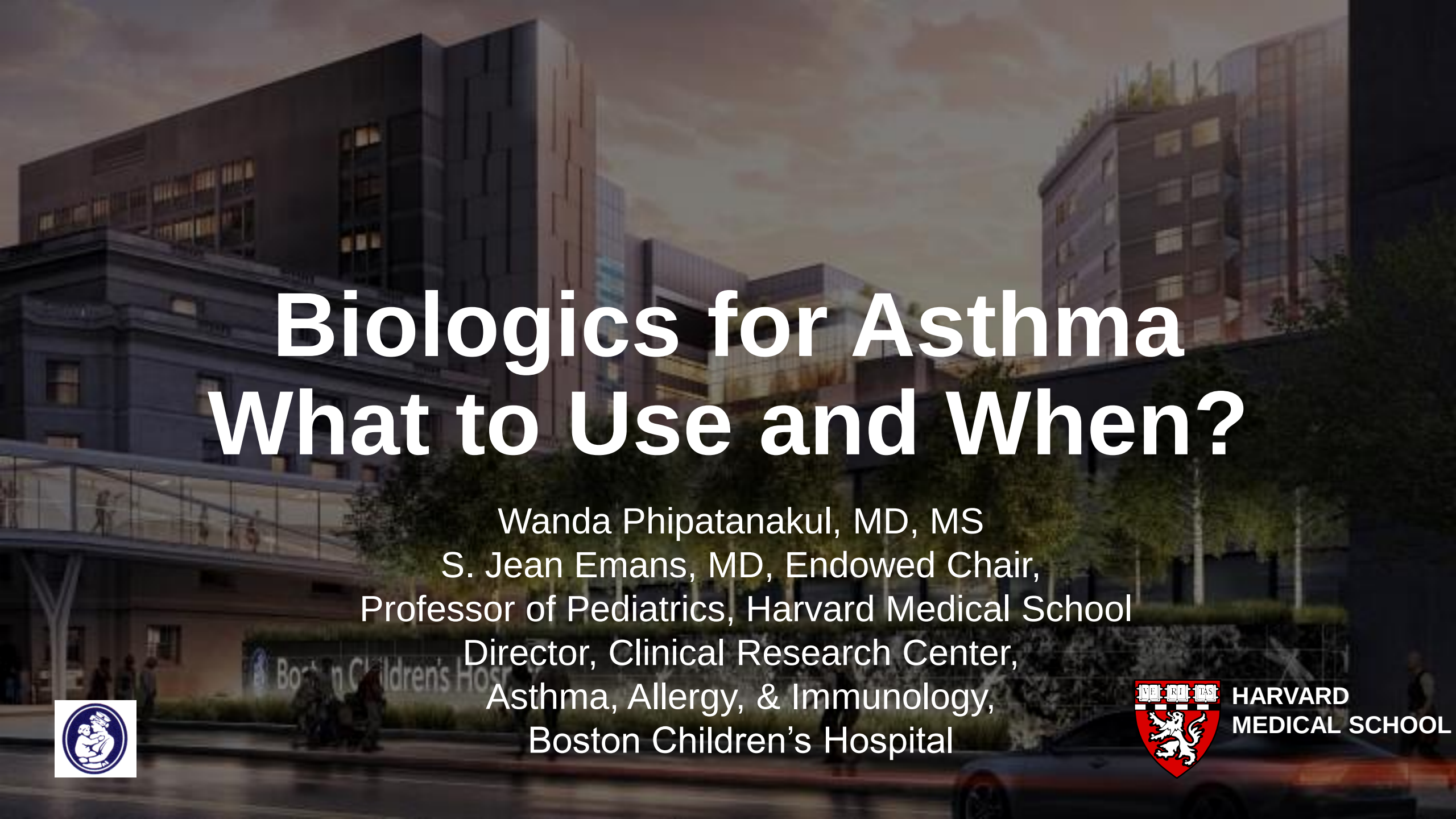


Biologics for Asthma What to Use and When?

Wanda Phipatanakul, MD, MS
S. Jean Emans, MD, Endowed Chair,
Professor of Pediatrics, Harvard Medical School
Director, Clinical Research Center,
Asthma, Allergy, & Immunology,
Boston Children's Hospital

HARVARD
MEDICAL SCHOOL

Learning Objectives

- Review the Landscape of Biologics in Asthma
- Discuss Strategies on Choice
- Discuss immune based personalized approaches and consideration of prevention/disease modification as future approaches

PATIENT ASSESSMENT

Age at asthma diagnosis (years)	3
Exacerbations in past year requiring OCS burst	5
Serious exacerbations in past year requiring hospitalization	3
FEV_1 (% predicted)	70%
Body mass index	22 kg/m^2
ACT score	12
ACQ score	2.8
Symptoms	>3 days/week

Sophie
6 y/o female

LAB RESULTS

Blood eosinophils (cells/µL)	500
Sputum eosinophils (%)	Not evaluated
FeNO (ppb)	31
IgE (IU/mL)	**400**
Allergen-specific IgE†	**House dust mites**

MEDICATION HISTORY

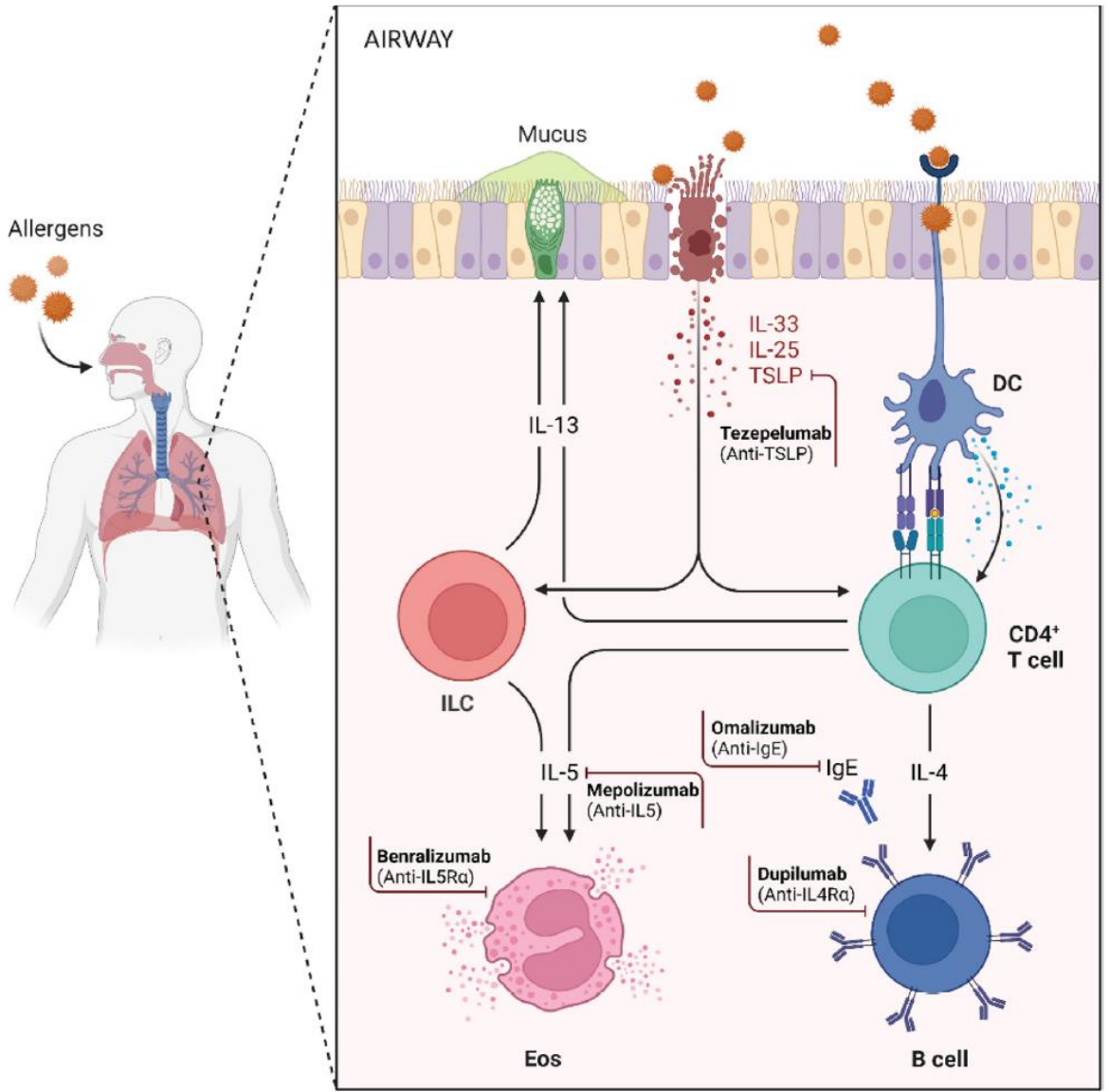
- High-dose ICS + LABA
- OCS – 5 bursts/y
- Intranasal corticosteroids

