PUTTING TOGETHER THE PIECES:

THE IMPACT OF THE LATEST INSIGHTS INTO THE PATHOPHYSIOLOGY OF THERAPEUTIC STRATEGIES TO ADDRESS THE UNMET NEEDS IN EOSINOPHILIC ESOPHAGITIS

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DISCLOSURES

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Consulting Fees – Adare/Ellodi, Allakos, Amgen, Arena, AstraZeneca, Calypso, Celgene/Receptos/Bristol Myers Squibb, Eli Lilly, EsoCap Biotech, Gossamer Bio, Parexel, Regeneron, Sanofi, Shire/Takeda
Contracted Research – Adare/Ellodi, Allakos, AstraZeneca, Meritage, Receptos/Bristol Myers Squibb, Regeneron, Shire, Takeda

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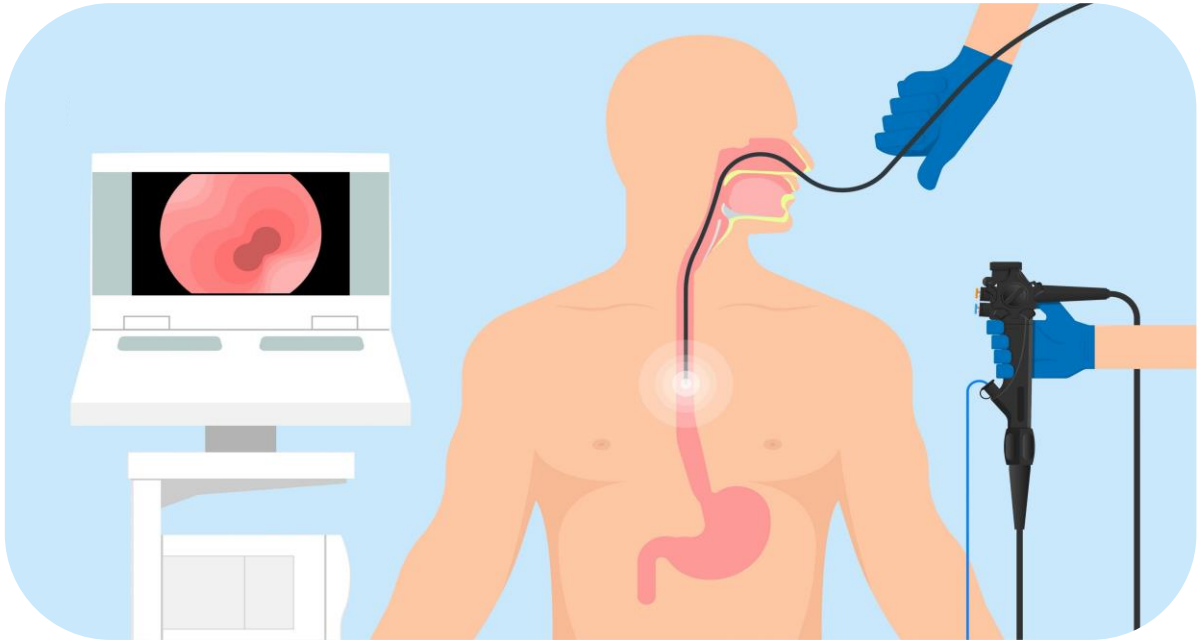
Consulting Fees - Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, Avir Pharma

LEARNING OBJECTIVES

- **Summarize** criteria and diagnostic tests to accurately diagnose eosinophilic esophagitis (EoE) in a timely manner.
- **Interpret** the recently updated guidelines for the treatment and management of EoE
- **Articulate** the latest insights into pathophysiology on therapeutic strategies to address the unmet needs in EoE
- **Evaluate** the utility of biologic agents in overcoming limitations of available treatment and in addressing the pathophysiology of EoE
- **Employ** patient-centered approaches to improve outcomes in EoE

COMPLEX DISEASE CONDITIONS: EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

DEFINING EoE



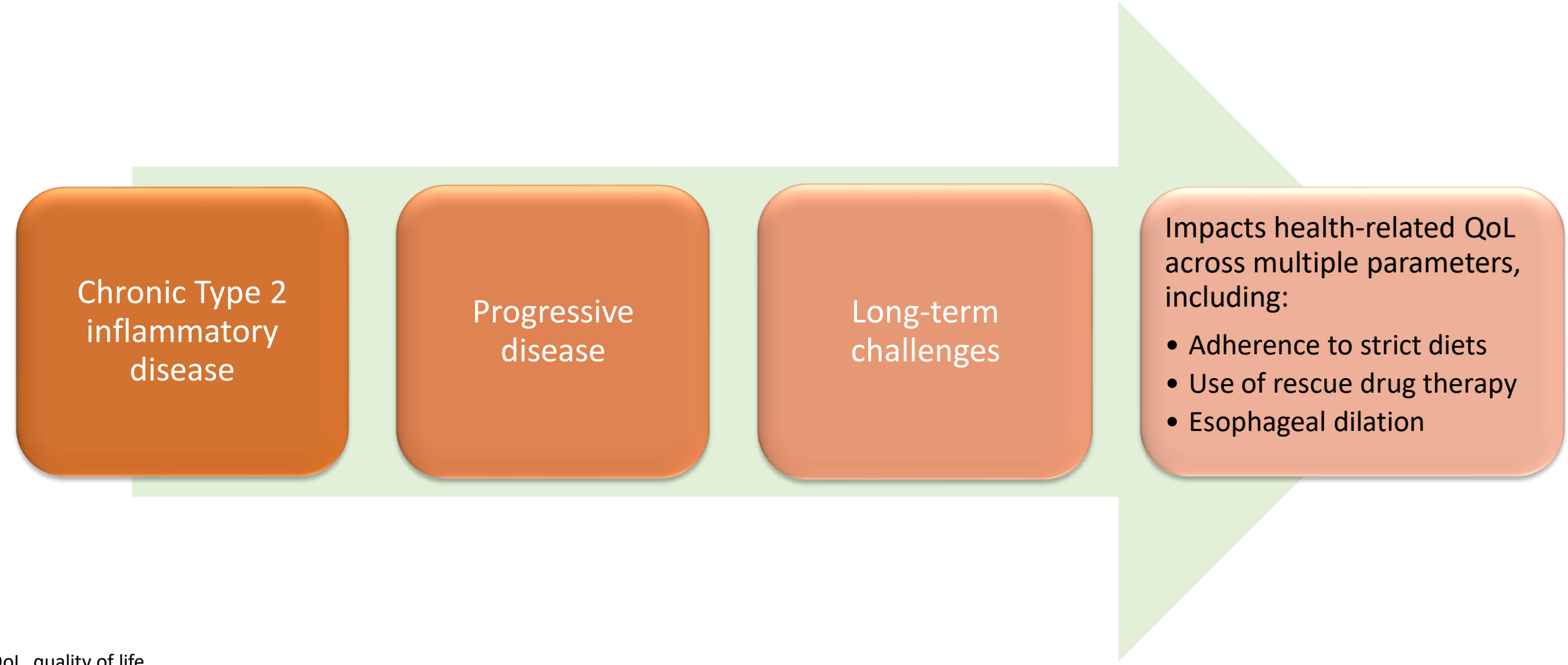
Large numbers of white blood cells (eosinophils) found in inner lining of the esophagus

Eosinophils release substances into surrounding tissues that cause inflammation (normally, no eosinophils in esophagus)

Chronic inflammation of EoE leads to symptoms that vary with age

Surdea-Blaga T, et al. *J Gastrointestin Liver Dis*. 2020;doi:10.15403/jgld-768. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5:335-358. doi:10.1177/2050640616689525. James C, et al. *Clin Rev Allergy Immunol*. 2018;55:99- 105. doi:10.1007/s12016-018-8683-2. Spergel JM, et al. *J Pediatr Gastroenterol Nutr*. 2009;48:30-36. doi:10.1097/ MPG.0b013e3181788282.

UNDERSTANDING EoE



QoL, quality of life.

O'Shea KM, et al. *Gastroenterology.* 2018;154(2):333-345. Mukkada V, et al. *Clin Gastroenterol Hepatol.* 2018;16(4):495-503.e8. Franciosi JP, et al. *Child Care Health Dev.* 2012;38(4):477-483. Lucendo AJ, et al. *United European Gastroenterol J.* 2018;6(1):38-45. Furuta GT, Katzka DA. *N Engl J Med.* 2015;373(17):1640-1648.

EPIDEMIOLOGY: A CHRONIC TYPE 2 INFLAMMATORY DISEASE

Approximately 1 in 2000 people in the US live with EoE

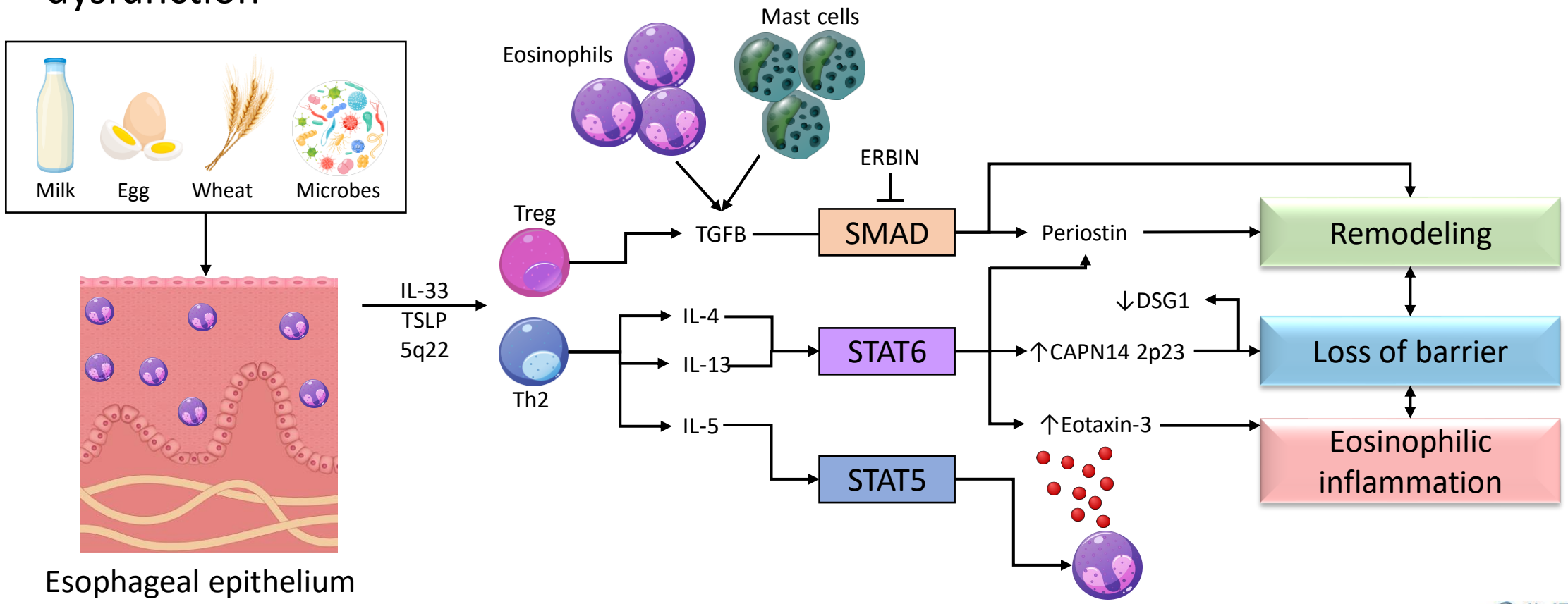
Patients often have multiple Type 2 inflammatory diseases

~75% of patients have at least one comorbid Type 2 inflammatory disease

O'Shea KM, Aceves SS, Dellon ES, et al. *Gastroenterology.* 2018;154(2):333-345. van Rhijn BD, Bredenoord AJ. *J Clin Gastroenterol*. 2017;51(8):659-668. Jyonouchi S, Brown-Whitehorn TA, Spergel JM. *Immunol Allergy Clin North Am*. 2009;29(1):85-97. Padia R, Curtin K, Peterson K, Orlandi RR, Alt J. *Laryngoscope*. 2016;126(6):1279-1283. https://www.type2inflammation.com/eosinophilic-esophagitis/

