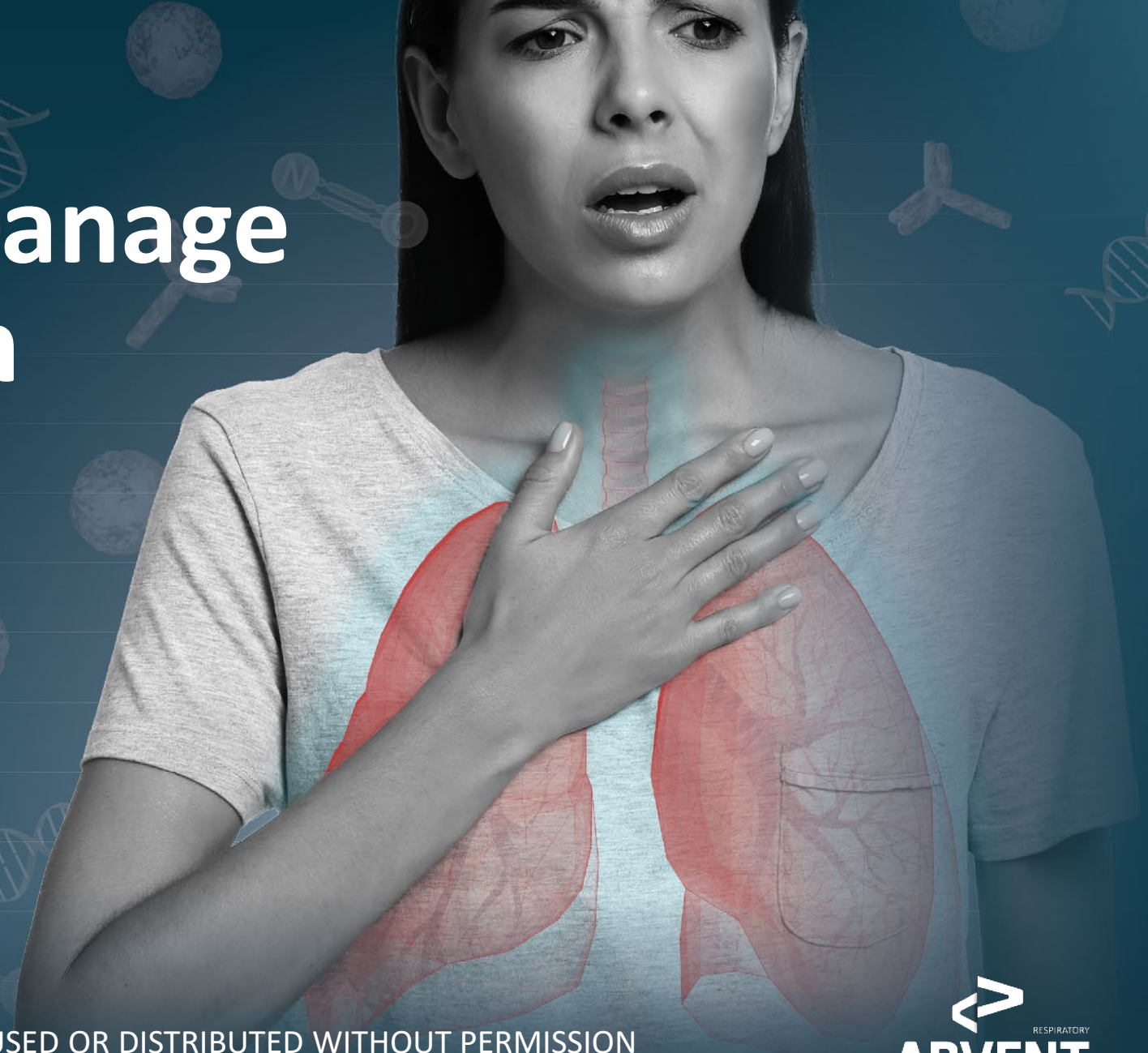
Biomarkers to manage severe asthma in clinical practice



MAT-AU-2300328 | Date of preparation March 2023| Sanofi Australia (Macquarie Park, NSW)

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

CHAIR

Prof Brian Oliver

Distinguished Professor of Respiratory Medicine at UTS and a Research Leader at the Woolcock Institute of Medical Research

Professor Brian Oliver investigates the causes and consequences of respiratory diseases. His research focuses on asthma and COPD and spans basic to clinical.

Brian's scientific training began at the National Heart and Lung Institute, UK. He then had further training in both molecular biology (University of Leeds), and respiratory virology at Professor Sebastian Johnston's laboratory at Imperial College, London, before commencing his PhD at the University of Sydney (supervised by Professor Judith Black).

Brian also serves the research community as President of the Thoracic Society of Australia and New Zealand's NSW branch, and he is a regular expert commentator in the media

SPEAKER

Prof Ian Pavord

Professor of Respiratory Medicine, University of Oxford and

Honorary Consultant Physician at the Oxford University Hospitals

Professor Pavord has a particular interest in asthma, chronic pulmonary disease and chronic cough. He is an internationally renowned researcher in these areas and has played a lead role in developing three of the most promising emerging treatments. He has published 350 scientific papers, including three of the 20 most cited papers in the field in the last 10 years. He has an H-index of 74. His main contribution has been to develop new methods to assess and treat airway inflammation and airway diseases. He has been joint Chief Medical Advisor to Asthma UK since May 2008 and joint Editor of Thorax since 2010. In 2016 Professor Pavord was awarded The ERS Gold Medal in Asthma in recognition of his outstanding contribution in the field of asthma research.

SPEAKER

Prof Peter Wark

Senior staff specialist in Respiratory, Sleep & General Medicine John Hunter Hospital and Hunter New England Local Health District

Prof Peter Wark is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital & Hunter New England Local Health District. He is a conjoint Professor with the University of Newcastle. In addition, Prof Wark is a senior member of the Priority Research Centre for Healthy Lungs and a member of the Vaccines Immunology Viruses and Asthma research group at the Hunter Medical Research Institute. He has been a member of the TSANZ executive board and chairman of the clinical care and resources subcommittee since 2011.

AGENDA

19:00	**Opening & Speaker Introduction**	Prof Brian Oliver (Chair)
19:05	**Challenges & Advances in Severe Asthma Management – UK Perspective (Clinical Utility of ORACLE scale and Sub-Stratification of Type-2 High Airway Disease for Therapeutic Decision-Making)**	Prof Ian Pavord
19:30	**Biomarkers for Asthma in Australia**	Prof Peter Wark
19:55	**Panel Discussion - Facilitated by Prof Brian Oliver**	All
20:25	**Final Remarks**	Prof Brian Oliver (Chair)
20:30	**Meeting Close**	

RESPIRATORY ADVENT
ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

Biomarkers to Manage Severe Asthma in Clinical Practice: UK Perspective

Ian Pavord

Professor of Respiratory Medicine, University of Oxford

Honorary Consultant Physician, University of Oxford Hospitals NHS Trust

Disclosures

Speaker's honoraria:
AstraZeneca, Boehringer Ingelheim, Aerocrine, Chiesi, Novartis, Sanofi, Regeneron, and GSK

Advisory panels:
Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp, Sanofi, and Regeneron

Sponsorship:
Boehringer Ingelheim, GSK, AstraZeneca, Chiesi, and Napp

Disclaimer

This case study was selected by Prof Pavord independently of the sponsor

It gives general information on treatment considerations based on recent data and the individual case study. The presenter is providing their own experiences

Nothing in this presentation should be construed as medical advice since each patient is different

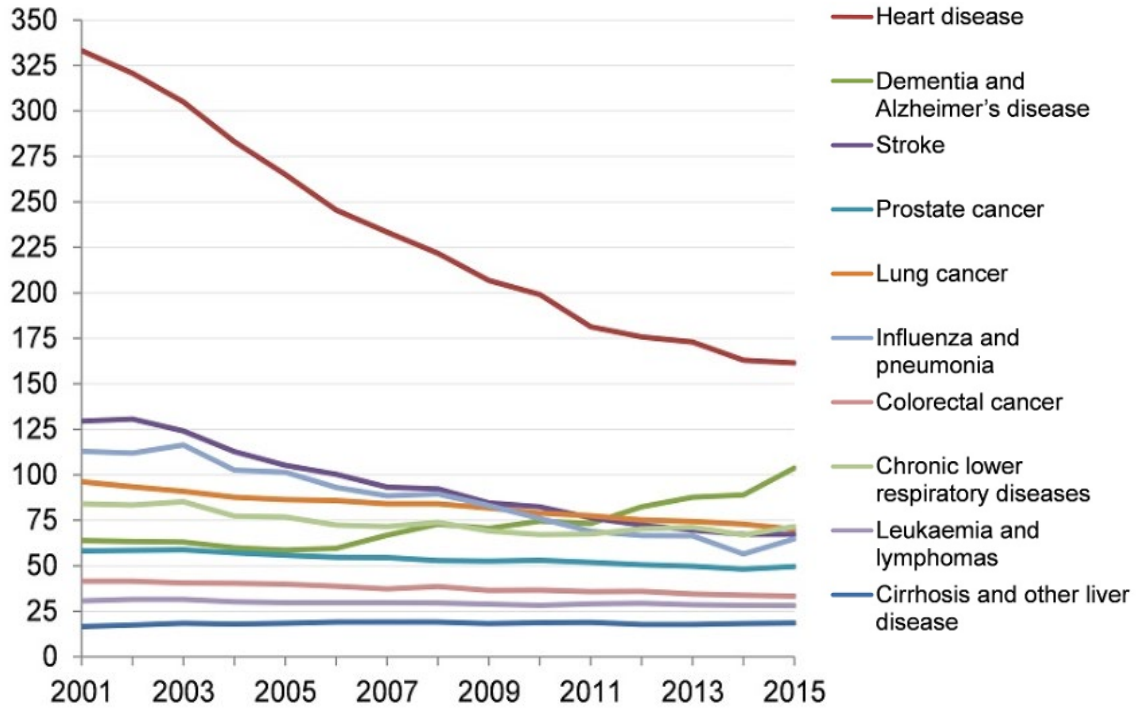
Since each patient is an individual case, you should use your own medical judgment to choose the appropriate treatment for each patient

Why is it important to diagnose type 2 asthma?

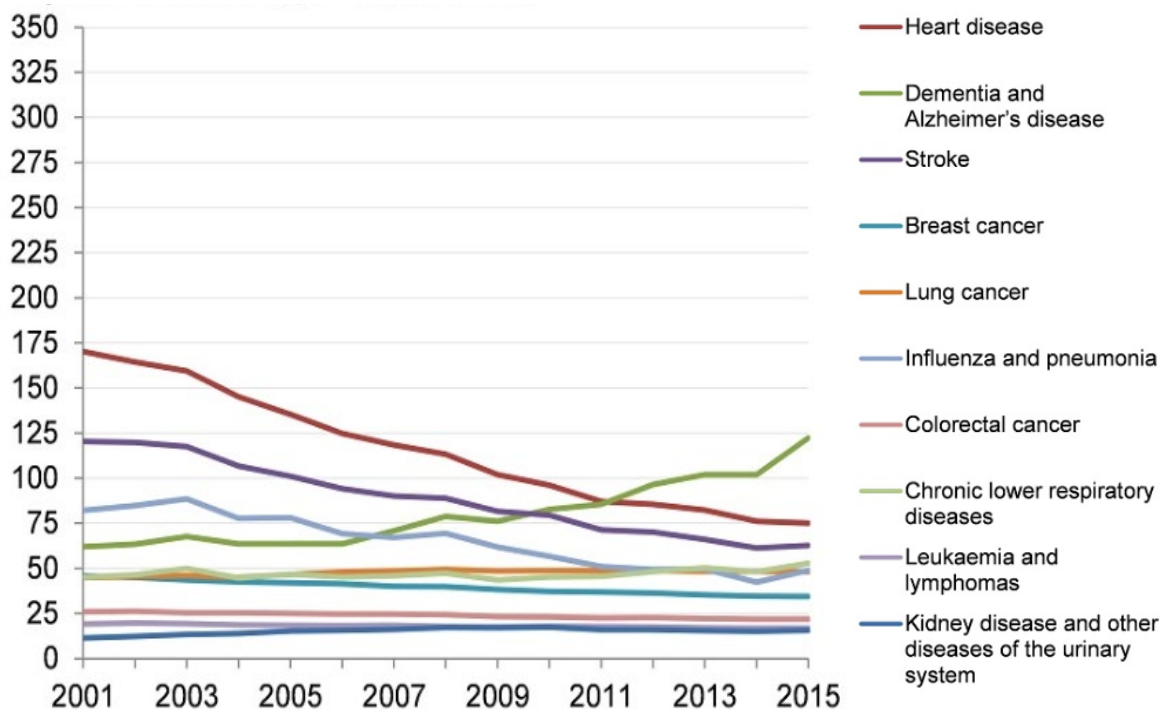
- Progress against key outcomes has stalled
- New methods to measure airway inflammation have exposed several damaging assumptions/over-simplifications in our current approach to assessment and management of asthma
- There is a growing consensus that we need to move to a new approach focusing on treatable traits, of which type 2 inflammation is the most important
- Management guided by biomarkers of type 2 inflammation looks feasible and is more effective than our current approach
- New treatment options have inflammatory phenotype-specific benefits

Mortality rates in England 2001–15

Age-standardised rate, per 100,000 males



Age-standardised rate, per 100,000 females



Gov.UK. Health profile for England: 2017. Available at https://www.gov.uk/government/publications/health-profile-for-england/chapter-2-major-causes-of-death-and-how-they-have-changed Accessed March 2023

Yasmin's story: A case report

- 34-year-old full-time mother of two children < 5 years
- Presented to A&E with acute wheeze and SOB
- Widespread polyphonic expiratory wheeze; PEF 250 (50% predicted)
- Mild childhood asthma and eczema. Never smoked. No pets
- Had a course of prednisolone for acute worsening 8 months earlier
- Taking BDP 100 2 puffs bd and salbutamol when needed
- Improved quickly with prednisolone and nebulizers. PEF 450 on discharge
- Maintenance treatment stepped up to BDP/formoterol 100/6 2 puffs bd

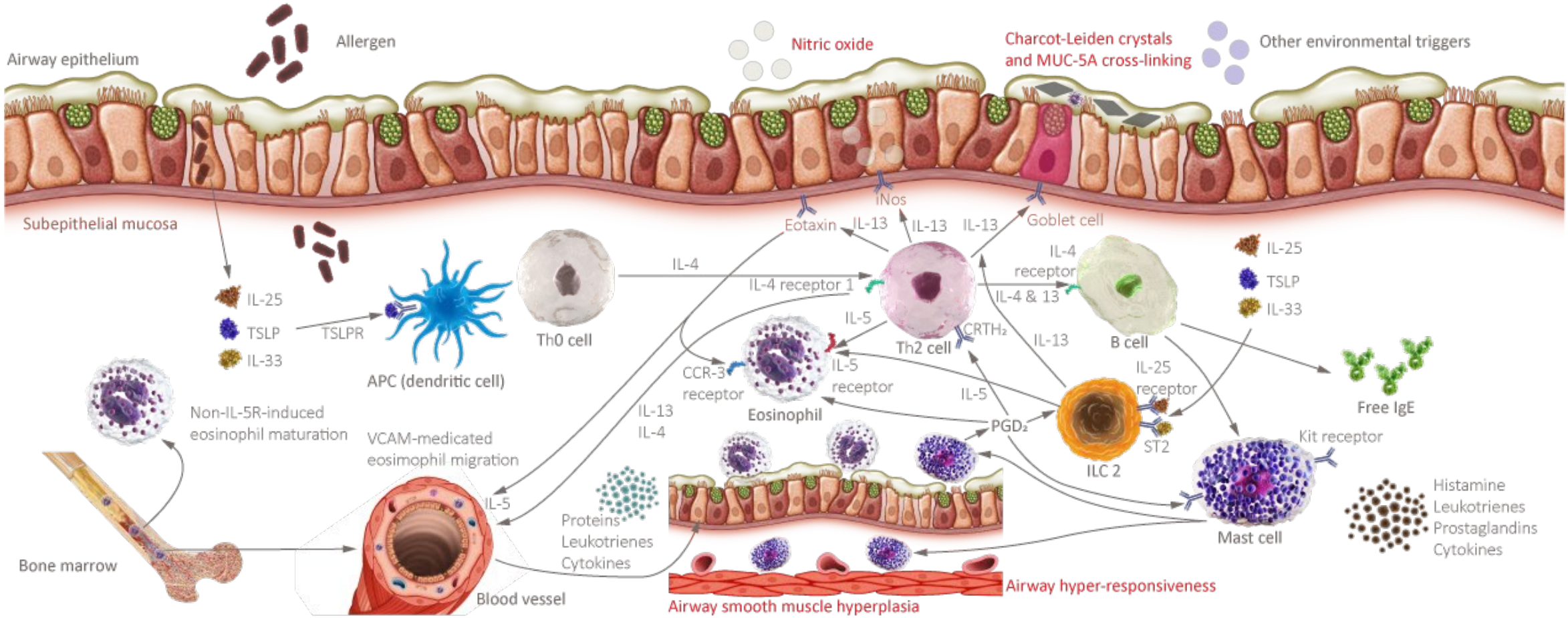
A&E, Accident and Emergency; **bd,** twice a day; **BDP,** budesonide dry powder; **PEF,** peak expiratory flow; **SOB,** shortness of breath

Yasmin's story: A case report (2)

- 6 weeks later, presented with extreme SOB and wheeze coming on over 24 hours
- Distressed, sweaty, unable to do PEF, silent chest
- pO_2 3 kPa, pCO_2 12 kPa
- Cardiorespiratory arrest. Difficult to intubate and ventilate. Taken to ITU
- Recovered with severe anoxic brain damage. Dependent on long-term care

ITU, intensive therapy unit; **kPa**, kilopascal; **PEF**, peak expiratory flow; **pO_2**, partial pressure of oxygen, **pCO_2**, partial pressure of carbon dioxide; **SOB**, shortness of breath

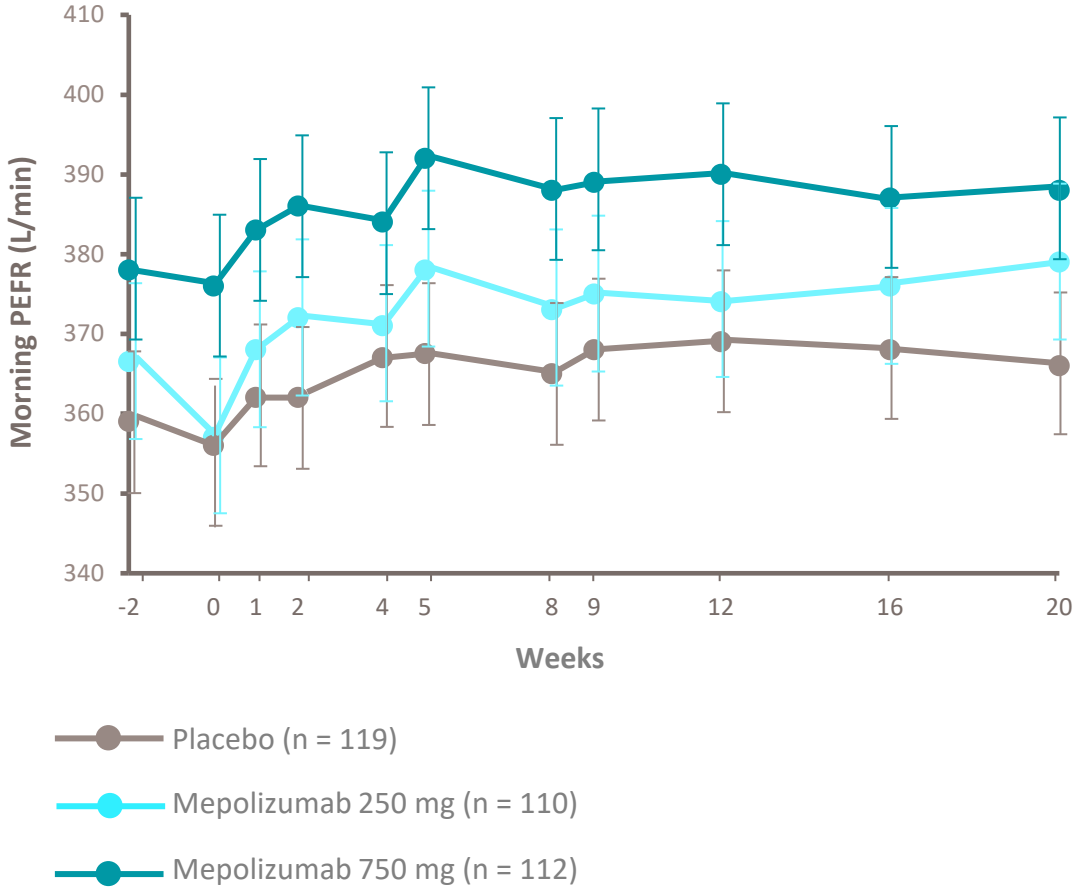
Type 2 airway inflammation in asthma

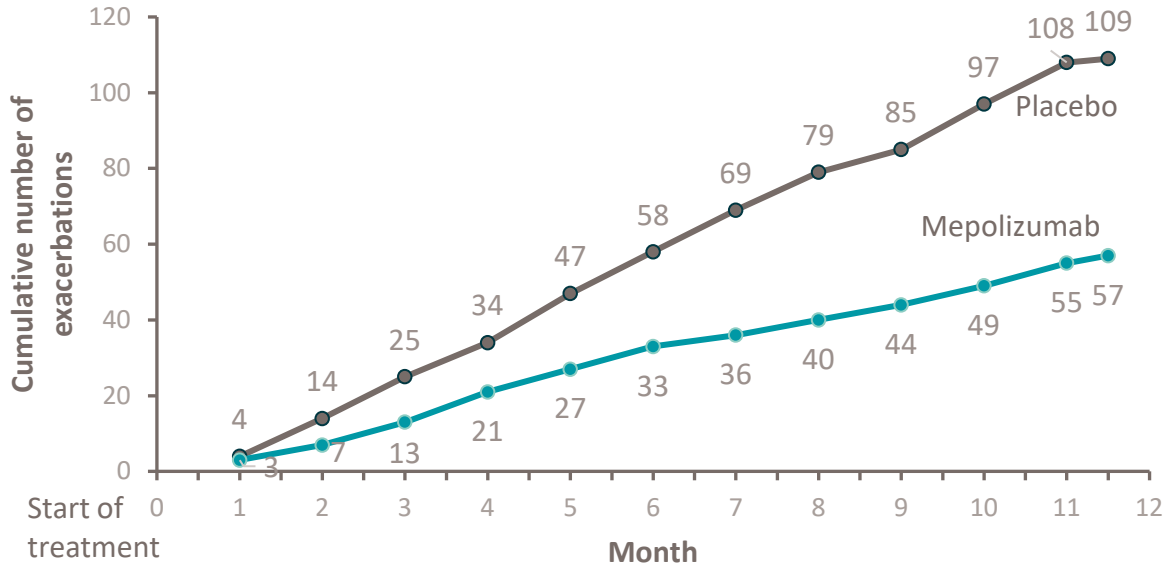


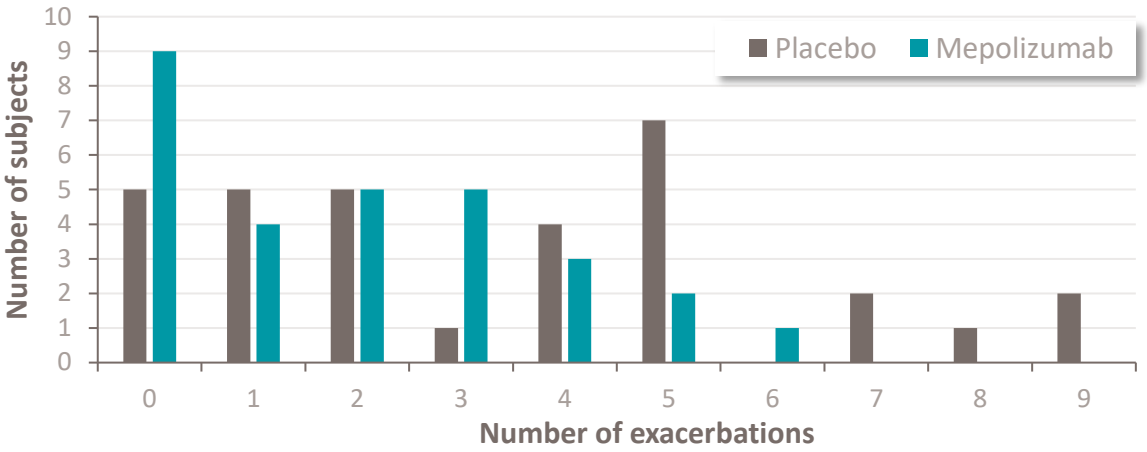
APC, antigen presenting cell; **CCR-3,** C chemokine receptor type 3; **$CRTH_2$,** prostaglandin D2 receptor 2; **ILC2,** type 2 innate lymphoid cell; **IgE,** immunoglobulin E, **IL,** interleukin; **iNOS,** inducible nitric oxide synthase; **MUC-5A,** mucin 5A; **PGD_2,** prostaglandin D2; **ST2,** IL-2 receptor-like 1; **Th0,** naïve T cell; **Th2,** T helper 2 cell; **TSLP,** thymic stromal lymphopoietin; **TSLPR,** thymic stromal lymphopoietin receptor; **VCAM,** vascular cell adhesion molecule

Couillard S, et al. Respirology. 2022;27:573–577.

