Food Allergy (MONDO:0700226) — Comprehensive Disease Characteristics Report

Summary

Food allergy is a common, complex, polygenic immune-mediated disease with no single causal gene. Unlike Mendelian disorders named after one locus, food allergy (MONDO:0700226) arises from the interaction of many susceptibility genes — primarily **epithelial-barrier genes** (*FLG*/filaggrin, the *SERPINB* clade B serpin cluster at 18q21.3) and **type-2 immune genes** (the *HLA* region [peanut-specific], the *IL4/IL13* cytokine cluster at 5q31.1, and *C11orf30/EMSY* at 11q13.5) — with a large environmental/exposome contribution. Because the research template requests a "causal gene" but food allergy is categorized as **Complex**, the correct answer is that susceptibility is distributed polygenically; the most robustly replicated genome-wide significant loci are *FLG*, the *SERPINB* cluster, *HLA*, the 5q31.1 cytokine cluster, and *C11orf30/EMSY* (PMID: 29051540, PMID: 29030101, PMID: 39698764).

The classic IgE-mediated form of the disease results from a failure of oral tolerance. Allergen crosses a compromised epithelial barrier, pathogenic Th2 lymphocytes drive B-cell class-switching to allergen-specific IgE, IgE arms mast cells and basophils via FcεRI, and on re-exposure the cross-linking of surface IgE triggers explosive degranulation — releasing histamine and proteases that produce urticaria, angioedema, gastrointestinal, respiratory and cardiovascular symptoms, and potentially fatal anaphylaxis. Food allergy affects as many as **8% of young children and 2% of adults** in Western countries and its prevalence is rising. The disease spans IgE-mediated, non-IgE-mediated (e.g., FPIES, allergic proctocolitis), and mixed (eosinophilic esophagitis) subtypes, and it imposes a heavy psychosocial and quality-of-life burden on patients and caregivers.

Management rests on allergen avoidance plus emergency intramuscular adrenaline (epinephrine) for acute reactions, with two disease-modifying strategies now established: **oral immunotherapy (OIT)** and **omalizumab** (anti-IgE, now FDA-approved for food allergy). The single most important advance in prevention is the paradigm shift demonstrated by the LEAP

and EAT trials: **early oral introduction of allergenic foods in infancy prevents food allergy**, reversing decades of avoidance-based advice. This report synthesizes 14 confirmed findings across all 15 requested sections, grounded in 58 reviewed papers.

Key Findings

Finding 1 — Food allergy is polygenic: barrier genes + type-2 immune genes

Food allergy has no single Mendelian cause. A genome-wide association study of oral-food-challenge–diagnosed food allergy (497 cases / 2,387 controls) identified **five loci at genome-wide significance**: the clade B serpin (*SERPINB*) gene cluster at 18q21.3, the cytokine gene cluster at 5q31.1 (which includes *IL4/IL13*), the filaggrin gene (*FLG*), the *C11orf30/LRRC32* locus, and the *HLA* region. Notably the HLA association is peanut-specific (PMID: 29051540):

> *"We identify five loci at genome-wide significance, the clade B serpin (SERPINB) gene cluster at 18q21.3, the cytokine gene cluster at 5q31.1, the filaggrin gene, the C11orf30/LRRC32 locus, and the human leukocyte antigen (HLA) region."*

A multi-population meta-analysis established **C11orf30/EMSY** as a genetic risk factor for food allergy generally and found *ITGA6* near genome-wide significance for peanut allergy; several implicated genes (*C11orf30/EMSY, SKAP1, CTNNA3*) are involved in epigenetic regulation of gene expression (PMID: 29030101). A 2025 review consolidates the picture: **16 genome-wide significant variants and 32 epigenome-wide significant loci**, with implicated genes falling into two functional groups — epithelial barrier function (*FLG, SERPINB7*) and immune function (*HLA, IL4*) (PMID: 39698764):

> *"Identified genes for food allergy are mainly involved in epithelial barrier function (e.g., FLG, SERPINB7) and immune function (e.g., HLA, IL4)."*

Gene/ontology annotations: *FLG* (HGNC:3748), *IL4* (HGNC:6014), *IL13* (HGNC:5973), *HLA-DQ/DR* region, *SERPINB7* (HGNC:8951), *C11orf30/EMSY* (HGNC:18071). Inheritance is **multifactorial/polygenic** (MONDO category: Complex). Evidence source: human GWAS.

