Wheat Allergy

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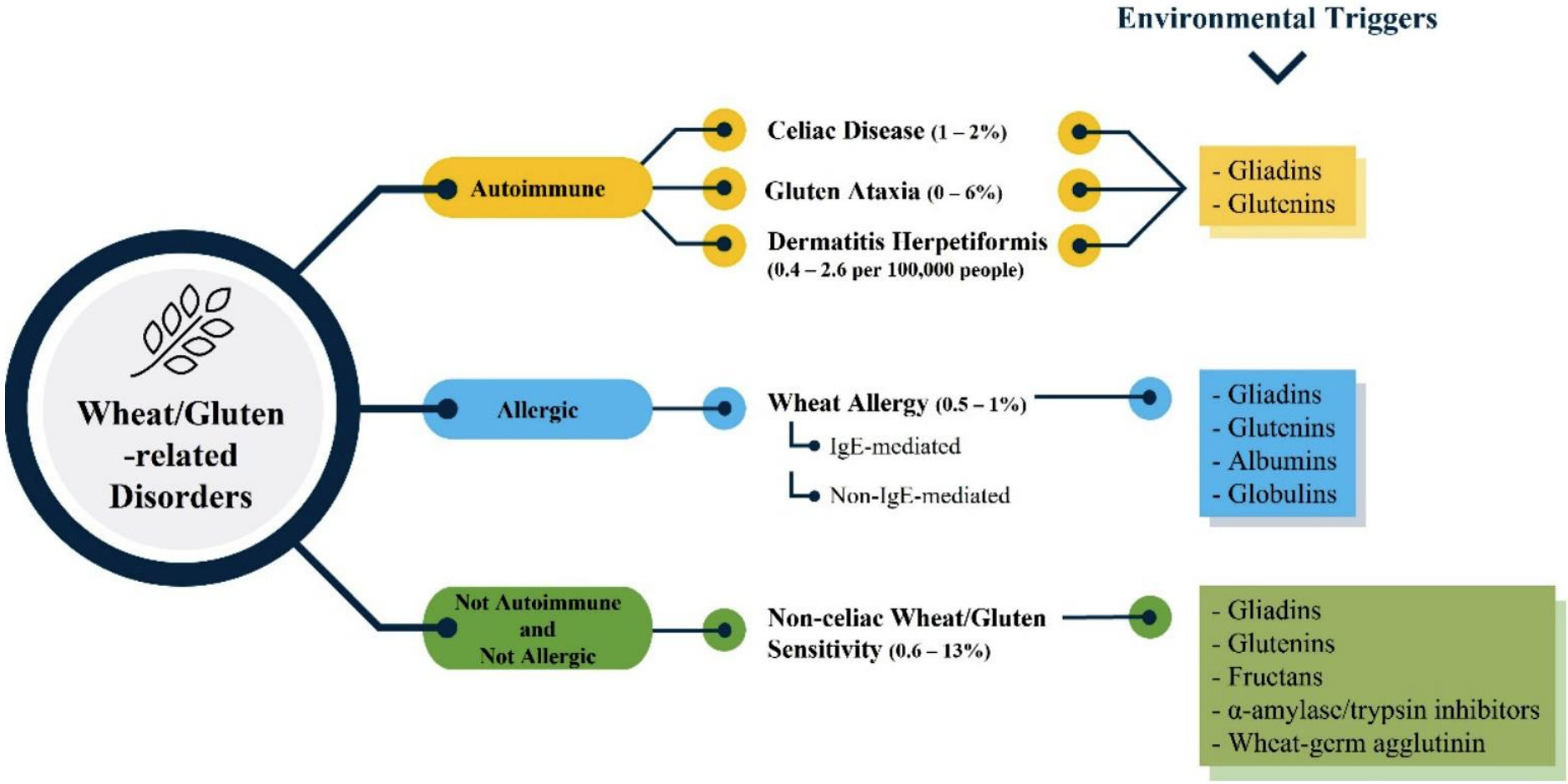
Wheat related diseases



Foods 2021, *10*, 1765.

Wheat allergy

IgE-mediated

Generalized: anaphylaxis, WDEIA

Gastrointestinal: GI anaphylaxis, pollen-related WA

Cutaneous: urticaria, angioedema, contact urticaria

Respiratory: Baker's asthma, rhinitis

Non-IgE mediated

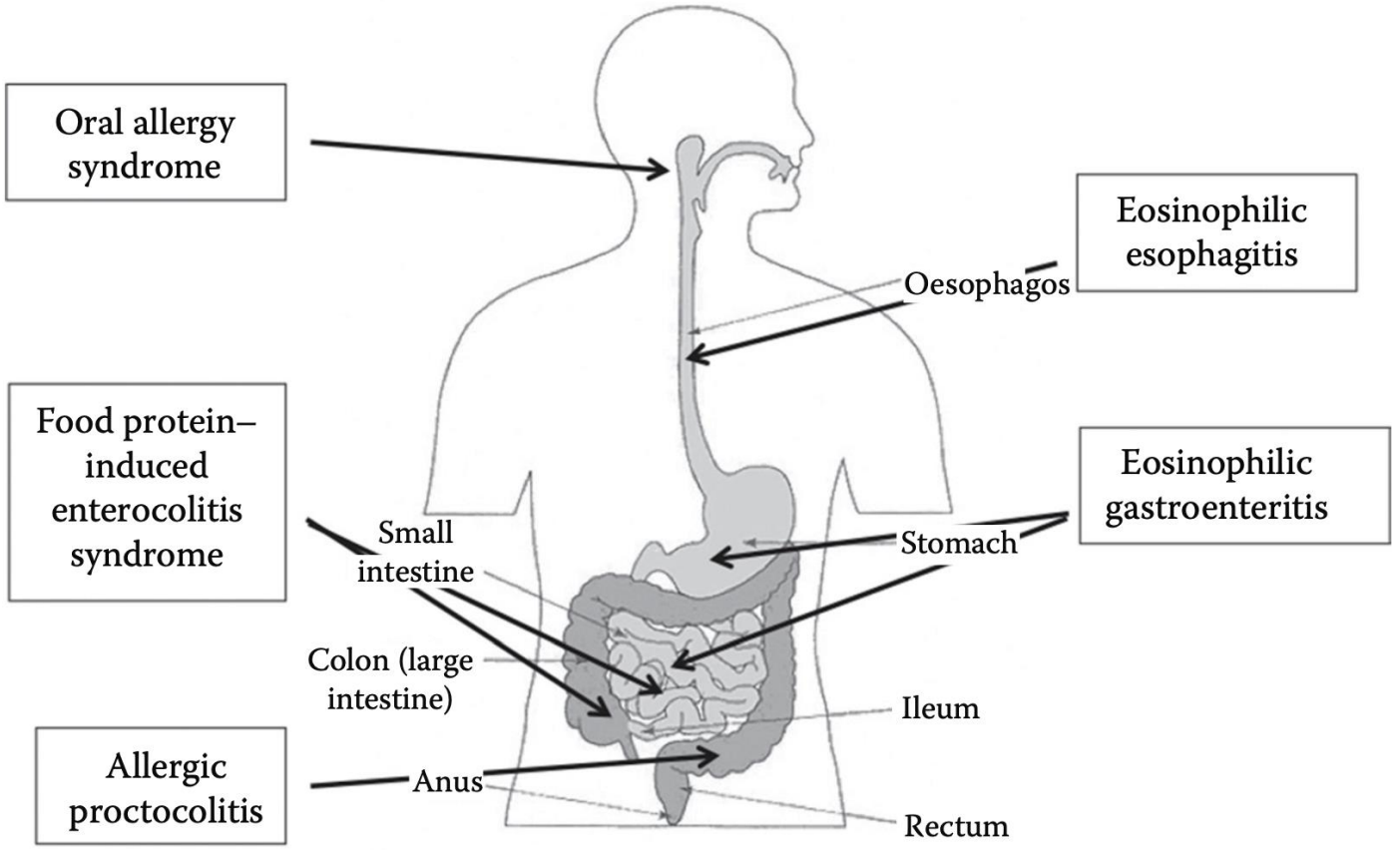
GI: FPIES, proctocolitis, CD, EoE, EG

Cutaneous: Atopic dermatitis

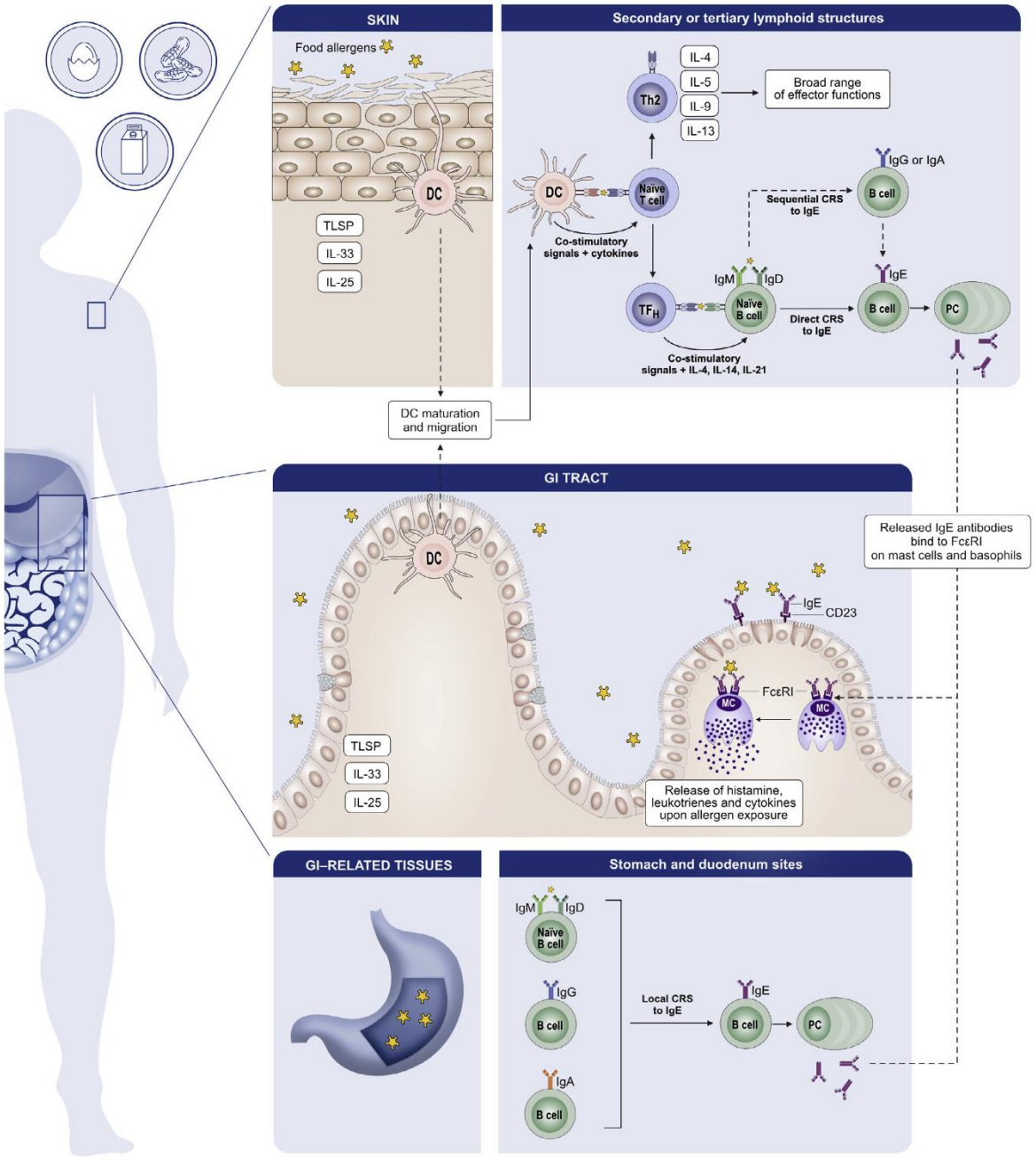
Respiratory: asthma



Gastrointestinal wheat allergies



Mechanisms of allergic sensitization



Allergy. 2021;76:1707–1717.