Mepolizumab (anti-IL-5): Effect in 'asthma' and eosinophilic airways disease[1,2]

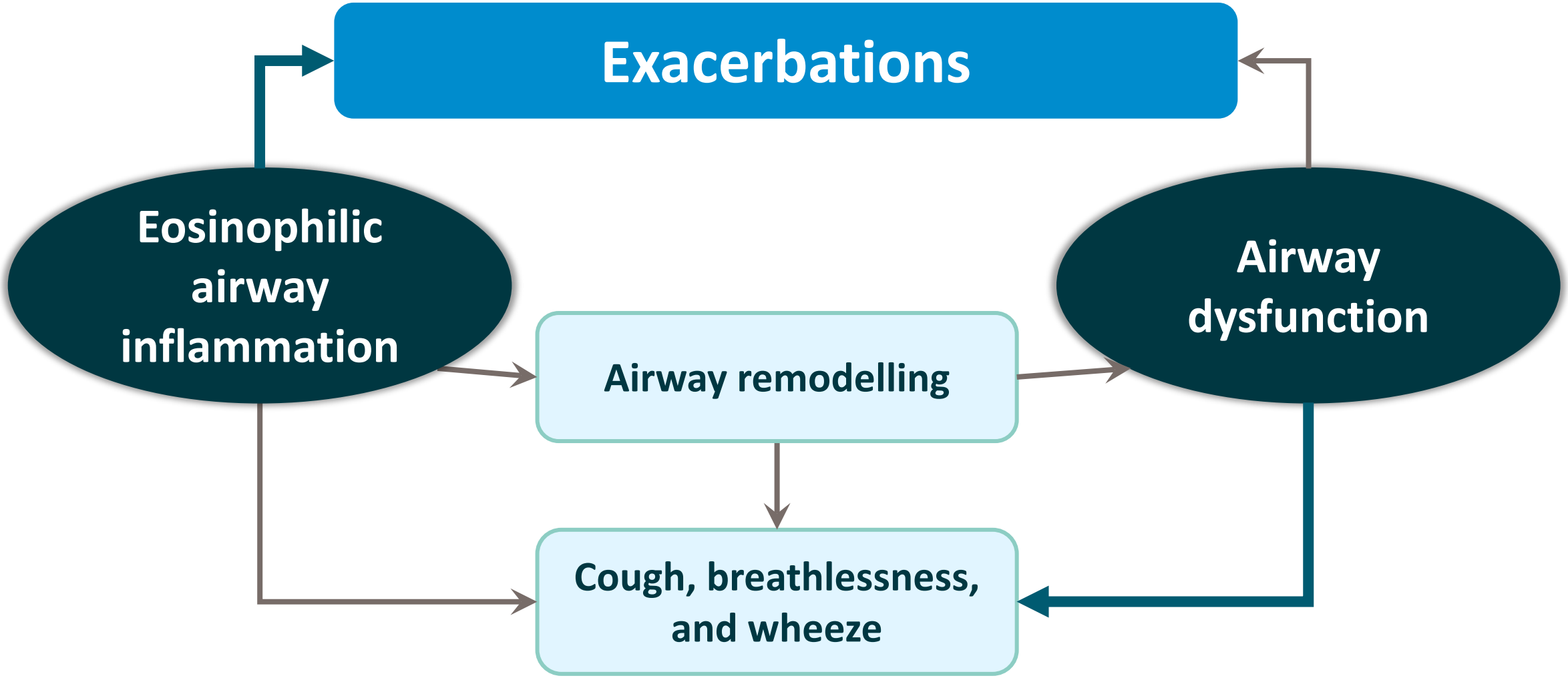






IL, interleukin; **PEFR**, peak expiratory flow rate

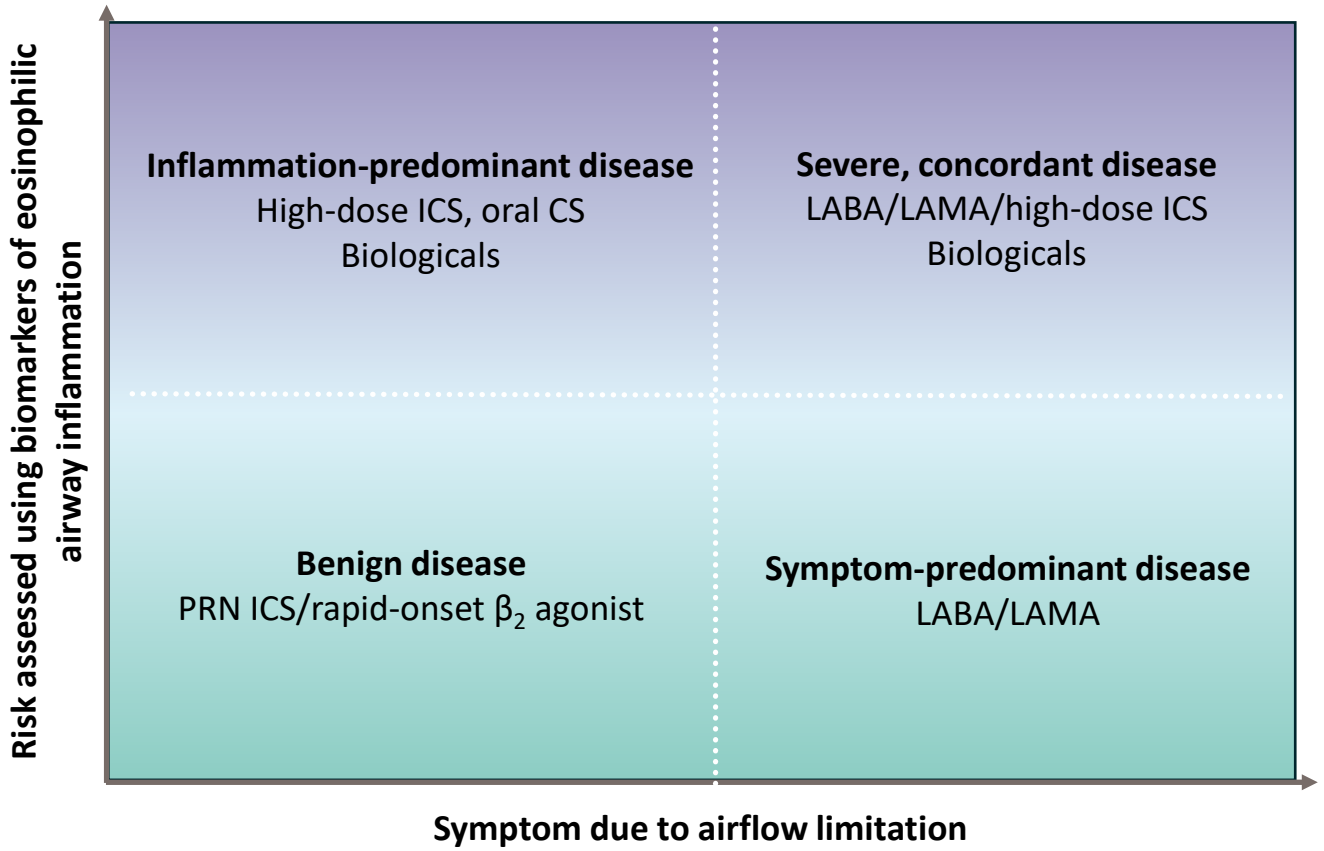
1. Flood-Page P, et al. Am J Respir Crit Care Med. 2007;176:1062–1071. **2.** Haldar P, et al. N Engl J Med. 2009;360:973–984.



Shaw DE, et al. Lancet Respir Med. 2021;9:786–794.

Treatable traits: A new approach to airway disease

Treatable trait is a measurable aspect of the disease that can be modified with resultant patient benefit



CS, corticosteroids; **ICS,** inhaled corticosteroids; **LABA**, long-acting β_2-agonists; **LAMA,** long-acting muscarinic agonists; **PRN**, as needed

Pavord ID and Agusti A. Eur Respir J. 2016;47:1299–1303.

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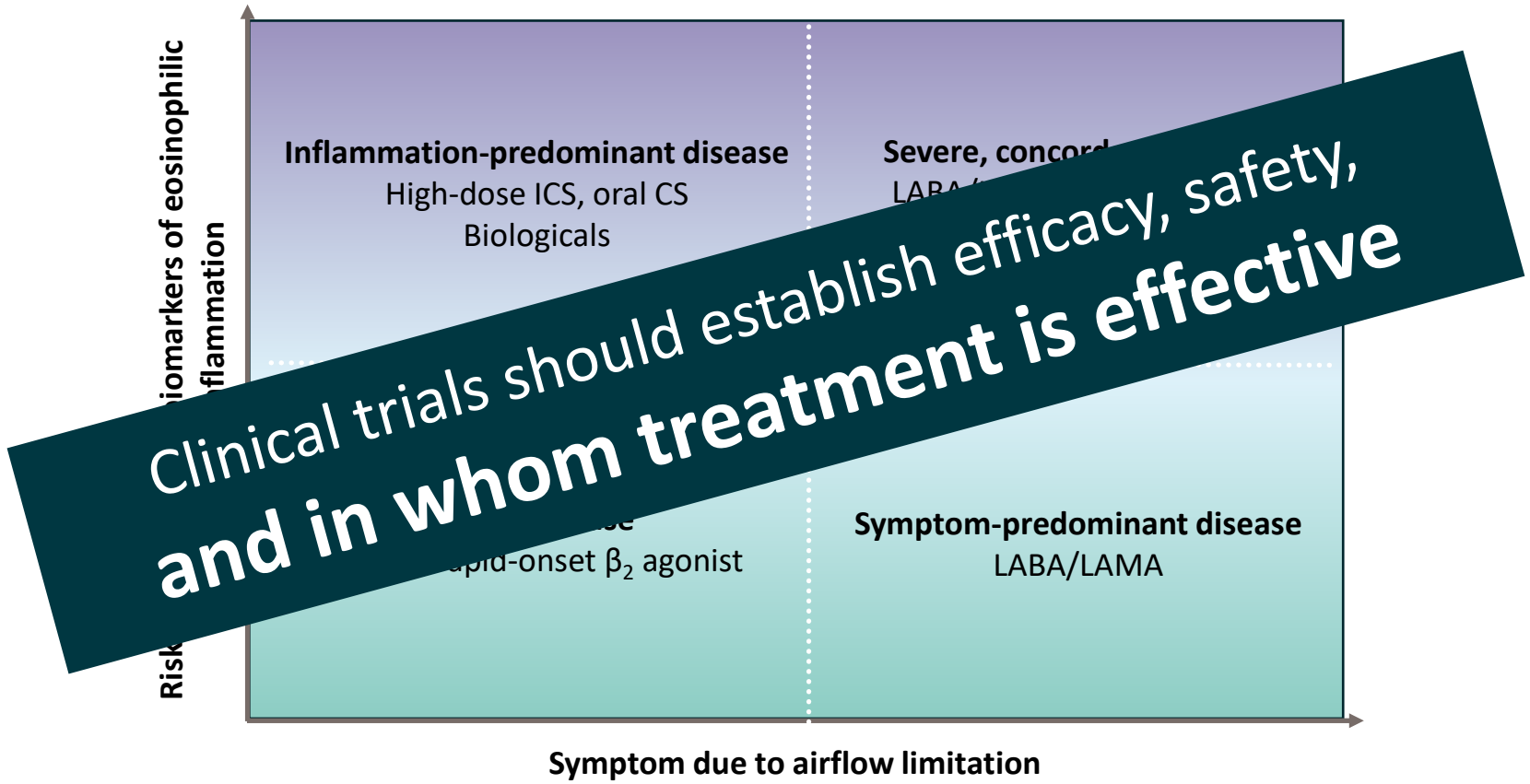

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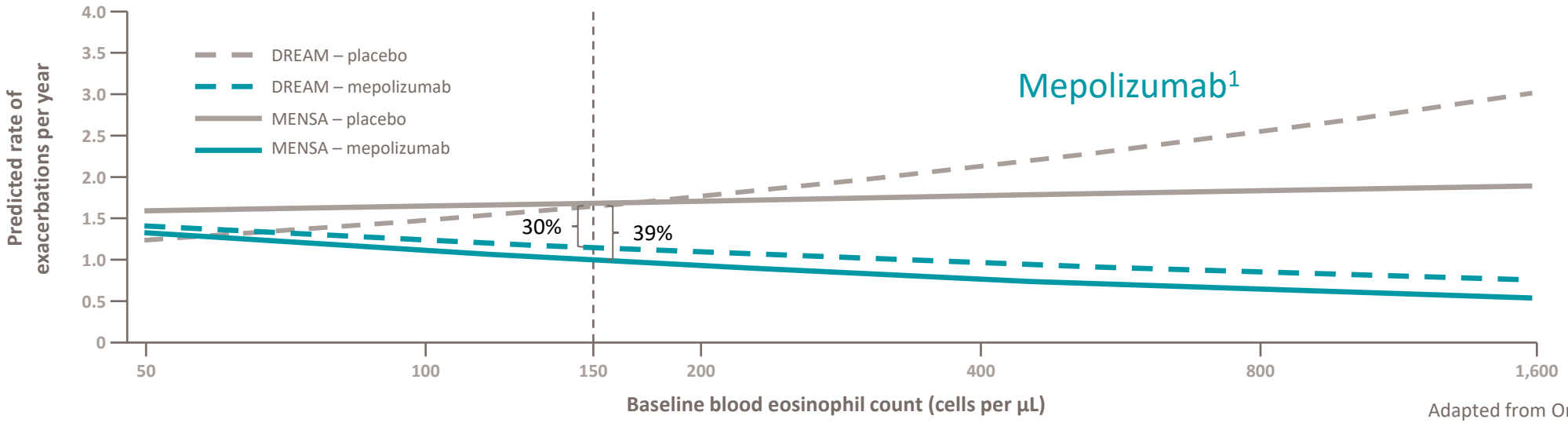
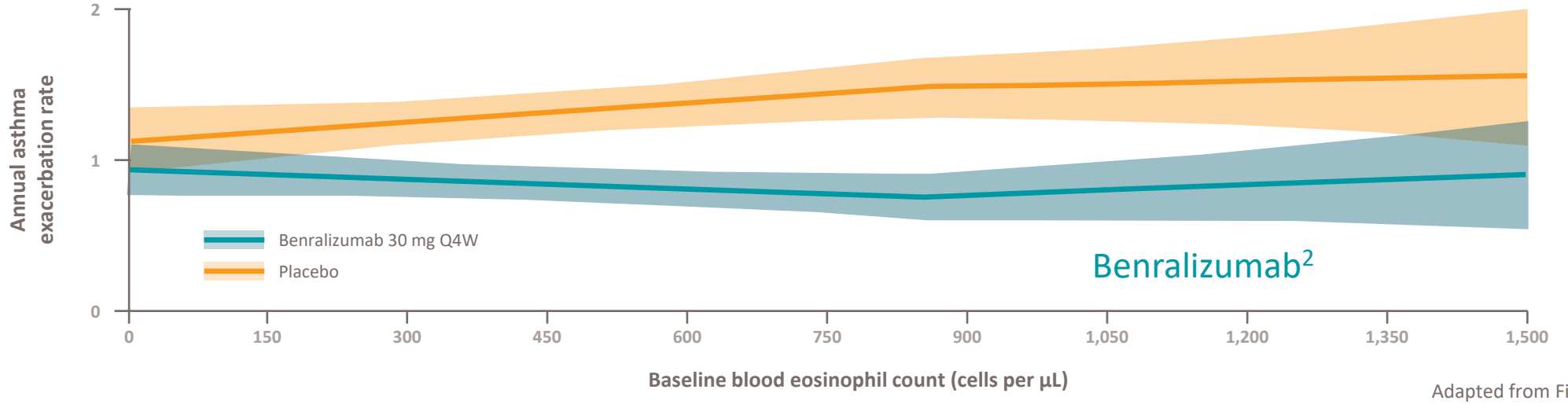
Pavord ID and Agusti A. Eur Respir J. 2016;47:1299–1303.

Relationship between blood eosinophils and response to anti-IL-5[1,2]



Adapted from Ortega HG et al, 2016[1]

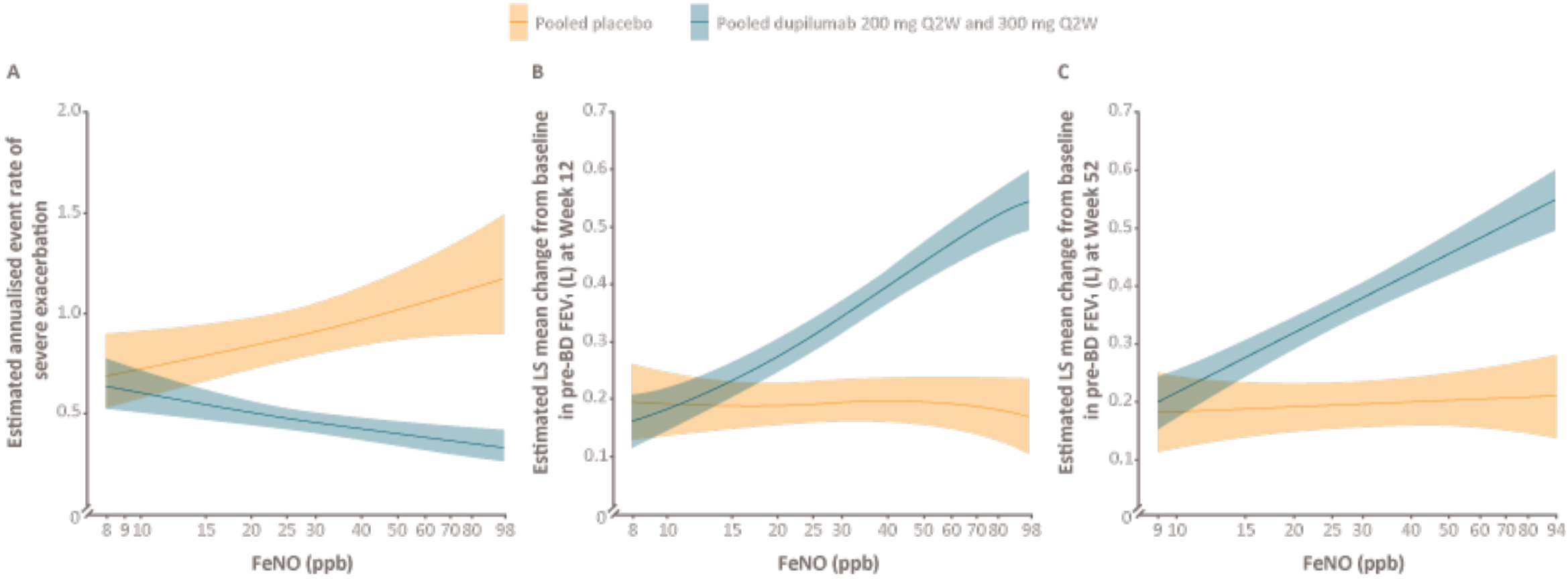


Adapted from FitzGerald JM et al, 2018[2]

IL, interleukin; **Q4W**, every 4 weeks

1. Ortega HG, et al. Lancet Respir Med. 2016;4:549–556. **2.** FitzGerald JM, et al. Lancet Respir Med. 2018;6:51–64.

Relationship between effects of dupilumab in moderate-to-severe asthma and baseline FeNO



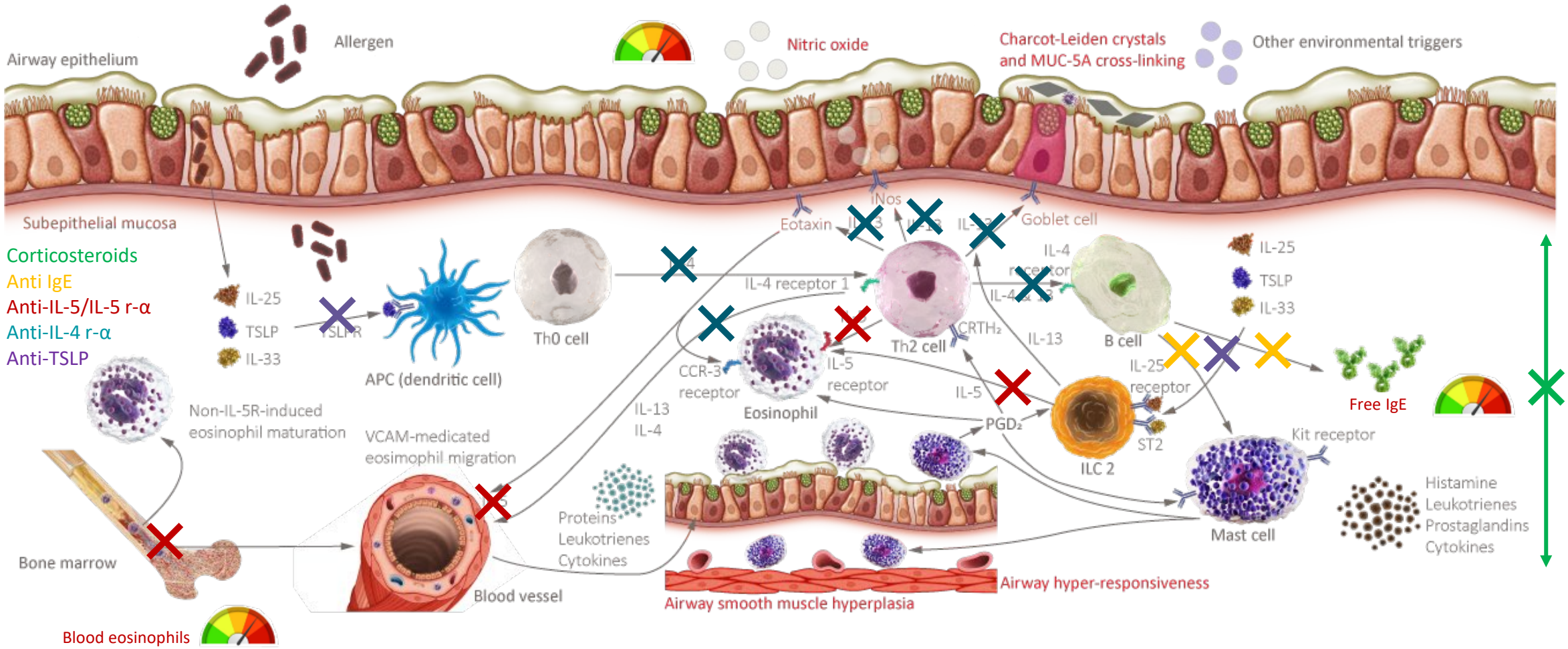
Shaded areas correspond to 95% CIs

Adapted from Pavord ID, et al, 2022.

BD, bronchodilator; **CI,** confidence interval; **FeNO,** fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second; **LS,** least squares; **ppb**, parts per billion; **Q2W,** every 2 weeks

Pavord ID, et al. J Allergy Clin Immunol Pract. 2022. Epub ahead of print: DOI: 10.1016/j.jaip.2022.11.043.

Targeted anti-inflammatory therapies work at different levels



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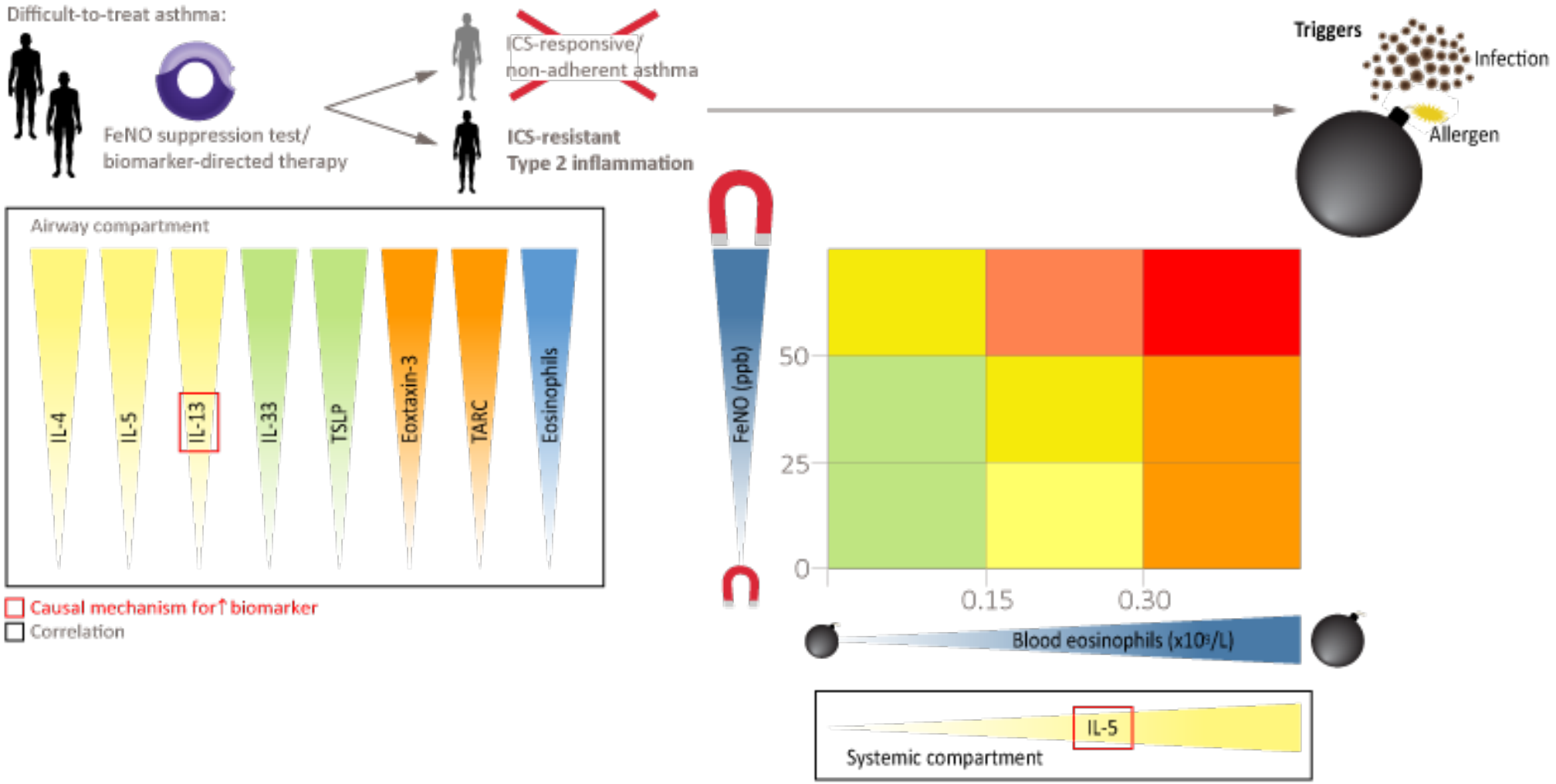
Couillard S, et al. Respirology. 2022;27:573–577.