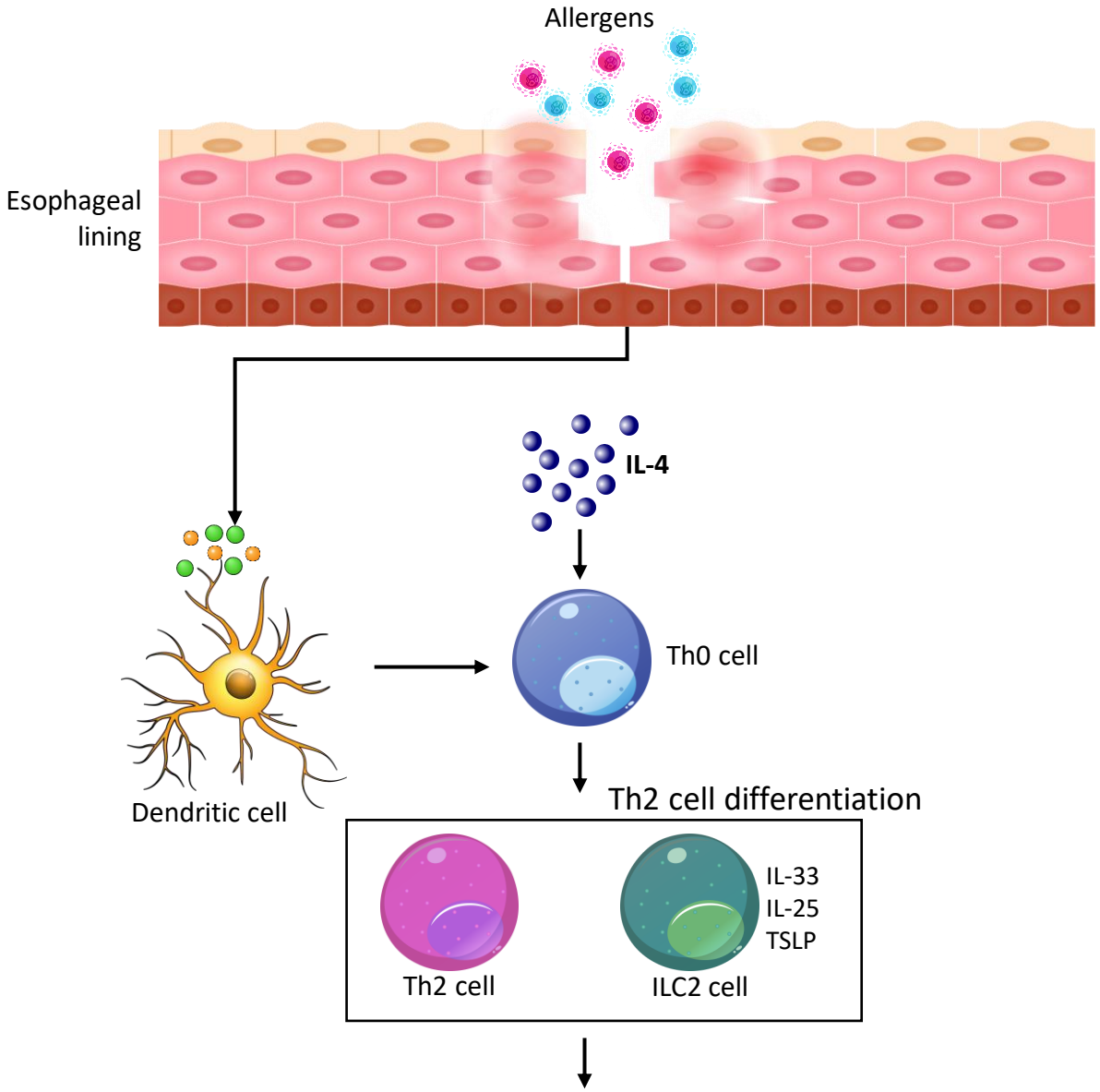
CLINICAL, PATHOLOGIC, AND THERAPEUTICS OF EOE

- Allergens drive EoE
- Presenting symptoms lead to esophageal inflammation, remodeling, rigidity, and dysfunction



O'Shea KM, Aceves SS, Dellon ES, et al. *Gastroenterology.* 2018;154(2):333-345.

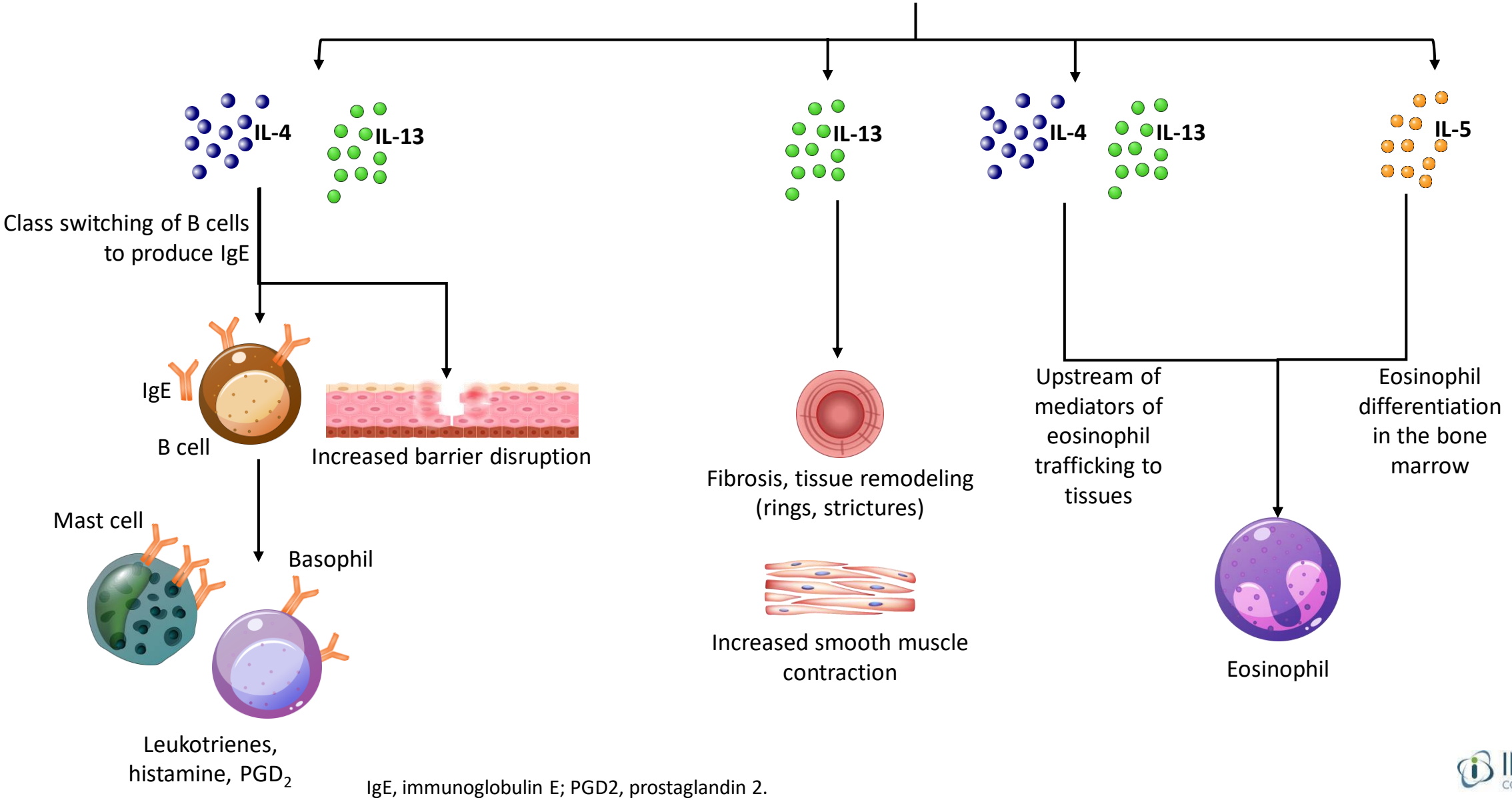
KEY TYPE 2 CYTOKINES IN EoE: IL-4, IL-13, AND IL-5



Th, T-helper cell; IL, interleukin; TSLP, thymic stromal lymphopoietin.

https://www.type2inflammation.com/eosinophilic-esophagitis/ Hill DA, Spergel JM. *Curr Allergy Asthma Rep.* 2016;16(2):9. doi:10.1007/s11882-015-0592-3 Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. *Nat Rev Drug Discov.* 2016;15(1):35-50. Furuta GT, Katzka DA. *N Engl J Med.* 2015;373(17):1640-1648. D'Alessandro A, et al. *World J Gastrointest Pathophysiol.* 2015;6(4):150-158. Davis BP, Rothenberg ME. *Annu Rev Pathol.* 2016;11:365-393. Malhotra N, Levine J. *Curr Probl Pediatr Adolesc Health Care.* 2014;44(11):335-340. 7. Siracusa MC, et al. *J Allergy Clin Immunol.* 2013;132(4):789-801.

KEY TYPE 2 CYTOKINES IN EOE: IL-4, IL-13, AND IL-5 (CONT)



IgE, immunoglobulin E; PGD2, prostaglandin 2.

RISK FACTORS ASSOCIATED WITH EoE

Climate	Season	Sex	Family history	Allergies and asthma	Age	Race
• People who live in a cold or dry climate are more likely to be diagnosed	• More likely to be diagnosed between spring and fall	• More common in males than in females	• Possible genetic component; if family members have EoE, greater chance of diagnosis	• People with food or environmental allergies, asthma, atopic dermatitis, or a chronic respiratory disease are more likely to be diagnosed	• The majority of cases are in children, adolescents, and adults ≤50, but can affect all ages	• More common among Caucasians, but can affect all races

Surdea-Blaga T, et al. *J Gastrointestin Liver Dis*. 2020;doi:10.15403/jgld-768. Spechler SJ. *J Gastroenterol*. 2019; doi:10.1007/s00535-019-01604-7. Gómez-Aldana A, et al. *World J Gastroenterol*. 2019; doi:10.3748/wjg.v25.i32.4598. Brown AY. Allscripts EPSi. Mayo Clinic. June 24, 2020. Alexander JA (expert opinion). Mayo Clinic. Aug. 27, 2020.

DIFFERENT MANIFESTATIONS OF EoE ACROSS PATIENTS

Different manifestations across patients, including:

Fibrosis of the esophagus (narrowing and scarring)	• Present in 89% of patients with EoE with features including uniformity and hyalinization
Esophageal dysfunction, particularly dysphagia	• A primary symptom directly associated with a diagnosis of EoE, characterized by difficulty swallowing
Food impaction	• One of the main symptoms of EoE, food impaction is a direct consequence of the esophageal fibrosis and mucosa remodeling
Chest pain	• Present in many patients with EoE

O'Shea KM, Aceves SS, Dellon ES, et al. *Gastroenterology.* 2018;154(2):333-345. D'Alessandro A, Esposito D, Pesce M, Cuomo R, De Palma GD, Sarnelli G. *World J Gastrointest Pathophysiol.* 2015;6(4):150-158. https://www.type2inflammation.com/eosinophilic-esophagitis

POSSIBLE COMPLICATIONS OF EoE

Scarring and narrowing of the esophagus	• Makes it difficult to swallow; more likely food will get stuck
Damage to the esophagus	• Tearing in connection with retching when food is stuck • Due to inflammation of the esophagus, endoscopy **may** cause perforation or tears in tissue lining esophagus
Malnutrition	• Food avoidance due to symptoms can lead to malnutrition

Surdea-Blaga T, et al. *J Gastrointestin Liver Dis*. 2020;doi:10.15403/jgld-768. Spechler SJ. *J Gastroenterol*. 2019; doi:10.1007/s00535-019-01604-7. Gómez-Aldana A, et al. *World J Gastroenterol*. 2019; doi:10.3748/wjg.v25.i32.4598. Acid reflux. American College of Gastroenterology. https://gi.org/topics/acid-reflux/. Brown AY. Allscripts EPSi. Mayo Clinic. June 24, 2020. Alexander JA (expert opinion). Mayo Clinic. Aug. 27, 2020.

THE BURDEN OF EoE: ANXIETY AND DEPRESSION SYMPTOMS

Increased Risk

- Affects both adult and pediatric patients with EoE
- May reduce HRQoL and treatment adherence
- Impacts eating and food-specific anxieties
- Important to screen for restrictive behaviors (ie, ARFID)

Causes

- Disease process and dietary treatments
- Lack of treatment options (eg, patients who follow strict elimination diets indefinitely)

ARFID, avoidant restrictive food intake disorder; HRQoL, health-related quality of life.

Taft TH, Guadagnoli L, Edlynn E. *J Asthma Allergy*. 2019 Dec 9;12:389-399. doi: 10.2147/JAA.S193045. Zimmerman J, Fisher M. *Curr Probl Pediatr Adolesc Health Care*. 2017;**47**:95–103. doi:10.1016/j.cppeds.2017.02.005

THE BURDEN OF EoE: QOL AND ECONOMIC IMPACT OF ASSOCIATED CONDITIONS

Incidence and Prevalence

- Rapidly increasing disease
- Not known: real increase in incidence or better recognition?
- Reported incidence varies from 1 to 20 new cases per 100,000 inhabitants per year with mean value of 7
- Prevalence ranges 13 - 49 cases per 100,000 inhabitants

Burden in the USA

- Estimated annual burden of ~1.4 billion US dollars

Dellon ES. *Gastroenterol Clin North Am.* 2014;43:201-218. doi:10.1016/j.gtc.2014.02.002. Jensen ET, Kappelman MD, Martin CF, Dellon ES. *American J Gastroenterol.* 2015;110:626- 632. doi:10.1038/ajg.2014.316. Whitney-Miller CL, Katzka D, Furth EE. *Am J Clin Pathol.* 2009;131:788-792. doi:10.1309/AJCPOMPXJFP7EB4P Vanderheyden AD, Petras RE, DeYoung BR, Mitros FA. *Arch Pathol Lab Med.* 2007;131:777-779.

