Modern Management of COPD.

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THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

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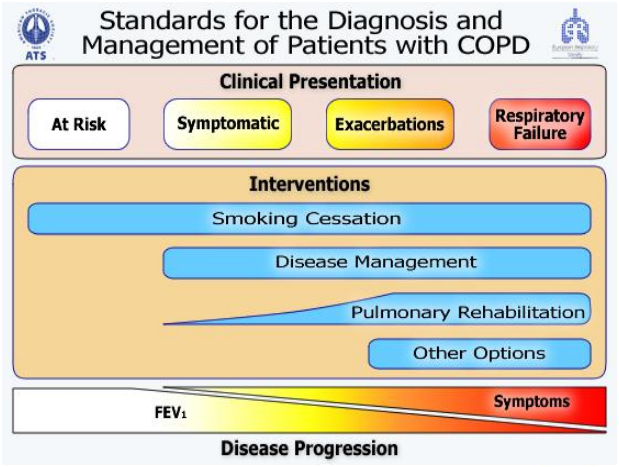
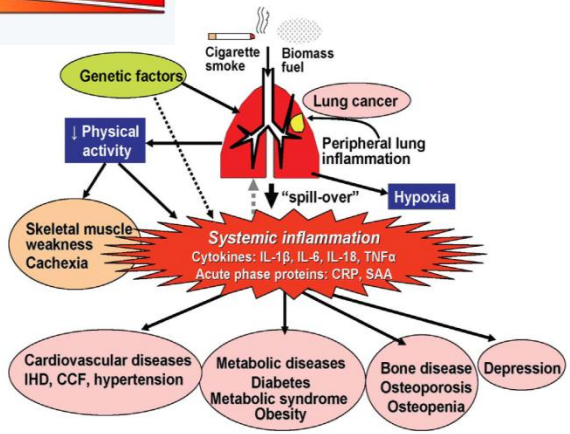
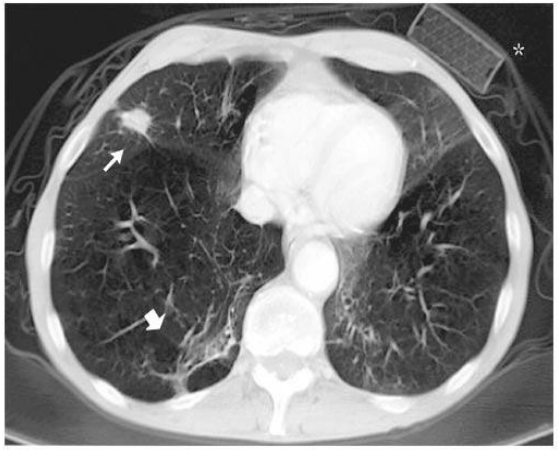






Disclosures: Dr Robert Young

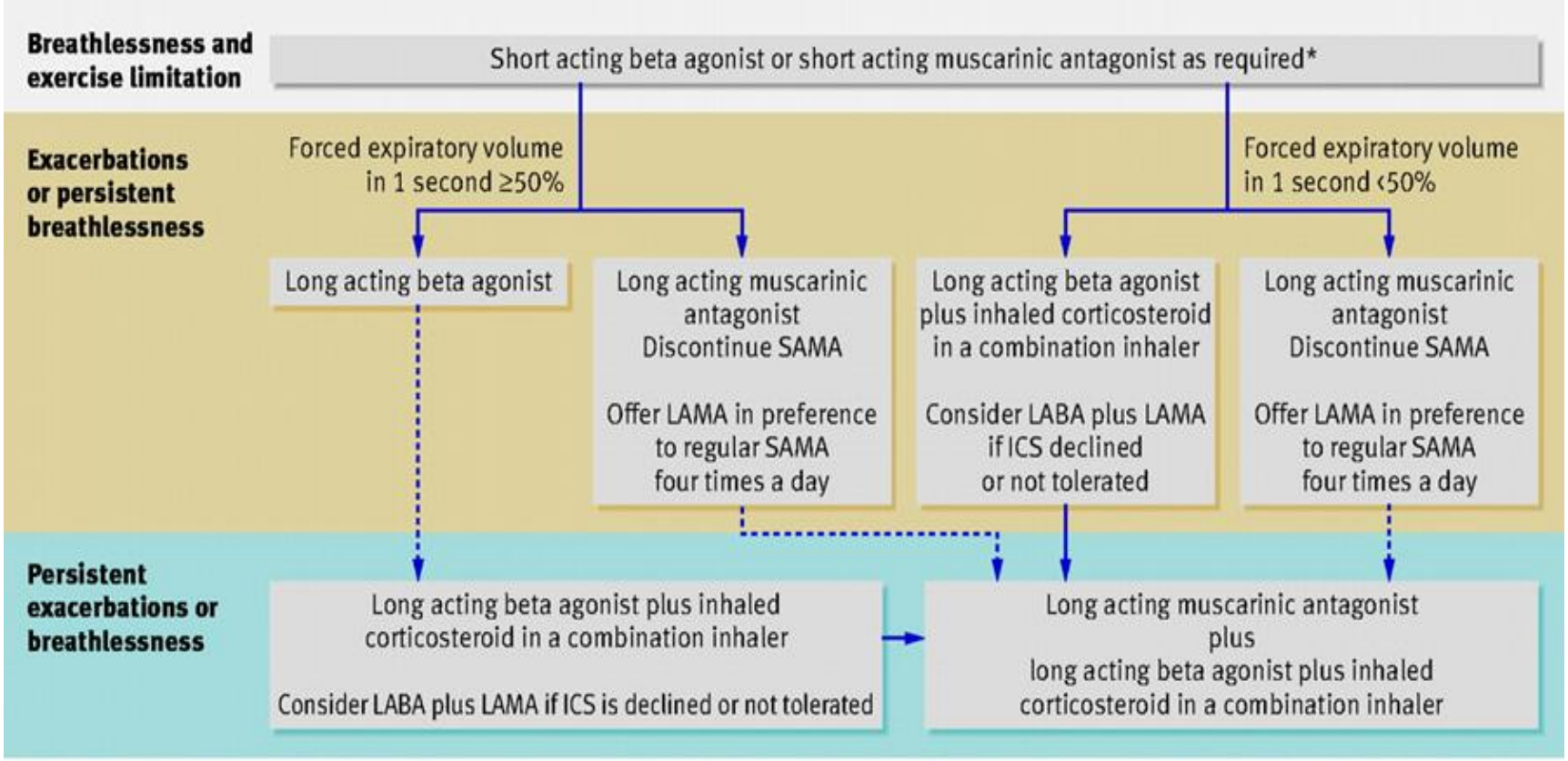
Never received funding
from the tobacco industry

Associate Professor in Medicine
and Molecular Genetics,
University of Auckland, NZ

eceived travel grant and honorarium
for talks on COPD and
smoking cessation from GSK

Chief Scientific Officer of
Synergenz BioScience who
helped fund development of a
lung cancer risk score (Respiragene)

COPD Management - ?confused

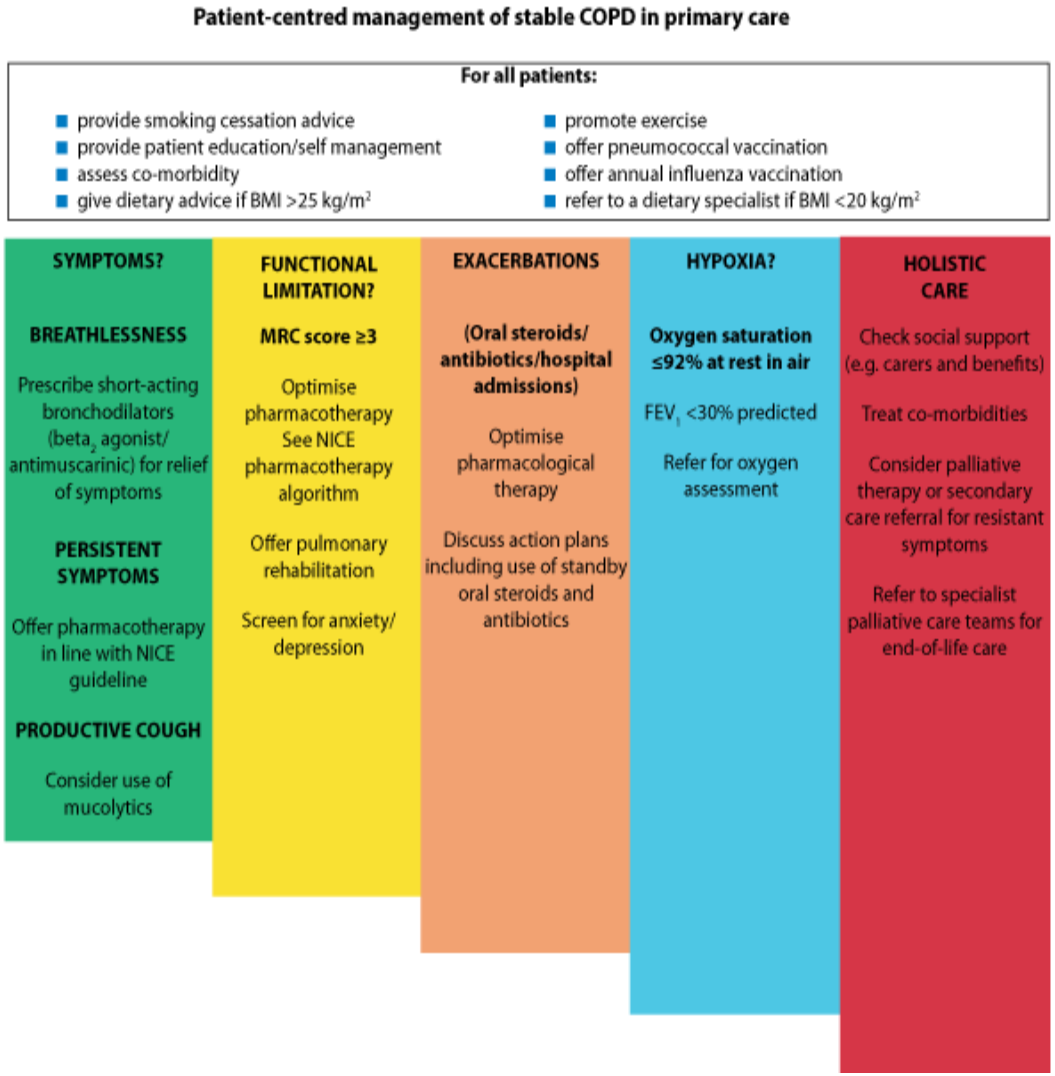


Abbreviations: SAMA = short acting muscarinic antagonist, LAMA = long acting muscarinic antagonist, LABA = long acting beta agonist, ICS = inhaled corticosteroid

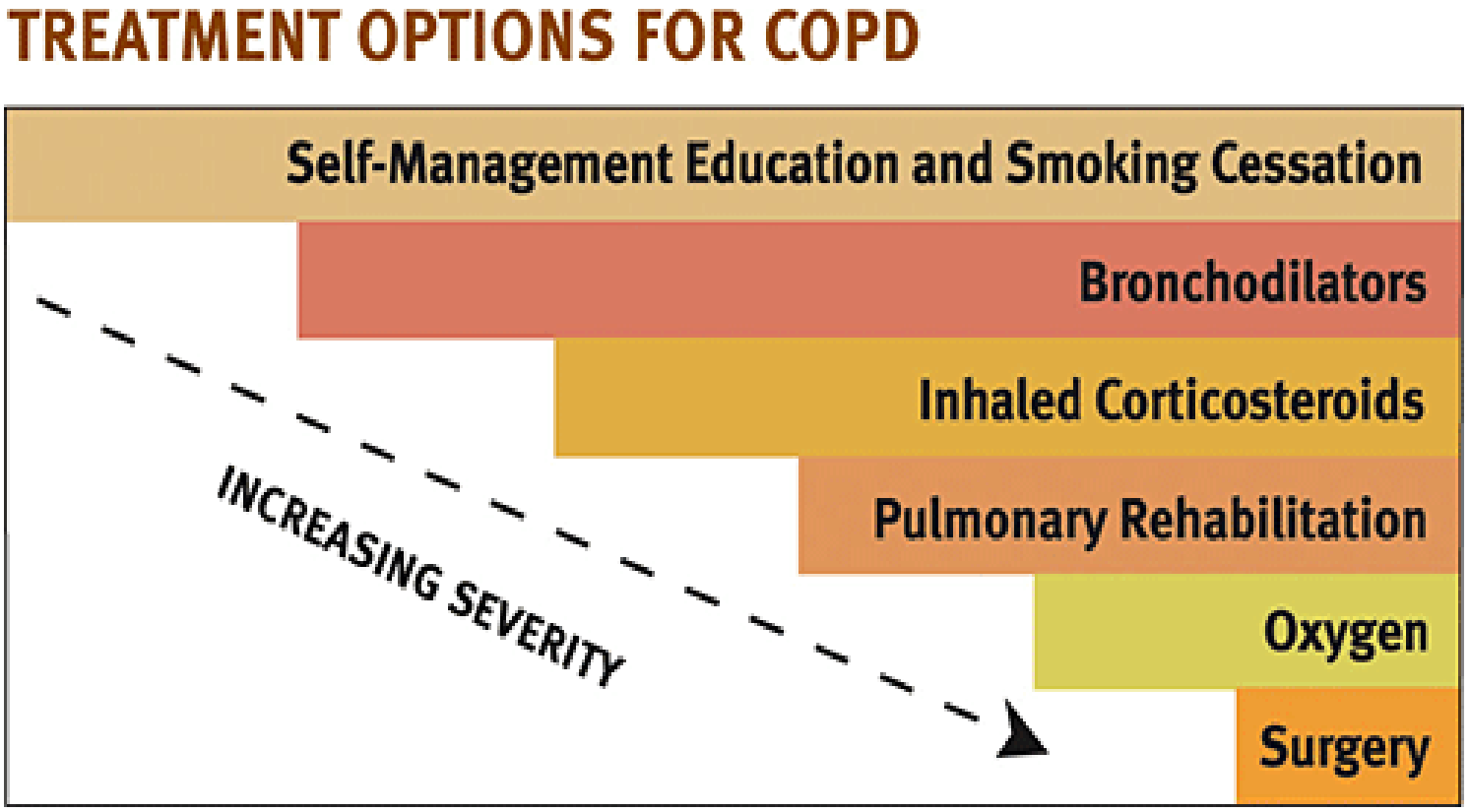
* Short acting beta agonist (as required) may continue at all stages

→ Offer therapy (strong evidence) ⇢ Consider therapy (less strong evidence)

COPD Management - ?confused



COPD - simplified



But how do you define severity?

Topics

1. What is COPD and why diagnose it
2. Treatment options in COPD – a symptom based approach
3. Treatment options in COPD – when to add the inhaled steroids
4. Treatment options – beyond the airways
5. Management options in the future

1. What is COPD and why diagnose it

What is COPD and why diagnose it

- Affects 8% of adult population (1 in 12)
- Affects 20% of adult smokers (1 in 5)
- Affects 30% of adult general medical admissions
- Affects 50% of pneumonia over 65 yrs old

COPD and asthma are very different diseases

COPD health status in New Zealand

- Prevalence COPD
  - 6.6% equivalent to 96,100 adults (formal diagnosis)
- COPD hospitalisation rates
  - 2,021 per 100,000 – Maori
  - 484 per 100,000 – non-Maori
- COPD Mortality rates
  - 129 per 100,000 – Maori
  - 46 per 100,000 – Non-Maori

MOH. A Portrait of Health – Key Results of the 2006/07 NZ Health Survey. Wellington. 2008
MOH. Tatau Kajukura:Maori Health Chart Book 2010. 2nd Ed. Wellington 2010

“COPD is highly prevalent, underdiagnosed, undertreated and underpercieved”

Bart Celli 2008

"COPD is highly prevalent, underdiagnosed, undertreated and underpercieved"

Bart Celli 2008

50-80% of COPD is undiagnosed

Diagnosis and management of COPD

- Diagnose - assess airflow limitation (spirometry, PEFR)
- Assess symptoms (CAT and mMRC score)
- Assess exacerbation risk (PHx of exacerbation, FEV_1%pred)
- Assess COPD comorbidities (anxiety/depression, muscle wasting/fatigue)
- Assess COPD-related comorbidities (CHD/CHF, lung cancer, osteoporosis)
- Manage – reduce risk and reduce symptoms

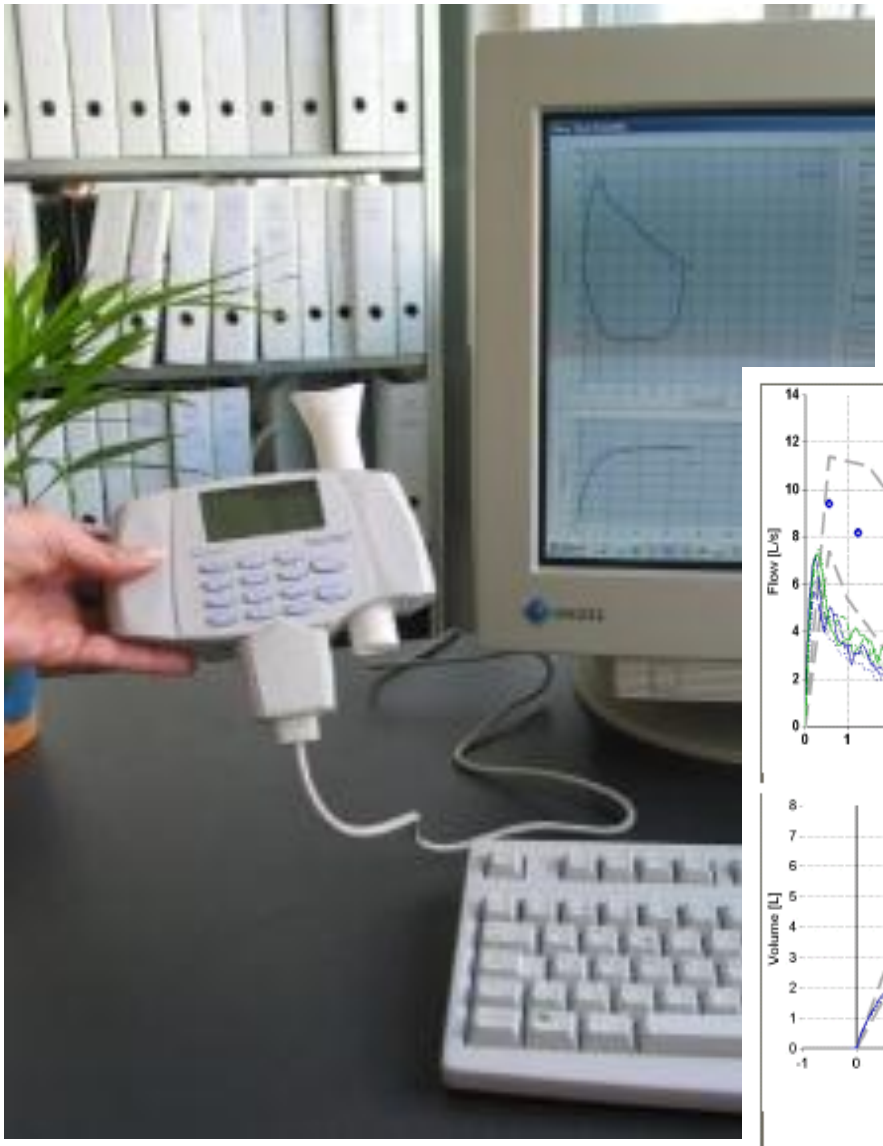
Diagnosis and management of COPD

- Diagnose - n (spirometry, Pl
- Assess syr e)
- Assess risk f exacerbation)
- Assess CC //depression, muscle wastin
- Assess CC s (CHD/CHF, lung cancer, osteoporosis)
- Manage – reduce risk and reduce symptoms