Prevalence of Wheat Allergy:

A meta-analysis including 56 studies

Sensitization vs Clinical allergy

- Self-reported: 0.63%
- Self-reported physician-diagnosed: 0.70%
- Skin prick test positive to wheat allergens: 0.22%
- sIgE positive to wheat allergens: 0.97%
- Food-challenge confirmed: 0.04%

Nutrients 2023, 15, 1564

Phylogenetics of allergenic grasses



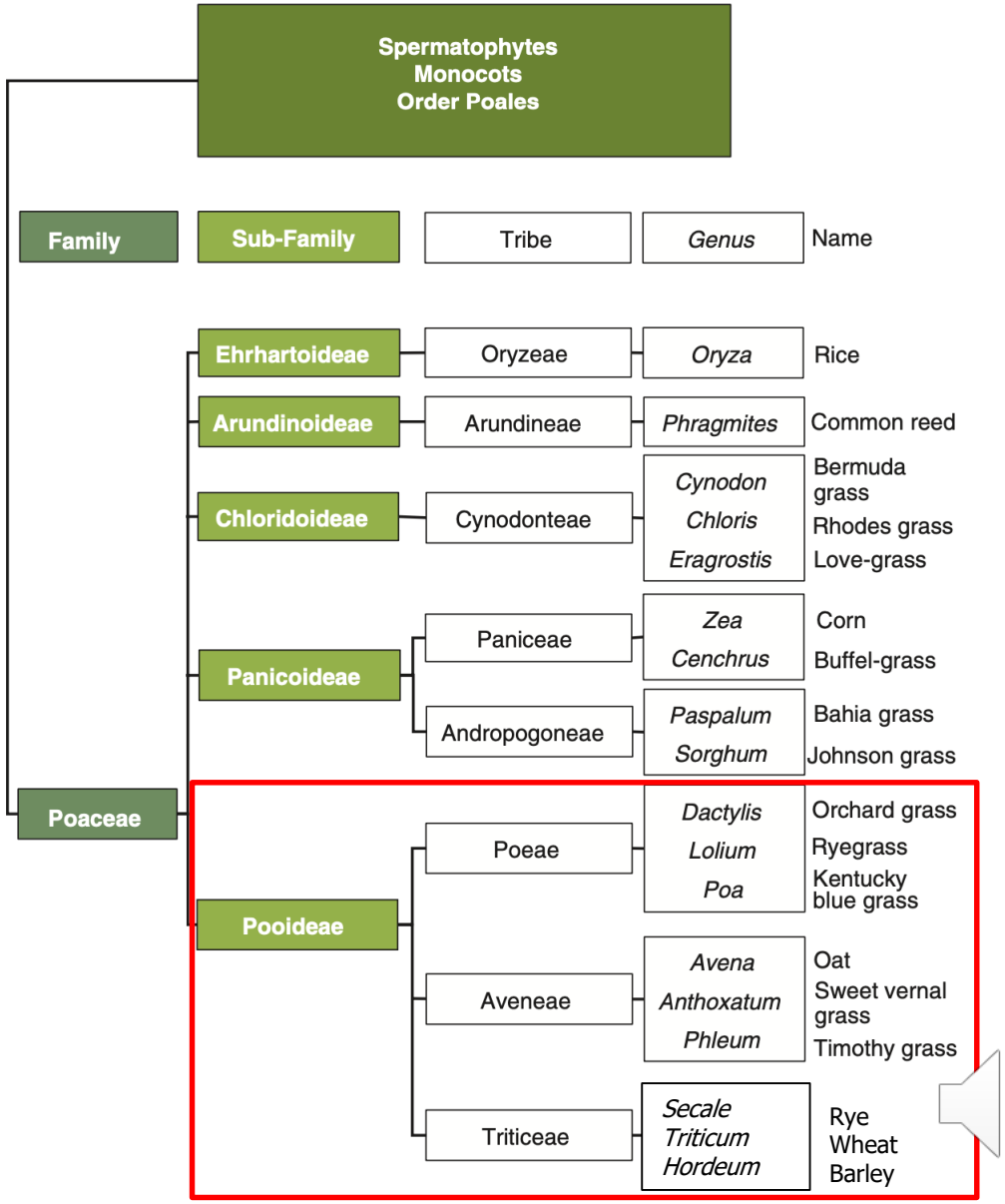
Timothy



Sweet vernal

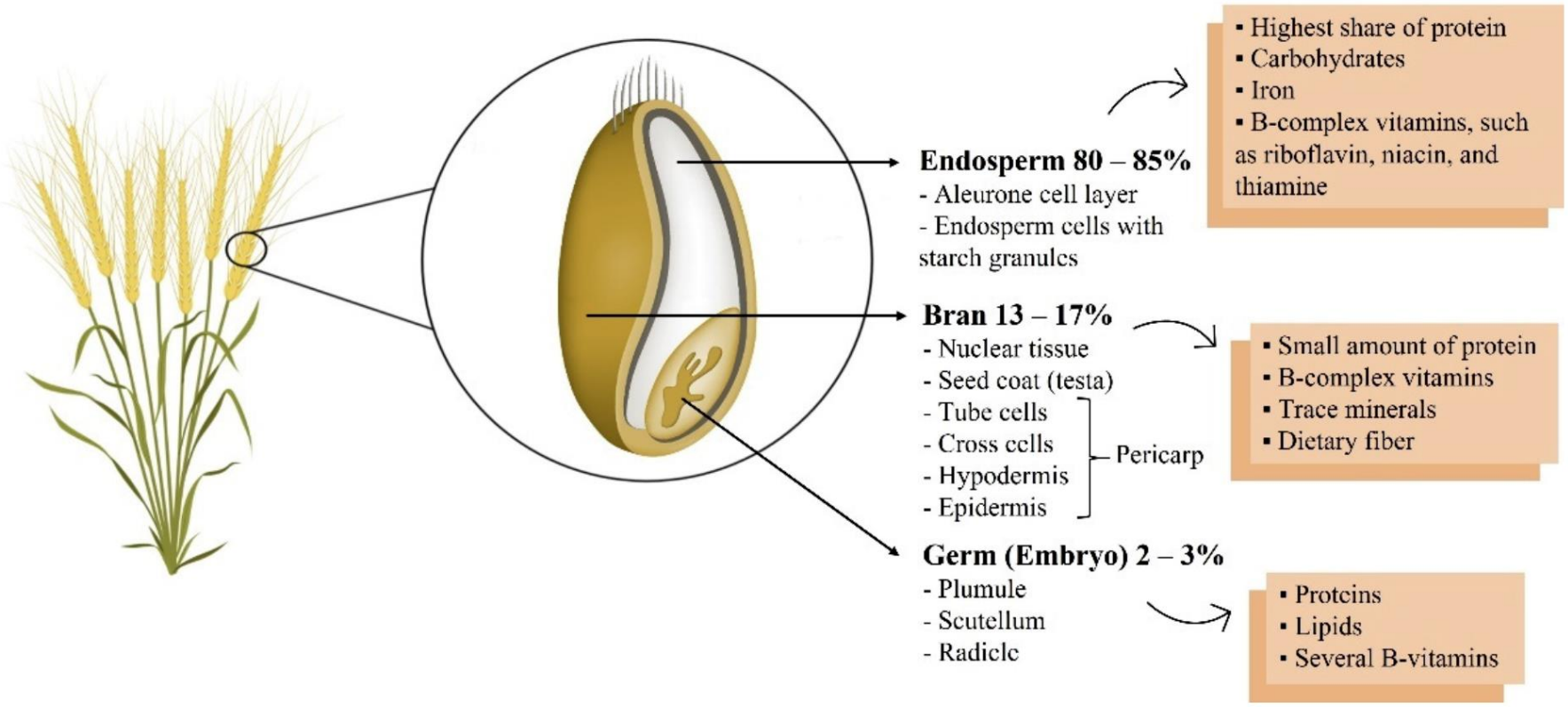


Ryegrass



Wheat grain constitution

Triticum aestivum



Foods 2021, *10*, 1765.

