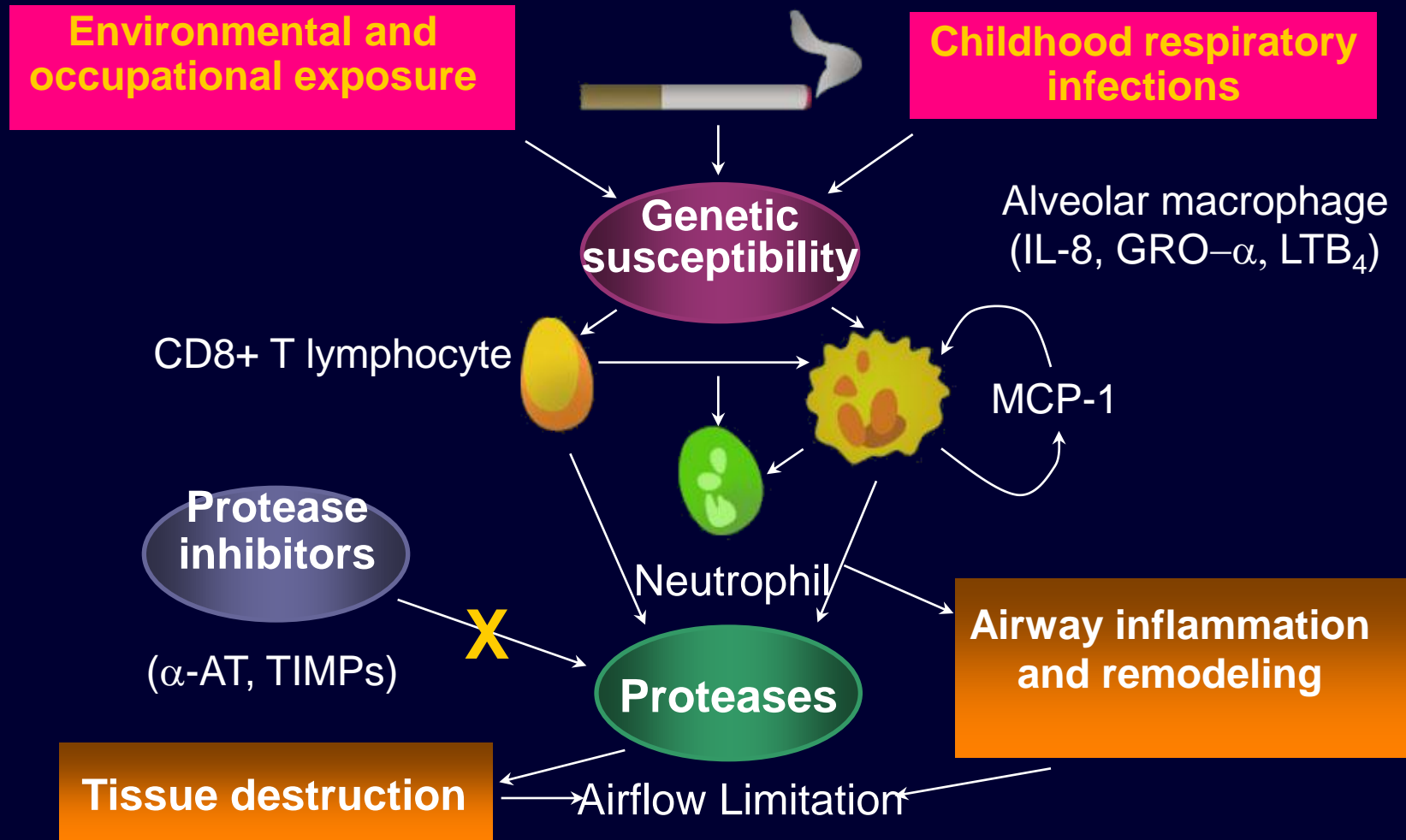
- Long-term exposure to chemicals, dust, or fumes in the workplace or second-hand smoke
- Household exposures (eg, biomass cooking)



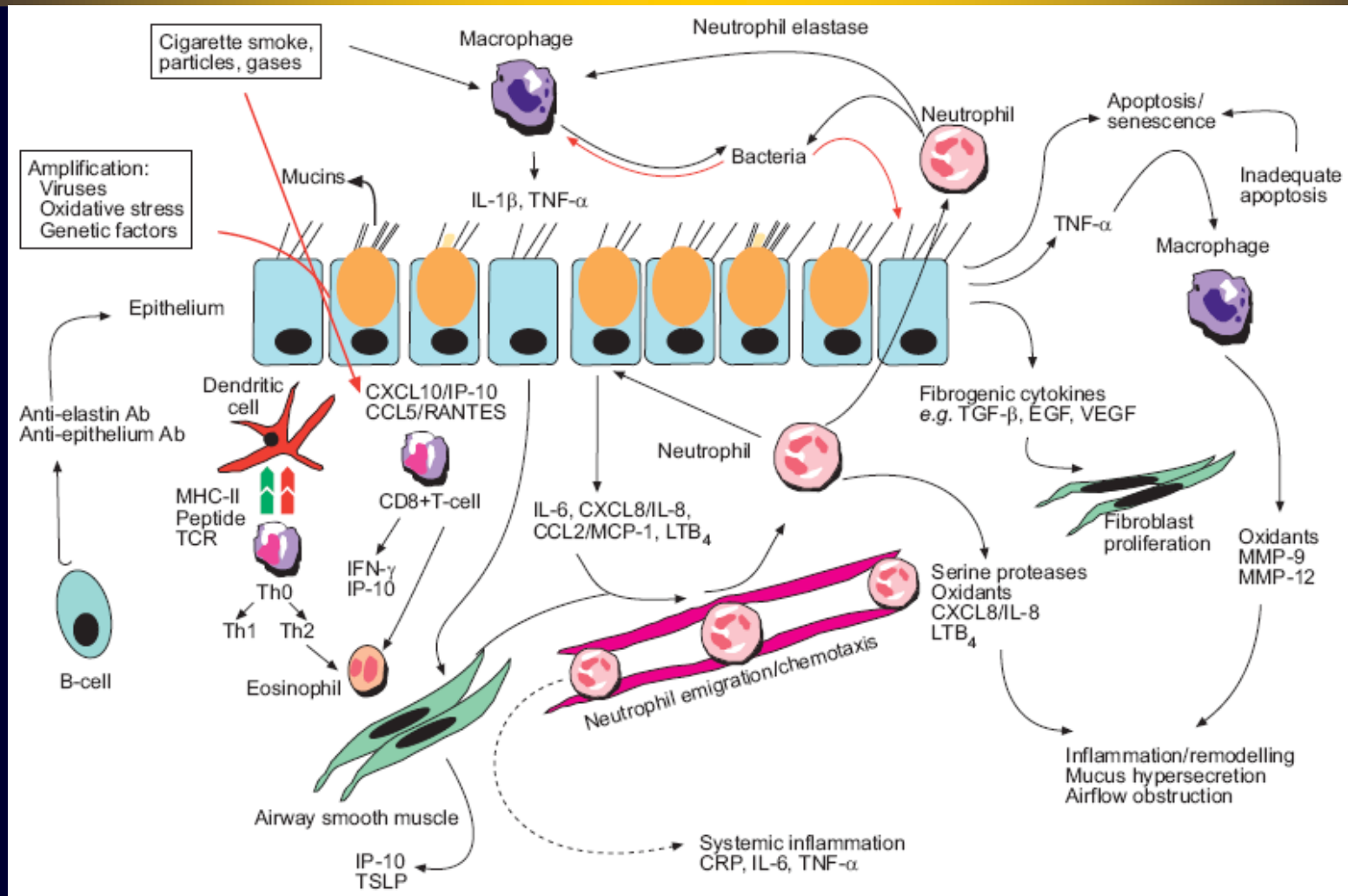
1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. Updated 2014. <http://www.goldcopd.org>.
2. American Lung Association. COPD Fact Sheet. Updated May 2014. <http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html>



