# Precision Medicine approach
# And
# Obstructive Airway Diseases

Prof Ye Tun

Department of Respiratory Medicine

Thingunkyun General Hospital

# Obstructive airway diseases

- Asthma and COPD

- Have a great personnel and social impact

- May share biological mechanisms (i.e. endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (i.e. phenotypes) which require individualised treatment

# Precision medicine

Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations

# Final objective of precision medicine

To improve clinical outcomes for individual patients while minimizing unnecessary side effects for those less likely to respond to a given treatment

President Barack Obama launched a research initiative aimed at accelerating progress toward a new era of "precision medicine"

The State of the Union Address on January 20, 2015

# Asthma and COPD

- Both asthma and COPD are "complex" and "heterogeneous"
- Complex
  - They have several components with nonlinear dynamic interactions
- Heterogenous
  - Not all of these components are present in all patients or, in a given patient, at all time points

# "Oslerian diagnostic labels"
## Asthma and COPD

- Do not consider novel genetic, molecular or imaging information

- May be valid for the "stereotypical" patients, but it may be of much less clear value in "intermediate" (and frequent) cases

- The pattern of airway inflammation even in classical cases may not be as distinct as has been assumed

# "Oslerian diagnostic label" approach to airway diseases

- Fails to provide optimal care in a significant number of patients because it does not consider the biological complexity of airway diseases and does not consider the distinct endotypes present in each patient

- Does not appreciate common patterns of disease (e.g. chronic cough)
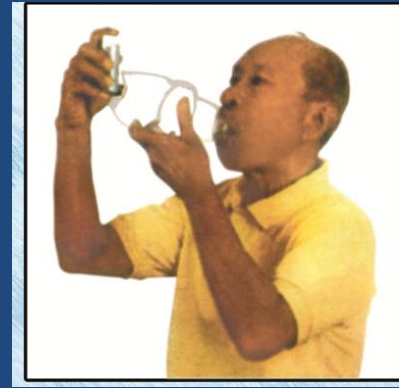
- Can increase clinical practice variability and enhance inappropriate prescription of some drugs (e.g. inhaled corticosteroids) in some patients

- Can contribute to treatment failure and high rates of hospital readmissions

- Inhibits research progress
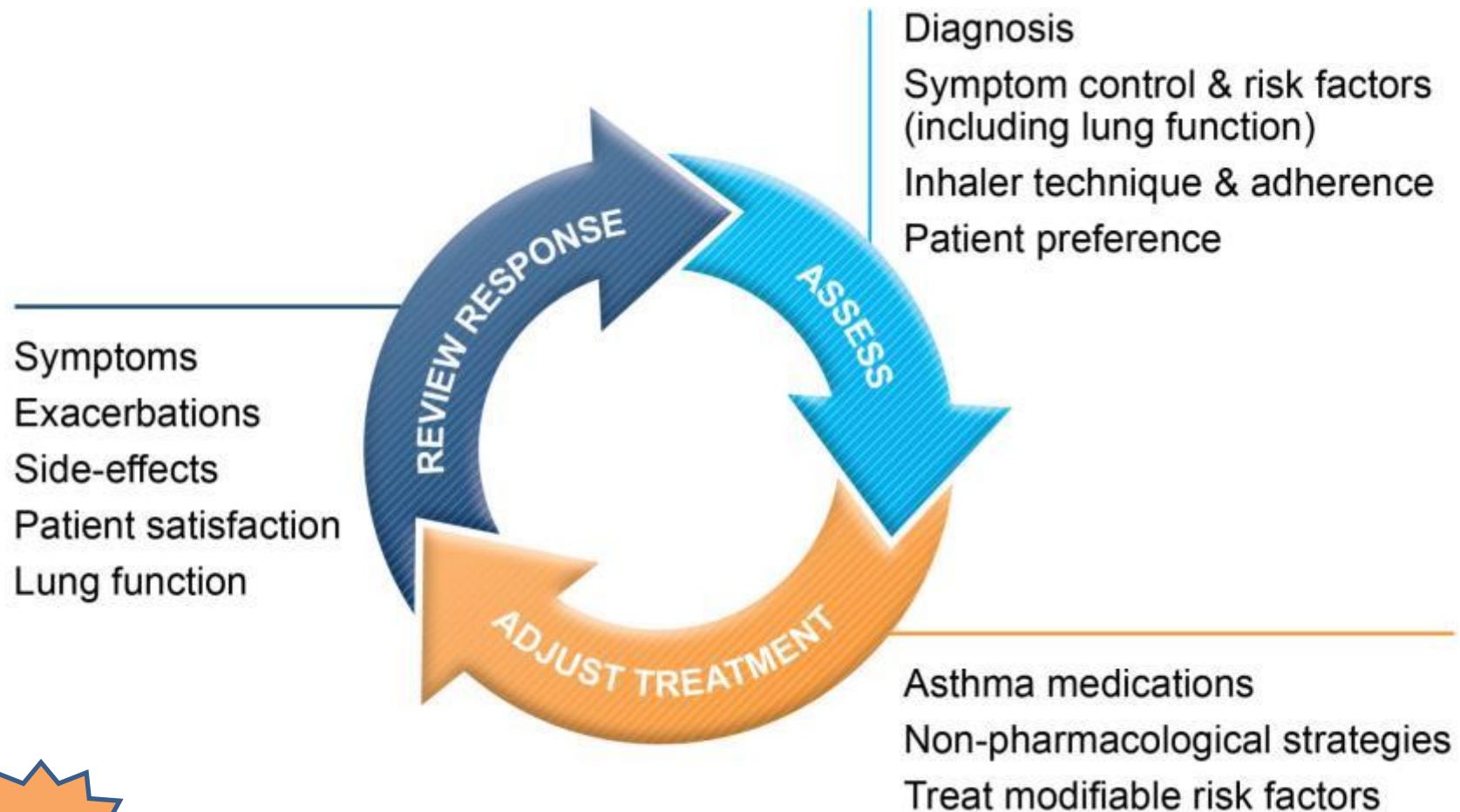
Agusti A, et al, Eur Respir J 2016
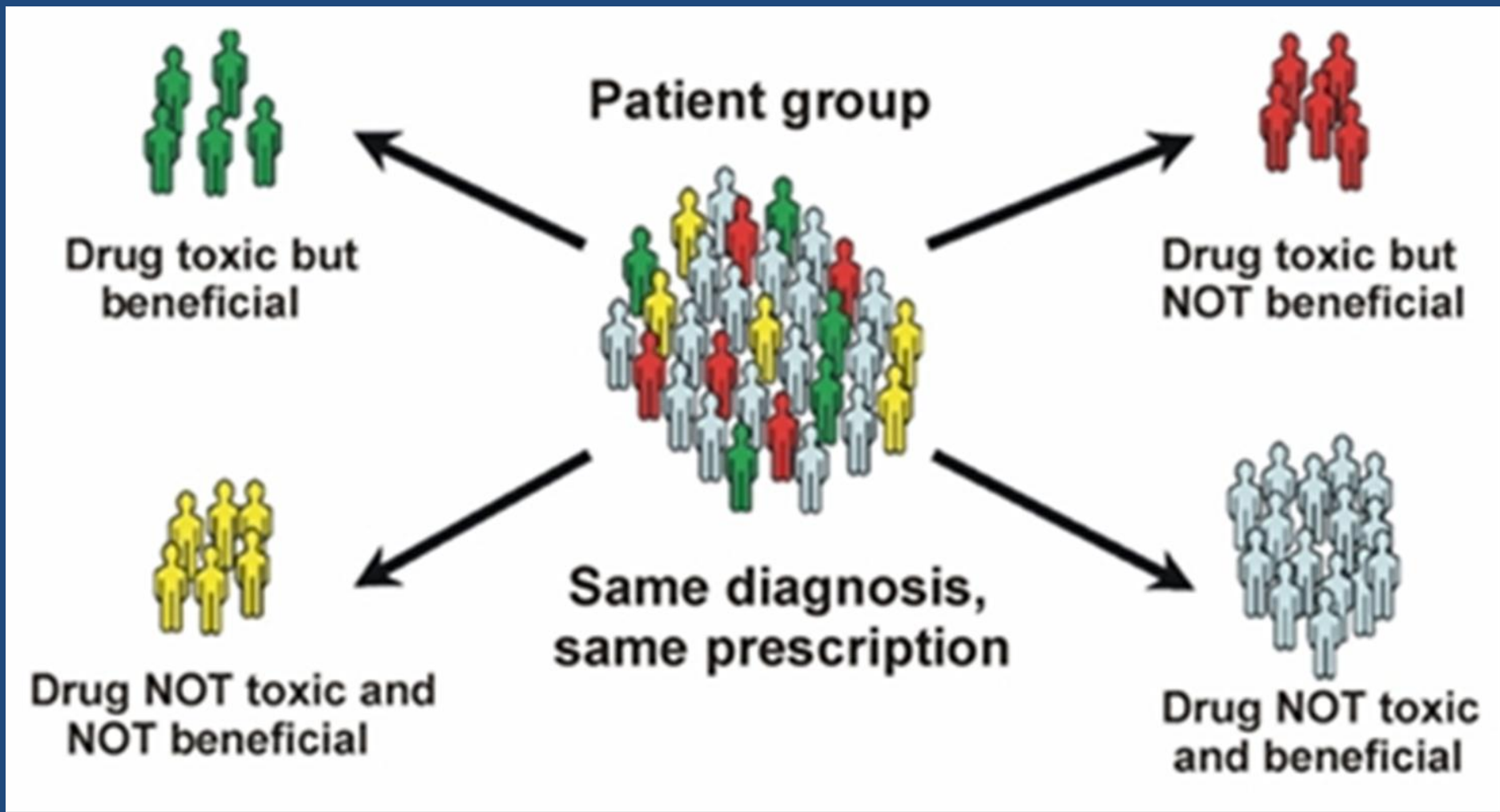
Chakma Justin (Journal of Young Investigators, 2009)