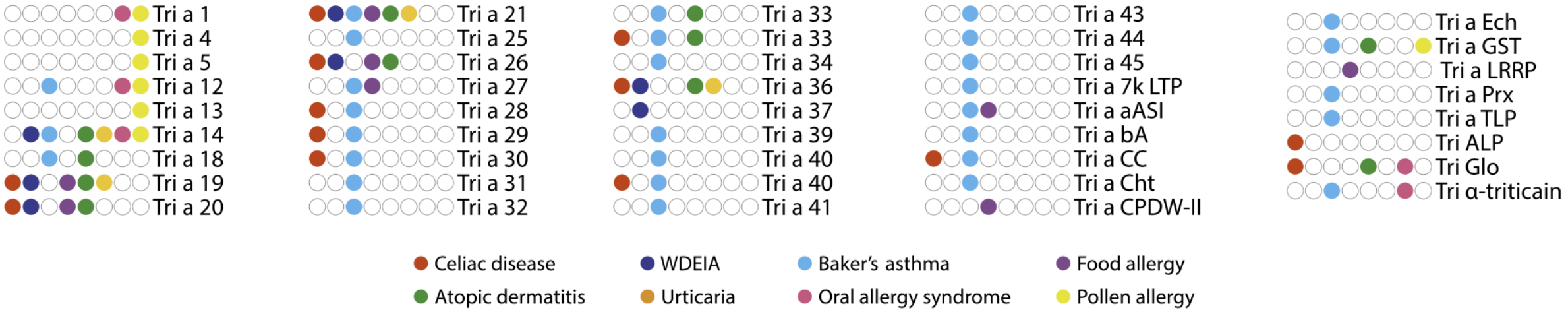
Wheat protein allergens

Triticum aestivum



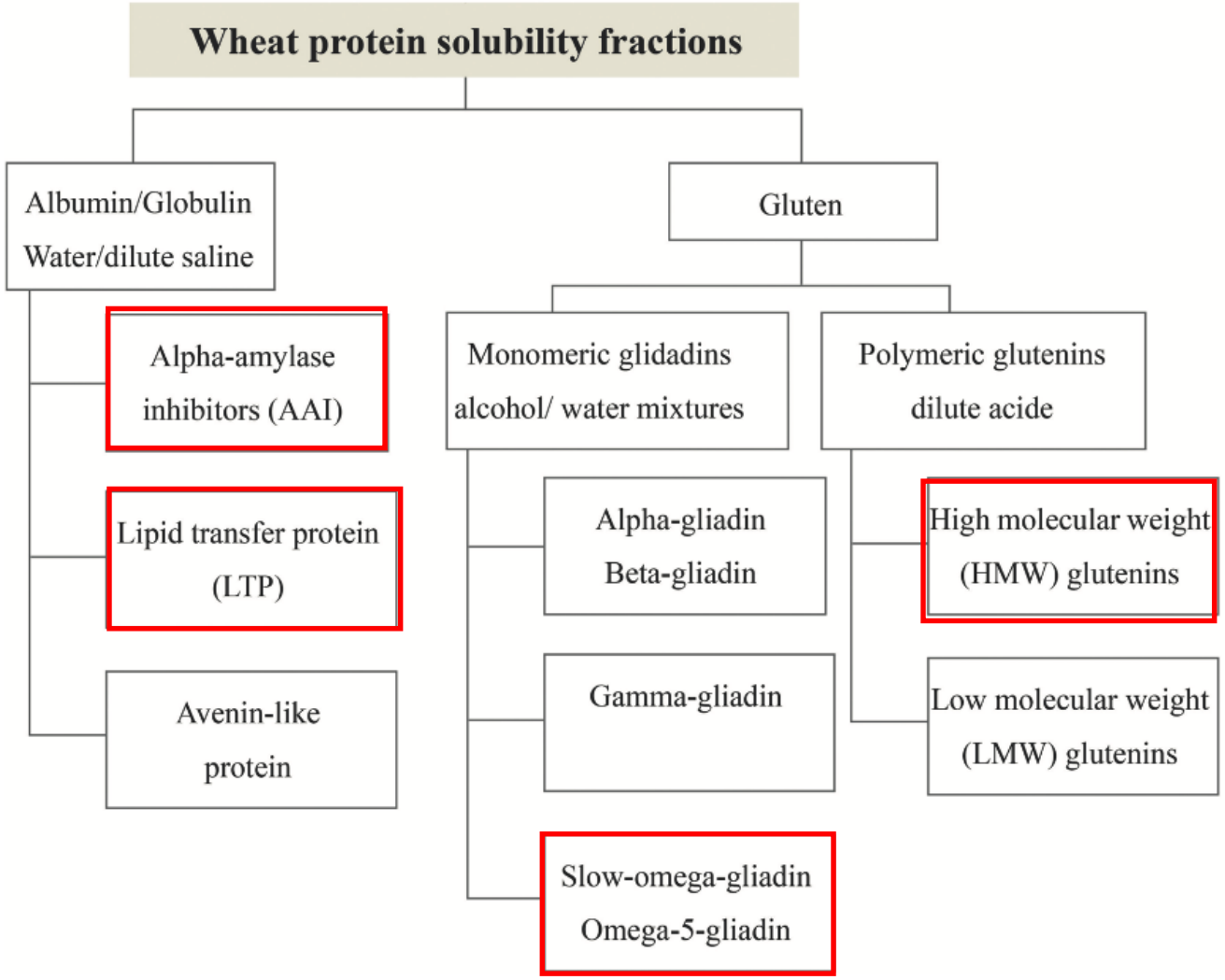
Species	Allergen	Biochemical name	MW(SDS-PAGE)	Route of Allergen Exposure	Date Created	Modified Date
Triticum aestivum (Wheat)						
	Tri a 12	Profilin	14 kDa	Food	25-03-2003	2019-09-27
	Tri a 14	Non-specific lipid transfer protein 1 (nsLTP-1)	9 kDa	Airway	18-02-2007	2023-09-19
	Tri a 15	Monomeric alpha-amylase inhibitor 0.28		Airway	07-04-2011	2019-09-27
	Tri a 17	beta-amylase	56 kDa	Food	10-09-2018	2019-09-27
	Tri a 18	Agglutinin isolectin 1		Food	06-03-2003	2010-04-29
	Tri a 19	Omega-5 gliadin	65 kDa	Food	06-03-2003	2023-09-19
	Tri a 20	Gamma gliadin	35 to 38 kDa	Food	02-07-2014	2023-09-21
	Tri a 21	Alpha/beta gliadin		Airway	07-04-2011	2023-09-21
	Tri a 25	Thioredoxin		Food	13-10-2006	2019-09-27
	Tri a 26	High molecular weight glutenin	88 kDa	Food	13-10-2006	2019-09-27
	Tri a 27	Thiol reductase homologue	27 kDa	Airway	15-10-2009	2021-12-12
	Tri a 28	Dimeric alpha-amylase inhibitor 0.19	13 kDa	Airway	15-10-2009	2021-12-12
	Tri a 29	Tetrameric alpha-amylase inhibitor CM1/CM2	13 kDa	Airway	15-10-2009	2020-05-12
	Tri a 30	Tetrameric alpha-amylase inhibitor CM3	16 kDa	Airway	15-10-2009	2020-05-12
	Tri a 31	Triosephosphate-isomerase		Airway	07-04-2011	2020-05-12
	Tri a 32	1-cys-peroxiredoxin		Airway	07-04-2011	2020-05-12
	Tri a 33	Serpin		Airway	07-04-2011	2020-05-12
	Tri a 34	Glyceraldehyde-3-phosphate-dehydrogenase		Airway	07-04-2011	2020-05-12
	Tri a 35	Dehydrin		Airway	07-04-2011	2020-05-12
	Tri a 36	Low molecular weight glutenin	40 kDa	Food	23-05-2011	2023-09-21
	Tri a 37	Alpha purothionin	12 kDa	Food	08-11-2011	2019-09-27
	Tri a 39	Serine protease inhibitor-like protein		Airway	09-01-2013	2019-09-27
	Tri a 40	Tetrameric alpha-amylase inhibitor CM17	15.96 kDa	Airway	07-08-2015	2023-09-19
	Tri a 41	Mitochondrial ubiquitin ligase activator of NFKB 1 (fragment)		Airway	23-09-2015	2023-09-21
	Tri a 42	Tapetum determinant 1 (TPD1) fragment		Airway	23-09-2015	2023-09-21
	Tri a 43	Transcriptional corepressor SCAI	12 kDa	Airway	23-09-2015	2023-09-21
	Tri a 44	Endosperm transfer cell specific PR60 (nsLTP-like protein)	10 kDa	Airway	23-09-2015	2023-09-21
	Tri a 45	Transcription elongation factor 1 (EIF1)	10 kDa	Airway	23-09-2015	2023-09-21

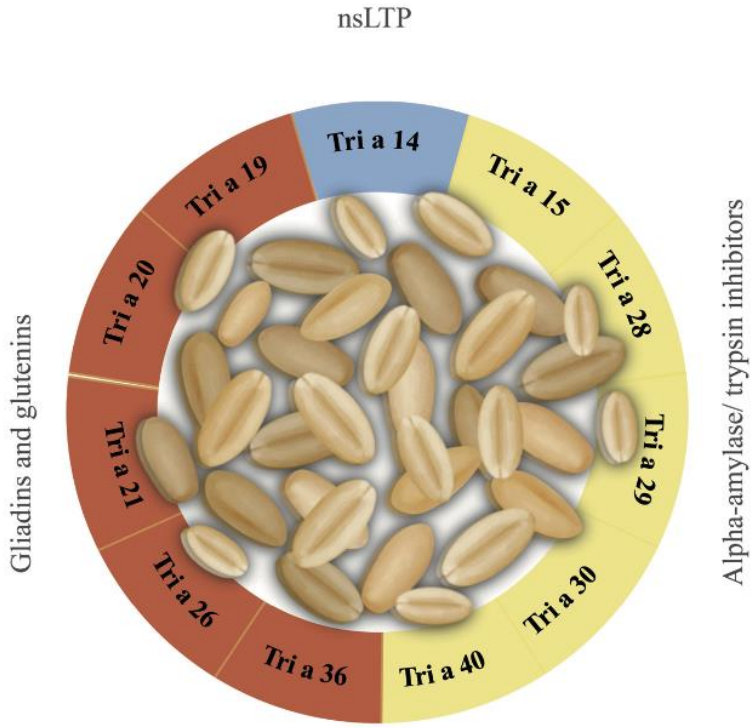
Reference allergen map of bread wheat :
disease associations



Sci. Adv. 2018; **4** : eaar8602

Wheat allergens grouped according to their solubility





Pediatr Allergy Immunol. 2023 Mar:34 Suppl 28:e13854.

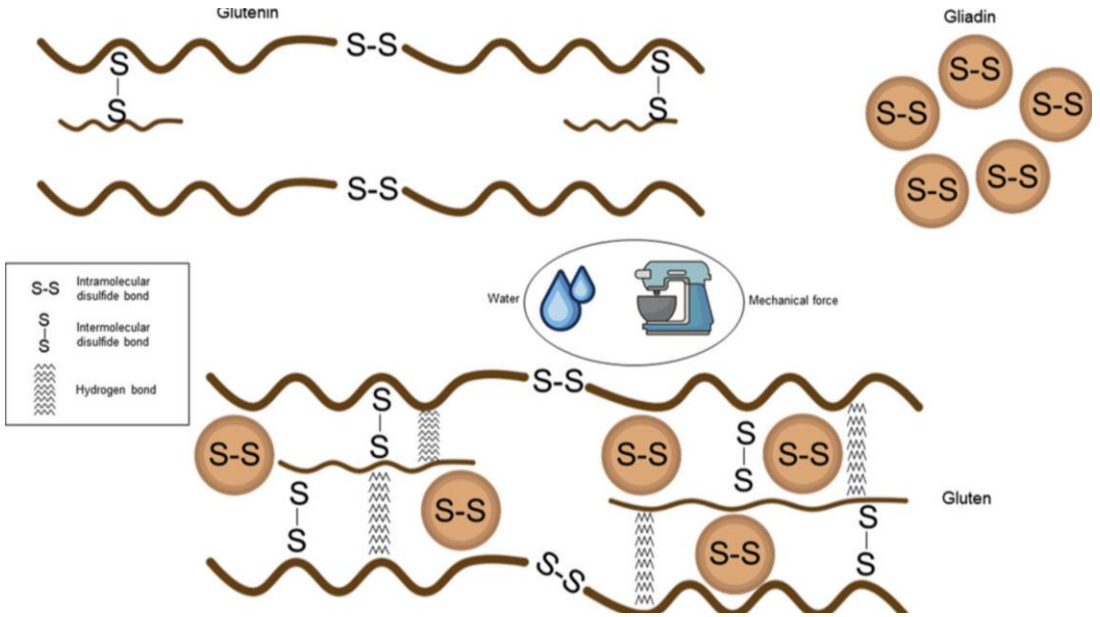
Albumin/Globulins (Water/dilute saline)

- α-amylase/trypsin inhibitor (ATI): Tri a 15, 28, 29, 30, 40
  - Prolamin superfamily
  - Natural defense against pests and pathogens
  - Can trigger the innate immune system
  - Baker's asthma, and immediate-type allergy

- Lipid transfer protein (LTP): Tri a 14
  - Prolamin superfamily
  - Natural defense against pests and pathogens
  - Baker's asthma, and immediate-type allergy

- α-purothionin: Tri a 37
  - A plant toxin
  - IgG/IgE can differentiate sensitization and true allergy (highly specific)
  - Wheat-induced anaphylaxis

Water/salt insoluble proteins



- **Gluten** (Prolamin superfamily):
  - **Gliadin** (α/β/γ/ω):
    - ω–5 gliadin (Tri a 19)
      - Wheat induced anaphylaxis
      - Wheat-dependent exercise-induced anaphylaxis (WDEIA)
  - **Glutenin:**
    - LMW
    - HMW
      - Tri a 26
      - Wheat induced anaphylaxis
      - Wheat dependent exercise induced anaphylaxis (WDEIA)

Scenarios of IgE-mediated hypersensitivity

1. *Typical IgE-mediated form of food allergy*

-A 6-month-old girl developed wheezing and urticaria after introduction of wheat cereal.
-Her wheat skin prick test was 6 mm and her wheat specific IgE was 25 kUA/L.
-Wheat avoidance was instituted.
-At 18 months her wheat IgE was 48 kUA/L and continued wheat avoidance was recommended. She continued with yearly allergy follow-up to discuss entry to daycare and elementary school, as well as review of management of accidental exposures.
-At age 5 her wheat IgE level was 40 kUA/L. A wheat challenge was performed, which she passed with no reaction. Wheat was then successfully introduced into her diet.

This represents a typical case of wheat allergy: early onset with a high chance of resolution by school age, often with wheat-specific IgE levels that remain significantly elevated.

Scenarios of IgE-mediated hypersensitivity

1. *Typical IgE-mediated form of food allergy*

- Infancy
- within minutes to 1–2 h
- Cutaneous: urticaria, angioedema, erythema, pruritus,
- Gastrointestinal: vomiting, abdominal pain,
- Respiratory: persistent cough, hoarse voice, wheeze, stridor, respiratory distress, nasal congestion
- Anaphylaxis
- may be associated also with delayed-type symptoms, which include the worsening of atopic dermatitis

Scenarios of IgE-mediated hypersensitivity

2. *Wheat-dependent, exercise-induced anaphylaxis (WDEIA)*

-A 16-year-old young woman develops diffuse hives, difficulty breathing, and vomiting after completing the 400-meter sprint at her track and field competition.

-She has a history of asthma but has not had any recent exacerbations.

-She reports that she ate an "energy bar" before the competition started, which she has had many times before at school without any symptoms but never before a sports competition.