Finding 2 — Early oral introduction prevents food allergy (LEAP/EAT): a primary-prevention paradigm shift

The **LEAP randomized controlled trial** (n=640 high-risk infants) demonstrated that early, sustained peanut consumption from infancy to age 5 prevents peanut allergy, and the protective effect **persists to 12 years of age** (144 months): peanut allergy was 15.4% in the original avoidance group vs 4.4% in the consumption group (P<0.001) (PMID: 38804779):

> *"At age 144 months, peanut allergy remained significantly more prevalent in participants in the original peanut avoidance group than in the original peanut consumption group (15.4% [38 of 246 participants] vs. 4.4% [11 of 251 participants]; P<0.001)."*

A pooled intention-to-treat analysis of LEAP + EAT showed a **75% reduction in peanut allergy (p<.0001)** among children randomized to early peanut consumption, with earlier introduction more effective (PMID: 36435990). Modeling estimated that a **77% population-level reduction** in peanut allergy could be achieved by introducing peanut at 4 months (with eczema) / 6 months (without eczema), with the benefit diminishing for each month of delay (PMID: 36521802). Meta-analyses provide **high-certainty evidence for peanut and egg** (PMID: 41967460).

Analysis	Population	Effect	PMID
LEAP 12-yr follow-up	497 high-risk	15.4% vs 4.4% peanut allergy (P<0.001)	38804779
LEAP+EAT pooled ITT	High-risk + general	75% reduction (p<.0001)	36435990
Population model	All infants	77% reduction if introduced early	36521802
Meta-analysis	Multiple RCTs	High-certainty for peanut & egg	41967460

Mechanistic basis — the *dual-allergen-exposure hypothesis*: cutaneous exposure through an inflamed/disrupted skin barrier (e.g., atopic dermatitis) promotes sensitization, whereas early oral intake induces tolerance (PMID: 38740132, PMID: 41967460). Evidence source: human RCT + modeling.

Finding 3 — Pathophysiology: IgE-mediated type-2 immune cascade with mast-cell degranulation

Experimental food allergy demonstrates the causal chain. Allergen is taken up across the GI epithelium (facilitated when IgE–antigen complexes bind **CD23** on epithelial cells) → pathogenic **Th2 lymphocytes** are activated (IL-4, IL-5, IL-13) → B cells class-switch to allergen-specific **IgE** → IgE binds **FcεRI** on mast cells and basophils → re-exposure cross-links surface IgE → mast-cell/basophil **degranulation** (histamine, mast cell protease MMCP-1) → anaphylaxis and local GI manifestations (PMID: 19079331):

> *"antigen uptake can be facilitated by immunoglobulin-E (IgE)-antigen complexes binding to CD23 on the epithelial cell surface. Studies on systemic anaphylaxis or local gastrointestinal manifestations of food allergy in mice have highlighted the contribution of IgE, mast cells, and pathogenic Th2 lymphocytes in experimental food allergy."*

In mouse models, ovalbumin-specific serum IgE correlates with jejunal MMCP-1+ mast-cell density and predicts diarrhea, accompanied by increased IL-4/IL-6 (PMID: 19450258). Mast-cell-deficient W/Wv mice and IL-4/IL-10 neutralization studies confirm the dependence of the response on mast cells and Th2 cytokines (PMID: 12951468, PMID: 9003216). Evidence source: in vitro + model organism + human.

GO/CL ontology suggestions: GO:0016068 (type I hypersensitivity), GO:0043303 (mast cell degranulation), GO:0002639 (positive regulation of immunoglobulin production), GO:0042092 (type 2 immune response); CL:0000097 (mast cell), CL:0000767 (basophil), CL:0000546 (T-helper 2 cell), CL:0000236 (B cell). CHEBI: histamine (CHEBI:18295).

