The Practice of Food Allergy
AAAAI Diagnostic Symposium

A Diagnostic Algorithm for Food Allergy

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Disclosures

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Objectives

- Understand how to select the most appropriate tests for diagnosing food allergy
- Understand how to interpret tests to more accurately diagnose food allergy

Spectrum of Possible Food Allergic Reactions

- 10 m/o vomits repetitively 2 hrs. after ingesting rice cereal
- 43 y/o gets bloating & diarrhea after eating pizza & ice cream
- 12 y/o develops hives, SOB & emesis after ingesting a “trail bar”
- 4 family members develop pruritus, facial erythema & vomiting after eating tuna at a local restaurant
- 3 y/o with atopic dermatitis has eczematous flare after eating eggs
- 24 y/o seen in ER after steak “gets stuck going down”
- 32 y/o hunter develops anaphylaxis 4 hrs. after eating steak

Getting to the Right Diagnosis

Requires an understanding of –

- Pathophysiology
- Epidemiology
- Careful history
- Choosing the right tests

Step 1: Pathophysiology

Adverse reactions (not hypersensitivity)

- Bacterial food poisoning
- Scombroid fish poisoning

Non-Allergic/Intolerance

- Lactase enzyme deficiency
- Delayed maturation of fructase enzyme
- Galactosemia

Allergy (Immune-mediated)

IgE-Mediated

- Anaphylaxis
- Urticaria

IgE?

- Atopic Dermatitis
- Eosinophilic esophagitis

“Non-IgE” mediated

- Isolated gastrointestinal reactions
- Skin rashes

Step 2: Epidemiology

- **Of foods**

Common in Adults
- peanut
- tree nuts
- seafood
- (fruits/vegetables)

Common in Children
- egg
- milk
- soy
- wheat
- peanut
- tree nuts
- seafood

- **Of disorders**

Often associated with food
- anaphylaxis
- acute urticaria
- atopic dermatitis (~35%)
- syndromes of gastrointestinal allergy

Not usually associated with food
- asthma
- allergic rhinitis
- chronic urticaria

Step 2:

Epidemiology

- Cross-reactivity within food groups
- Cross-reactivity with pollens

If Allergic to:	Risk of Reaction to at Least One:	Risk:
A legume* (peanut)	Other legumes (peas, lentils, beans)	5%
A tree nut (walnut)	Other tree nuts (brazil, cashew, hazelnut)	37%
A fish* (salmon)	Other fish (swordfish, sole)	50%
A shellfish (shrimp)	Other shellfish (crab, lobster)	75%
A grain* (wheat)	Other grains (barley, rye)	20%
Cow's milk*	Beef (hamburger)	10%
Cow's milk*	Goat's milk (goat)	92%
Cow's milk*	Mare's milk (horse)	4%
Pollen (birch, ragweed)	Fruits/vegetables (apple, peach, honeydew)	55%
Peach*	Other Rosaceae (plum, pear, apple, cherry)	55%
Melon* (cantaloupe)	Other fruits (avocado, watermelon, banana)	92%
Latex* (latex glove)	Fruits (avocado, kiwi, banana)	35%
Fruits (banana, kiwi, avocado)	Latex (latex glove)	11%

Sicherer SH, *JACI* 2003; 108(6):881-90

Step 3: Careful History

- History is key:
  - Timing (minutes to a few hours)
  - Symptoms
  - Quantity & preparation of food (e.g. raw vs. cooked vs. baked)
  - Reproducibility (previously or subsequently tolerated?)
  - Treatment (resolution/outcome)
  - Co-factors (exercise, alcohol, medications [e.g. NSAIDs])
- History informs testing – provides “pre-test probability””
- Diagnostic testing serves to support/refute diagnosis of suspected allergy based on history

Pre-test Probability

Likelihood of allergy from clinical history: History \ Lab Test		Likelihood of allergy from test results: Low	Intermediate	High
	High	*Possible allergy*	***Probably allergic***	***Likely to be allergic***
	Intermediate	*Possible allergy*	*Possible allergy*	***Probably allergic***
	Low	***Unlikely to be allergic***	*Possible allergy*	*Possible allergy*

Santos AF et al. EAACI Guidelines on the diagnosis of food allergy. *Allergy* 2023; xx: 1-20.