THE BURDEN OF EoE: FOLLOW-UP MAINTENANCE

Current therapies for EoE patients:

- Elimination diet
- Proton pump inhibitors (PPI)
- Swallowed topical corticosteroids
- Esophageal dilation

Lucendo AJ, Molina-Infante J, Arias Á, et al. *United European Gastroenterol J.* 2017;5(3):335-358. O'Shea KM, Aceves SS, Dellon ES, et al. *Gastroenterology.* 2018;154(2):333-345. Wolf WA, Dellon ES. *Gastroenterol Hepatol (N Y).* 2014;10(7):427-432. D'Alessandro A, Esposito D, Pesce M, Cuomo R, De Palma GD, Sarnelli G. *World J Gastrointest Pathophysiol.* 2015;6(4):150-158. Watts A, Alexander JA, Gupta SK. *Gastrointest Endosc.* 2016;83(2):307-308. Baker RD, Baker SS. Towards better diagnosis and monitoring of eosinophilic esophagitis: are we there yet? *J Pediatr Gastroenterol Nutr.* 2020;70(4):410.
https://www.type2inflammation.com/eosinophilic-esophagitis

DIAGNOSTIC CHALLENGES AND CURRENT SCREENING RECOMMENDATIONS

DIAGNOSTIC CONSIDERATIONS AND CHALLENGES

Patients with EoE face diagnostic delay (median 4-6 years)

Diagnostic delay seems to increase with increasing age

Median [IQR] time between symptom onset and diagnosis

Age	Years, median [IQR]
<11 yo	*1 [0.5-2.3]*
11-17 yo	*2 [1-4]*
>=18 yo	*4 [1-12]*

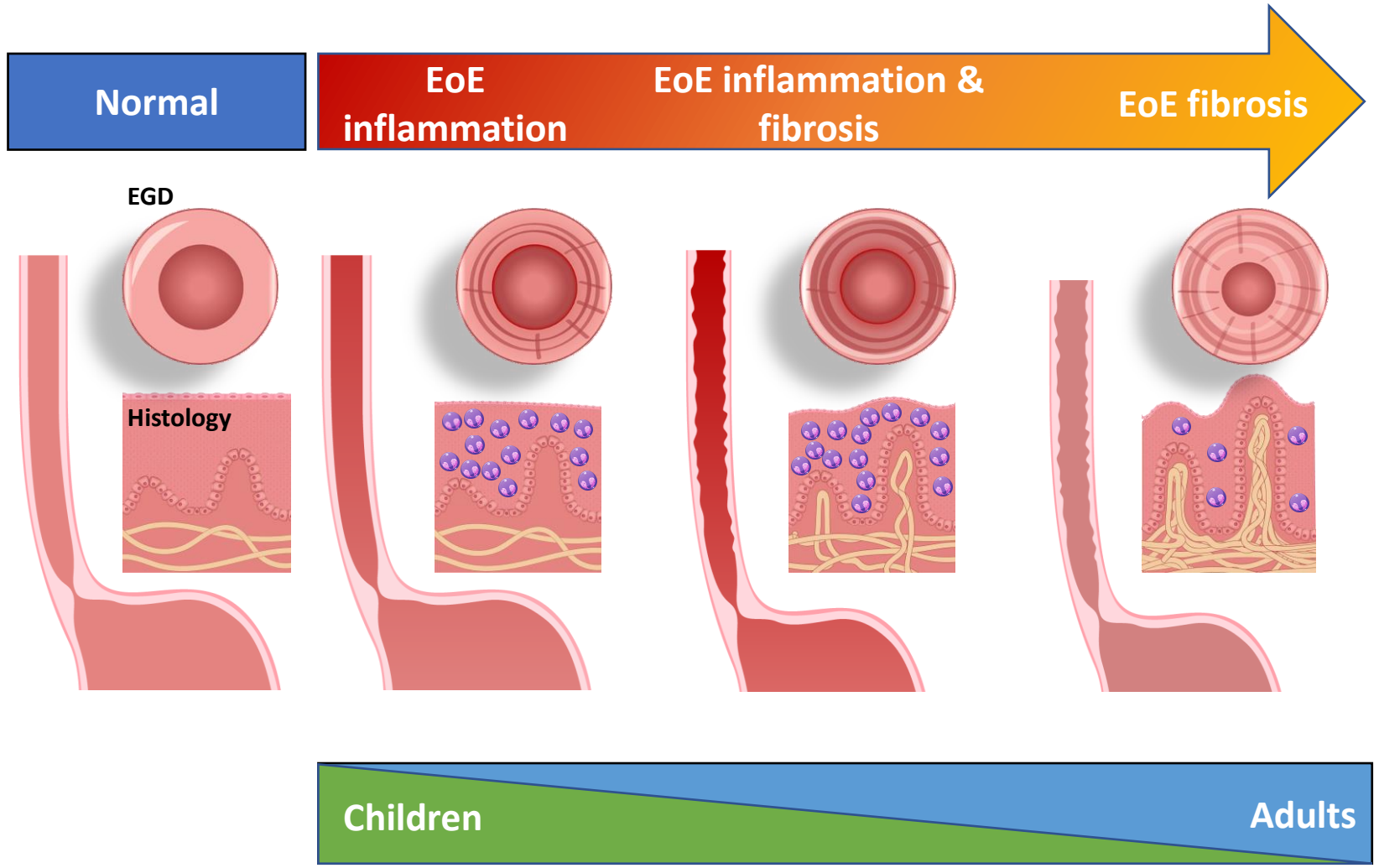
History of food allergy and atopic dermatitis reduces diagnostic delay

IQR, interquartile range.

Schoepfer et al. *Gastroenterology*. 2013;145(6):1230-6.e62. doi:10.1053/j.gastro.2013.08.015; Chehade M, et al. *J Allergy Clin Immunol Pract*. 2018;6(5):1534-1544.e5. doi:10.1016/j.jaip.2018.05.038

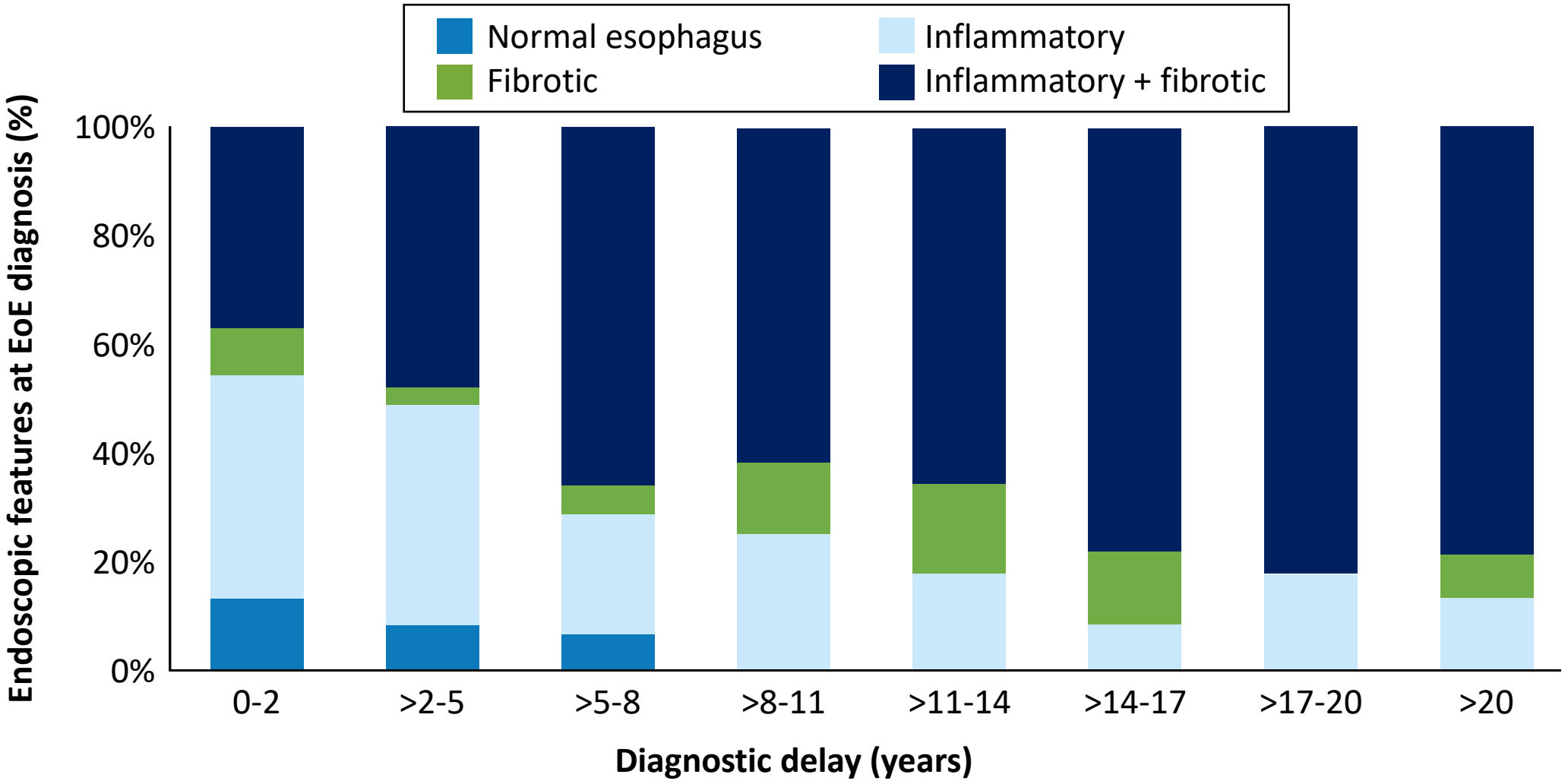
DIAGNOSTIC DELAYS: DISEASE PROGRESSION

Data in adults suggest potential for inflammation to progress into strictures in some EoE patients with untreated disease.



Hirano I, et al. *Gastroenterol Clin North Am*. 2014;43(2):297-316. doi:10.1016/j.gtc.2014.02.015

DIAGNOSTIC DELAYS: INCREASED RISK OF FIBROSTENOTIC COMPLICATIONS



Schoepfer AM, et al. *Gastroenterology*. 2013;145(6):1230-6.e62. doi:10.1053/j.gastro.2013.08.015.

INTEGRITY CONTINUING EDUCATION

OVERCOMING DIAGNOSTIC DELAYS: MULTIDISCIPLINARY AWARENESS

Assessment of the following is **important**:

- Symptoms
- Endoscopy
- Histopathology

Requires awareness of symptoms and **collaboration:**

- Gastroenterologists
- Allergists
- Primary care clinicians
- Pathologists

Lucendo AI, Molina-Infante J, Arias A, et al. *United European Gastroenterol J*. 2017;5(3):335-358. Dellon ES, Jones PD, Martin NB, et al. *Dis Esophagus*. 2013;26(1):7-13. Hirano I. *Gastroenterology.* 2018;155:601-606.

DIAGNOSTIC CRITERIA AND TESTING

In combination with

Symptoms

- May vary with age

Endoscopy and Histopathology

- Upper endoscopy looking for features of EoE
- Esophageal biopsies demonstrating eosinophilic infiltration
- Guidelines suggest ≥15 eosinophils/hpf

hpf, high-power field.

Dellon ES, Liacouras CA, Molina-Infante J, et al. *Gastroenterology*. 2018;155(4):1022-1033.e10. Lucendo AI, Molina-Infante J, Arias A, et al. *United European Gastroenterol J*. 2017;5(3):335-358. Safroneeva E, Straumann A, Coslovsky M, et al. *Gastroenterology*. 2016;150(3):581-590.e4. Straumann A, Aceves SS, Blanchard C, et al. *Allergy*. 2012;67(4):477-490.

DIAGNOSING EoE: SYMPTOMS ACCORDING TO AGE

Infants & Toddlers

- Food refusal
- Coughing/gagging with food
- Vomiting
- Failure to thrive

Children

- Food refusal
- Coughing/gagging with food
- Decreased appetite
- Nausea
- Vomiting/regurgitation
- Abdominal pain/chest pain
- Dysphagia
- Food impaction
- Failure to thrive

Adults

- Dysphagia
- Food impaction
- Food avoidance
- Substernal chest pain
- Intractable heartburn
- Regurgitation

Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, Schoepfer AM, Simon D, Simon H-U. *Allergy* 2012;67:477–490. Eosinophilic esophagitis – Symptoms and causes - Mayo Clinic. Accessed on Aug 19, 2021. Carr S, Chan ES, Watson W. *Allergy Asthma Clin Immunol*. 2018;14(Suppl 2):58. Wong S, Ruszkiewicz A, Holloway RH, et al. *World J Gastrointest Pathophysiol*. 2018;9(3):63-72. Chehade M, et al. Ann Allergy Asthma Immunol. 2019;122(6):603-609. doi:10.1016/j.anai.2019.03.020

DIAGNOSTIC TESTING: ENDOSCOPY

- Used to identify morphologic features associated with EoE
- Includes a validated scoring system that relies on assessment of:
  1. Edema
  2. Rings
  3. Exudates
  4. Furrows
  5. Stricture

EoE endoscopic reference score (EREFS)

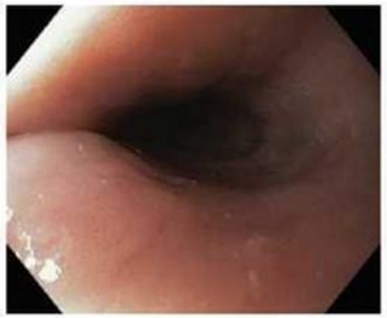
Edema (vascular pattern)
- Grade 0: normal
- Grade 1: reduced
- Grade 2: absent

Rings
- Grade 0: none
- Grade 1: mild (some)
- Grade 2: moderate (trachealized)
- Grade 3: severe (the endoscope cannot pass)

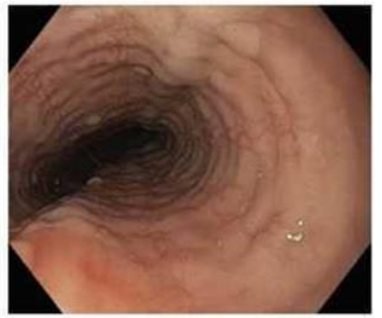
Exudates
- Grade 0: none
- Grade 1: mild (less than 10% of the surface)
- Grade 2: severe (more than 10% of the surface)

Furrows (vertical)
- Grade 0: none
- Grade 1: mild
- Grade 2: severe (deep)

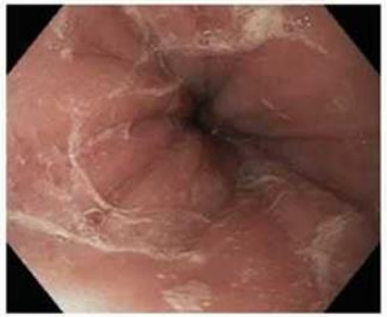
Stricture
- Grade 0: absent
- Grade 1: present



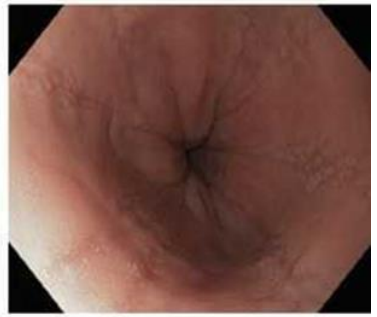
Edema grade 1



Rings grade 2



Exudates grade 2



Furrows grade 1

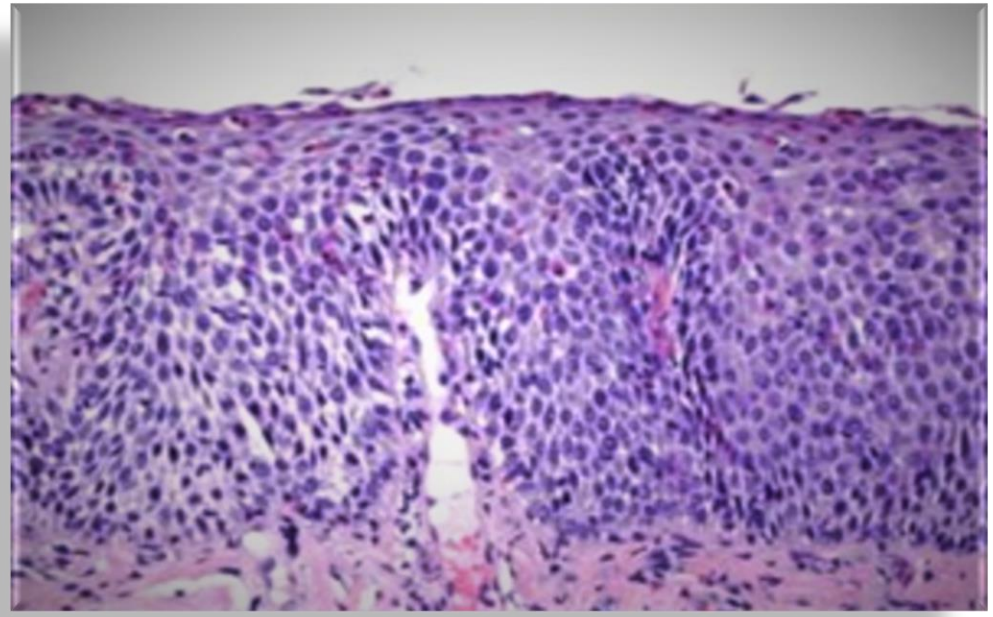
Modified with permission from the author:
Hirano I, Moy N, Heckman MG, *et al.* Gut 2013; 62: 489-95

Rev Gastroenterol Mex 2017;82:5–12

Hirano I, et al. *Gut.* 2013;62:489-95.