# Precision medicine approach to the diagnosis and management of chronic airway diseases

- "Label-free"

- Based on the identification of "treatable traits" in each patient

- These traits can be "treatable" based on "phenotypic" recognition or on deep understanding of the critical causal pathways (e.g. true "endotypes")

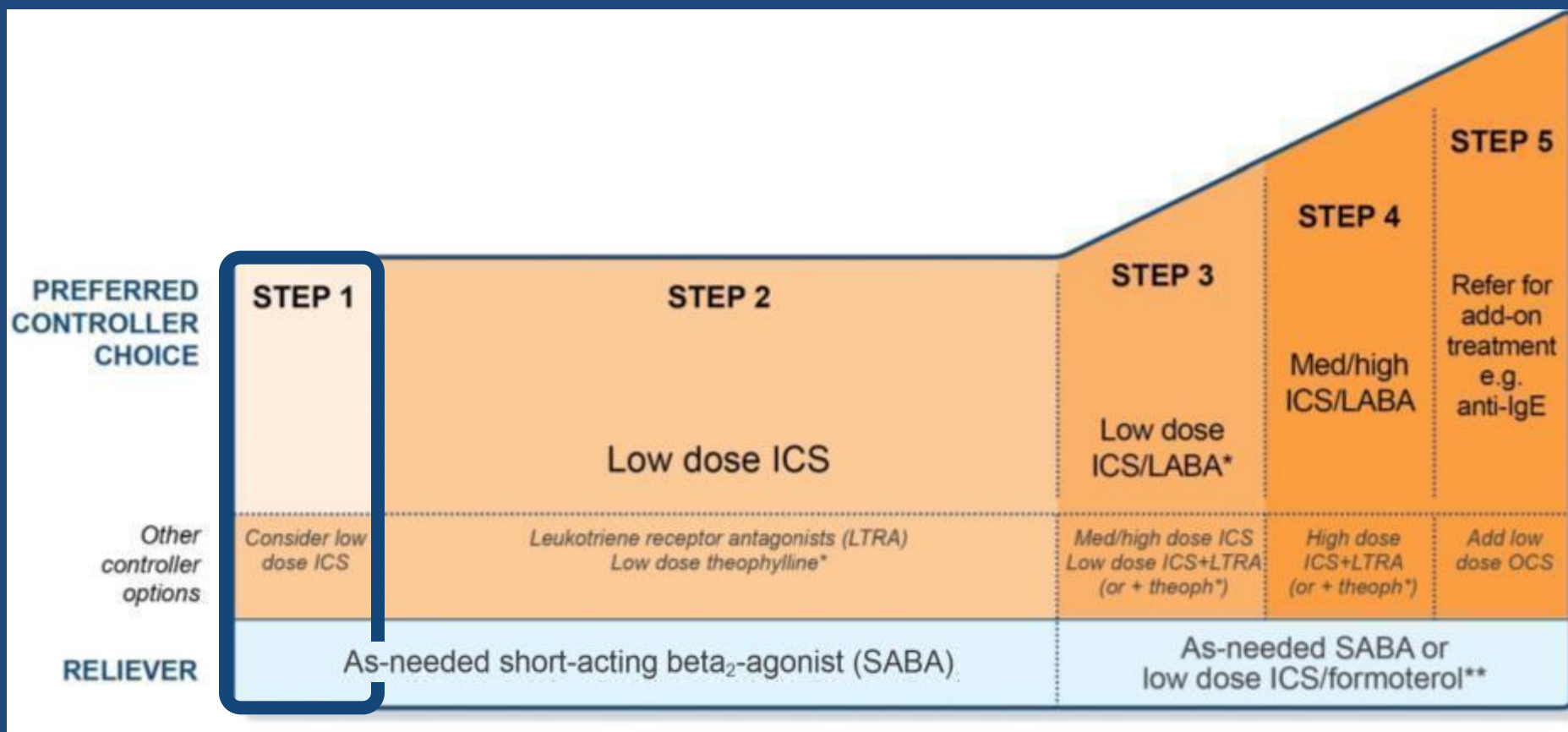# "Oslerian diagnostic label" approach

# The control-based asthma management cycle



Diagnosis

Symptom control & risk factors (including lung function)

Inhaler technique & adherence

Patient preference

Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

Asthma medications

Non-pharmacological strategies

Treat modifiable risk factors

REVIEW RESPONSE

ASSESS

ADJUST TREATMENT

NEW!

**GINA 2014**

# Stepwise management – pharmacotherapy for Asthma

# Combined Assessment of COPD
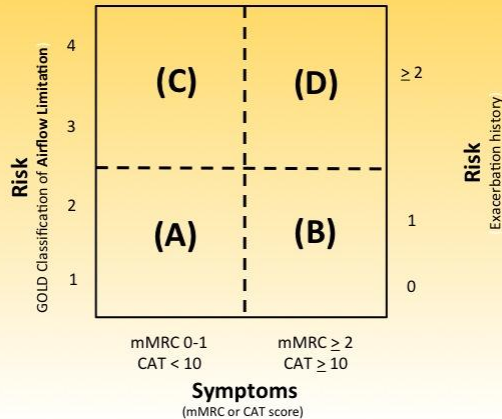


When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history

| Patient | Characteristic | Spirometric Classification | Exacerbations per year | mMRC | CAT |
|---------|----------------|---------------------------|------------------------|------|-----|
| A | Low Risk Less Symptoms | GOLD 1-2 | ≤ 1 | 0-1 | < 10 |
| B | Low Risk More Symptoms | GOLD 1-2 | ≤ 1 | ≥2 | ≥ 10 |
| C | High Risk Less Symptoms | GOLD 3-4 | ≥2 | 0-1 | < 10 |
| D | High Risk More Symptoms | GOLD 3-4 | ≥2 | ≥2 | ≥ 10 |

# Severity of Airflow Limitation in COPD

In patients with $FEV_1/FVC < 0.70$

GOLD 1: Mild  $FEV_1 \geq 80\%$ predicted

GOLD 2: Moderate  $50\% \leq FEV_1 < 80\%$ predicted

GOLD 3: Severe  $30\% \leq FEV_1 < 50\%$ predicted

GOLD 4: Very Severe  $FEV_1 < 30\%$ predicted

*Based on Post-Bronchodilator $FEV_1$*

# Combined assessment

✓ Assess symptoms

✓ Assess degree of airflow limitation using spirometry

✓ Assess risk of exacerbations

*Combine these assessments for the purpose of improving management of COPD*

# Manage Stable COPD:  Non-pharmacologic treatment

| Patient | Essential | Recommended | Depending on local guidelines |
|---------|-----------|-------------|-------------------------------|
| **A** | Smoking cessation (can include pharmacologic treatment) | Physical activity | Flu vaccination Pneumococcal vaccination |
| **B, C, D** | Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation | Physical activity | Flu vaccination Pneumococcal vaccination |