-What is the most likely diagnosis and how should she be treated and further evaluated?



Scenarios of IgE-mediated hypersensitivity

2. *Wheat-dependent, exercise-induced anaphylaxis (WDEIA)*

- Adolescents
- Intermittent urticaria, angioedema, and anaphylaxis
- When wheat is ingested less than 4 hours before or after occurrence or consumption of cofactors:
  - Exercise
  - NSAIDs
  - Alcohol
- ω–5 gliadin (Tri a 19)
- Lipid transfer protein (LTP):Tri a 14



Scenarios of IgE-mediated hypersensitivity

3. *Baker's allergy or asthma*

-A 30-year-old male cook who later studied to become pastry chef/ baker.

-After 2 years of working as a baker, the patient started experiencing nasal symptoms first from rye flour and later from wheat. No asthmatic symptoms at any time.

-Wheat IgE 2.1 kU/l, rye 0.8 kU/l. In SPT, whole-wheat extract 0 mm as were the other cereals.

-Chamber challenge with wheat flour induced nasal symptoms and also increase in nasal resistance (acoustic rhinomanometry).

-Occupational allergic rhinitis due to wheat and rye (baker's allergy).

-Primarily a respiration filter and change of the station in the kitchen. This did not help this patient enough, so she is considering to learn a new profession.

Scenarios of IgE-mediated hypersensitivity

3. *Baker's allergy or asthma*

- Adults (male)
- Comes from inhalation of the wheat flour
- The test allergen with most sensitivity but low specificity is whole-wheat flour
- CRD:
  - α-amylase/trypsin inhibitor (ATI):Tri a 15, 28, 29, 30, 40
  - Lipid transfer protein (LTP):Tri a 14

Scenarios of IgE-mediated hypersensitivity

4. *Contact Urticaria*

-a 24-year-old non-atopic beautician developed urticarial lesions on the hands shortly after application of an anti-ageing solution to a client's face



-SPT:
+ve: with the product and HWP
-ve: commercial extracts of wheat

Scenarios of IgE-mediated hypersensitivity

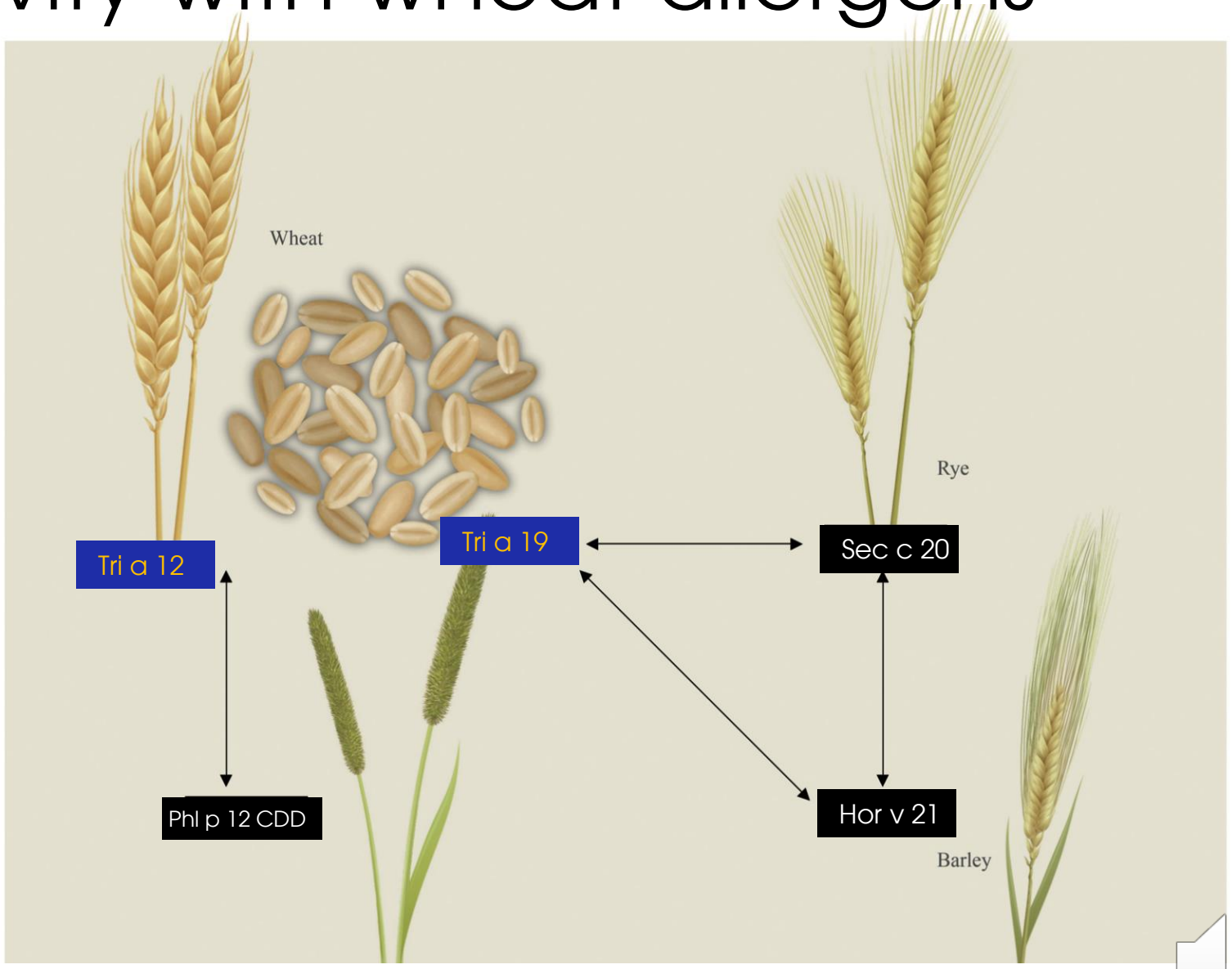
4. *Contact Urticaria*

- Use of cosmetics and also sometimes together with food allergy
- Exposure to hydrolyzed wheat protein
- Contact urticaria
- Even anaphylaxis

Cross-reactivity with wheat allergens

Most people with a wheat allergy (about 80%) can tolerate other grains, such as barley and rye

Half of wheat-allergic children reacted to barley. Omega-5 gliadin-sIgE predicts cross-reactive barley allergy in children allergic to wheat (95% positive predictive value for barley allergy was 4.6 kU_A /L)



Pediatr Allergy Immunol. 2022 Nov;33(11):e13878.
Pediatr Allergy Immunol. 2023 Mar;34 Suppl 28:e13854.

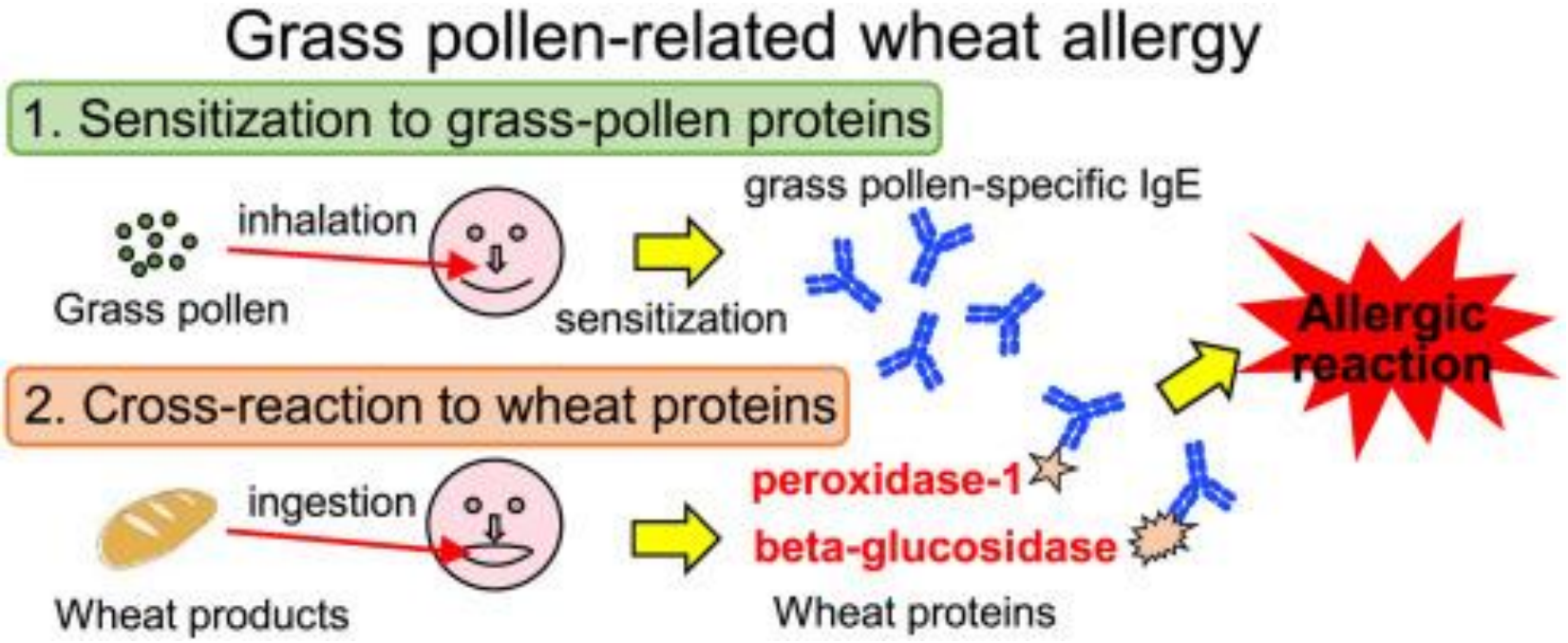
Grass pollen and wheat allergy

- **Cross-sensitization:**
  - 65% of patients with grass pollen allergy has positive results for wheat-specific IgE test
  - Tri a 12 and Phl p 12 cross-reaction (CCD)

- Grass pollen-related wheat allergy:
  - Urticaria, rhinitis, or anaphylaxis
  - Peroxidase-1 and beta-glucosidase

Grass pollen-related wheat allergy (GPWA)