Finding 4 — Treatment: avoidance + epinephrine; OIT and omalizumab are disease-modifying

Intramuscular **adrenaline (epinephrine)** is the only life-saving treatment for food-induced anaphylaxis but is frequently delayed or underused; patients should carry autoinjectors (PMID: 40719286, PMID: 42262574):

> *"Intramuscular adrenaline continues to be the primary treatment, yet its administration is often delayed or insufficiently used."*

Oral immunotherapy (OIT) achieves desensitization (e.g., sesame OIT ~85–97%) with mostly mild-to-moderate adverse events (PMID: 42808451); earlier initiation of cow's-milk OIT (<24 months) is associated with fewer severe reactions and no maintenance-phase anaphylaxis (PMID: 41616970). **Omalizumab** (anti-IgE monoclonal) raises reaction thresholds and improves OIT tolerability; in the OUtMATCH trial, post-omalizumab dietary consumption success reached **61–70% for milk/egg/wheat vs 38–56% for peanut/tree nuts** (PMID: 40447195):

> *"greater success was observed for milk, egg, or wheat (61%-70%) than for peanut or tree nuts (38%-56%)"*

Omalizumab monotherapy is now **FDA-approved** for food allergy.

NCIT treatment terms: Epinephrine (NCIT:C377), Omalizumab (NCIT:C2175), immunotherapy (NCIT:C15299), antihistamine (NCIT:C265), corticosteroid (NCIT:C2271). Evidence source: human clinical trials + reviews.

Finding 5 — Substantial psychosocial burden and reduced quality of life

Food allergy imposes measurable psychological and quality-of-life costs on patients and caregivers. Mothers of children with food allergy had significantly higher state anxiety (STAI-S, P<0.001) and caregiver burden (Zarit, P<0.001) and lower quality of life (EUROHIS-QOL, P=0.009) than controls; cow's-milk protein allergy specifically increased trait anxiety (P=0.035) (PMID: 40923420):

> *"Mothers in the FA group had significantly higher state anxiety (STAI-S) (P < 0.001) and ZCBS scores (P < 0.001) compared to controls."*

In a national US sample (N=5,940 food-allergy households), **69.9% screened at-risk for food insecurity**, and FA-related anxiety was the most common psychosocial experience (25.4%/30.1% of children/adults), higher among food-insecure households (p<.0001) (PMID: 38288585):

> *"FA-related anxiety was the most common (25.4%/30.1% of children/adults)"*

Disease-specific instruments include the **Food Allergy Quality of Life Questionnaire (FAQLQ)** and **Food Allergy Independent Measure (FAIM)** (PMID: 37695230, PMID: 38288585). Evidence source: human cross-sectional/survey.

Finding 6 — Gut dysbiosis and reduced short-chain fatty acids: the gene-environment axis

Reduced gut bacterial diversity and abundance are epidemiologically associated with food allergy. Mechanistically, microbial **short-chain fatty acids (SCFAs)** steer CD4 T-cell differentiation toward anergic **regulatory T cells (Treg, Foxp3+)** versus allergic **Th2** responses, acting through GPR41/GPR43/GPR109a receptors and histone-deacetylase inhibition (PMID: 39571752):

> *"T-cell differentiation poses an opportunity to direct the immune cells towards an anergic regulatory T cell (Treg) or allergic T helper 2 (Th2) response."*

Early-life microbial exposures — particularly rural/farming environments — may protect against food allergy by stimulating innate immune pathways and shaping the gut microbiome, while air pollutants (PM, NO2), synthetic barrier-disrupting chemicals, and ultra-processed foods increase risk (PMID: 42670723):

> *"Early-life microbial exposures, especially those associated with rural and farming environments, may protect against food allergies by stimulating innate immune pathways and shaping the gut microbiome."*

Probiotic evidence is inconclusive overall but more promising in cow's-milk protein allergy (PMID: 39571752). **CHEBI:** short-chain fatty acid (CHEBI:26666), butyrate (CHEBI:17968). **CL:** CL:0000815 (regulatory T cell). Evidence source: human epidemiology + mechanistic review.

Finding 7 — Epidemiology: ~8% of children / ~2% of adults, rising; three immunologic subtypes

Food-allergic conditions affect **as many as 8% of young children and 2% of adults** in Western countries, with rising prevalence (PMID: 39257598):

> *"Food allergic (FA) conditions have been classified as immunoglobulin E (IgE) and non-IgE-mediated reactions that affect as many as 8% of young children and 2% of adults in Western countries, and their prevalence seems to be rising."*

A systematic review/meta-analysis of US pediatric data showed prevalence rose from **5.6% (2012) to 6.6% (2018)** — a 1.6 percentage-point increase per decade (95% CI 0.5–2.7) — with stabilization between 2021 (7.9%) and 2024 (7.2%); the largest increase was among 10–17-year-olds, with no difference by race/ethnicity (PMID: 42887634):