# Manage Stable COPD:  Pharmacologic Therapy

| Patient | First choice | Second choice | | Alternative choices |
|---------|--------------|---------------|---|---------------------|
| **A** | SAMA  prn *or* SABA prn | LAMA *or* LABA *or* SABA and SAMA | | Theophylline |
| **B** | LAMA *or* LABA | LAMA and LABA | | SABA *and/or* SAMA Theophylline |
| **C** | ICS +LABA *or* LAMA | LAMA and LABA | | PDE4-inh. SABA and/*or* SAMA Theophylline |
| **D** | ICS + LABA *or* LAMA | ICS andLAMA *or* ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh.*or* LAMA and LABA *or* LAMA and PDE4-inh. | | *Carbocysteine* SABA and/*or* SAMA Theophylline |

# Precision medicine approach
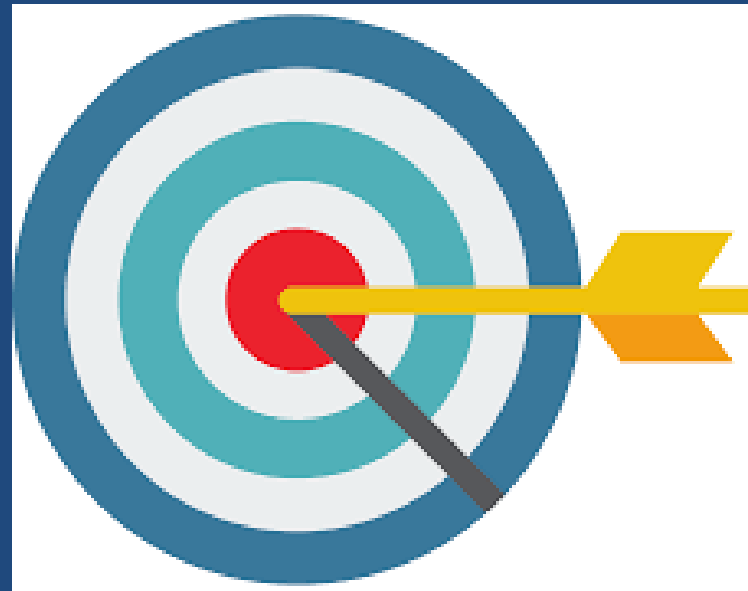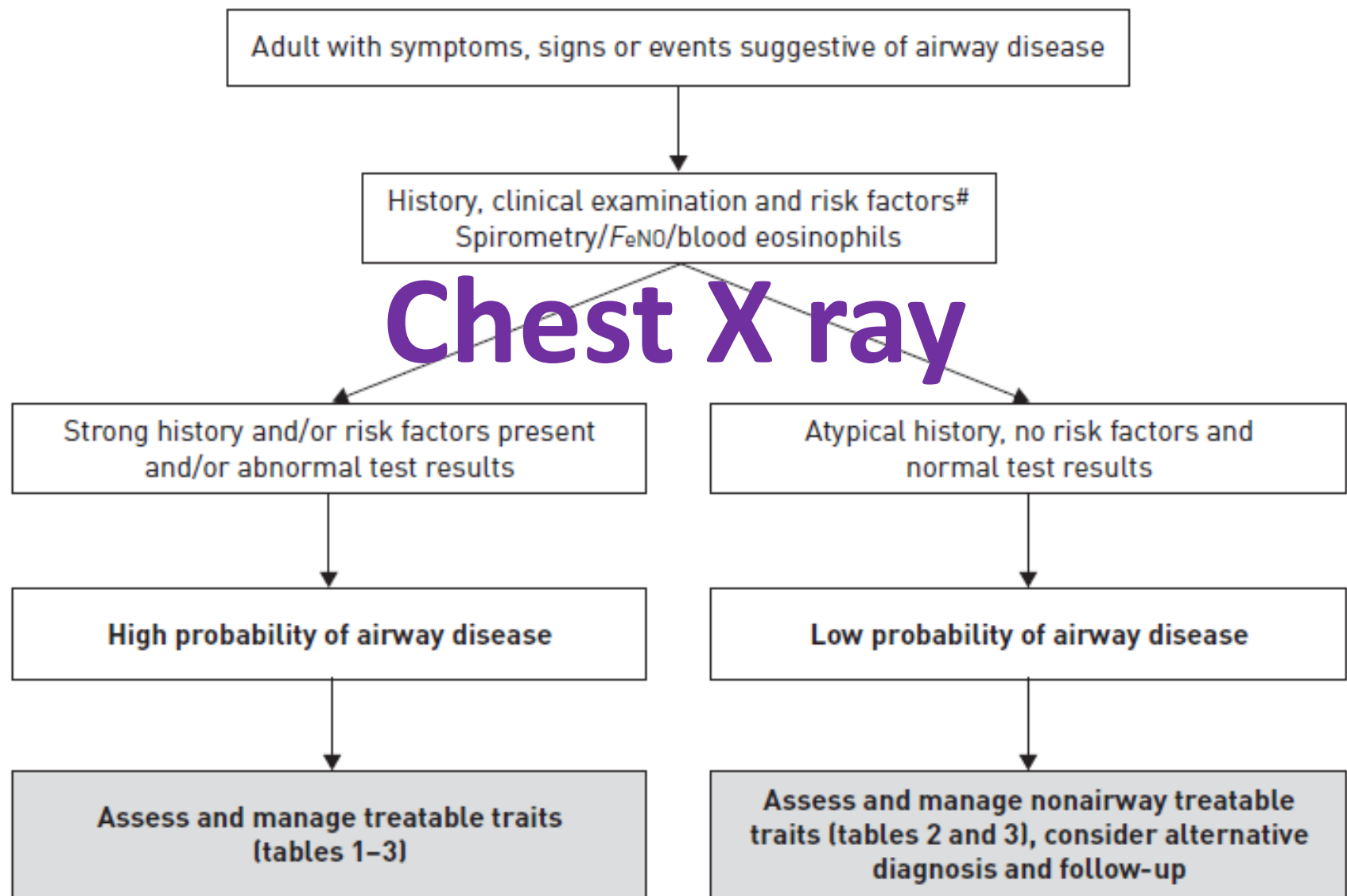
**FIGURE 1** Proposed diagnostic strategy for an adult with symptoms, signs or events suggestive of airway disease. For further explanations, see text. FeNO: exhaled nitric oxide fraction. #: smoking, allergies, sputum production, occupation, lung development and growth.