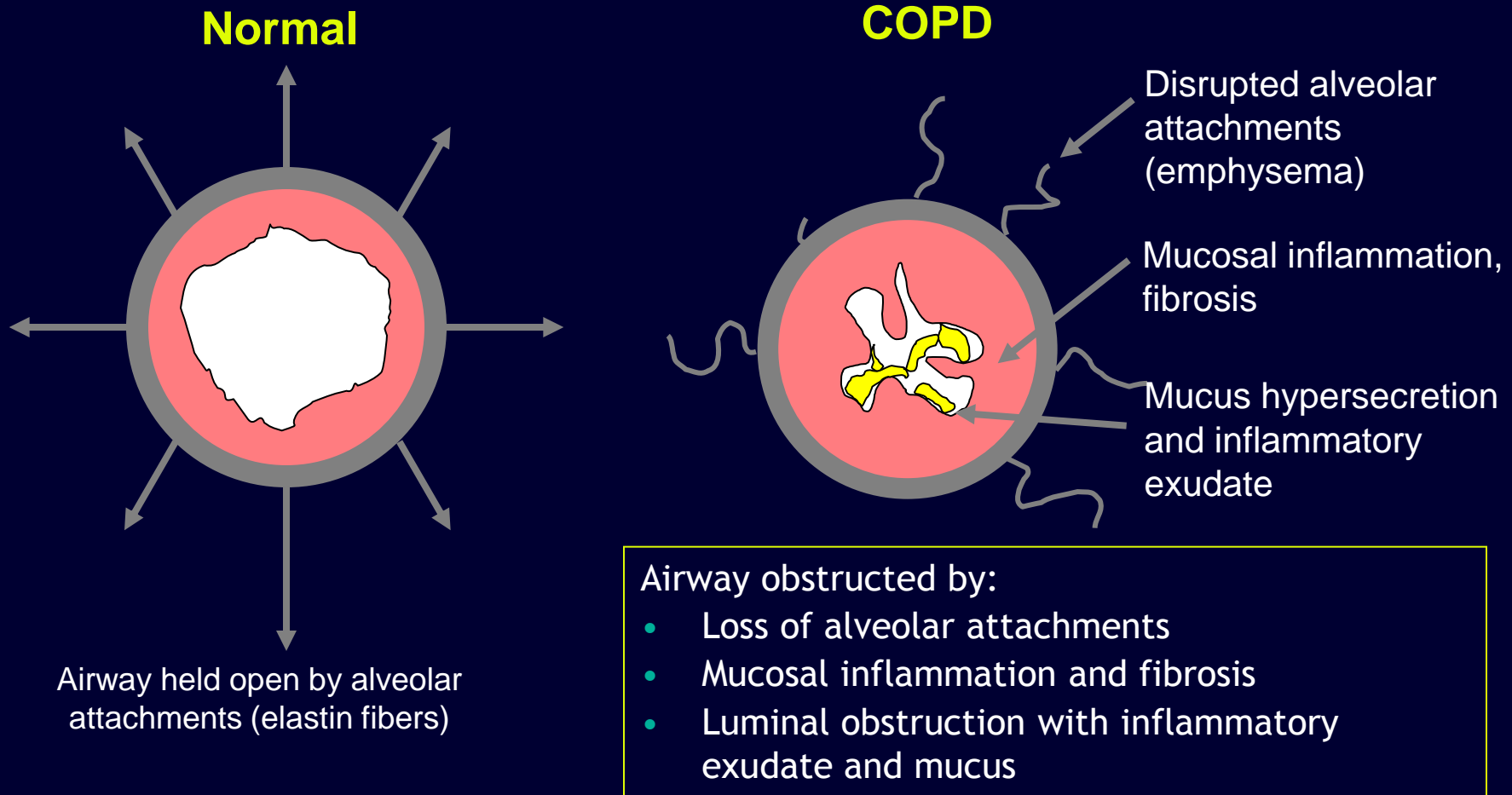
# Pathophysiology of COPD



# Inflammatory and Cellular Mechanisms in COPD due to Cigarette Smoking



# Emphysema and Small Airways Disease Contribute to Total Airflow Limitation in COPD





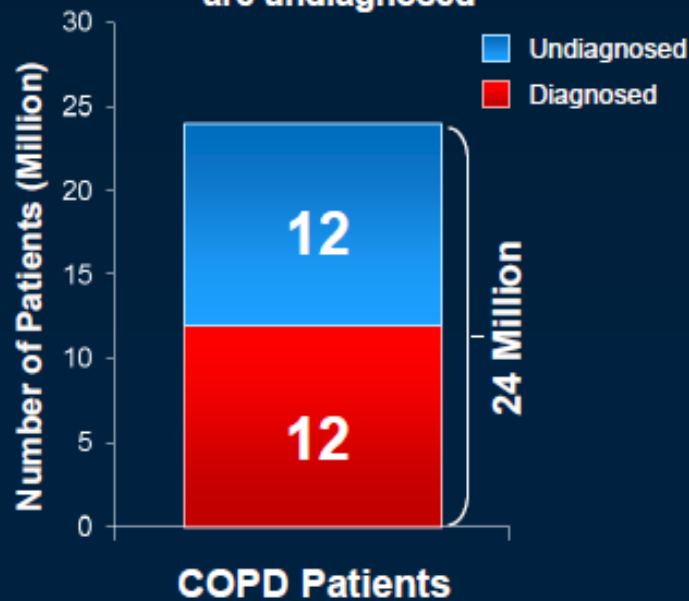
# Improving Outcomes in COPD

- Early diagnosis and accurate assessment

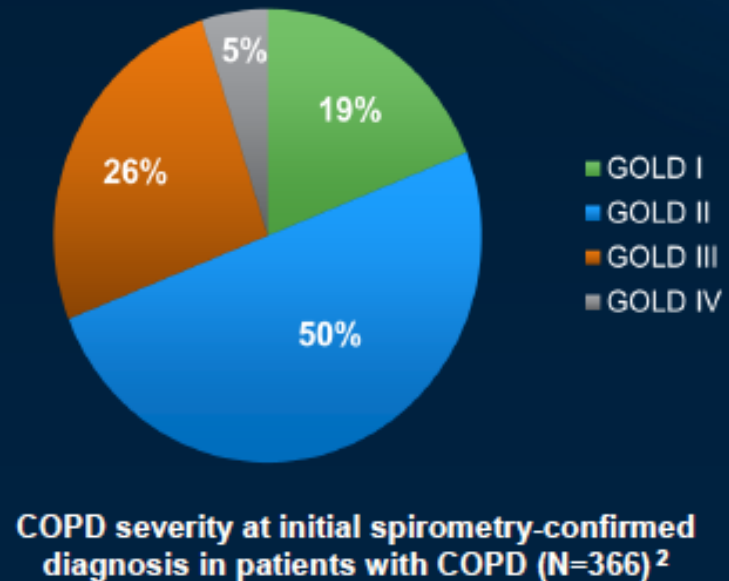
# COPD Is Underdiagnosed and Undertreated