> *"FA increased from 5.6% in 2012 to 6.6% in 2018 (1.6 percentage-point increase per decade; 95% CI: 0.5-2.7), with stabilization between 2021 (7.9%) and 2024 (7.2%)."*

Classification spans three types: IgE-mediated FA (Th2/IgE basis), non-IgE-mediated FA (e.g., FPIES, food protein-induced allergic proctocolitis), and mixed IgE/non-IgE (eosinophilic esophagitis). **Regional triggers differ:** peanuts/tree nuts predominate in Western countries, hen's egg/cow's milk in East Asia, seafood in Southeast Asia (PMID: 40719286). Evidence source: human epidemiology.

Finding 8 — Prognosis: usually non-fatal; rare fatal anaphylaxis with identifiable risk factors

Anaphylaxis case-fatality is estimated at **0.65–2% in children**; food is the main trigger (cow's milk, peanuts, tree nuts); mucocutaneous signs occur in >90% of cases and death is usually secondary to laryngeal edema (seen in 40–50%). Risk factors for severe/fatal reactions include personal asthma history, peanut/tree-nut allergy, and adolescence (PMID: 33236416):

> *"Anaphylaxis fatality rate is estimated to be 0.65% to 2%. Food is the main anaphylaxis trigger in children, notably cow's milk, peanuts, and tree nuts. Mucocutaneous manifestations are observed in more than 90% of cases"*

A systematic review of 32 studies found that young adults with asthma and known peanut/tree-nut allergy are at higher risk of fatal anaphylaxis; delayed adrenaline injection is associated with fatal outcomes, though timely adrenaline alone may be insufficient; cofactors include alcohol, exercise, medications, and mast cell disorders (PMID: 30288817). Many IgE-mediated childhood allergies (milk, egg) resolve with age, whereas peanut/tree-nut/seafood allergies more often persist; SPT and sIgE thresholds imperfectly predict resolution (PMID: 24132133). Evidence source: human epidemiology + systematic review.

Finding 9 — Animal models: adjuvant-based and adjuvant-free (epicutaneous) mouse models

Mouse models (e.g., Balb/c, C3H/HeJ) sensitized to ovalbumin or peanut — orally with mucosal adjuvants such as cholera toxin, or epicutaneously (adjuvant-free) — then orally challenged, reproduce allergen-specific IgE, intestinal mast-cell activation (MMCP-1), Th2 cytokines, and systemic anaphylaxis (PMID: 19079331, PMID: 19450258). Mast-cell-deficient W/Wv mice and IL-4/IL-10 neutralization establish mast-cell and Th2-cytokine dependence (PMID: 12951468, PMID: 9003216). In C3H/HeJ mice, epicutaneous immunotherapy (OVA-Viaskin patches) induced sustained protection against anaphylaxis via gastrointestinal-homing LAP+/Treg cells, demonstrating **skin–gut immune crosstalk** and a tissue-specific GI Treg deficiency in allergic mice (PMID: 27417020):

> *"epicutaneous application of antigen generated a population of gastrointestinal-homing LAP"*

Phenotype recapitulation: good for IgE, mast-cell activation, Th2 cytokines, and anaphylaxis; **limitations:** adjuvants are artificial, and murine oral tolerance differs from human timing. **NCBI Taxon:** *Mus musculus* (10090). Evidence source: model organism.

Finding 10 — Natural (spontaneous) food allergy in companion animals

Adverse food reactions occur naturally in dogs and cats, affecting mainly the integument and GI tract. In dogs, pruritus of distal limbs/face/ears/ventrum predominates, presenting as recurrent bacterial skin infections, otitis externa, and atopic dermatitis; four breeds (German shepherds, West Highland white terriers, Labrador and golden retrievers) account for ~40% of affected dogs, with onset by 6–12 months in 22–38% (PMID: 31072328):

> *"Four breeds (German shepherd dogs, West Highland white terriers, Labrador and golden retrievers) accounted for about 40% of affected dogs. Most dogs diagnosed with a CAFR were pruritic"*

Non-cutaneous signs include GI (diarrhea, vomiting), conjunctivitis, and even anaphylaxis (PMID: 30419909). As in humans, elimination diet followed by oral food challenge is the diagnostic gold standard (PMID: 29871756, PMID: 32448251):

> *"An elimination diet over several weeks using a protein source and a carbohydrate source previously not fed is still the diagnostic tool of choice."*

NCBI Taxon: *Canis lupus familiaris* (9615), *Felis catus* (9685). Evidence source: veterinary clinical.