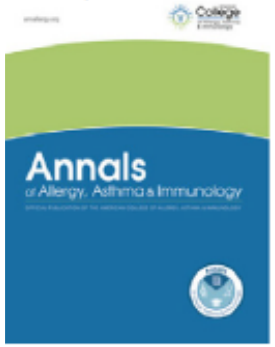
What can we do for this patient?

Future of biologics in pediatric asthma

Optimizing response, early introduction, and equitable access to treatment

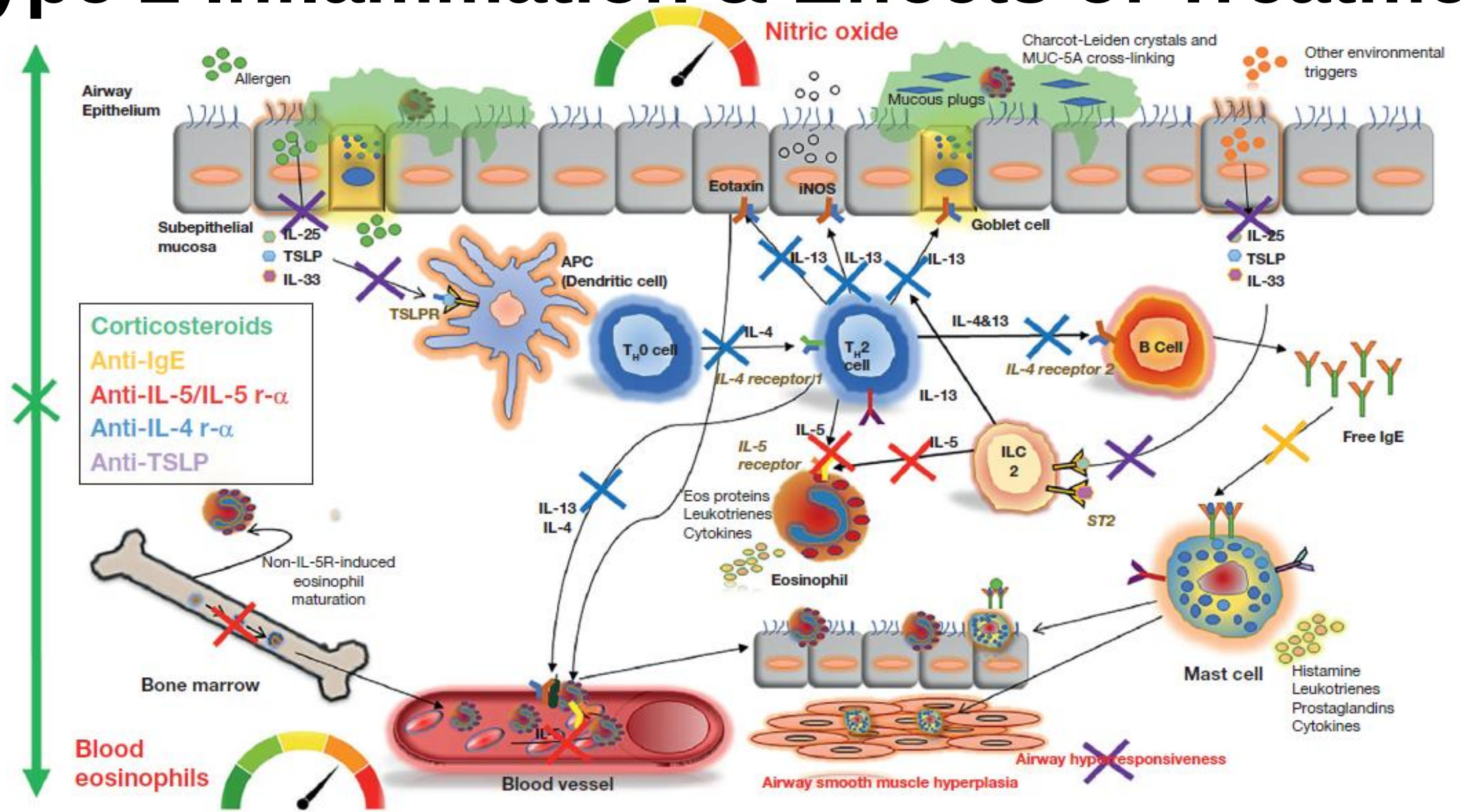
Ianthe R.M. Schepel, BMBCh, MPhil, MS*; Tina M. Banzon, MD†; Wanda Phipatanakul, MD, MS†





2023

Type 2 Inflammation & Effects of Treatment



Coullard S, et al CHEST 2025

And a number of questions arise:

- What are the opportunities that these new agents offer?
- In which patients should we really use these expensive agents?
- What do we need to do before starting a biological?

- …and also, which one to choose…

	Omalizumab(Xolair)	Mepolizumab (Nucala)	Dupilumab(Dupixent)	Benralizumab(Fasenra)	Tezepelumab(Tezspire)	Depemokimab (Exdensur)
Age	≥6 years old	≥6 years old	≥6 years old	≥6 years old	≥12 years old	≥12 years old
Asthma Indication	moderate-to-severe asthma with perennial aeroallergen sensitization	severe asthma with an eosinophilic phenotype	moderate-to-severe asthma with an eosinophilic phenotype or OCS-dependent asthma	severe asthma with an eosinophilic phenotype	severe asthma with no specific phenotype	severe asthma with an eosinophilic phenotype
Mechanism	binds free IgE	binds IL-5	binds IL-4 receptor (IL-4Rα)	binds IL-5 receptor (IL-5Rα)	binds TSLP	binds IL-5
Biomarkers	IgE = 30-700 IU/mL (or 30-1300 IU/mL) aeroallergen sensitization	No strict eosinophil cutoff; generally ≥150-300 cells/µL used	No strict eosinophil cutoff; generally ≥150-300 cells/µL used	No strict eosinophil cutoff; generally ≥300 cells/µL used	No biomarker cutoff	No strict eosinophil cutoff; generally ≥150-300 cells/µL used
Dosing	Every 2 weeks or every 4 weeks	Every 4 weeks	Every 2 weeks	Every 4 weeks (x 3), then every 8 weeks	Every 4 weeks	Every 6 months
Location	office or home	office or home	office or home	office or home	office or home	office
Other FDA Indications and Dosing	CIU (≥12 years old); Nasal Polyps (≥18 years old) Food allergy ≥ 1 y/o	HES (≥12 years old) w/o CA; CRSwNP (≥18 years old); EGPA (≥18 years old), COPD adults	AD (≥6 months); CRSwNP (≥12 years old); EoE (≥1 years old) CSU, prurigo nodularis & COPD &bullousP ≥18	EGPA adults	CRS w/ NP (≥12 years old)	NA
Common side effects	Headache, upper abdominal pain, pyrexia, injection site reaction (pain, swelling, erythema, pruritus)	Headache, injection-site reaction; back pain; fatigue	Conjunctivitis, oral herpes, eosinophilia, arthralgia, injection-site reactions	Headache, pharyngitis, injection-site reactions.	Pharyngitis, arthralgia, back pain	injection-site reaction; upper respiratory infections; pharyngitis

How do we choose a biologic?