## 50%

of COPD patients in the United States are undiagnosed<sup>1</sup>



Majority of patients are diagnosed at later stages of COPD<sup>2</sup>



1. NIH, NHLBI. Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung and Blood Diseases.

2. Make B et al. *Int J Chron Obstruct Pulmon Dis*. 2012;7:1-9.

3. Mapel DW et al. *Int J Chron Obstruct Pulmon Dis*. 2011; 6:573-581.

# Key Indicators for COPD Diagnosis

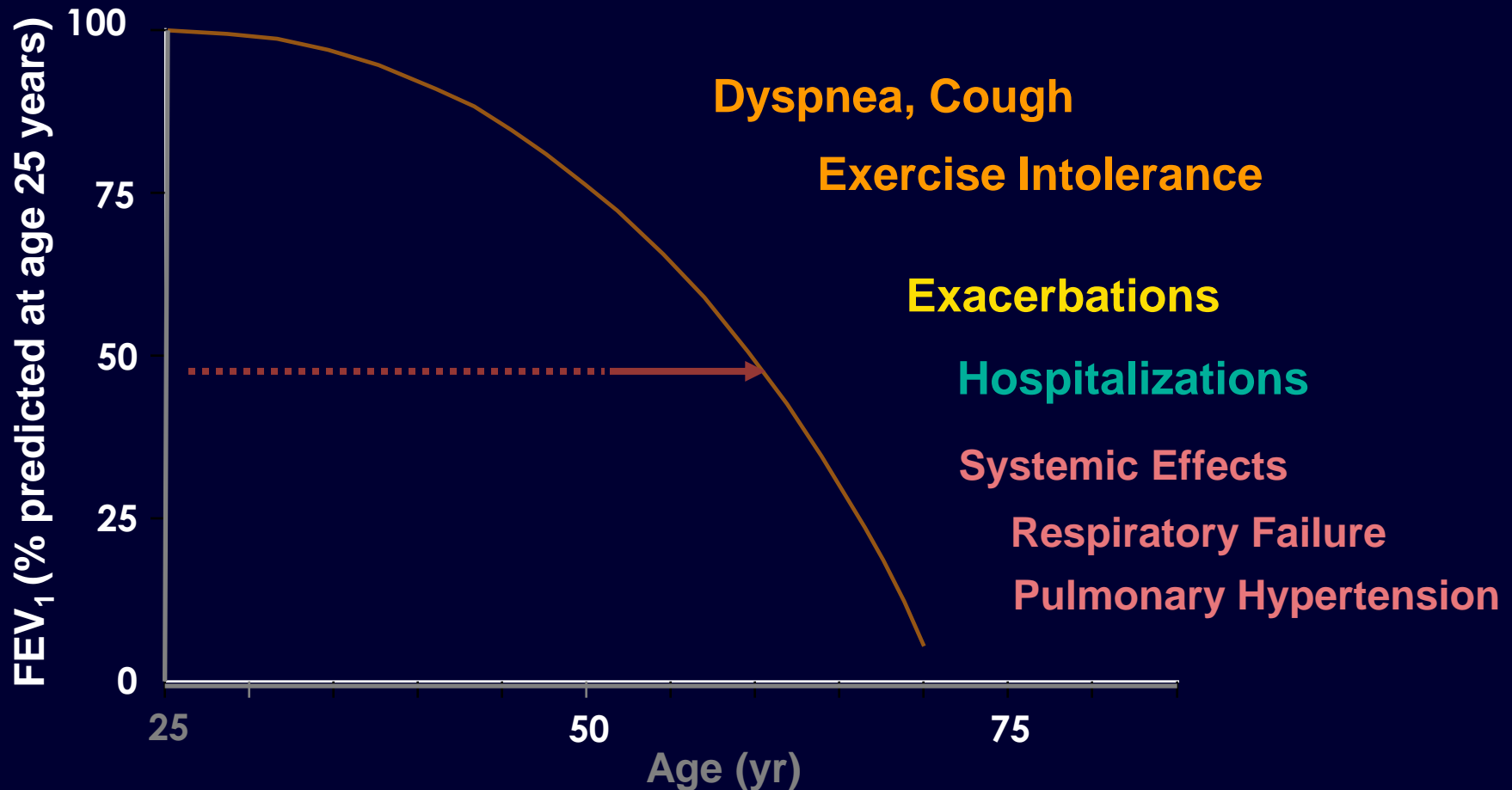
- Consider a diagnosis of COPD, and perform spirometry, if any of these indicators\* are present in an individual >40 years of age
  - Exertional dyspnea
  - Chronic cough
  - Chronic sputum production
  - History of exposure to risk factors (eg, tobacco smoke)
- Spirometry is required to make the diagnosis
  - Post-bronchodilator  $FEV_1/FVC < 0.70$  confirms persistent airflow limitation and COPD diagnosis

\*These indicators are not diagnostic in themselves, but the presence of multiple key indicators increases the probability of a COPD diagnosis.  $FEV_1$  = forced expiratory volume in 1 second; FVC = forced vital capacity.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. Updated 2014.

# Diagnostic Challenges: Natural History of COPD

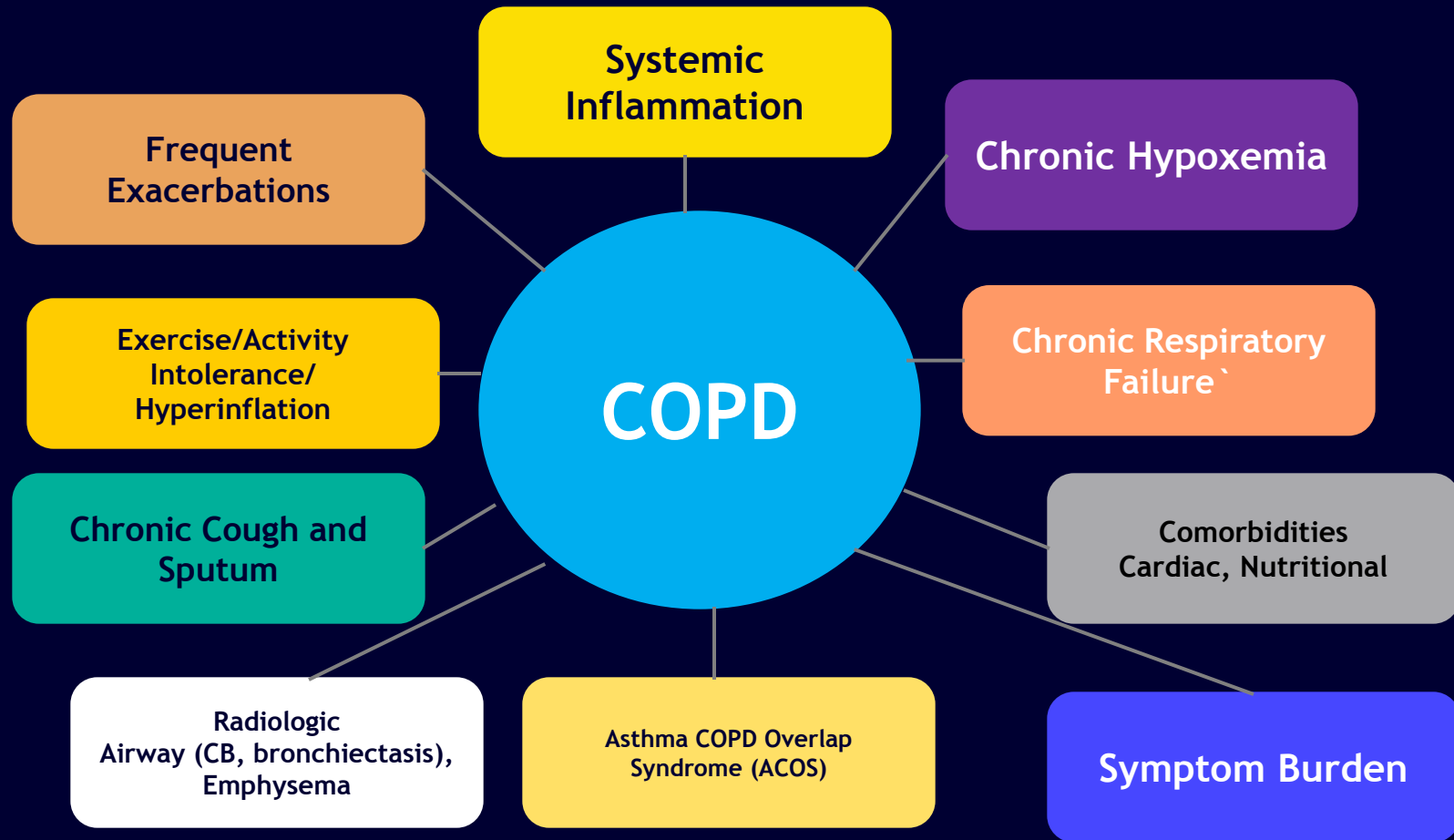
Significant drops in lung function often required for patients to become severely symptomatic