Diagnose

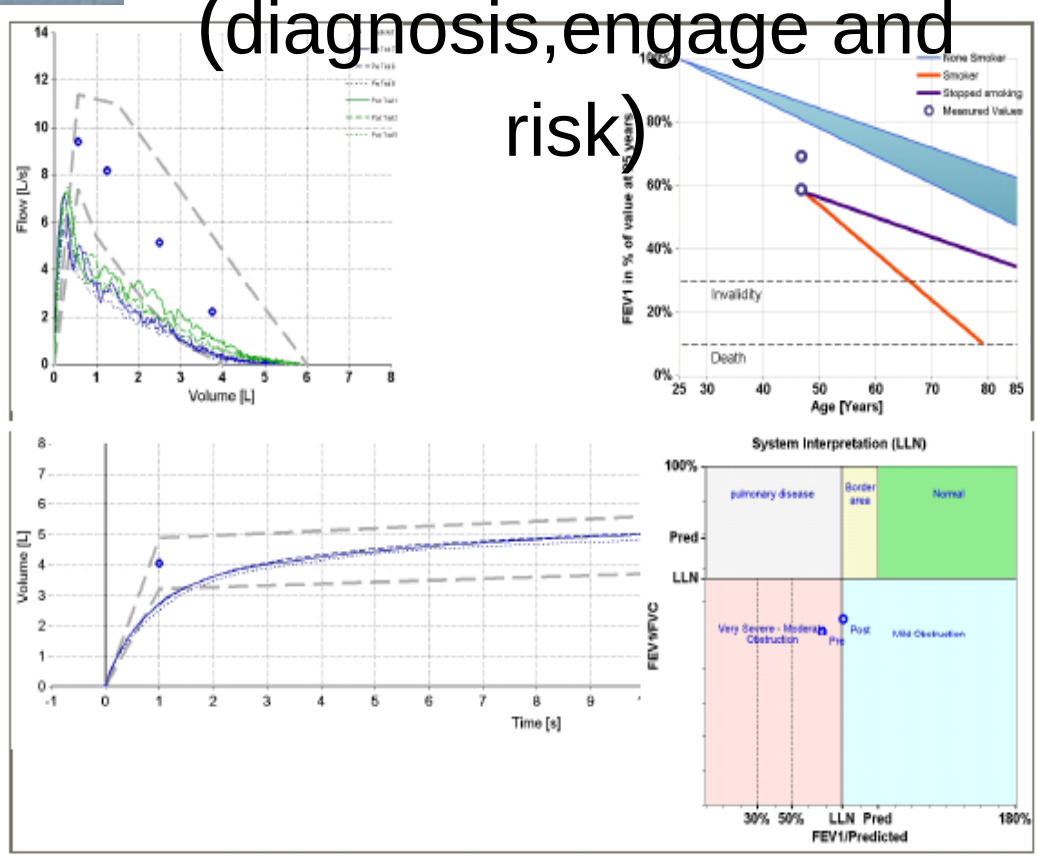
Assess

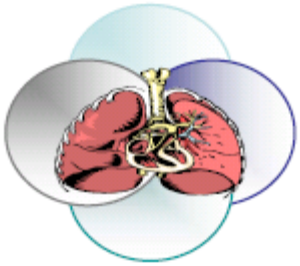
Manage



Diagnosis

Spirometry and lung age (diagnosis,engage and risk)





Lung Health Clinic (Auckland)

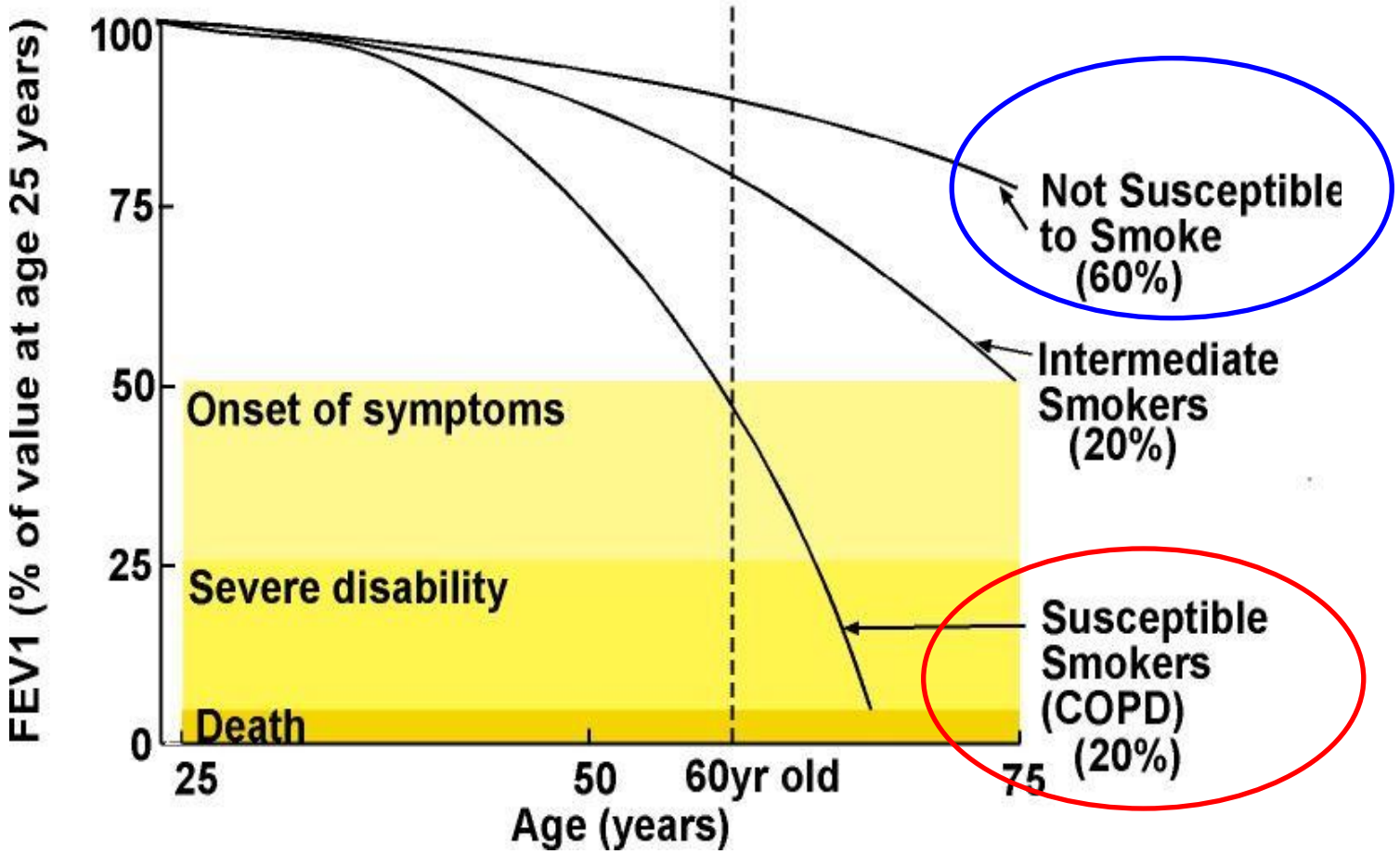
Contact us: Ph 0800 789999 or 09 630 9967 or Fax 09 623 6456
or email: lunghealthclinic@adhb.govt.nz

For assessment of patients with breathlessness or suspected of asthma or COPD (especially those exposed to smoking or aero-pollutants).

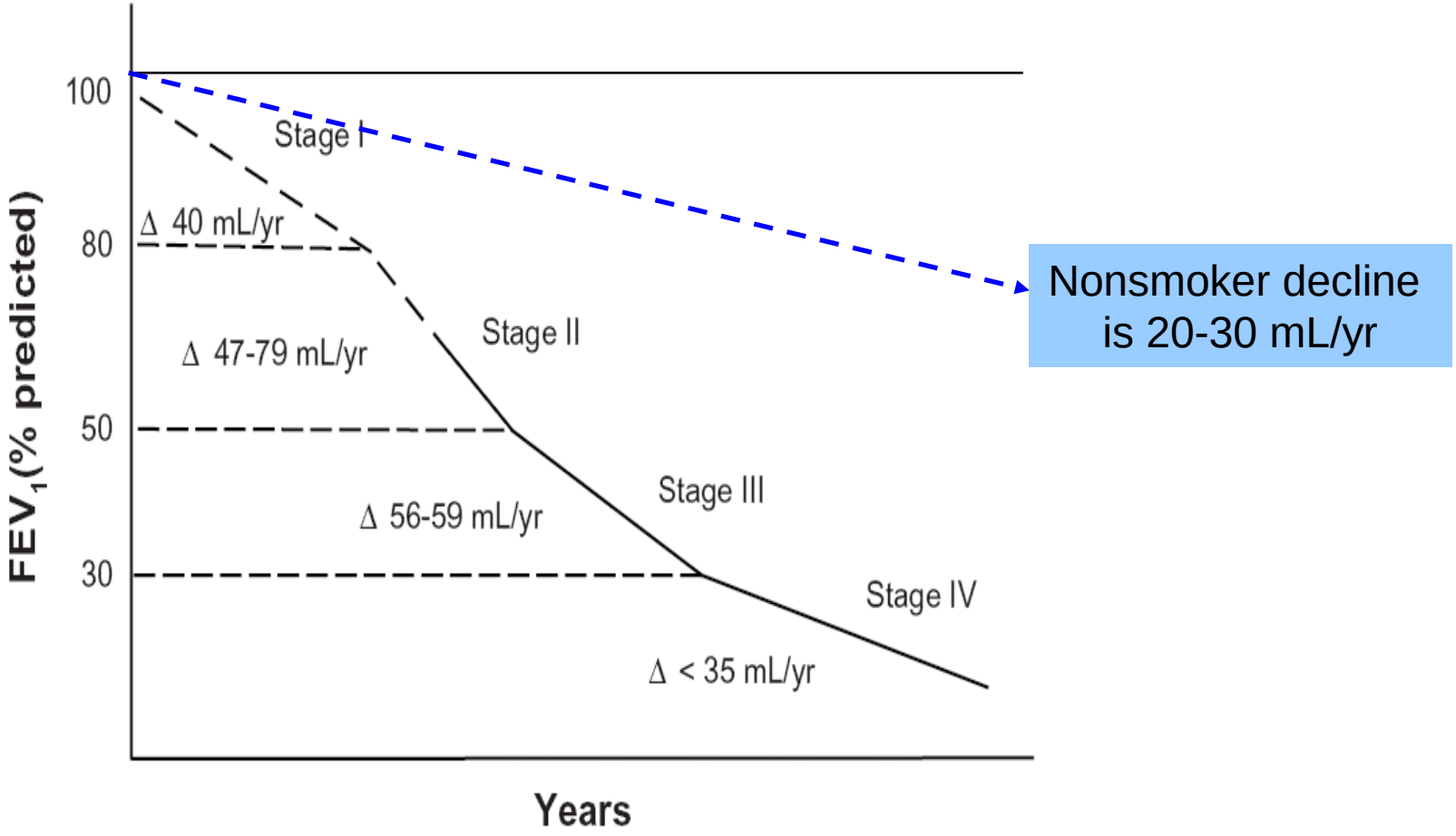
For lung function testing, medication review, smoking cessation, inhaler technique, COPD unresponsive to treatment and lung cancer screening.

Refer your patient for a personal consultation with **Raewyn Hopkins** (BN, MPH) or **Associate Professor Robert Young**, Consultant Physician (FRACP, PhD)

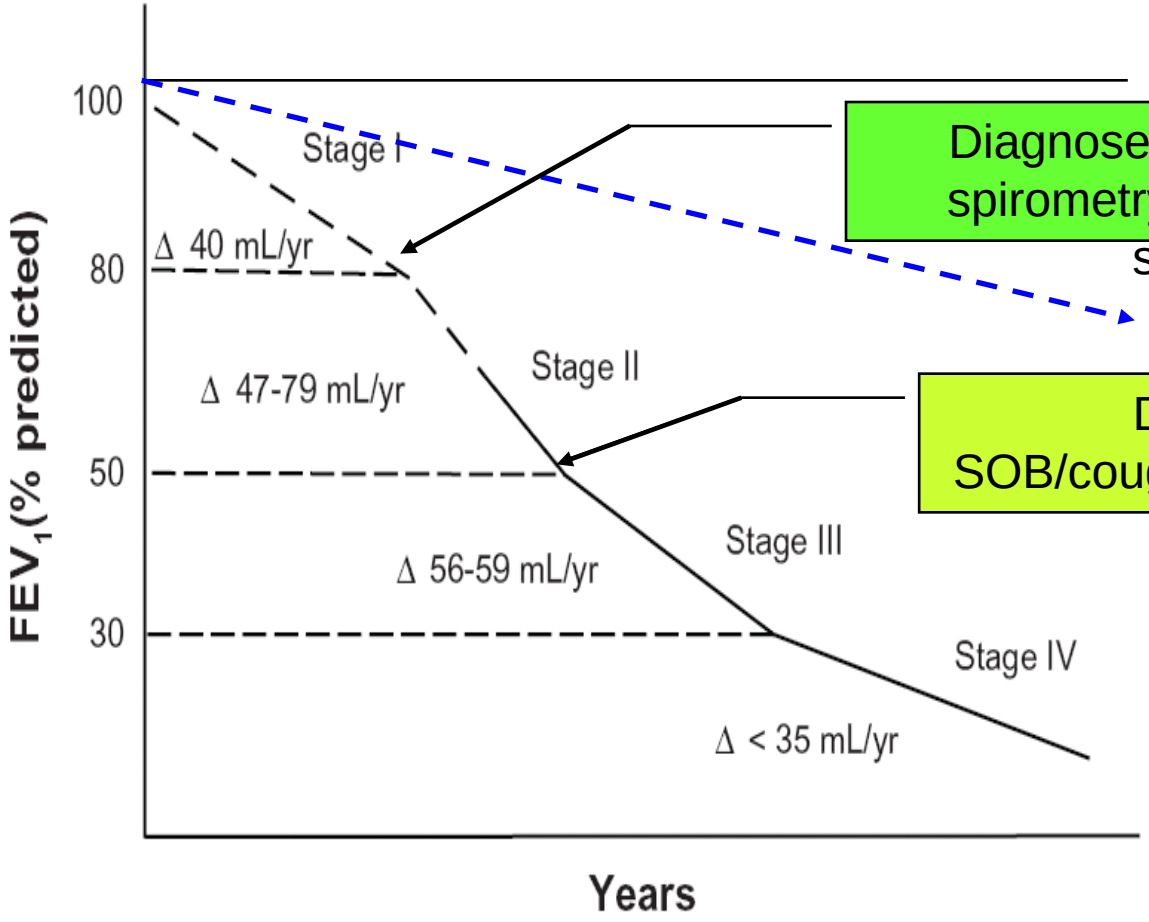
Decline of Lung Function: variable susceptibility



Decline in lung function with COPD severity



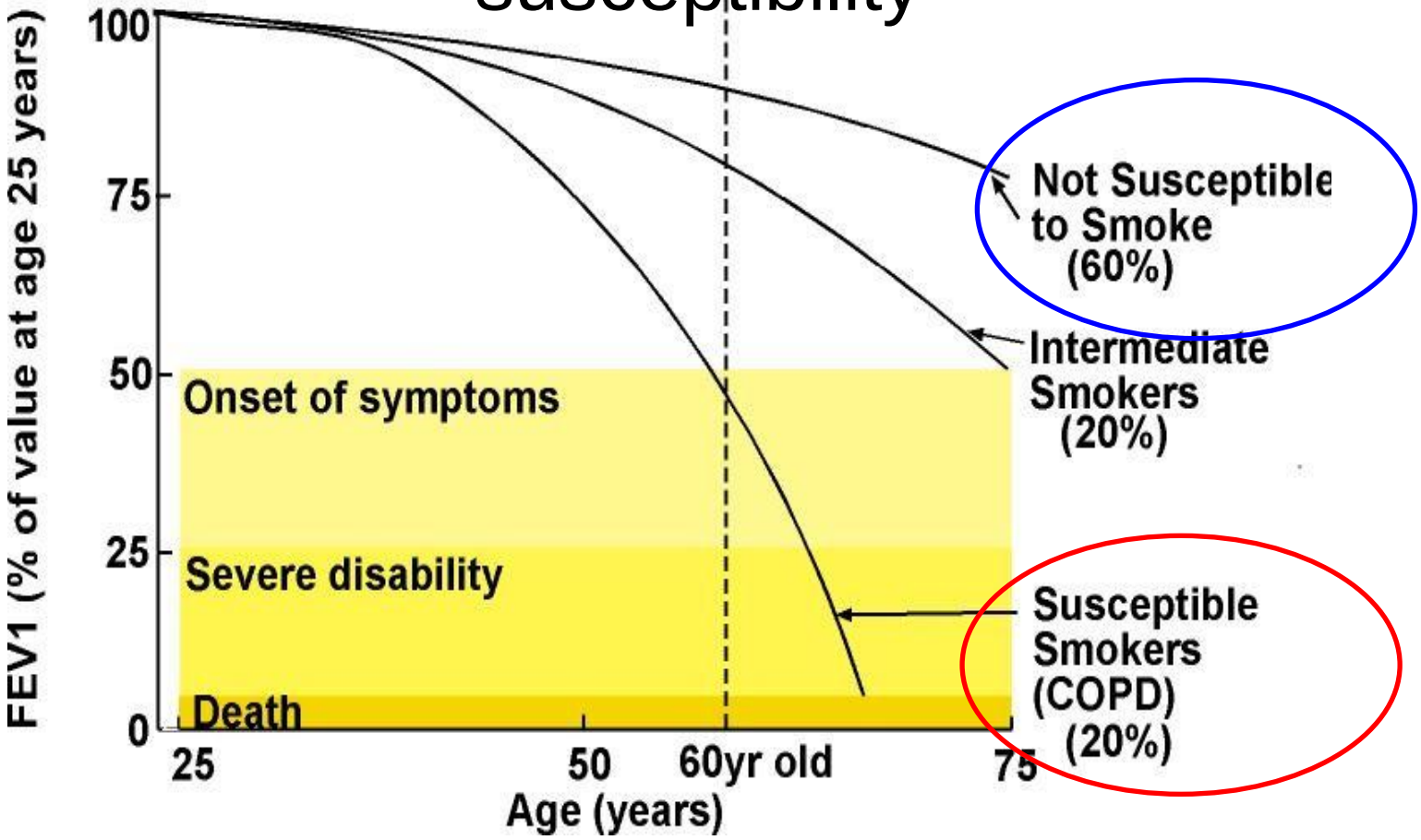
Decline in lung function with COPD severity



Diagnosed with screening spirometry of smokers/ex-smokers

Diagnosed with SOB/cough/sputum and wheeze (AECOPD)

Decline of Lung Function: variable susceptibility



↓FEV1: other morbidities apart from COPD

- 5x ↑Lung cancer

-5x ↑ heart attack

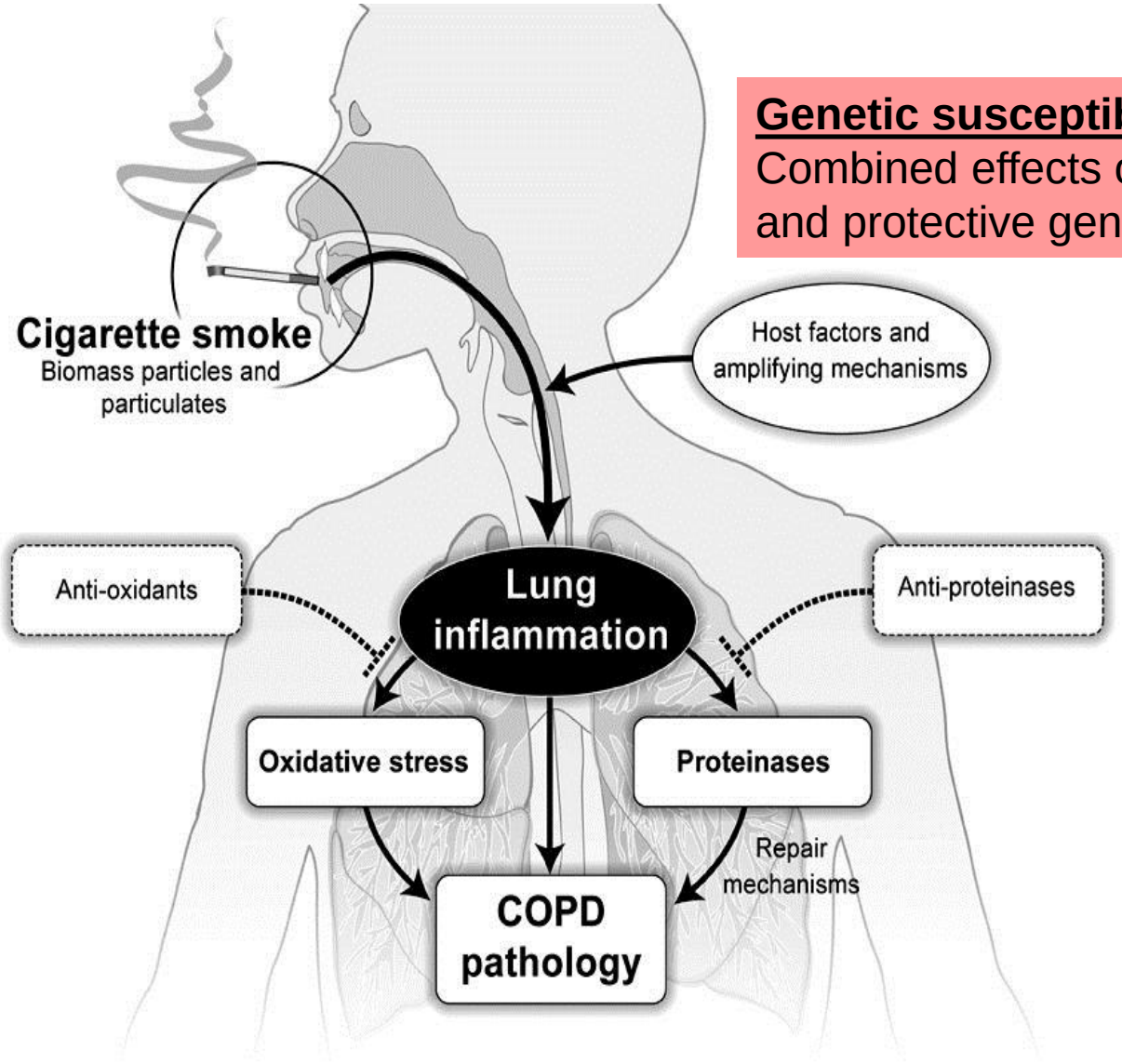
- 2-3x ↑ stroke (Young et al. ERJ 2007)