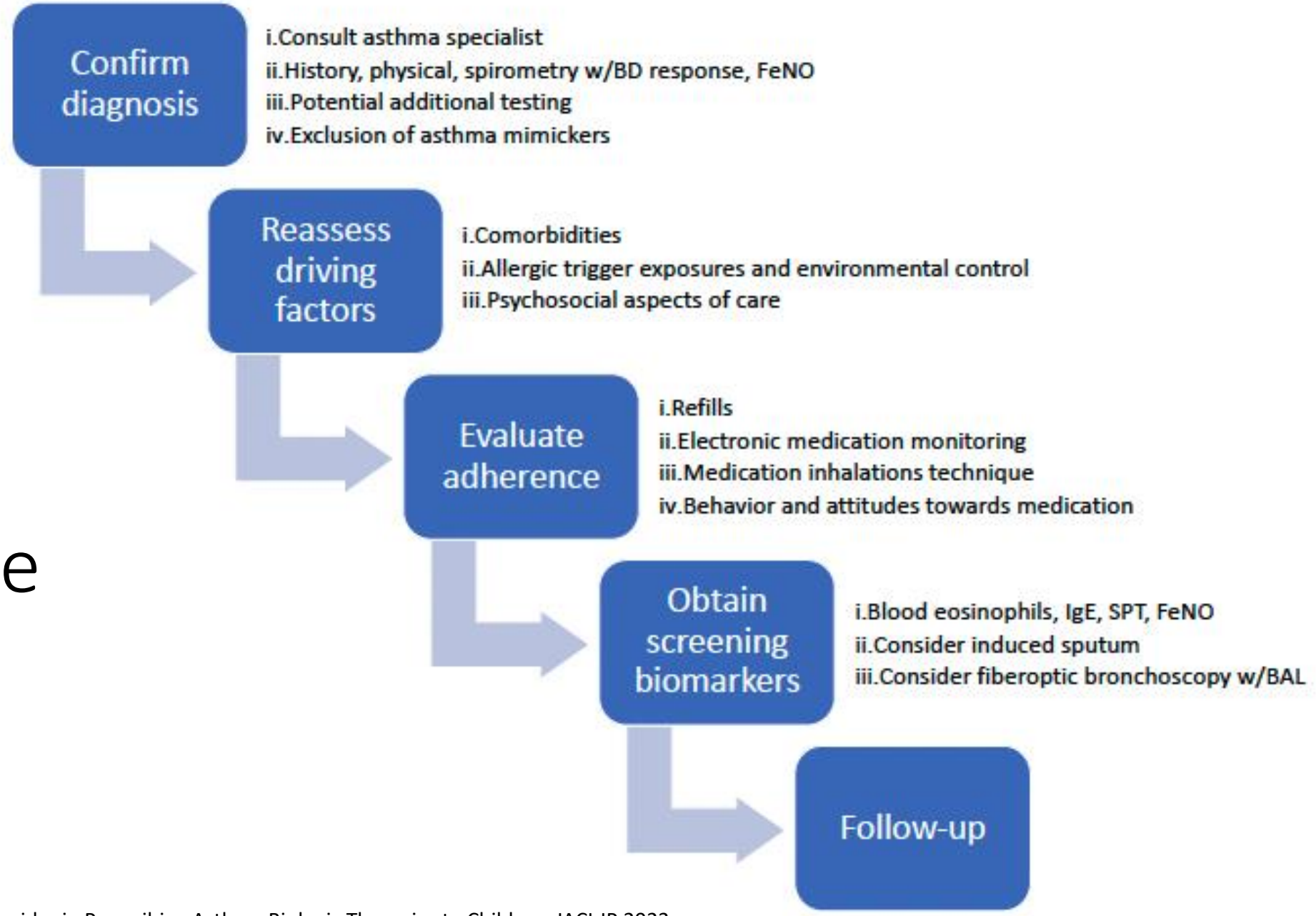
Factors to Consider in Prescribing Asthma Biologic Therapies to Children

William C. Anderson III, MD[a], Tina M. Banzon, MD[b], Bo Chawes, MD, PhD, DMSc[c], Nikolaos G. Papadopoulos, MD, PhD[d], Wanda Phipatanakul, MD, MS[e], and Stanley J. Szefler, MD[f] *Aurora, Colo; Boston, Mass; Copenhagen, Denmark; and Athens, Greece* JACI Practice 2023

- Clinical history: control (impairment & risk), current therapy step
- Basic labs CBC w/ Diff (eos count), total IgE
- Aeroallergen sensitization, skin prick testing and/or specific Ige
- Spirometry, FENO
- Family consideration (adherence, schedule) office vs. home, dosing frequency
- # of injections, fear of needles
- Comorbid conditions/competing diagnosis

- Atopic dermatitis, chronic idiopathic urticarial, chronic rhinosinusitis with nasal polyps, other skin conditions (prurigo nodularis, bullous pemphigoid)

A stepwise approach



Anderson WC et al. Factors to Consider in Prescribing Asthma Biologic Therapies to Children. JACI-IP 2023

Safety Considerations for Biologic Therapies

Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
• Anaphylaxis	• Hypersensitivity (rare) • Herpes zoster infection	• Anaphylaxis	• Hypersensitivity (rare)	• Hypersensitivity (rare) • Injection site reactions • Hypereosinophilia