# Diagnostic Challenges: COPD Phenotypes

Disease attributes that describe the diverse symptoms and outcomes of patients



# Patient-Related Diagnostic Challenges

- Patients lack of awareness of the disease
- Patients under-report symptoms
- Symptoms are chronic and slowly progressive, often misattributed to aging
- SOB leads to activity reduction to reduce symptom impact (thus, need to assess level of activity which requires time-consuming focused questions)
- Availability of healthcare resources/insurance issues
- Social stigma of COPD

# Clinician-Related Diagnostic Challenges

- Myths about COPD
- Nihilistic attitude about COPD/Awareness of COPD guidelines suboptimal
- Diagnosis of exclusion and overlap with other diseases
- Underuse and paucity of validated assessment tools
- Inadequate utilization of spirometry

# Global Strategy for Diagnosis, Management, and Prevention of COPD: Assessment of COPD

1. Assess symptoms
2. Assess degree of airflow limitation using spirometry
3. Assess risk of exacerbations

# GOLD: Combined COPD Assessment

Assessment Using Symptoms, Breathlessness, Spirometric Classification, and Risk of Exacerbations<sup>a</sup>

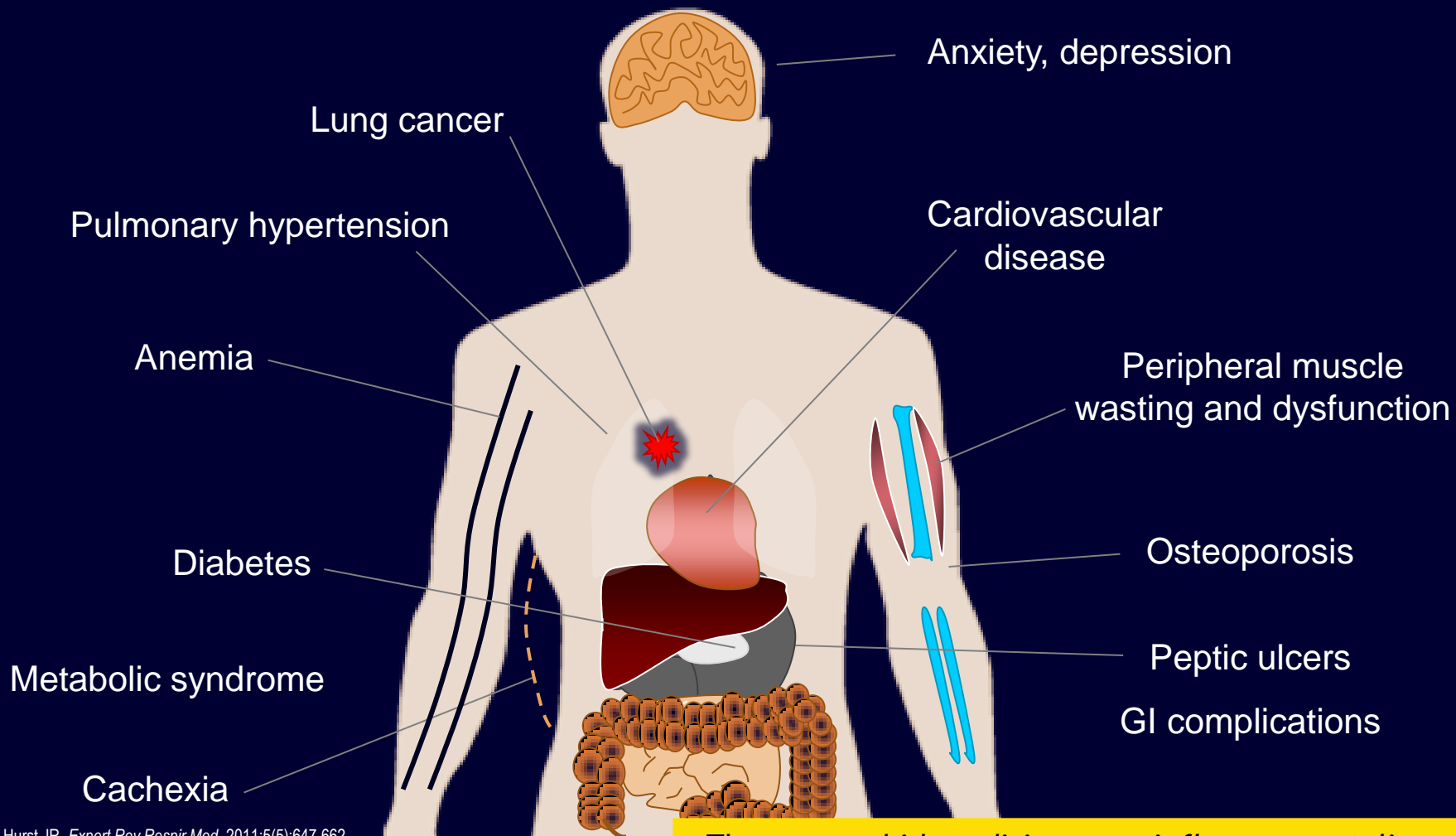
|  |          |                                      |                                      |  |                                     |
|--|----------|--------------------------------------|--------------------------------------|--|-------------------------------------|
| <b>Risk</b><br>(GOLD Classification of Airflow Limitation) | <b>4</b> | <b>C</b><br>High risk, Less symptoms | <b>D</b><br>High risk, More symptoms | <b>≥2</b><br>or<br><b>≥1</b> leading to hospital admission<br><b>1</b> (not leading to hospital admission)<br><b>0</b> | <b>Risk</b><br>(Exacerbations/Year) |
|  | <b>3</b> |                                      |                                      |  |                                     |
|  | <b>2</b> | <b>A</b><br>Low risk, Less symptoms  | <b>B</b><br>Low risk, More symptoms  |  |                                     |
|  | <b>1</b> |                                      |                                      |  |                                     |
|  |          | <b>CAT &lt; 10</b> <b>CAT ≥ 10</b>   |                                      |  |                                     |
|  |          | <b>Symptoms</b>                      |                                      |  |                                     |
|  |          | <b>mMRC 0-1</b> <b>mMRC ≥ 2</b>      |                                      |  |                                     |
|  |          | <b>Breathlessness</b>                |                                      |  |                                     |

<sup>a</sup> When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.