Finding 11 — Phenotype spectrum: multi-system disease, urticaria/ angioedema most frequent

Food allergy is a multi-system disease. In an anaphylaxis cohort, organ involvement was **cutaneous 95.7%, cardiovascular 76.8%, respiratory 74.6%**; the most common manifestations were urticaria (81.9%), dyspnea (71.3%), and angioedema (69.4%); 2.2% had biphasic reactions (PMID: 18254479):

> *"The organs most frequently involved in the anaphylaxis were cutaneous (95.7%), cardiovascular (76.8%), and respiratory (74.6%). The most common manifestations were dyspnea (71.3%), urticaria (81.9%), and angioedema (69.4%)."*

In childhood food allergy the most common skin manifestations were angioedema (48%), urticaria (31%), and atopic dermatitis (21%) (PMID: 9252873). Across food anaphylaxis, mucocutaneous signs occur in >90% and laryngeal edema in 40–50% (PMID: 33236416).

Phenotype	Frequency	HPO term
Urticaria	81.9% (anaphylaxis); 31% (childhood)	HP:0001025
Angioedema	69.4%; 48% (childhood)	HP:0100665
Dyspnea/respiratory	71.3–74.6%	HP:0002094
Cardiovascular/hypotension	76.8%	HP:0002615 / HP:0001635
Atopic dermatitis/eczema	21% (childhood)	HP:0001047
Anaphylaxis	—	HP:0100845
Diarrhea/vomiting (GI)	—	HP:0002014 / HP:0002017
Laryngeal edema	40–50%	HP:0012027

Evidence source: human clinical cohorts.

Finding 12 — Epigenetics: DNA-methylation signatures distinguish clinical allergy from sensitization

A machine-learning study on DNA-methylation (DNAm) data narrowed 405,000+ CpGs to an **18-CpG signature mapping to 13 genes** (many immune-associated; 7 previously linked to food allergy) that achieved high classification accuracy distinguishing food-allergic from merely sensitized individuals — addressing the <50% accuracy of standard tests and the reliance on oral food challenges (PMID: 31216310):

> *"The 18-CpG signature mapped to 13 genes, on which biological insights were collected. Notably, many of the FA-discriminating genes found in this study were strongly associated with the immune system, and seven of the 13 genes were previously associated with FA."*

A 2025 review reports **32 epigenome-wide significant loci** in food allergy (PMID: 39698764). This positions epigenetic marks as both a mechanism and a candidate diagnostic. Evidence source: human computational/epigenomics.

Finding 13 — Alpha-gal syndrome: a tick-bite-induced, delayed, adult-onset red-meat allergy

Alpha-gal syndrome (AGS) is a **delayed IgE-mediated food allergy** to galactose-α-1,3-galactose (α-Gal), a carbohydrate epitope ubiquitously expressed in non-primate mammalian tissues. Sensitization follows tick bites and produces delayed (often 2–6 h) reactions to red meat and mammalian products (PMID: 42571940, PMID: 42808634):

> *"α-Gal has emerged as the causative antigen of alpha-gal syndrome (AGS), a delayed IgE-mediated food allergy to mammalian-derived products, including red meat."*
>
> *"Alpha-gal syndrome (AGS) is an emerging red meat allergy, IgE-mediated, with delayed reactions to a carbohydrate derived from mammals: α-gal (galactose-α-1,3-galactose). Sensitization follows a tick bite."*

α-Gal epitopes are thermostable, so conventional cooking may not reduce allergenicity, and AGS epidemiology is shaped by tick distribution with likely under-diagnosis (PMID: 42571940). Sensitized individuals show elevated innate-immune markers and reduced regulatory

cytokines (IL-10, IL-35) (PMID: 42877672). AGS is an important example of an **environmentally triggered, carbohydrate-directed, adult-onset** food allergy that departs from the classic protein-sensitization, childhood-onset paradigm. **CHEBI:** galactose-α-1,3-galactose. Evidence source: human clinical/review.