Agusti A, et al, Eur Respir J 2016

# The relationships between the exposome and the genome (via complex Biological networks)
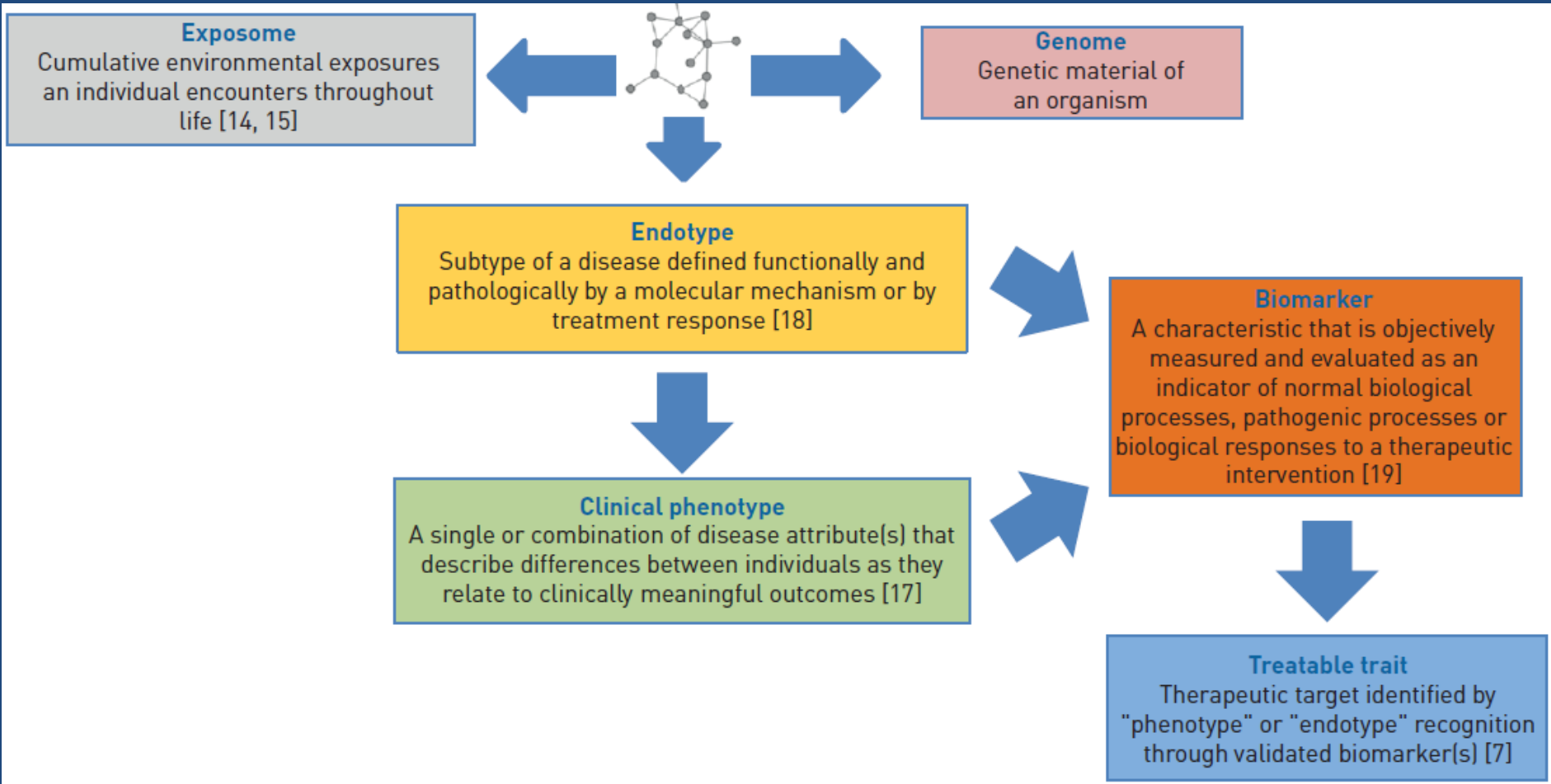
# Treatable traits

- Pulmonary
  - Airflow limitation
  - Eosinophilic airway inflammation
  - Chronic bronchitis
  - Airway bacterial colonisation
  - Bronchiectasis
  - Cough reflex hypersensitivity
  - Pre-capillary pulmonary hypertension
  - Chronic respiratory failure
- Extrapulmonary
- Behaviour/lifestyle risk factors

# Airflow limitation

$FEV_1/FVC < 0.7$ (or lower limit of normal

- Airway smooth muscle contraction

- Loss of elastic recoil (emphysema)

- Airway mucosal oedema

# Airway smooth muscle contraction

## Diagnostic criteria

- Bronchodilator reversibility
- peak expiratory flow variability
- positive PC20

# Treatment

**First choice**

- Maintenance:
  - long-acting β2-adrenergic agonists/muscarinic antagonists;
- Rescue:
  - short-acting β2-adrenergic agonists/muscarinic antagonists

**Second choice**

- Inhaled corticosteroids
- Bronchial thermoplasty

# Loss of elastic recoil (emphysema)

**Diagnostic criteria**

- Chest computed tomography
- DLCO, compliance

**First choice**

- Smoking cessation

**Second choice**

- Lung volume reduction surgery
- lung transplantation
- $\alpha$1-anti-trypsin replacement if deficient, valves, coils

# Airway mucosal oedema

Diagnostic criteria

- Chest computed tomography
- Spirometry-induced bronchoconstriction

**First choice**

- Inhaled corticosteroids

**Second choice**

- Oral corticosteroids,
- Anti-interleukin-5, -13, -4

# Eosinophilic airway inflammation

## Diagnostic criteria

- Sputum eosinophils
- Blood eosinophils
- FeNO, (periostin)

**First choice**

- Inhaled corticosteroids

**Second choice**

- Oral corticosteroids
- Leukotriene receptor antagonists
- Anti-IgE
- Anti-interleukin-5, -13, -4

# Chronic bronchitis

## Diagnostic criteria

- Cough and sputum 3 months × 2 years (no eosinophilic airway inflammation)

**First choice**

- Smoking cessation

**Second choice**

- Carbocysteine,
- Macrolides
- Roflumilast

# Airway bacterial colonisation

Diagnostic criteria

- Sputum culture,
- Quantitative PCR

**First choice**
- Antibiotics

**Second choice**
- Long-term low-dose macrolides
- vaccination

# Bronchiectasis

Diagnostic criteria

- Chest X ray
- Chest computed tomography

**First choice**

- Drainage

**Second choice**

- Macrolides, nebulised antibiotics
- Surgery
- Vaccination

# Cough reflex hypersensitivity

Diagnostic criteria

- Capsaicin challenge, cough
- counts, cough questionnaire

**First choice**

- Speech and language treatment

**Second choice**

- Gabapentin

# Pre-capillary pulmonary hypertension

Diagnostic criteria

- Doppler echocardiography,
- Brain natriuretic peptide,
- Right heart catheterisation

**First choice**

- Long-term (domiciliary) oxygen therapy

**Second choice**

- Noninvasive ventilation
- Lung transplantation

# Chronic respiratory failure

- Arterial hypoxemia

- Arterial hypercapnia

# Arterial hypoxemia

Diagnostic criteria

- PaO$_2$ <55 mmHg

**First choice**

- Long-term (domiciliary) oxygen therapy

# Arterial hypercapnia

Diagnostic criteria

- $PaCO_2$ >45 mmHg

**First choice**

- Optimized medical therapy

**Second choice**

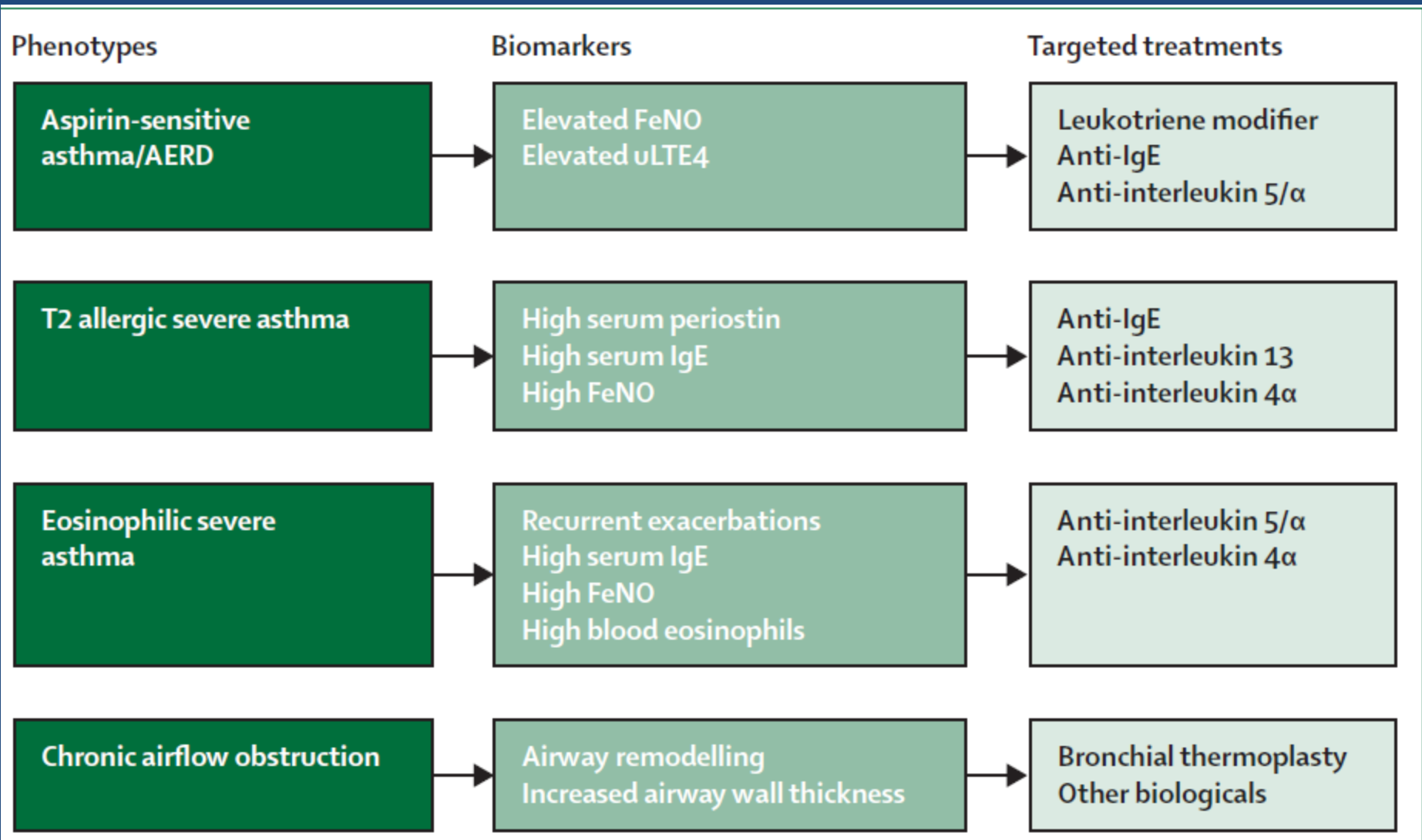- Noninvasive ventilation
- Lung transplantation