Translating type 2 biomarkers in severe asthma: A two-compartment, two-hit theory

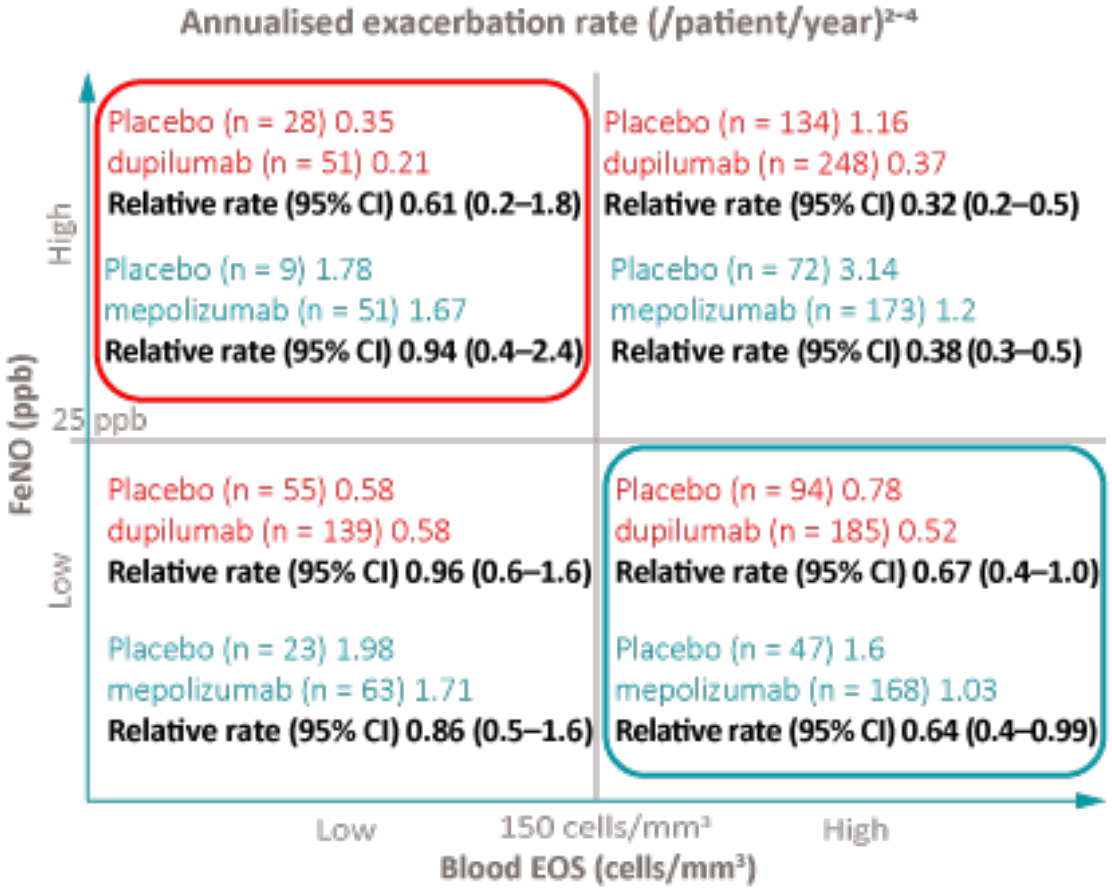


ICS, inhaled corticosteroids; **IL,** interleukin; **FeNO,** fractional exhaled nitric oxide; **ppb,** parts per billion; **TARC,** thymus and activation-regulated chemokine; **TSLP,** thymic stromal lymphopoietin

Couillard S, et al. Respirology. 2022;27:573–577.

Sub-stratifying type 2 airways disease: Magnet and bomb patients

Magnet[1]	Bomb[1]
Early onset	Late onset
Allergy	No allergy
AHR++	Less AHR
AD, rhinitis	CRSNP, EGPA
FeNO > blood EOS	Blood EOS > FeNO
ICS > OSC	OCS >ICS
Teze > Benra	Benra > Teze



Adapted from Shrimanker R, et al. 2019.[4]

AD, atopic dermatitis; **AHR**, airway hyper-responsiveness; **Benra,** benralizumab; **CI**, confidence interval; **CRSNP,** chronic rhinosinusitis with nasal polyposis; **EGPA,** eosinophilic granulomatosis with polyangiitis; **EOS**, eosinophils; **FeNO,** fractional exhaled nitric oxide; **ICS,** inhaled corticosteroids; **OCS,** oral corticosteroids; **Teze,** Tezepelumab

1. Couillard S, et al. Respirology. 2022;27:573–577. **2.** Castro M, et al. N Engl J Med. 2018;378:2486–2496. **3.** Pavord ID, et al. Lancet. 2012;380:651–659. **4.** Shrimanker R, et al. Am J Respir Crit Care Med. 2019;200:1308–1312.

Useful and useless ways to identify type 2 airway inflammation

Useful

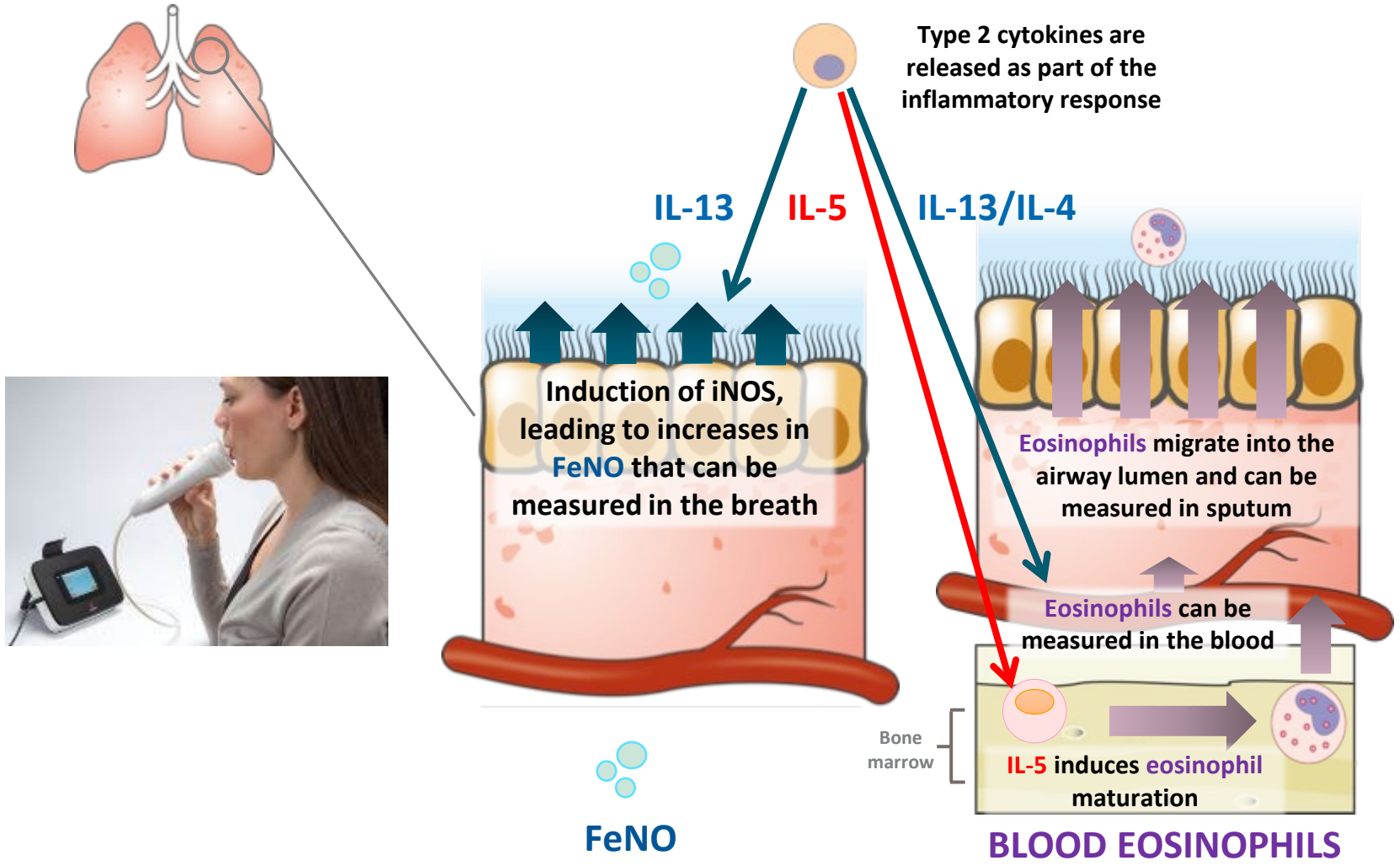
- Sputum eosinophils
- Blood eosinophils
- Exhaled nitric oxide (FeNO)
- Good response to steroids
- Frequent attacks
- Nasal polyposis
- Symptoms triggered by allergens

Useless

- FEV_1
- Bronchodilator reversibility
- Airway hyper-responsiveness
- Diagnostic label
- Symptoms
- Allergy and serum IgE
- Age of onset of airway disease

FeNO, fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second; **IgE,** immunoglobulin E

Simple tests of type 2 airway inflammation[1–4]

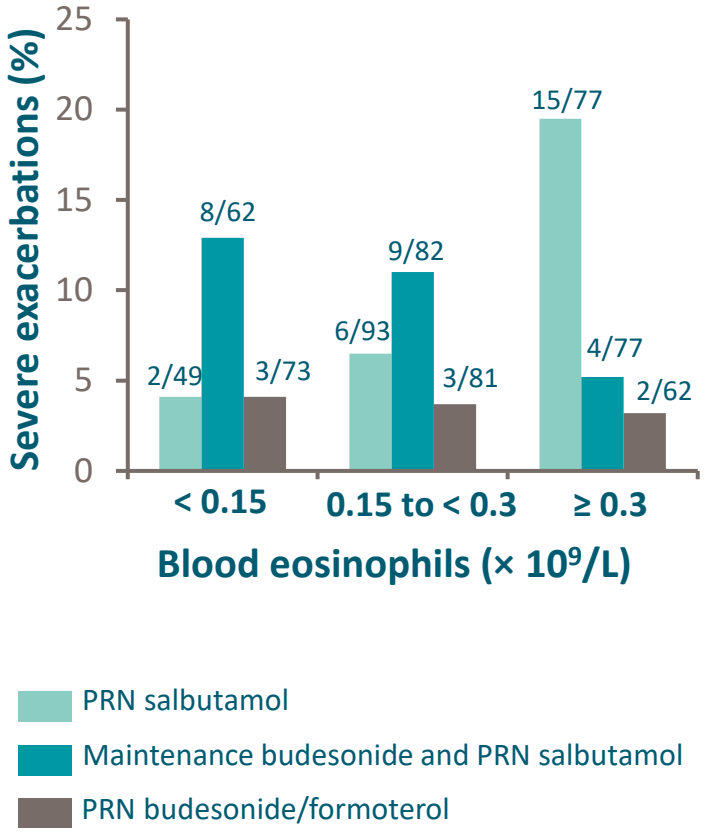


FeNO, fractional exhaled nitric oxide; **IL,** interleukin; **iNOS,** inducible nitric oxide synthase

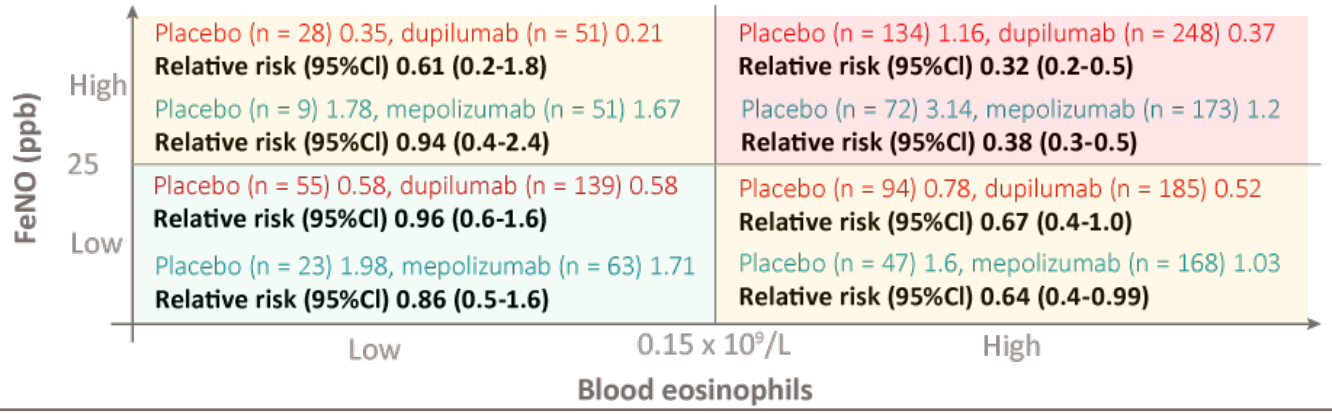
1. Sidhu SS, et al. Proc Natl Acad Sci U S A. 2010;107:14170–14175. **2.** Suresh V, et al. Am J Respir Cell Mol Biol. 2007;37:97–104. **3.** Menzies-Gow A, et al. J Allergy Clin Immunol. 2003;111:714–719. **4.** Hershey GK. J Allergy Clin Immunol. 2003;111:677–690; quiz 91.

Biomarkers, risk stratification, and precision medicine in airway disease[1-4]

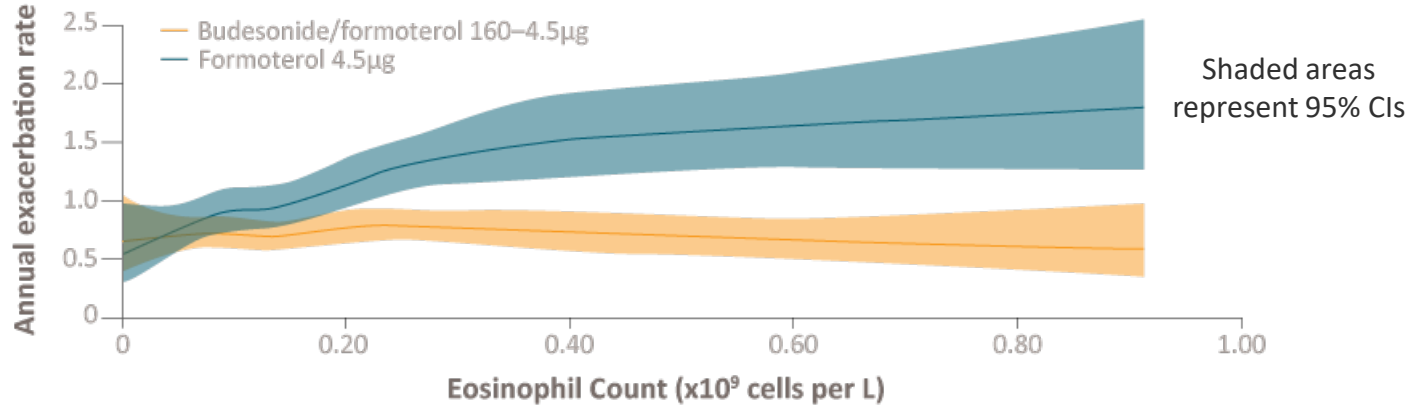
Mild asthma[1,2]



Moderate-to-severe asthma[3]



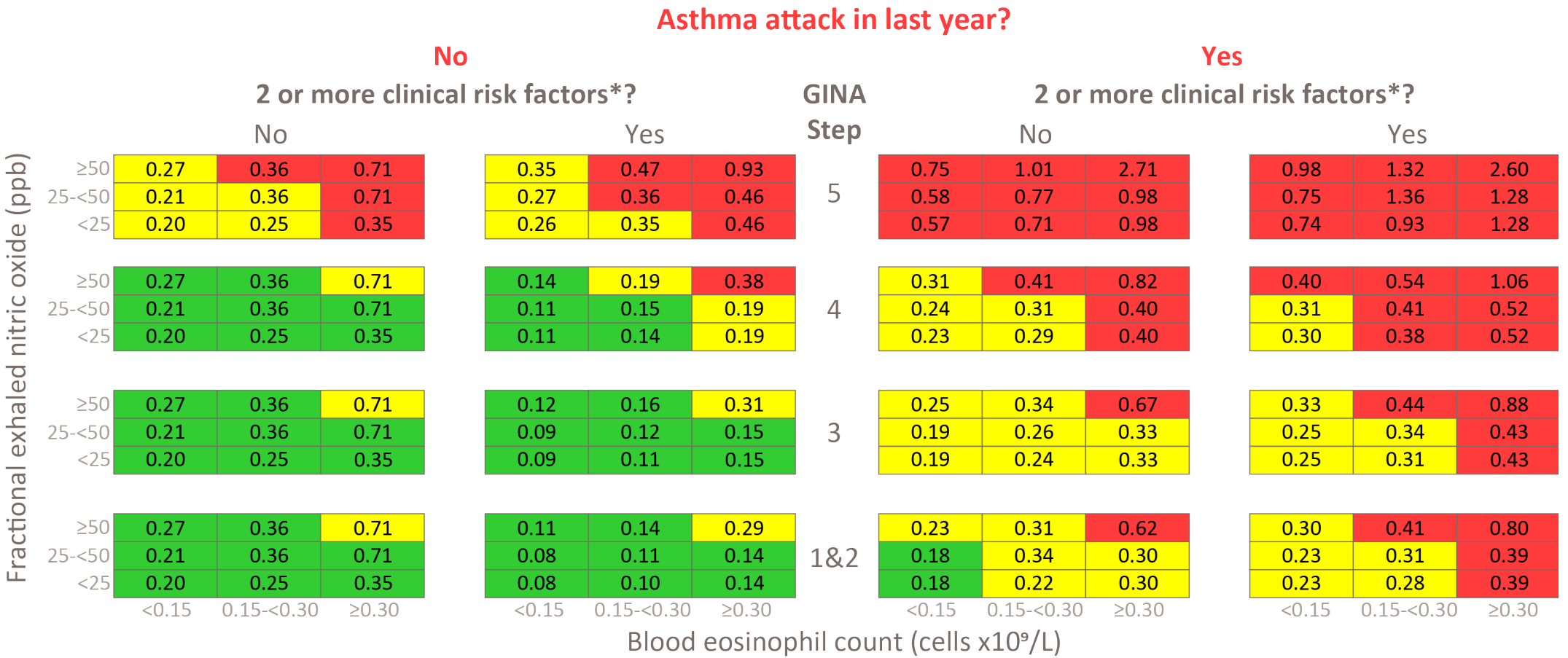
COPD[4]



CI, confidence interval; **COPD,** chronic obstructive pulmonary disease; **FeNO,** fractional exhaled nitric oxide**; ppb,** parts per billion; **PRN**, as needed

1. Beasley R, et al. N Engl J Med. 2019;380:2020–2030. **2.** Pavord ID, et al. Lancet Respir Med. 2020;8:671–680. **3.** Shrimanker R, et al. Am J Respir Crit Care Med. 2019;200:1308–1312. **4.** Bafadhel M, et al. Lancet Respir Med. 2018;6:117–126.

OxfoRd Asthma attaCk risk scaLE (ORACLE): Blood eosinophils and FeNO are the airway equivalent of blood pressure and cholesterol



Numbers in each cell are predicted annual asthma attack rates for patients over the age of 12 years if treatment is not changed

FeNO, fractional exhaled nitric oxide; **GINA,** Global Initiative for Asthma; **ORACLE,** OxfoRd Asthma attaCk risk scaLE; **ppb,** parts per billion

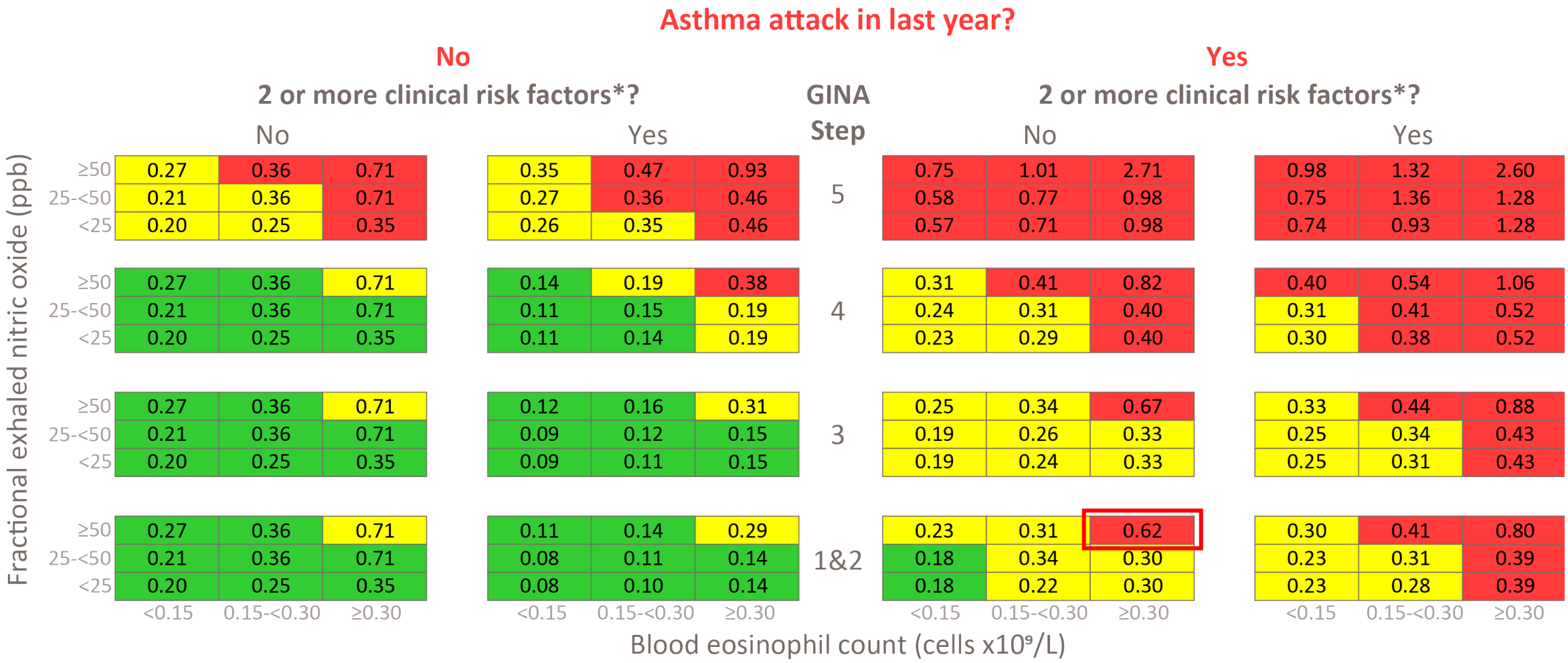
Couillard S, et al. Thorax. 2022;77:199–202.

Yasmin's story: A case report

- 34-year-old full-time mother of two children < 5 years
- Presented to A&E with acute wheeze and SOB
- Widespread polyphonic expiratory wheeze; PEF 250 (50% predicted)
- Mild childhood asthma and eczema. Never smoked. No pets
- Had a course of prednisolone for acute worsening 8 months earlier
- Taking BDP 100 2 puffs bd and salbutamol when needed
- Improved quickly with prednisolone and nebulizers. PEF 450 on discharge
- Blood eosinophils 0.89 × 10^9/L; FeNO 165 ppb (normal < 25 ppb)

A&E, accident and emergency; **bd,** twice a day; **BDP,** budesonide dry powder; **FeNO**, fractional exhaled nitric oxide, **PEF,** peak expiratory flow; **SOB,** shortness of breath; **ppb**, parts per billion

OxfoRd Asthma attaCk risk scaLE (ORACLE)



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Couillard S, et al. Thorax. 2022;77:199–202.

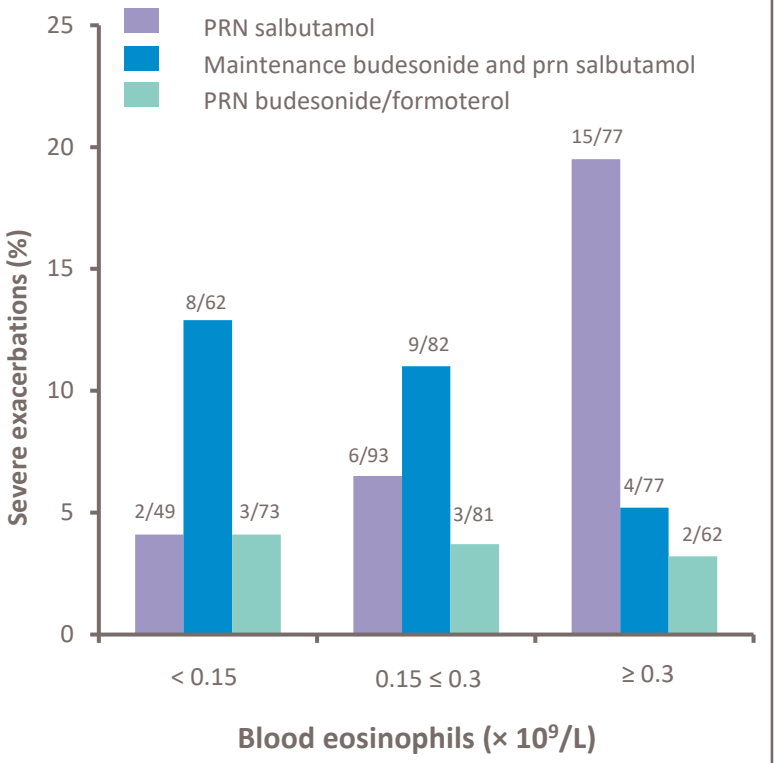
Yasmin's story: A case report

- BDP increased to 400 mcg bd with electronic monitoring
- On follow-up well. Good adherence with treatment
- No further attacks
- FeNO 32 ppb; PEF 500

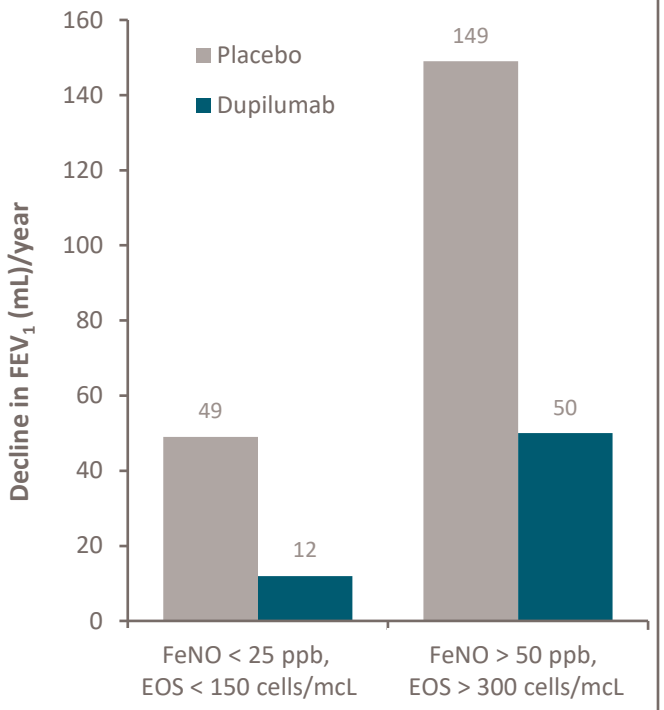
BDP, budesonide dry powder; **FeNO,** fractional exhaled nitric oxide; **PEF,** peak expiratory flow; **ppb,** parts per billion

Type 2 airway inflammation is associated with an uncertain future

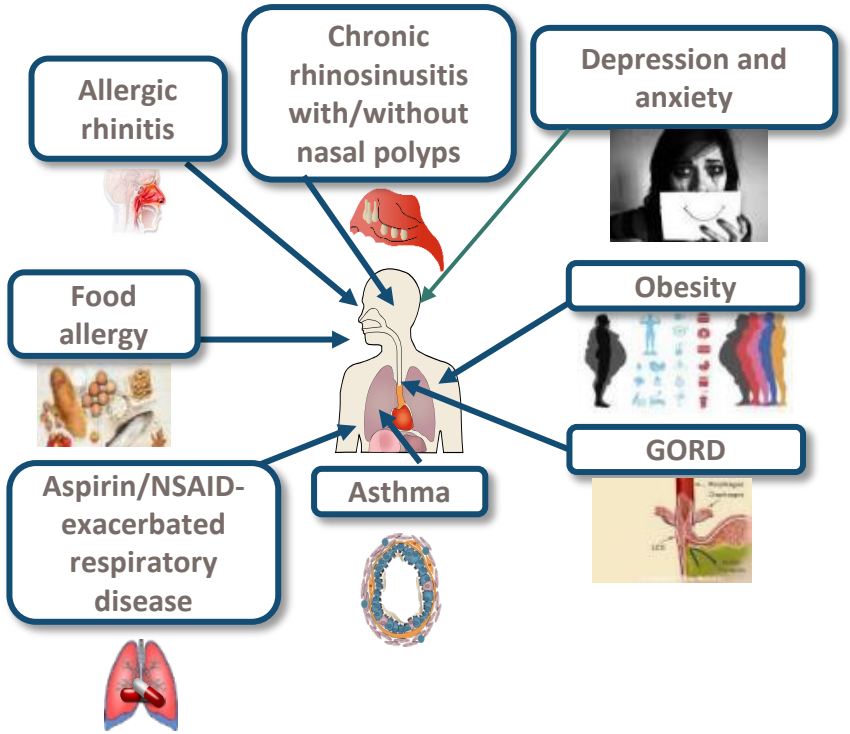
Asthma attack risk[1]



Airway remodelling[2]



People remodelling[3]



EOS, eosinophils; **FeNO,** fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second; **GORD,** gastro-oesophageal reflux disease; **NSAID,** non-steroidal anti-inflammatory drug; **ppb,** parts per billion; **PRN**, as needed

1. Pavord ID, et al. Lancet Respir Med. 2020;8:671–680. **2.** Pavord I, et al. Am J Respir Crit Care Med, 2022;205:A3418. **3.** Kaplan A, et al. NPJ Prim Care Respir Med. 2020;30:36.