What is COPD and why diagnose it

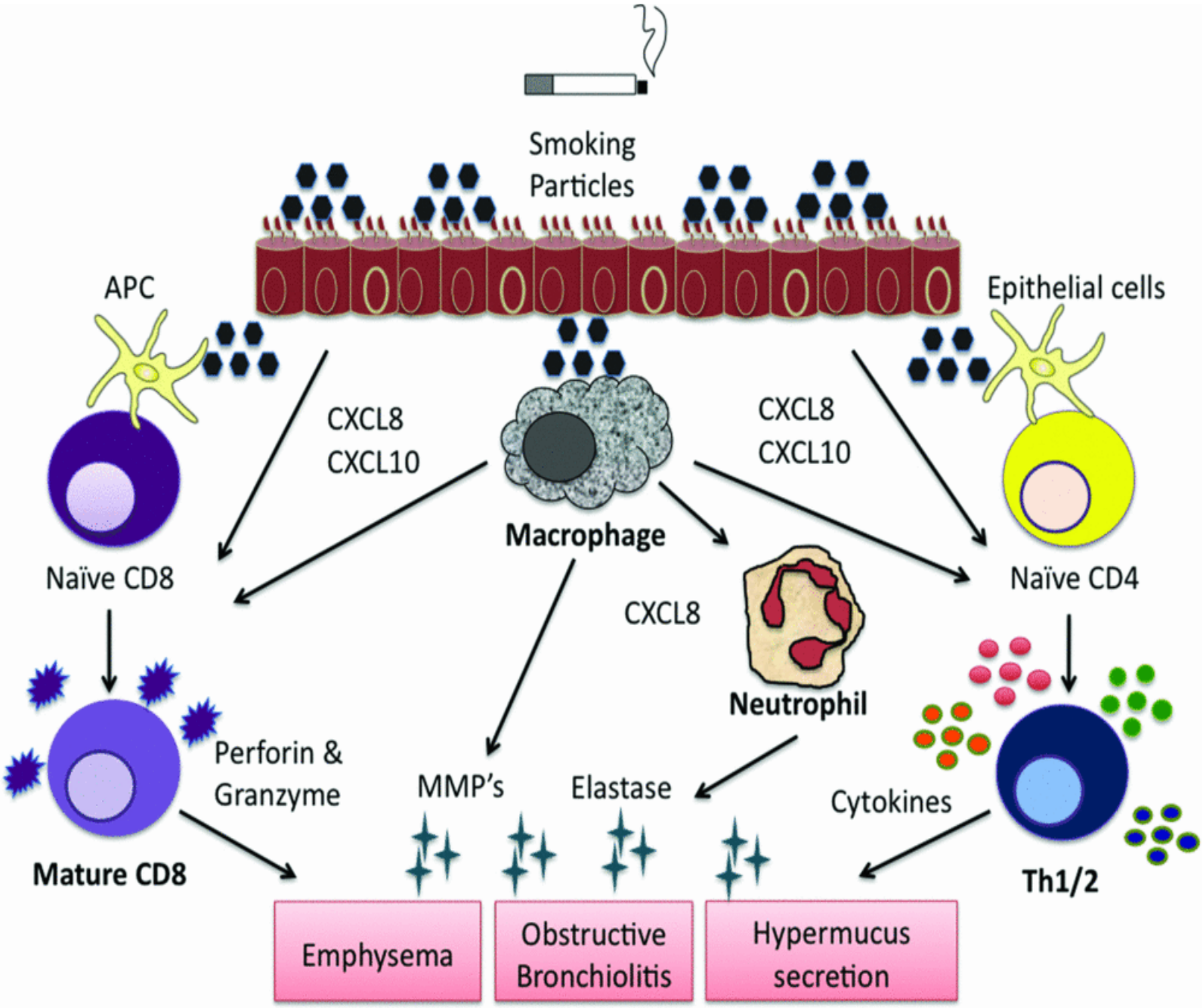
- Results from genetic susceptibility and aero-pollutant (smoking) exposure
- Neutrophilic airway inflammation
- Presents with
  - exertional breathlessness and LRTI (cough, sputum, wheeze and SOB)
  - Fatigue and poor exercise tolerance
- Systemic inflammation and co-morbidities
- Precursor illness to 70-80% of all lung cancer

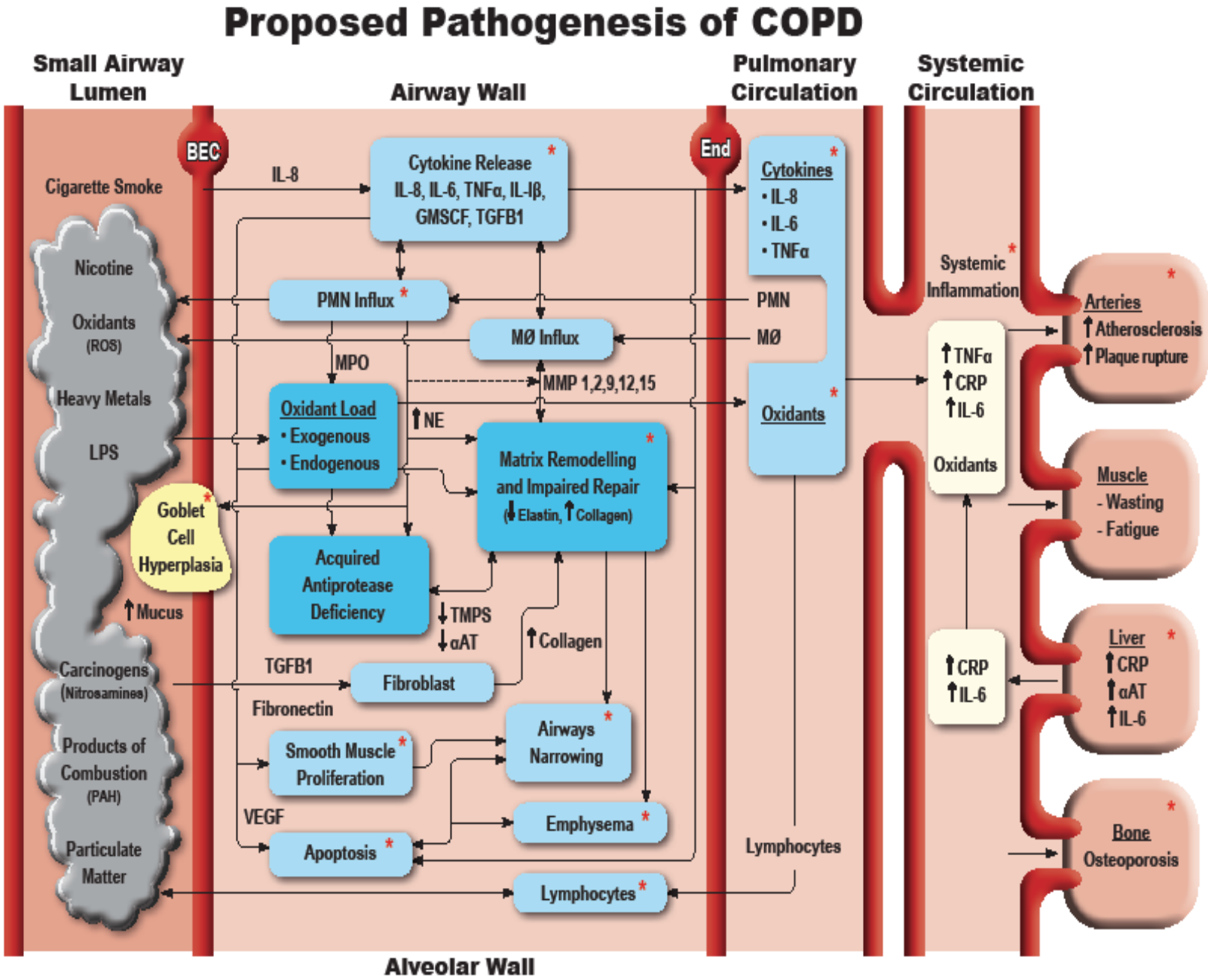
Genetic susceptibility

Combined effects of susceptibility and protective genetic effects



Reprinted with permission from the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009. Available from: http://www.goldcopd.org.


Smoking
Particles
APC
Epithelial cells
CXCL8
CXCL10
CXCL8
CXCL10
Macrophage
Naïve CD8
Naïve CD4
CXCL8
Neutrophil
Perforin &
Granzyme
MMP's
Elastase
Cytokines
Mature CD8
Th1/2
Emphysema
Obstructive
Bronchiolitis
Hypermucus
secretion



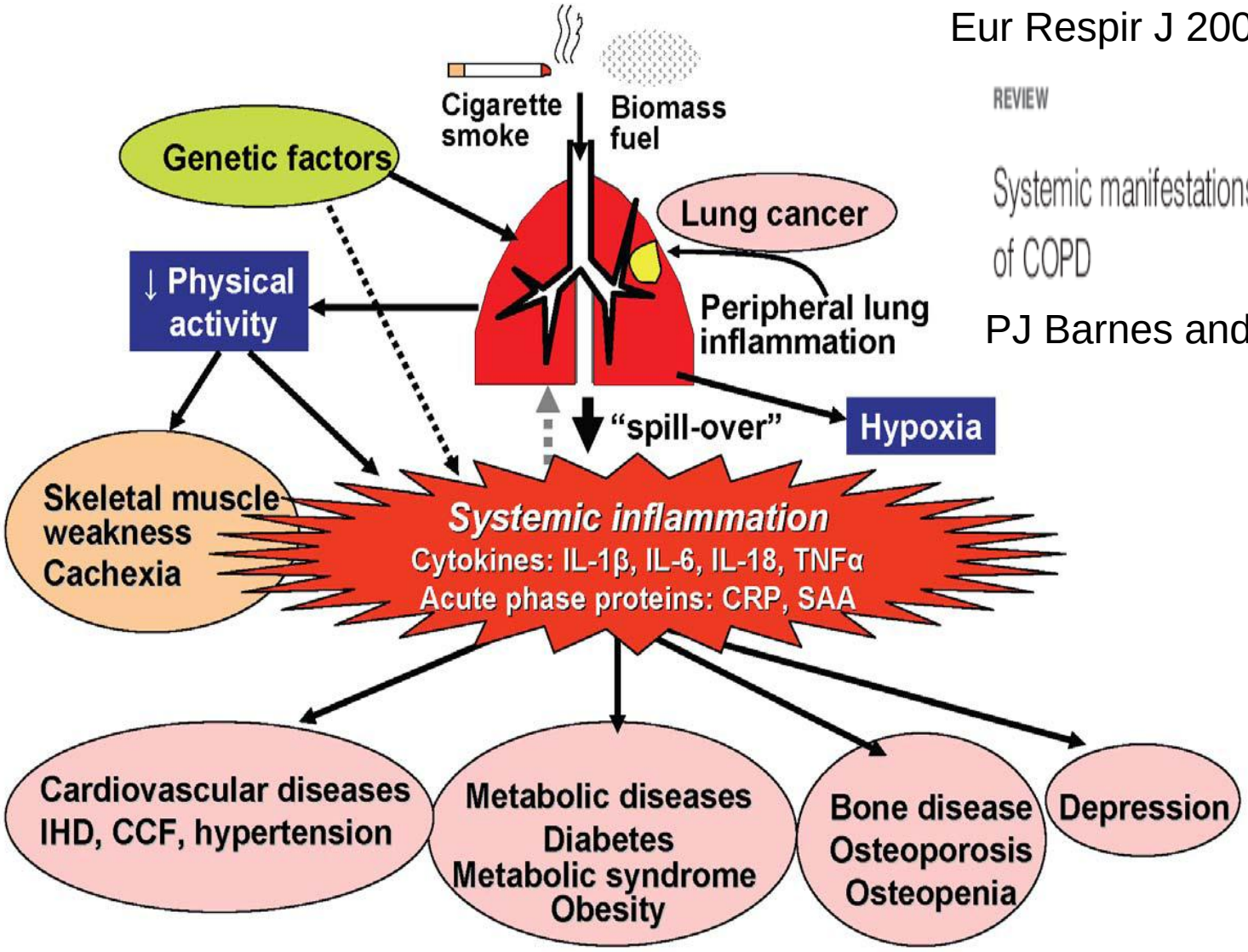
Young RP, et al. (European Respir Review 2009)

Eur Respir J 2009; 33: 1165-85.

REVIEW

Systemic manifestations and comorbidities of COPD

PJ Barnes and BR Celli



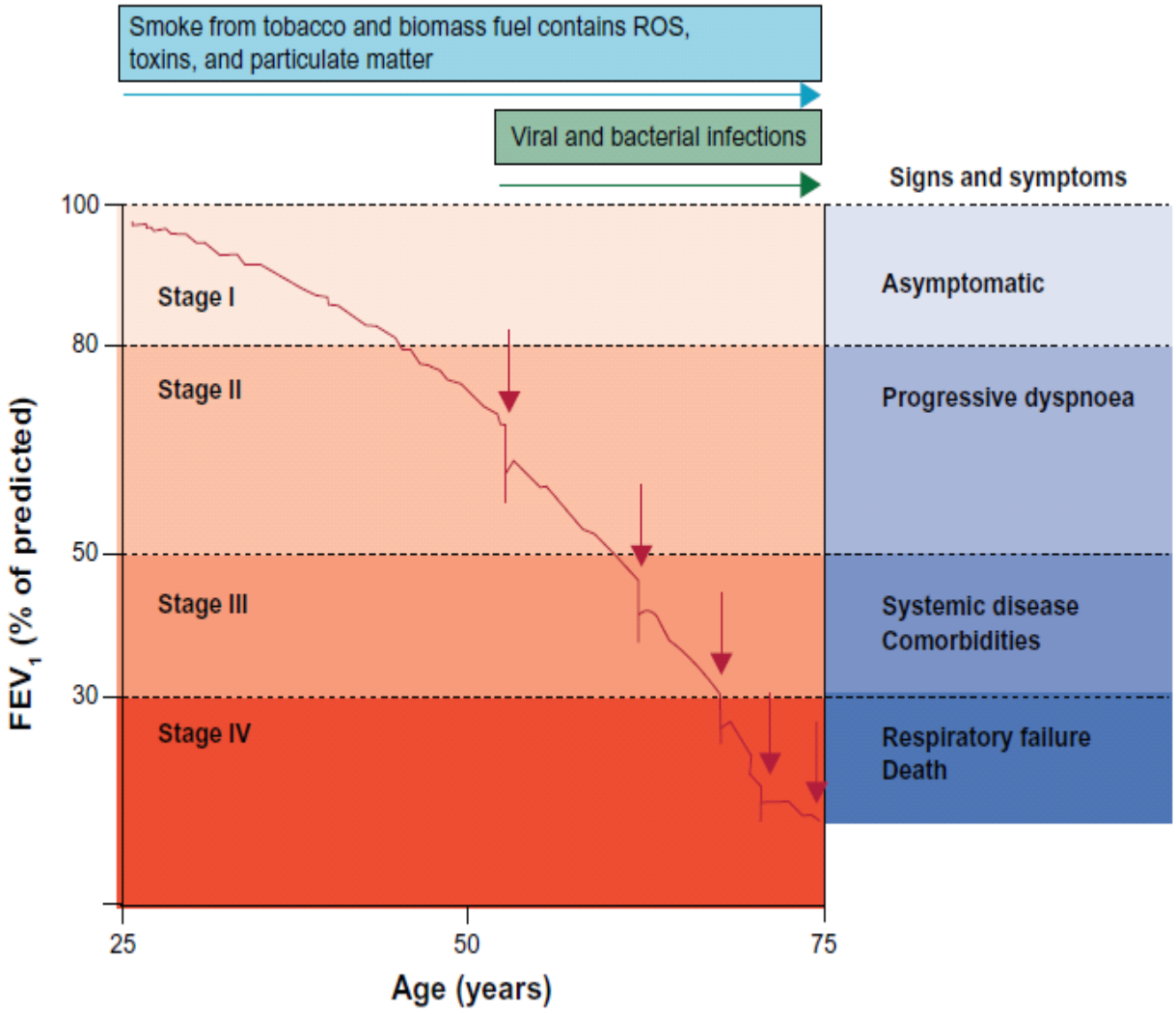
2. A symptom based approach (**Assess**)

Management of COPD – the aims

Reduce symptoms	Relieve symptoms Improve exercise tolerance Improve health status
Reduce risk	Prevent disease progression Prevent and treat exacerbations Reduce mortality

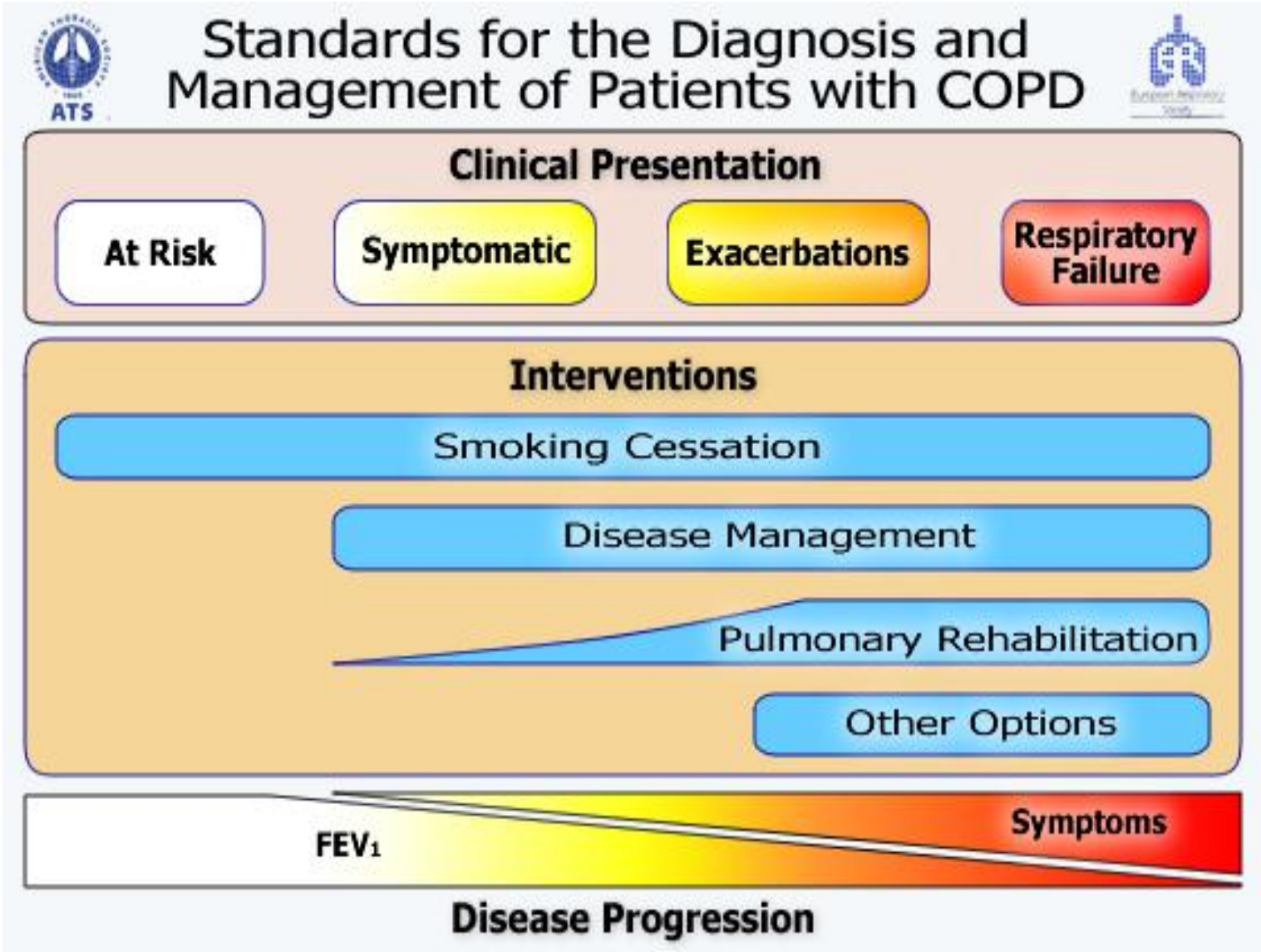
GOLD Strategy Document 2011 (http://www.goldcopd.org/)

