Diagnosing Food Allergies in Infants and Children

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Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

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	clinical area for above: pediatric allergies

Learning Objectives

- Evaluate test methods for detection and diagnosis of food allergy
- Incorporate diagnostic test results to manage food allergies

MODULE 1: INTRODUCTION

- Define what are food allergies
- Review the importance of clinical history and a physical exam

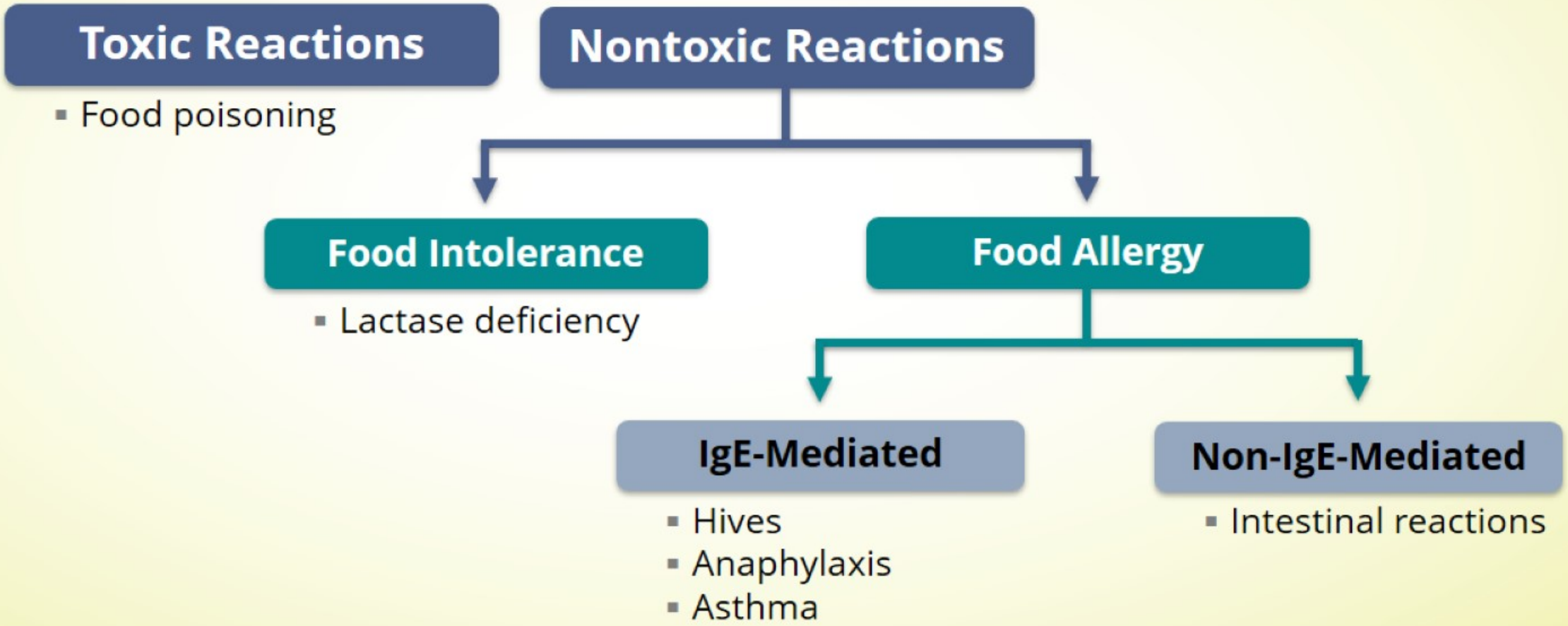
Defining Food Allergies

- A **food** is any substance—whether processed, semiprocessed, or raw—intended or adapted for human consumption

- A **food allergy** is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food

- **Food allergens** are specific components of food recognized by allergen-specific cells that elicit specific immune reactions

Adverse Reactions to Foods



Adapted from Cianferoni A, Spergel JM. *Allergol Int.* 2009;58(4):457-466.