Severe eosinophilic asthma: A patient's journey

- 34-year-old female presenting with episodic cough, wheeze, and breathlessness
- Nasal stuffiness, anosmia, clinical evidence of nasal polyps
- ACQ 1.4; FEV_1 2.54 (90% predicted); FEV_1/FVC 74%; FeNO 165 ppb; blood eosinophils 0.77×10^9/L
- Partial response to BDP. Noticed complete response to prednisolone

Treatment	ICS	ICS/LABA		Montelukast	+Tiotropium	+Uniphyllin	+Prednisolone		+Dupilumab
People remodelling	CRSwNP		Depression						Osteoporosis, obesity, NIDDM
Airway remodelling (post-BD FEV_1)	2.54		2.15			1.82			1.66
Asthma attacks		x		x	x	x	x	x	x

2003 — **2018**

ACQ, Asthma Control Questionnaire; **BD,** bronchodilator; **BDP**, budesonide dry powder; **CRSwNP,** chronic rhinosinusitis with nasal polyps; **FeNO,** fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second; **FVC,** forced vital capacity; **ICS,** inhaled corticosteroids; **LABA,** long-acting β_2-agonists; **NIDDM,** non-insulin-dependent diabetes

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- ACQ 1.4; FEV_1 2.54 (90% predicted); FEV_1/FVC 74%; FeNO 165 ppb; blood eosin
- Partial response to BDP. Noticed complete response to prednisolone

What if biologic was started here instead of 'everything but the kitchen sink', futile GINA management?

Treatment	ICS	ICS/LABA		Montelukast	+Tiotropium	+Uniphyllin							
People remodelling	CRSwNP		Depression										
Airway remodelling (post-BD FEV_1)	2.54		2.15			1.82							1.66
Asthma attacks	x		x		x		x	x	x	x	x	x	x	x	x

2003 — **2018**

ACQ, Asthma Control Questionnaire; **BD,** bronchodilator; **BDP**, budesonide dry powder; **CRSwNP,** chronic rhinosinusitis with nasal polyps; **FeNO,** fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second; **FVC,** forced vital capacity; **GINA,** Global Initiative for Asthma; **ICS,** inhaled corticosteroids; **LABA,** long-acting β_2-agonists; **NIDDM,** non-insulin-dependent diabetes

Conclusions

- Airway dysfunction and type 2 airway inflammation are disconnected. Both need to be assessed for optimum risk stratification and management
- Inflammatory biomarkers have been necessary to identify efficacy of new biologicals
- The blood eosinophil is an excellent ‘theragnostic’ biomarker for anti-IL-5 and FeNO for anti-IL-13 and -4
- Biomarkers of type 2 inflammation identify risk in asthma and COPD
- This risk can be reduced effectively with targeted treatment
- Inflammatory biomarkers are ready for prime time

COPD, chronic obstructive pulmonary disease; **FeNO,** fractional exhaled nitric oxide; **IL,** interleukin

Acknowledgements

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Samantha Thulborn
Tim Powell
Jenny Kane
Katie Borg
Clare Connelly
Our patients

Prescribing information

PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥ 12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Please review full Product Information before prescribing. Full Product Information is available from sanofi-aventis australia pty ltd at http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swpdupix or by contacting 1800 818 806.

Atopic dermatitis*:* **Adults and adolescents:** Treatment of moderate to severe atopic dermatitis in patients aged 12 years and older who are candidates for chronic systemic therapy. Not intended for episodic use. **Children 6 to 11 years of age:** Dupixent is indicated for the treatment of severe atopic dermatitis in patients aged 6 to 11 years old who are candidates for chronic systemic therapy. Dupixent is not intended for episodic use. **Asthma:** Add on maintenance treatment in patients aged 6 years and older with moderate to severe asthma with type 2 inflammation (elevated eosinophils or elevated FeNO) that is inadequately controlled despite therapy with other medicinal products for maintenance treatment. **Chronic rhinosinusitis with nasal polyposis (CRSwNP):** Dupixent is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). **DOSAGE AND ADMINISTRATION: Atopic dermatitis – Adults:** Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites), followed by 300 mg given every other week. Refer to full PI for preparation, handling and administration. Treatment should be initiated and supervised by a dermatologist or immunologist **Atopic Dermatitis – Paediatric and Adolescent patients aged 6-17 years: Patients 15 kg to < 30 kg:** Initial dose of 600 mg (two 300 mg injections consecutively in different injection sites) followed by 300 mg every four weeks. **Patients 30 kg to < 60 kg:** Initial dose of 400 mg (two 200 mg injections consecutively in different injection sites) followed by 200 mg given every other week. **Patients ≥ 60 kg:** Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites) followed by 300 mg given every other week. **Asthma – Adults and adolescents:** Initial dose of 400 mg by subcutaneous injection (two 200 mg injections consecutively in different injection sites) followed by 200 mg given every other week. Refer to full PI for preparation, handling and administration. **Oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis** or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis: Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites) followed by 300 mg given every other week. **Asthma – Paediatric patients aged 6-11: Patients 15 kg to < 30 kg:** Initial dose of 100 mg followed by 100 mg given every other week, or an initial dose of 300 mg followed by 300 mg given every four weeks. **Patients 30 kg to < 60 kg:** Initial dose of 200 mg followed by 200 mg given every other week, or an initial dose of 300 mg followed by 300 mg given every four weeks. **Patients ≥ 60 kg:** Initial dose of 200 mg followed by 200 mg given every other week. **Chronic Rhinosinusitis with Nasal Polyposis:** The recommended dose of Dupixent for adult patients is an initial dose of 300 mg followed by 300 mg given every other week. Dupixent is intended for long-term treatment. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. If after 24 weeks of treatment a patient's disease is stable, Dupixent may be given at a dose of 300 mg every four weeks in patients with CRSwNP who do not have comorbid asthma. **CONTRAINDICATIONS** Hypersensitivity to dupilumab or any of its excipients **PRECAUTIONS** Record the tradename and the batch number to improve traceability. Hypersensitivity, angioedema, helminth infections, conjunctivitis and keratitis, comorbid asthma, concomitant atopic conditions, eosinophilic conditions, acute asthma or deteriorating disease, gradual corticosteroid dose reduction. Refer to full PI. **INTERACTIONS** Live vaccines, No safety data on co-administration with other immunomodulators. Refer to full PI. **ADVERSE EFFECTS Atopic dermatitis:** Injection site reactions, conjunctivitis, conjunctivitis allergic, oral herpes, conjunctivitis bacterial, herpes simplex, eosinophilia, eye pruritus, blepharitis, dry eye, hypersensitivity – refer to full PI. **Asthma:** Injection site reactions, oropharyngeal pain, eosinophilia – refer to full PI. **Chronic Rhinosinusitis with Nasal Polyposis:** Injection site reactions, injection site swelling, conjunctivitis – refer to full PI. **Post marketing experience:** Angioedema, arthralgia, keratitis, ulcerative keratitis, facial rash. **NAME OF SPONSOR** sanofi-aventis australia pty ltd, 12-24 Talavera Road, Macquarie Park, NSW 2113. Based on Full Product Information with TGA date of approval of 29 June 2022 Date of Preparation: 30 June 2022

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

RESPIRATORY
ADVENT
ADVANCES IN
TYPE 2 INFLAMMATORY DISEASES

Using biomarkers to manage asthma in Australia

Prof Peter Wark

Centre for Healthy Lungs Hunter Medical Research Institute, University of Newcastle

Department of Respiratory and Sleep Medicine, John Hunter Hospital

Disclosures

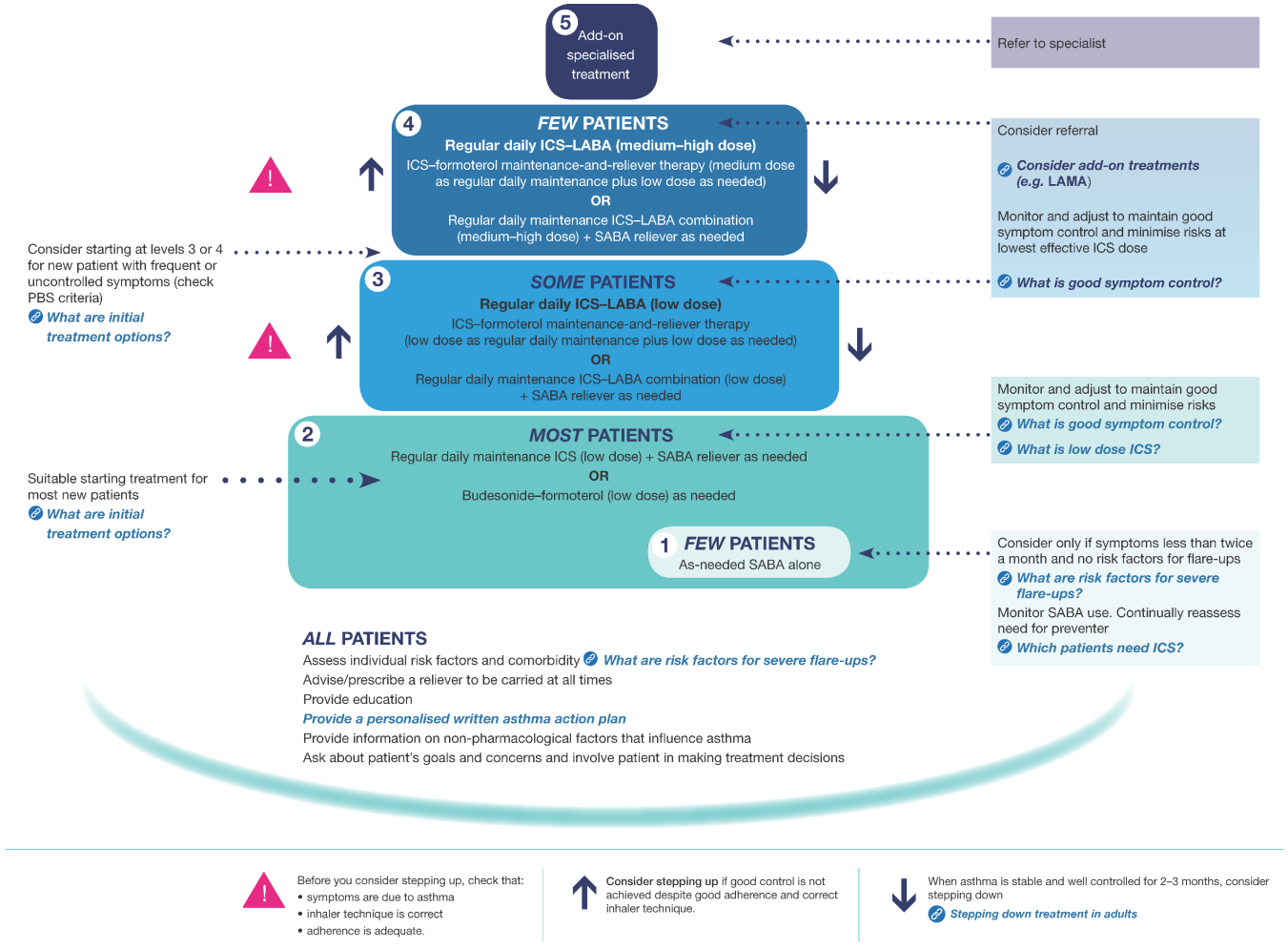
- Employee of NSW Health
- Spoken at or organised meetings sponsored by: AstraZeneca, GSK, Boehringer Ingelheim, Mundipharma, Menarini, Novartis, CSL, Chiesi, Sanofi, Vertex
- Advisory board member for: AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, Vertex, PBAC Australia

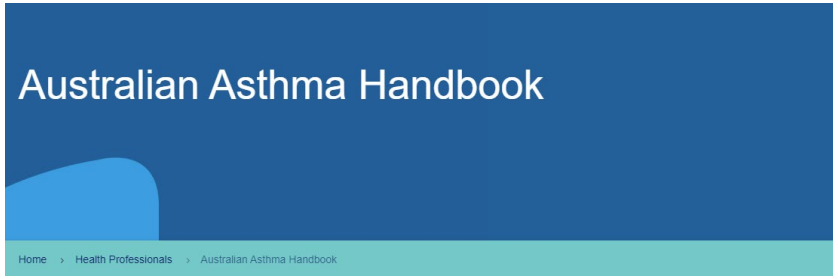
NSW, New South Wales; **PBAC**, Pharmaceutical Benefits Advisory Committee

Outline

- The evolution of asthma understanding and the importance of inflammation
- Type 2 inflammation: an endotype of disease that can be treated and identified
  - Steps 1–2 (mild disease) type 2 inflammation and treatment
  - Steps 3–4 (moderate disease) type 2 inflammation and treatment
  - Steps 4–5 (severe disease) type 2 inflammation and treatment, and when to treat with biologics

A step wise approach to asthma, but at every step consider the biomarkers!





Australian Asthma Handbook

The Australian Asthma Handbook is Australia's national guidelines for asthma management and National Asthma Council Australia's flagship publication, forming the foundation of all our health professional resources.

> *"The Australian Asthma Handbook was developed by primary care for primary care. It contains exactly what primary carers need — practical and useful information in plain English, underpinned by the latest evidence."* *Prof. A. Barnard*

The Australian Asthma Handbook Website

Providing best practice, evidence-based guidance, the *Handbook* is an innovative, easy-to-use and searchable website.

ICS, inhaled corticosteroid; **LABA**, long-acting β_2-agonist; **LAMA**, long-acting muscarinic antagonist; **PBS,** Pharmaceutical Benefits Scheme; **SABA**, short-acting β_2-agonist

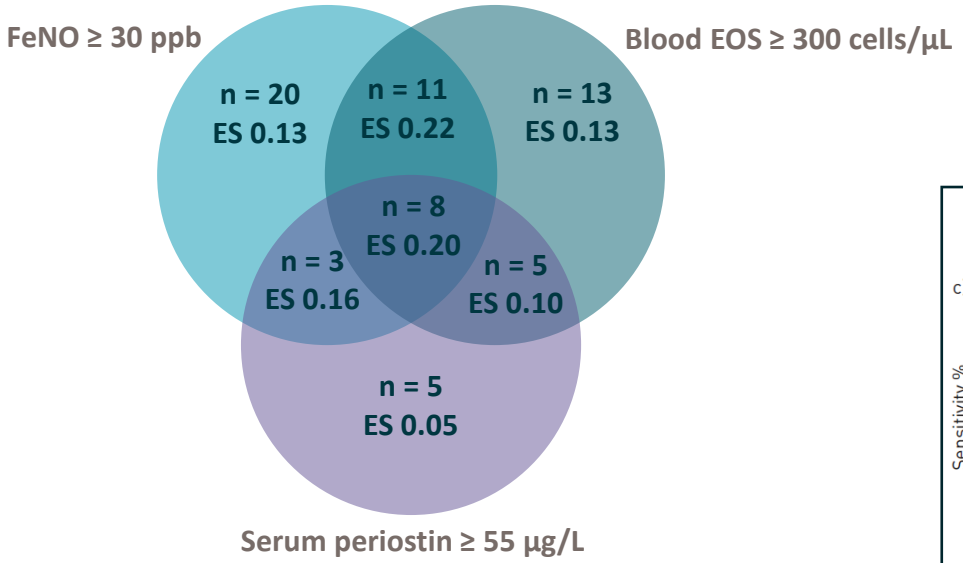
Australian Asthma Handbook V2.2, published April 2022. Available at https://www.asthmahandbook.org.au/ Accessed March 2023.

Predicting type 2 high inflammation with biomarkers

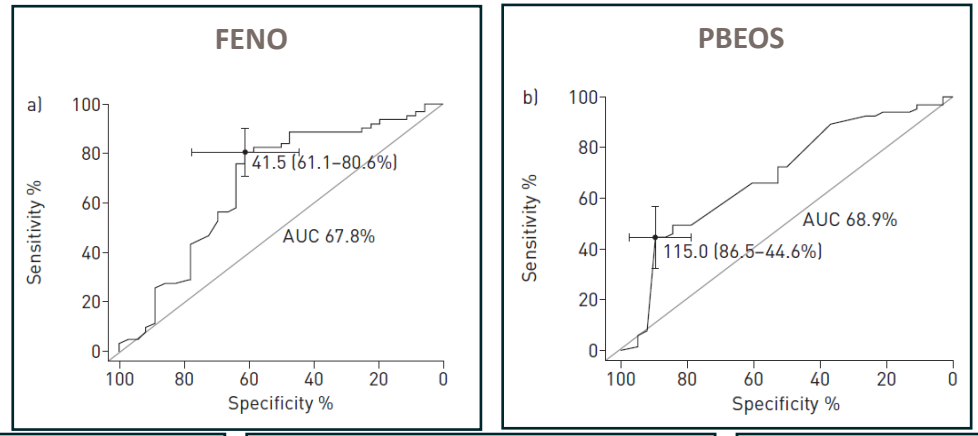
Transcriptome profile of airway epithelial cells exposed to T2GM (U-BIOPRED)

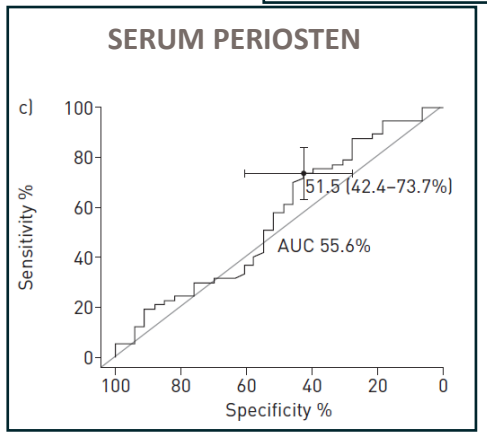
Correlated T2GM high

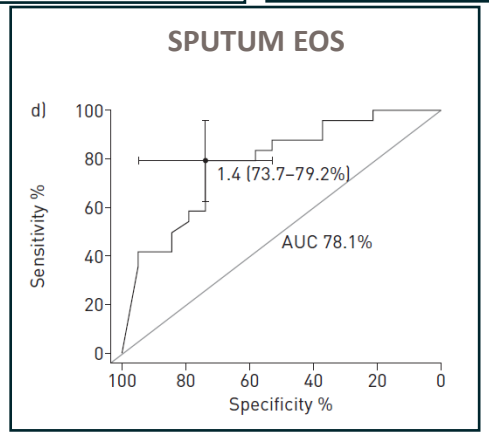
- Sputum eosinophilia correlated best
- FeNO (≥ 30 ppb)
- Blood EOS (≥ 300 cells/µL) moderate prediction

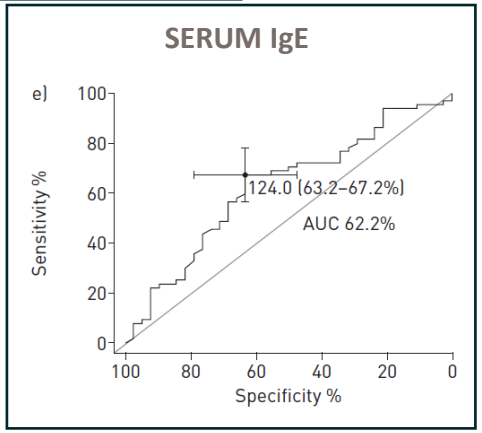


Receiver operating characteristic (ROC) curves





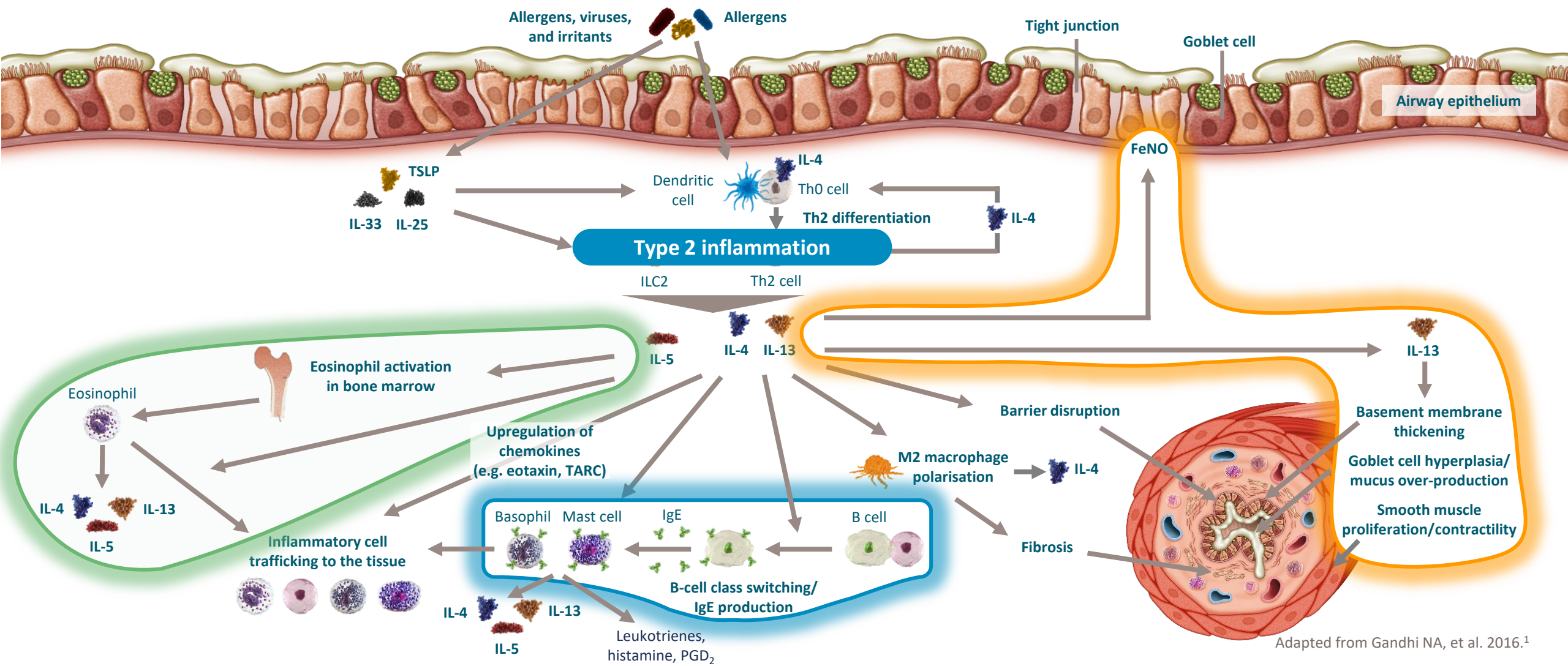




AUC, area under the curve**; EOS**, eosinophils; **ES**, enrichment score; **FeNO**, fractional exhaled nitric oxide; **IgE**, immunoglobulin E; **PBEOS**, peripheral blood eosinophils; **ppb**, parts per billion; **T2GM**, type 2 gene mean; **U-BIOPRED**, Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Pavlidis S, et al. Eur Respir J. 2019;53:1800938.

Can we measure type 2 high asthma?[1–4]



Adapted from Gandhi NA, et al. 2016.[1]

Ig, Immunoglobulin; **IL**, Interleukin; **ILC2**, type 2 innate lymphoid cell; **FeNO**, fractional exhaled nitric oxide; **PDG_2**; prostaglandin D2; **TARC**, thymus and activation-regulated chemokine; **Th**, T helper; **TSLP**, thymic stromal lymphopoietin

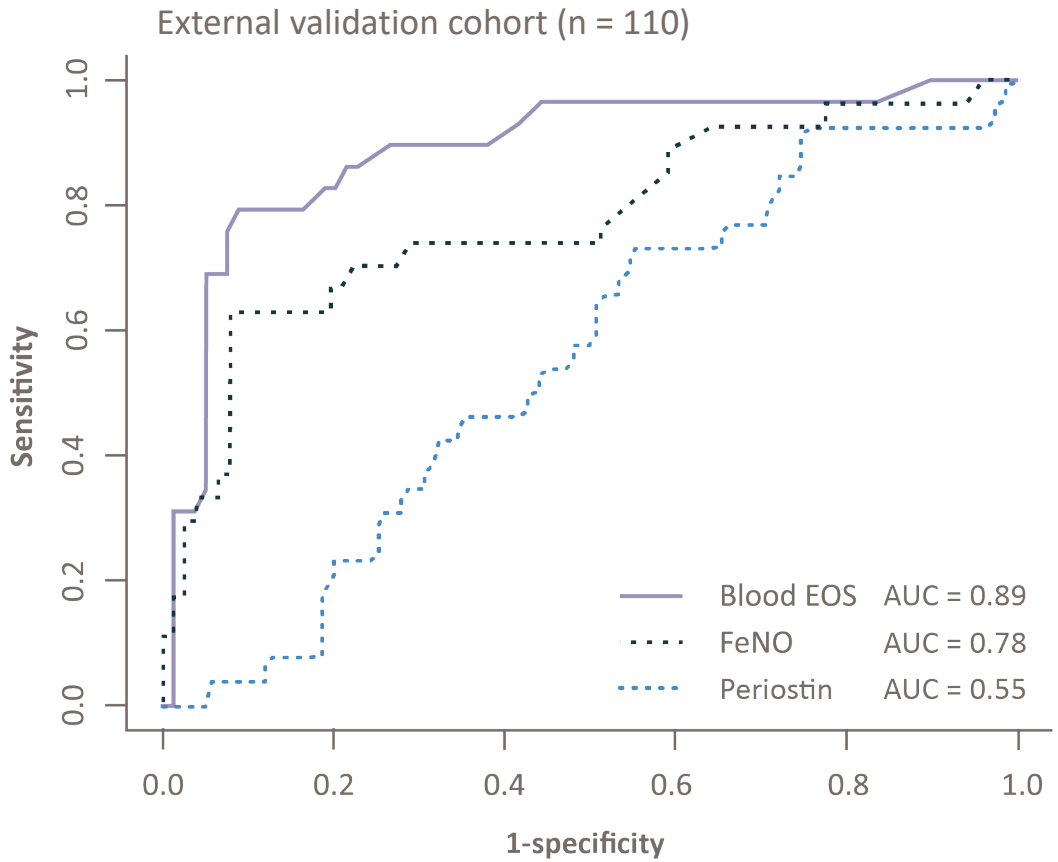
1. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35–50. **2.** Fahy JV. Nat Rev Immunol. 2015;15:57–65. **3.** Nonaka M, et al. Int Arch Allergy Immunol. 2010;152:327–341. **4.** GINA. Global strategy for asthma management and prevention. 2022. Available at https://ginasthma.org/gina-reports/ Accessed March 2023.