DIAGNOSTIC TESTING: HISTOLOGY

Histology: increased eosinophils in the esophageal mucosa (≥ 15 per hpf)



hpf, high-power field . Esophagus. Esophageal Structure - презентация онлайн (ppt-online.org). Accessed on August 18, 2021. R Brun. Gastroenterology Dept. Rambam Health Care Campus.

DIFFERENTIAL DIAGNOSIS FOR ESOPHAGEAL EOSINOPHILIA

Clinicians must rule out other causes of esophageal eosinophilia before confirming EoE:

- GERD
- Parasitic infection
- Crohn's disease
- Eosinophilic gastroenteritis
- Hypereosinophilic syndrome
- Drug hypersensitivity
- Vasculitis
- Connective tissue diseases

GERD, gastroesophageal reflux disease.

Furuta GT, et al. *Gastroenterology*. 2007;133(4):1342-1363. doi:10.1053/j.gastro.2007.08.017. Liacouras CA, Furuta GT, Hirano I, et al. *J Allergy Clin Immunol*. 2011;128(1):3-22. doi:10.1016/j.jaci.2011.02.040

DIAGNOSTIC TESTING: WHEN TO TEST PATIENTS WITH EOE

EoE Causes: Food Triggers +/- Environmental Allergens

Current food allergy testing identifies IgE-mediated sensitization, not EoE triggers.

ONLY consider testing for EoE triggers to expand already restricted diet.

OR test to identify immediate/anaphylactic food allergy or environmental allergens.

Consider testing for allergic sensitization with skin prick testing or blood testing for allergen-specific IgE

Important for EoE patients with symptoms of immediate IgE-mediated food allergy

Discourage allergy testing if patient is eating foods without a history of immediate reactions

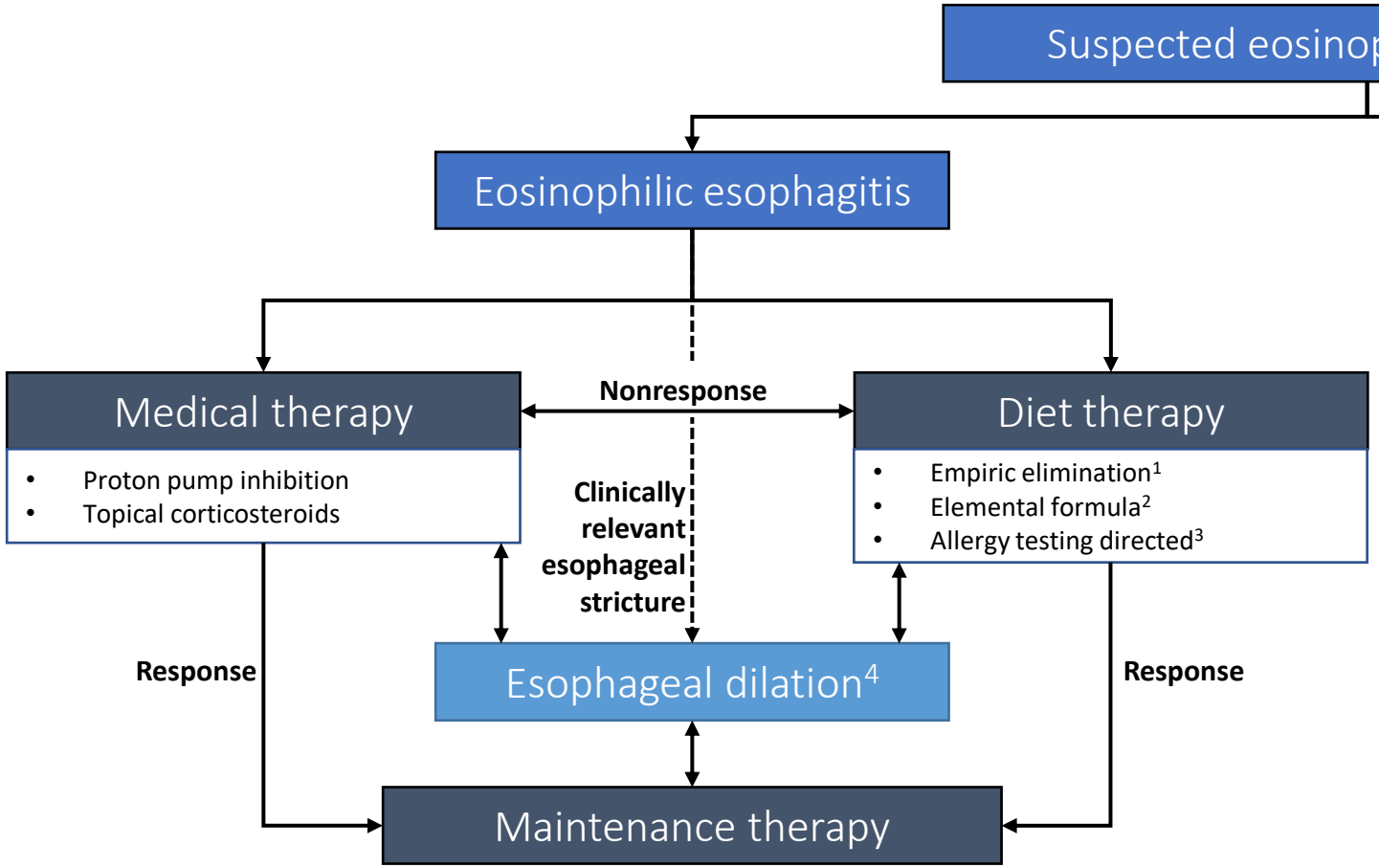
Consider testing to expand restricted diet

- Overly restricted diet by patients based on symptoms associations
- Before individual food challenges following prolonged elimination diet

Carr S, et al. *Allergy Asthma Clin Immunol*. 2019;15:22. doi:10.1186/s13223-019-0336-3; Ho HE, et al. *J Allergy Clin Immunol Pract*. 2018;6(2):649-650. doi:10.1016/j.jaip.2017.08.014; Chehade M, et al. *Expert Rev Clin Immunol*. 2020;16(7):679-687. doi:10.1080/1744666X.2020.1801419

THERAPEUTIC MANAGEMENT OF EoE FOR OPTIMAL OUTCOMES

EoE TREATMENT ALGORITHM : CLINICAL DECISION SUPPORT TOOL



Secondary causes of eosinophilic esophagitis

- Gastroesophageal reflux disease
- Eosinophilic gastrointestinal disease
- Achalasia
- Hypereosinophilic syndrome
- Esophageal Crohn's disease
- Infections (fungal, viral)
- Connective tissue disorders
- Autoimmune disorders
- Vasculitis
- Drug hypersensitivity reactions
- Pill esophagitis
- Stasis esophagitis
- Graft versus host disease
- Marfan syndrome type II
- Hyper-IgE syndrome
- PTEN hamartoma tumor syndrome
- Netherton's syndrome
- Severe atopy metabolic wasting syndrome

1. Recommendation in favor of empiric elimination diets is based on the published experience with the six food elimination diet (SFED). Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option. Emerging data on less restrictive diets (4 food, milk elimination, 2-4-6 step up diet) may increase both provider and patient preference for diet therapy.
2. Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.
3. Due to the potential limited accuracy of the currently available, allergy-based testing for the identification of specific food triggers for eosinophilic esophagitis, patients may prefer alternative medical or dietary therapies to an exclusively testing-based elimination diet.
4. Esophageal dilation does not address the esophageal inflammation associated with EoE.

Hirano I, et al. *Gastroenterology*. 2020;158(6):1776-1786. doi:10.1053/j.gastro.2020.02.038

LONG-TERM ADHERENCE TO RESTRICTED DIET IS LIMITED

Allergen avoidance with elimination and elemental diets

Effective first-line treatment

Limitations:

- Difficult for patients and families
- Cost concerns for allergen-free options or elemental diets
- Need for feeding tubes for elemental diet
- Potential nutritional deprivation
- Psychological burden created by the avoidance of major food groups
- Unnecessary food aversion
- Challenges of long-term adherence

Relapse upon discontinuation of the diet is common

Hirano I, Chan ES, Rank MA, et al. *Ann Allergy Asthma Immunol*. 2020;124(5):416-423.

UPDATED GUIDELINES AND RECOMMENDATIONS FOR ASSESSMENT AND MANAGEMENT OF EoE

Proton pump inhibition	Swallowed topical corticosteroids (budesonide or fluticasone)	Systemic glucocorticoids	Endoscopic dilation
• **AGA JTF: Conditional recommendation, very low quality; low effectiveness 42%** • Effectiveness lower, more heterogeneous vs other available therapies	• **AGA JTF: Strong recommendation, moderate quality; overall effectiveness 65%** • Consistent histologic benefits demonstrated in multiple PBO-controlled, randomized trials • Current use limited to off-label administration of products developed for asthma	• **AGA JTF: Swallowed topical steroids rather than oral systemic steroids. Conditional recommendation, moderate quality** • Expected systemic AEs with systemic therapy	• **AGA JTF: Conditional recommendation for dysphagia from a stricture, very low quality** • Dilation does not address underlying inflammation

AE, adverse event; AGA, American Gastroenterological Association; JTF, Joint Task Force for Allergy-Immunology Practice Parameters; PBO, placebo.
Hirano I, Chan ES, Rank MA, et al. *Ann Allergy Asthma Immunol*. 2020;124(5):416-423.

AGA GUIDELINES: DIET THERAPY OPTIONS

Diet Therapies: AGA Recommendations & Quality of Evidence

- **Elemental diet: Conditional recommendation/ Moderate**
- **6-food elimination diet: Conditional recommendation/Low**
- **Allergy testing based elimination diet: Conditional recommendation/Very low**

Limitations per Class

- **Elemental diet:** Challenges of adherence to diet & prolonged process of dietary reintroduction
- **Empiric, 6-food elimination:** Challenges of adherence to diet & need for multiple endoscopies during dietary reintroduction
- **Allergy testing-based elimination diet:** Poor sensitivity & specificity of currently available, IgE-based allergy tests for identifying trigger foods

Hirano I, et al. *Gastroenterology*. 2020;158:1776–1786. doi:https://doi.org/10.1053/j.gastro.2020.02.038

NEW INSIGHTS INTO PATHOPHYSIOLOGY, NOVEL TREATMENT TARGETS, AND EMERGING AGENTS

2020 AGA/JTF ALLERGY/IMMUNOLOGY GUIDELINES: MANAGEMENT OF EoE

Biologic Therapies: **Anti-IgE**

- Recommendation: In patients with EoE the AGA/JTF suggests against the use of anti-IgE therapy (conditional recommendation; very low-quality evidence)

Biologic Therapies: **Anti-IL-5**

- Recommendation: In patients with EoE the AGA/JTF recommends to use anti-IL-5 therapy only in the context of a clinical trial (no recommendation; knowledge gap).

Biologic Therapies: **Anti-IL-13**

- Recommendation: In patients with EoE the AGA/JTF recommends to use anti-IL-13 or anti-IL-4 receptor alpha therapy only in the context of a clinical trial (no recommendation; knowledge gap).

Misc Therapies: **Montelukast, Cromolyn, Immunomodulator, Anti-TNF**

- Recommendation: In patients with EoE the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF only in the context of a clinical trial (no recommendation; knowledge gap).

Hirano I et al. *Gastroenterology*. 2020; 158: 1776-1786; Rank MA et al. *Gastroenterology*. 2020; 158: 1789-1810; Hirano I et al. *Ann Allergy Asthma Immunol*. 2020; 124: 416-423; Rank MA et al. *Ann Allergy Asthma Immunol*. 2020; 124: 424-440.

MEPOLIZUMAB

US FDA approval as an add-on maintenance treatment for severe eosinophilic asthma in patients ≥12 yo, 2015

US FDA approval for the treatment of adults with EGPA, a rare autoimmune disease that causes vasculitis, 2017

Add-on maintenance treatment of patients ≥6 years with severe asthma with an eosinophilic phenotype

Treatment of adult and pediatric patients ≥12 years with HES for ≥6 months without an identifiable non-hematologic secondary case

Most common AEs (≥5%) in clinical trials in patients with severe asthma (100 mg mepolizumab): headache, injection site reaction, back pain, and fatigue

EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome.
Nucala website. https://nucalahcp.com/severe-eosinophilic-asthma.