Pollen Food Allergy Syndrome
Oral Allergy Syndrome



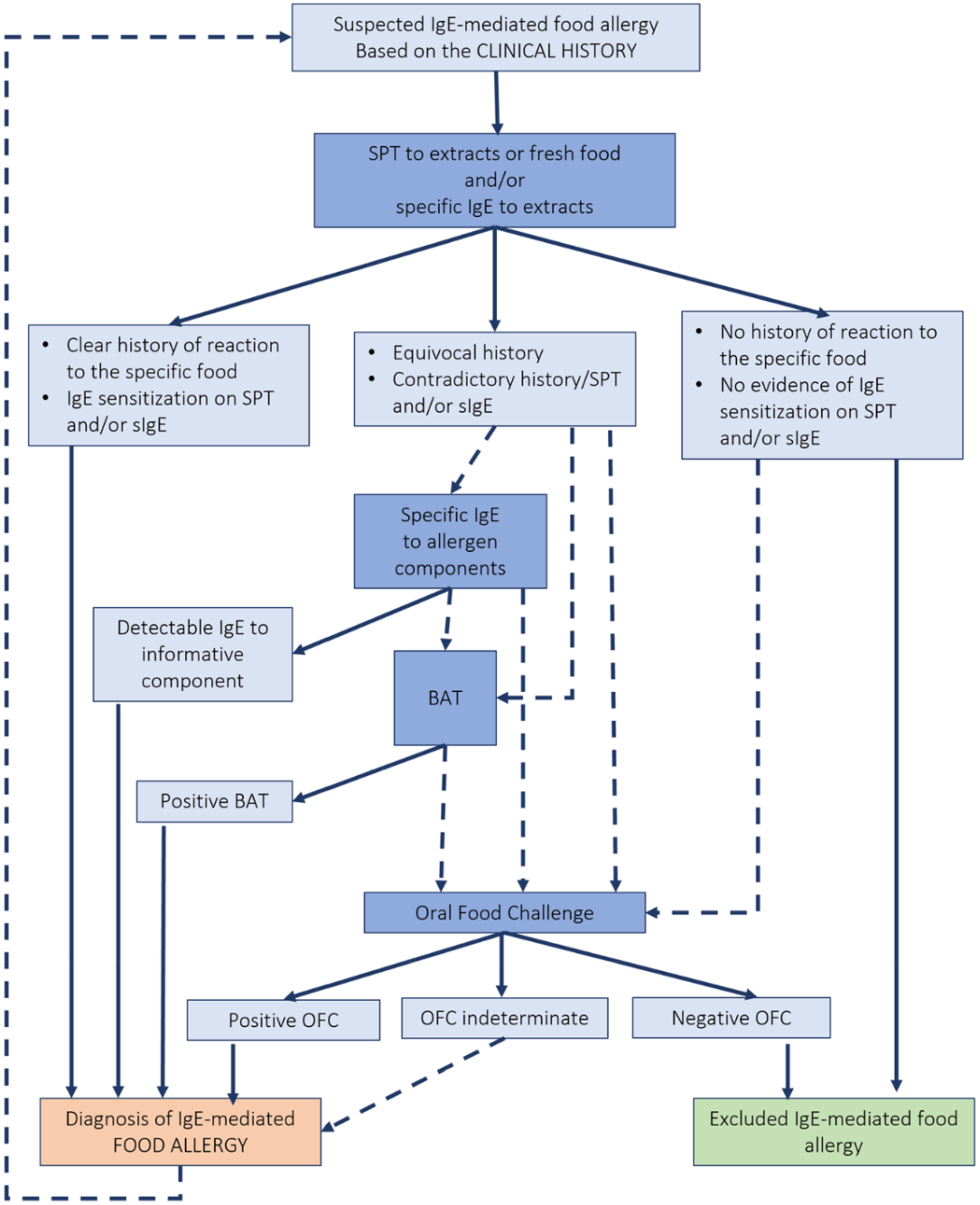
Allergology International 70 (2021) 215e222

Diagnosis of wheat allergy

- Clinical features
- Skin Prick Test (SPT)
- Specific IgE measurement
- Oral Food challenge (OFC)

IgE-mediated food allergy

EACCI guideline



Allergy. 2023;78:3057–3076.

Skin Prick Test

-Wheat sensitization is much more common than true clinical allergy

-Used extracts:

- Commercial wheat extract
- ω-5 gliadin (dissolved in ethanol, in-house preparation
- Hydrolyzed wheat protein (for contact urticaria)



Wheat specific IgE

- Whole wheat-specific IgE:
  - Low specificity
  - Common among atopic children without true food allergies
  - up to 65% of the patients with grass pollen allergy have false-positive IgE test
- ω–5 gliadin (Tri a 19)
- Lipid transfer protein (LTP):Tri a 14
- α-amylase/trypsin inhibitor (ATI):Tri a 15, 28, 29, 30, 40



Food-specific sIgE highly predictive of clinical reactivity

Allergen	Diagnostic Decision Level kU_A/L[a]	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Egg white[185]	7	61	95	98	38
Infants ≤2 yr[186]	0.35	91	77	95	68
Ovomucoid for baked egg[56]	10.8	55	96	88	80
Cow's milk[185]	15	57	94	95	53
Infants ≤1 yr[187]	5	30	99	95	64
Casein for baked milk[188]	20.2	30	95	69	78
Peanut[185]	14	57	99	99	36
Fish[185]	20	25	100	99	89
Soybean[185]	30	44	94	73	82
Wheat[185]	26	61	92	74	87
Tree nuts[189]	15	Other values were not calculated and are not available.		95	

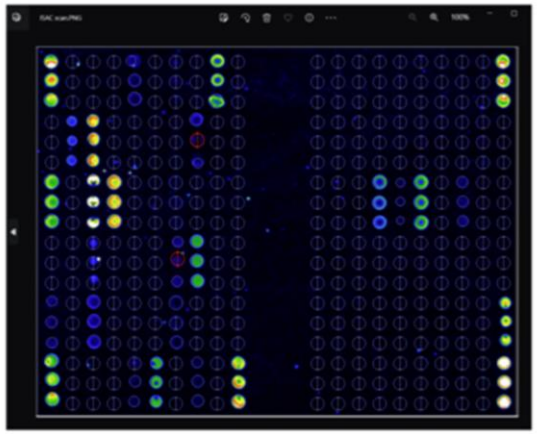
[a] kU_A/L = allergen-specific kilo units per liter.

Multiplex solid-phase immunoassays

A



B



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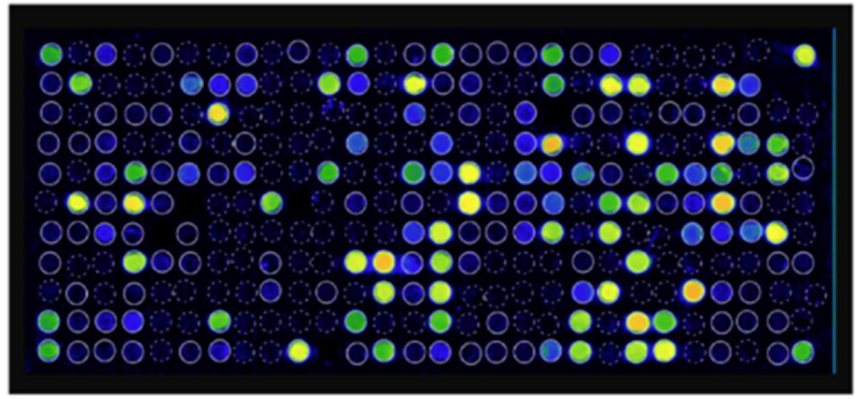
A



B



ALEX2

Oral food challenge (OFC)

BOX 2. An example of preparation for oral food challenge for IgE-mediated wheat allergy and calculation of doses consumed

1. Weigh* 10 g (2 teaspoons† = 10 mL) wheat flour.
2. Mix in 5 g (1 teaspoon = 5 mL) sugar.
3. Mix ingredients in applesauce for a total weight of 100‡ g (1/2 cup less 3 teaspoon or 115 mL).
4. Record timing, amount ingested, and any objective/subjective symptoms.

Cumulative dosing§:

Time (min)	% of total food	Amount of challenge food, g	Amount of wheat flour, g
00	0.1%	0.1	0.01
05	0.5%	0.5	0.05
20	1%	1	0.1
35	4%	4	0.4
50	10%	10	1
60	20%	20	2
70	20%	20	2
80	20%	20	2
90	24.4%	24.4	2.44
Total	100%	100 g	10 g

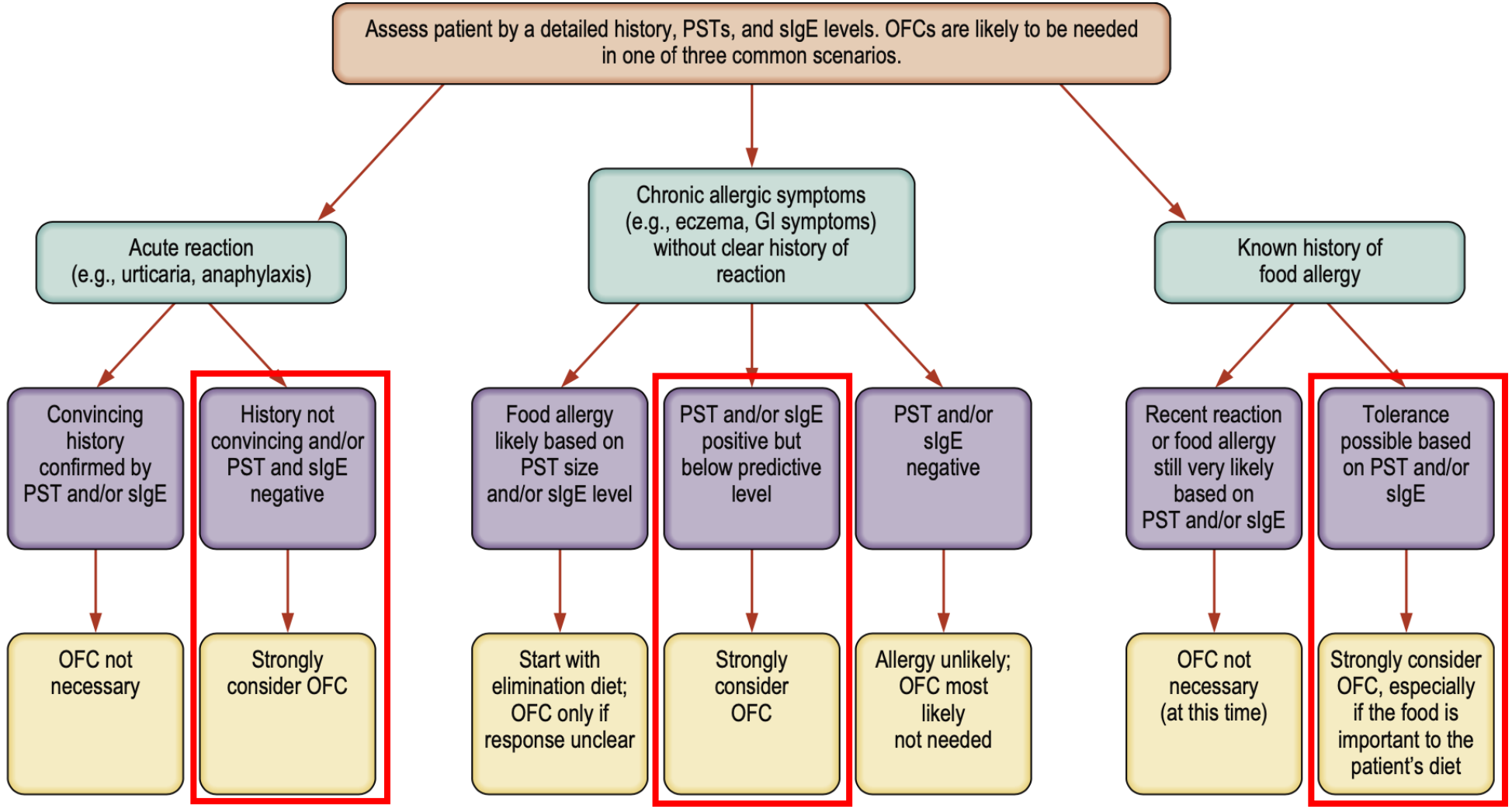
Indications for an OFC

- Identify foods causing acute reactions for initial diagnosis of food allergy and for monitoring resolution of food allergy
- Determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic esophagitis will cause immediate reactions
- Expand the diet in persons with multiple dietary restrictions, usually because of subjective complaints such as headaches or hyperactive behavior
- Assess the status of tolerance to cross-reactive foods
- Assess the effect of food processing on food tolerability, eg, fruits and vegetables that may be tolerated in cooked form in the pollen-food allergy syndrome

J Allergy Clin Immunol 2009;123:S365-83.



Oral food challenge (OFC)



Middleton E. Middleton's Allergy : Principles and Practice. Ninth. Elsevier; 2020.