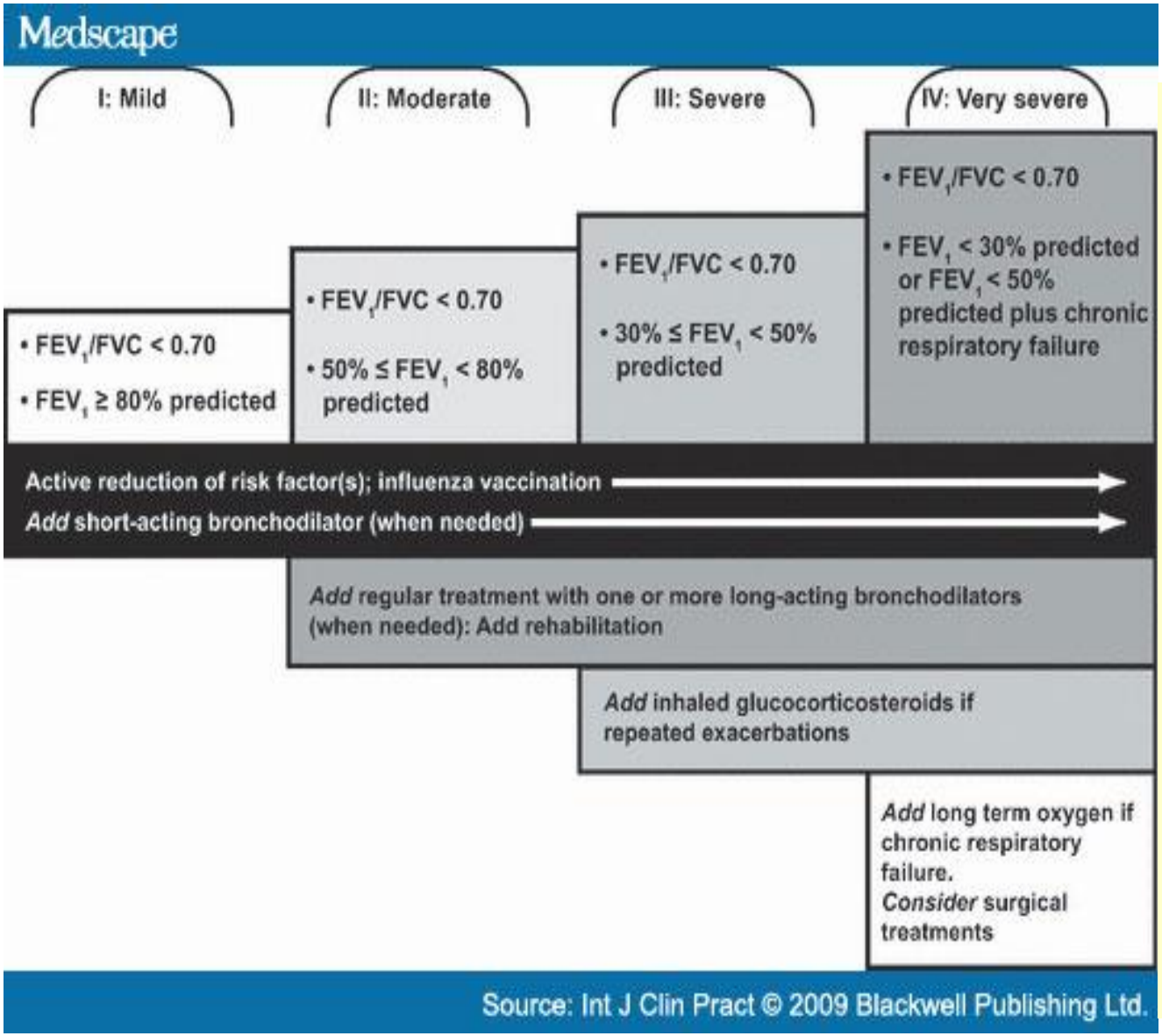
Development and progression of COPD – FEV_1 vs symptoms



Treatment options in COPD – a symptom based approach

- Spirometry – document severity of airways obstruction (confirm diagnosis, end organ damage)
- Establish – symptom profile (CAT) , tendency to LRTI, AECOPD, hospitalisation for acute exacerbations (direct inhaler treatment).
- Consider COPD a CVS risk factor
- Consider COPD a precursor to lung cancer


Standards for the Diagnosis and Management of Patients with COPD
ATS
Clinical Presentation
At Risk
Symptomatic
Exacerbations
Respiratory Failure
Interventions
Smoking Cessation
Disease Management
Pulmonary Rehabilitation
Other Options
FEV1
Symptoms
Disease Progression



SABA/SAMA prn

then LABA/LAMA bd

then LABA + ICS bd

then LABA /ICS + LAMA

Plus

•Oral AB/Prednisone

•Pulmonary rehab

•LTOT and surgery/valves

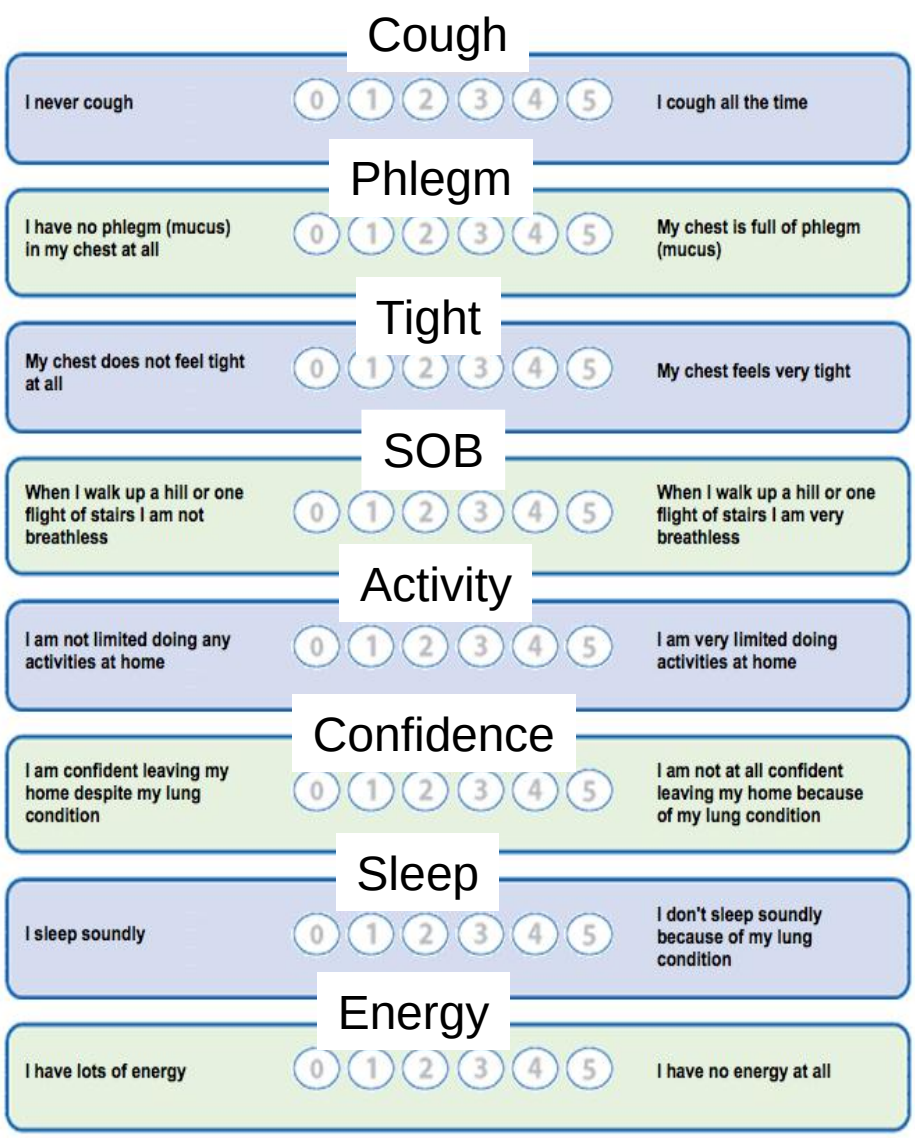
A symptom based approach

HEED study

- Lung function alone is a poor predictor of symptoms
- Symptoms of COPD should be assessed regularly in patients with COPD (self administered CAT questionnaire, www.catestonline.co.uk)
- Reduced exercise tolerance was seen in 70% with mild disease (%predFEV1>80%) and 74% with moderate disease (%predFEV1 50-80%).

Jones P et al. Respir Med. 2010;105(1):57-66

The CAT questionnaire **(download from - www.catestonline.co.uk)**



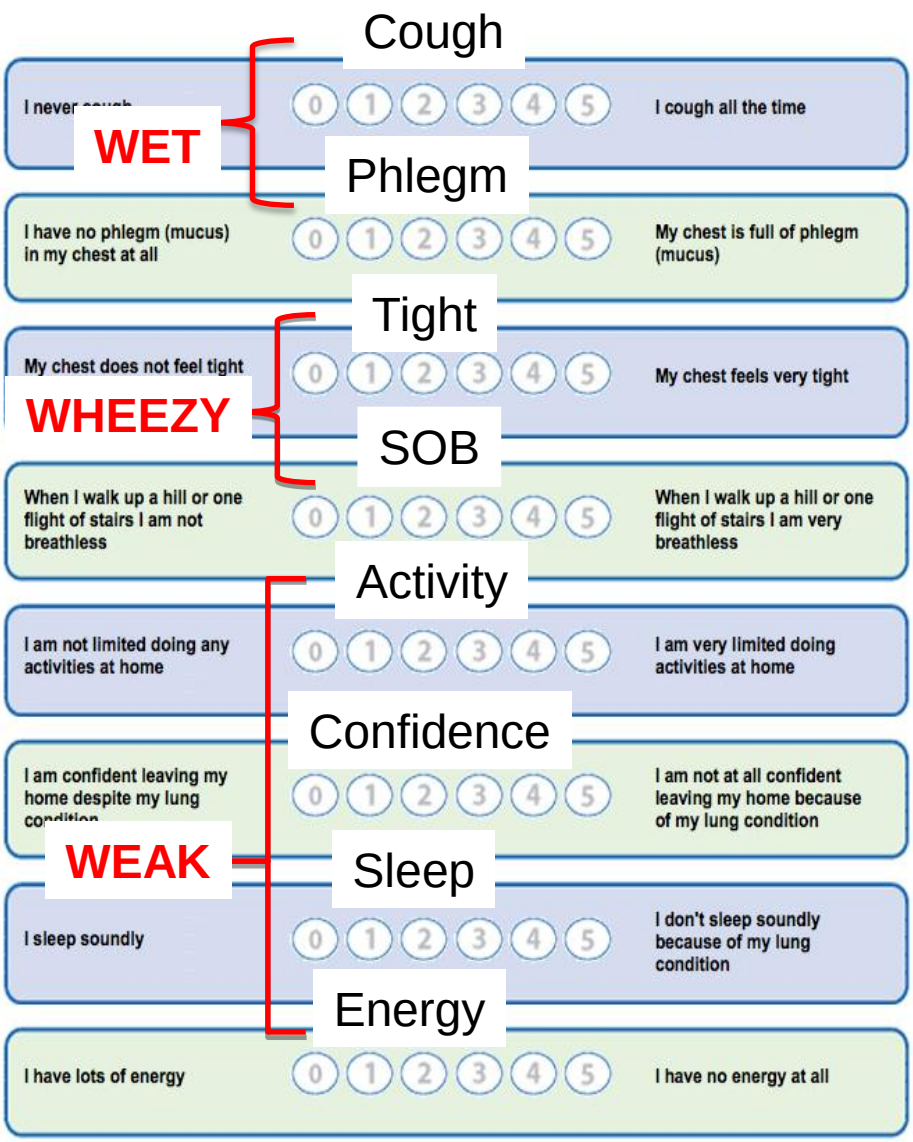
A symptom based approach – CAT

COPD **Self** Assessment Test

Score/40
- mild 0-10
- mod 10-15
- severe 15-25
- very severe 25-40

Basis on which to establish
- overall disability
- specific disabilities and
- response to treatments

The CAT questionnaire **(download from - www.catestonline.co.uk)**



A symptom based approach – CAT

COPD **Self** Assessment Test

Score/40
- mild 0-10
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- severe 15-25
- very severe 25-40

Basis on which to establish
- overall disability
- specific disabilities and
- response to treatments

CAT Score – patient data

	I never cough	0 X 2 3 4 5	I cough all the time	1
	I have no phlegm (mucus) in my chest at all	0 X 2 3 4 5	My chest is completely full of phlegm (mucus)	1
	My chest does not feel tight at all	0 1 X 3 4 5	My chest feels very tight	2
WHEEZY	When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 X 5	When I walk up a hill or one flight of stairs I am very breathless	4
	I am not limited doing any activities at home	0 1 2 X 4 5	I am very limited doing activities at home	3
	I am confident leaving my home despite my lung condition	0 1 2 3 X 5	I am not at all confident leaving my home because of my lung condition	4
	I sleep soundly	0 1 X 3 4 5	I don't sleep soundly because of my lung condition	2
WEAK	I have lots of energy	0 1 2 3 4 X	I have no energy at all	5

Scoring range 0-40

Total score 2 2

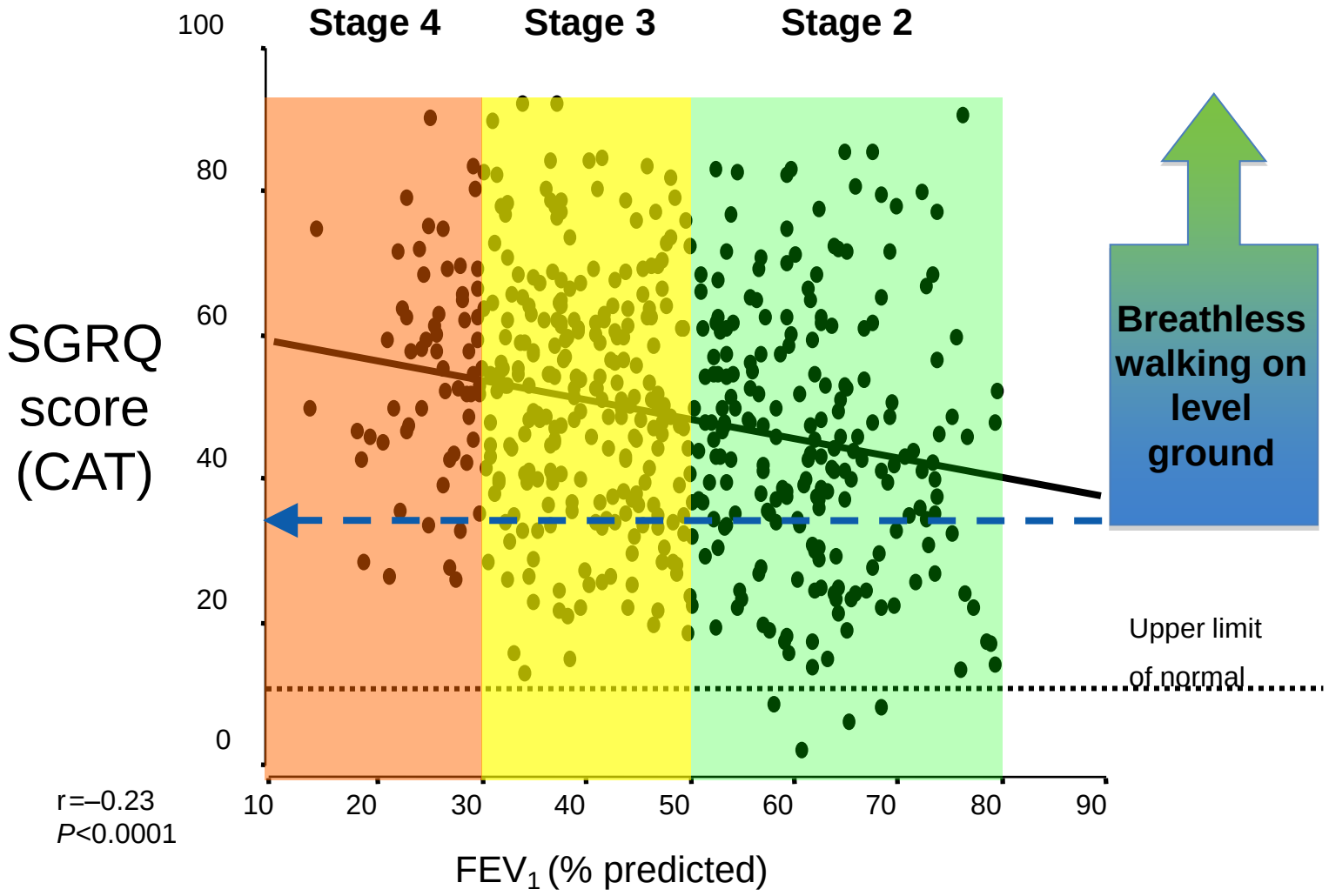
CAT Score/40
- mild 0-10
- mod 10-15
- severe 15-25
- very severe 25-40

Severe

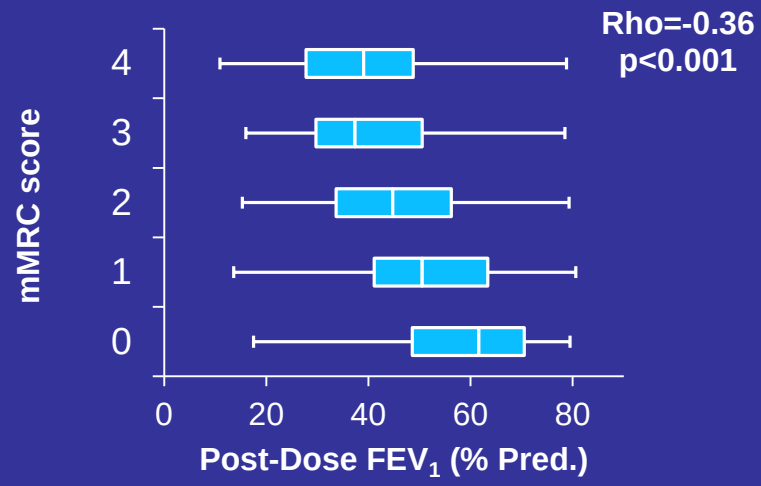
Modified MRC Breathlessness Score

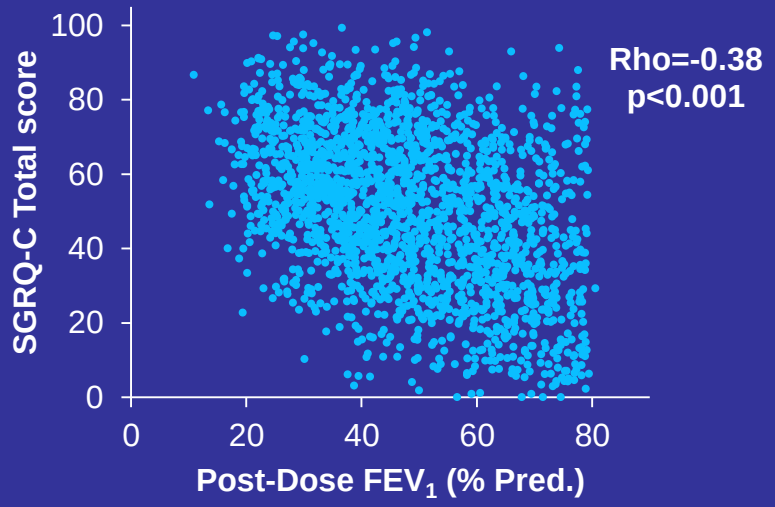
Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

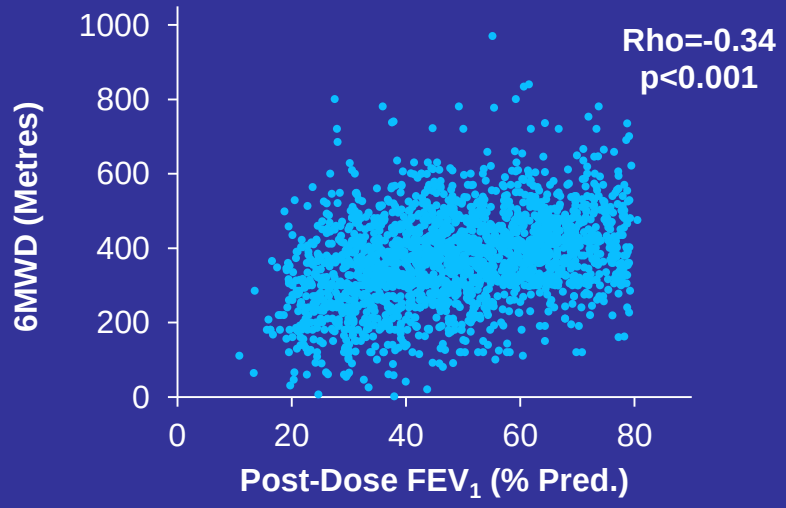
No correlation between QOL and FEV_1 severity