# Global Strategy for the Diagnosis, Management, and Prevention of COPD: Assessment of COPD

1. Assess symptoms
2. Assess degree of airflow limitation using spirometry
3. Assess risk of exacerbations
4. Assess comorbidities

# Comorbidities of COPD



*These comorbid conditions may influence mortality and hospitalizations; the patient should be assessed for them routinely and treated appropriately.*

Patel AR, Hurst JR. *Expert Rev Respir Med.* 2011;5(5):647-662.

Sinden NJ, Stockley RA. *Thorax.* 2010;65(2):43-57.

Chatila WM, et al. *Proc Am Thorac Soc.* 2008;5:549-555.

Watz H, et al. *Chest.* 2009;136:1039-1046.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2009. [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report2014\\_Feb07.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf).

# Improving Outcomes in COPD

- Early diagnosis and accurate assessment<sup>1</sup>
- Implementing optimal management<sup>2</sup>

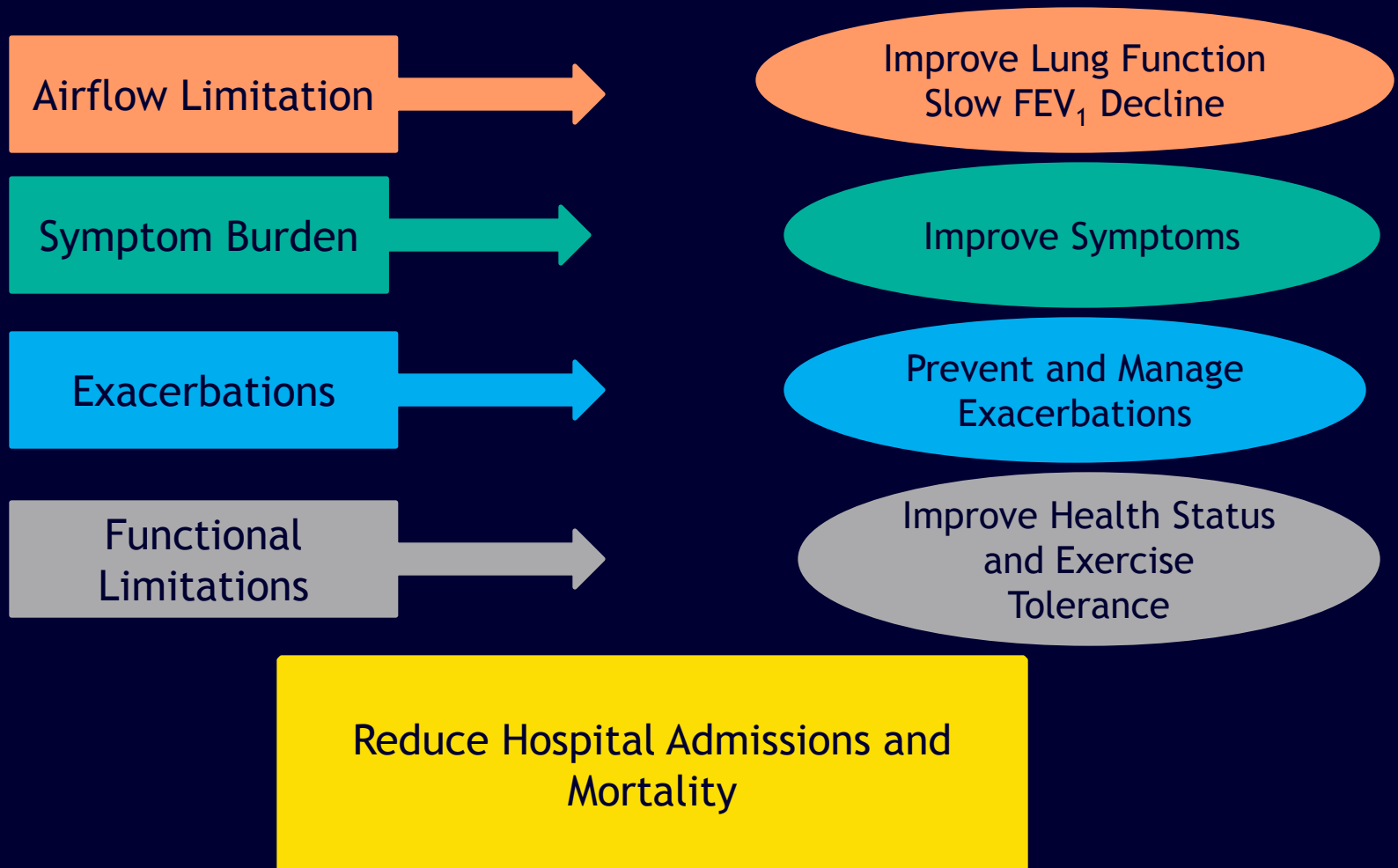
1. Decramer M, et al. *Respir Med*. 2011;105(11):1576-1587.

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. Updated 2009.

[http://www.goldcopd.org/uploads/users/files/GOLD\\_Report2014\\_Feb07.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf).



# Goals of Management



# Nonpharmacologic Therapy To Manage COPD

**Smoking Cessation**



**Patient Education**



**Vaccination**



**Oxygen Therapy**



**Pulmonary Rehabilitation**



**Surgical and Non-surgical Alternatives**



# Nonpharmacological Options for COPD

| Patient Group                 | A<br>Low risk,<br>fewer symptoms  | B<br>Low risk,<br>more symptoms                      | C<br>High risk,<br>fewer symptoms                      | D<br>High risk,<br>more symptoms                      |
|-------------------------------|---|--|--|---|
| Description                   | GOLD 1-2<br>≤1 Exacerbation<br>mMRC 0-1 or<br>CAT <10   | GOLD 1-2<br>≤1 Exacerbation<br>mMRC ≥2 or<br>CAT >10 | GOLD 3-4<br>≥2 Exacerbations<br>mMRC 0-1 or<br>CAT <10 | GOLD 3-4<br>≥2 Exacerbations<br>mMRC ≥2 or<br>CAT >10 |
| Essential                     | <p>Smoking cessation for all patients who smoke</p> <ul style="list-style-type: none"> <li>• The key intervention for smokers</li> <li>• Can include pharmacologic treatment</li> </ul> |  |  |   |
| Recommended                   | Pulmonary rehabilitation  |  |  |   |
| Depending on local guidelines | <p>Physical activity</p> <p>Influenza vaccination<br/>Pneumococcal vaccination</p>  |  |  |   |

# Smoking Cessation

- Ask about tobacco use
- Advise to quit
- Assess willingness to make an attempt
  - Motivational intervention
- Assist in quit attempt
- Arrange follow-up
- Smoking status and willingness to quit assessed at every health visit
- Individual readiness to quit is variable
  - May be related to acute health care events
- Exploit windows of opportunity
  - Acute health problems are associated with increasing cessation rates

# Pharmacologic Therapy: First Line

- NRT, bupropion and varenicline are superior to placebo
- Bupropion and NRT show equal efficacy when compared head to head
  - Bupropion has not been shown to enhance the effect of NRT compared with NRT alone
- Varenicline is superior to bupropion and single forms of NRT
  - Varenicline is not more effective than combination NRT

# Pharmacologic: Alternative Therapy

- Second line (off label use) but have documented efficacy and are recommended as alternative therapies
  - Nortriptyline
    - Nortriptyline did not enhance the effect of NRT compared with NRT alone
  - Clonidine
    - Clonidine increased the chances of quitting, but this was offset by a dose-dependent rise in adverse events
- Nonpharmacologic options
  - Acupuncture (effects due to positive expectations )
  - Hypnosis (no common technique to analyze)