Affect of Pre-test Probability: Positive History

- Evaluated 169 children with suspected peanut allergy
  - Group 1 had a history of a past reaction to peanut
  - Group 2 avoiding peanut without a history of a past reaction

- Compared outcome of OFC to peanut-specific IgE levels

Peanut

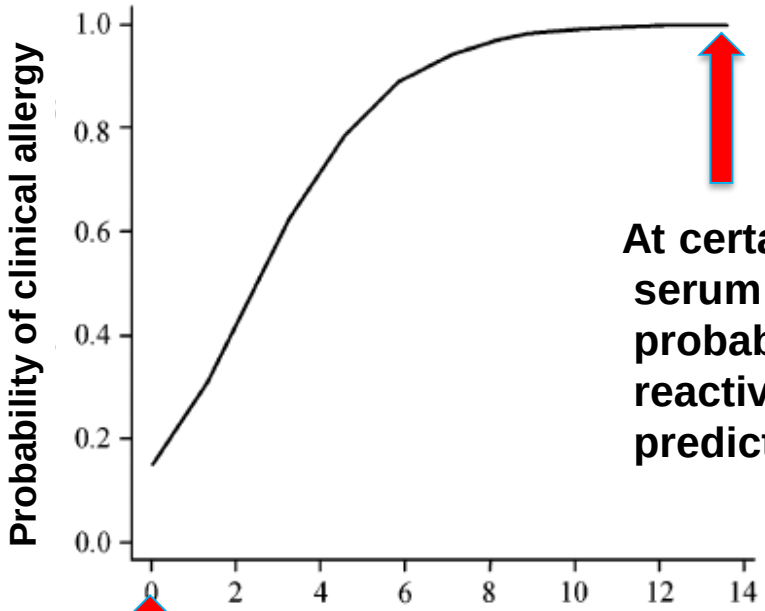
	Group 1 (n = 110)		Group 2 (n = 59)	
IgE level	Total	Passed	Total	Passed
<0.35	38	29 (76%)	17	15 (88%)
0.36 to <2	38	17 (44%)	21	15 (71%)
2 to 4.9	27	11 (40%)	12	4 (33%)
≥5	7	0 (0%)	9	7 (77%)

Perry et al *JACI* 2004;114:144

Step 4: Food Allergy Testing

- **Skin prick testing & food-specific IgE testing**
  - **Avoid panel testing (poor positive predictive value → overdiagnosis, unnecessary avoidance)**
  - **Sensitization (+ test) alone is <u>not</u> diagnostic without convincing history of clinical reaction**
  - **The larger the wheal diameters on SPT or the higher the food-specific IgE, the greater the likelihood of allergic reactivity (not severity of reaction)**
  - **Negative results → allergy unlikely**

Curve varies by –
- **Food**
- **Patient age**
- **Assay (brand)**



At certain wheal size or serum IgE level, probability of clinical reactivity exceeds 95% predictability

Negative test is not zero risk of reactivity

Sporik R et al. *Clin Exp Allergy* 2000; 30:1541-46; Sampson HA. *JACI* 2001; 107:891-96.

Step 4: Food Allergy Testing

TABLE I. Diagnostic cutoffs for specific IgE and skin prick testing with 95% positive predictive

	Specific IgE[1,5-8]		Skin prick test[1,6,9]
Foods	**95% PPV**	**50% NPV**	**95% PPV**
Cow's milk*	15 kU/L (32 also reported) Infants ≤2 y: 5 kU/L	2 kU/L	≥8 mm Infants ≤2 y: 6 mm
Egg*	7 kU/L Infants ≤2 y: 2 kU/L	2 kU/L	≥7 mm Infants ≤2 y: 4-5 mm
Peanut	15-34 kU/L	2 kU/L if history of reaction 5 kU/L is no history of reaction	≥8 mm Infants ≤2 y: 4 mm
Fish	20 kU/L	–	
Tree nuts	20 kU/L		≥8 mm for walnut ≥12 mm for cashew
Sesame	50 kU/L (86% PPV)		≥8 mm

NPV, Negative predictive value; *PPV*, positive predictive value.
*These numbers were derived from uncooked milk and direct egg and do not apply to baked milk or baked egg.