Consider giving all age appropriate vaccines prior to starting biologics

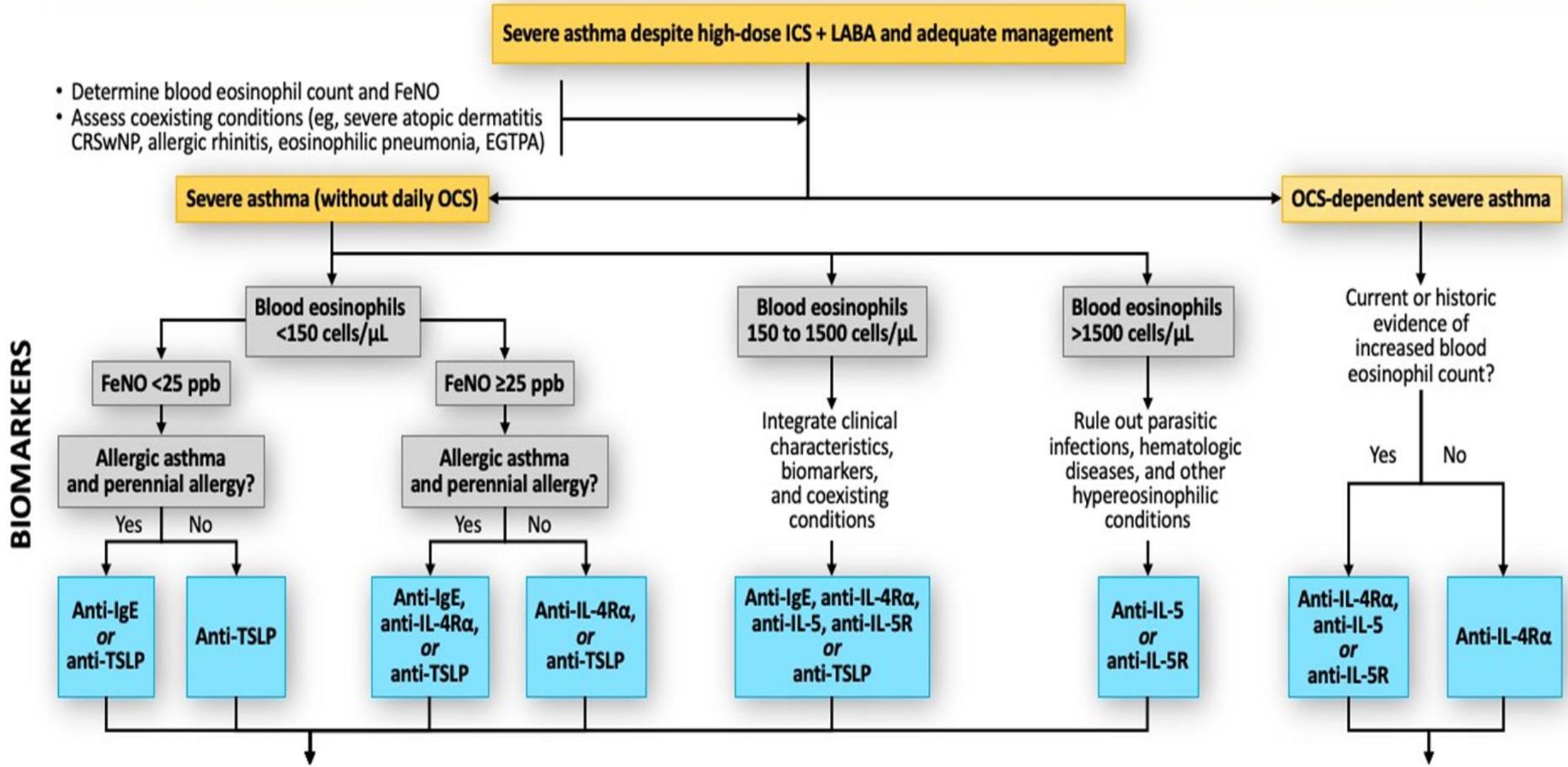
The package insert suggests avoid live vaccines during treatment with biologics but there is no data

One suggestion - hold biologic for 12 weeks & wait to restart for 4 weeks after vaccination.

Limited available evidence suggests that holding biologic for 4 weeks or more before immunization may also lead to safe and effective vaccination.

Safety overall well tolerated- Give time for a few months to determine efficacy

McGregor MC et al. *Am J Respir Crit Care Med*. 2019;199:433-445
Pelaia C et al. *Ther Adv Resp Dis*. 2018;12:1-6.
Holguin F et al. *Eur Resp J.* 2019; in press (https://doi.org/10.1183/13993003.00588-2019)..



Brusselle G et al. *N Engl J Med* 2022; 386:157-71.

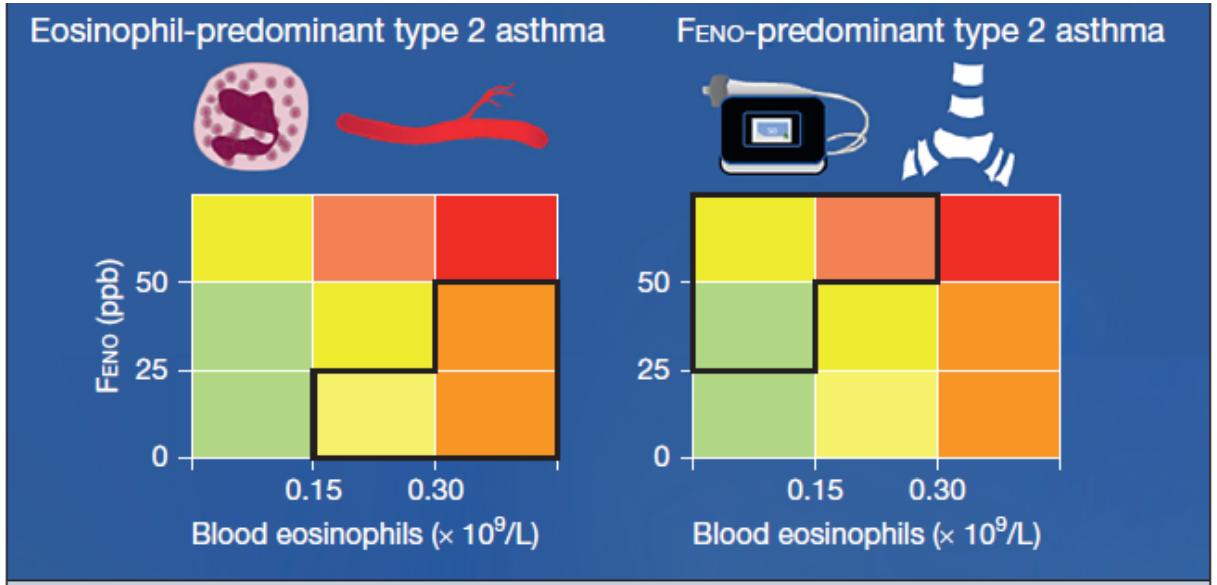
How can we predict response??

FeNO and Eosinophils and Increased Airway Bronchial Hyperresponsiveness- HOT/HOT

Ian Pavord

"Measure eos and FeNO in all patients with severe asthma"

- Type II biomarkers are additive with patients that have more than one biomarkers have high T2 inflammation and more BHR/exacerbations
- Isolated elevations in FeNO can indicate ongoing type II inflammation



Greater % of late-onset asthma	Greater % of early onset
Less allergy	Allergy
Less AHR	AHR ++
Less atopic. More CRSwNP, EGPA	Eczema, atopic rhinitis > CRSwNP
Blood eos signal > FENO signal	FENO signal > blood eos signal
OCS > ICS sensitivity	ICS > OCS sensitivity
Anti-IL-5/-5R ~ Anti-IL-4R ~ Anti-TSLP response	Anti-IL-4R/Anti-TSLP > Anti-IL-5/-5R response
← Many patients have features of both →	
↑Eosinophils and/or ↑FENO = ↑risk of attacks, ↑response to biologics	

Coullard S, et al CHEST 2025

1. Workup

Woman, 35 y of age

Asthma diagnosis confirmed ✓

Asthma is uncontrolled ✓

Environmental triggers optimized ✓

Adherence and inhaler technique ?