# E-Cigarettes

- Rationale behind E-cigarettes
  - Cigarette smoke contains up to 7000 chemicals
  - Nicotine is not among the most important toxic compounds
  - Nicotine replacement using a preparation that does not contain the health-compromising toxins
- Harm reduction - supporting an addiction
  - Nicotine delivery is unregulated
  - Contain flavorants and other additives whose effects are unknown
  - Concern many smokers who would have quit switch to E-cigarettes
  - Some persons may start e-cigarettes because of perceived safety
    - After becoming addicted may be at higher risk to switch to conventional cigarettes

# Defining Pulmonary Rehabilitation: Official ATS/ERS Statement

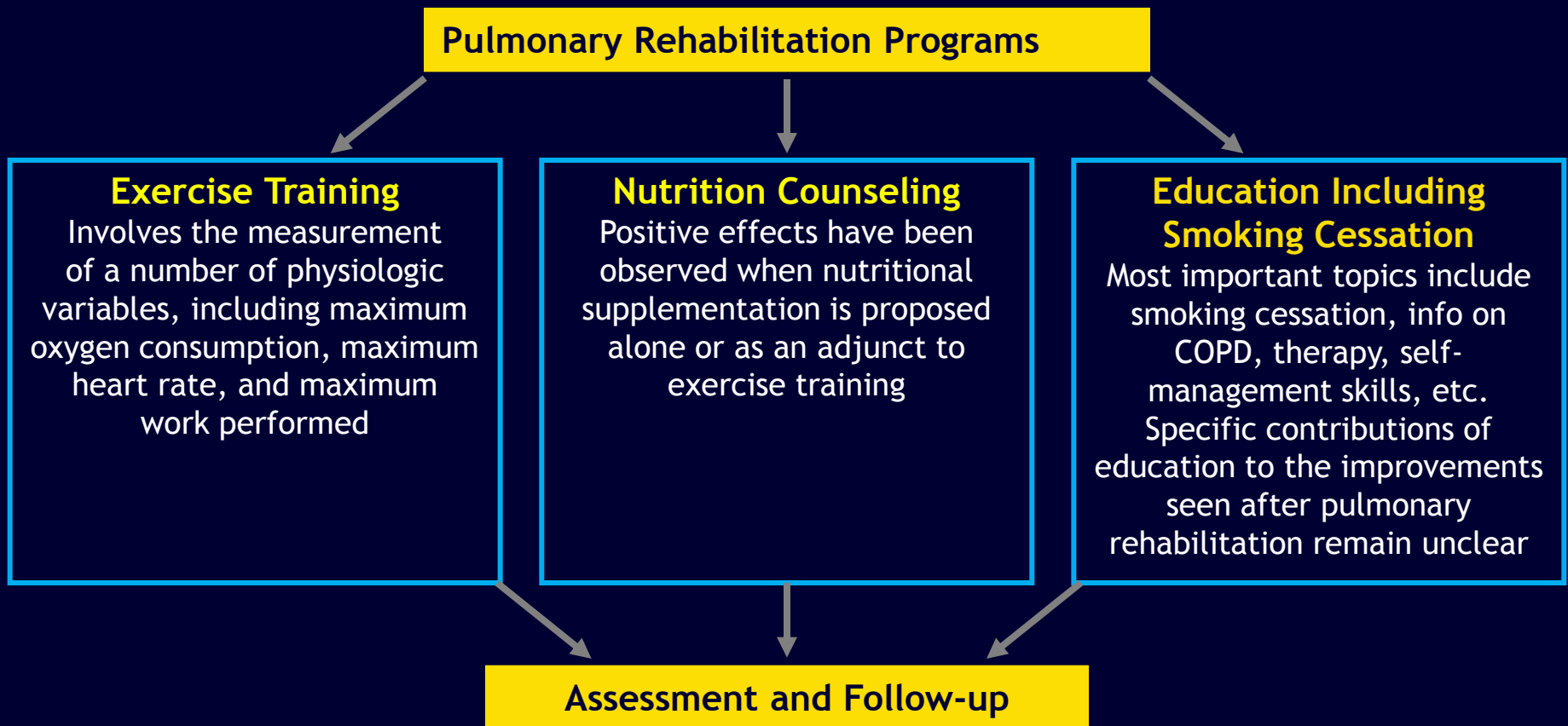
“Pulmonary rehabilitation is a **comprehensive intervention** based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, **exercise training, education, and behavior change**, designed to improve the **physical and psychological** condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.”

ATS = American Thoracic Society; ERS = European Respiratory Society

Spruit MA, et al. *Am J Respir Crit Care Med*. 2013;188(8):e13-64.



# Components of Pulmonary Rehabilitation Programs



# Pharmacological Management of COPD

- Guideline-recommended COPD treatment
  - Improves lung function
  - Minimizes symptoms
  - Improves QoL
  - Prevents exacerbations
- Wide variety of options including new agents
  - Appropriate treatment selection hinges on GOLD staging
  - Before stepping up/modifying treatment, re-evaluate
    - Treatment goals
    - Clinical phenotype
    - Comorbidities
    - Adherence

# Rationale for Early Treatment in COPD

- The effect of treatment on lung function may be more marked in patients who are younger and in those with less severe disease<sup>1-4</sup>
- Lung function deteriorates more rapidly during the less severe, early stages of COPD<sup>3</sup>
- LABA and LAMA are recommended initial maintenance therapy for patients who are symptomatic but at low risk of exacerbations<sup>5</sup>
- Lack of data in treatment-naïve patients with mild or moderate airflow limitation<sup>1</sup>

# COPD Pharmacological Agents Approved

## Bronchodilators

### Short-acting

#### $\beta$ -Agonists (SABA)

Albuterol  
Pirbuterol  
Levalbuterol

#### Anticholinergic (SAMA)

Ipratropium

### Long-acting

#### $\beta$ -Agonists (LABA)

Salmeterol  
Formoterol  
Arformoterol  
Indacaterol  
Olodaterol

#### Anticholinergic (LAMA)

Tiotropium  
Aclidinium  
Umeclidinium

#### LABA +LAMA

Umeclidinium +Vilanterol  
Tiotropium +Olodaterol

#### Theophylline

## Anti-Inflammatory

### ICS+LABA

Fluticasone + Salmeterol  
Budesonide +Formoterol  
Fluticasone Fuorate +Vilanterol

### PDE-4 Inhibitors

Roflumilast

### Systemic Steroids

Prednisone  
Methylprednisolone

# COPD Pharmacological Treatment Options

|                    | A  | B                             | C  | D             |
|--------------------|--|-------------------------------|--|---------------|
| First Choice       | Short-acting<br>(SAMA OR SABA)                                       | Long-acting<br>(LAMA OR LABA) | LAMA<br>OR<br>ICS + LABA   |               |
| Second Choice      | Long-acting<br>(LAMA OR LABA)<br>OR<br>Short-acting<br>(SAMA + SABA) | Long-acting<br>(LAMA + LABA)  | Combinations of:<br>• LAMA<br>• LABA<br>• ICS<br>• PDE4 Inhibitor* |               |
| Alternative Choice | Theophylline   |                               |  |               |
|                    |  |                               | Short-acting<br>(SAMA +/-OR SABA)                                  |               |
|                    |  |                               | PDE4 Inhibitor*  | Carbocysteine |

Adapted from: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2011.