Foong R-X et al. *JACI-In Pract* 2021; 9:71-80

Step 4: Food Allergy Testing – Components

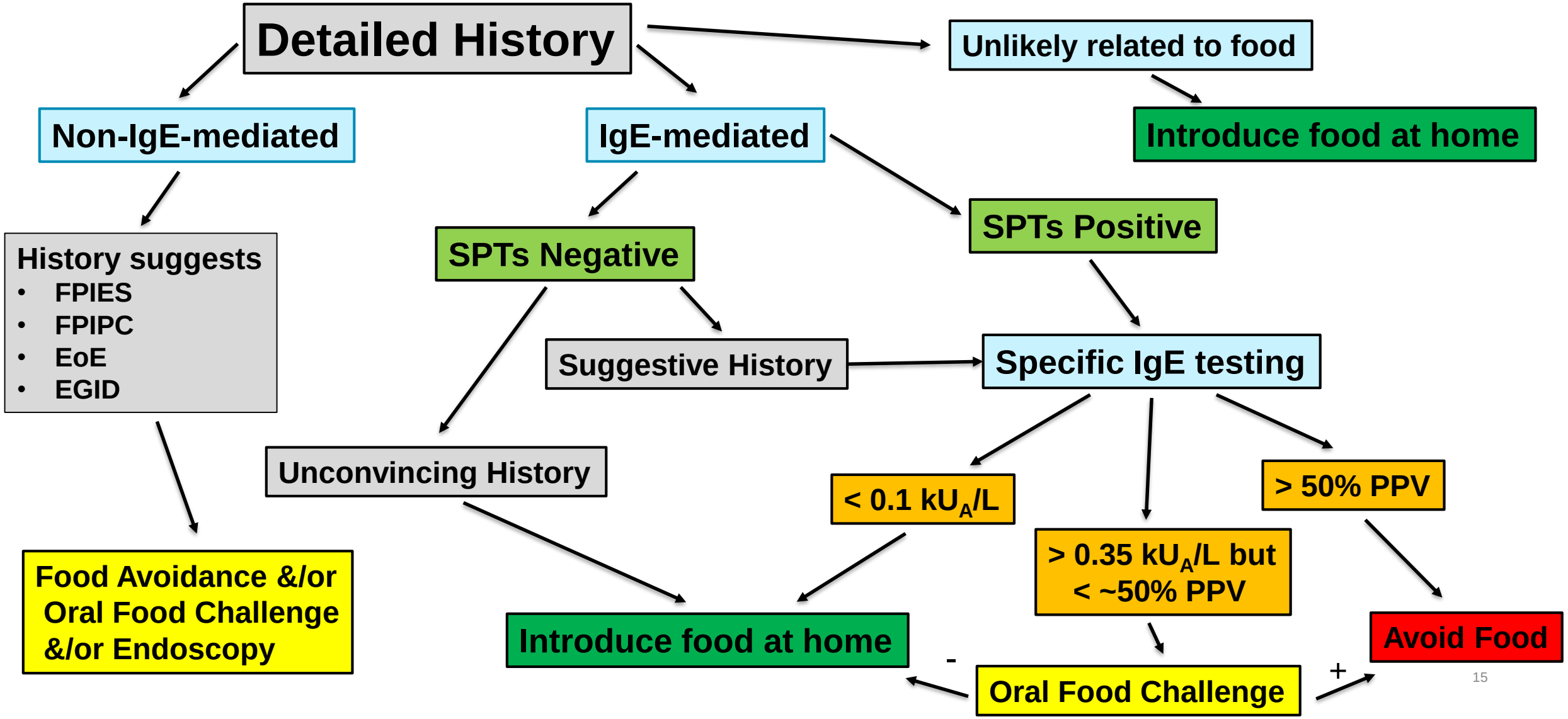
TABLE II. Proposed diagnostic cutoff levels and positive predictive value (PPV) for specific IgE to individual allergen components