Validating biomarkers to diagnose airway eosinophilic inflammation

Sensitivity, specificity, PPV, and NPV of different surrogate markers using alternative cut-points to diagnose eosinophilic airway inflammation (< 3%, ≥ 3% sputum eosinophils)

	Threshold	Sensitivity	Specificity	PPV	NPV
Blood EOS	> 0.22 × 10^9/L	86	79	60	93
Blood EOS	≥ 0.25 × 10^9/L	79	84	64	91
Blood EOS	≥ 0.27 × 10^9/L	78	91	79	91
FeNO level	> 20 ppb	74	57	40	87
FeNO level	≥ 24 ppb	74	63	42	87
FeNO level	≥ 42 ppb	63	92	74	89
FeNO level	> 50 ppb	56	92	67	84
Serum periostin[a]	> 26 ng/mL	54	57	29	77

ROC curve analyses of the sensitivity and specificity of blood EOS, FeNO, and serum periostin[a] for the diagnosis of airway eosinophilic inflammation

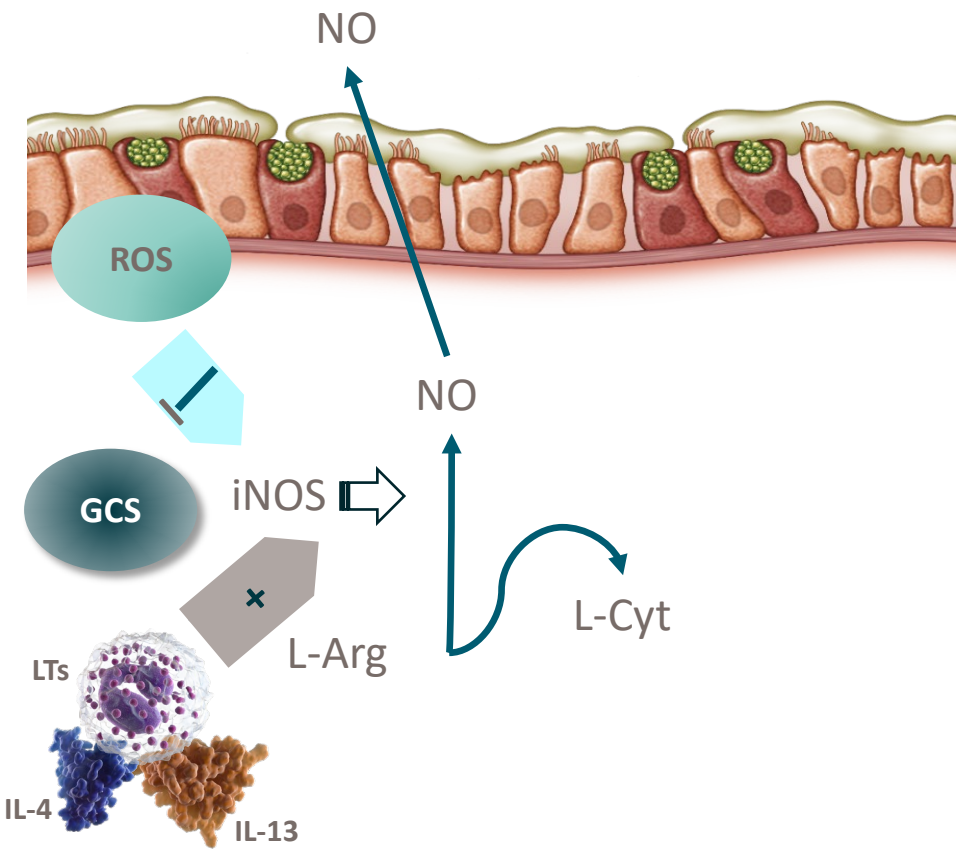


[a]By in-house ELISA.

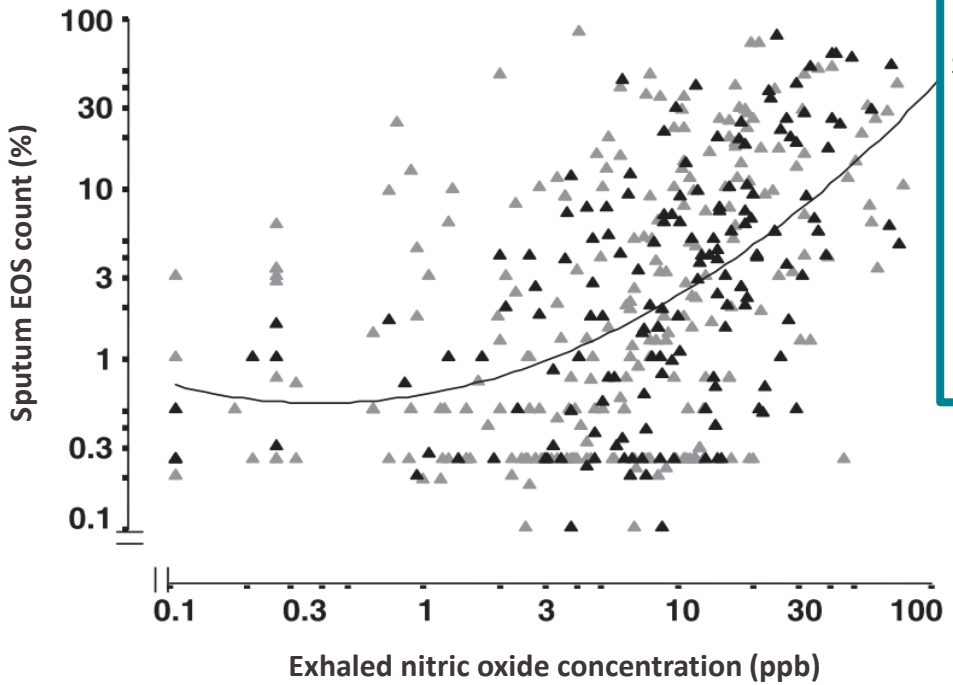
AUC, area under the curve; **ELISA,** enzyme-linked immunosorbent assay; **EOS,** eosinophils; **FeNO,** fractional exhaled nitric oxide; **NPV**, negative predictive value; **ppb**, parts per billion; **PPV**, positive predictive value; **ROC**, receiver operating curve

Wagener AH, et al. Thorax. 2015;70:115–120.

FeNO—what does it measure in asthma?



Scatter plot of sputum EOS count vs exhaled nitric oxide[1]



Mild-to-moderate asthma

Significant correlation with sputum eosinophilia

$R^2 = 0.26$, $P < 0.001$

For non-smokers, exhaled NO of 8.3 ppb identifies sputum EOS

Sensitivity 71%

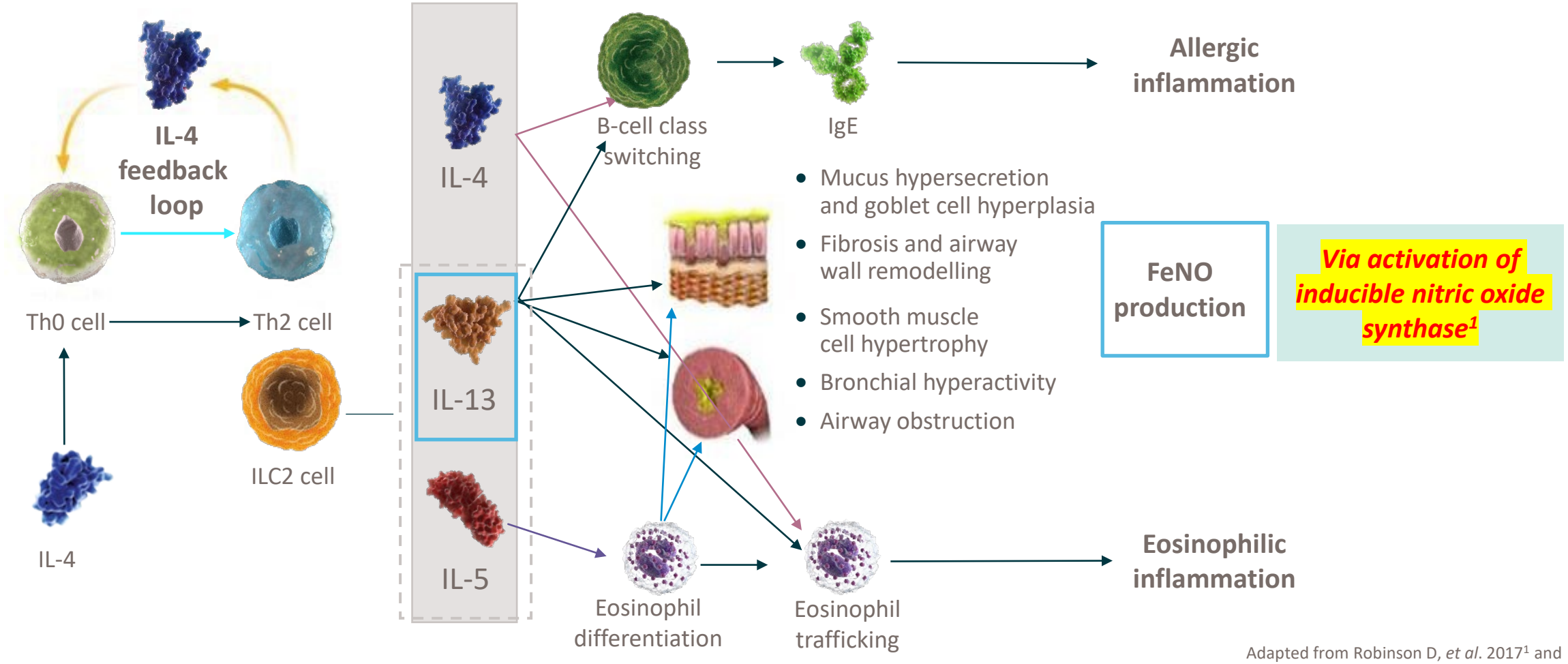
Specificity 72%

In severe asthma, FeNO is a relatively poor predictor of sputum eosinophilia, AUC 0.72[2]

AUC, area under the curve; **EOS,** eosinophil; **FeNO**, fractional exhaled nitric oxide; **GCS**, glucocorticosteroids; **IL**, interleukin; **iNOS**, inducible nitric oxide synthase; **L-Arg**, L-arginine; **L-Cyt**, L-citrulline; **LT**, leukotriene; **NO**, nitric oxide; **ppb**, parts per billion; **ROS**, reactive oxygen species

1. Berry MA, et al. Clin Exp Allergy. 2005;35:1175–1179. **2.** Hastie AT, et al. J Allergy Clin Immunol. 2013;132:72–80.

IL-4 and IL-13 are key and central drivers of type 2 inflammation[1–3]



Adapted from Robinson D, *et al*. 2017[1] and Hammad H and Lambrecht BN. 2008[2]

FeNO, fractional exhaled nitric oxide; **IgE**, immunoglobulin E; **IL**, interleukin; **ILC2**, type 2 innate lymphoid cell; **Th0**, naïve T; **Th2**, T helper 2

1. Robinson D, et al. Clin Exp Allergy. 2017;47:161–75. **2.** Hammad H and Lambrecht BN. Nat Rev Immunol. 2008;8:193–204. **3.** Australian Approved Product Information for DUPIXENT (dupilumab). 29 June 2022. http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swpdupix

FeNO is reimbursable on MBS (11507) when done with spirometry and reported

Category 2 - DIAGNOSTIC PROCEDURES AND INVESTIGATIONS

11507

Group D1 - Miscellaneous Diagnostic Procedures And Investigations

Subgroup 4 - Respiratory

Measurement of spirometry:

(a) that includes continuous measurement of the relationship between flow and volume during expiration or during expiration and inspiration, performed before and after inhalation of a bronchodilator; and

(b) fractional exhaled nitric oxide (FeNO) concentration in exhaled breath;

if:

(c) the measurement is performed:

(i) under the supervision of a specialist or consultant physician; and

(ii) with continuous attendance by a respiratory scientist; and

(iii) in a respiratory laboratory equipped to perform complex lung function tests; and

(d) a permanently recorded tracing and written report is provided; and

(e) 3 or more spirometry recordings are performed unless difficult to achieve for clinical reasons;

each occasion at which one or more such tests are performed

Not applicable to a service associated with a service to which item 11503 or 11512 applies

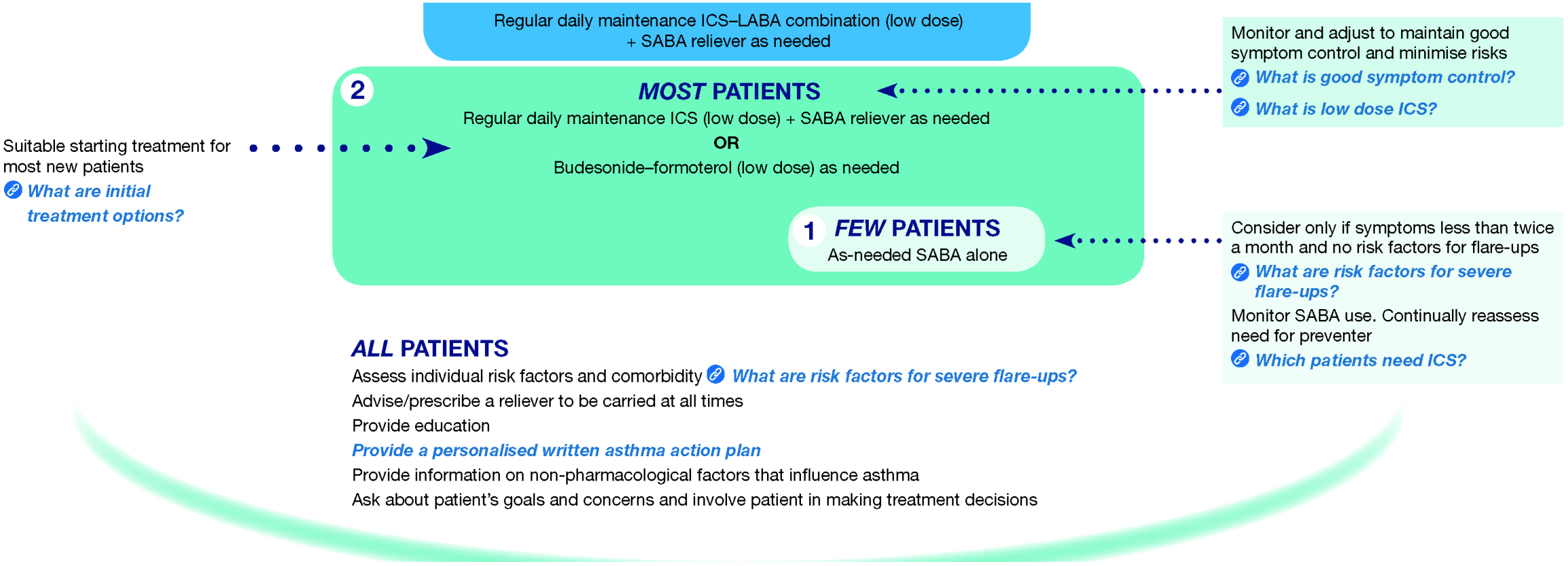
Fee: $105.95 **Benefit:** 75% = $79.50 85% = $90.10

(See para DN.1.21 of explanatory notes to this Category)

FeNO, fractional exhaled nitric oxide; **MBS,** Medicare Benefits Schedule

Australian Government. Department of Health and Aged Care. MedicareBenefits Schedule– Item 11507 . Available at http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=11507&qt=item Accessed March 2023.

Steps 1–2 (mild disease) type 2 inflammation and treatment Australian Asthma Handbook 2022

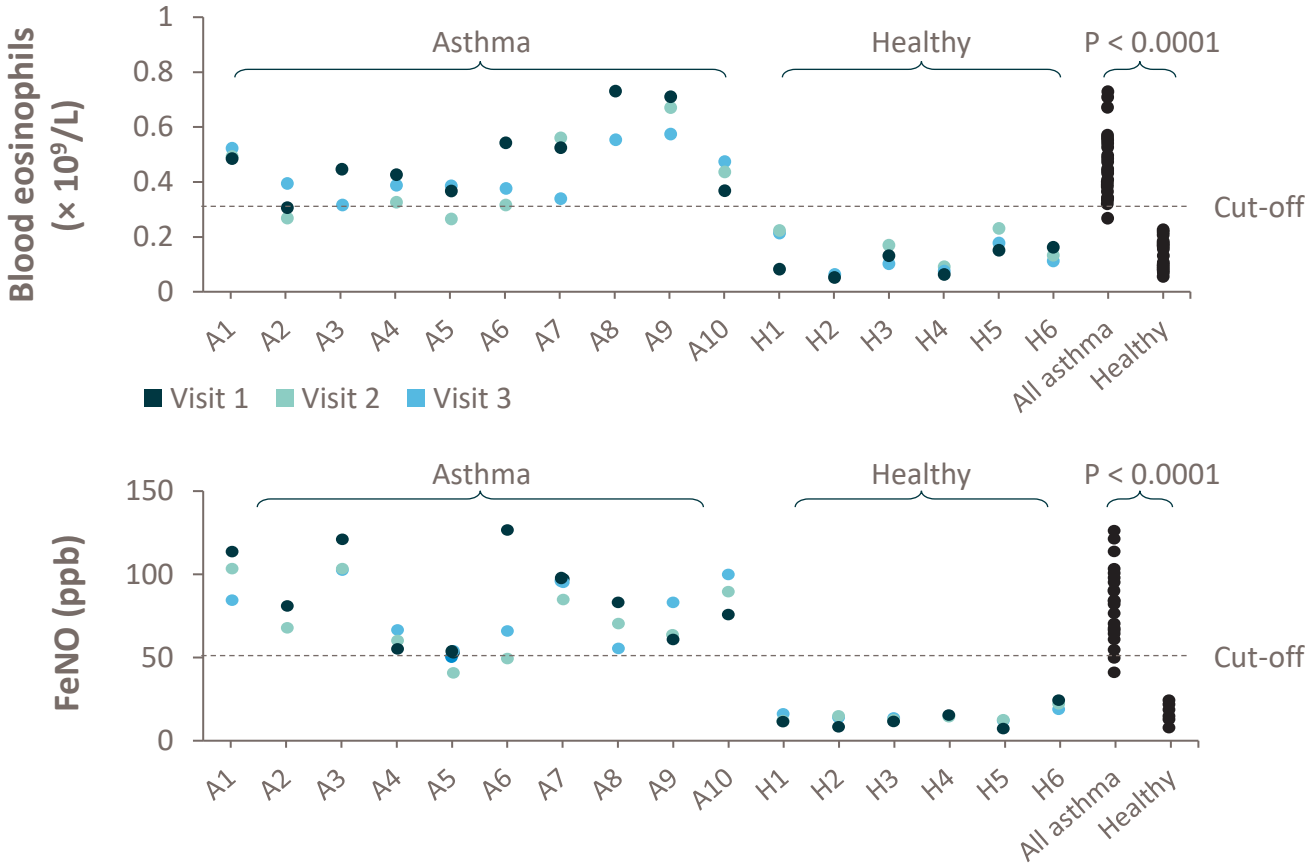


ICS, inhaled corticosteroid; **LABA,** long-acting β_2-agonist; **SABA,** short-acting β_2-agonist

Australian Asthma Handbook V2.2, published April 2022. Available at https://www.asthmahandbook.org.au/ Accessed March 2023.

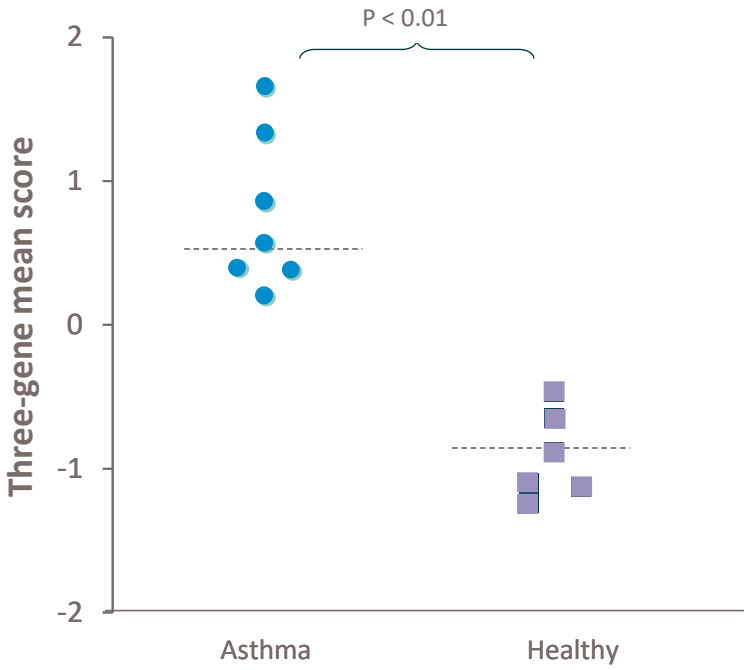
Blood eosinophil and FeNO in mild asthma predict type 2 disease

- 10 ICS-naive patients with eosinophil counts (> 0.3 × 10^9/L) and high FeNO levels (> 50 ppb) were selected along with six healthy subjects



Bronchial brushings

- SERPINB2
- POSTN
- CLCA1



FeNO, fractional exhaled nitric oxide; **ICS**, inhaled corticosteroid; **ppb**, parts per billion; **CLCA1**, chloride channel accessory 1

Southworth T, et al. Clin Transl Sci. 2021;14:1259–1264.

Figures adapted from Southworth T, et al. 2021.

ICS modify the disease

ICS reduce AHR

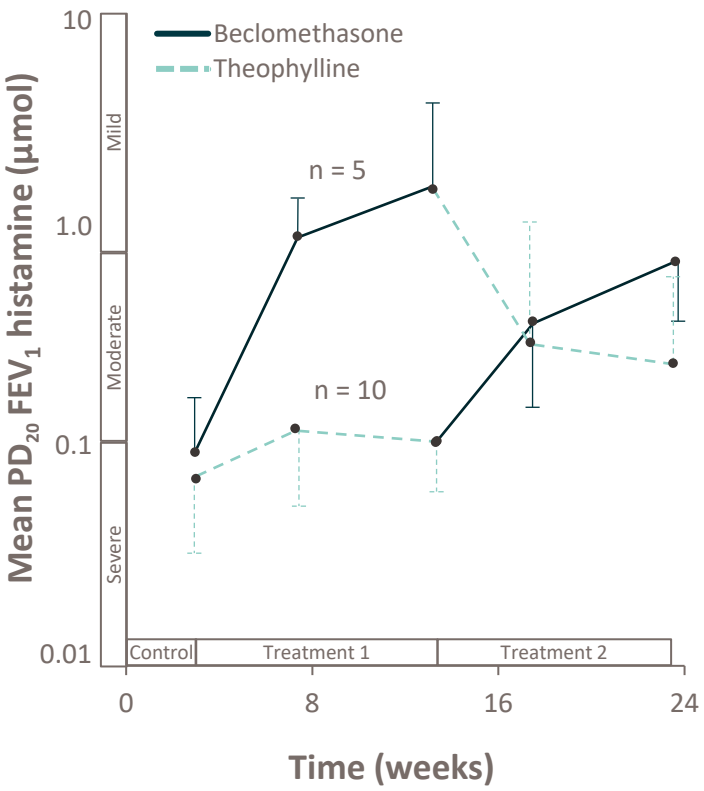


Figure adapted from Dutoit JI, et al. 1987.[1]

ICS improve PEF and AHR

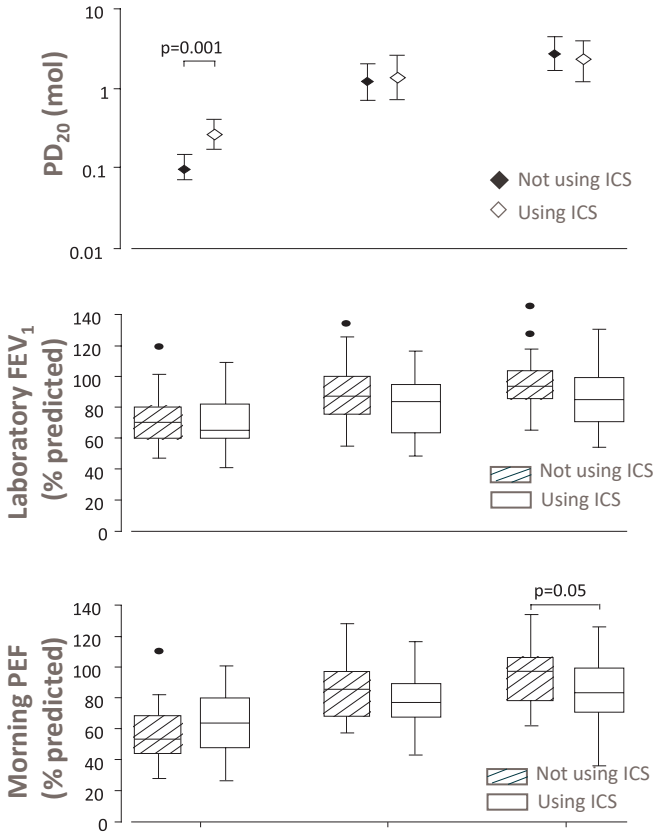
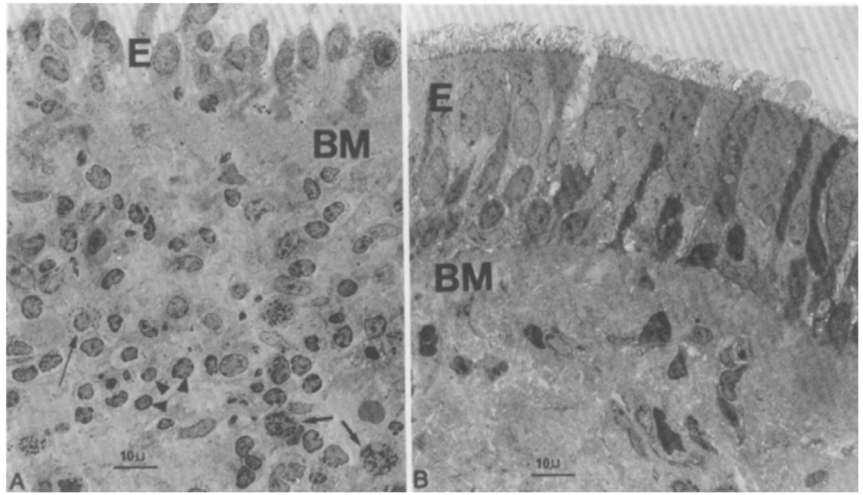