# Extrapulmonary treatable traits of airway diseases

- Deconditioning
- Obesity
- Cachexia
- OSA
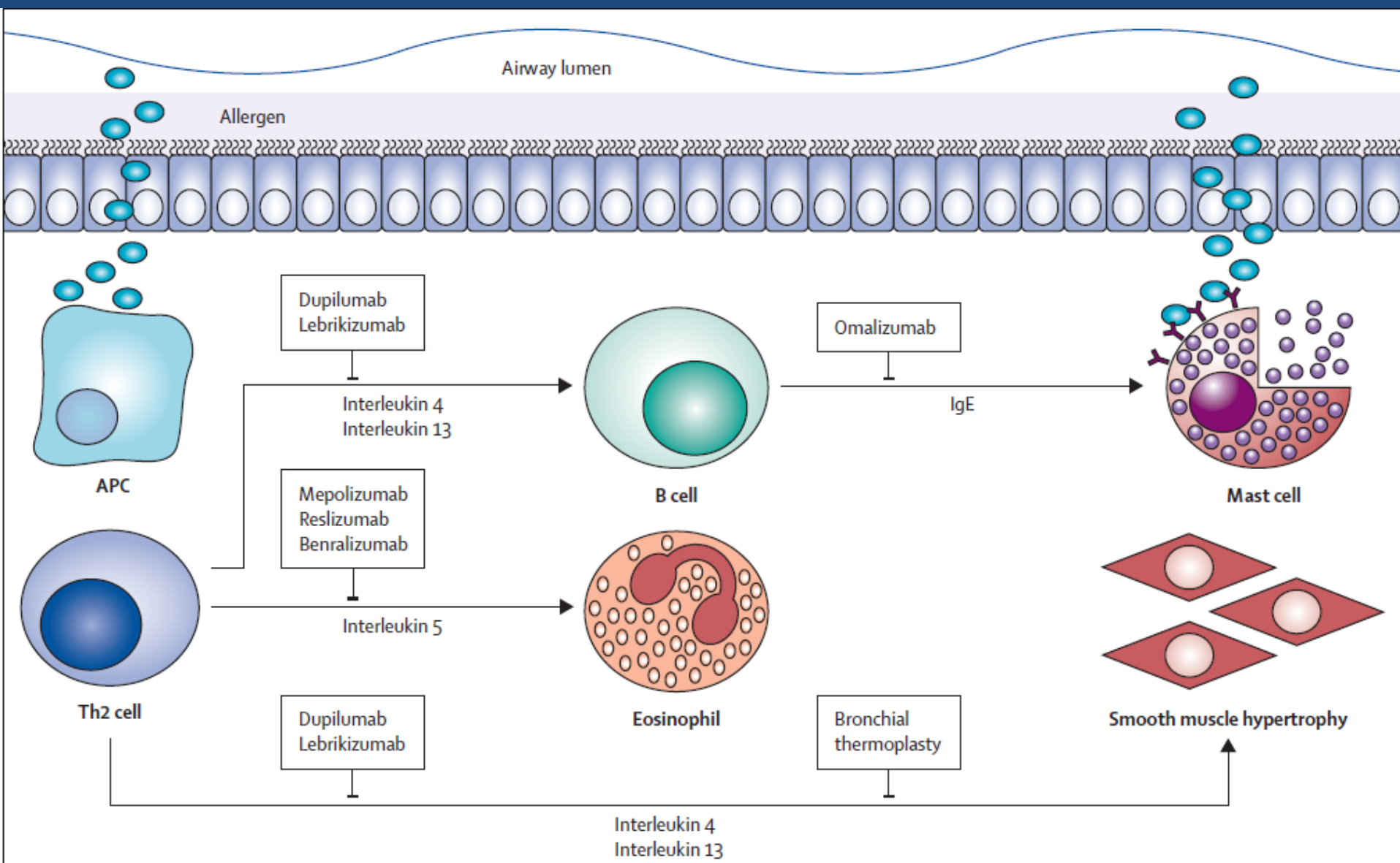- CVD
- GERD
- Rhino-sinusitis
- Psychiatric disorders

- Persistent systemic inflammation
- Smoking and others
- Exposure to sensitizing agents/pollution
- Symptom perception
- Inhaler device
- Adherence to treatment
- Family and social support

| Trait | Treatment |
|---|---|
| **Pulmonary treatable traits** | |
| Airway smooth muscle contraction | Bronchodilators |
| Eosinophilic airway inflammation | Corticosteroids/Type 2 biologics |
| Chronic sputum production | Smoking cessation, macrolides, PDE4 inhibitors |
| Bacterial colonisation | Macrolides, tetracyclines |
| Bronchiectasis | Macrolides, tetracyclines, nebulised antibiotics/aminoglycosides |
| Cough reflex hypersensitivity | Gabapentin, P2X3, speech pathology intervention |
| Chronic respiratory failure | Oxygen/NIV/lung transplant |
| Pulmonary hypertension | Oxygen/NIV/lung transplant |
| Emphysema | Lung volume reduction/transplant |
| **Extrapulmonary treatable traits** | |
| Rhinosinusitis | Topical steroids/surgery |
| Deconditioning | Rehabilitation |
| Cachexia | Diet/physical activity |
| Obesity | Diet/physical activity/bariatric surgery |
| Cardiovascular disease | ACE inhibitors/diuretics/$\beta$-blockers |
| Vocal cord dysfunction | Speech pathology therapy |
| Depression | Cognitive and behavioural therapy |
| Anxiety | Anxiolytics |
| Systemic inflammation | Statins? |
| **Treatable behavioural/lifestyle factors** | |
| Poor inhalation technique | Education |
| Nonadherence to treatment | Reassurance/education/periodic check-up |
| Smoking | Cessation support |
| Exposure to sensitising agents | Avoidance/desensitisation |
| Side-effects of treatments | Treatment optimisation |
| Polypharmacy | Medication review |
| Poor family and social support | Family therapy education/self-management support |