MEPOLIZUMAB (IL-5 MAB) IN PEDIATRIC EOE

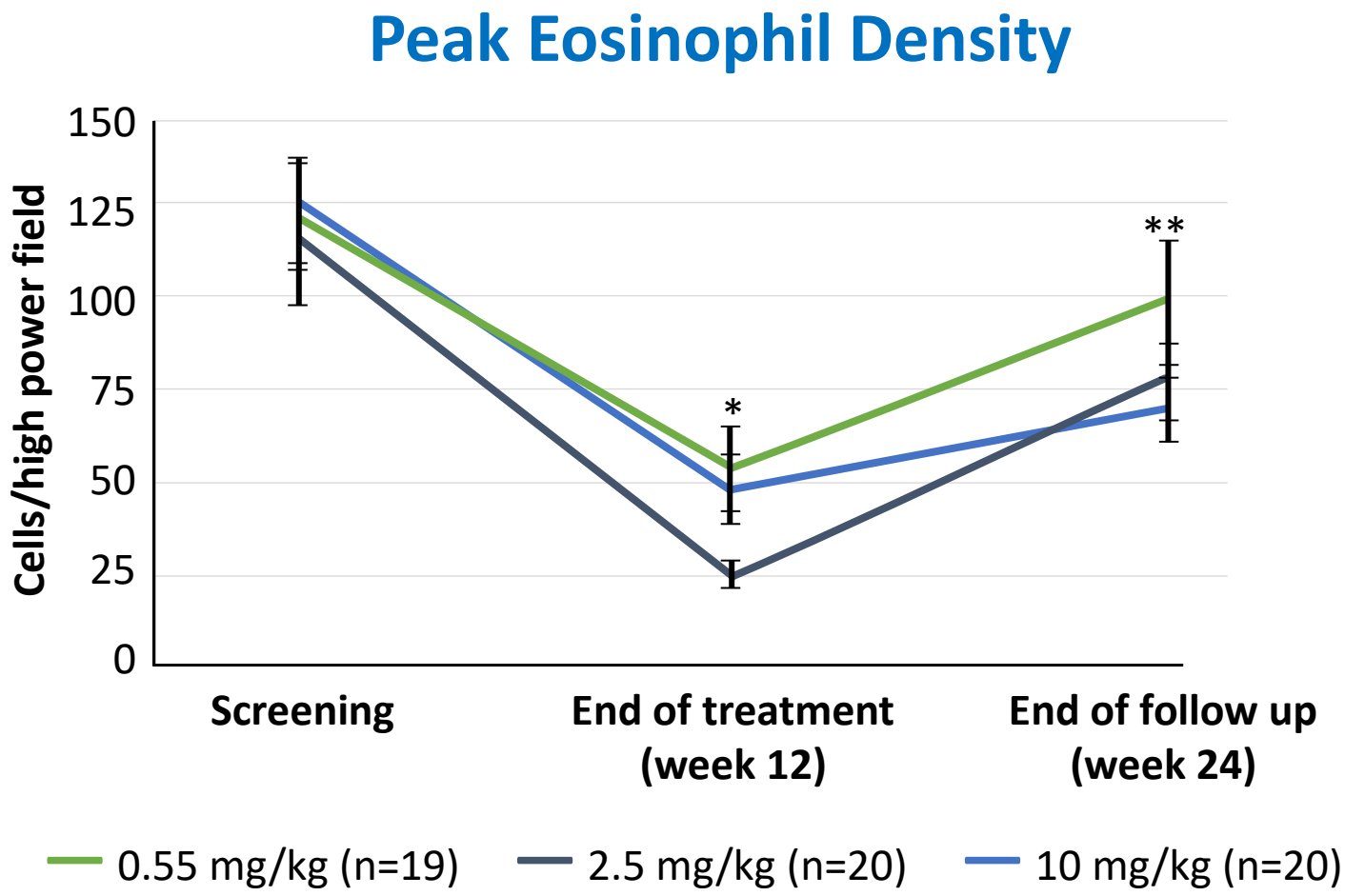
- International, multicenter, double blind randomized trial
- 59 patients ages 2-17
- Inclusion criteria: ≥20 eos/hpf
- Mepolizumab 0.55, 2.5, 10 mg/kg IV at weeks 0, 4, 8
- No placebo but low dose was selected to be minimally effective
- Primary endpoint: Proportion with peak < 5 eos/hpf at week 12
- Symptom assessment: nonvalidated daily PRO completed by proxy <7 yo and by patient >8 years
- Mepolizumab well tolerated

IV, intravenous; PRO, patient-reported outcome.

Assa'ad AH, et al. *Gastroenterology.* 2011;141(5):1593-15604.

MEPOLIZUMAB IN TREATMENT OF PEDIATRIC EoE (CONT)

- 8.8% achieved primary endpoint of <5 eos/hpf
- No significant improvement in symptoms comparing dosing arms (19% without symptoms at baseline)



*Significant decrease from baseline in the overall peak eosinophil count at week 12 (*P* <.0001).
**Significant decrease from baseline in the overall peak eosinophil count at week 24 (*P* =.0002).

Assa'ad AH, et al. *Gastroenterology*. 2011;141(5):1593-15604.

RESLIZUMAB

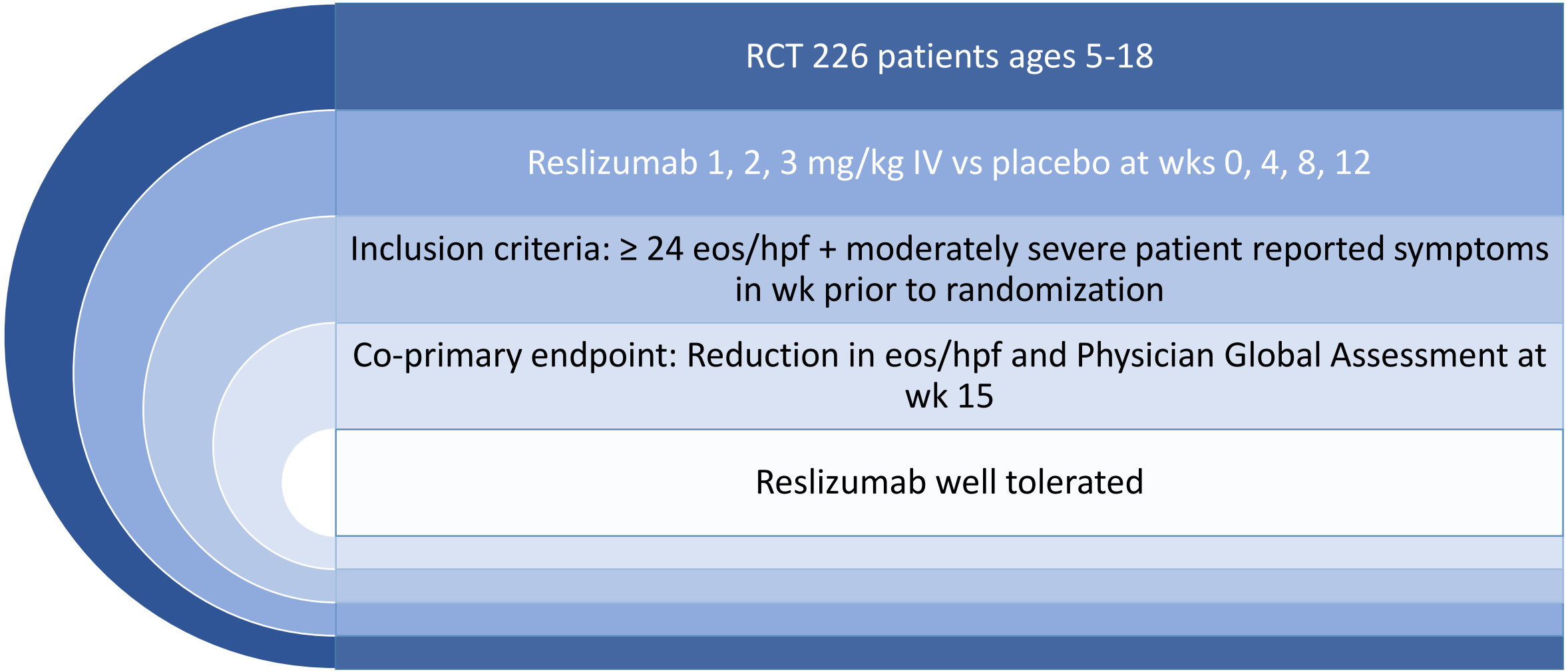
US FDA approval 2016

Add-on maintenance for treatment of patients with severe asthma ≥18 years with an eosinophilic phenotype

Limitation of use: Not indicated for treatment of other eosinophilic conditions or for relief of acute bronchospasm or status asthmaticus

Cinquair website. https://hcp.cinqair.com/.

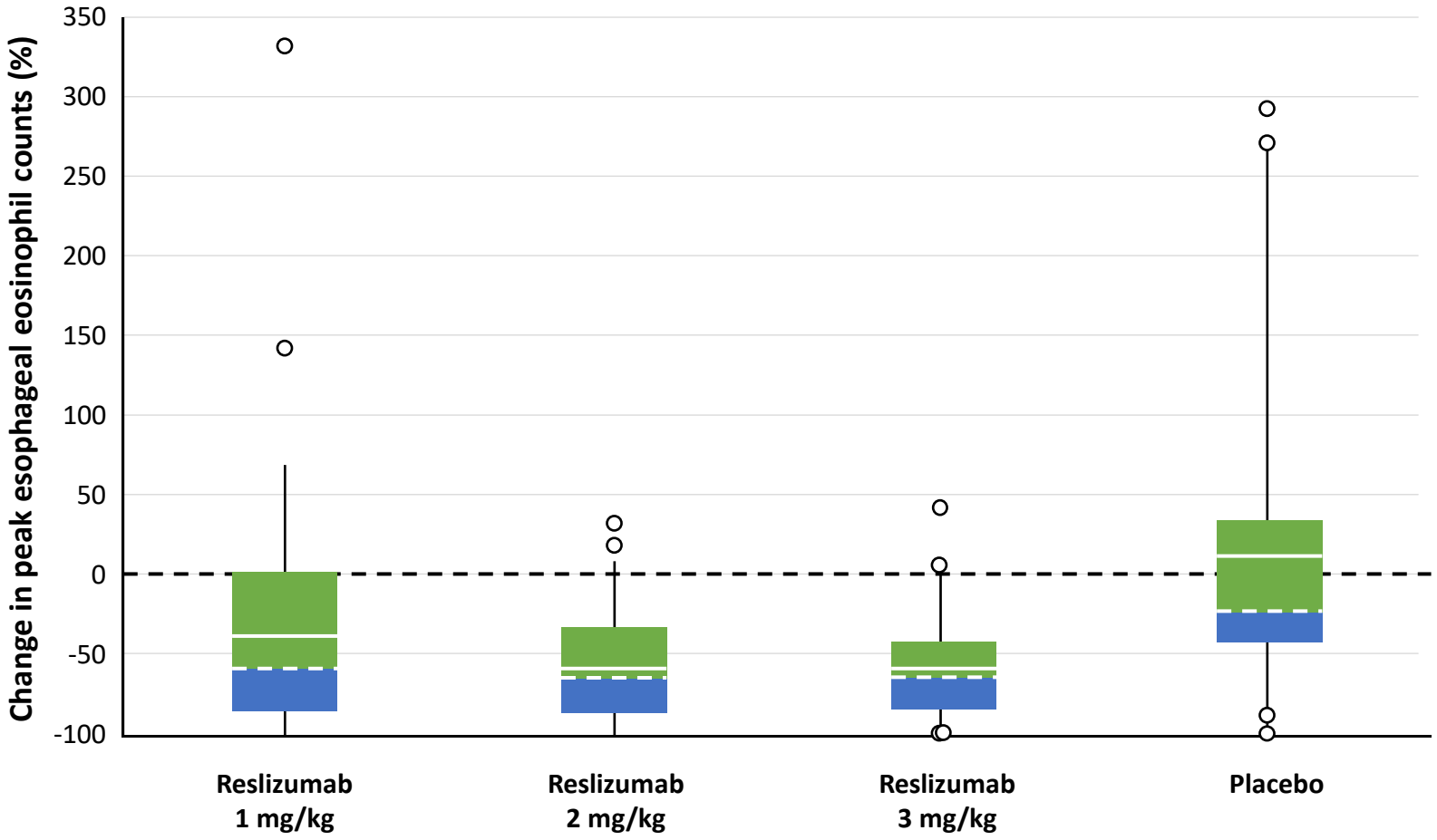
RESLIZUMAB IN TREATMENT OF PEDIATRIC EoE



IV, intravenous. wk, week. Spergel JM, et al. *J Allergy Clin Immunol*. 2012;130(2);461-7.e5.