Figure adapted from Reddel HK, et al. 2000.[2]

ICS reduce airway inflammation



Terbutaline alone

Budesonide

Figure from Laitinen LA, et al. 1992.[3]

AHR, airway hyperresponsiveness; **BM,** basement membrane; **E,** airway epithelium; **FEV_1**, forced expiratory volume in 1 second; **ICS,** inhaled corticosteroids; **PEF**, peak expiratory flow; **PD_{20}**, provocation dose of histamine causing a 20% decline in FEV_1

1. Dutoit JI, et al. Am Rev Respir Dis. 1987;136:1174–1178. **2.** Reddel HK, et al. Eur Respir J. 2000;16:226–235. **3.** Laitinen LA, et al. J Allergy Clin Immunol. 1992;90:32–42

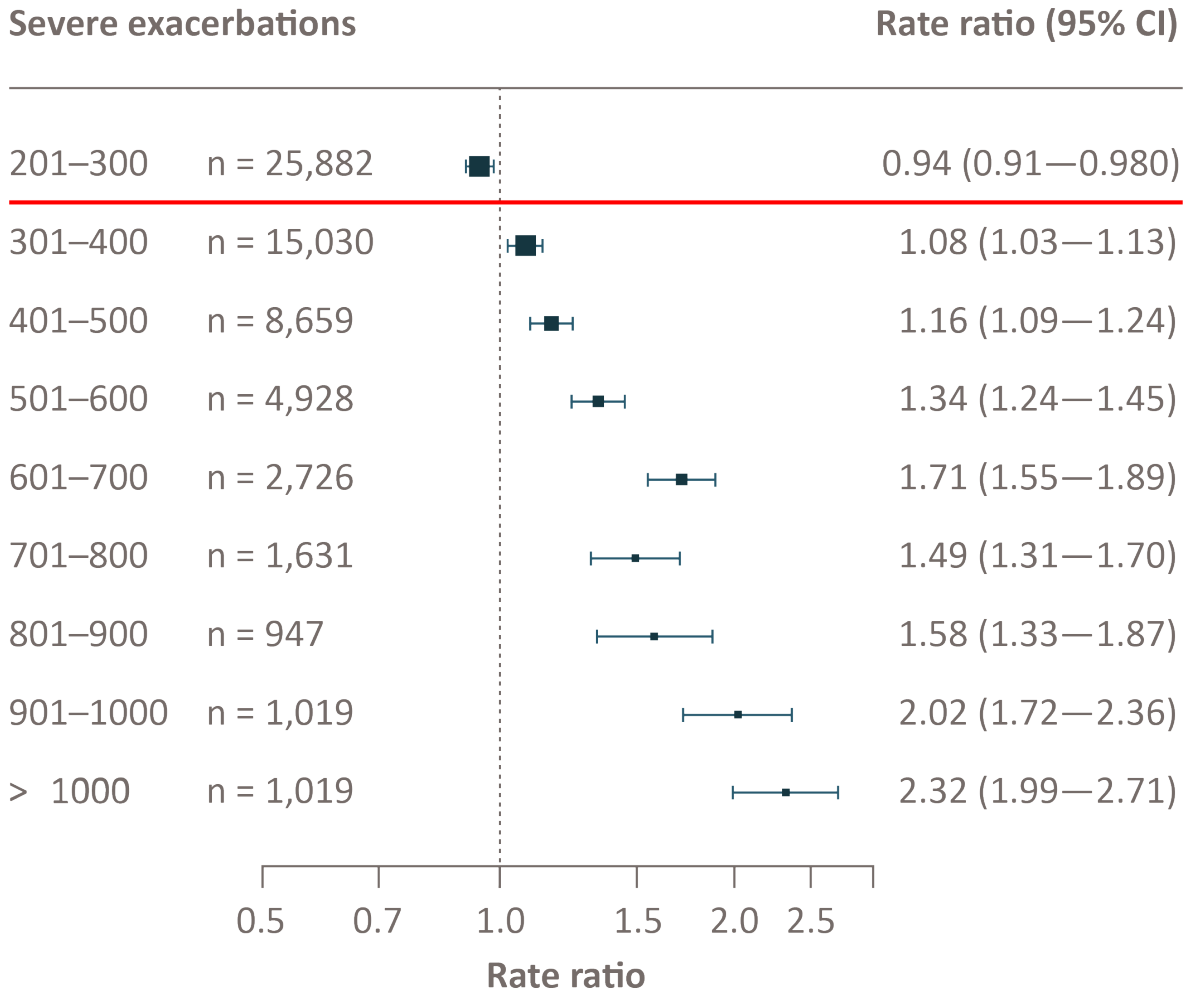
Blood eosinophils and asthma disease burden

Primary care cohort of 130,248 patients aged 12–80 years

Blood eosinophil count ≤ 400/µL or > 400/µL

Blood eosinophil high

- Exacerbation adjusted rate ratio: 1.42, 95% CI 1·36–1·47; P < 0.0001
- Lower odds of achieving overall asthma control (OR 0.74, 95% CI 0.72–0.77; P < 0.0001)



CI, confidence interval; **OR**, odds ratio

Price DB, et al. Lancet Respir Med. 2015;3:849–858.

Figure adapted from Price, DB et al. 2015.

FeNO (and spirometry) assists in diagnosis of asthma in primary care

- Cross-sectional diagnostic study of 219 adult patients attending 10 general practices for the first time with complaints suspicious for OAD[1]
- Study aimed to evaluate the sensitivity, specificity, and predictive values of FeNO for the diagnosis of asthma[1,2]
- 90 (41.1%) patients had asthma, 50 (22.8%) had COPD, and 79 (36.1%) had no OAD[1]
- Asthma could be ruled in with a FeNO > 46 ppb[2]
- Asthma could be ruled out with a FeNO < 12 ppb[2]
- NNT (investigate): three patients with FeNO to prevent the need for one bronchial provocation challenge[2]

Asthma diagnoses	FeNO (ppb)	LR+ (95% CI)	LR– (95% CI)
Borderline BHR, mild BHR, moderate-to-severe BHR, positive bronchodilator reversibility (n = 75)	> 12	1.12 (0.96–1.30)	0.62 (0.32–1.22)
	> 20	1.55 (1.12–2.14)	0.65 (0.47–0.91)
	> 35	1.94 (1.09–3.48)	0.81 (0.68–0.98)
	> 46	4.53 (1.96–10.49)	0.73 (0.62–0.86)
	> 76	Not calculable	Not calculable

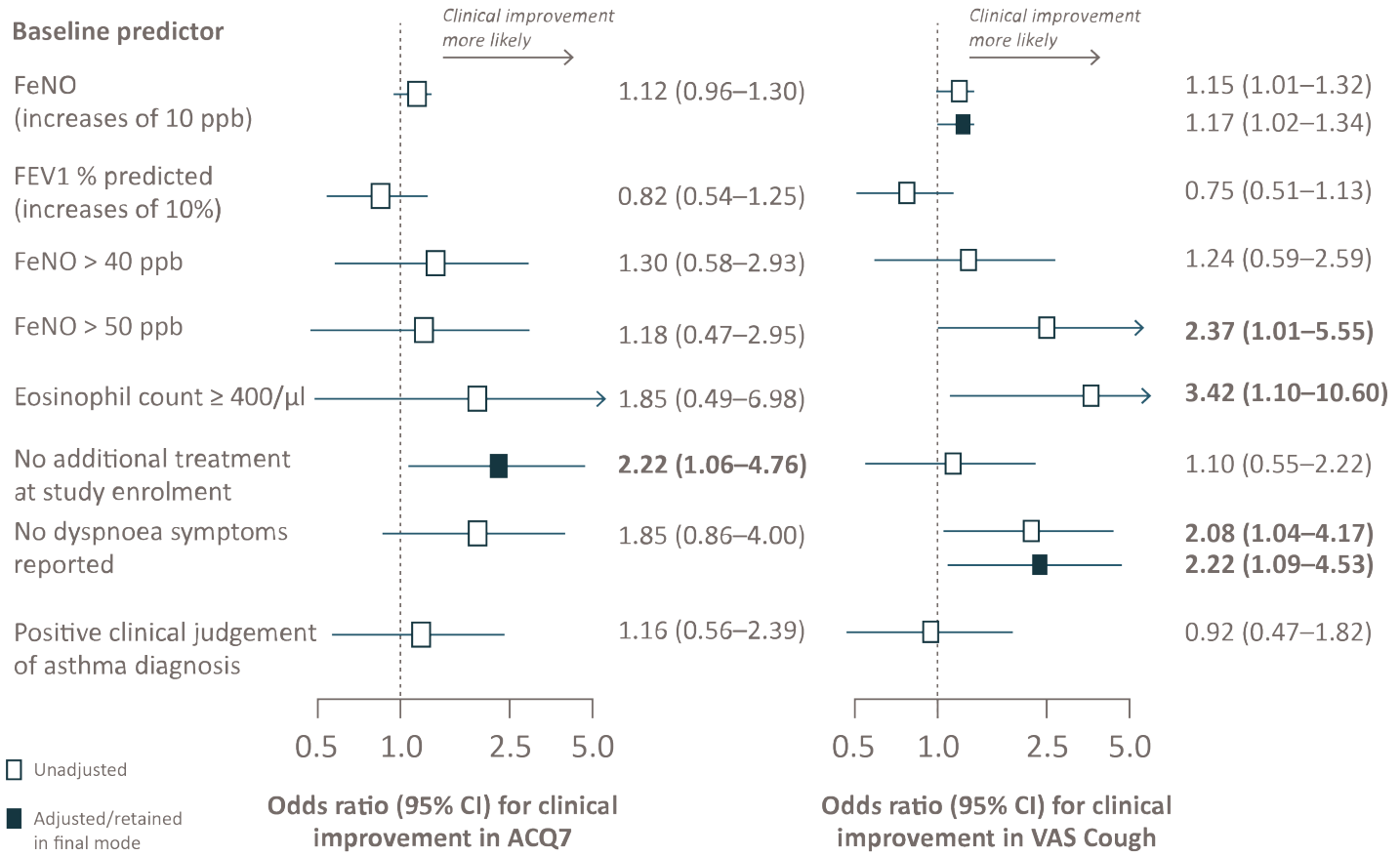
Table adapted from Schneider A, et al. 2009.[2]

BHR, bronchial hyperresponsiveness; **CI,** confidence interval; **COPD,** chronic obstructive pulmonary disease; **FeNO**, fractional exhaled nitric oxide; **LR+**, positive likelihood ratio, **LR–**, negative likelihood ratio; **NNT**, number needed to treat; **OAD**, obstructive airway disease; **ppb**, parts per billion

1. Schneider A, et al. BMC Pulm Med. 2009;9:3. **2.** Schneider A, et al. Respir Res. 2009;10:15.

FeNO predicts response to ICS, in the absence of bronchodilator response to salbutamol

- Undiagnosed > 18 years, cough, wheeze, dyspnoea, BDR < 20%
- 294 patients randomised to ICS or placebo; due to protocol violations, 214 patients were analysed
- Size of the treatment response was predicted by baseline FeNO
- FeNO (continuous and binary [> 50 ppb]), blood eosinophils, and reports of dyspnoea predicted response to ICS
- FeNO stronger response to improvement in cough



Adapted from Price D, et al. 2018.

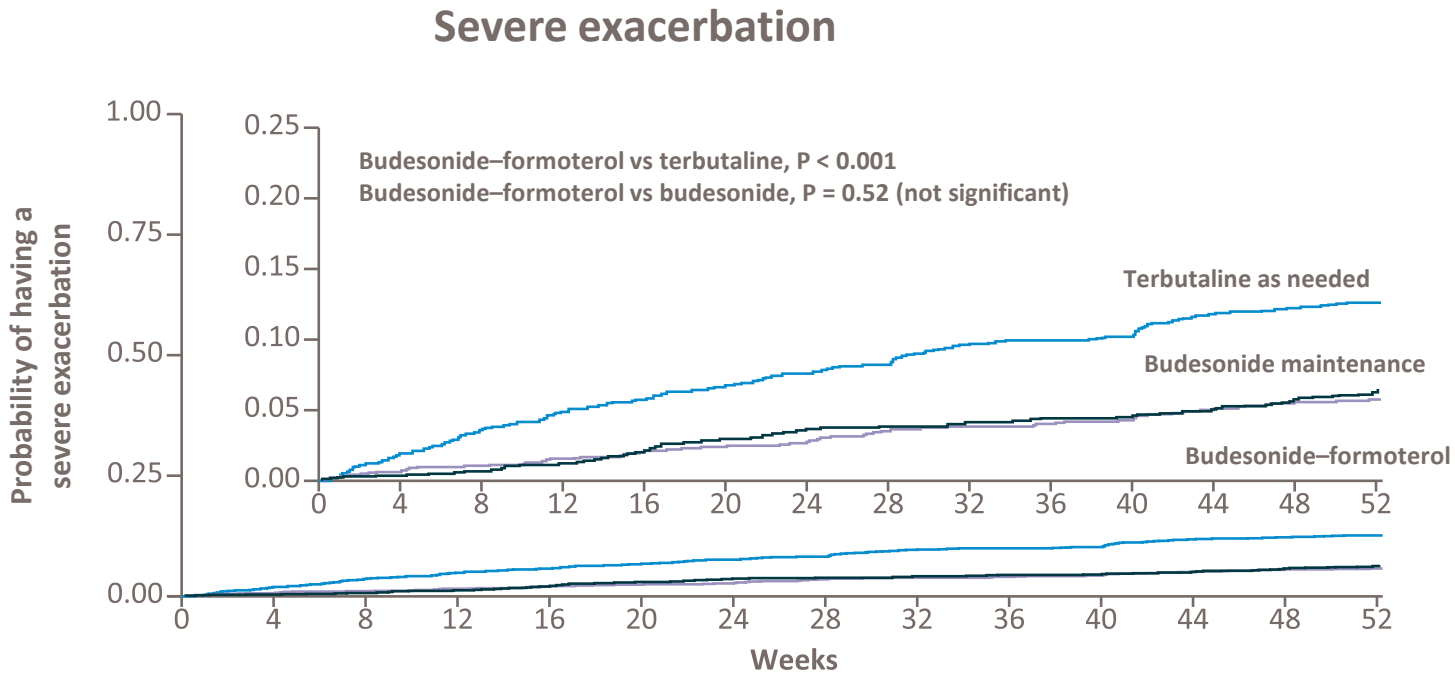
Clinical improvement defined as a decrease of ≥ 0.5 for ACQ-7 and a decrease of ≥ 20 mm for VAS cough

ACQ, Asthma Control Questionnaire; **BDR**, bronchodilator response; **CI**, confidence Interval; **FeNO**, fractional exhaled nitric oxide; **FEV_1**, forced expiratory volume in 1 second; **ICS**, inhaled corticosteroids; **ppb**, parts per billion; **VAS**, visual analogue scale

Price D, et al. Lancet Respir Med. 2018;6:29–39.

ICS regularly or ICS/LABA PRN reduces exacerbation risk in step 2 asthma

- 12 years and older
- Asthma, BDR > 12% or 200 mL
- Step 2; uncontrolled on SABA PRN or controlled on ICS
- Post BD FEV_1pp > 80%
- In the run-in used SABA 3-6 per week



Number at risk

Terbutaline as needed	1,277	1,237	1,190	1,153	1,131	1,102	1,084	1,067	1,038	1,024	1,017	987	977	731
Budesonide–formoterol as needed	1,277	1,258	1,235	1,218	1,207	1,179	1,172	1,159	1,138	1,127	1,119	1,097	1,086	822
Budesonide maintenance	1,282	1,264	1,238	1,226	1,201	1,172	1,159	1,150	1,136	1,123	1,110	1,088	1,076	811

Figure and table adapted from O'Byrne PM, et al. 2018.

BD, bronchodilator; **BDR**, bronchodilator response; **FEV_1pp**, forced expiratory volume in 1 second percent predicted; **ICS**, inhaled corticosteroid; **LABA**, long-acting β_2-agonists; **PRN**, as needed; **SABA**, short-acting β_2-agonists

O'Byrne PM, et al. N Engl J Med. 2018;378:1865–1876.

Mild asthma, as-needed BUD–formoterol effect on exacerbations *independent* of biomarker profile (in those with demonstrable BDR)

- 675 participants > 18 years, blood EOS and FeNO, GINA step 2
- Risk exacerbation three times greater in those with blood EOS > 0.3×10^9/L compared with those with blood EOS < 0.15×10^9/L
- In patients with blood EOS > 0.3×10^9/L, regular BUD + SABA PRN was more effective than PRN SABA for severe exacerbations (risk odds ratio 0.11, 95% CI 0.03–0.45)
- Compared to PRN SABA group, however, maintenance BUD more effective than SABA alone in patients with FeNO < 20 ppb compared with > 50 ppb (p=0.0040)
- Benefits of maintenance inhaled BUD are greater in patients with high blood EOS counts

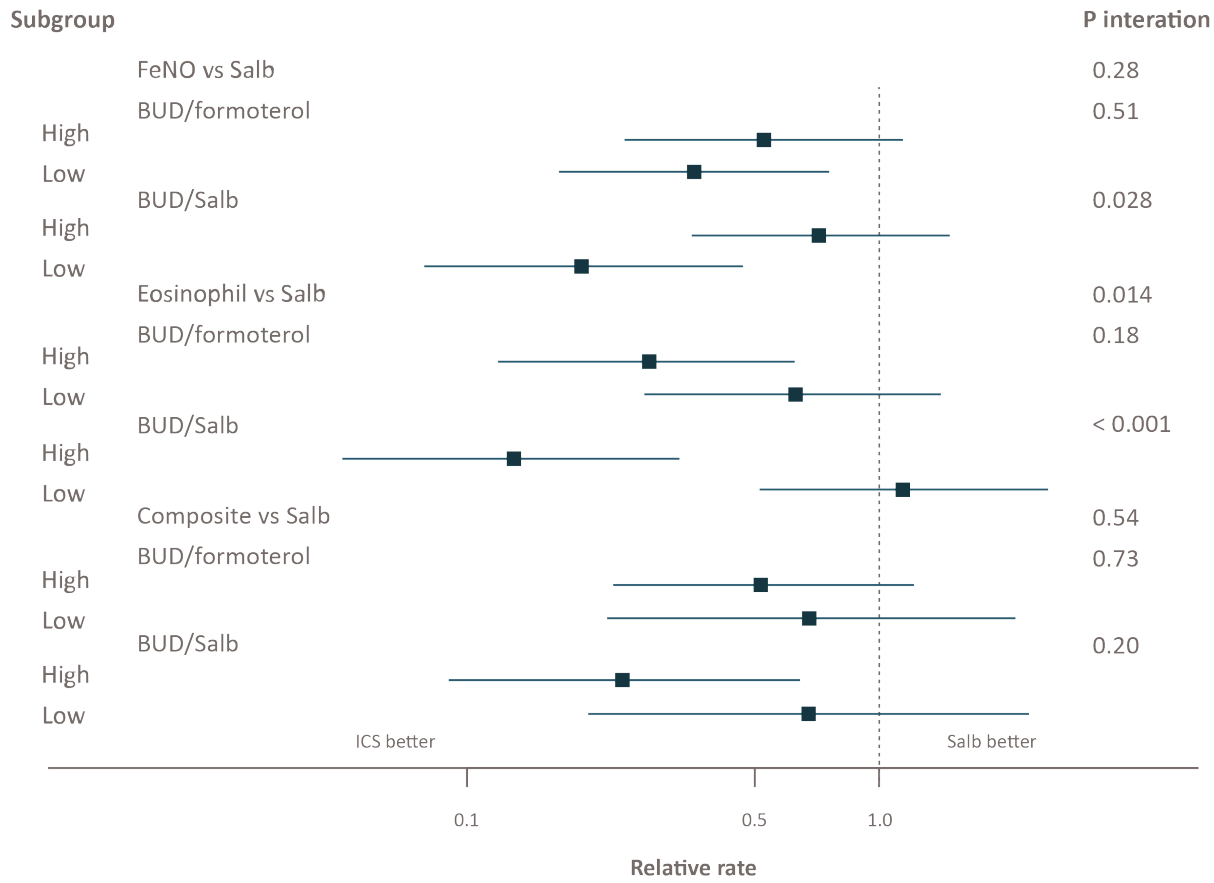


Figure taken from Pavord, ID et al. 2020.[1]

BDR, bronchodilator response; **BUD**, budesonide; **CI**, confidence Interval; **EOS**, eosinophils; **FeNO**, fractional exhaled nitric oxide; **GINA**, Global Initiative for Asthma; **ICS**, inhaled corticosteroid; **PRN**, as needed; **SABA**, short-acting β_2-agonists; **Salb**, salbutamol

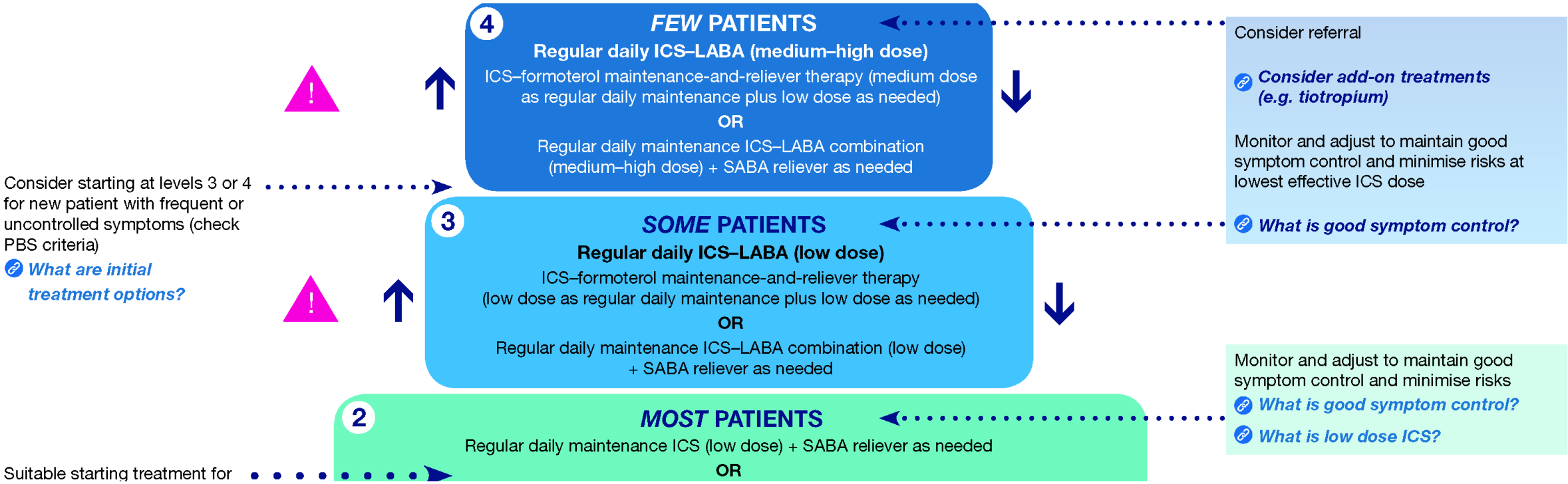
Pavord ID, et al. Lancet Respir Med. 2020;8:671–680.

In mild asthma

- History and variable airflow obstruction predict disease that will respond to ICS
- The majority of these patients are likely to have type 2 airway inflammation and justify the use of either low-dose ICS regularly or ICS–formoterol as needed
- Blood eosinophils and FeNO are biomarkers of active type 2 inflammation and reflect risk of exacerbations and poor control, even in mild asthma

FeNO, fractional exhaled nitric oxide; **ICS**, inhaled corticosteroid

Step 3-4 (moderate disease)
Type 2 inflammation and treatment - Australian Asthma Handbook

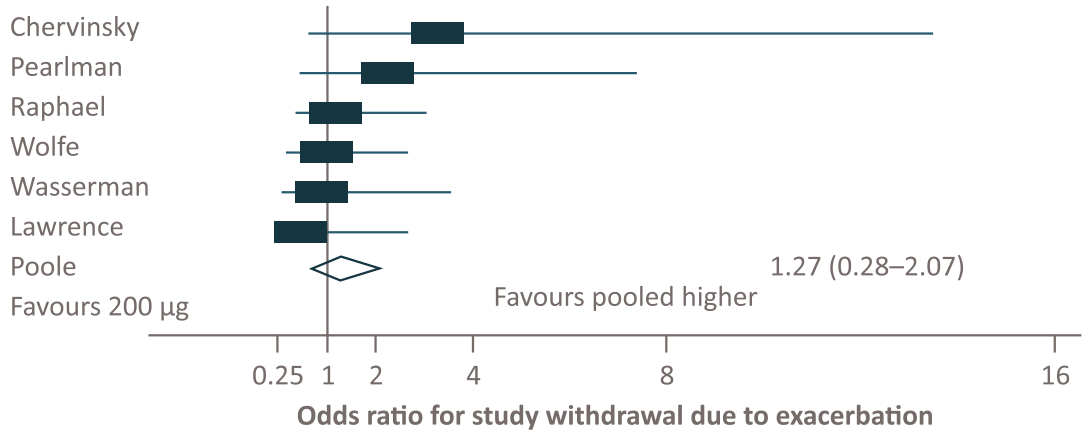


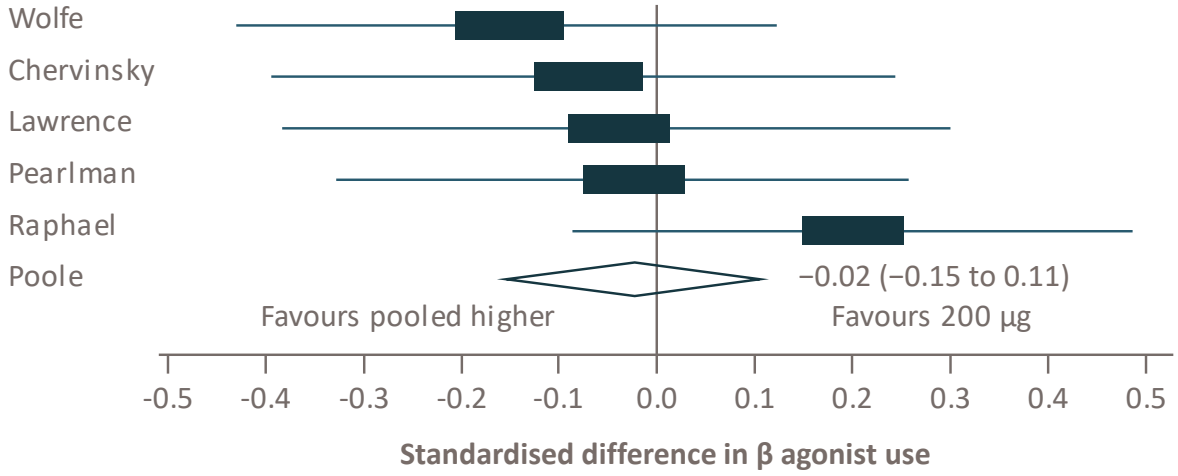
ICS, inhaled corticosteroid; **LABA**, long-acting β_2-agonist; **PBS,** Pharmaceutical Benefits Scheme; **SABA**, short-acting β_2-agonist

Australian Asthma Handbook V2.2, published April 2022. Available at https://www.asthmahandbook.org.au/ Accessed March 2023.