Natural course of IgE-mediated Wheat allergy

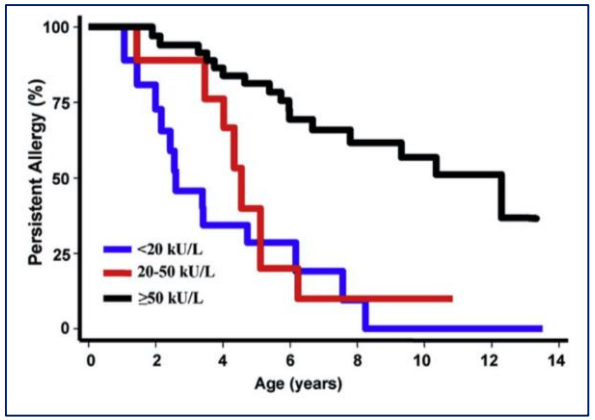
Food	Age or rates of resolution	Criteria for resolution	Study type, country	Year
Cow's milk	19% by 4 ears, 42% by 8 years, 64% by 12 years, and 79% by 16 years[25]	Passed OFC or sIgE <3 kU/L with no symptoms within 12 months	Retrospective, US	2007
	57.4% during 48- to 60-month follow-up[69]	Passed OFC or successful consumption history	Prospective, Israel	2012
	52.6% at a median age of 63 months[9]	Passed OFC or ingestion of uncooked milk products in serving size quantities	Observational cohort, USA	2013
	57% after 1 year from the diagnosis[32]	Passed OFC	Birth cohort, Europe	2015
	25% by 43 months, 50% by 104.8 months[33]	Passed OFC or successful consumption history	Retrospective, Korea	2020
	81.8% by 6 years[70]	Passed OFC or successful consumption history	Retrospective, Singapore	2022
Hen's egg	11% by 4 years, 41% by 8years, 65% by 12 years, 82% by 16 years[8]	Passed OFC or sIgE < 2 kU/L with no symptoms within 12 months	Retrospective, USA	2007
	49.3% at a median age of 74 months[71]	Passed OFC or ingestion of whole, concentrated egg products in serving size quantities	Observational cohort, USA	2014
	30% by 3 years, 59% by 5 years, and 73% by 6 years[35]	Passed OFC	Retrospective, Japan	2016
	83.9% by 4 years[26]	Passed OFC	Longitudinal cohort, Australia	2019
	25% by 46.7 months, 50% by 67.6 months[33]	Passed OFC or successful consumption history	Retrospective, Korea	2020
	14.6% by 7 years, 40.8% by 9 years, 60.5% by 12 years[a),36]	Passed OFC	Prospective, Japan	2022
	89% by 6 years[34]	Passed OFC or SPT < 3 mm or SPT 3–7 mm with successful consumption history	Longitudinal cohort, Australia	2022
Wheat	29% by 4 years, 56% by 8 years, 65% by 12 years[27]	Passed OFC or successful consumption history	Retrospective, USA	2009
	20% by 4 years, 52% by 8years, 66% by 12 years, 76% by 18 years[38]	Passed OFC	Prospective, Poland	2014
	14.7% at 2 years, 27% at 4 years, 45.7% at 5 years, 69% at 9 years[37]	Passed OFC	Prospective, Thailand	2017

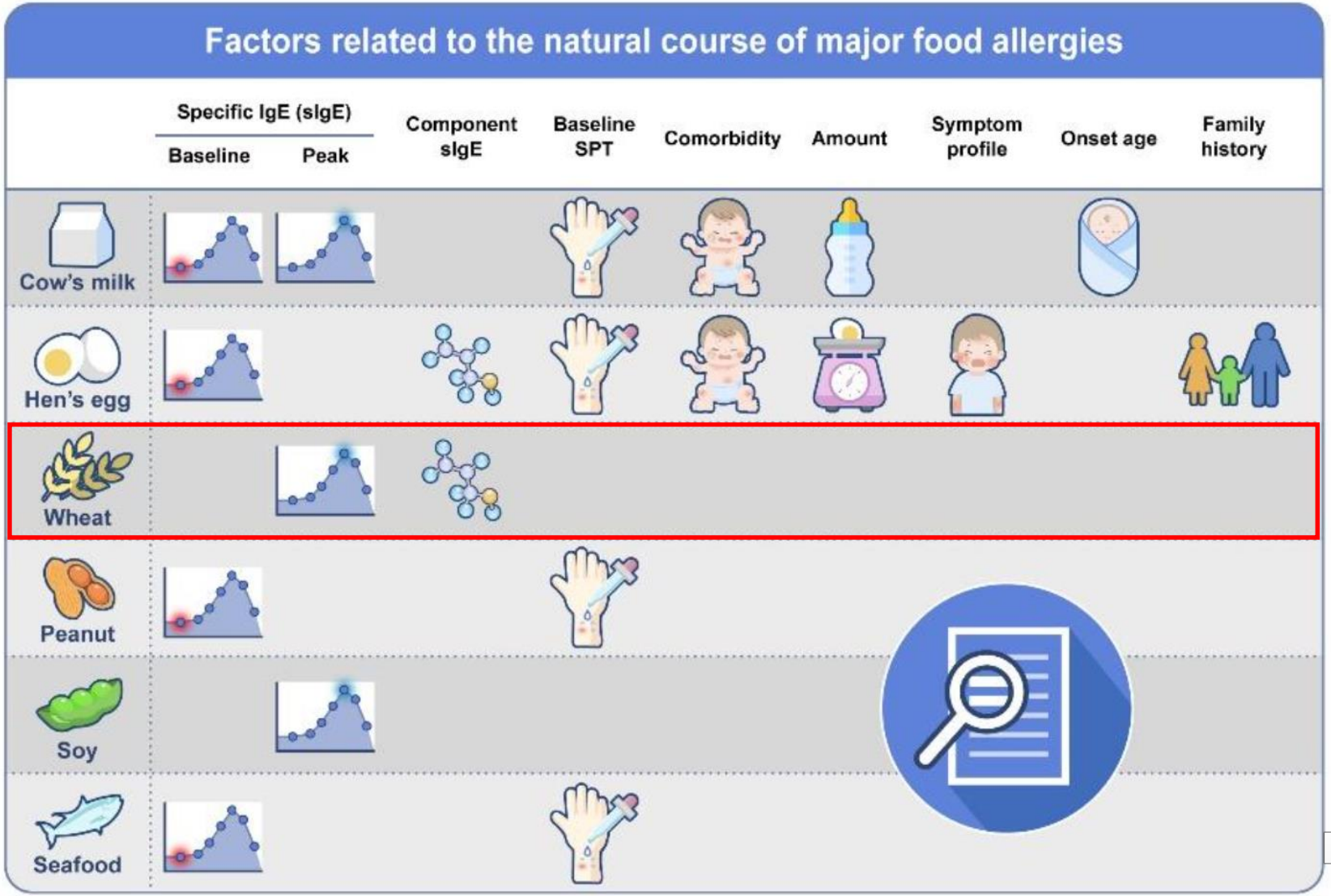
OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.
[a)]Among children with a definitive immediate-type reaction to hen's eggs at 6 years of age.

Clin Exp Pediatr Vol. 66, No. 12, 504–511, 2023

Factors associated with persistent wheat allergy

ω-5-gliadin-sIgE (≥0.35 kU/L)[37]
High peak wheat-sIgE (≥50 kU/L)[27]





Clin Exp Pediatr Vol. 66, No. 12, 504-511, 2023

Clinical management of wheat allergy

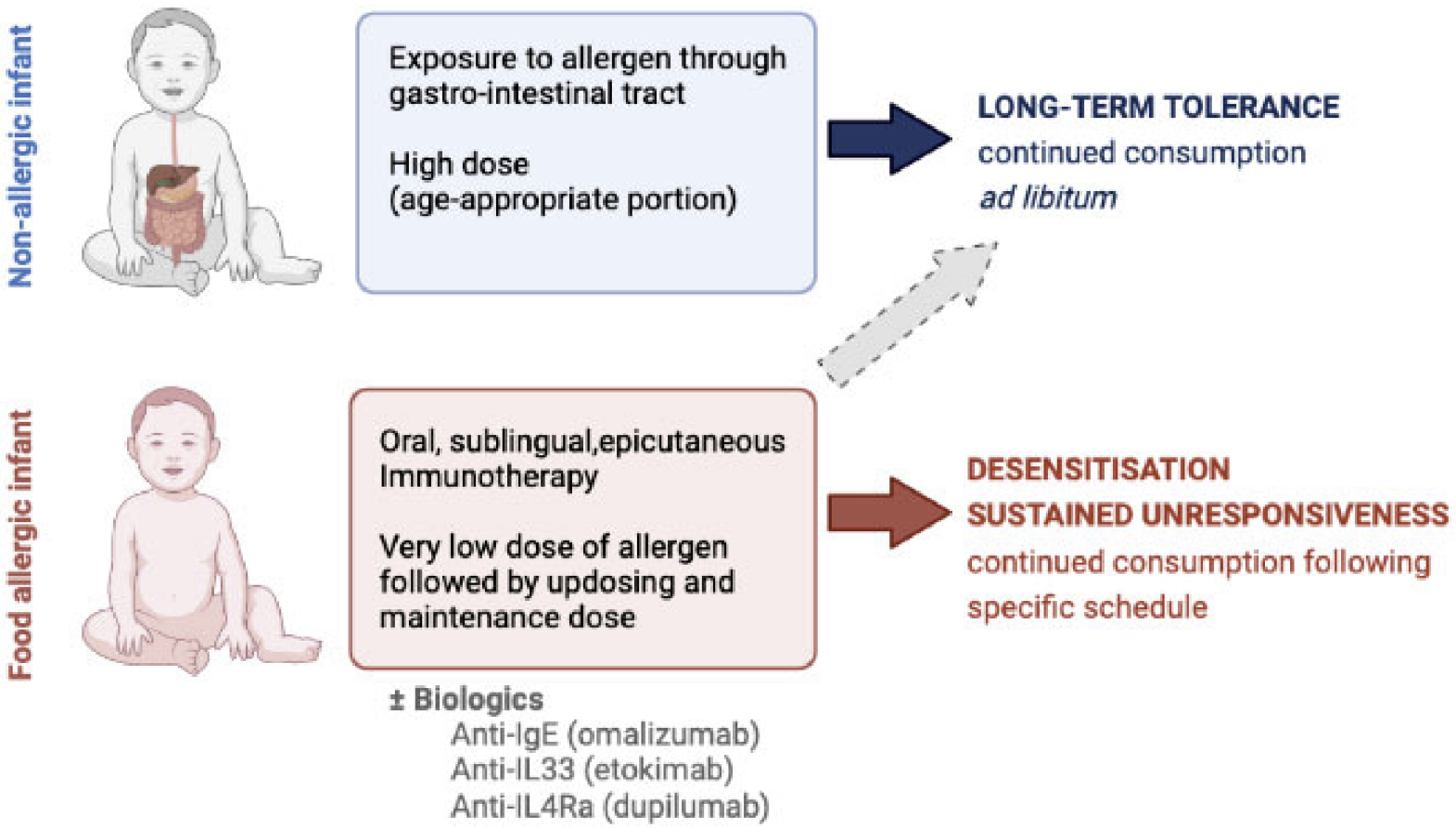
- **Advice and avoidance:**
  - Avoidance of all wheat-containing products
  - Avoidance of all gluten-containing wheat especially if co-factors present
  - Avoidance of inhalation of wheat containing proteins
  - Avoidance of cosmetics with hydrolyzed wheat protein

- **Pharmacotherapy for treatment of accidental reactions:**
  - Adrenaline autoinjector
  - Symptomatic treatment as required for mild systemic reactions, rhinitis/asthma