RESLIZUMAB IN TREATMENT OF PEDIATRIC EoE

Significant reduction in eosinophilic inflammation
Median reduction in peak eos/hpf:
1 mg/kg 59%;
2 mg/kg 67%;
3 mg/kg 64%;
Placebo 24%
(*P*<0.001)

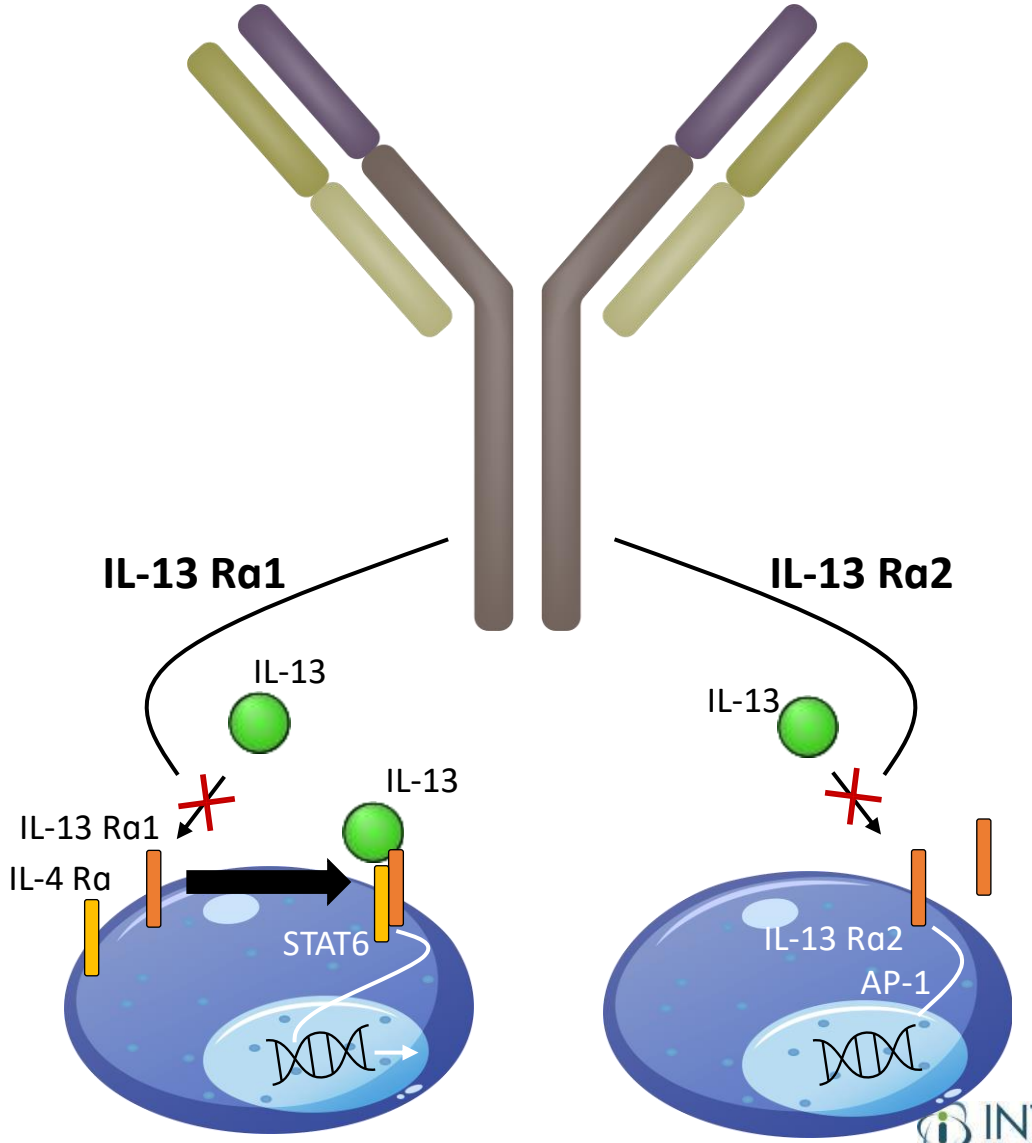


P <.0001 for all comparisons of reslizumab to placebo.

Spergel JM, et al. *J Allergy Clin Immunol*. 2012;130(2);461-7.e5.

ANTI-IL-13 MAB (RPC4046) IN TREATMENT OF EoE

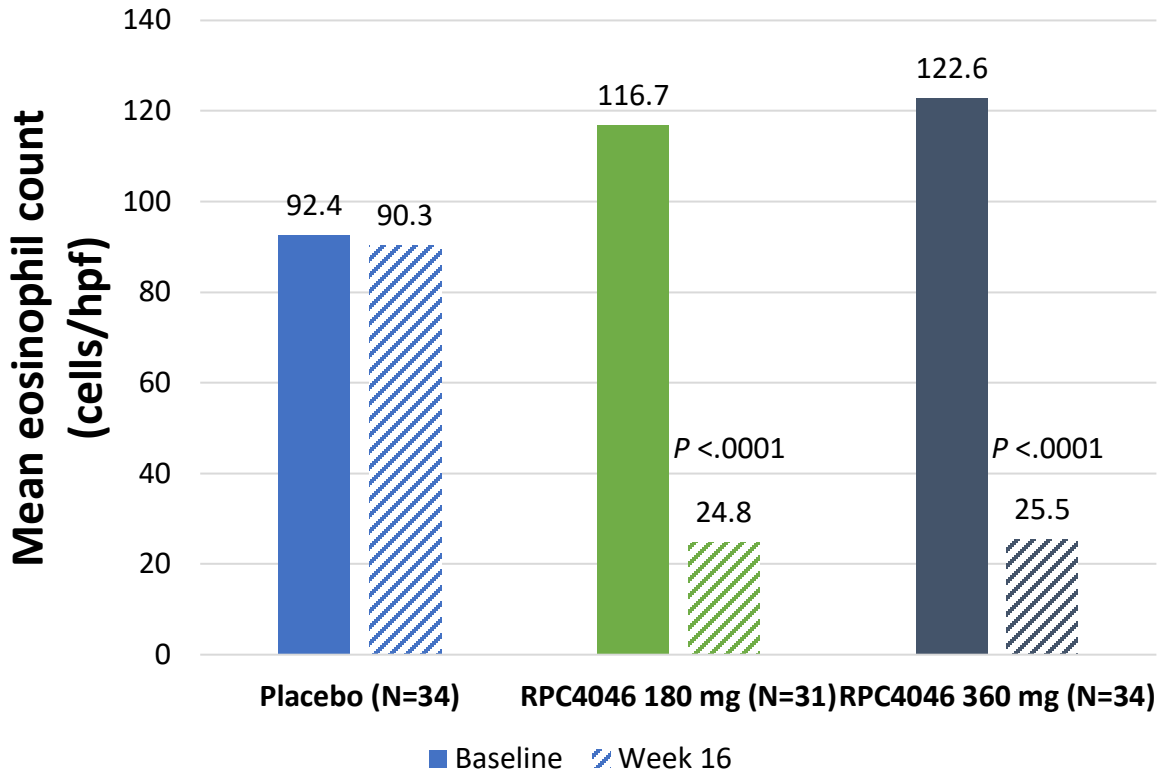
- Recombinant, humanized monoclonal (IgG1κ) antibody, highly selective for IL-13
- Inhibits binding of IL-13 to the IL-13Rα1 and IL-13Rα2 receptors
- Phase 2 double-blind, placebo-controlled trial conducted in 99 adults (18-65 years)
- Administered as a weekly subcutaneous injection at 2 doses (180 mg, 360 mg) vs placebo for 16 weeks

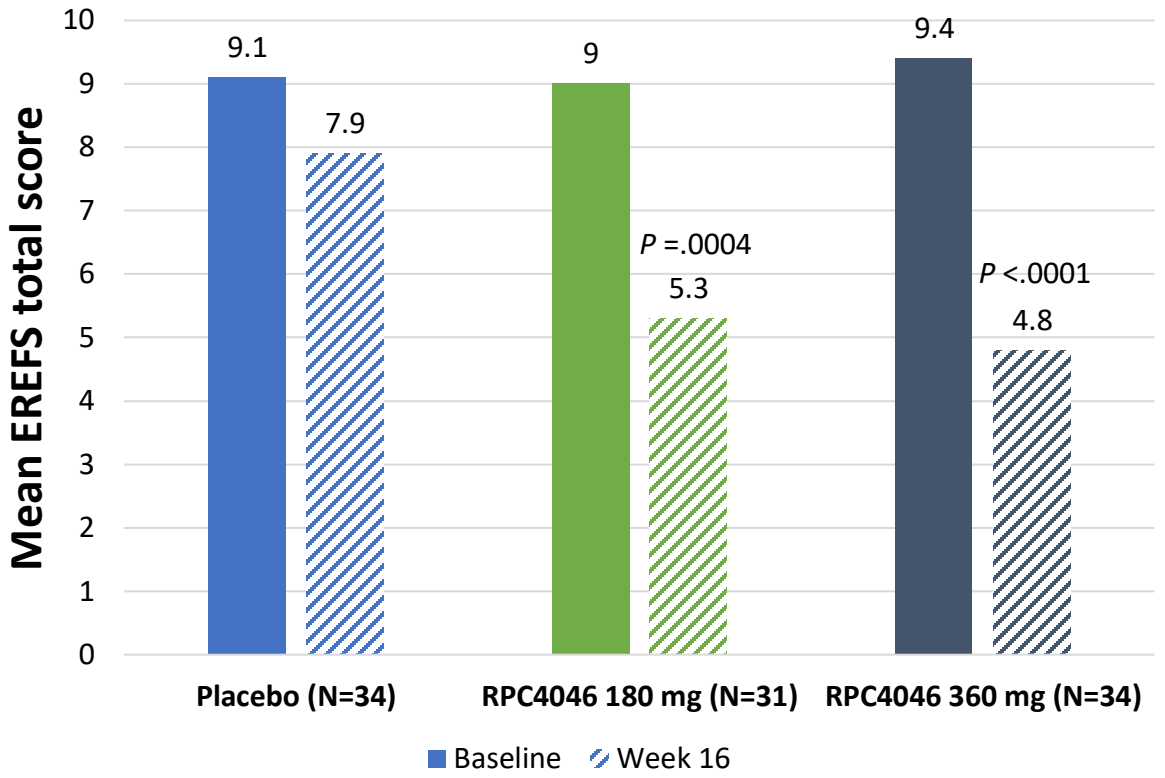


Hirano I, et al. *Gastroenterology*. 2019;156(3):592-603.e10.

ANTI-IL-13 MAB (RPC4046) REDUCED EOSINOPHILIC INFLAMMATION

Randomized, double blind, placebo-controlled trial; Primary Endpoint: Change in mean esophageal eosinophil count



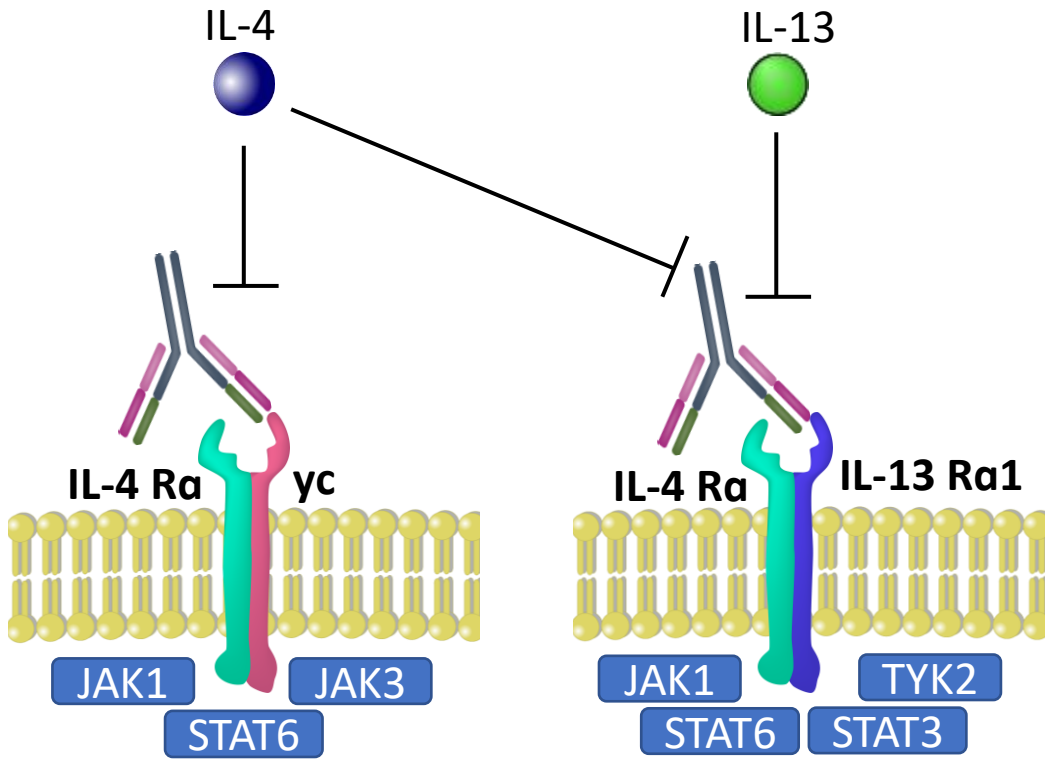


Hirano I, et al. Gastroenterology. 2019;156(3):592-603.e10.

INTEGRITY CONTINUING EDUCATION

DUPILUMAB (ANTI-IL-4RA) IN TREATMENT OF EoE

- IL-4 receptor α monoclonal antibody
- Inhibits signaling of IL-4 and IL-13
- US FDA approval for moderate-to-severe atopic dermatitis, 2017; approved for moderate - severe asthma, late 2018; chronic rhinosinusitis with nasal polyps



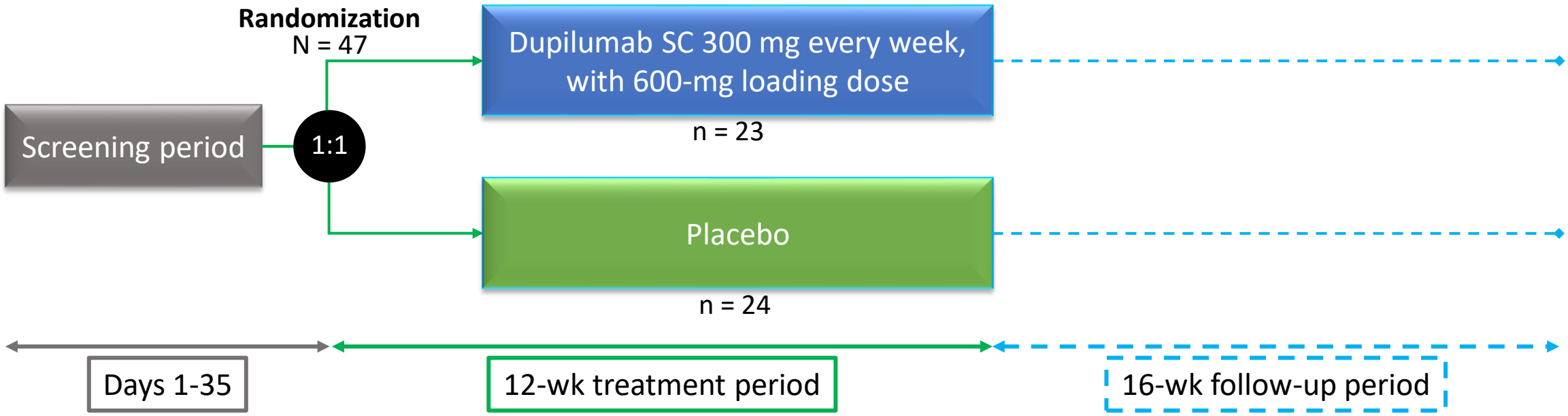
Type 1 receptor
B cells, T cells, monocytes, eosinophils, fibroblasts

Type 2 receptor
Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

Gandhi N, et al. *Expert Rev Clin Immunol*. 2017;13(5);425-437. Simpson E, et al. *N Engl J Med*. 2016;375;2335-2348. Wenzel S, et al. *Lancet*. 2016;388;31-44. Bachert C, et al. *JAMA*. 2016;315(5);469-479.