IgE to individual allergen components	IgE (kU_A/L)	PPV	When I do an OFC in clinic*
Milk casein to diagnose baked milk allergy[19]	20.2	69%	< 10 kU_A/L
Egg ovomucoid			
to diagnose baked egg allergy[20]	50	95%	≤ 5 kU_A/L
to diagnose cooked egg allergy[21]	26.6	95%	≤ 2 kU_A/L
to diagnose raw egg allergy[22]	5.21	95%	< 1 kU_A/L
Peanut Ara h 2[10,18,23]	0.35-42.2	90%-95%	< 1 kU_A/L
Hazelnut Cor a 9[23-25]	1-2	79%-100% specificity	< 2 kU_A/L
Hazelnut Cor a 14[23,26]	0.72-47.8	87%-90% specificity	< 1 kU_A/L
Cashew Ana o 3[27,28]	0.16	98% specificity	
	2	95%	< 0.5 kU_A/L
Soya Gly m 8 [29]	1	89%	
	3.55	74%	< 1 kU_A/L
Wheat Tri a 19[30,31]	0.04	100%	
	0.41	81%	

* < 30% reaction rate; mostly mild

Foong R-X et al. *JACI-In Pract* 2021; 9:71-80

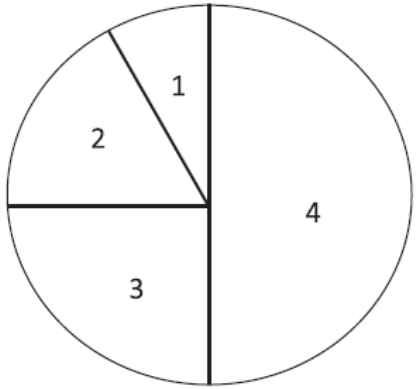
Diagnostic Algorithm



Step 5: Oral Food Challenge

- **Performing the OFC**
  - DBPCFC - gold standard, used mostly in research settings
  - Open OFC- most commonly used in clinical setting
  - Age-appropriate serving size for the food (may use masking agents if patient is highly anxious)
    - Divided doses q 15-30 minutes:
      - use more doses & lower starting dose if history of severe reaction
- **When to stop an OFC**

Four Dose Protocol	Six Dose Protocol
Divide the serving as outlined below. Dose 1 = 1/12th of the total serving Dose 2 = 1/6th of the total serving Dose 3 = 1/4 of the total serving Dose 4 = 1/2 of the total serving	Dose 1 = 1% of total dose Dose 2 = 4% of total dose Dose 3 = 10% of total dose Dose 4 = 20% of total dose Dose 5 = 30% of total dose Dose 6 = 35% of total dose



Bird JA et al, *JACI* 2020; 8(1):75-90.e17

Diagnosis of Food Allergy: Emerging Tests

- May limit need for oral food challenges
  - **Epitope mapping**
    - Identification of specific amino acid sequences bound by IgE
    - Immunodominant epitopes, diversity and number of epitopes predict clinical reactivity
      - *Allergenis* BBEA™ - >93% accurate for diagnosing peanut allergy & provides likelihood of tolerating various eliciting doses
  - **Basophil & Mast cell activation tests (BAT & MAT)**
    - Flow cytometry (CD63 or CD203c) after incubation with allergen
    - BAT requires fresh sample (must perform within 24 hours); MAT uses serum
    - High sensitivity, specificity, PPV and NPV; requires validation in a variety of patient cohorts and not commercially available
    - 10 – 15% BAT non-responders

Foong R-X et al. *JACI-In Pract* 2021; 9:71-80

Summary

- A detailed clinical history is critical for informing the diagnostic work-up and for arriving at the correct diagnosis

- No laboratory test is by itself diagnostic of food allergy

- While the oral food challenge remains the “gold standard” for diagnosing food allergy, the majority cases can be diagnosed with a thorough medical history & appropriate lab studies

THANK YOU