Comorbidities reviewed ✓

Phenotyped ✓
- Allergic/childhood onset
- Corticosteroid dependence: 0

Biomarkers measured ✓
- IgE 350 kU/L (↑)
- F_{ENO} 45 ppb (↑)
- Blood Eos 0.35×10^9/L (↑)

Physiologic features/Imaging reviewed ✓
- FEV_1 65%, FEV_1 to FVC ratio 0.57
- Normal findings on chest radiograph

2. Considering which biologic

- All options below are reasonable choices - status quo is not.
- The following features should be discussed and weighed with the patient
- Payer reimbursement criteria may need to be considered

Options	Features	Comments
Omalizumab	• Young woman of child-bearing age • Fits prescription criteria • Allergic / childhood onset	• Most data in pregnancy • IgE↑, sensitised • Modest effect on attacks
Dupilumab or tezepelumab	• Eos and F_{ENO} raised • Spirometry results obstuctive • History of severe asthma attacks • Childhood onset	• Only mAbs to ↓↓ F_{ENO} and ↑↑ FEV_1 • Large effect on attacks • First choice here if no plans for children
Mepolizumab or benralizumab	• Eos raised • History of severe asthma attacks	• Large effect on attacks
Reslizumab	• Eos raised	• Intravenous therapy, no • subcutaneous option

3. Making a choice

- Shared decision-making is essential.
- If no short-term plans for pregnancy, dupilumab or tezepelumab are preferred for their broad clinical impacts (Attacks, FEV_1)
- Failure to achieve optimal response within 6 mo should prompt reevaluation

Coullard S, et al CHEST 2025

PEDIATRIC ASTHMA MONITORING PLAN

PeARL
PEDIATRIC ASTHMA IN REAL LIFE

1 IN EVERY VISIT, EVALUATE AS PRIORITY:

- Symptoms
- Control
- Comorbidities
- Adherence
- Growth

2 EVERY VISIT OR TWO, PERFORM:

- Lung function
- QoL
- FeNO (if feasible)

3 ONCE OR TWICE A YEAR:

- Do reversibility
- Review biomarkers

4 IF INDICATED, CONSIDER:

- Irritant exposures
- Allergen exposures
- Psychological evaluation
- Nutritional evaluation
- Tests for steroid adverse events
- Smoking cessation advice to parents

5 PLAN NEXT VISIT

2-6 months ahead
(sooner in severe/uncontrolled disease)

6 BETWEEN VISITS CONSIDER:

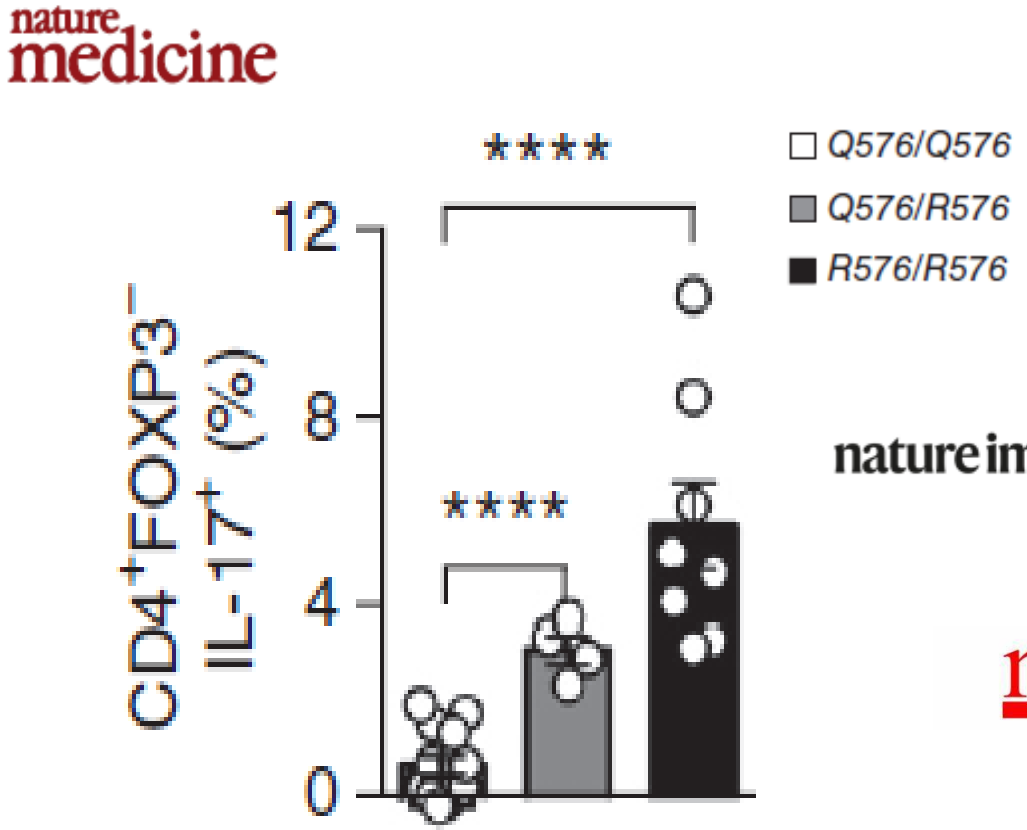
- eHealth apps
- Smart inhalers

Papadopolous N, et al Ped Allergy Immunol 2024

Future-Precision Biomarker Driven Therapy

An asthma associated IL4R polymorphism Increases Airway Inflammation by Conversion of regulatory T cells to Th_{17}-like Cells

- IL-4Rα-Q576R polymorphism- (glutamine (Q) to arginine R substitution at position 576 of the IL-4Rα)
  - R allele frequency 68% (blacks/hispanics); 20% (whites)
  - R allele associated with severe asthma
  - Unique among *IL4R* polymorphisms, directly drives T_H2 to T_H17 inflammatory response in the airways
  - Dose response relation with severity
  - Augmented by obesity



nature immunology

nature
International weekly journal of science

Massoud et al, Nat Med 2016; 22(9):1013-22

Hani H, et al Nature Immunol November, 2020

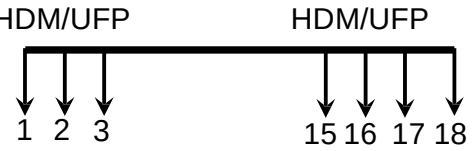
Babat, S, et al Nature March 2021

Cohort

IL4R$^{Q576/Q576}$
IL4R$^{Q576/R576}$
IL4R$^{R576/R576}$

Study design

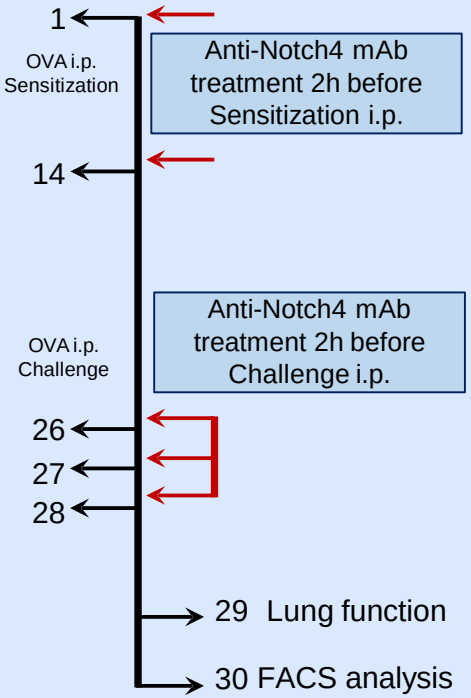
Il4ra^{R576} *Foxp3*^{YFPCre}
Il4ra^{R576} *Foxp3*^{YFPCre} *Notch4* $^{\Delta/\Delta}$
Il4ra^{R576} *Foxp3*^{YFPCre} *Grb2* $^{\Delta/\Delta}$
Il4ra^{R576} *Foxp3*^{YFPCre} *Il6ra* $^{\Delta/\Delta}$