- **Allergen-specific immunotherapy:**

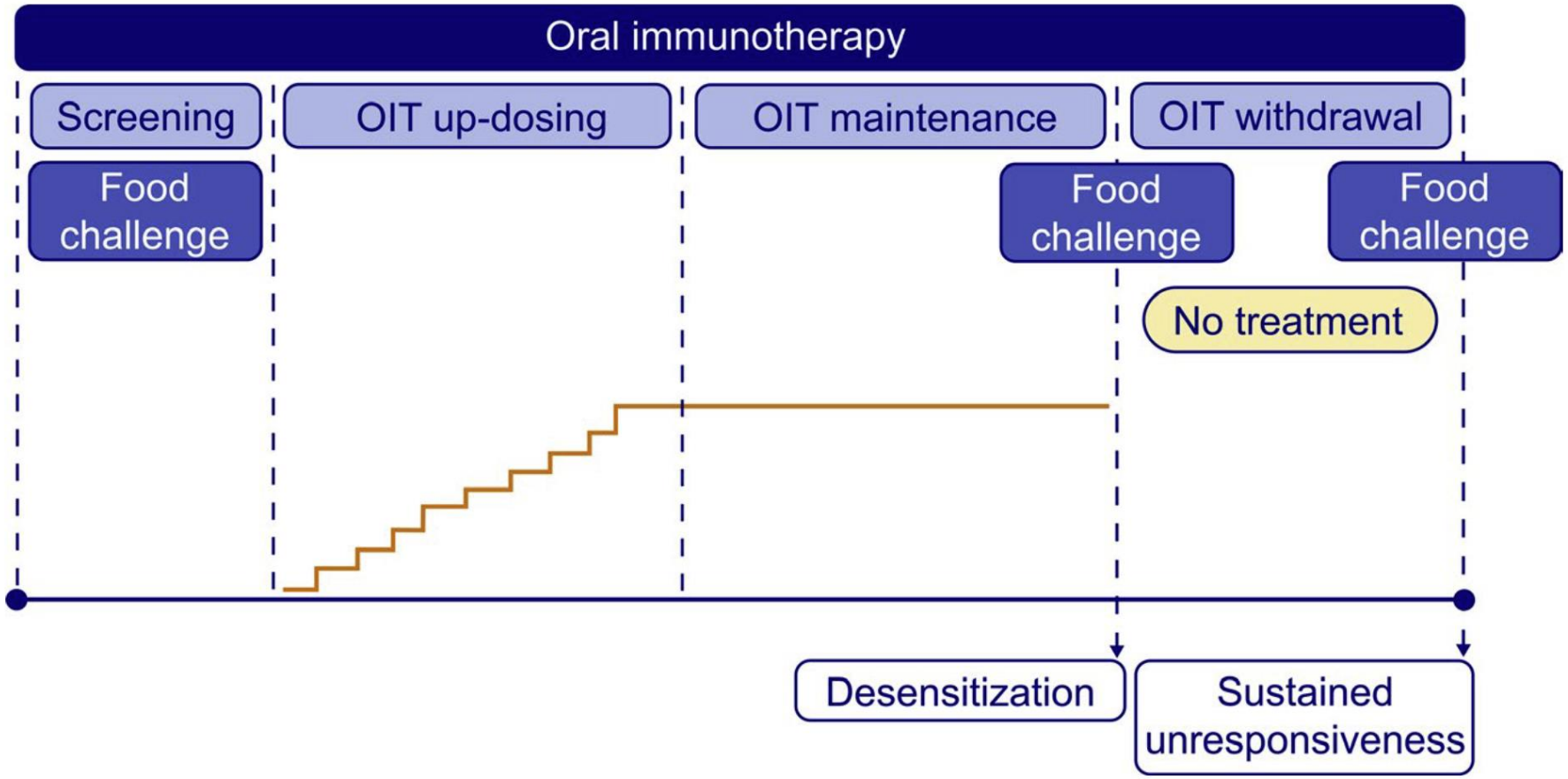
Pediatr Allergy Immunol. 2023 Mar:34 Suppl 28:e13854.

Oral tolerance induction



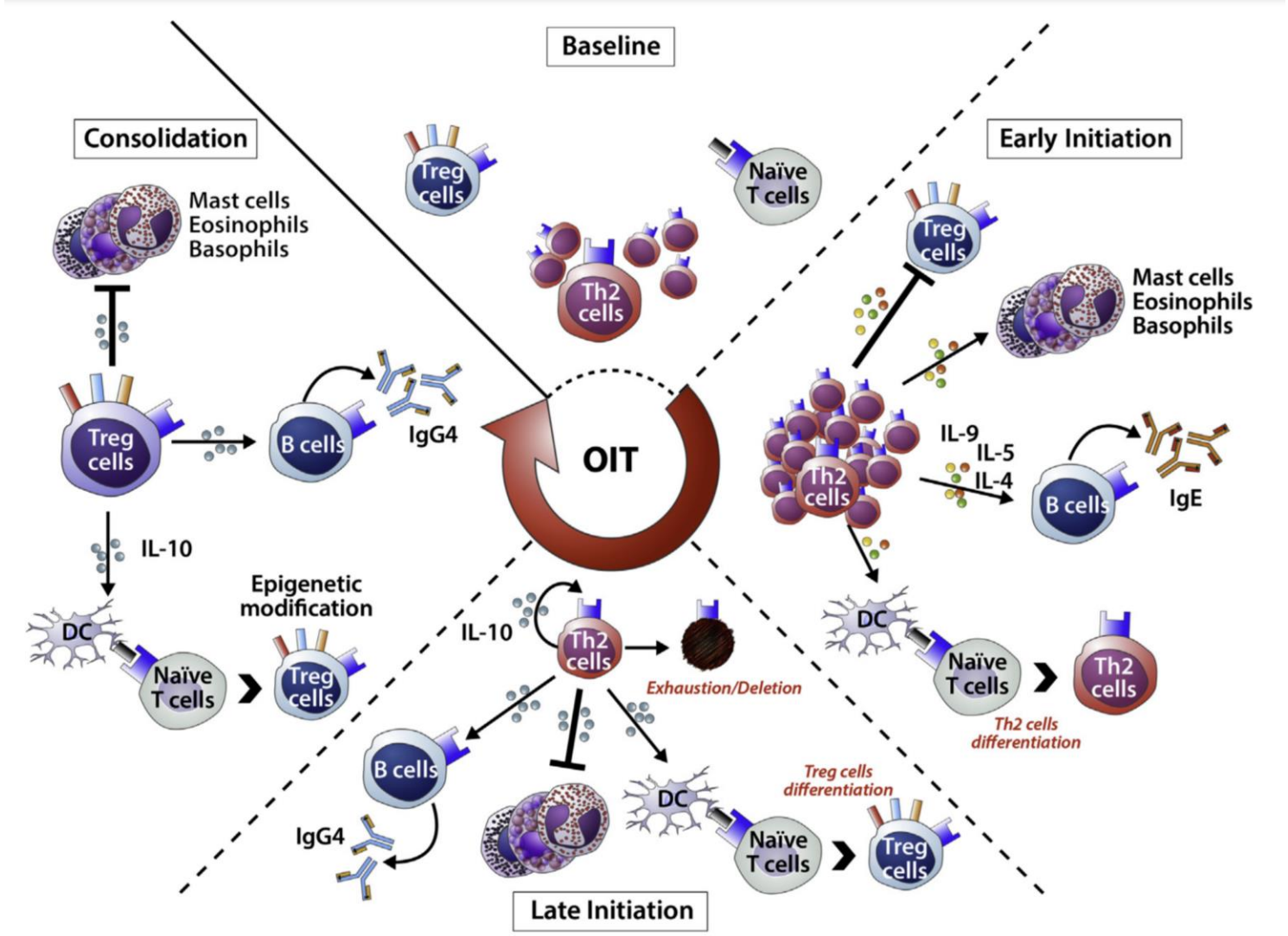
Foods 2022, 11, 3386. h

Oral Immunotherapy (OIT)



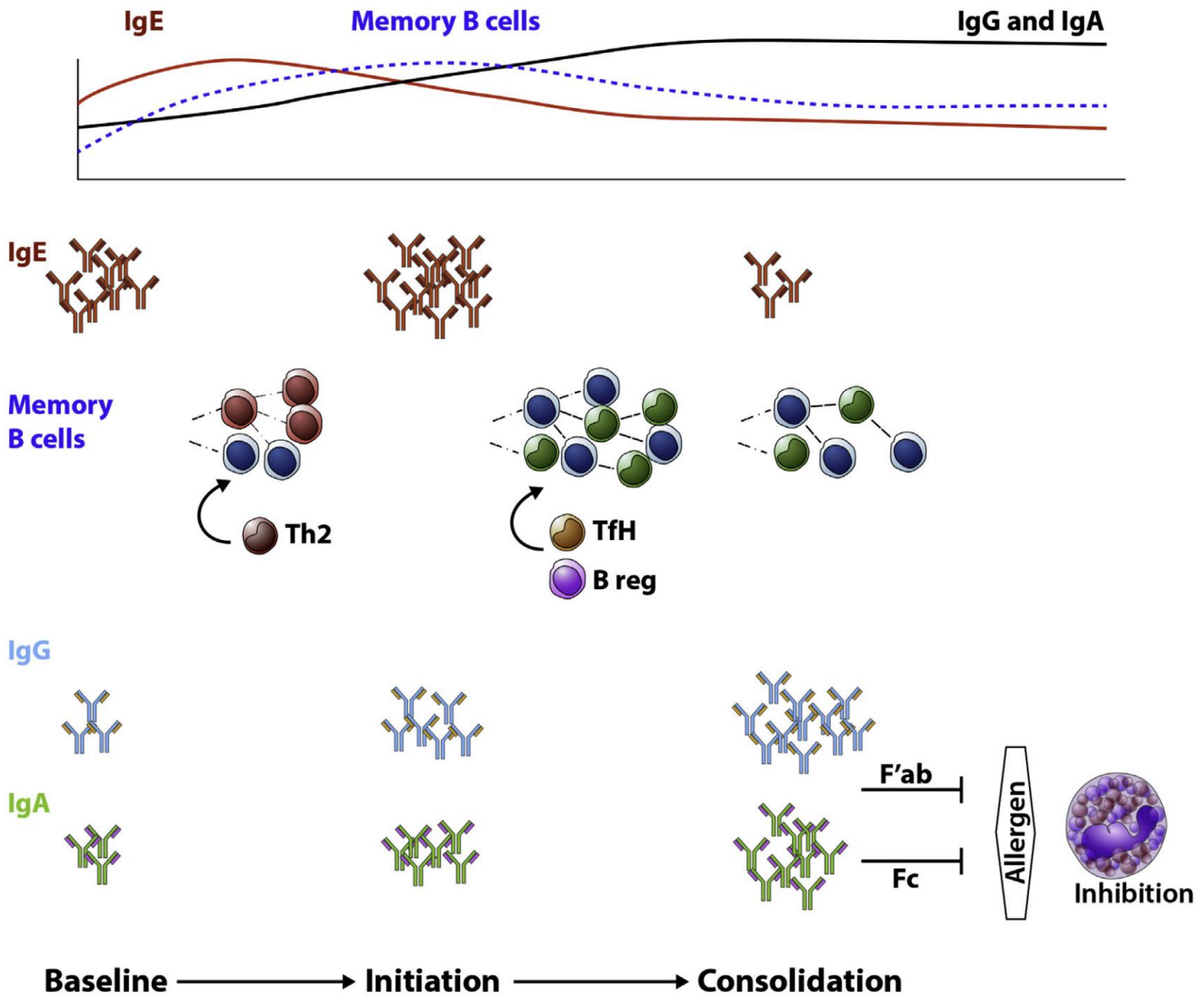
Allergy. 2020;75:1316–1326

Sequential immune mechanisms of OIT



J Allergy Clin Immunol 2018;141:491-8.