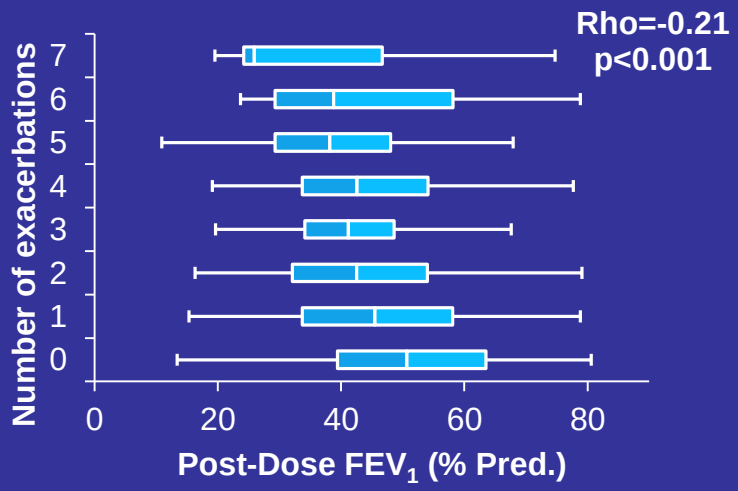


ECLIPSE showed weak correlation between disease outcome parameters & FEV_1





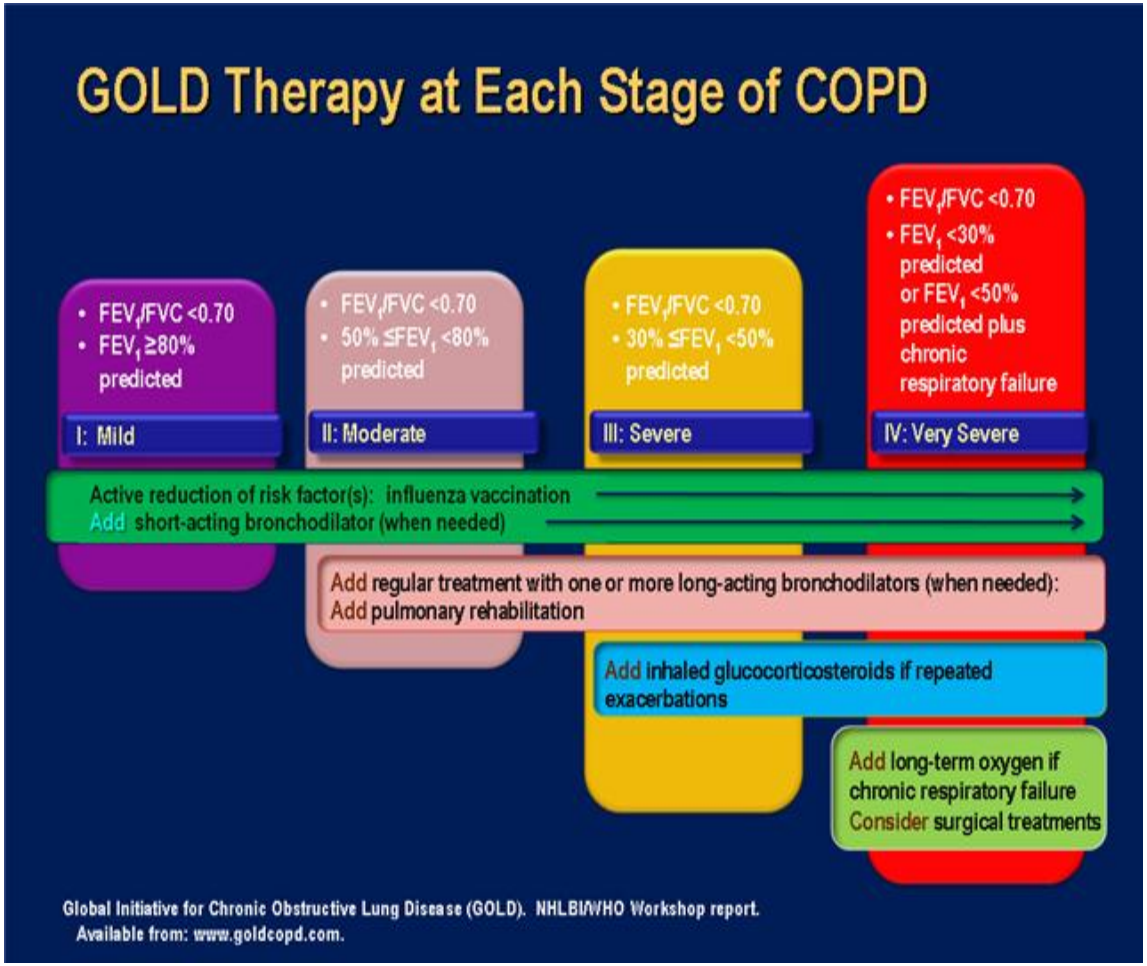




Agusti et al. Resp Res 2010

3. When to start long acting bronchodilators and when to add steroids (**Manage**)

COPD Management – adding inhalers



A symptom based approach

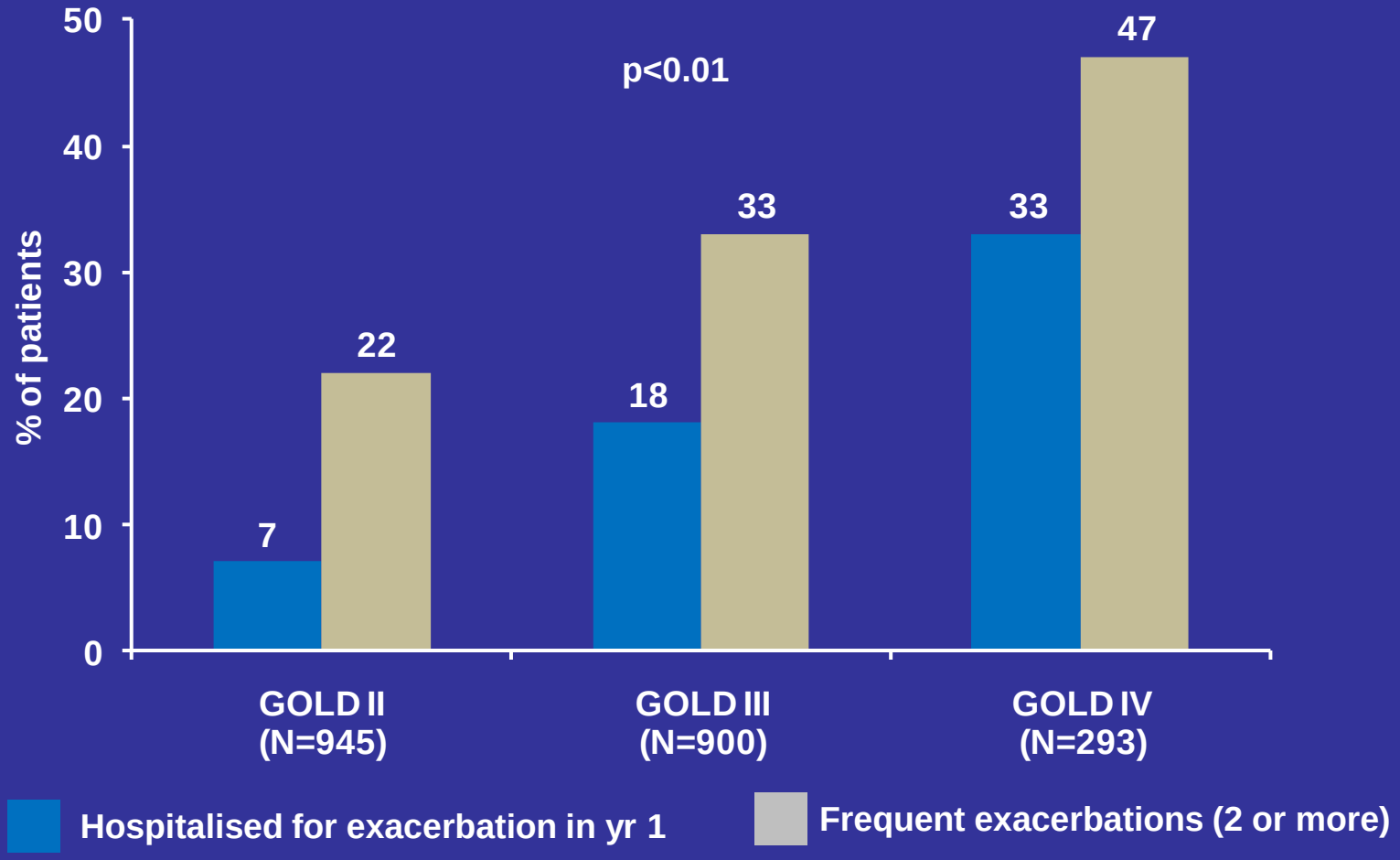
Eclipse study

- “Frequent exacerbator*” is a specific type of COPD that requires aggressive treatment with combination therapy (preferably fixed dose ICS and LABA)
- “Frequent exacerbators” may be found in those with moderate COPD (22%) and not just severe disease (30-50%).

* 2+ exacerbations per year

Hurst J et al. N Engl J Med. 2010;363:1128-1138

The ‘frequent exacerbator phenotype’: Frequency/severity by GOLD Category (1)

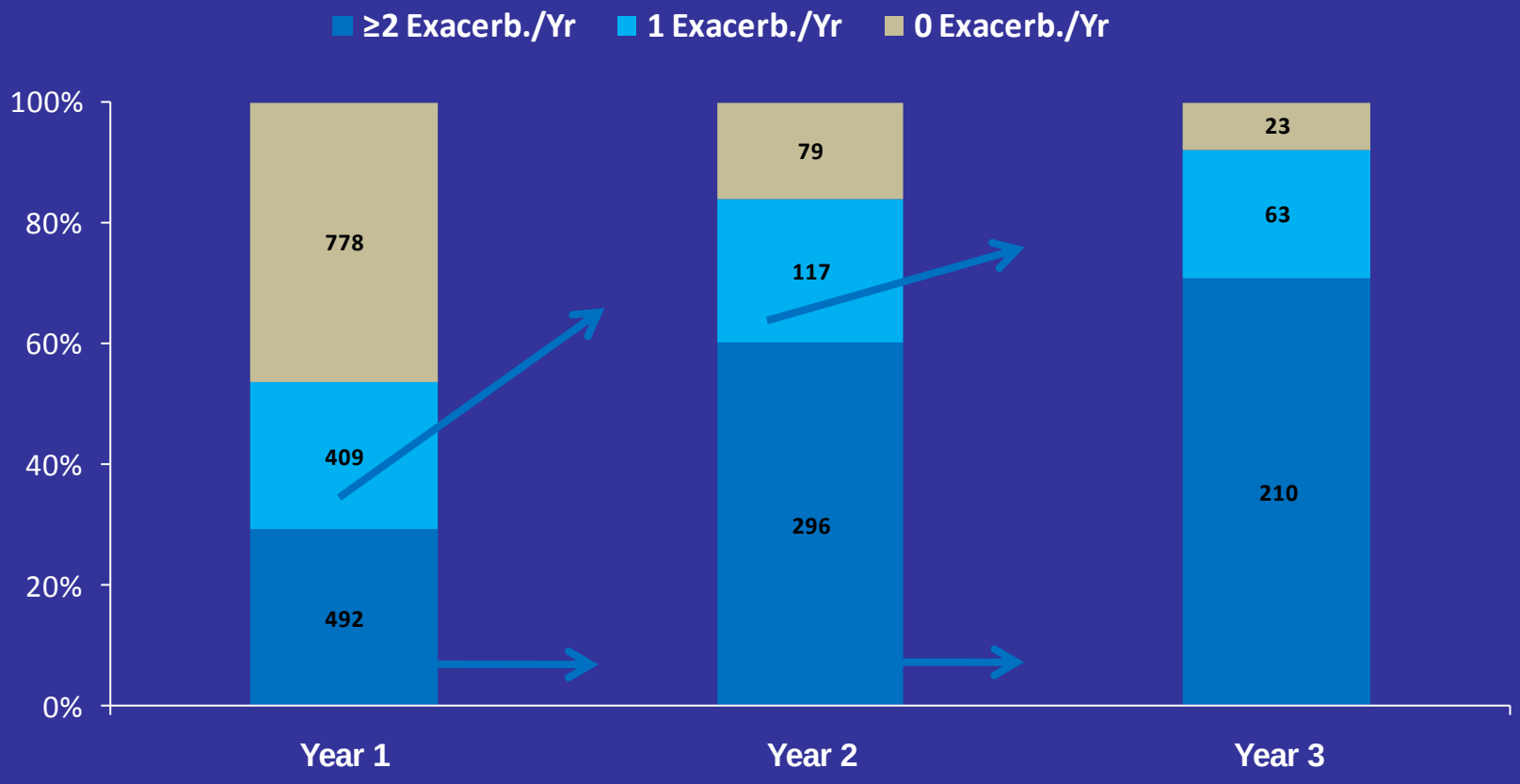


ECLIPSE 1 year data

Hurst et al. N Engl J Med 2010

Frequent exacerbators represent stable COPD phenotype - independent of severity

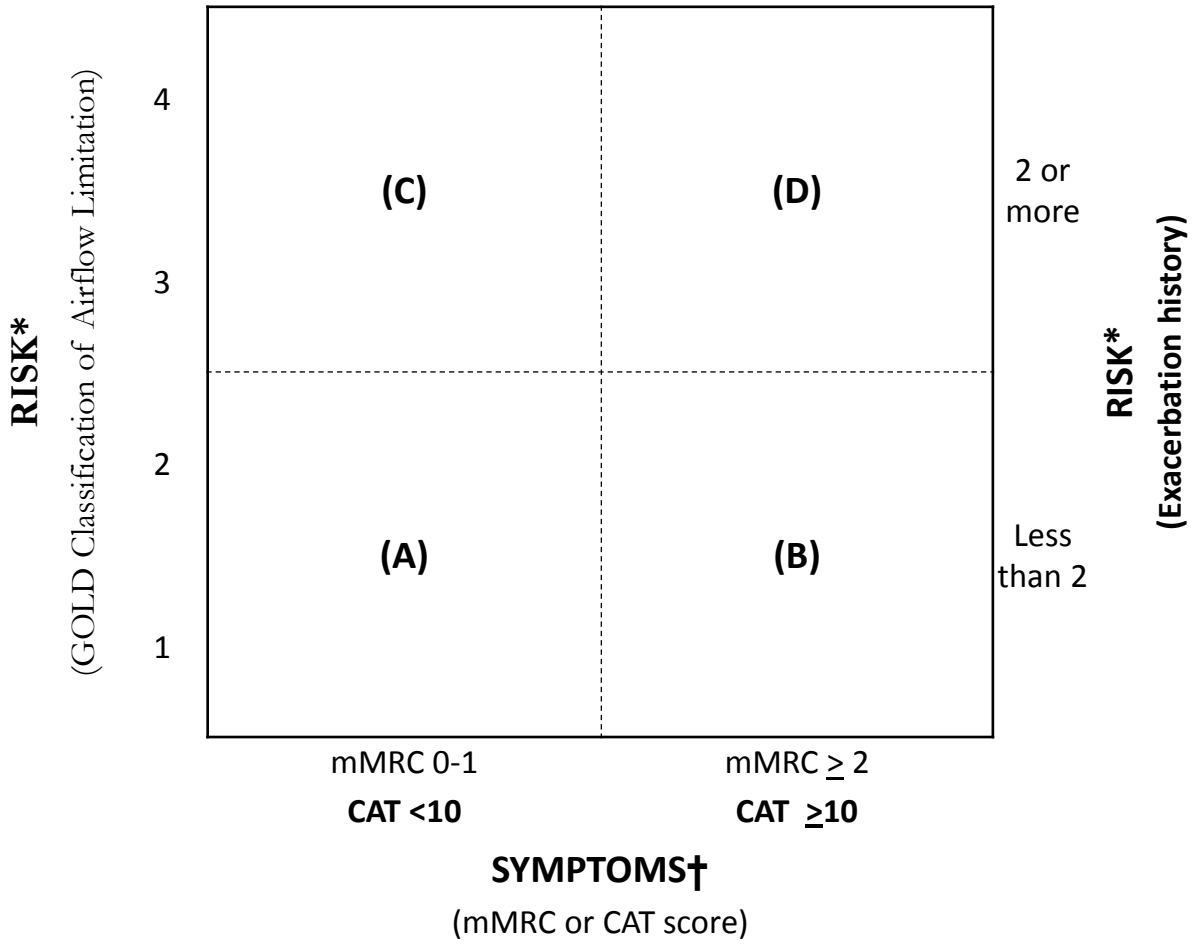
- Proportion of subjects experiencing ≥2 exacerbations/year increases year-on-year
- Stable population provides potential to understand the cause(s) of the phenotype