Finding 14 — Food allergy–eosinophilic esophagitis continuum: antigen exposure shapes immune phenotype

IgE-mediated food allergy and **eosinophilic esophagitis (EoE)** are interconnected manifestations on a continuum determined by antigen exposure patterns, dose, and chronicity. Among children with IgE-mediated food allergy, **EoE prevalence is ~4.7% (nearly 100-fold higher than the general population)**, and during oral immunotherapy confirmed EoE develops in **1–10% of participants**. Mechanistically, antigen avoidance favors IgE-mediated responses via T follicular helper cells, whereas sustained exposure promotes a shift toward eosinophilic/EoE-type inflammation (PMID: 42575621):

> *"Among children with IgE-mediated food allergy, EoE prevalence is nearly 100-fold higher than the general population at 4.7%. During oral immunotherapy, gastrointestinal symptoms are common, with confirmed EoE developing in 1% to 10% of participants."*

This finding clarifies a key safety consideration for OIT and links the IgE-mediated and mixed subtypes mechanistically. **CL:** CL:0000771 (eosinophil); **UBERON:** UBERON:0001043 (esophagus). Evidence source: human clinical/review.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

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1. GENETIC + ENVIRONMENTAL PREDISPOSITION
   Barrier genes (FLG, SERPINB7) + immune genes (HLA, IL4/IL13, C11orf30/EMSY)
   + exposome (pollution, dysbiosis/low SCFA, timing of allergen exposure)
        │  leads to
        ▼
2. EPITHELIAL BARRIER DYSFUNCTION
   Impaired skin and/or gut barrier allows allergen penetration
   (CD23-mediated transepithelial uptake in the gut)
        │  results in
        ▼
3. BRANCH POINT — SITE & TIMING OF FIRST EXPOSURE (dual-allergen-exposure hypothesis)
   ├── Cutaneous exposure through INFLAMED skin → SENSITIZATION  ──┐
   └── Early ORAL exposure through HEALTHY gut   → TOLERANCE (Treg) │ [protective; LEAP/EAT]
                                                                   ▼
4. TH2 POLARIZATION  (sensitization pathway)
   Dendritic cells present allergen → pathogenic Th2 cells (IL-4, IL-5, IL-13)
   [Low SCFA tips the Treg/Th2 balance toward Th2 — inferred from models]
        │  drives
        ▼
5. IgE CLASS-SWITCH
   B cells produce allergen-specific IgE
        │  which binds
        ▼
6. EFFECTOR-CELL ARMING
   IgE occupies FcεRI on mast cells and basophils
        │  then on RE-EXPOSURE
        ▼
7. DEGRANULATION
   Allergen cross-links surface IgE → histamine, tryptase, MMCP-1 release
        │  causing
        ▼
8. CLINICAL MANIFESTATION (multi-system)
   Cutaneous (urticaria 82%, angioedema 69%), respiratory (dyspnea 71%),
   cardiovascular (hypotension 77%), GI → ANAPHYLAXIS (fatality 0.65–2%)

   BRANCH (chronic sustained exposure): shift toward EOSINOPHILIC inflammation
   → eosinophilic esophagitis (EoE), the "mixed" phenotype
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Upstream vs downstream. Upstream drivers are genetic barrier/immune variants and environmental/exposome factors (steps 1–3). The Th2→IgE axis (steps 4–6) is the central, intermediate mechanism — the node targeted by both omalizumab (sequesters IgE) and OIT (reprograms the T-cell/antibody response toward IgG4/Treg). Downstream (steps 7–8) is effector-cell degranulation and the clinical syndrome — the node targeted by adrenaline.

Cell types involved: epithelial cells (CL:0000066), dendritic cells (CL:0000451), Th2 cells (CL:0000546), B cells (CL:0000236), mast cells (CL:0000097), basophils (CL:0000767), regulatory T cells (CL:0000815), eosinophils (CL:0000771).

Anatomical structures (UBERON): skin (UBERON:0002097), gastrointestinal tract / small intestine–jejunum (UBERON:0001052 / UBERON:0002115), esophagus (UBERON:0001043), respiratory tract / larynx (UBERON:0001004 / UBERON:0001737), cardiovascular system (UBERON:0004535). Body systems: integumentary, digestive, respiratory, cardiovascular, immune.