## Many Patients Remain Symptomatic on “Mono-Bronchodilator” Therapy

- A significant proportion of patients with COPD remain symptomatic when receiving a single bronchodilator<sup>1</sup>

*Current guidelines recommend adding a second bronchodilator to treatment regimens in moderate COPD to optimize symptom benefit for patients<sup>2</sup>*

- Combining bronchodilators of different pharmacologic classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator<sup>2</sup>
- As airflow obstruction becomes more severe, a LAMA plus a LABA combination has been advocated<sup>3</sup>

# Improving Outcomes in COPD

- Early diagnosis and accurate assessment<sup>1</sup>
- Implementing optimal management<sup>2</sup>
- Incorporating self-management skills through education and collaboration with a healthcare team<sup>3</sup>

1. Decramer M, et al. *Respir Med*. 2011;105(11):1576-1587.

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. [www.goldcopd.org](http://www.goldcopd.org)

3. Rice K, et al. *Clin Chest Med*. 2014;35(2):337-351

# Patient Education: Key Educational Messages for COPD

- Basic facts about COPD
  - Contrast normal and COPD airways
- Roles of medications and potential adverse events
  - Long-term maintenance and quick-relief medications
- Relevant environmental triggers and reducing exposures
- Building an action plan: when and how to take rescue actions
- Skills
  - Inhalers, nebulizers, spacers, symptoms, and early warning signs



# Adherence to COPD Medications Is Poor

- More than half of patients with COPD will stop new prescriptions after the first month<sup>1</sup>
- Sustained adherence continues to decay over time<sup>1</sup>
- Strategies to support adherence
  - Educate patients about COPD and treatments<sup>2</sup>
  - Set treatment goals<sup>2</sup>
  - Urge patients to complete treatment course<sup>2</sup>
  - Train patients on proper use of devices periodically<sup>2</sup>
  - Support self-efficacy; encourage and praise success<sup>3</sup>
  - Ask about side effects<sup>2</sup>
  - Ask about device preference<sup>4</sup>

1. Bender B et al. *J Allergy Clin Immunol.* 2006;118(4):899-904.

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. [www.goldcopd.org](http://www.goldcopd.org)

3. Cecere LM et al. *COPD* 2012;9:251-258

4. Dolovich MD, et al. *CHEST* 2005;127:335-371.

# Inhaler Devices Available in the U.S.



**A large proportion (49-76%) of patients use their inhalers incorrectly**  
GOLD guidelines recommend rechecking inhaler technique at each patient visit

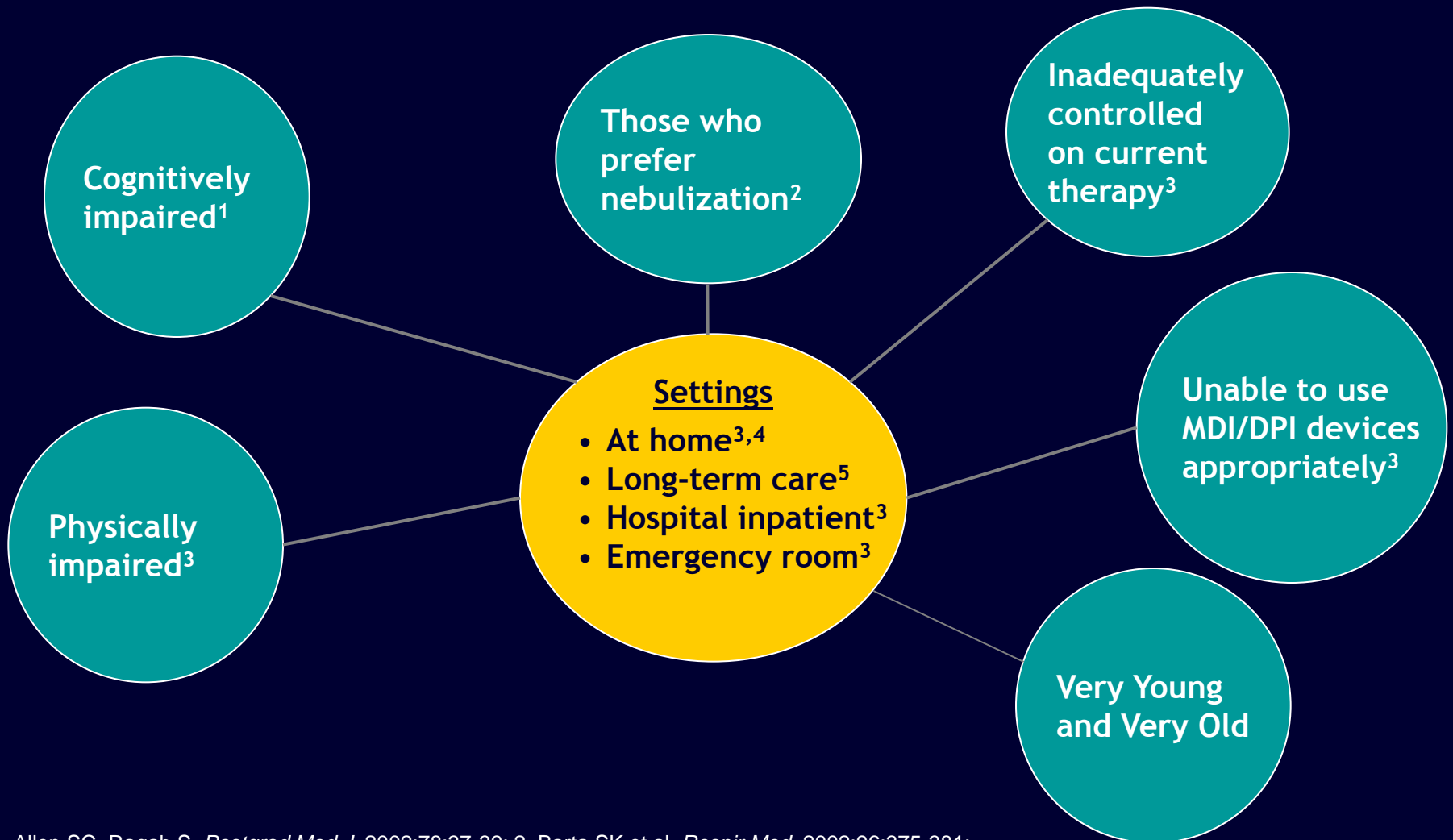


1. Newman SP. *Eur Respir Rev.* 2005;14:96,102-108.

2. Molimard M, et al. *J Aerosol Med.* 2003;16(3):249-54.

3. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2011

# Nebulization Has a Role for Many Patients and in Multiple Settings



1. Allen SC, Ragab S. *Postgrad Med J.* 2002;78:37-39; 2. Barta SK et al. *Respir Med.* 2002;96:375-381;

3. Dolovich MB et al. *Chest.* 2005;127:335-371; 4. American Thoracic Society. *Am J Respir Crit Care Med.* 2005;171:1443-1464; 5. American Medical Directors Association. *COPD Management in the Long-Term Care Setting.* Clinical Practice Guideline. Columbia, MD: AMDA; 2010.