DUPILUMAB EOE PHASE 2 TRIAL

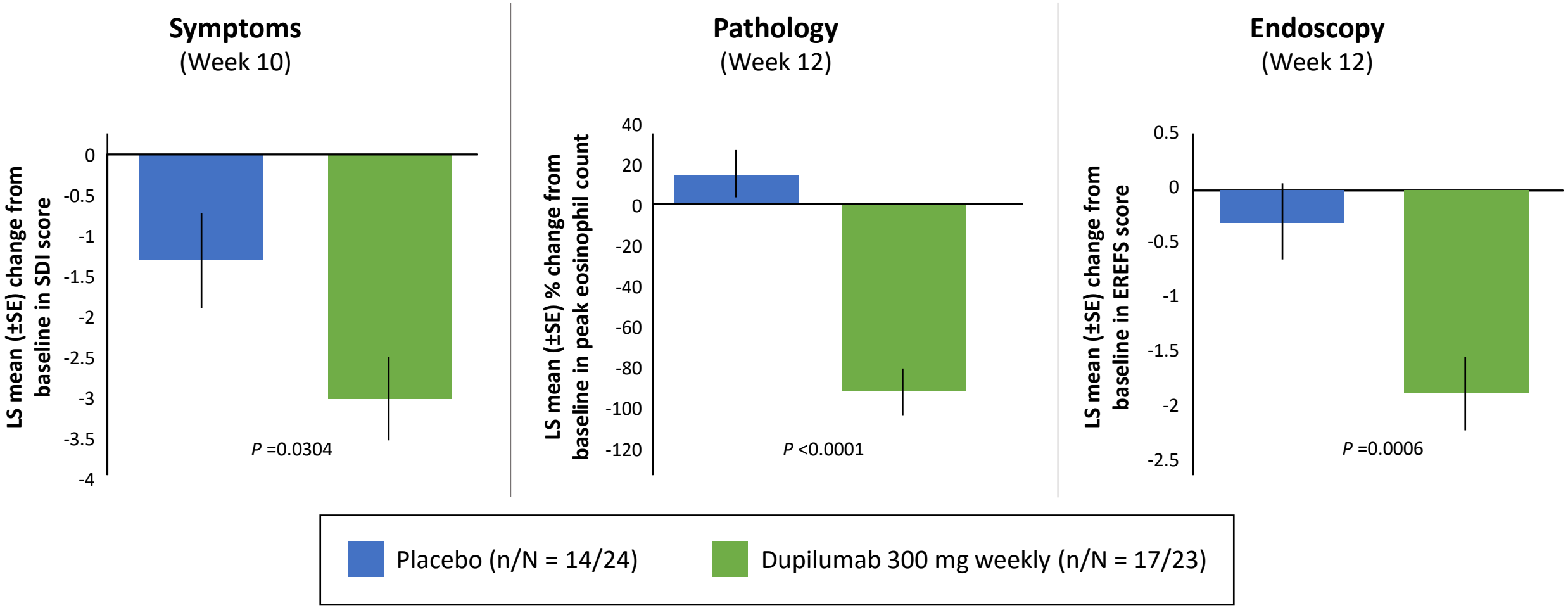
Phase 2, multicenter, double-blind, randomized, placebo-controlled study in 47 adults with active EoE



mAB, monoclonal antibody; SC, subcutaneous; wk, week.

Hirano I, et al. *Gastroenterology*. 2020;158:111–122

DUPILUMAB PHASE 2 STUDY IN ADULTS WITH EoE: REDUCED DYSPHAGIA, EOE, AND ENDOSCOPIC ACTIVITY



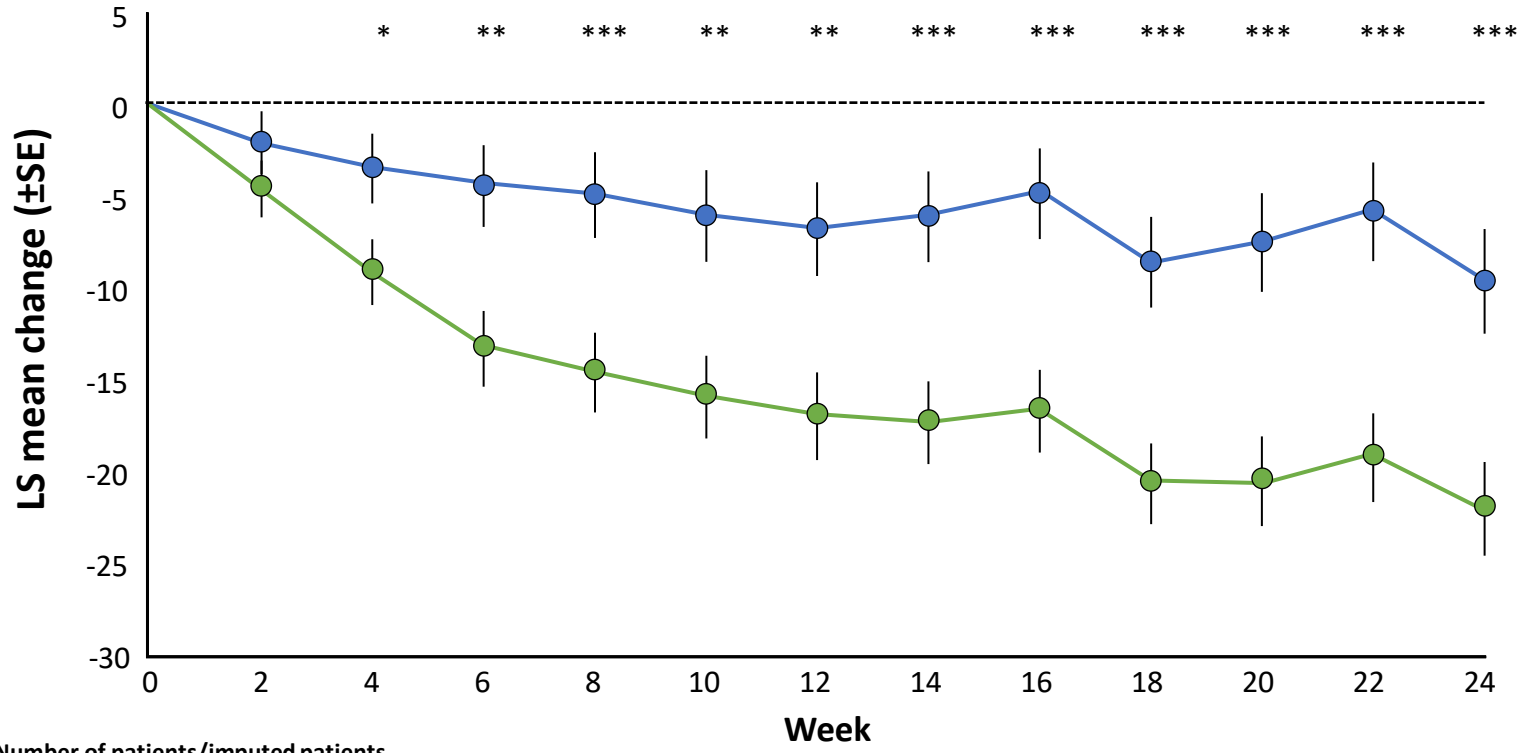
Hirano I, et al. *Gastroenterology*. 2020;158:111–122.

INTEGRITY CONTINUING EDUCATION

DUPILUMAB PHASE 3 STUDY: PART A RANDOMIZED TRIAL

Coprimary endpoints: Dupilumab significantly reduced dysphagia and intraepithelial eosinophil counts at Wk 24 (n=81)

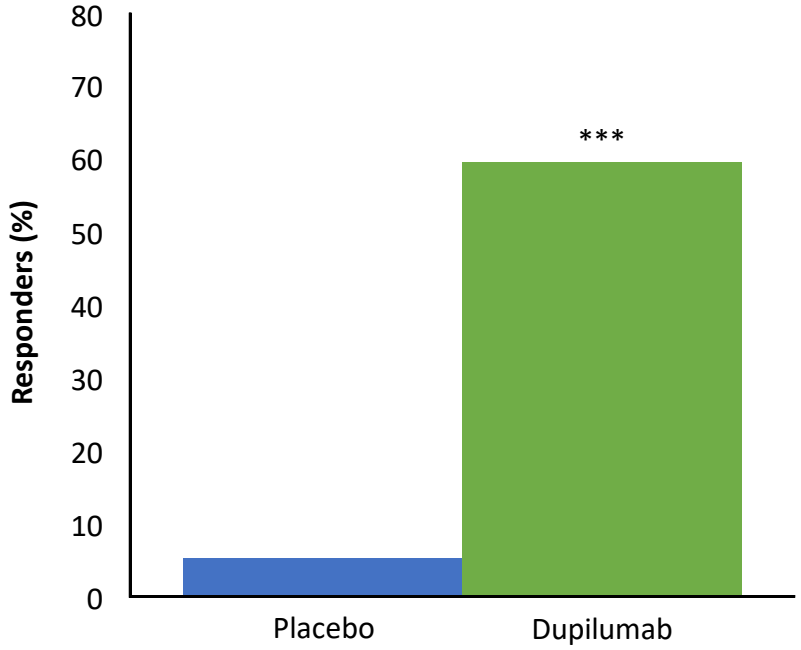
Absolute change in DSQ total score from baseline



Number of patients/imputed patients

Placebo	39/0	37/2	35/4	33/6	34/5	33/6	33/6	30/9	27/12	29/10	29/10	26/13	28/11
Dupilumab	42/0	42/0	42/0	40/2	41/1	41/1	40/2	40/2	37/5	38/4	38/4	38/4	38/4

Proportion of patients achieving peak esophageal intraepithelial eosinophil counts of ≤6 eos/hpf at Wk 24



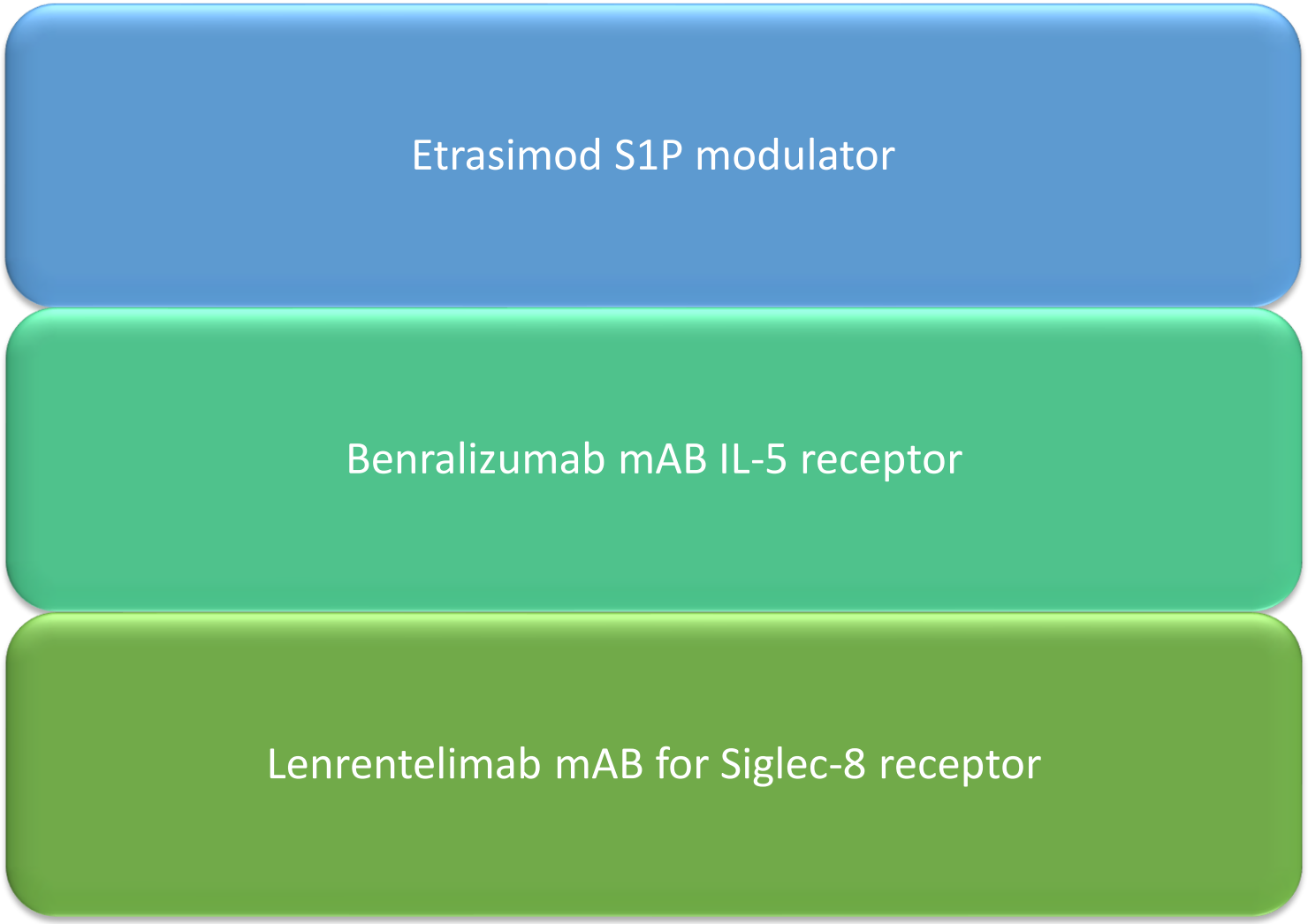
Number of patients	39	42
Number of responders (%)	2 (5.1)	25 (59.5)

Placebo Dupilumab 300 mg qw

*P<0.05, ** P<0.01; *** P<0.001.