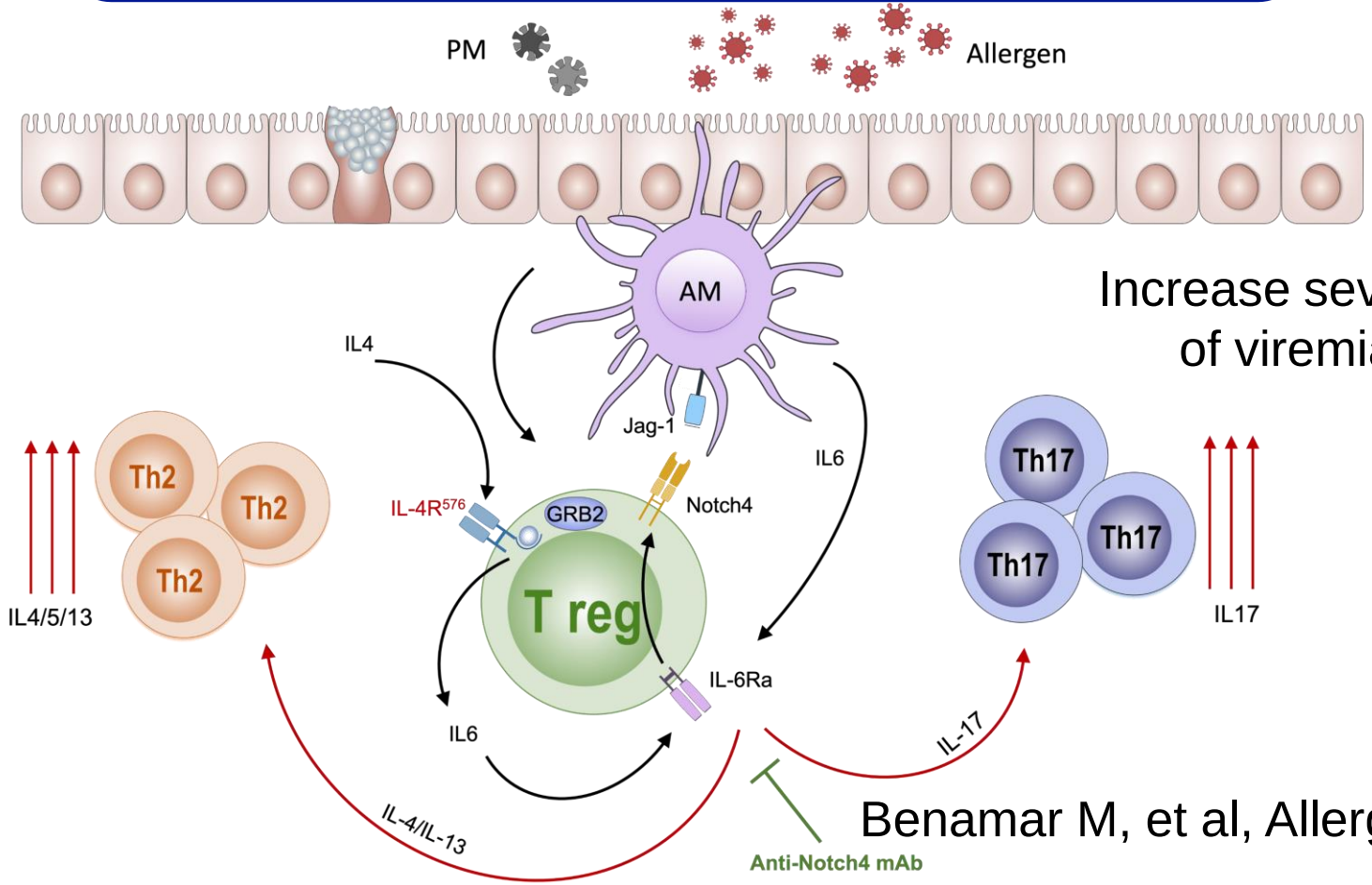
Lung function analysis

FACS analysis

Therapy



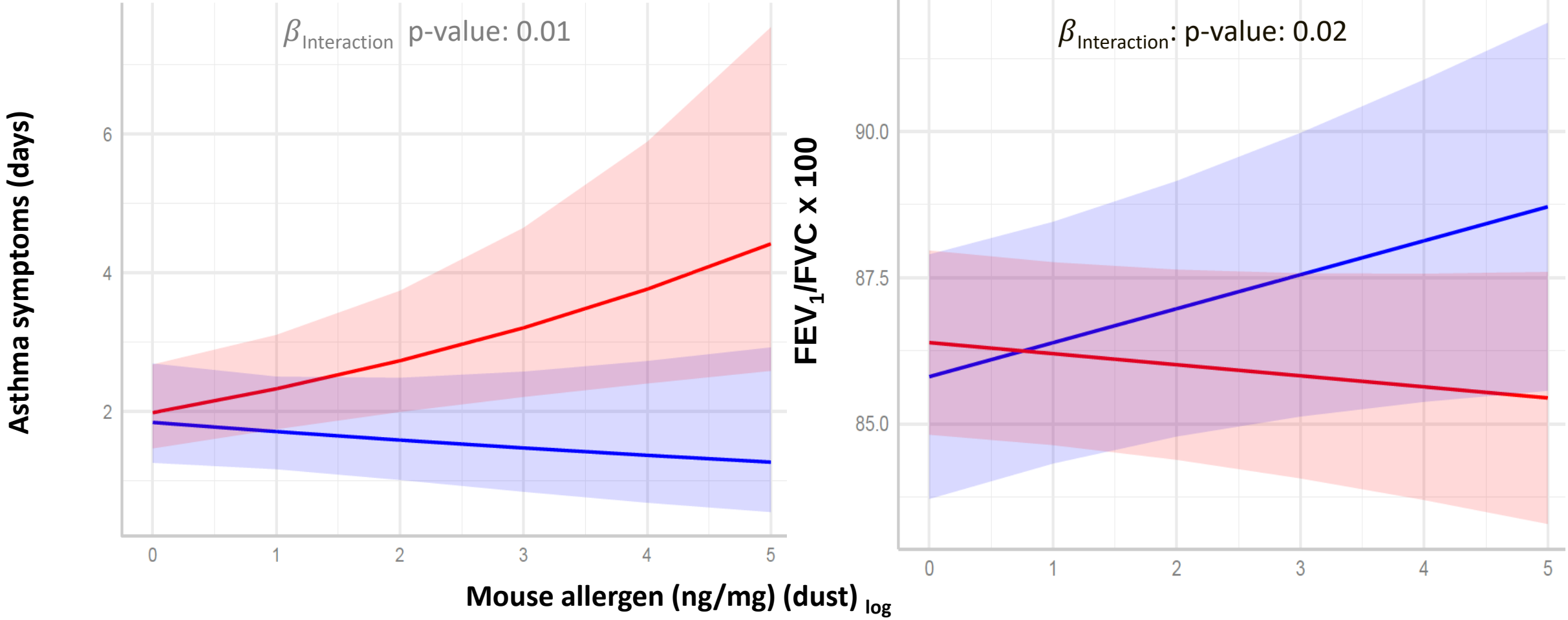
The IL4-Ra-R576 variant exacerbates asthmatic inflammation via a T_{reg} Cell GRB2-IL-6-Notch4 Circuit



Increase severity of viremia

Benamar M, et al, Allergy, 2022

Gene by Environment Interactions with School Mouse Exposure and Asthma Symptoms & Lung Function