Most of the therapeutic effect is seen with low-to-moderate dose inhaled corticosteroid

- Meta-analysis, seven RCTs, 2,431 adults or adolescents, treated with fluticasone
- Most of the therapeutic benefit of fluticasone is achieved with a total daily dose of 200 µg/day, with minimal further clinical benefit achieved with higher doses





RCT, randomised controlled trial

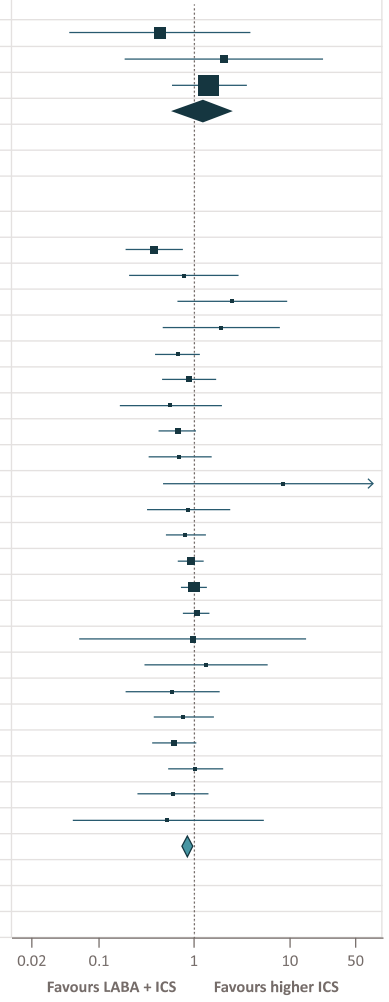
Masoli M, et al. Thorax. 2004;59:16–20.

Figures adapted from Masoli M, et al. 2004.

Step 3 – addition of LABA to ICS

- 48 studies > 15,000 participants including 1,155 children and 14,000 adults
- Inadequately controlled on ICS
- ICS/LABA vs high-dose ICS
- Exacerbations (RR 0.88, 95% CI 0.78–0.98; P = 0.02)
- Dominated by adult data (40 studies, six in children)
- Why difference in children? An effect of more dominant type 2 high inflammation?

	LABA + ICS		Increased ICS			RR	RR
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M–H, fixed, 95% CI**	**M–H, fixed 95% CI**
2.1.1 Children							
LOCCS	1	17	3	22	24.6%	0.43 (0.05–3.79)	
SAM104926	2	160	1	161	9.4%	2.01 (0.18–21.97)	
Verberne 1998	10	60	7	60	66.0%	1.43 (0.58–3.50)	
Subtotal (95% CI)		**237**		**243**	**100%**	**1.24 (0.58–2.66)**	
Total events	13		11				
Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² = 0%							
Test of overall effect: *Z* = 0.55 (P = 0.59)							
2.1.2 Adults							
Baraniuk 1999	11	231	28	223	5.2%	0.38 (0.19–0.74)	
Bateman 2006	4	246	5	228	0.9%	0.77 (0.21–2.85)	
Bouros 1999	8	69	3	65	0.6%	2.51 (0.70–9.06)	
Busse 2003	6	281	3	277	0.5%	1.97 (0.50–7.80)	
Condemi 1999	21	221	31	216	5.7%	0.66 (0.39–1.12)	
Greening 1994	18	220	19	206	3.6%	0.89 (0.48–1.64)	
Johansson 2001	4	176	7	173	1.3%	0.56 (0.17–1.88)	
Kelsen 1999	26	239	40	244	7.2%	0.66 (0.42–1.05)	
Kips 2000	8	29	12	31	2.1%	0.71 (0.34–1.49)	
Li 1999	3	13	0	16	0.1%	8.50 (0.48–151.05)	
LOCCS	7	143	8	144	1.4%	0.88 (0.33–2.37)	
Murray 1999	29	260	35	254	6.4%	0.81 (0.51–1.28)	
O'Byrne 2001	58	323	61	312	11.3%	0.92 (0.66–1.27)	
O'Byrne 2005	145	789	149	819	26.5%	1.01 (0.82–1.24)	
Pauwels 1997	62	210	60	214	10.8%	1.05 (0.78–1.42)	
SAM30022	1	34	1	33	0.2%	0.97 (0.06–14.88)	
SAM40090	4	242	3	241	0.5%	1.33 (0.30–5.87)	
SAM40026	5	295	8	279	1.5%	0.59 (0.20–1.79)	
SFCF4026	12	154	16	156	2.9%	0.76 (0.37–1.55)	
SLGA5021	20	246	32	243	5.8%	0.62 (0.36–1.05)	
Van Noord 1999	16	139	15	135	2.8%	1.04 (0.53–2.01)	
Vermetten 1999	8	113	14	120	2.5%	0.61 (0.26–1.39)	
Wallin 2003	1	18	2	19	0.4%	0.53 (0.05–5.33)	
Subtotal (95% CI)		**4,691**		**4,658**	**100%**	**0.87 (0.78–0.97)**	
Total events	477		552				
Heterogeneity Chi² = 22.93, df = 22 (P = 0.41); I² = 4%							
Test for overall effect *Z* = 2.47 (P = 0.01)							



CI, confidence interval; **LABA**, long-acting β_2-agonists; **ICS**, inhaled corticosteroids; **M-H,** Mantel–Haenszel; **RR**, risk ratio

Ducharme FM, et al. Cochrane Database Syst Rev. 2010(4):Cd005533.

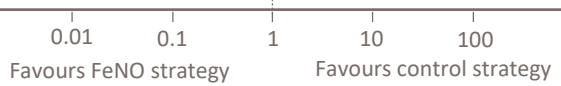
ICS and ICS/LABA adjusted by FeNO

- FeNO-adjusted treatment reduced exacerbations in adults

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma
Comparison: 1 Asthma treatment tailored on FeNO vs clinical symptoms
Outcome: 1 Number of participants who had ≥ 1 exacerbations over study period

Study or subgroup	FeNO strategy N	Control strategy N	Log [odds ratio] (SE)	Odds ratio IV, fixed (95% CI)	Weight	Odds ratio IV, fixed (95% CI)
Honkoop 2014	189	203	–0.4463 (0.4546)		14.3%	0.64 (0.26–1.56)
Powell 2011	111	109	–0.7344 (0.2926)		34.4%	0.48 (0.27–0.85)
Shaw 2007	58	60	–0.5746 (0.4267)		16.2%	0.56 (0.24–1.30)
Smith 2005	46	48	0.3863 (0.4697)		13.4%	1.47 (0.59–3.69)
Syk 2013	93	88	–0.7244 (0.3679)		21.8%	0.48 (0.24–1.00)
Total (95% CI)	**497**	**508**			**100%**	

Heterogenity: Chi^2 = 4.61, df = 4 (P = 0.33); I^2 = 13%
Test for overall effect: *Z* = 3.00 (P = 0.0027)
Test for subgroup differences: Not applicable



Adapted from Petsky HL, et al. 2016.[1]

- Significantly decreased the number of children who had one or more exacerbations but did not impact on the day-to-day clinical symptoms or ICS doses

Review: Exhaled nitric oxide levels to guide treatment for children with asthma
Comparison: 1 Asthma treatment tailored on FeNO vs clinical symptoms
Outcome: 1 Number of participants who had ≥ 1 exacerbations over study period

Study or subgroup	FeNO strategy n/N	Control strategy n/N	Odds ratio IV, fixed (95% CI)	Weight	Odds ratio M–H, fixed (95% CI)
De Jongste 2008	9/75	12/72		7.0%	0.64 (0.27–1.73)
Peirsman 2014	11/49	22/50		10.9%	0.37 (0.15–0.88)
Pestsky 2015	6/31	15/32		7.7%	0.27 (0.09–0.84)
Pijnenburg 2005	7/42	10/47		5.1%	0.74 (0.25–2.16)
Pike 2013	37/44	38/46		3.8%	1.11 (0.37–3.38)
Szefler 2008	102/276	118/270		48.7%	0.76 (0.54–1.06)
Verini 2010	16/32	26/32		8.4%	0.23 (0.07–0.71)
Voorend-van bergen 2015	9/92	14/89		8.3%	0.58 (0.24–1.42)
Total (95% CI)	**641**	**638**		**100%**	**0.62 (0.49–0.80)**

Heterogenity: Chi^2 = 4.61, df = 4 (P = 0.33); I^2 = 13%
Test for overall effect: *Z* = 3.00 (P = 0.0027)
Test for subgroup differences: Not applicable

Adapted from Petsky HL, et al. 2016.[2]

CI, confidence interval; **FeNO**, fractional exhaled nitric oxide; **ICS**, inhaled corticosteroid; **IV,** inverse variance; **LABA**, long-acting β_2-agonists; **M-H,** Mantel–Haenszel; **SE**, standard error

1. Petsky HL, et al. Cochrane Database Syst Rev. 2016;9:Cd011440 **2.** Petsky HL, et al. Cochrane Database Syst Rev. 2016;11:CD011439.

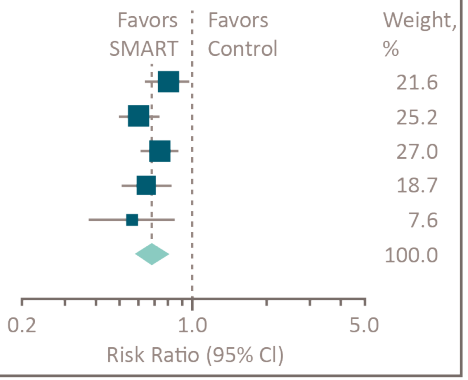
ICS/LABA (SMART) vs fixed-dose ICS

- 16 RCTs, 22,524 participants, most aged ≥ 12 years
- 15/16 BUD/FORM
- SMART vs equivalent ICS/LABA: RR 0.68 (95% CI 0.58–0.80)
- SMART vs high-dose ICS/LABA: RR 0.77 (95% CI 0.60–0.98)

Association of SMART with exacerbations requiring systemic corticosteroids, hospitalisation, or ED visits among patients aged 12 years or older vs the same dose of ICS and LABA controller therapy

Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI). %	Risk Ratio (95% CI)
Vogelmeier et al, 2012	1067	132	1076	167	-3.1 (-6.1 to -0.2)	0.80 (0.64 to 0.99)
Rabe et al, 2006	1107	143	1138	245	-8.6 (-11.7 to -5.5)	0.60 (0.50 to 0.72)
Atienza et al, 2013	1049	170	1042	229	-5.8 (-9.1 to -2.4)	0.74 (0.62 to 0.88)
Papi et al, 2013	852	99	849	152	-6.3 (-9.6 to -2.9)	0.65 (0.51 to 0.82)
Papi et al, 2013	151	28	152	50	-14.4(-24.1 to -4.6)	0.56 (0.38 to 0.84)
Overall (random-effects model)	4226	572	4257	843	-6.4 (-10.2 to -2.6)	0.68 (0.58 to 0.80)

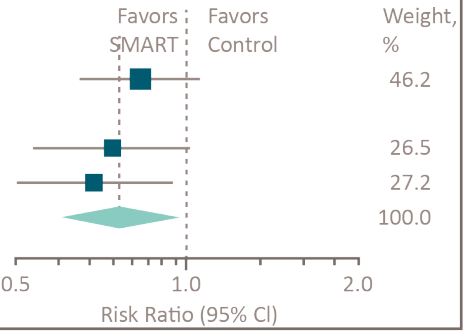
Heterogenity: I^2 = 29%, P=0.23
Test for overall effect: t_4 = -6.44, P<0.001



Association of SMART with exacerbations requiring systemic corticosteroids, hospitalisation, or ED visits among patients aged 12 years or older vs a higher dose of ICS and LABA controller therapy

Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI). %	Risk Ratio (95% CI)
Bousquet et al, 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)
Kuna et al, 2007						
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)

Heterogenity: I^2 = 0%, P=0.64
Test for overall effect: t_2 = -4.71, P=0.4

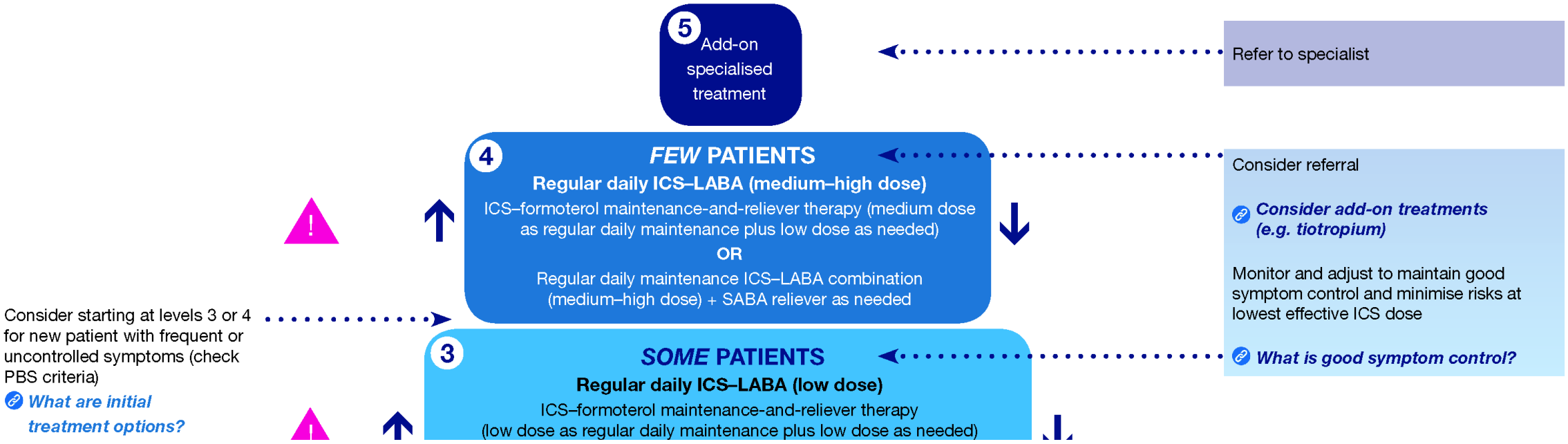


Taken from Sobieraj DM, et al. 2018.

BUD, budesonide; **CI**, confidence interval; **ED**, Emergency Department; **FORM,** formoterol; **ICS**, inhaled corticosteroid; **LABA**, long-acting β_2-agonists; **RCT**, randomised controlled trial; **RR**, risk ratio; **SMART**, single maintenance and reliever therapy

Sobieraj DM, et al. JAMA. 2018;319:1473–1484.

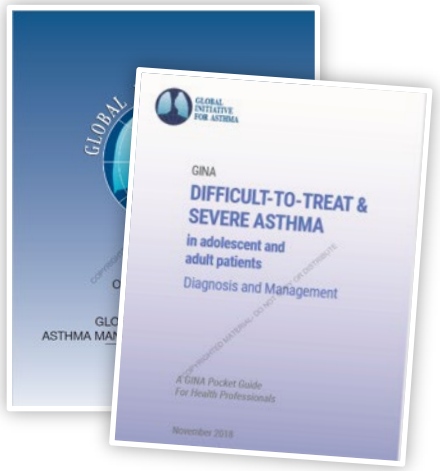
When to move from step 4 to step 5



ICS, inhaled corticosteroid; **LABA**, long-acting β_2-agonist; **PBS**, Pharmaceutical Benefits Scheme; **SABA**, short-acting β_2-agonist

Australian Asthma Handbook V2.2, published April 2022. Available at https://www.asthmahandbook.org.au/ Accessed March 2023.

GINA Guidelines (2022) characterising patients with type 2 Inflammation in asthma



GINA criteria for type 2 inflammation

- Blood eosinophils ≥ 150 cells/µL and/or
- FeNO ≥ 20 ppb and/or
- Sputum eosinophils ≥ 2% and/or
- Asthma clinically allergen driven

(Repeat blood eosinophils and FeNO up to three times on lowest possible OCS dose)

- High-dose ICS?
- Oral corticosteroids?
- Macrolides?
- Biologics?

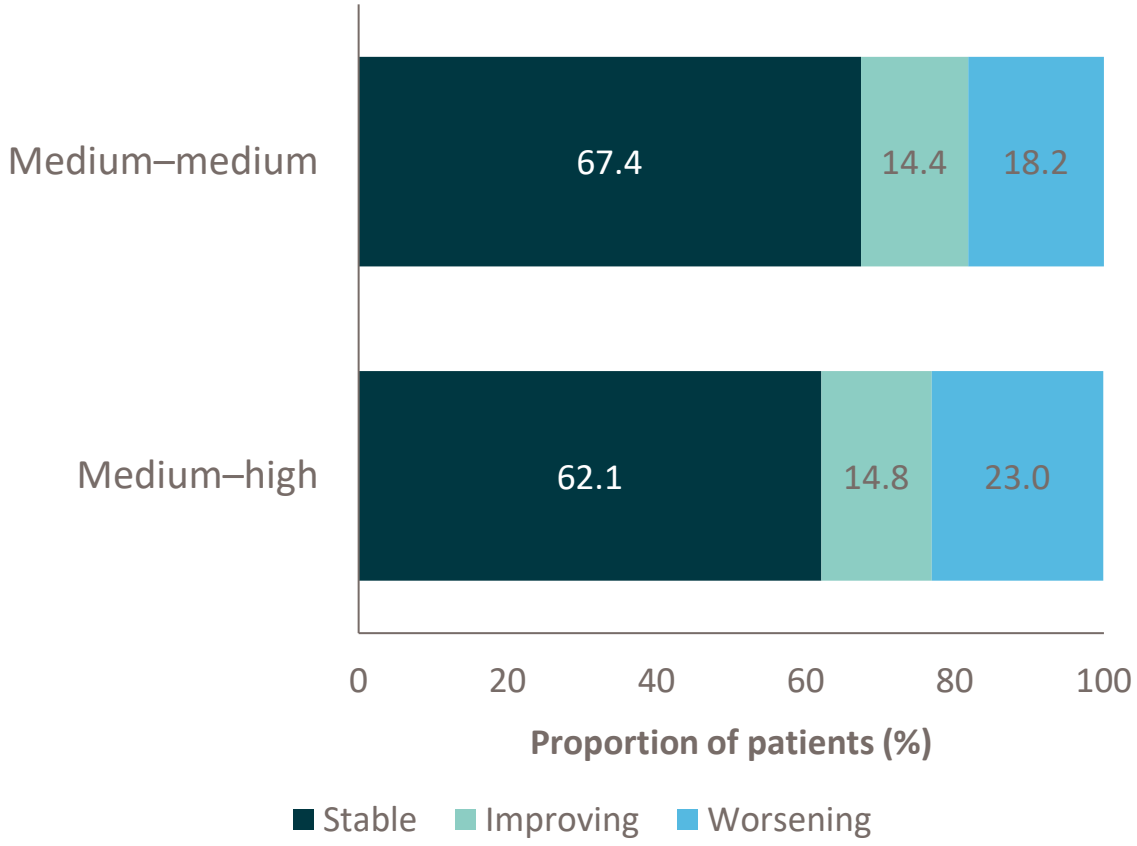
OCS use rapidly reduces biomarkers of type 2 inflammation, e.g. FeNO, blood eosinophils

FeNO, fractional exhaled nitric oxide; **GINA**, Global Initiative for Asthma; **ICS**, inhaled corticosteroid; **OCS**, oral corticosteroid; **ppb**, parts per billion

GINA. Global strategy for asthma management and prevention. 2022. Available at https://ginasthma.org/gina-reports/ Accessed March 2023.

Stepping up from medium- to high-dose ICS does NOT prevent exacerbations

- UK database study > 13 years followed for a mean 2 years
- Stepped up medium- to high-dose ICSs (n = 6879) had a higher risk of exacerbations (hazard ratio, 1.17; 95% CI, 1.12-1.22)
- High ICS adherence (≥ 80%) was associated with increased OCS use, add-on therapies and asthma-related healthcare visits (adult-onset asthma)
- A step-up to high-dose ICSs was also associated with a higher number of asthma exacerbations and antibiotics courses



Adapted from Pavord ID, et al. 2023.

CI, confidence interval; **ICS**, inhaled corticosteroids; **UK,** United Kingdom

Pavord ID, et al. J Allergy Clin Immunol Pract. 2023;11:532–543.

Clinical study of triple therapy FF/UMEC/VI in patients with asthma inadequately controlled by ICS/LABA

Baseline demographics		Total (N = 2,436) Mean (SD)/n (%)
Age (years)		53.2 (13.11)
Male		922 (38%)
BMI (kg/m^2)		29.35 (6.642)
Pre-study ICS dose at screening - mid		1,621 (67%)
CV history/risk factor		1,181 (48%)
Duration of asthma (years)		21.2 (15.31)
Smoking status	Never smoked	1,966 (81%)
	Former smoker	470 (19%)
	Current smoker	0
Number of exacerbations requiring oral/systemic corticosteroids and/or hospitalisation in previous 12 months	0	892 (37%)
	1	1,166 (48%)
	≥ 2	378 (16%)

Disease characteristics at screening		Total (N = 2,436)
FEV_1 %pred, Pre-bronchodilator (at screening)	n	2,423
	Mean (SD)	58.48 (12.787)
FEV_1 %pred, Pre-bronchodilator (at randomisation)	n	2420
	Mean (SD)	68.18 (14.760)
FEV_1/FVC ratio, Post-bronchodilator (at enrolment)	n	2,430
	Mean (SD)	0.66 (0.11)
	n	2,418
Reversibility* % (at screening)	Mean (SD)	29.92 (18.122)
Reversibility* mL (at Screening)	Mean (SD)	483.7 (274.16)

*Patients were required to meet the threshold for reversibility (defined as post-bronchodilator increase in FEV1 of ≥12% and ≥200 mL).

Adapted from Lee LA, et al. 2021.

BMI, body mass index; **CV**, cardiovascular; **FEV_1**, forced expiratory volume in 1 second; **FF**, fluticasone furoate; **FVC**, forced vital capacity; **ICS**, inhaled corticosteroids; **LABA**, long-acting β_s-agonists; **SD**, standard deviation; **UMEC**, umeclidinium; **VI**, vilanterol

Lee LA, et al. Lancet Respir Med. 2021;9:69–84.

Triple therapy (FF/UMEC/VI) in patients with asthma inadequately controlled by ICS/LABA

ICS escalation is required to reduce exacerbation rate vs continuing mid dose ICS/LABA

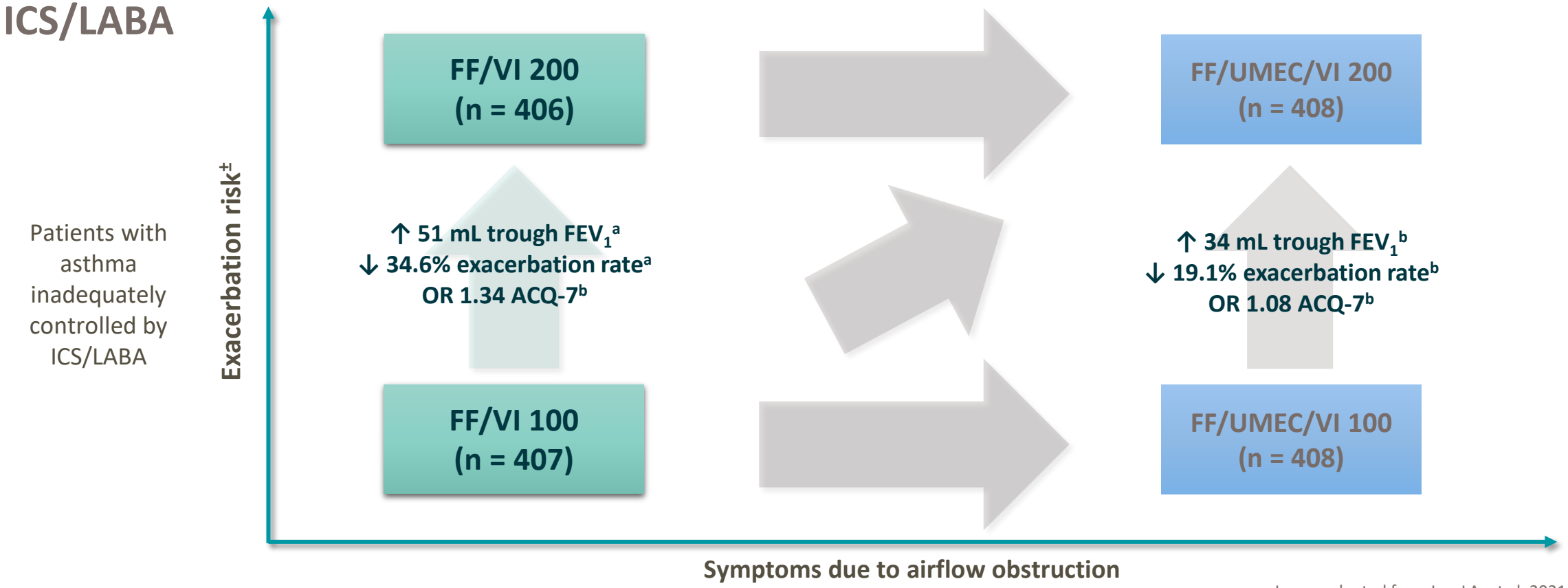


Image adapted from Lee LA, et al. 2021.[1]

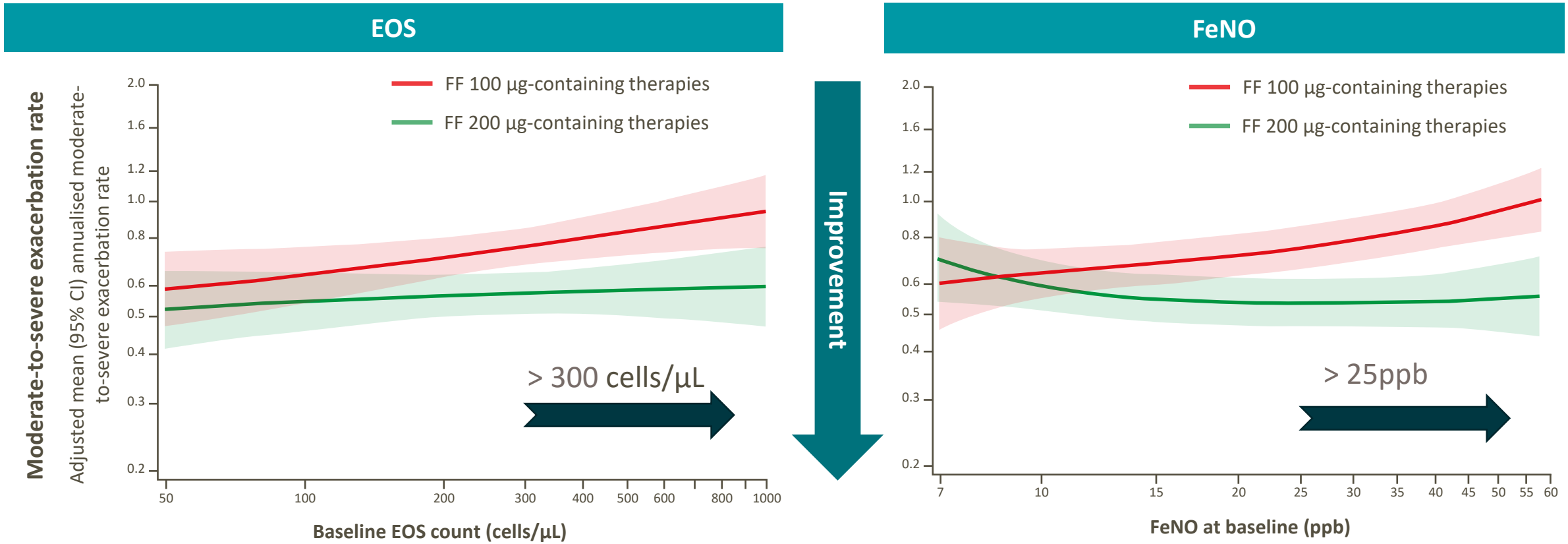
[a]Nominally statistically significant P ≤ 0.021; [b]Not significant.