Therapeutic logic mapped onto the chain

Intervention	Mechanistic node targeted	Effect
Early oral introduction (LEAP/EAT)	Step 3 branch point	Diverts to tolerance; **77% population reduction**
Allergen avoidance	Step 7 (prevents cross-linking)	Prevents reactions (but may favor IgE/EoE branch)
Oral immunotherapy (OIT)	Steps 4–6 (reprograms T/B response)	Desensitization ~85–97% (sesame)
Omalizumab (anti-IgE)	Step 6 (sequesters free IgE)	Raises thresholds; 38–70% consumption success
Adrenaline (epinephrine)	Step 8 (reverses effector physiology)	Life-saving acute rescue

Evidence Base

PMID	Title (abbrev.)	Supports finding	Evidence type
29051540	*SERPINB GWAS of food allergy*	F1 (core susceptibility loci)	Human GWAS
29030101	*Multi-population peanut GWAS; C11orf30/EMSY*	F1	Human GWAS/meta
39698764	*FA genetics & epigenetics review*	F1, F12	Review
38804779	*LEAP 12-yr follow-up*	F2	Human RCT
36435990	*Pooled LEAP+EAT causal inference*	F2	Human RCT pooled
36521802	*Window of opportunity model*	F2	Modeling
41967460	*Prevention by early introduction*	F2	Meta-analysis
19079331	*Immunophysiology of experimental FA*	F3, F9	Model organism
19450258	*IgE–MMCP-1 in jejunum*	F3, F9	Model organism
12951468	*W/Wv mast-cell-deficient mice*	F3, F9	Model organism
9003216	*Murine onset model, IL-4/IL-10*	F3, F9	Model organism
40719286	*Epidemiology & management of anaphylaxis*	F4, F7	Review
40447195	*OUtMATCH: foods after omalizumab*	F4	Human RCT
42808451	*Sesame immunotherapy review*	F4	Systematic review
41616970	*Cow's-milk OIT timing*	F4	Human cohort
40923420	*Maternal psychological effects*	F5	Human cross-sectional
38288585	*Food insecurity & psychosocial burden*	F5	Human survey
37695230	*QoL, FAQLQ, caregiver burden*	F5	Human cross-sectional
39571752	*Gut dysbiosis & probiotics*	F6	Review
42670723	*External exposome & FA*	F6	Review
39257598	*IgE & non-IgE mechanisms review*	F7	Review

PMID	Title (abbrev.)	Supports finding	Evidence type
42887634	*US pediatric FA temporal trends*	F7	Meta-analysis
33236416	*Anaphylaxis in children*	F8, F11	Review
30288817	*Food-induced fatal anaphylaxis*	F8	Systematic review
24132133	*Natural history; SPT/sIgE prediction*	F8	Systematic review
27417020	*Epicutaneous IT, GI LAP+ Tregs*	F9	Model organism
31072328	*Canine/feline AFR signalment*	F10	Veterinary
30419909	*Non-cutaneous AFR in pets*	F10	Veterinary
29871756	*AFR pathogenesis/diagnosis*	F10	Veterinary review
32448251	*Time to flare after OFC (pets)*	F10	Veterinary
18254479	*Anaphylaxis features in Korea*	F11	Human cohort
9252873	*Childhood FA skin manifestations*	F11	Human cohort
31216310	*ML epigenetic biomarker (18-CpG)*	F12	Human computational
42571940	*Alpha-gal syndrome mechanisms*	F13	Review
42808634	*Alpha-gal syndrome overview*	F13	Review
42877672	*Alpha-gal immunologic comparison*	F13	Human cohort
42575621	*FA–EoE continuum*	F14	Review
38740132	*Cutaneous allergen exposure in AD*	F2 (dual-allergen)	Review

Diagnostics (cross-cutting). The diagnostic standard is **oral food challenge (OFC)** — skin prick tests and serum-specific IgE are sensitive but poorly specific, frequently identifying clinically irrelevant sensitization (PMID: 42358594, PMID: 42545935). **Component-resolved diagnostics** (e.g., Ara h 2 for peanut, casein for milk, ovomucoid for egg) improve risk stratification; casein-specific IgE ≥2.55 kUA/L predicted milk-OFC positivity with AUC 0.878 (PMID: 42451187). Emerging functional assays include the **basophil activation test (BAT)** and

mast cell activation test (MAT) (PMID: 42358594). Food-specific **IgG testing is not a validated diagnostic** for IgE-mediated allergy (PMID: 42818614). Note that skin prick testing itself can rarely provoke generalized reactions in infants (PMID: 11152165).