# Targeted treatments for Asthma



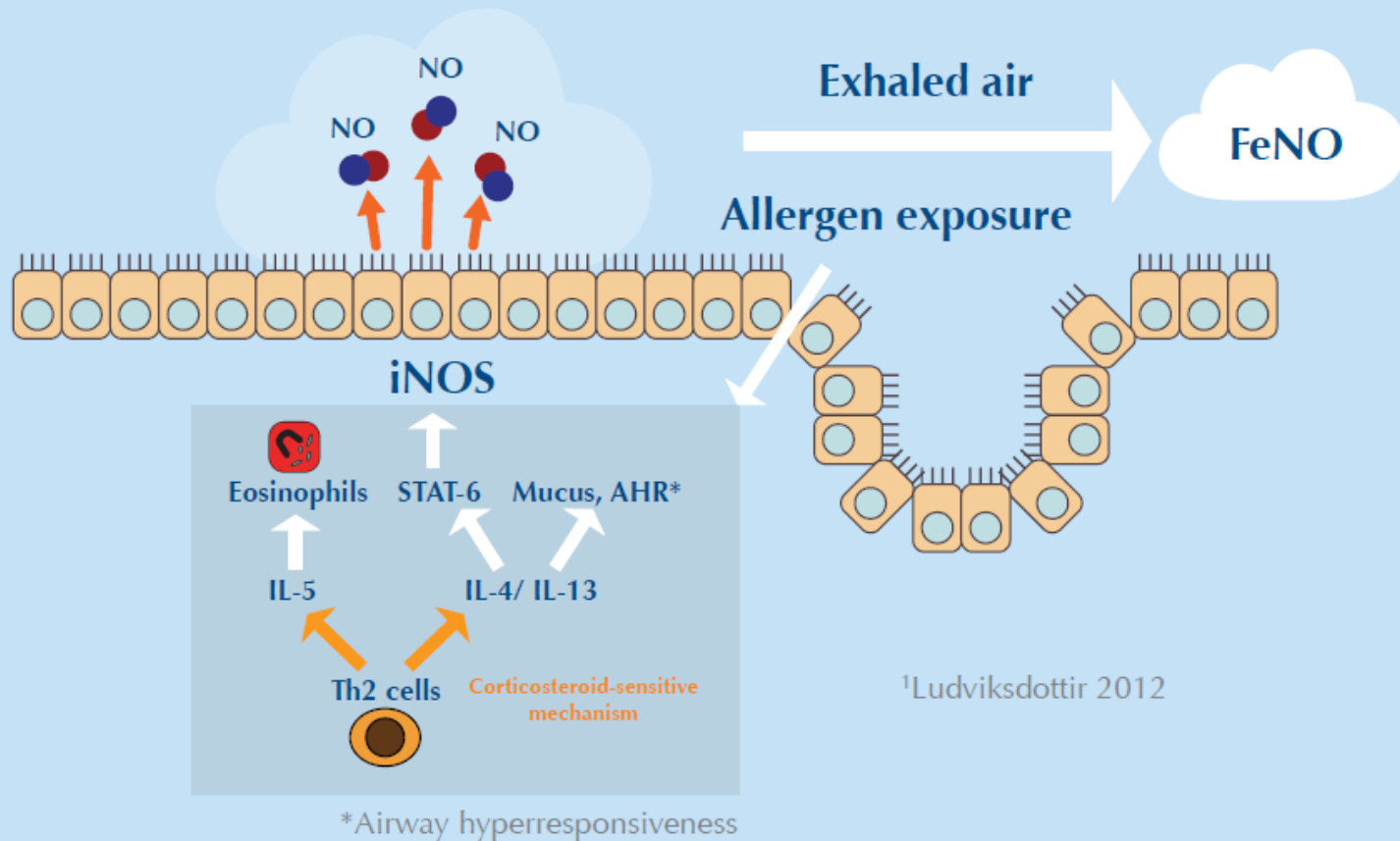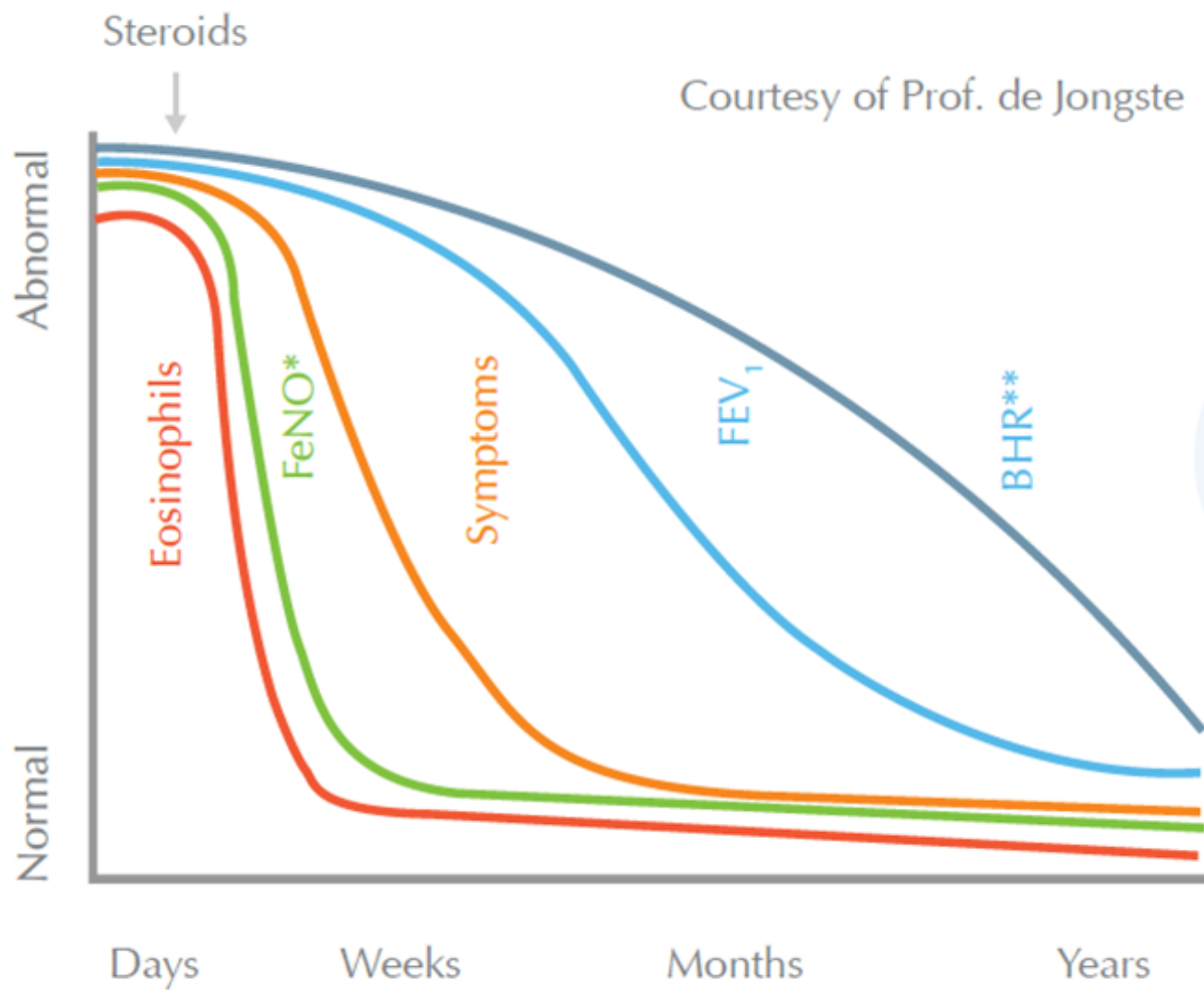| Phenotypes | Biomarkers | Targeted treatments |
|---|---|---|
| Aspirin-sensitive asthma/AERD | Elevated FeNO<br>Elevated uLTE4 | Leukotriene modifier<br>Anti-IgE<br>Anti-interleukin 5/α |
| T2 allergic severe asthma | High serum periostin<br>High serum IgE<br>High FeNO | Anti-IgE<br>Anti-interleukin 13<br>Anti-interleukin 4α |
| Eosinophilic severe asthma | Recurrent exacerbations<br>High serum IgE<br>High FeNO<br>High blood eosinophils | Anti-interleukin 5/α<br>Anti-interleukin 4α |
| Chronic airflow obstruction | Airway remodelling<br>Increased airway wall thickness | Bronchial thermoplasty<br>Other biologicals |

Trivedi A, et al, Lancet Respir Med 2016

# FENO, Fractional exhaled Nitric Oxide

- A reliable indicator of corticosteroid-responsive (Th2 driven) airway inflammation
- Monitor anti-inflammatory treatment effectiveness
- FeNO* testing of asthma patients or suspected asthma measures allergic airway inflammation

# FeNO IS A BIOMARKER OF INFLAMMATION



NO
NO    NO

Exhaled air → FeNO

Allergen exposure

iNOS

Eosinophils    STAT-6    Mucus, AHR*

IL-5    IL-4/ IL-13

Th2 cells    Corticosteroid-sensitive mechanism

[1]Ludviksdottir 2012

*Airway hyperresponsiveness

Courtesy of Prof. de Jongste

Steroids

Abnormal

Normal

Eosinophils — FeNO* — Symptoms — FEV₁ — BHR**

Days — Weeks — Months — Years

NIOX

**FeNO\* Test:** Initial Patient Visit

*Fractional exhaled Nitric Oxide

Help reveal if ICS will benefit patient

Assessment of inflammation

Is it steroid responsive inflammation?