ACQ, Asthma Control Questionnaire; **FEV_1**, forced expiratory volume in 1 second; **FF**, fluticasone furoate; **FF/VI 100,** FF/VI 100/25 µg; **FF/UMEC/VI 100,** FF/UMEC/VI 100/62.5/25 µg; **FF/VI 200,** FF/VI 200/25 µg; **FF/UMEC/VI 200,** FF/UMEC/VI 200/62.5/25 µg; **ICS**, inhaled corticosteroids; **LABA**, long-acting β_2-agonists; **OR**, odds ratio; **UMEC**, umeclidinium; **VI**, vilanterol

1. Lee LA, et al. Lancet Respir Med. 2021;9:69–84. **2.** Kerstijens, et al. Am J Respir Crit Care Med 2020;201:A4209.

Triple therapy (FF/UMEC/VI) in patients with asthma inadequately controlled by ICS/LABA (CAPTAIN trial)

Effect of increasing ICS on exacerbation rate across the EOS/FeNO range



Adapted from Lee LA, et al. 2021.

Pooled analysis.

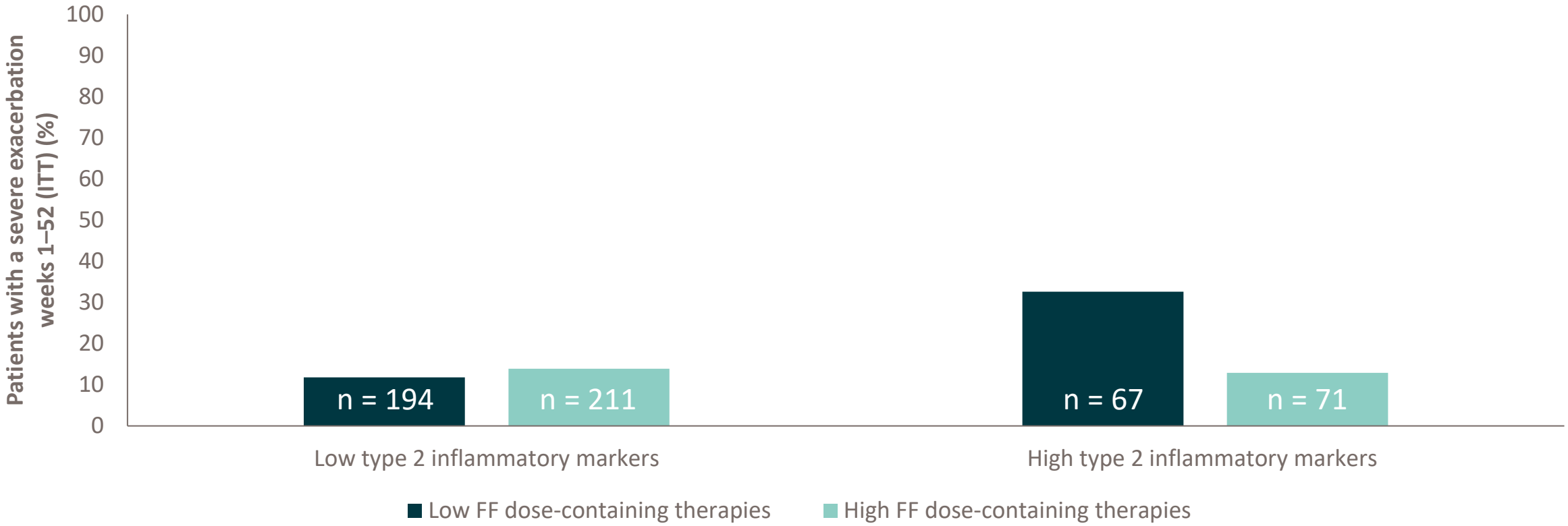
Unpooled analyses show similar trends for clinic trough FEV_1 and moderate-to-severe exacerbation rate. Pooled analyses were performed *post hoc*. Best-fitting fractional polynomial models from 36 pre-defined models are presented.

CI, confidence interval; **EOS**, eosinophils; **FeNO**, fractional exhaled nitric oxide; **FEV_1**, forced expiratory volume in 1 second; **FF**, fluticasone furoate; **ICS**, inhaled corticosteroids; **LABA**, long-acting β-agonists; **ppb**,parts per billion; **UMEC**, umeclidinium; **VI**, vilanterol

Lee LA, et al. Lancet Respir Med. 2021;9:69–84.

Triple therapy (FF/UMEC/VI) in patients with asthma inadequately controlled by ICS/LABA

Type 2 high group had more exacerbations, but also greater impact with increased ICS dose



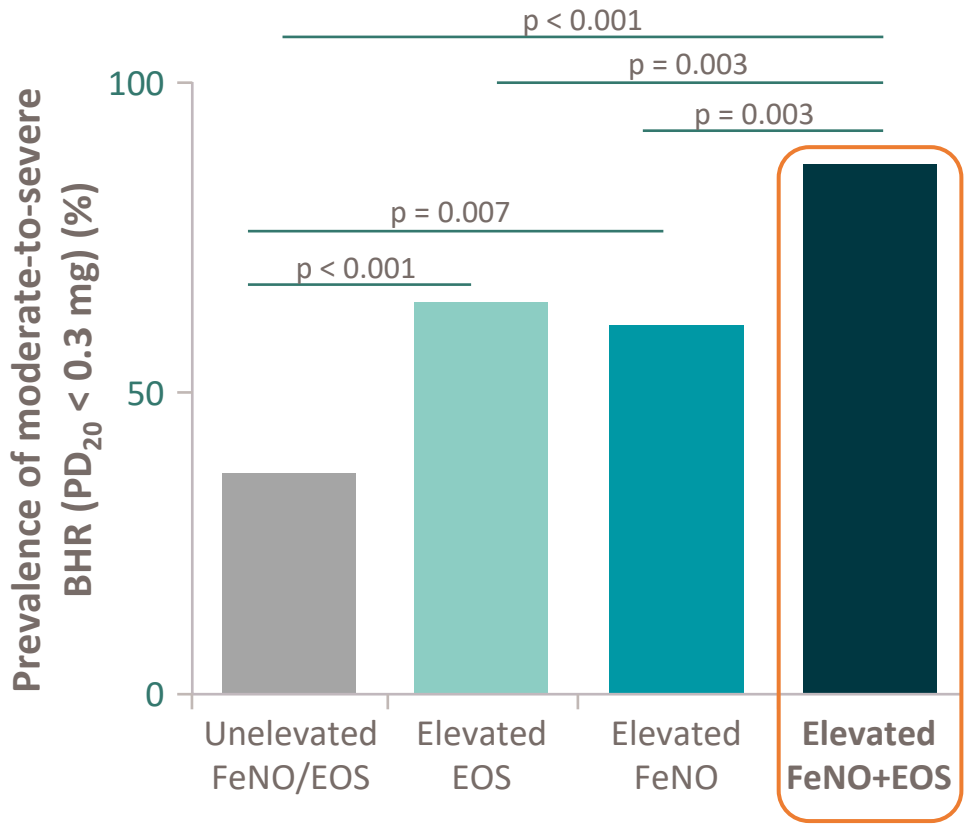
Post-hoc pooled analysis; n = patients with analysable data. Low type 2 inflammatory markers defined as eosinophils $< 0.15 \times 10^9$/L and FeNO < 20 ppb at baseline. High type 2 inflammatory markers defined as eosinophils $\geq 0.3 \times 10^9$/L and FeNO > 50 ppb.

FeNO, fractional exhaled nitric oxide; **FF**, fluticasone furoate; **ICS**, inhaled corticosteroid; **ITT**, intention-to-treat; **LABA**, long-acting β_2-agonists; **ppb**, parts per billion; **UMEC**, umeclidinium; **VI**, vilanterol

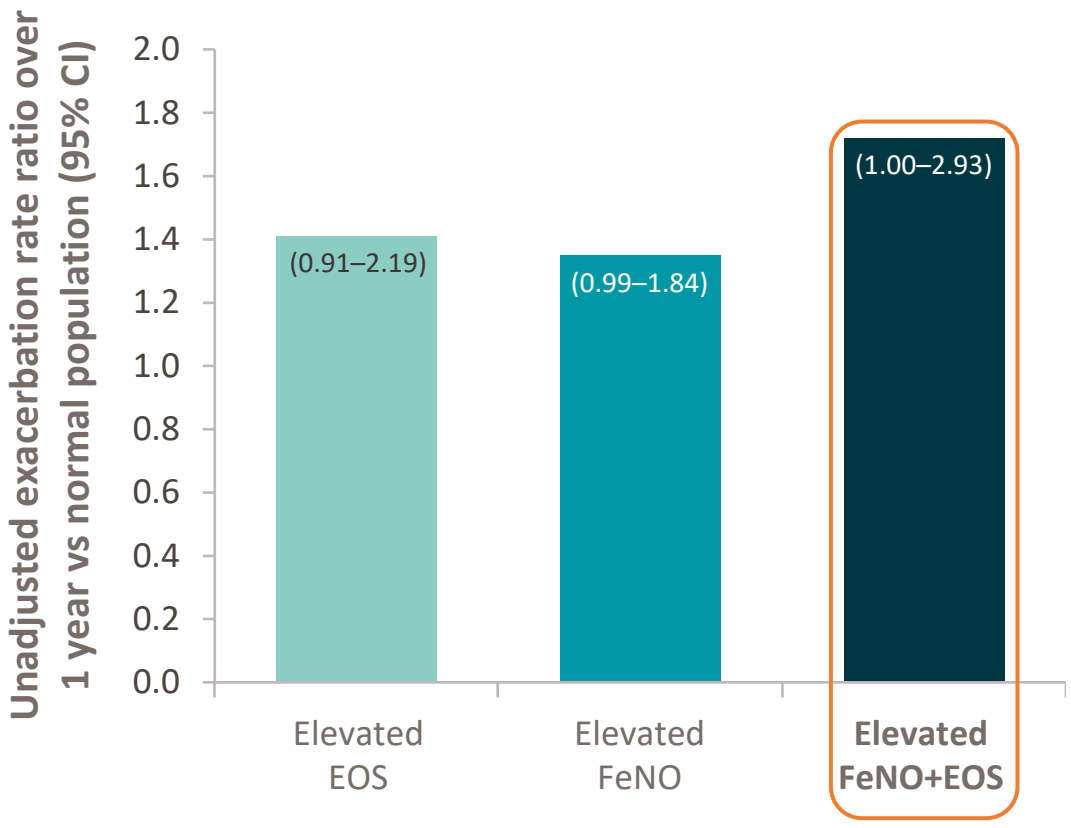
Lee LA, et al. Lancet Respir Med. 2021;9:69–84.

Refractory type 2 high disease (FeNO > 20 ppb and blood EOS ≥ 0.3 × 10^9/L) is associated with greater asthma disease burden

Increased bronchial hyperresponsiveness (n = 406)[1]



Greater severe exacerbation rates[a] vs normal controls (n = 610)[2]



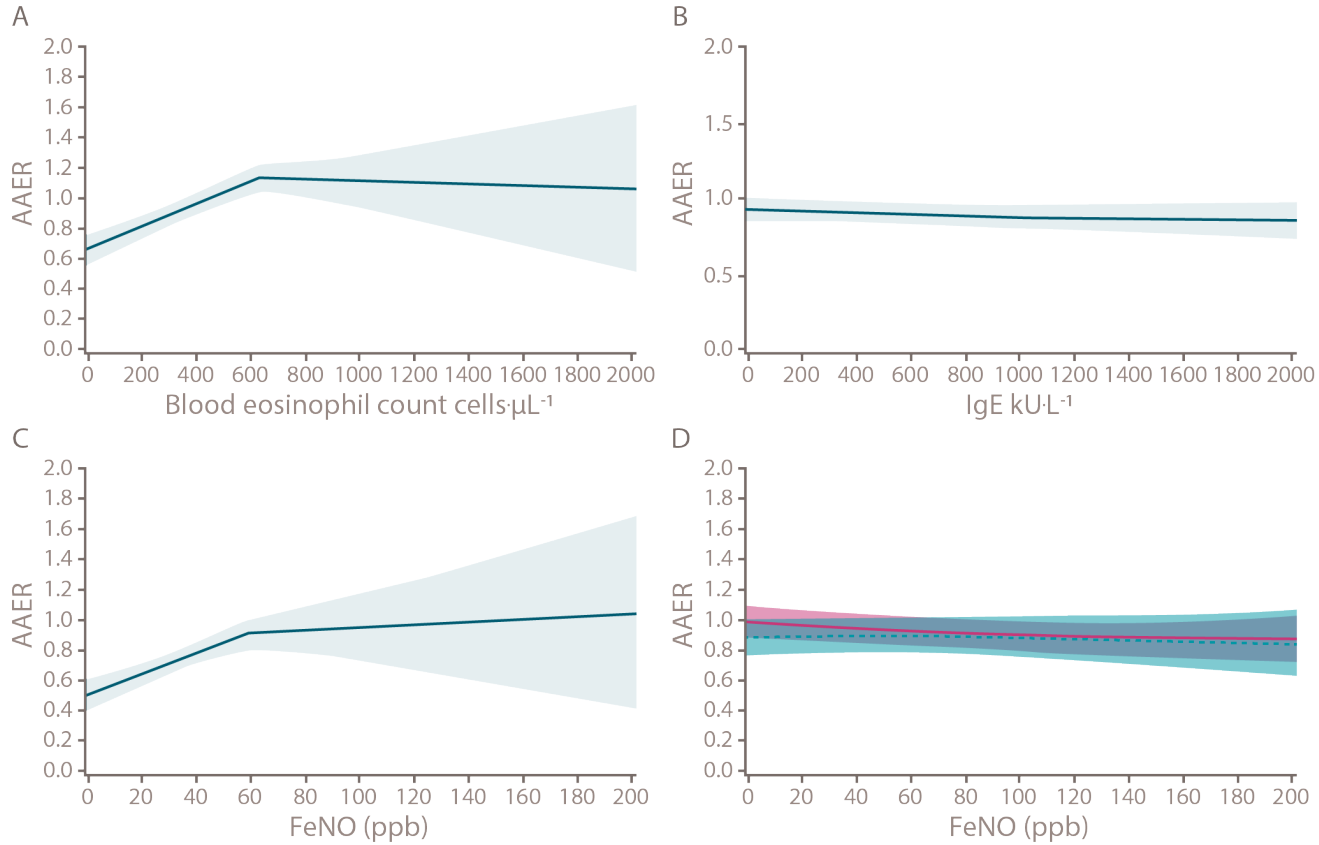
[a]Exacerbation: the occurrence of (1) respiratory-related hospitalisation (inpatient admission) AND/OR (2) emergency department attendance AND/OR (3) an acute course of OCS.

BHR, bronchial hyperresponsiveness; **CI,** confidence interval; **EOS**, eosinophils; **FeNO**, fractional exhaled nitric oxide; **OCS**, oral corticosteroids; **ppb**, parts per billion

1. Malinovschi A, et al. J Allergy Clin Immunol. 2016;138:1301–1308. e2. **2.** Rastogi S, et al. Thorax. 2017;72:A198.

Patient characteristics, biomarkers and exacerbation risk in severe, uncontrolled asthma

Seven Phase 2/3 RCTs of moderate-to-severe asthma, all had medium–high ICS+LABA, assessed annual exacerbations, 48 - 56 weeks



Images adapted from Kraft, *et al.* 2021[1]

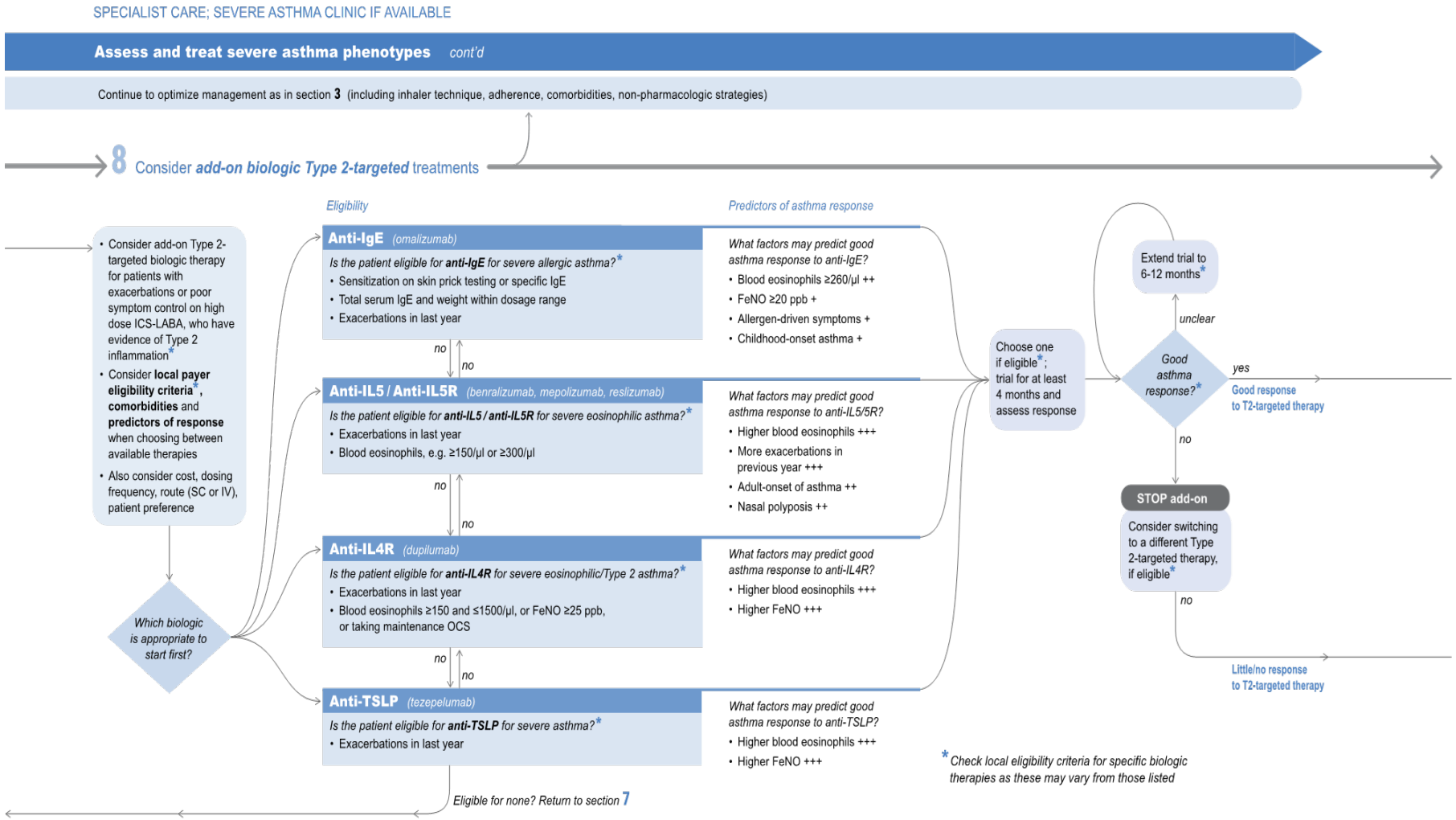
AAERs by eosinophil and FeNO subgroups

FeNO (ppb) \ Eosinophils cells·µL⁻¹	<150	≥150-<300	≥300
<20	0.58 (65/211, 30.8%)		
≥20 - <50	0.58 (157/467, 33.6%)		
≥50	0.83 (125/312, 40.1%)		1.00 (45/108, 41.7%)

ICS, inhaled corticosteroid; **LABA**: long-acting β_2-agonist; **RCT**, randomised controlled trial; **ppb**, parts per billion; **CI**, confidence interval; **IgE**, Immunoglobulin E; **FeNO**, fractional exhaled nitric oxide; **AAER**, annual asthma exacerbation rate.

1. Kraft M, et al. Eur Respir J. 2021;58(6).

Refractory type 2 asthma refractory to ICS, needs biologic therapy



Efficacy

1. Exacerbations reduced 25–50%
2. FEV_1 min change
3. ? Reduced OCS

1. Exacerbations reduced 50%
2. FEV_1 98–160 mL
3. Reduced OCS

1. Exacerbations reduced 70%
2. FEV_1 150–240 mL
3. Reduced OCS

FeNO, fractional exhaled nitric oxide; **FEV_1**, forced expiratory volume in 1 second; **ICS**, inhaled corticosteroid; **IgE**, immunoglobulin E; **IL**, interleukin; **IV,** intravenous; **LABA**, long-acting β_2-agonists; **OCS**, oral corticosteroids; **ppb**, parts per billion; **SC,** subcutaneous; **T2,** type 2; **TSLP,** thymic stromal lymphopoietin

GINA. Global strategy for asthma management and prevention. 2022. Available at https://ginasthma.org/gina-reports/ Accessed March 2023.

Prescribing Information

PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥ 12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Please review full Product Information before prescribing. Full Product Information is available from sanofi-aventis australia pty ltd at http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swpdupix or by contacting 1800 818 806.

Atopic dermatitis*:* **Adults and adolescents:** Treatment of moderate to severe atopic dermatitis in patients aged 12 years and older who are candidates for chronic systemic therapy. Not intended for episodic use. **Children 6 to 11 years of age:** Dupixent is indicated for the treatment of severe atopic dermatitis in patients aged 6 to 11 years old who are candidates for chronic systemic therapy. Dupixent is not intended for episodic use. **Asthma:** Add on maintenance treatment in patients aged 6 years and older with moderate to severe asthma with type 2 inflammation (elevated eosinophils or elevated FeNO) that is inadequately controlled despite therapy with other medicinal products for maintenance treatment. **Chronic rhinosinusitis with nasal polyposis (CRSwNP):** Dupixent is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). **DOSAGE AND ADMINISTRATION: Atopic dermatitis – Adults:** Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites), followed by 300 mg given every other week. Refer to full PI for preparation, handling and administration. Treatment should be initiated and supervised by a dermatologist or immunologist **Atopic Dermatitis – Paediatric and Adolescent patients aged 6-17 years: Patients 15 kg to < 30 kg:** Initial dose of 600 mg (two 300 mg injections consecutively in different injection sites) followed by 300 mg every four weeks. **Patients 30 kg to < 60 kg:** Initial dose of 400 mg (two 200 mg injections consecutively in different injection sites) followed by 200 mg given every other week. **Patients ≥ 60 kg:** Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites) followed by 300 mg given every other week. **Asthma – Adults and adolescents:** Initial dose of 400 mg by subcutaneous injection (two 200 mg injections consecutively in different injection sites) followed by 200 mg given every other week. Refer to full PI for preparation, handling and administration. **Oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis** or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis: Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites) followed by 300 mg given every other week. **Asthma – Paediatric patients aged 6-11: Patients 15 kg to < 30 kg:** Initial dose of 100 mg followed by 100 mg given every other week, or an initial dose of 300 mg followed by 300 mg given every four weeks. **Patients 30 kg to < 60 kg:** Initial dose of 200 mg followed by 200 mg given every other week, or an initial dose of 300 mg followed by 300 mg given every four weeks. **Patients ≥ 60 kg:** Initial dose of 200 mg followed by 200 mg given every other week. **Chronic Rhinosinusitis with Nasal Polyposis:** The recommended dose of Dupixent for adult patients is an initial dose of 300 mg followed by 300 mg given every other week. Dupixent is intended for long-term treatment. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. If after 24 weeks of treatment a patient's disease is stable, Dupixent may be given at a dose of 300 mg every four weeks in patients with CRSwNP who do not have comorbid asthma. **CONTRAINDICATIONS** Hypersensitivity to dupilumab or any of its excipients **PRECAUTIONS** Record the tradename and the batch number to improve traceability. Hypersensitivity, angioedema, helminth infections, conjunctivitis and keratitis, comorbid asthma, concomitant atopic conditions, eosinophilic conditions, acute asthma or deteriorating disease, gradual corticosteroid dose reduction. Refer to full PI. **INTERACTIONS** Live vaccines, No safety data on co-administration with other immunomodulators. Refer to full PI. **ADVERSE EFFECTS Atopic dermatitis:** Injection site reactions, conjunctivitis, conjunctivitis allergic, oral herpes, conjunctivitis bacterial, herpes simplex, eosinophilia, eye pruritus, blepharitis, dry eye, hypersensitivity – refer to full PI. **Asthma:** Injection site reactions, oropharyngeal pain, eosinophilia – refer to full PI. **Chronic Rhinosinusitis with Nasal Polyposis:** Injection site reactions, injection site swelling, conjunctivitis – refer to full PI. **Post marketing experience:** Angioedema, arthralgia, keratitis, ulcerative keratitis, facial rash. **NAME OF SPONSOR** sanofi-aventis australia pty ltd, 12-24 Talavera Road, Macquarie Park, NSW 2113. Based on Full Product Information with TGA date of approval of 29 June 2022 Date of Preparation: 30 June 2022

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

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