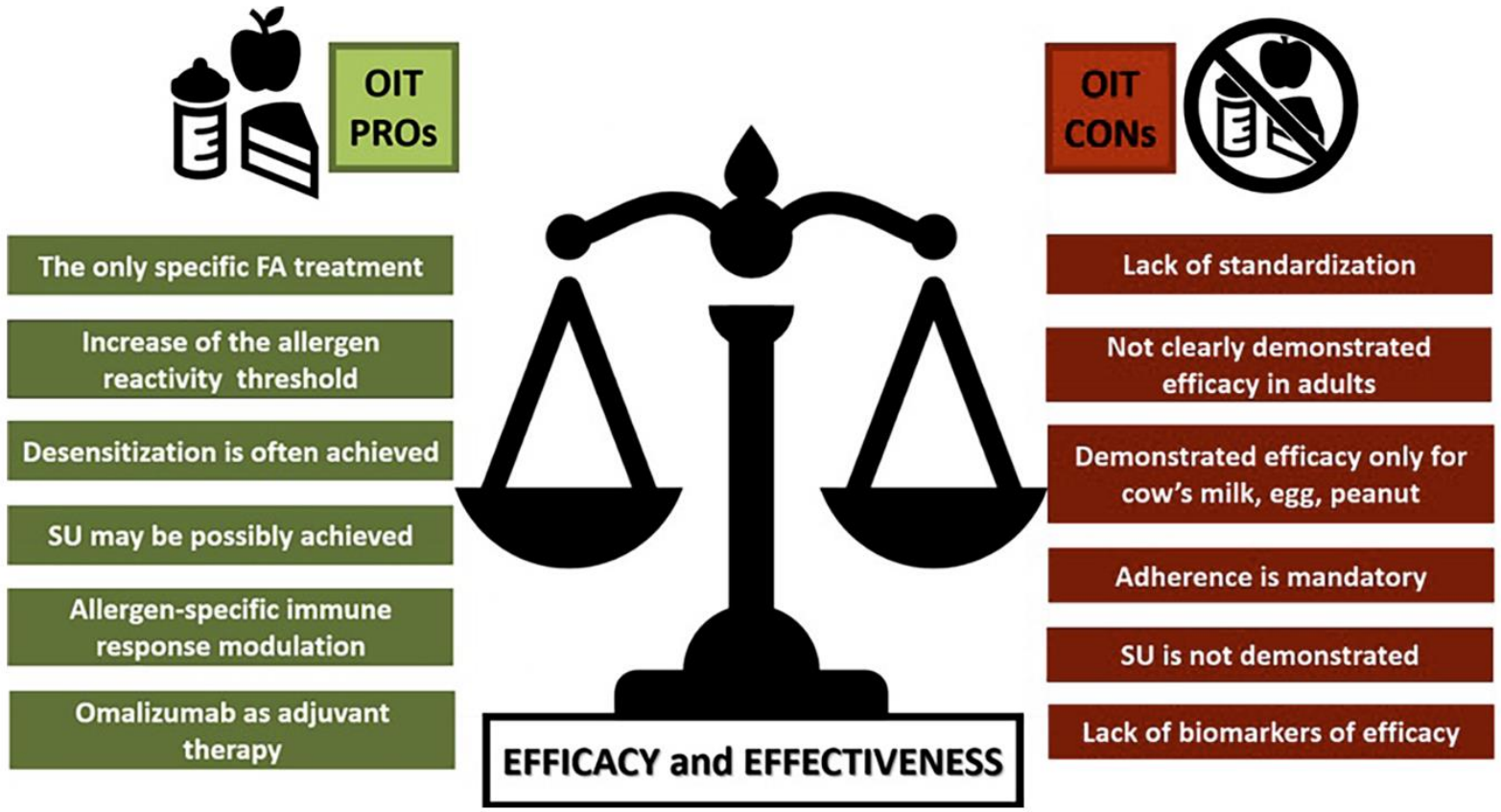
Humoral mechanisms of OIT



J Allergy Clin Immunol 2018;141:491-8.

Oral Immunotherapy (OIT)

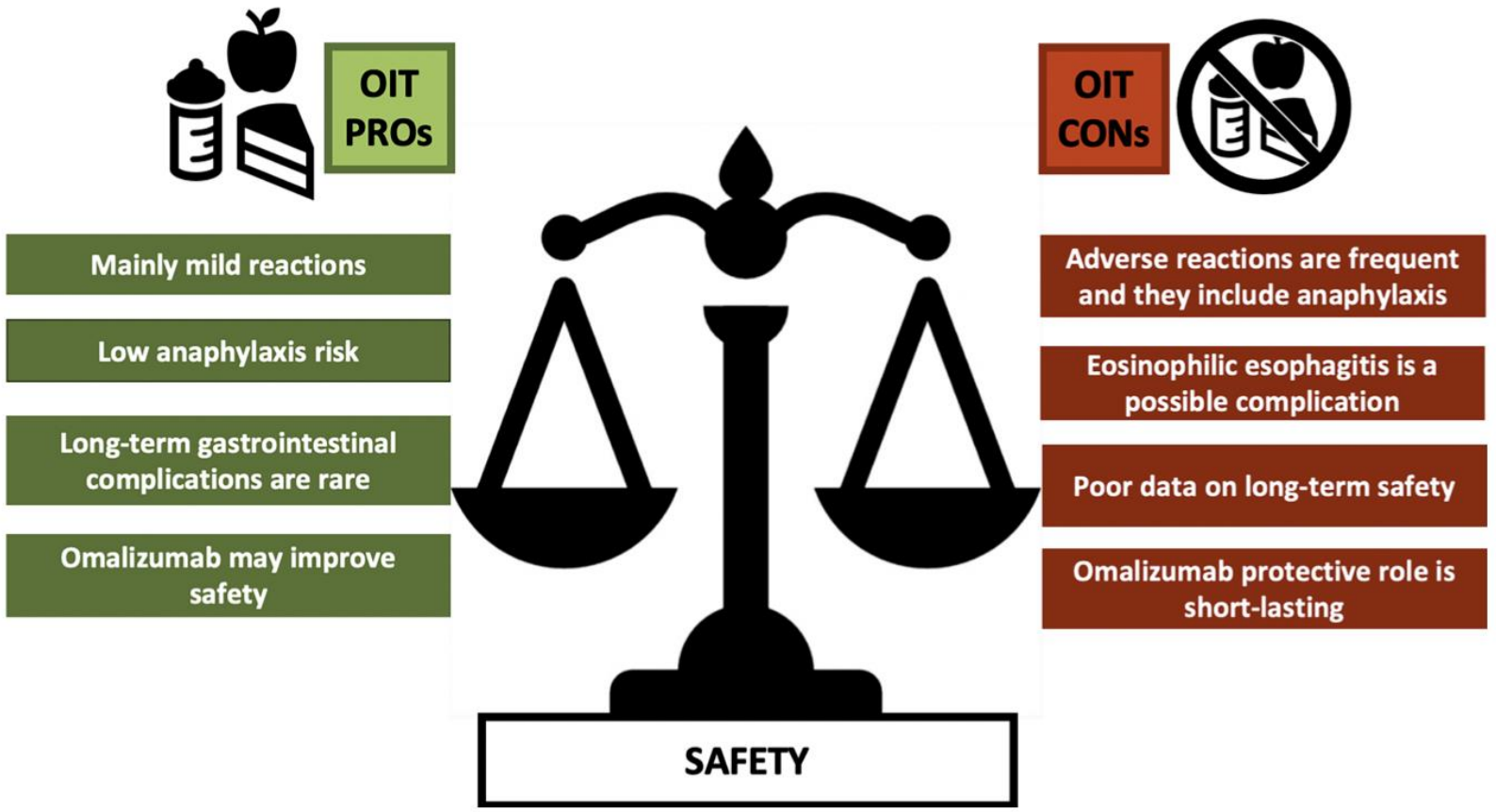
Efficacy and Effectiveness



Front. Immunol. 12:636612.

Oral Immunotherapy (OIT)

Safety



Front. Immunol. 12:636612.

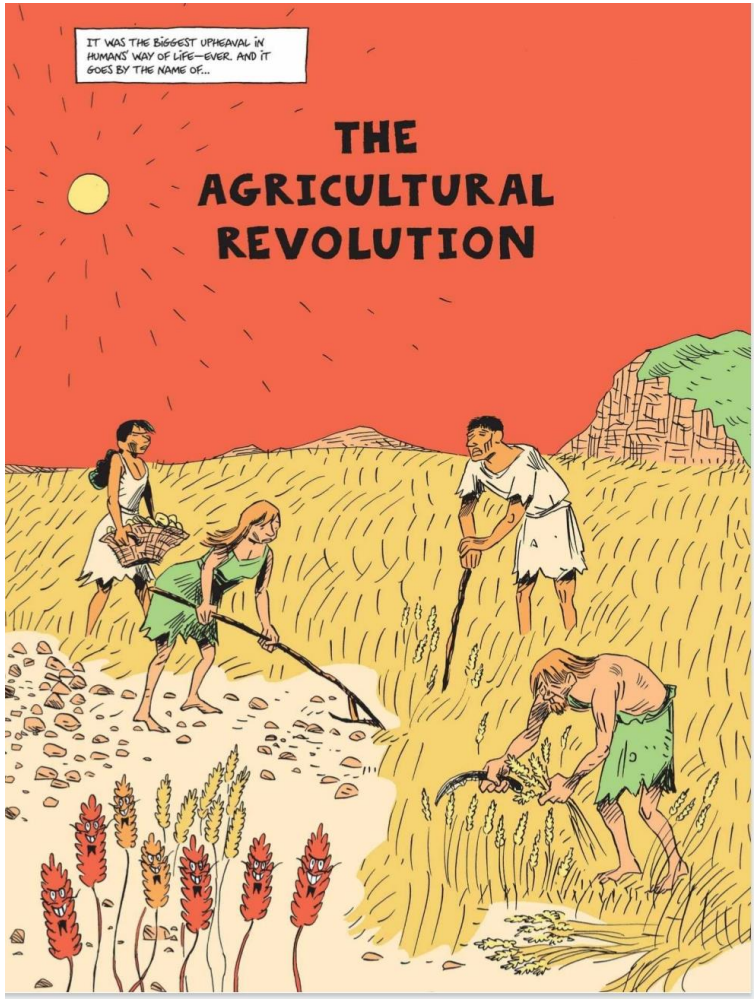
IgE-Dependent Allergy in Patients with Celiac Disease

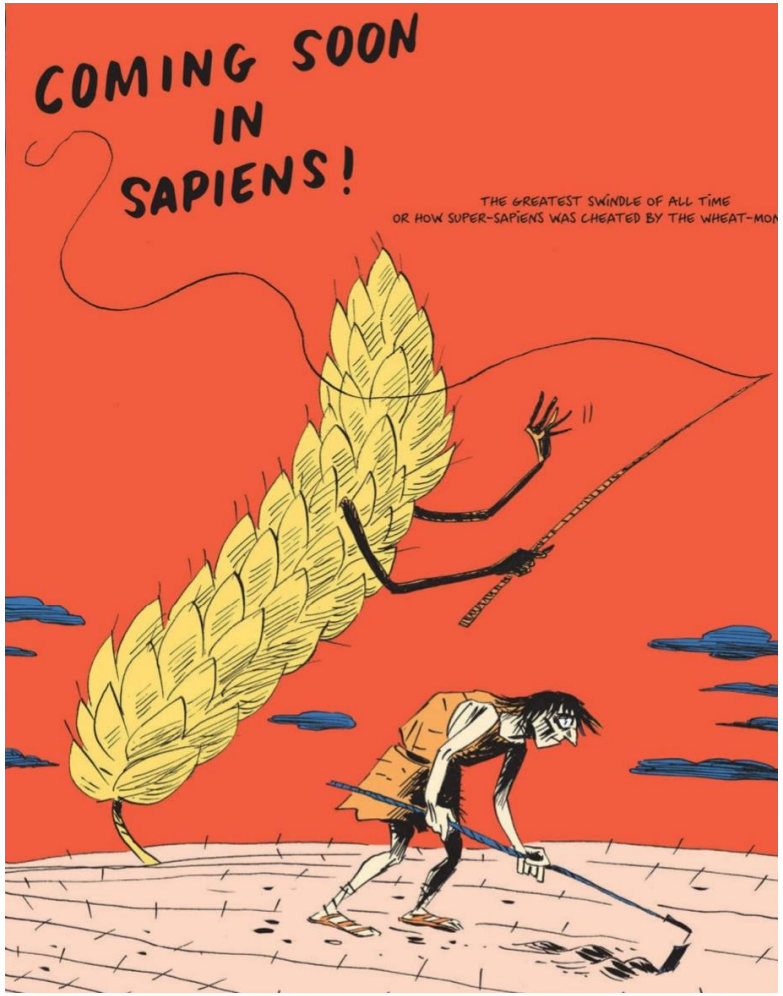
A Systematic Review

- Six original studies assessed the co-existence: 0 to 20.3% of CD were sensitized
- Eight reported cases of clinical allergy
- The potential risk of secondary sensitization after years of gluten-free diet

Nutrients 2023, *15*, 995.

“The Agricultural Revolution was history’s biggest fraud”





Sapiens A Graphic History