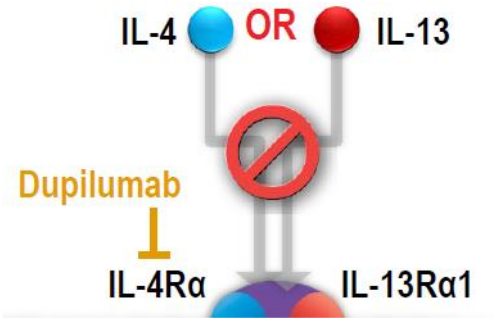


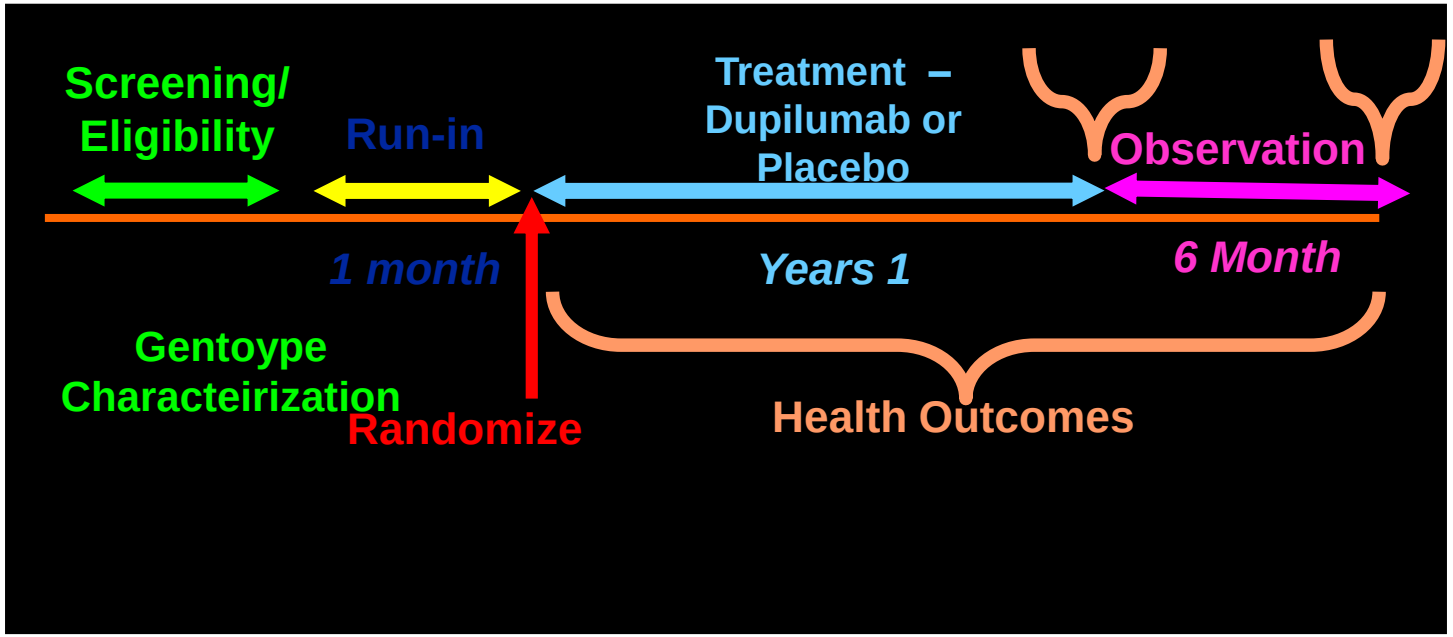
Ruran HB, et al JACI 2025

Investigating Dupilumab's Effect in Asthma by Genotype
IDEA Trial
https://ideaasthma.org

Boston- Phipatanakul/Israel
New Jersey- Oppenheimer
Michigan- Kim/Zoratti
Cleveland-Kaelber
NY-Montefiore- Jarwali
U Penn- Banerjee

U01 AI143514 – Phipatanakul/Chatila
3 Groups by Genotype 1: 1 Dupilumab vs. Placebo





Will investigate genotype driven (personalized) response to therapy and study preliminary mechanisms in disease modification

Trial for severe asthma targets a mutation common in children of color

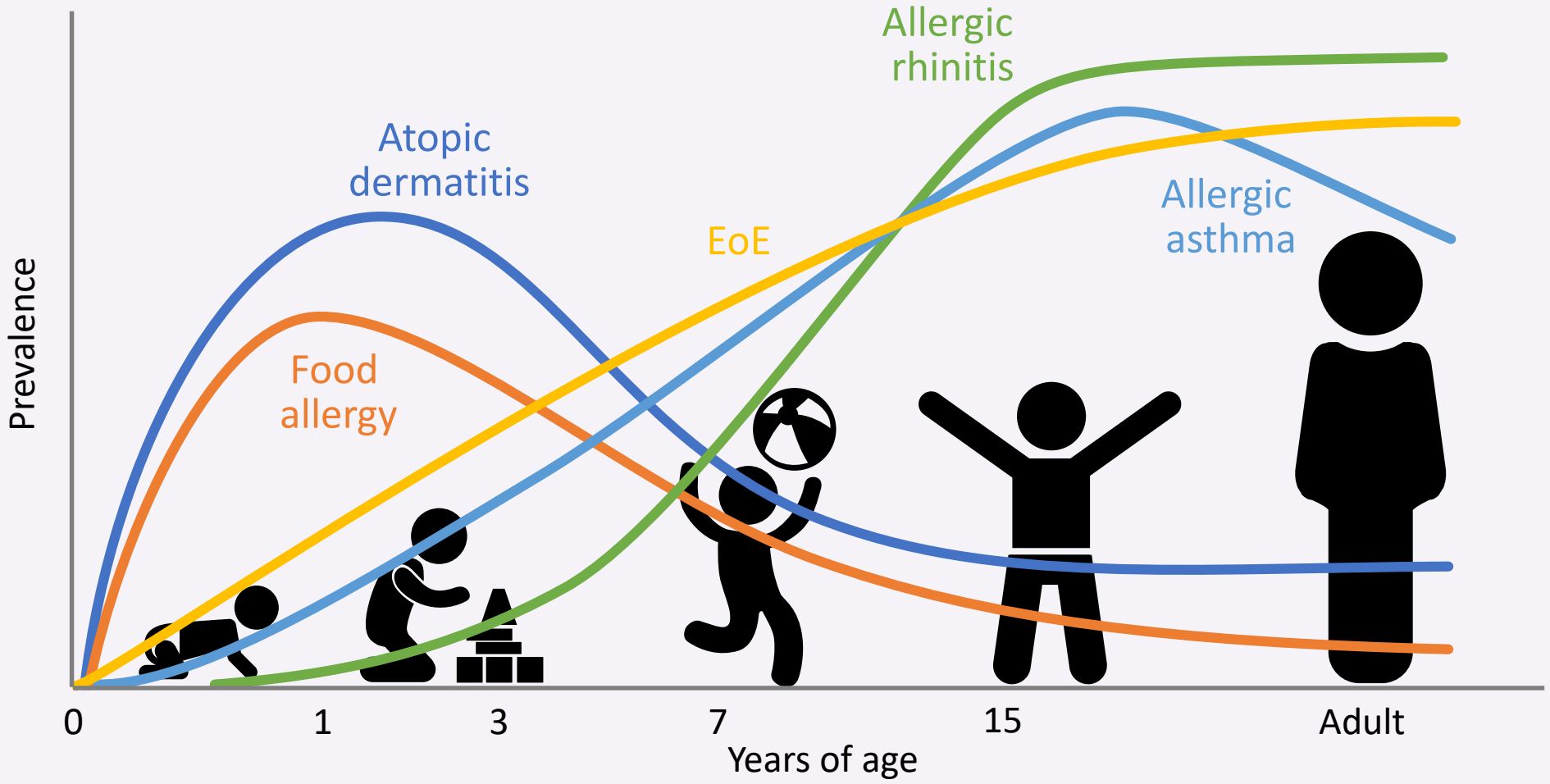
https://answers.childrenshospital.org/duplimab-asthma/