Key identifiers. MONDO:0700226; MeSH D005512 (Food Hypersensitivity); ICD-10 T78.0–T78.1 / Z91.01–Z91.018; ICD-11 4A85. Synonyms: IgE-mediated food allergy, food hypersensitivity, allergic disease from food material. Information is derived from **aggregated disease-level resources** (GWAS cohorts, registries, RCTs, reviews) rather than a single EHR patient series.

Limitations and Knowledge Gaps

1. **No single causal gene.** The research template field "causal gene(s): not recorded" is correct — food allergy is polygenic. GWAS to date explain only a modest fraction of heritability; effect sizes at individual loci are small, and most loci are regulatory rather than coding. Penetrance of susceptibility alleles is low and strongly environment-dependent.
2. **Mechanistic evidence is weighted toward murine models.** The core IgE/mast-cell/Th2 cascade (F3, F9) is best demonstrated in mice using artificial adjuvants; the exact triggers of human sensitization and the quantitative role of SCFA/microbiome in humans remain inferential rather than proven causally.
3. **Diagnostic imprecision.** SPT and sIgE have low specificity; OFC — the gold standard — is resource-intensive and carries reaction risk. Epigenetic (DNAm) and functional (BAT/MAT) biomarkers are promising but not yet in routine clinical use.
4. **Subtype heterogeneity.** Non-IgE-mediated forms (FPIES, proctocolitis) and the mixed EoE phenotype are mechanistically distinct and less well characterized than classic IgE-mediated allergy; this report is weighted toward IgE-mediated disease.
5. **Prevention generalizability.** High-certainty early-introduction evidence exists for peanut and egg; data for other allergens (milk, tree nuts, seafood) are weaker, and optimal dose/duration are undefined.
6. **Treatment durability.** OIT achieves desensitization but sustained unresponsiveness (true tolerance after stopping) is less certain; omalizumab requires ongoing administration. Long-term outcomes of combination strategies are still emerging.
7. **Epidemiologic measurement.** Much prevalence data is self-reported, likely over-estimating true (OFC-confirmed) food allergy; regional/ethnic variation is incompletely mapped.

Proposed Follow-up Experiments / Actions

1. **Polygenic risk score (PRS) development and validation.** Combine the 16 GWAS loci into a PRS and test whether it predicts (a) which sensitized children have clinical reactivity and (b) who benefits most from early introduction — enabling risk-stratified prevention. (Builds on F1, F2.)
2. **Prospective human microbiome–SCFA intervention trial.** Test whether butyrate/SCFA supplementation or defined probiotic consortia (beyond cow's-milk-allergy settings) shift the Treg/Th2 balance and prevent or treat food allergy, with stool metabolomics as a mechanistic readout. (F6.)
3. **Validate the 18-CpG DNA-methylation signature prospectively** against OFC outcomes in an independent multi-ethnic cohort, and benchmark it head-to-head against component-resolved IgE and BAT to reduce reliance on OFC. (F12.)
4. **Define the EoE-risk window during OIT.** Prospectively monitor esophageal eosinophilia (symptom-triggered endoscopy or non-invasive biomarkers) across OIT protocols to quantify dose/chronicity thresholds that tip patients into the eosinophilic branch. (F14.)
5. **Extend early-introduction RCTs to non-peanut/egg allergens** (tree nuts, sesame, seafood) with harmonized dosing to generate high-certainty evidence beyond peanut and egg. (F2.)
6. **Characterize alpha-gal syndrome epidemiology and mechanism** with tick-exposure cohorts, mapping geographic tick distribution to AGS incidence and dissecting the innate/regulatory cytokine imbalance (IL-10, IL-35) as therapeutic targets. (F13.)
7. **Comparative/One-Health studies** leveraging spontaneous canine and feline food allergy as a natural large-animal model to test tolerance-inducing interventions before human translation. (F10.)

Report compiled from a 5-iteration autonomous investigation: 14 confirmed findings, 58 papers reviewed. Evidence types span human GWAS/RCT/cohort/survey, model organism, veterinary clinical, and computational studies.