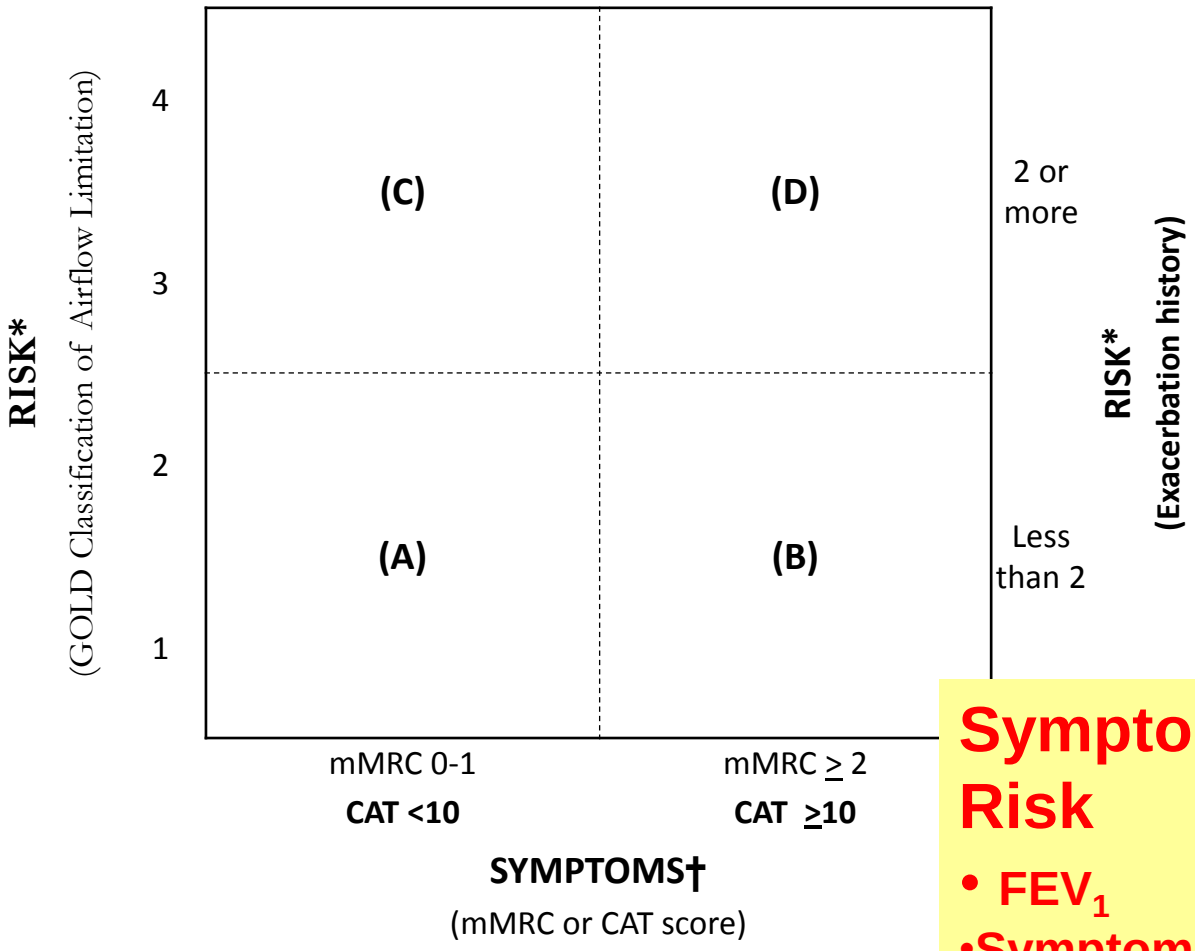
ECLIPSE 3 year data

Hurst et al. N Engl J Med 2010

New GOLD patient groups



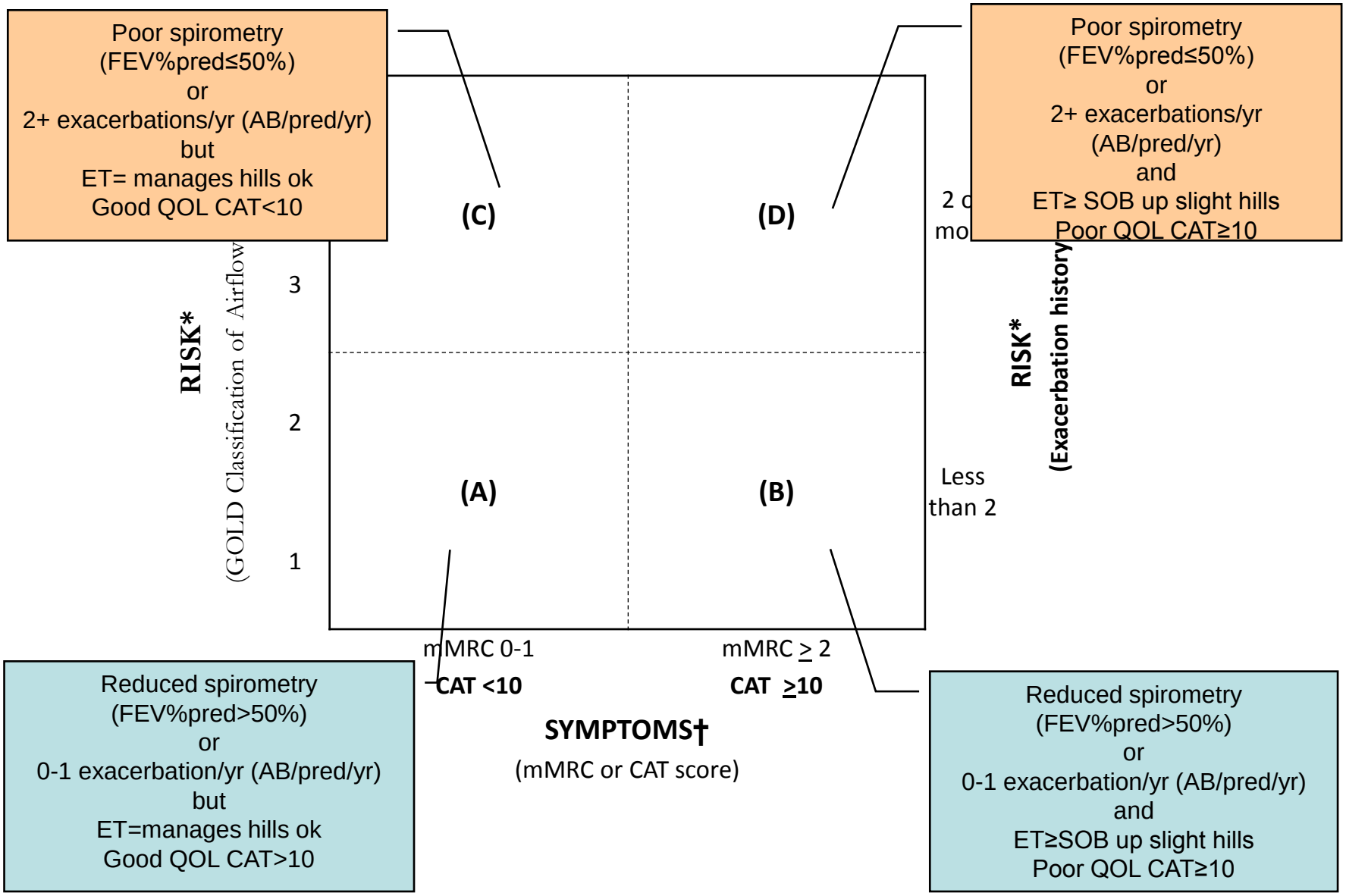
New GOLD patient groups



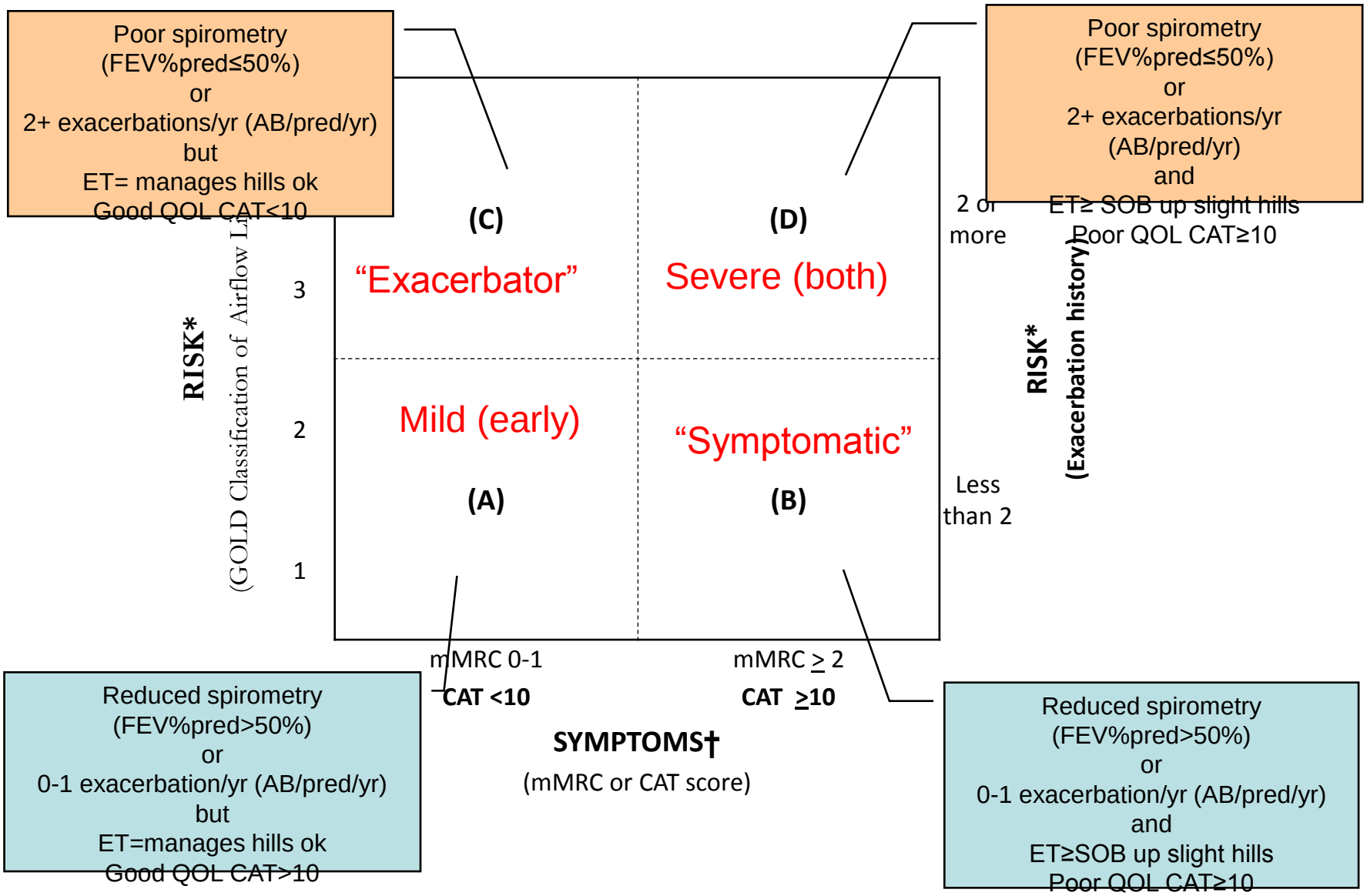
Symptoms and Risk

- **FEV_1**
- **Symptom score**
- **Exacerbation Hx**

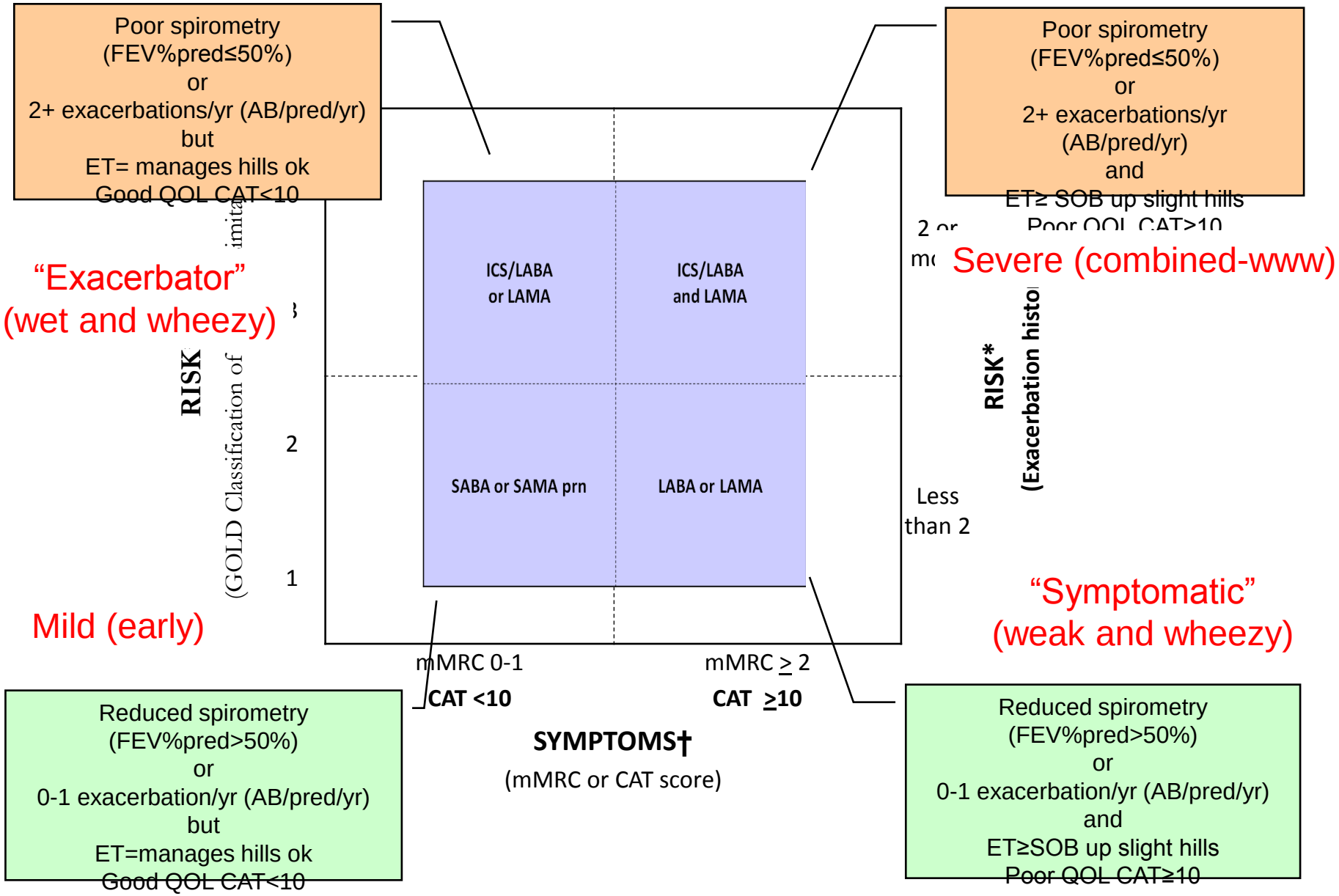
New GOLD-defined patient groups



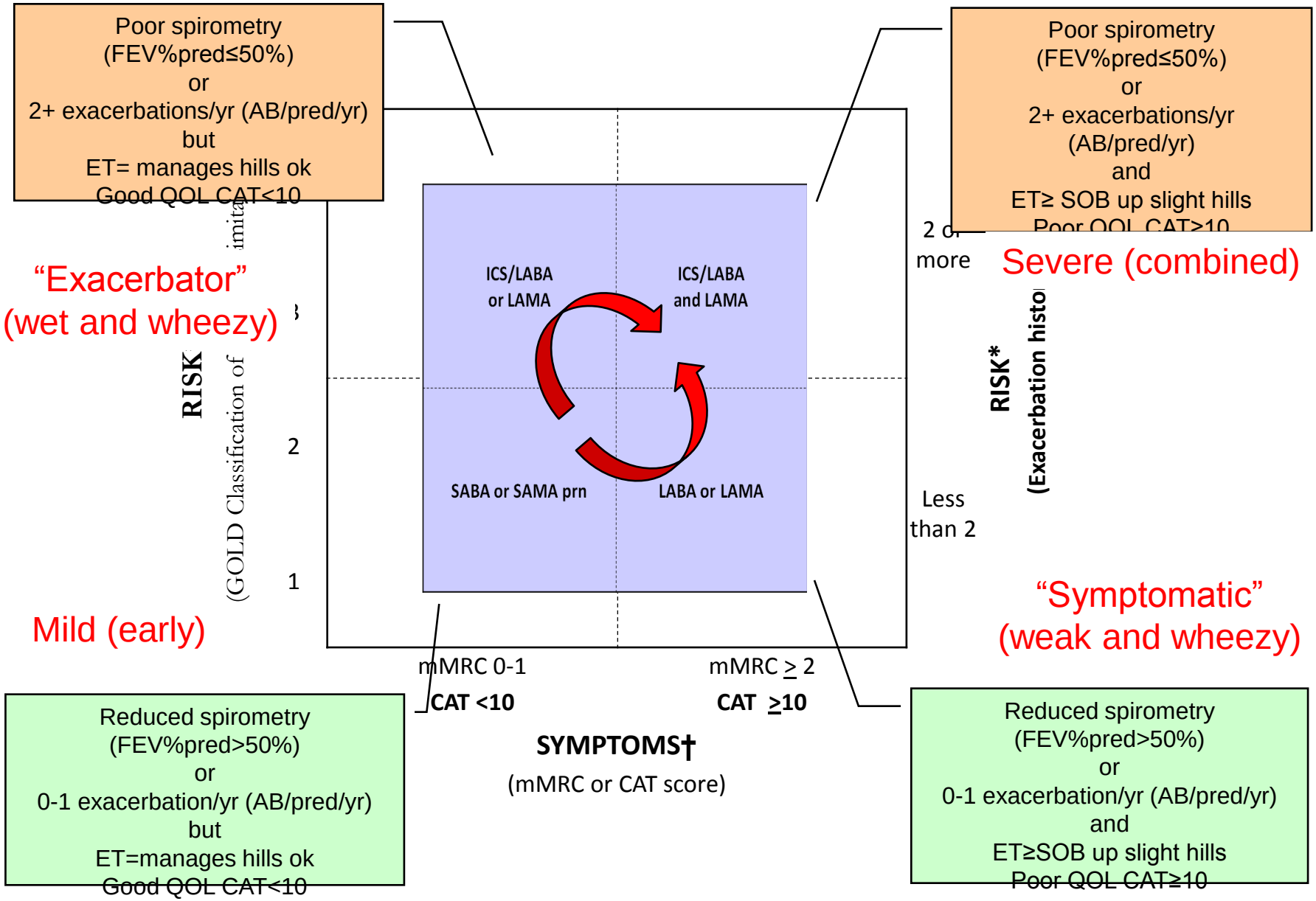
New GOLD-defined patient groups



New GOLD-defined patient groups



New GOLD-defined patient groups



CAT Score – patient data

WHEEZY

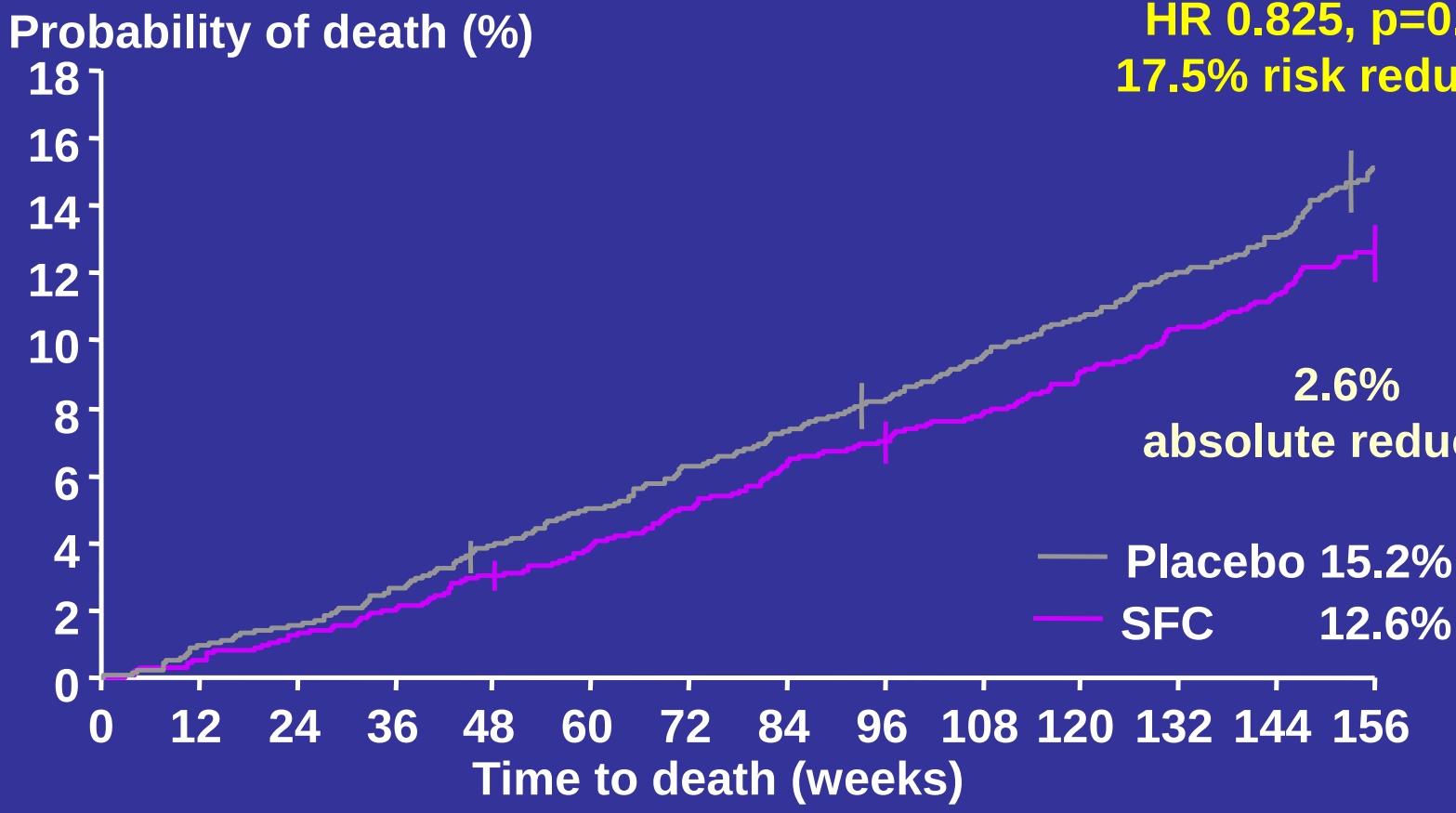
WEAK

"Symptomatic" (weak and wheezy)