Dellon et al. Am College of Gastro Annual Meeting Oct 2020.

ADDITIONAL AGENTS UNDER INVESTIGATION



S1P, sphingosine 1-phosphate.

Hirano I, Chan ES, Rank MA, et al. *Ann Allergy Asthma Immunol*. 2020;124(5):416-423.

A PATIENT-CENTRIC APPROACH TO OPTIMIZE OUTCOMES

COMPLEX UNMET NEEDS & UNIQUE BARRIERS

Survey of adult EGID patients and adult caregivers of children (<18 years) with EGIDs (88% with EoE)

- Medical domain: Only 19% reported that repeated endoscopies to monitor treatment response was convenient
- Healthcare domain: 67% indicated lack of insurance coverage for elemental formula as a barrier
- Social domain: Only 5% reported adequate awareness of EGIDs in schools
- Emotional domain: 64% had experienced significant stress due to EGID related out-of-pocket costs

EGID, eosinophilic gastrointestinal disease.

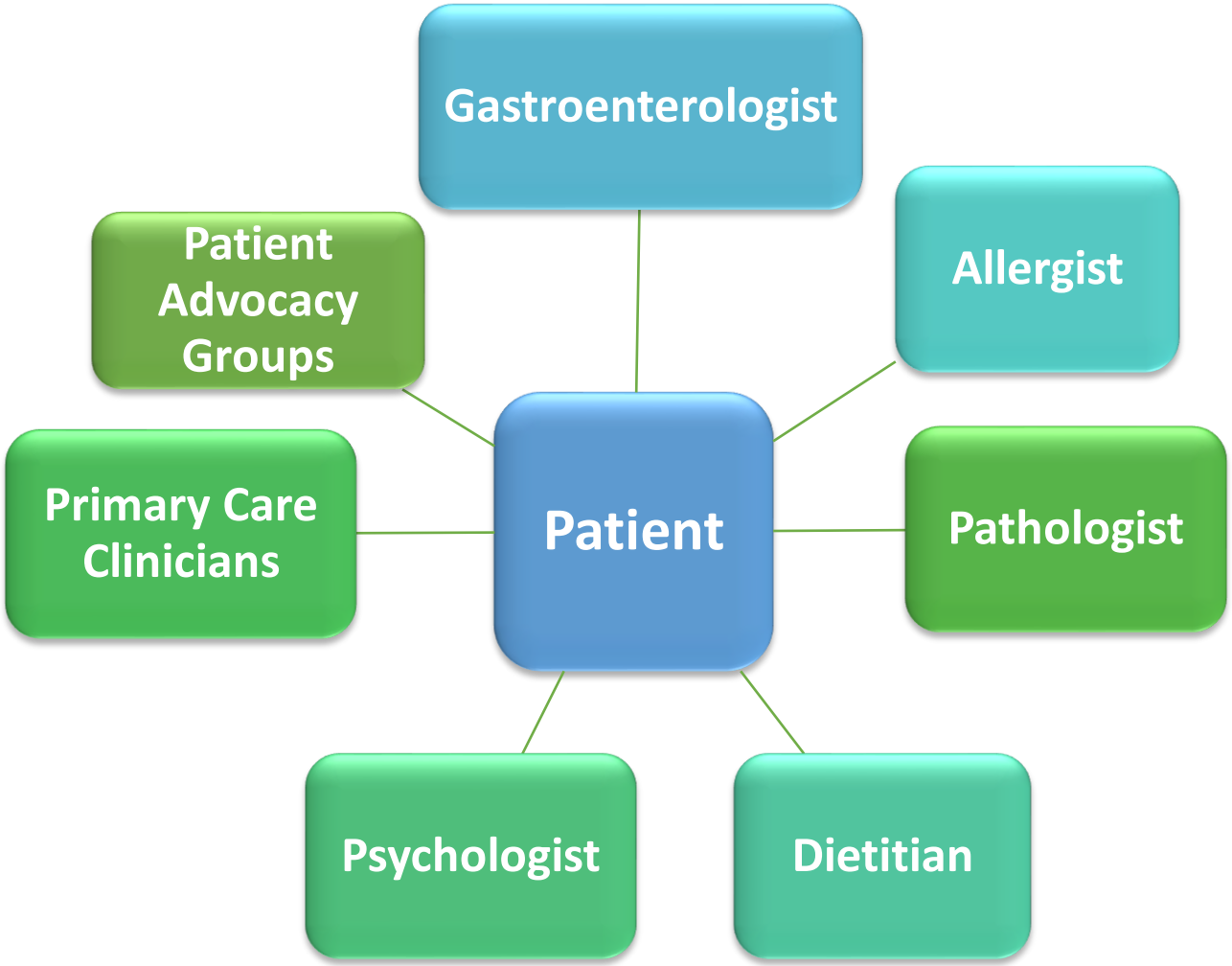
Hiremath G, et al. *Clin Res Hepatol Gastroenterol*. 2018;42:483-493.

IMPROVING ADHERENCE AND OUTCOMES THROUGH A PATIENT-CENTRIC APPROACH

Dellon ES. *Ann Allergy Asthma Immunol*. 2019;123(2):166-172. doi:10.1016/j.anai.2019.04.010.

INTEGRITY CONTINUING EDUCATION

COLLABORATIVE CARE OF PATIENTS WITH EoE



Lucendo AI, Molina-Infante J, Arias A, et al. *United European Gastroenterol J*. 2017;5(3):335-358. Dellon ES, Jones PD, Martin NB, et al. *Dis Esophagus*. 2013;26(1):7-13. Hirano I. *Gastroenterology.* 2018;155:601-606.

PATIENT CASE STUDY:

AN INTERACTIVE PATHOPHYSIOLOGY PUZZLE ACTIVITY

PUZZLE GAME INSTRUCTIONS

- You will now be taken to the interactive portion of the program
- The goal of this game is to earn puzzle pieces to build a 3D pathophysiology model of the EoE Pathway
- You will be given the opportunity to answer 4 case study-related questions

CASE PATIENT: BACKGROUND

Cheryl is a 28-year-old female patient who presents with eating concerns at a gastroenterologist practice. She complains of painful and difficult swallowing with food occasionally getting stuck in her throat. Recently, she worries about eating on a daily basis and has been avoiding certain dry, dense foods like meat.

PUZZLE QUESTION 1: PATIENT EVALUATION

For our case patient, what type of diagnostic testing should be considered initially?

A. Upper endoscopy with biopsies of the esophagus

B. Barium swallow

C. Peripheral blood eosinophil count

D. Esophageal manometry

PUZZLE QUESTION 1: PATIENT EVALUATION

For our case patient, what type of diagnostic testing should be considered initially?

A. Upper endoscopy with biopsies of the esophagus

B. Barium swallow

C. Peripheral blood eosinophil count

D. Esophageal manometry

CASE PATIENT: EVALUATION OF SYMPTOMS AND DIAGNOSTIC TESTING

Our patient's endoscopic presentation of EoE reveals a mix of inflammatory and fibrotic features, without severe stricture. Her histologic findings show an eosinophil-predominant inflammation with a peak value of 21 eosinophils per hpf. You confirm a diagnosis of EoE.

Cheryl has avoided peanut and tree nuts since childhood due to a history of anaphylaxis to both. She has mild atopic dermatitis and asthma, but moderately severe seasonal allergic rhinitis. She is referred to an allergist.

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PUZZLE QUESTION 2: ALLERGY TESTING

What should the allergist test to?

A. Panel of foods

B. Milk, egg, soy, wheat

C. Peanut and tree nuts

D. Peanut, tree nuts, and environmental allergens

PUZZLE QUESTION 2: ALLERGY TESTING

What should the allergist test to?

A. Panel of foods

B. Milk, egg, soy, wheat

C. Peanut and tree nuts

D. Peanut, tree nuts, and environmental allergens

CASE PATIENT: FURTHER EVALUATION OF SYMPTOMS AND DIAGNOSTIC TESTING

Our patient's allergy testing is positive to peanut, cashew, pistachio, hazelnut, walnut, pecan, tree pollen, and grass pollen.

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PUZZLE QUESTION 3: THERAPEUTIC OPTIONS

What therapeutic option is the least appropriate recommendation for Cheryl as she begins treatment of EoE?

A. Targeted dietary restrictions

B. Topical steroids

C. PPI 2x daily

D. Empiric 6 food elimination

PUZZLE QUESTION 3: THERAPEUTIC OPTIONS

What therapeutic option is the least appropriate recommendation for Cheryl as she begins treatment of EoE?

A. Targeted dietary restrictions

B. Topical steroids

C. PPI 2x daily

D. Empiric 6 food elimination

CASE PATIENT: THERAPEUTIC MANAGEMENT

Cheryl becomes nonadherent to topical steroids and experiences continued symptoms, with biopsy counts being persistently ≥ 15 eos/hpf.

PUZZLE QUESTION 4: CONTINUED DISEASE MANAGEMENT

What treatment and/or diagnostic option do you recommend to move forward with the management of EoE for our patient?

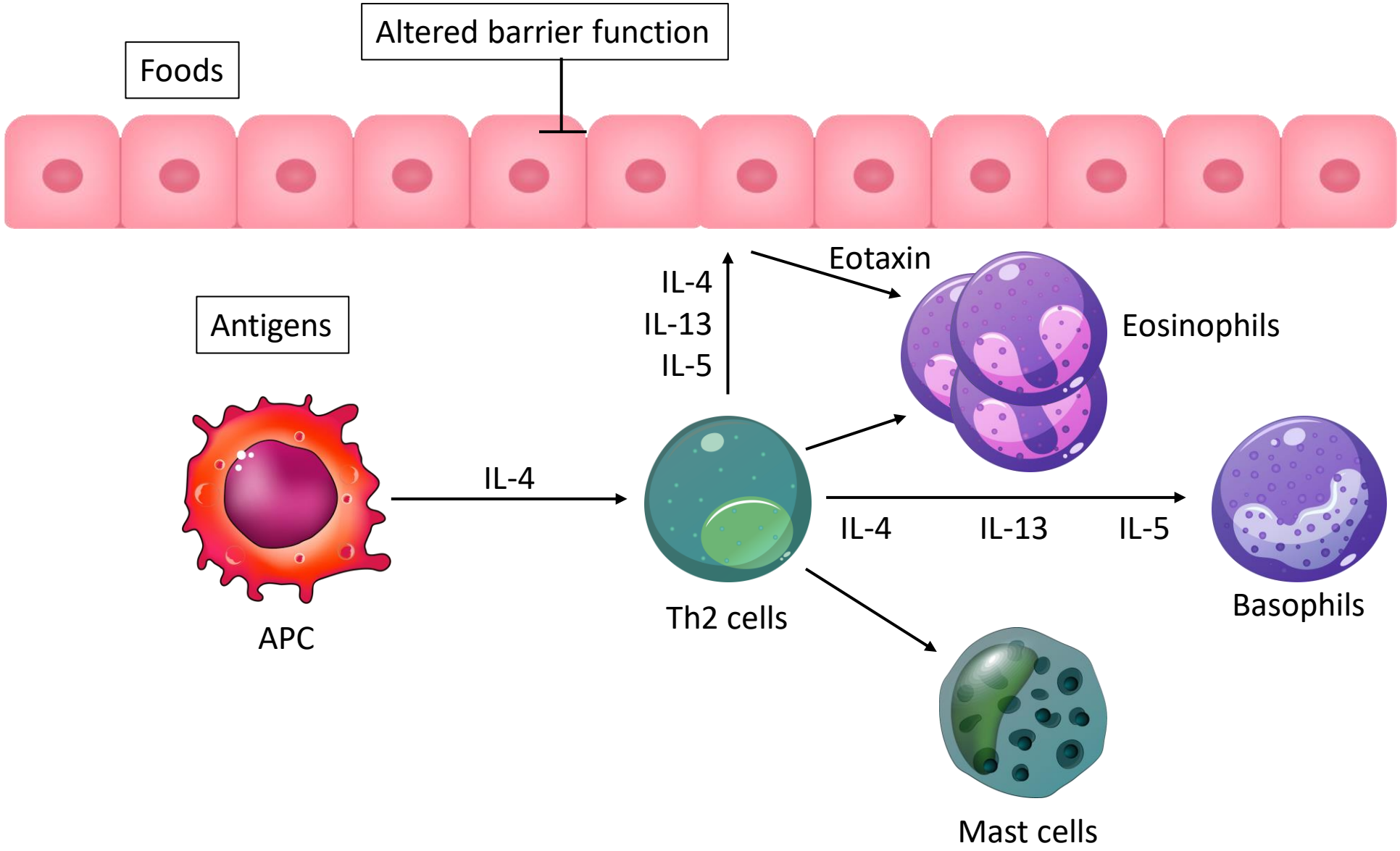
A. Repeat biopsies
B. PPI
C. Dietary eliminations
D. B & C
E. A &C

PUZZLE QUESTION 4: CONTINUED DISEASE MANAGEMENT

What treatment and/or diagnostic option do you recommend to move forward with the management of EoE for our patient?

A. Repeat biopsies
B. PPI
C. Dietary eliminations
D. B & C
E. A &C

PATHOPHYSIOLOGY PUZZLE IMAGE (SLIDE NOT SHOWN, FOR PUZZLE ONLY)



CASE PATIENT SUMMARY

PROGRAM SUMMARY

PROGRAM SUMMARY

- EoE is associated with a large healthcare burden, poor QoL, and rising incidence
- Currently available approaches are limited by lack of FDA approval, poor compliance with long-term use and variable effectiveness
- Although guidelines have been updated to direct the diagnosis, treatment, and management of EoE, current clinical practice remains highly variable and heterogeneous, precipitating dissatisfaction with therapy and poor outcomes
- Biologic agents are expected to overcome several important barriers to currently available treatment of EoE
- HCPs (gastroenterologists, allergists, immunologists, pediatric gastroenterologists, pediatric allergists/immunologists, and specialty NPs/PAs) who care for patients with EoE should be familiar with recent evidence and best-practice approaches to optimize therapeutic management and improve outcomes

THANK YOU!