Example values

FeNO 18 ppb — Unlikely

FeNO 54 ppb — Likely

Follow-up Visit

Help optimise ICS dose

Monitor treatment

Is anti-inflammatory therapy working?

Example values

FeNO 12 ppb — Likely

FeNO 62 ppb — Unlikely

Follow-up Visit

Help detect Non-adherence to ICS

Meaningful patient dialogue

Is the patient possibly not adhering to therapy?

Example values

FeNO 15 ppb — Unlikely

FeNO 78 ppb — Lik ely

# Bronchial Thermoplasty

- A non-drug procedure for severe persistent asthma in patients 18 years and older whose asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonists.



Bronchial Thermoplasty™ with the Alair® System by Asthmatx

Asthmatx
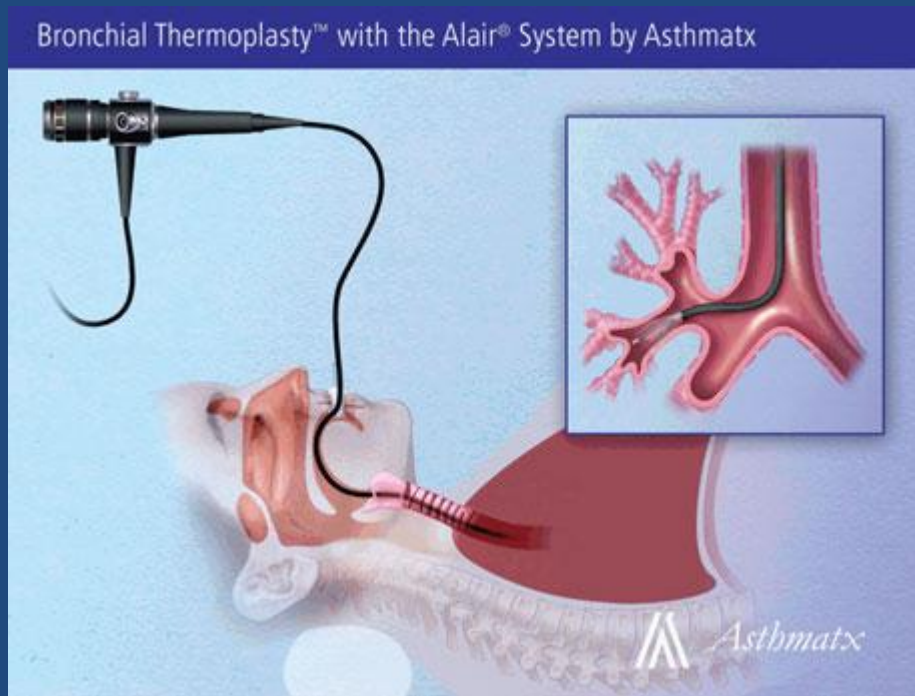
U.S. Food and Drug Administration (FDA) approved bronchial thermoplasty on April 27, 2010.

# Basic principle

- Delivers thermal energy  to the airway wall, in a precisely controlled manner, in order to <u>reduce excessive airway smooth muscle.</u>

- Reducing airway smooth muscle decreases the ability of the airways to constrict, thereby <u>reducing the frequency of asthma attacks.</u>
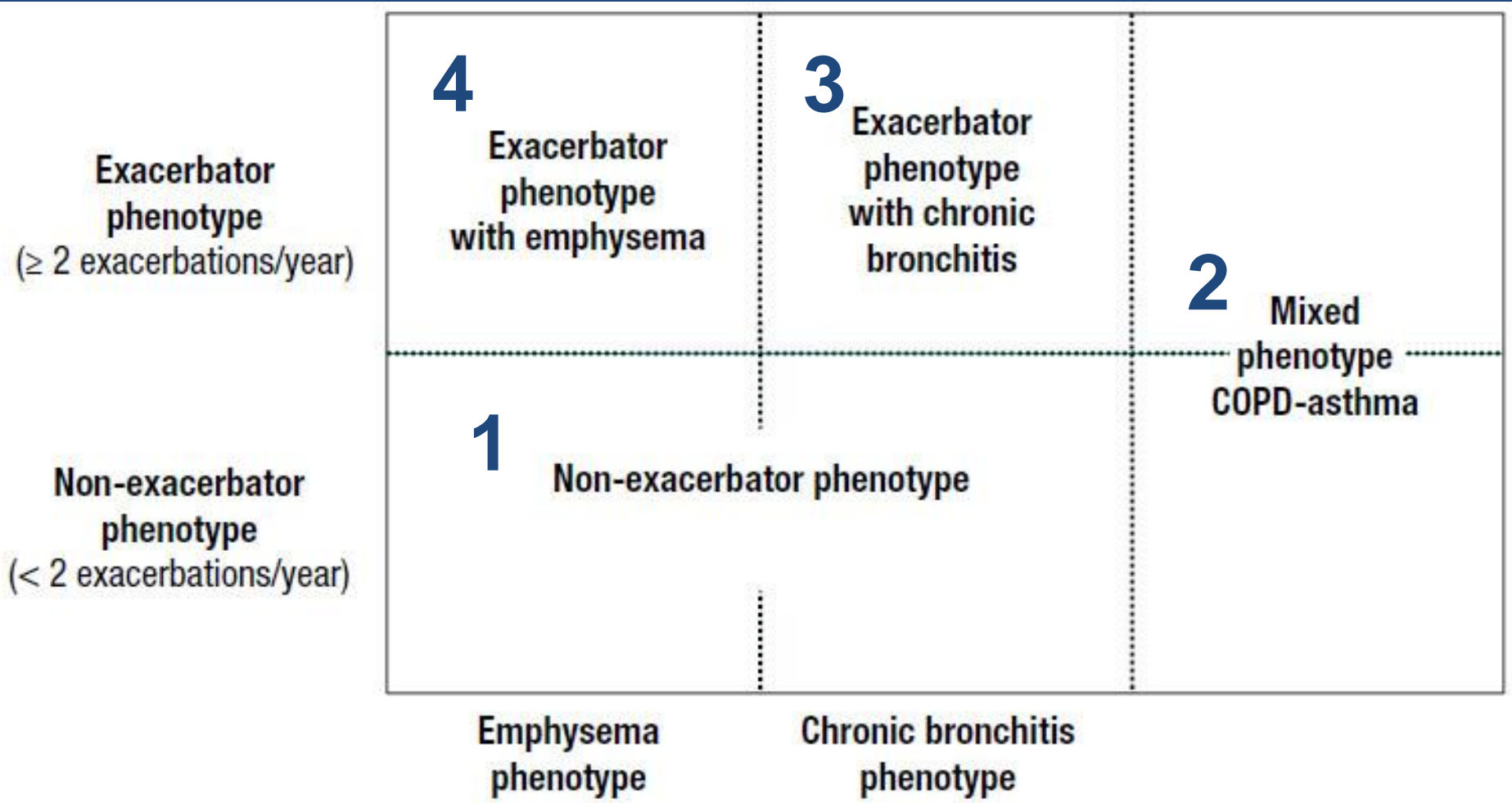
# Procedure

- Minimally invasive bronchoscopic procedure

- Performed in three outpatient procedure visits,

- Each treating a different area of the lungs

- Scheduled approximately three weeks apart.