CAT Score/40
- mild 0-10
- mod 10-15
- severe 15-25
- very severe 25-40

Severe

Primary analysis: all-cause mortality at 3 years

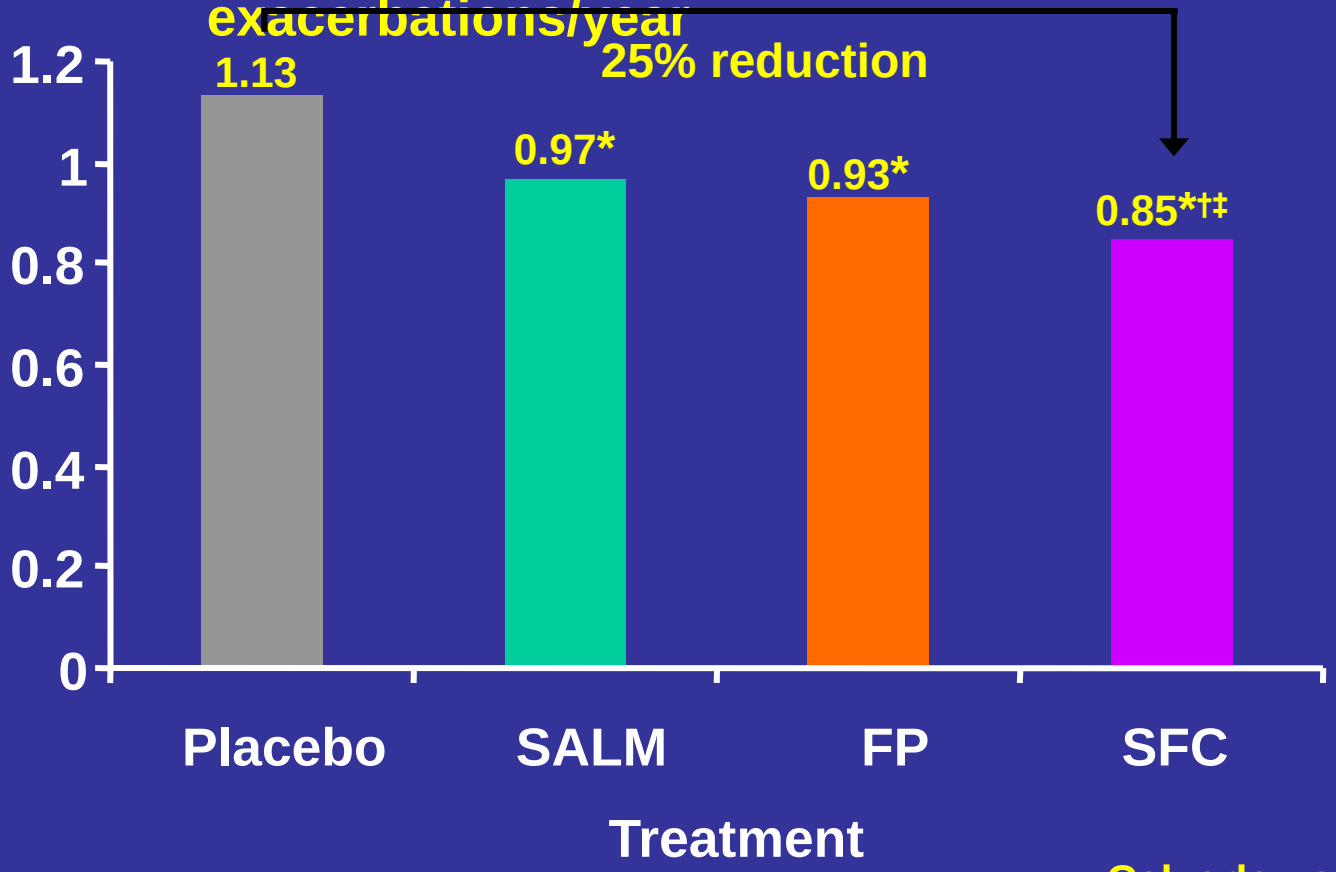


Vertical bars are standard errors

Calverley *et al.* NEJM 2007

Rate of moderate and severe exacerbations over three years

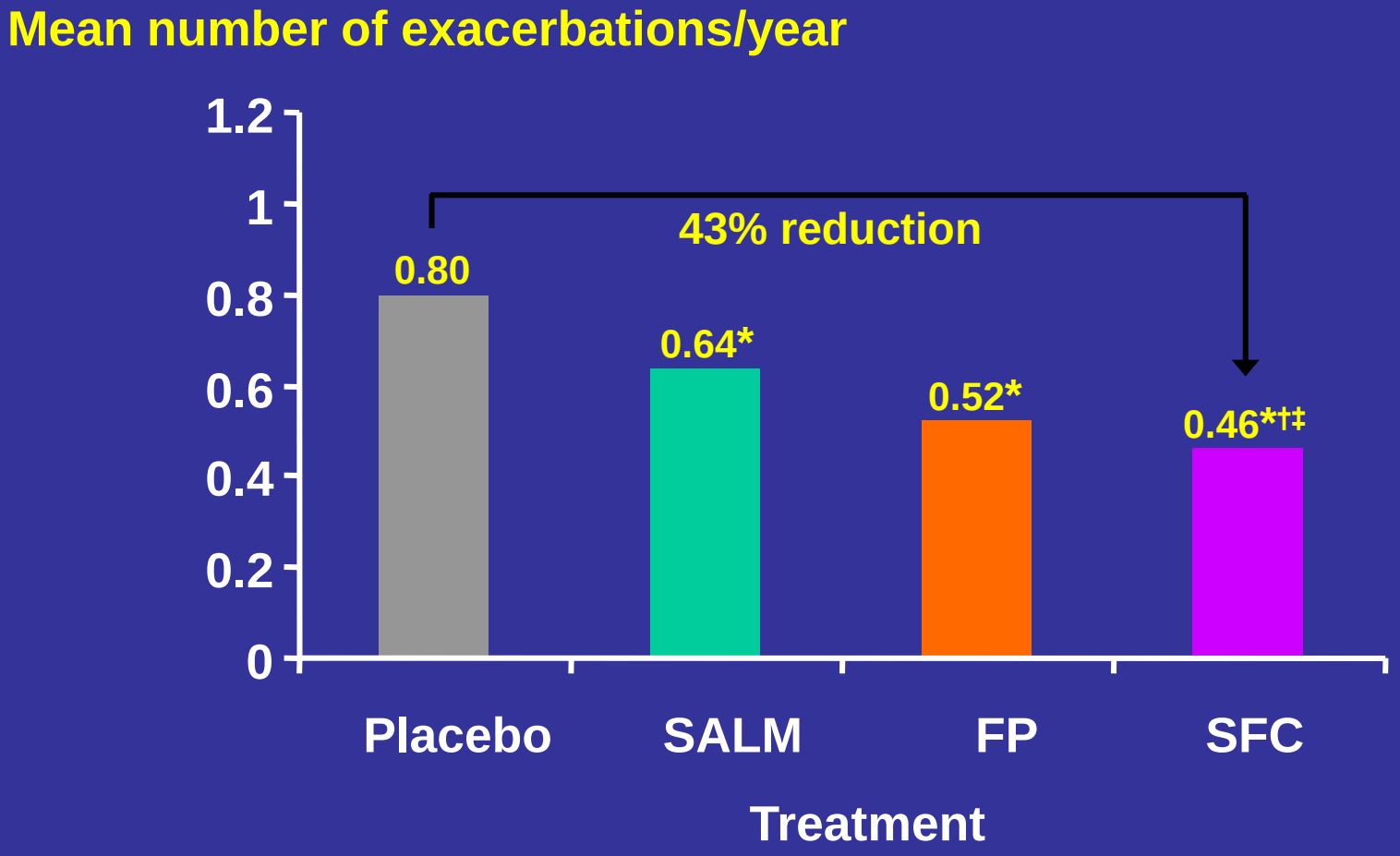
NNT to prevent 1 exacerbation in 1 year = 4



Calverley *et al.* NEJM 2007

*p < 0.001 vs placebo; †p = 0.002 vs SALM; ‡p = 0.024 vs FP

Rate of exacerbations requiring systemic corticosteroids over three years



*p < 0.001 vs placebo; †p < 0.001 vs SALM; ‡p = 0.017 vs FP

Calverley *et al.* NEJM 2007

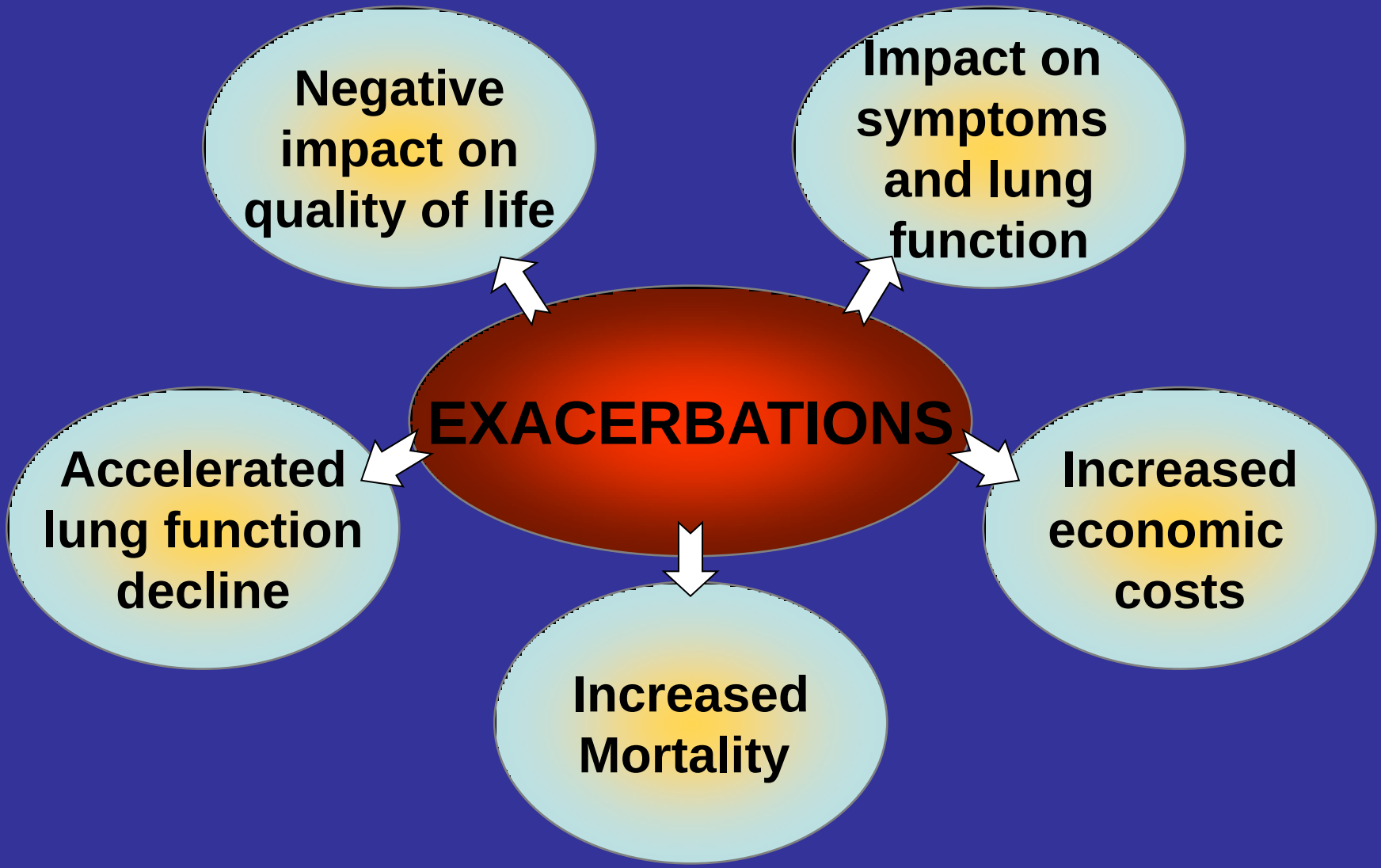
TORCH: Results summary

SFC 50/500, in COPD patients with FEV_1 < 60% predicted

- Had a trend towards improved survival vs placebo
- Significantly maintains and improves health status vs placebo and components
- Significantly reduces the rate of exacerbations vs placebo and components
- Significantly improves lung function vs placebo and components
- Is generally well tolerated over 3 years with a lack of significant effect on systemic effects of steroids such as bone and eye disorders in COPD patients
- Led to increase in cases of pneumonia, but with no corresponding increase in mortality with SFC treatment

Calverley *et al.* NEJM 2007

Consequences of COPD exacerbations



A symptom based approach

- Smoking and aero-pollutant (dust) avoidance
- Yearly Flu vaccination, 5 yearly pneumococcal vaccination and regular exercise
- Exertional SOB- prn bronchodilators (SABA/SAMA)
- Fatigue + poor ET – reg bronchodilators (LABA and LAMA (*FEV1<60% predicted for Tiotropium))
- LRTI/bronchitis/AECOPD – Inhaled corticosteroids with LABA or LAMA (*FEV1<60% predicted)
- 2+ Hospitalisations/yr – triple therapy

COPD Phenotypes and treatment

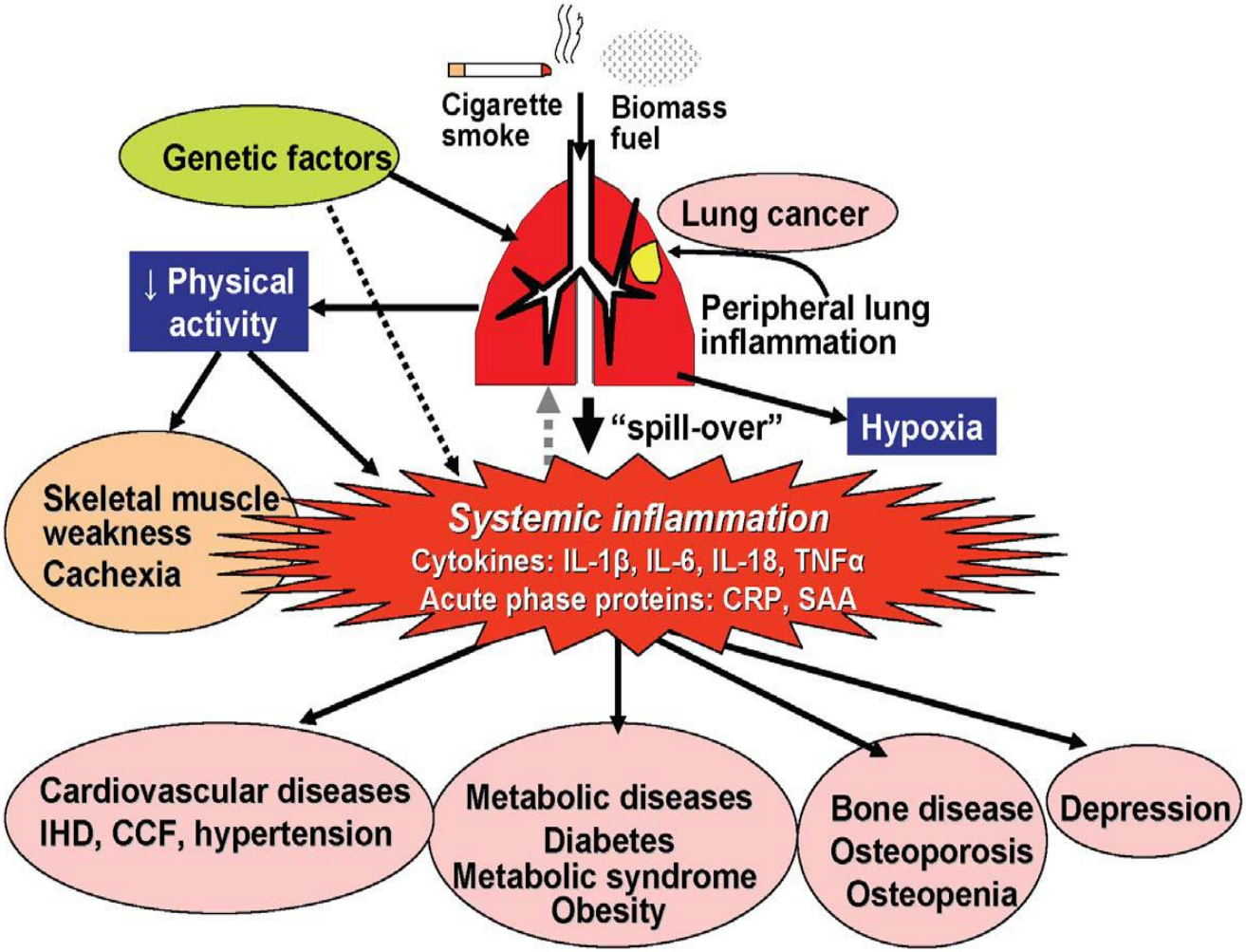
- Mild disease (FEV1%pred >50%) - few Sx (SABA/SAMA)
- Mild disease (FEV1%pred >50%) - persisting Sx (LABA or LAMA) or 2+ exacerbations/yr (ICS/LABA)
- Mod-Sev disease (FEV1%pred ≤50%) - few Sx (ICS/LABA or LAMA)
- Mod-Sev disease (FEV1%pred ≤50%) - persisting Sx (ICS/LABA and LAMA) and 2+ exacerbations/yr (ICS/LABA and LAMA)

When to add the steroids

- ICS are needed when patients suffer recurrent exacerbations characterised by productive cough and SOB.
- ICS with LABA are superior to ICS alone and shown to improve lung function, quality of life and survival as do LAMA (TORCH/UPLIFT study).
- Oral steroids for 3-10 days are useful for exacerbations characterised by SOB with productive cough.

4. COPD - Beyond the airways (**Manage – future**)

COPD - Beyond the airways



Beyond the airways

- Muscle fatigue, muscle weakness and cachexia (pulmonary rehab and optimised nutrition)
- Cardiovascular disease, stroke, CHF, pulmonary hypertension (aspirin, statin and β-blockers)
- Insulin resistance, metabolic syndrome, obesity (exercise, calorie restriction, wght loss)
- Osteoporosis (bisphosphonates)

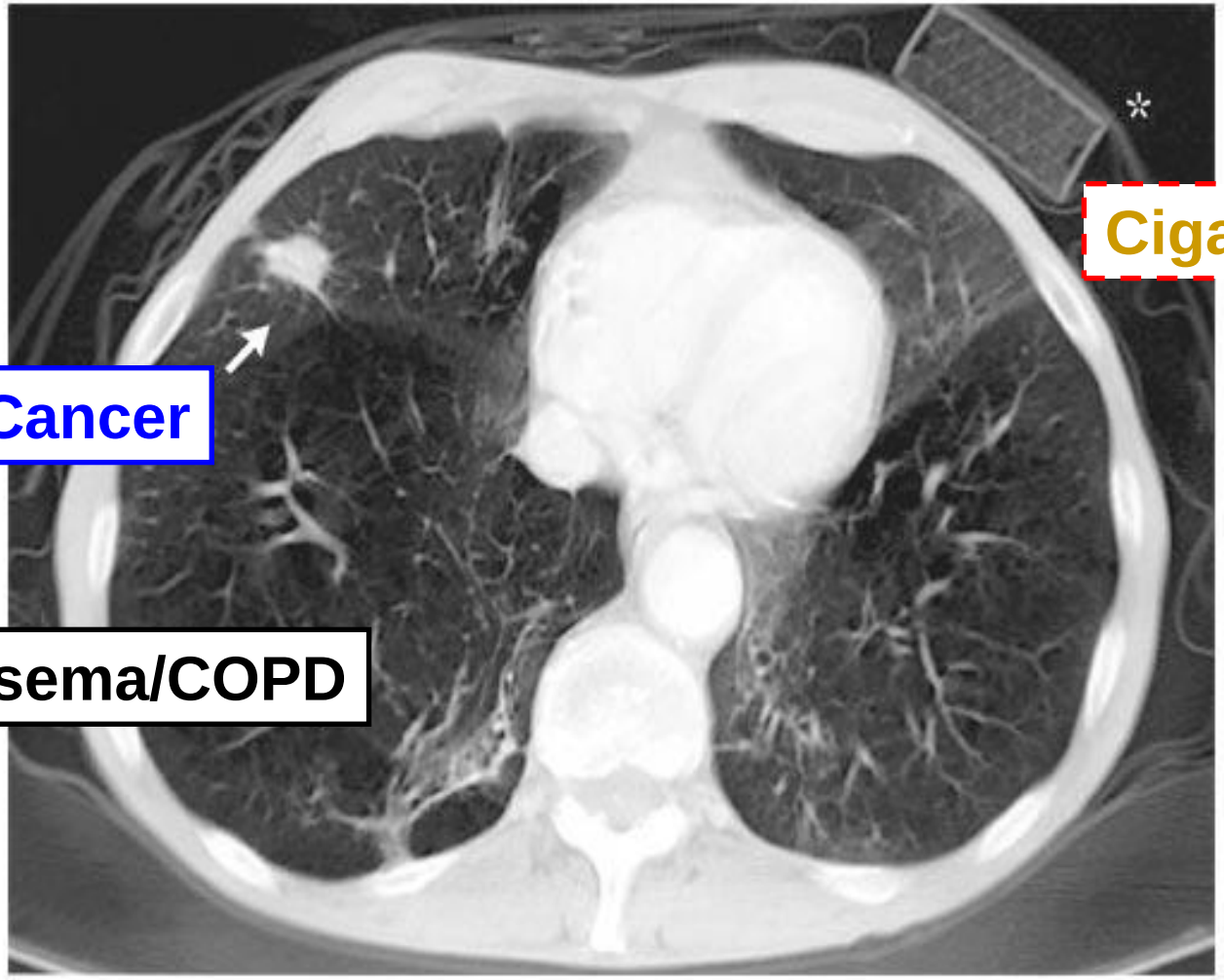
Beyond the airways

- Future treatments will look to reduce [dynamic] hyperinflation measured as IC/TLC ratio rather than to use FEV_1 as a measure of outcome.
- Recent studies suggest that statins reduce hyperinflation and dilate small airways by reducing pulmonary inflammation, and improve endothelial function by reducing systemic inflammation (clinical trials underway).

COPD and lung cancer

- COPD increases the risk of lung cancer by 4-6 fold compared to smokers with normal lung function.
- 70-80% of lung cancer has pre-existing COPD
- 20-30% of deaths in COPD are from lung cancer

COPD overlap with lung cancer

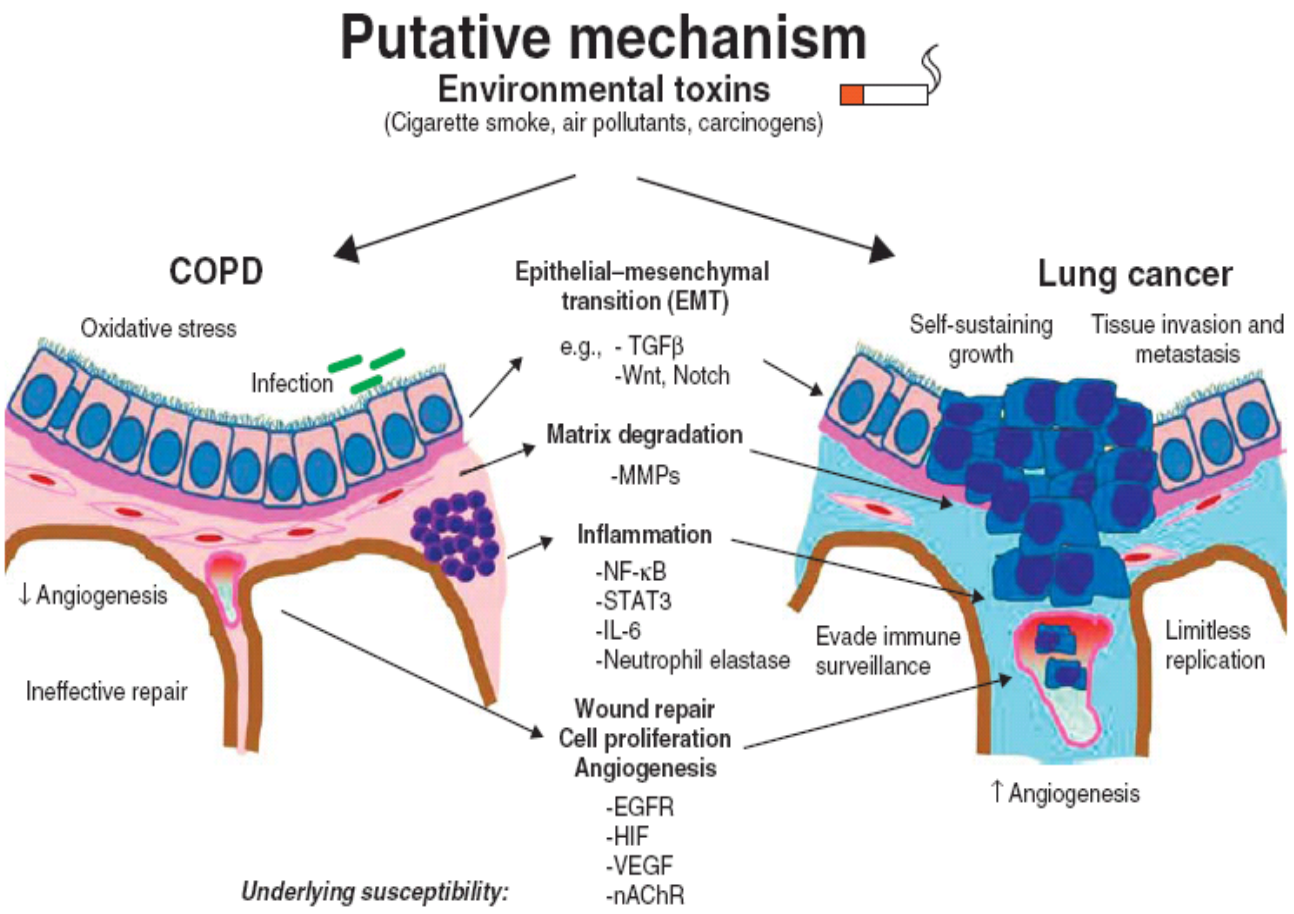


Common pathogenic mechanisms and pathways in the development of COPD and lung cancer