# Unmet Needs With Current Interventions

- Current pharmacotherapies do not change the natural history of COPD<sup>1</sup>
- Many patients remain symptomatic with current therapies<sup>2</sup>
- Inadequate adherence with inhaled therapy is a major cause of poor clinical outcomes in the treatment of COPD<sup>3</sup>
- Cost, compliance, and safety are significant issues<sup>3</sup>

1. Barnes PJ, Stockley RA. *Eur Respir J*. 2005;25:1084-1106.
2. Franssen FM et al. *Int J Chron Obstruct Pulmon Dis*. 2011;6:493-501.
3. Dransfield MT et al. *Prim Care Respir J*. 2011;20:46-53.
4. Restrepo RD et al. *Int J Chron Obstruct Pulmon Dis*. 2008;3:371-384

# Emerging Therapies in COPD Management

- Novel therapies
  - Novel formulations of existing medications
  - Novel classes of bronchodilators
  - Novel targets for pharmacologic therapy

# Novel Formulations of Existing Medications

- Novel Bronchodilators
  - Ultra LABAs
  - Ultra LAMAs
  - LABA/LAMA combinations
  - LABA/ICS combinations
  - Nebulized bronchodilators and combination therapies
  - MABAs

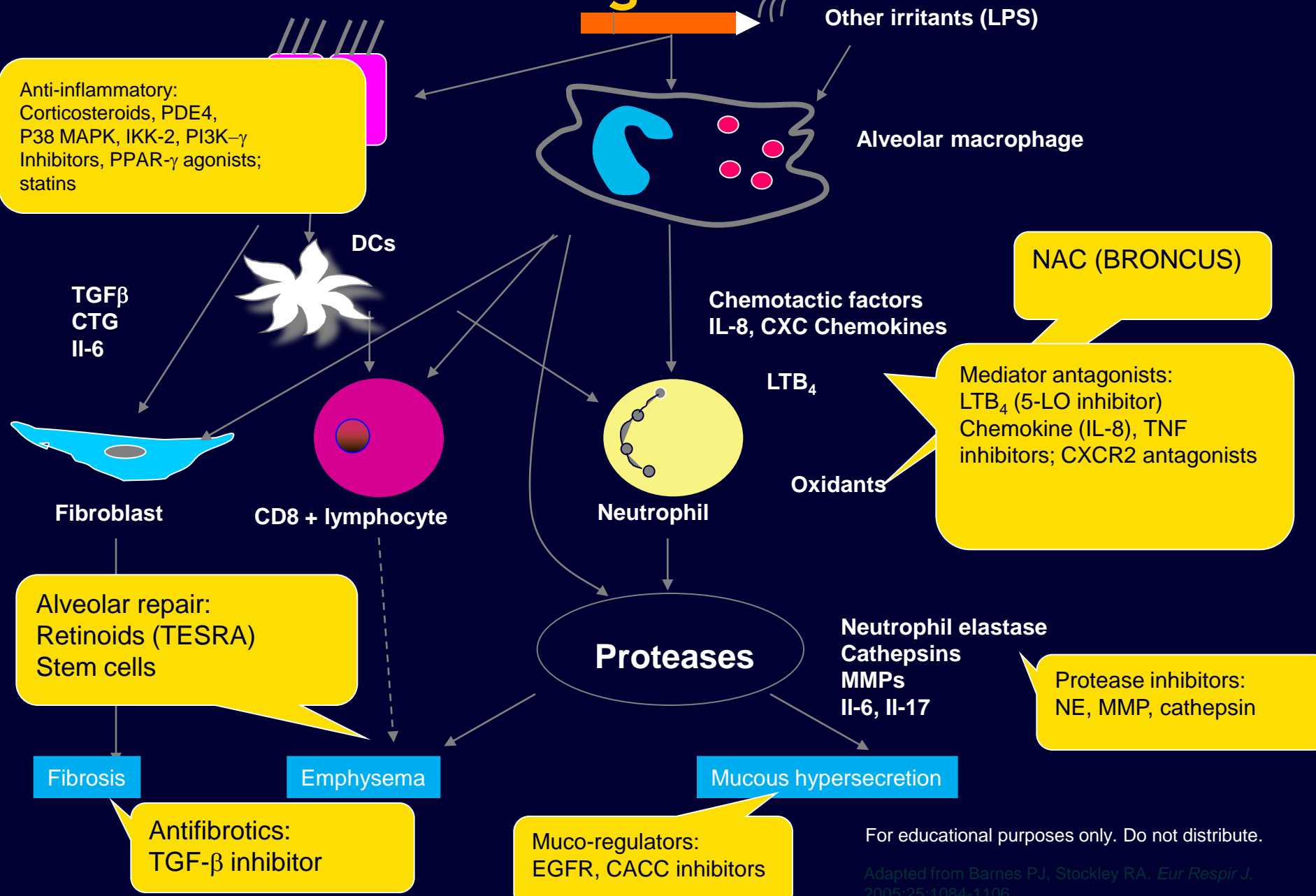
LABA: long acting beta-2 agonists; LAMA: long acting muscarinic antagonist;  
ICS; inhaled corticosteroid; MABA: bifunctional muscarinic beta-2 agonist

Cazzola M, et al. *Pharmacol. Rev.* 2012;64:450-504.

# Drugs Used in Treatment of Comorbidities That May Be Useful in COPD

- Statins
- ACE Inhibitors
- Beta-blockers
- Peroxisome proliferator-activated receptor (PPAR) agonists
- Macrolides

# Novel Targets in COPD



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Adapted from Barnes PJ, Stockley RA. *Eur Respir J.* 2005;25:1084-1106.

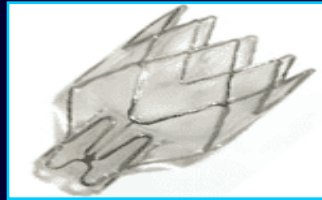


# Bronchoscopic Approaches to LVR

Flow regulation

Zephyr-  
Endobronchial  
Valves (EBV)

PulmonX



One-way valve leads to atelectasis.

Intrabronchial  
Valves (IBV)

Spiration



One-way valve leads to atelectasis.

Tissue compression

RePneu - Lung  
volume reduction  
coil (LVRC)

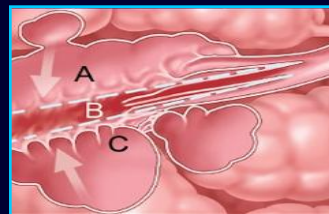
PneumRx



Coil reduces lung volume by coiling and compressing disease tissue.

AeriSeal -  
Polymeric Lung  
Sealant

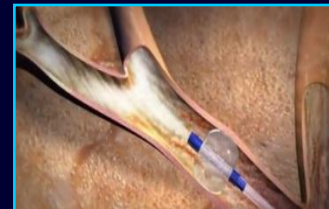
Aeris



Tissue sealant flows into alveolar compartment, polymerizes and seals target area.

InterVapor -  
Bronchoscopic  
Thermal Vapor  
Ablation (BTVA)

Uptake



Heated water vapor produces thermal reaction with localized inflammation followed by fibrosis.

# Summary (1) Improving Outcomes in COPD

- Early diagnosis and accurate assessment
  - Identifying patients at risk
  - Using appropriate diagnostic approaches, ruling out other mimickers
  - Early treatment
- Implementing optimal management
  - Reducing exposures to risk factors and triggers
  - Non-pharmacological approaches
  - Pharmacological treatments
- Incorporating self-management skills through education and collaboration with a health care team
  - Improve adherence

## Summary (2)

- Proper assessment of COPD should include assessment of symptoms, lung function, and exacerbation risk to determine appropriate treatment<sup>1</sup>
- Comorbidities are common and adversely affect outcomes<sup>1</sup>
- Phenotypic characterization of COPD will improve personalized approach to the disease<sup>2</sup>
- Smoking cessation, pulmonary rehabilitation can improve outcomes<sup>1</sup>
- Current and emerging therapeutic combinations may be more effective than monotherapy<sup>1</sup>

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. Updated 2014. <http://www.goldcopd.org>.

2. Chen X et al. *Front. Med.* 2013;7:425-432.