- Should never be applied without proper <u>anti-inflammatory pharmacotherapy in these patients.</u>

# Phenotypes of COPD

# Pharmacological treatment of COPD according to phenotypes

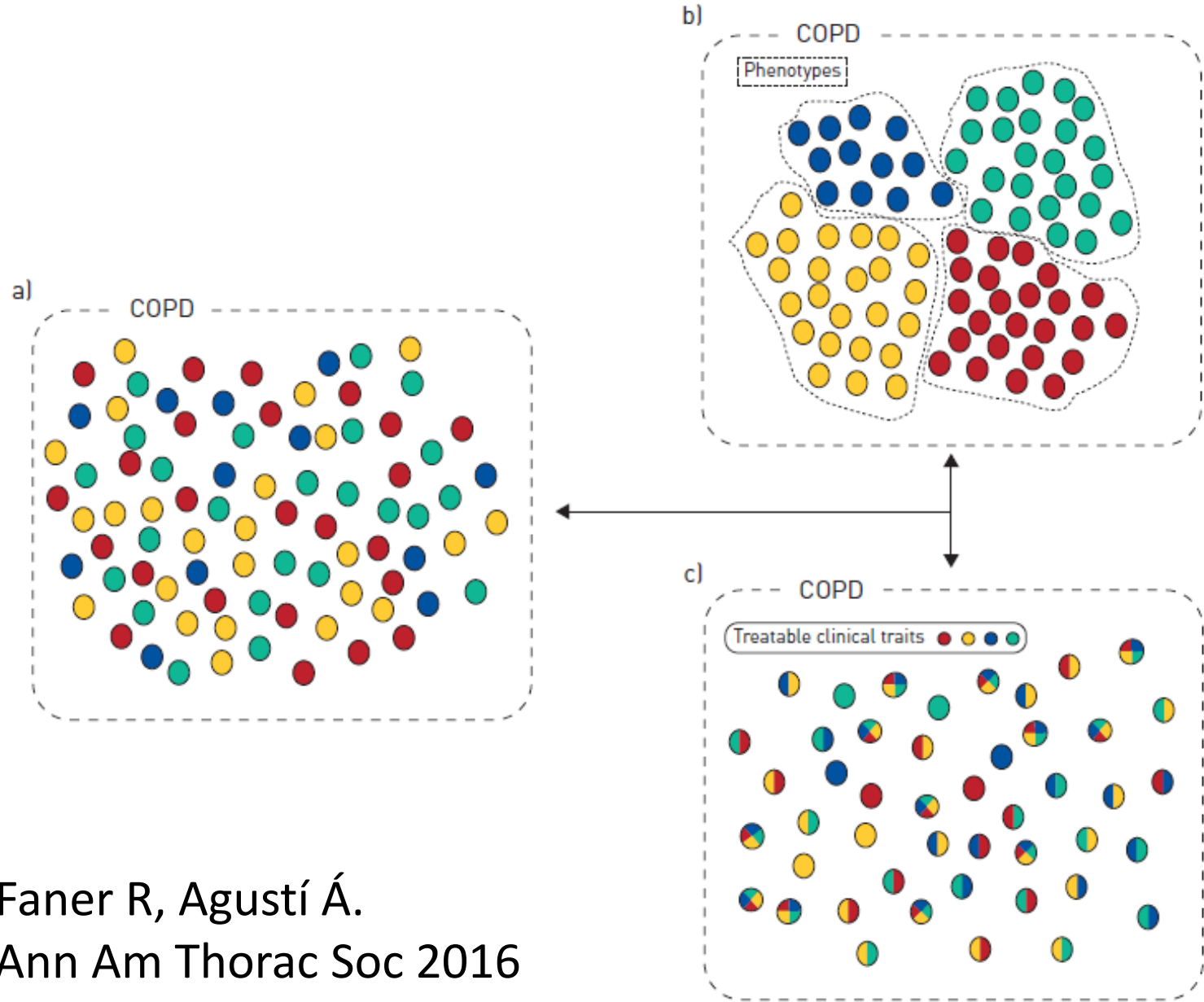| No exacerbator | Overlap COPD-asthma | Exacerbator with emphysema | Exacerbator with chronic bronchitis |
|---|---|---|---|
| Long-acting bronchodilators | | | |
| | Inhaled corticosteroids | | |
| | | Mucolytics | |
| | | | PDE$_4$ inhibitors |
| | | | Macrolides |

# COPD heterogeneity



Faner R, Agustí Á.
Ann Am Thorac Soc 2016

Rooney C and Sethi T, Ann. N.Y. Acad. Sci. 2015
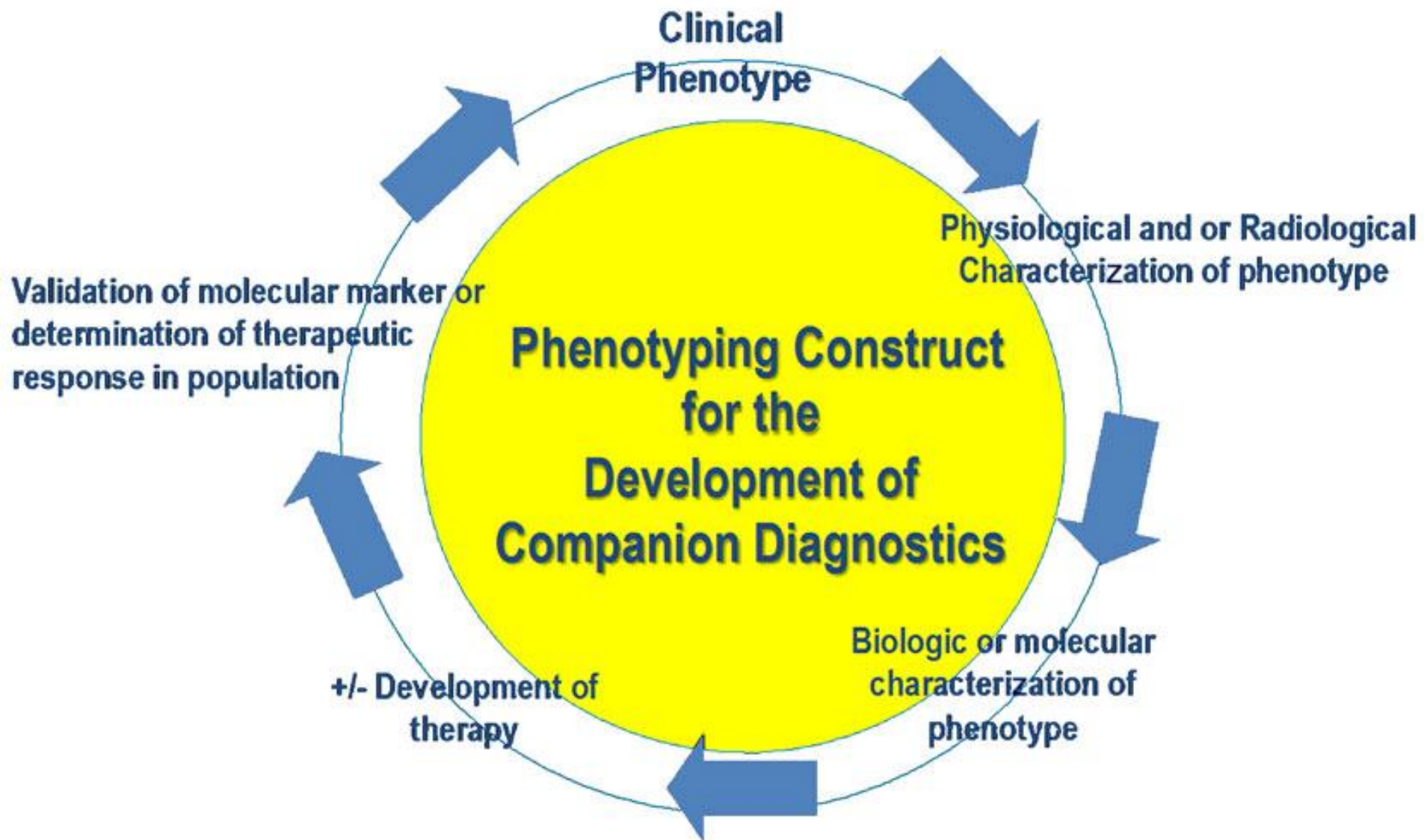
Physicians always try to be as precise as possible in relation to the needs of individual patients - Best care for patients

# Thank You for Your Attention!

# Questions?