2011 Exp Opin Ther Targets
Yang IA, et al.

Ian A Yang†, Vandana Relan, Casey M Wright, Morgan R Davidson,

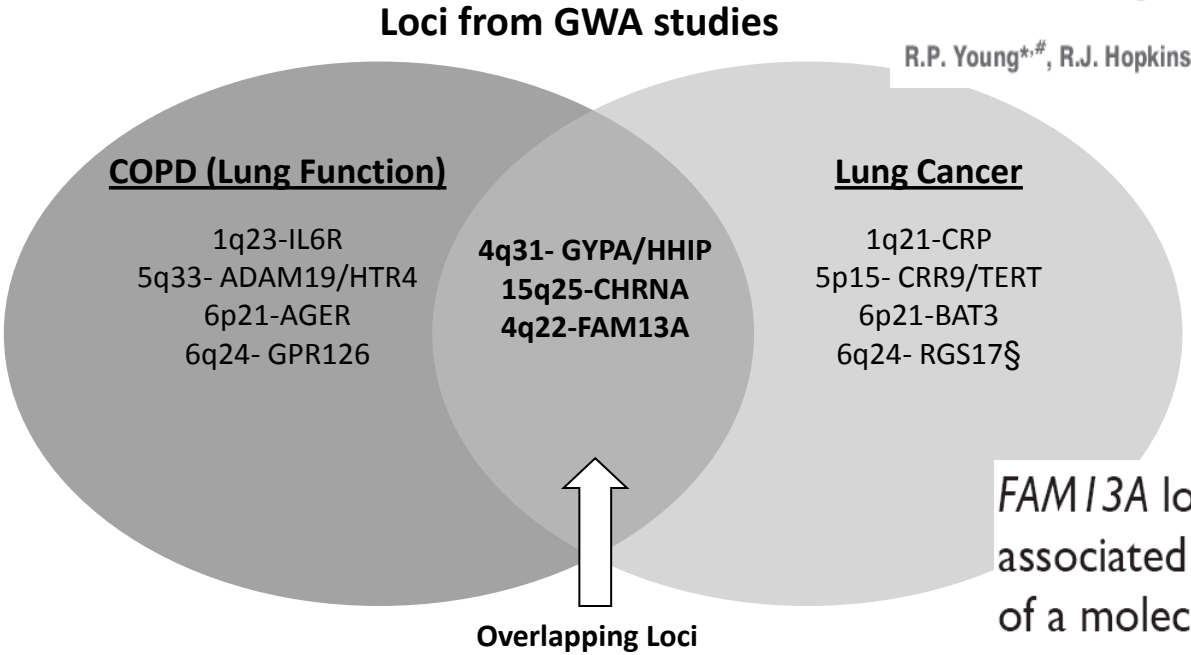
Common pathogenic mechanisms and pathways in the development of COPD and lung cancer



COPD-Lung Cancer Genetic overlap

Lung cancer gene associated with COPD: triple whammy or possible confounding effect? 2008

R.P. Young*,#, R.J. Hopkins*, B.A. Hay*, M.J. Epton¶, P.N. Black* and G.D. Gamble*



Chromosome 4q31 locus in COPD is also associated with lung cancer

R.P. Young*,#, C.F. Whittington*, R.J. Hopkins*, B.A. Hay*, M.J. Epton¶, P.N. Black*,† and G.D. Gamble*

2010

FAM13A locus in COPD is independently associated with lung cancer – evidence of a molecular genetic link between COPD and lung cancer

2011

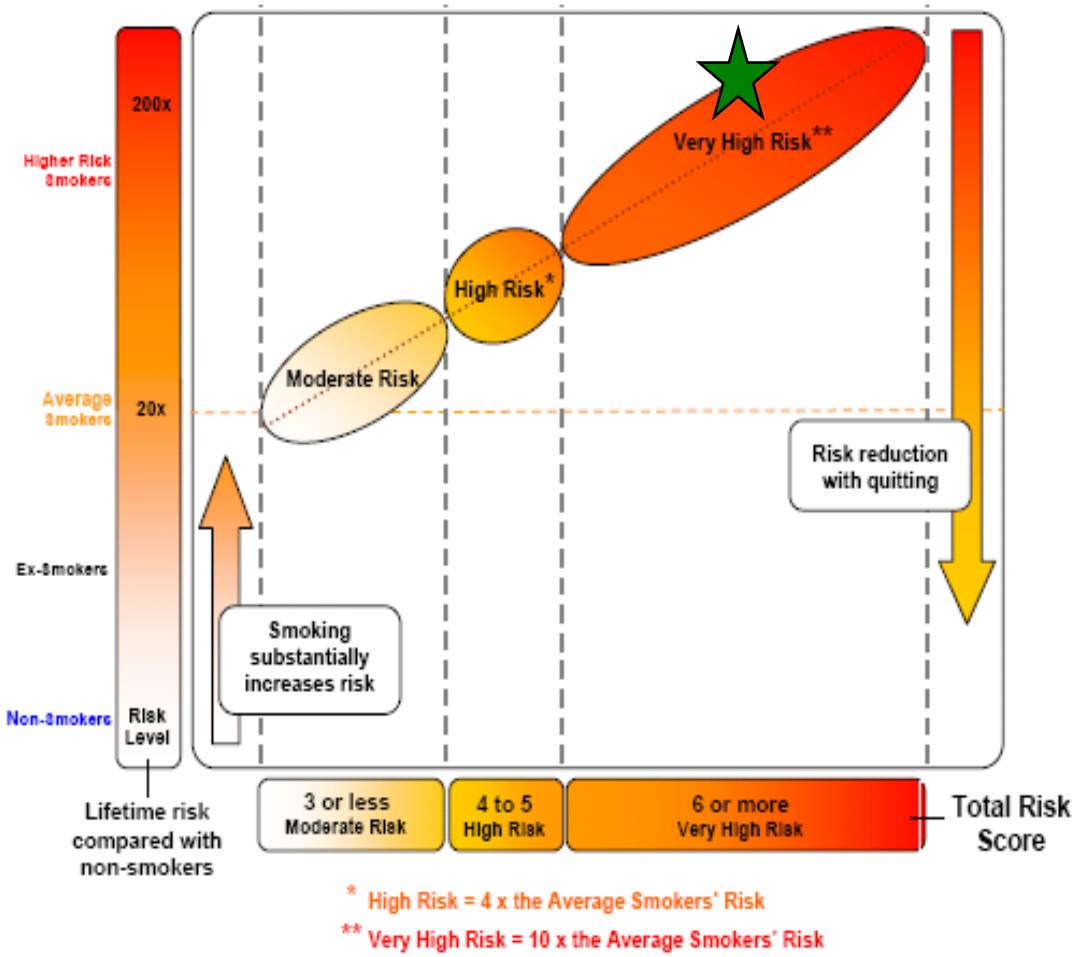
This article was published in the following Dove Press journal:
The Application of Clinical Genetics
21 December 2010
Number of times this article has been viewed

Robert P Young[1]
Raewyn J Hopkins[1]
Bryan A Hay[1]
Chris F Whittington[1]
Michael J Epton[2]
Gregory D Gamble[1]

Abstract: Recent genome-wide association studies have repor
chromosome 4q22.1 is associated with lung function and COPD.
in a case-control study of current or former smokers with chro
disease (COPD, n = 458), lung cancer (n = 454), or normal lung fi
and smoking history were comparable between groups. We conf
(rs7671167) confers a protective effect on smoking-related COPI
[OR] = 0.79, P = 0.013, and GG genotype OR = 0.71, P = 0.024)

Lung cancer risk score:

Lung cancer risk score: **Very High Risk** (6 or more)



In addition to smoking, the risk of lung cancer is further increased by

- genetic factors
- how much you smoked
- age
- COPD.

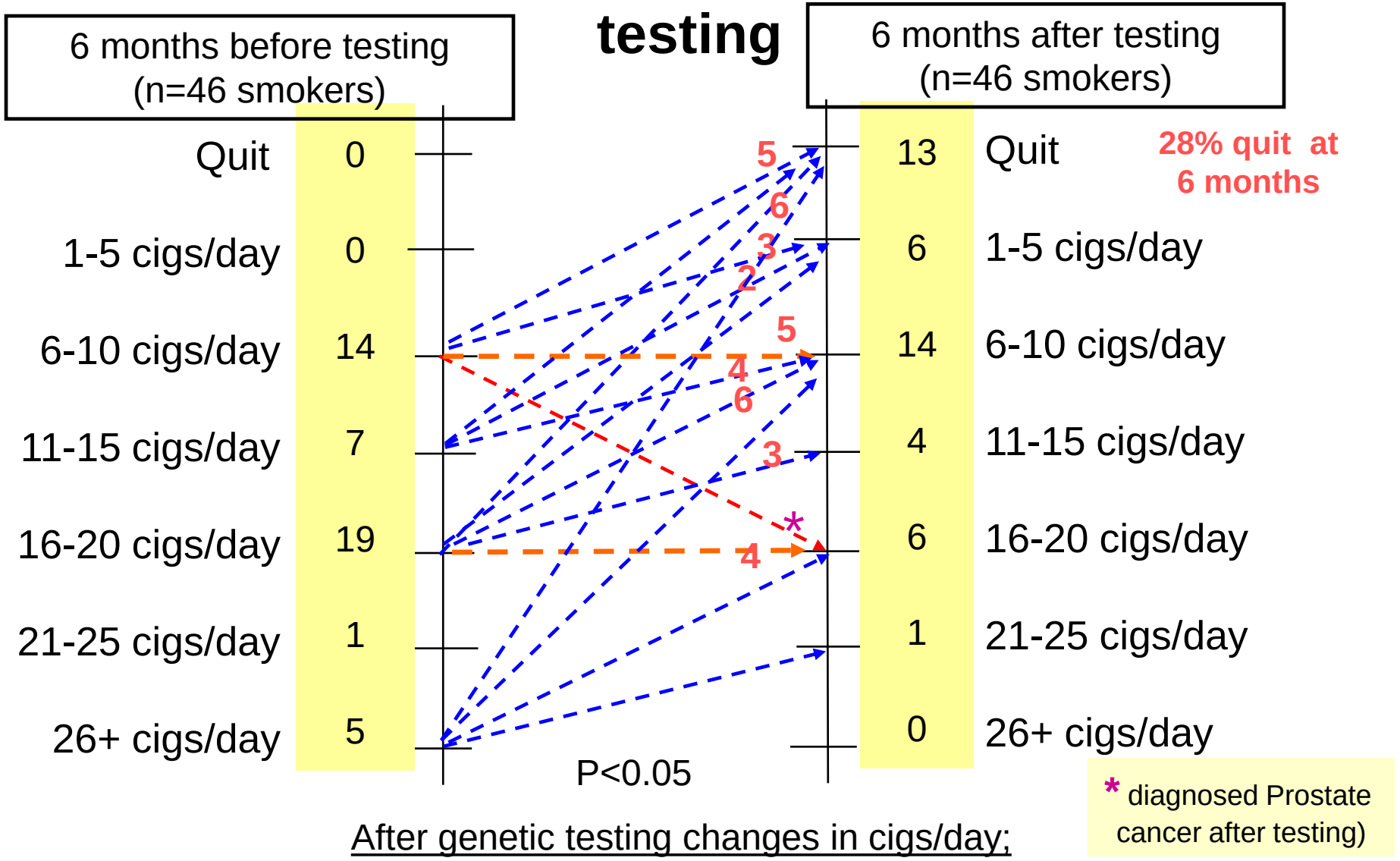
Respiragene Test* identifies those at greatest risk based on the above factors.

Life-long Smoker – has on average a 1 in 10 (10%) lifetime chance of getting lung cancer.

Non-smoker – has on average a 1 in 200 (0.5%) lifetime chance of getting lung cancer.

*Young RP, et al. PlosOne 2009; April 23.

Daily cigarette consumption pre- and post genetic testing



After genetic testing changes in cigs/day;

Overall 78% decreased cigs/day (blue), 13 (28%) Quit smoking, 2 lost to follow up, while 9 (20%) no change (orange) and 1 (2%) increased (red) consumption *

CT screening for lung cancer

NLST trial (NEJM August, 2011)

- RCT of >50,000 current and former smokers in the US aged 55-74 yr and with 30+ pack year history
- Compared yearly CT screening with CXR screening over 3 years
- Showed a 20% reduction in lung cancer mortality
- Concerns remain over low pick up rates, costs and harms from radiation and unnecessary investigation of low risk smokers → **need to better target high risk smoker**

Diagnosis and management of COPD

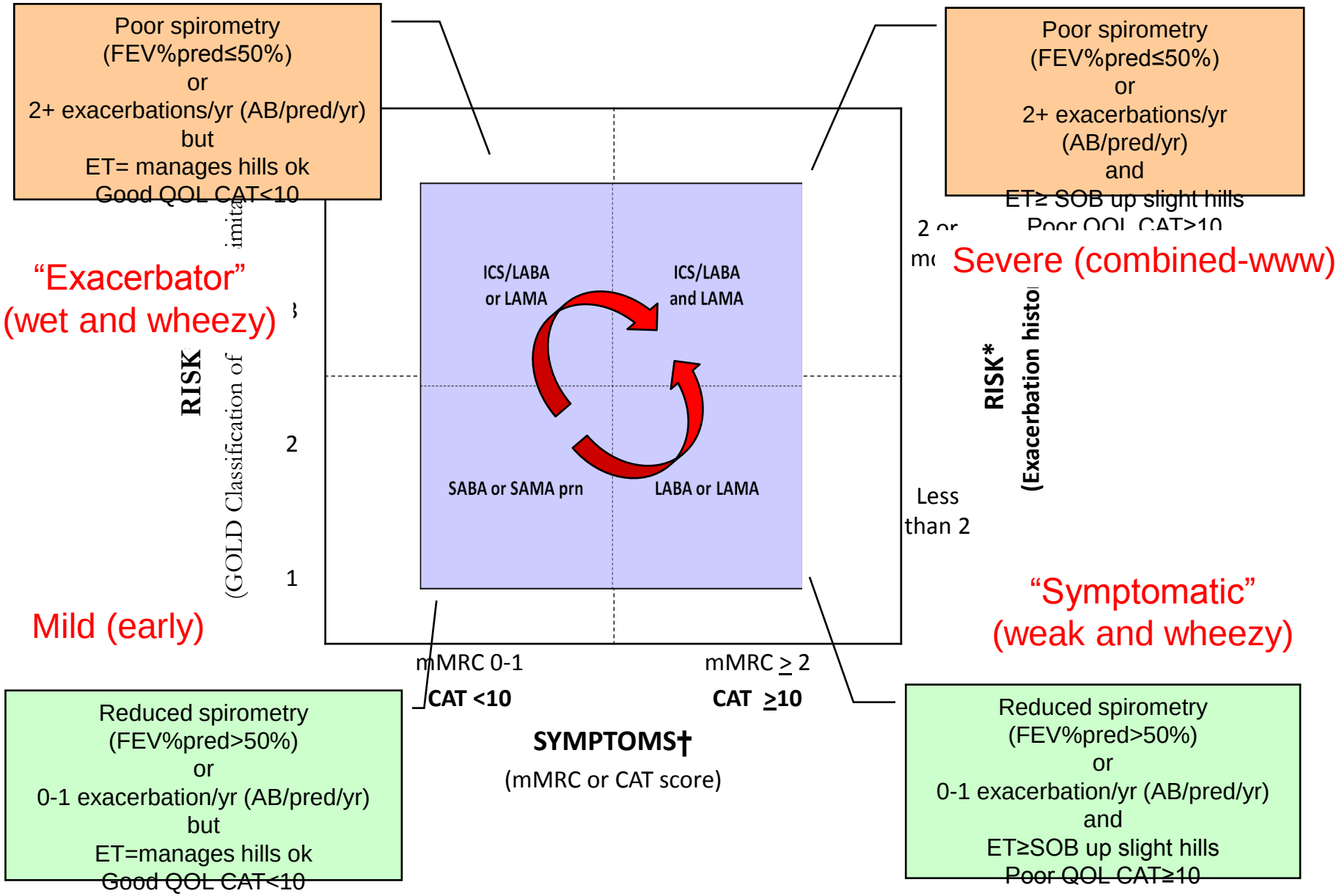
- Diagnose - assess airflow limitation (spir
- Ass
- Ass exac
- Ass musc
- Assess COPD-related comorbidities (CHD/CHF, lung cancer, osteoporosis)
- Manage – reduce risk and reduce symptoms

Diagnose – spirometry

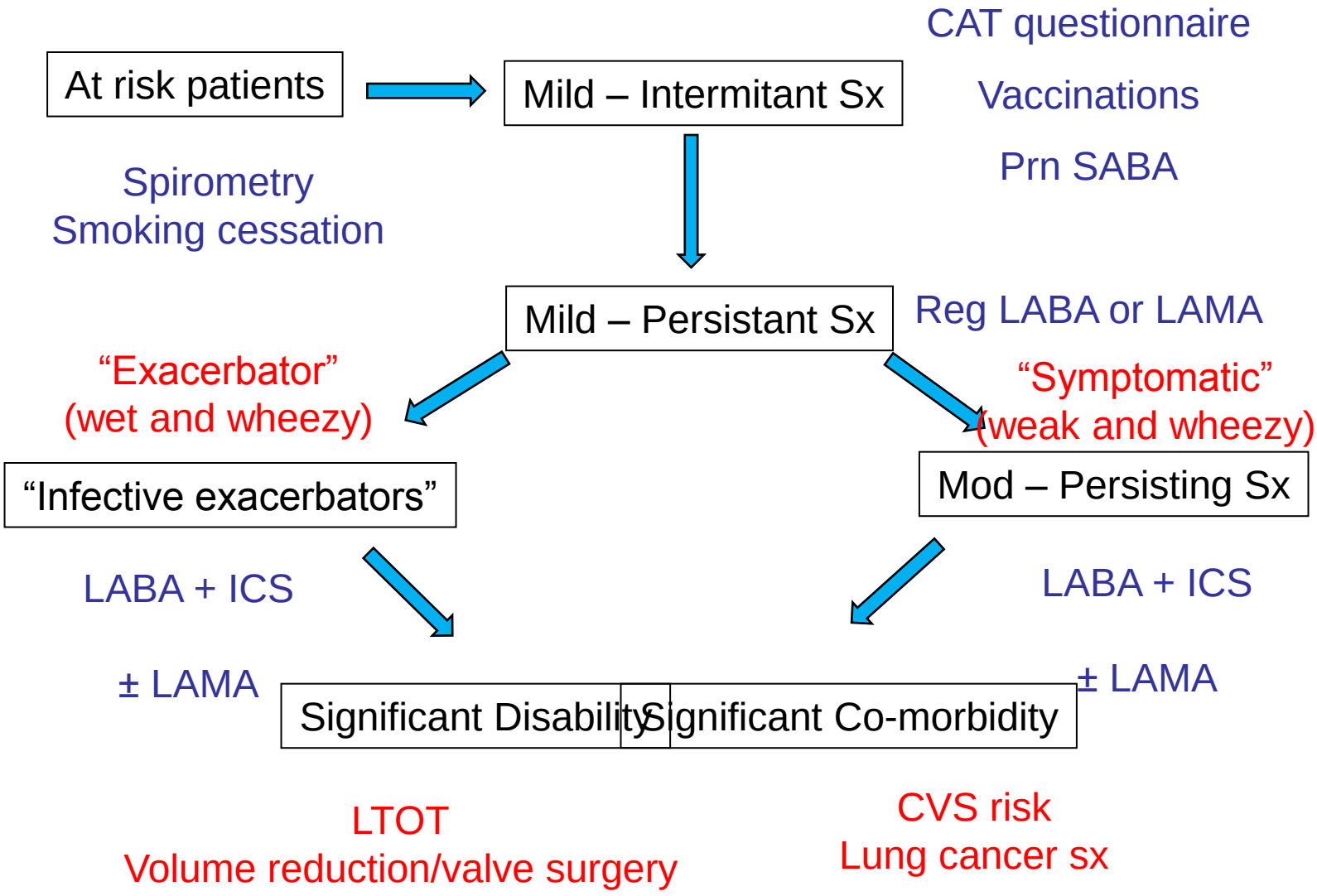
Assess – CAT or mMRC score

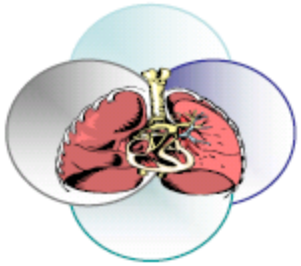
Manage – reduce Sx/exacerbations

New GOLD-defined patient groups



Management of COPD - summary





Lung Health Clinic (Auckland)

Contact us: Ph 0800 789999 or 09 630 9967
or Fax 09 623 6456
or email: lunghealthclinic@adhb.govt.nz

For assessment of patients with breathlessness or suspected of asthma or COPD (especially those exposed to smoking or aero-pollutants).

For lung function testing, medication review, smoking cessation, inhaler technique, COPD unresponsive to treatment and lung cancer screening.

Associate Professor Robert Young,
Consultant Physician (FRACP, PhD)