Posted on ospital.org/duplimab-asthma/

https://ideaasthma.org

Biologics in Disease Modification and Prevention

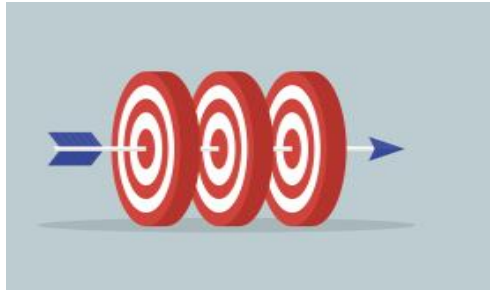
IgE Mediated “Allergic/Atopic March”[1,2]



1. Tsuge M, et al. *Children (Basel).* 2021;8(11):1067. 2. Meyer R, et al. *Pediatr Allergy Immunol*. 2019;30(2):149-158.

Triple Threat: Important in the Development of Asthma

Can we hypothesize immune based treatment in young children that acts on the “triple threat” will prevent the atopic allergic asthma march

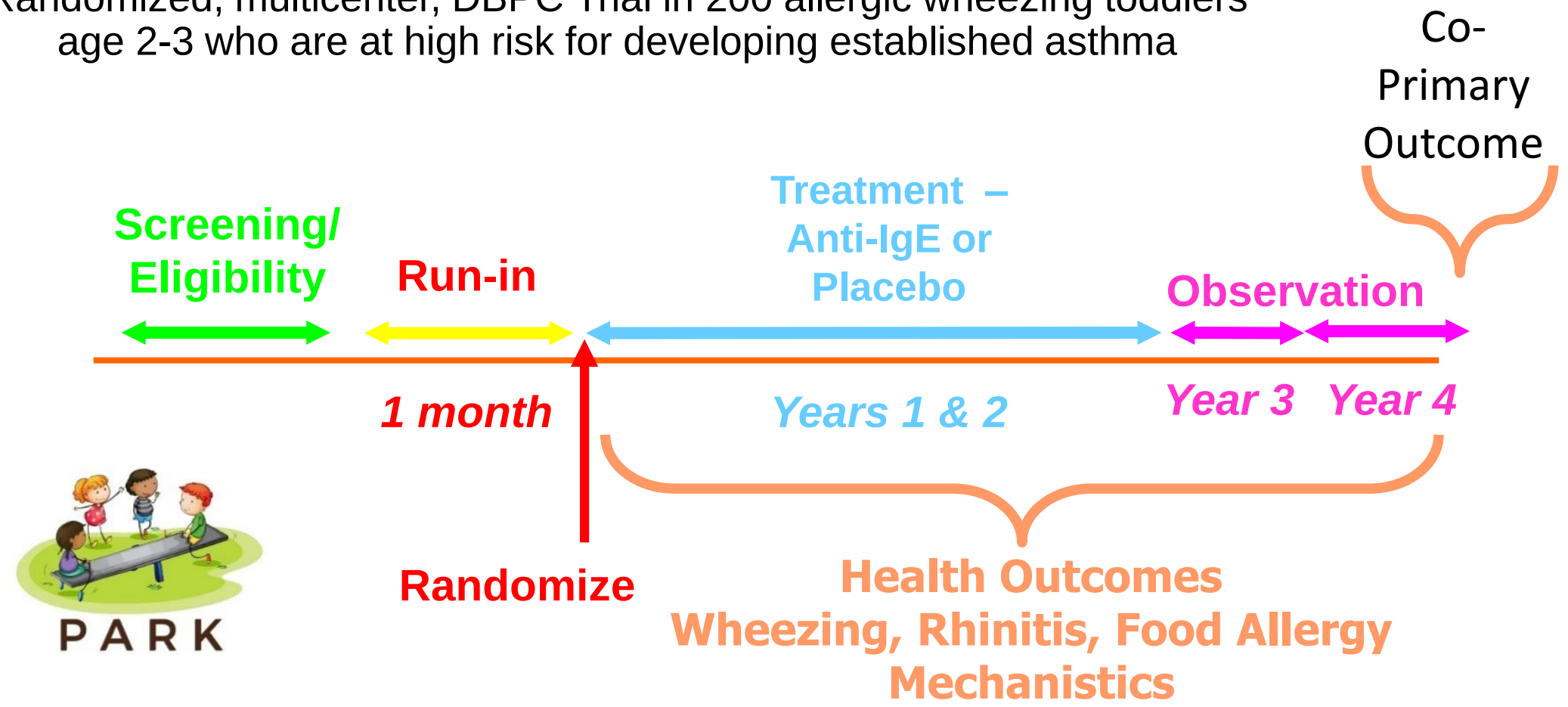


Preventing Asthma in High Risk Kids- PARK

https://answers.childrenshospital.org/asthma-prevention-xolair/

U01AI126614/ U01 AI179563- Principal Investigator Phipatanakul- NCT02570984

Randomized, multicenter, DBPC Trial in 200 allergic wheezing toddlers age 2-3 who are at high risk for developing established asthma



Can asthma be nipped in the bud?

Posted on August 2, 2016 by Nancy Fliesler Posted in Pediatrics, Therapeutics

More On: asthma, clinical trials, Division of Allergy and Immunology, Wanda Phipatanakul

A multicenter randomized trial is testing omalizumab (Xolair) in wheezy toddlers. (FDA/Wikimedia Commons)

Will early intervention prevent asthma in school-age children?

Posted on September 30, 2024 by Nancy Fliesler | Clinical, Research

Tags: allergy, asthma, clinical trials, research

The randomized, double-blind **Preventing Asthma in High Risk Kids (PARK)** trial is supported by a seven-year, $20 million Asthma Prevention Grant from the NIH's National Institute of Allergy and Infectious Diseases (NIAID). By its end, it will enroll 250 wheezy 2- and 3-year-olds with a positive allergy test. The children will receive either Xolair or placebo and will be followed for four years — two years on the treatment, then two years off — to see what proportion of each group develops active asthma as defined by NIAID.

https://answers.childrenshospital.org/preventing-asthma/

https://www.youtube.com/watch?v=PQrdNB7lM5U

Conclusions

- We now have an increasing list of biologics, targeting the key pathways in asthma, necessitating Precision-Biomarker Driven Approaches
- Critical steps, such as diagnosis confirmation, adherence, phenotyping and evaluation of alternative treatments are steps that need to be taken before biological initiation
- Choice of agent should be guided by indication, phenotype, outcome expectations and shared decision making,
  - Logistical considerations (availability, cost, center experience) should also be taken into account

Future Directions

- Approved therapies for non type 2 asthma lacking- many in pipeline
- Better predictive biomarkers are needed
- Head to head studies would be useful (but limited)
- NIH has several ongoing major efforts in Precision Medicine 1)genotype stratified precision therapy (IDEA), 2) novel therapies in an adaptive trial design (PreCISE)
- Understanding the role of IgE targeted biologics in allergic and rhinovirus induced disease have paved the way to consider immune based strategies to prevention (PARK)
- SOON, we will have major advancements in understanding what may work in prevention and modifying disease progression
- Stay tuned!

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R01HL137192 (Phipatanakul) EASY-SLEEP
U01AI126614/U01AI179563(Phipatanakul) PARK
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https://bchasthmaresearch.com

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