IgE-Mediated Food Allergy and Anaphylaxis

- Primary cause of anaphylaxis in children[1]
- Incidence has increased[2-4]
  - **1983-1987**: 21/100,000 person-years annually
  - **1990-2010**: 49.8/100 000 person-years annually
- Symptoms have rapid onset, may be localized or generalized, and can be potentially fatal
- Common severe allergens: peanuts, milk, and tree nuts

1. Lee S, et al. *J Allergy Clin Immunol*. 2017;139(1):182–188.e2.
2. Sicherer SH, et al. *J Allergy Clin Immunol*. 2010;125(6):1322-1326.
3. Yocum MW, et al. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):452-456.
4. Decker WW, et al. *J Allergy Clin Immunol*. 2008;122(6):1161-1165.

Symptoms of IgE-Mediated Food Allergy Reactions

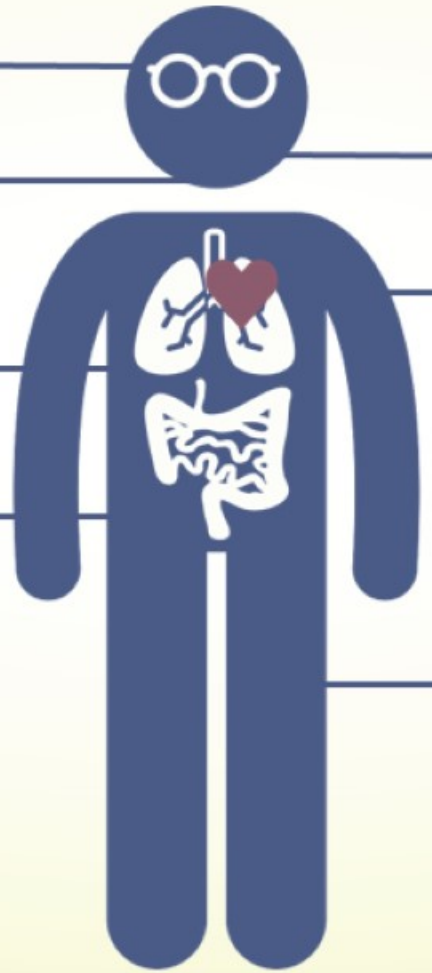
Ocular: Pruritus, conjunctival erythema, tearing, periorbital edema

Oral: Angioedema of the lips, tongue, or palate; oral pruritus; tongue swelling

Lower respiratory: Cough, chest tightness, dyspnea, wheezing, intercostal retractions, accessory muscle use

Gastrointestinal: Nausea, abdominal pain, reflux, vomiting, diarrhea, irritability and food refusal with weight loss over time

Other: Uterine contractions, sense of "impending doom"



Upper respiratory: Nasal congestion, pruritus, rhinorrhea, sneezing, laryngeal edema, hoarseness, dry staccato cough

Cardiovascular: Tachycardia (occasionally bradycardia in anaphylaxis), hypotension, dizziness, fainting, loss of consciousness

Cutaneous: Erythema, pruritus, urticaria, morbilliform eruption, angioedema, eczematous rash

Yawn BP, Fenton MJ. *Am Fam Physician*. 2012;86(1):43-50.

Clinical History and Physical Exam

- Clinical history and physical examination are used to determine testing strategies and interpretation of results
- History can include timing of reactions, common culprit foods, related allergic conditions, other known food allergies, and symptoms
- Physical examination can differentiate between acute presentation and chronic symptoms

Questions to Ask: Food Allergen

What food is suspected of triggering the reaction?

What other foods were ingested at the time? Are all ingredients known?

How much of the suspected food was ingested?

How was the food prepared and served?

Questions to Ask: Symptoms

What symptoms were involved in the reaction?

What was the duration between exposure and symptom onset?

How was the reaction treated?

Was the reaction with cutaneous or inhalation exposure?

Did similar symptoms develop on previous occasions when the food was ingested?

Does the patient have a history of avoiding the suspected food?

Questions to Ask: Contributing Factors

Was the patient exercising prior to reaction?

Has the patient recently undergone a blood transfusion or organ transplant?

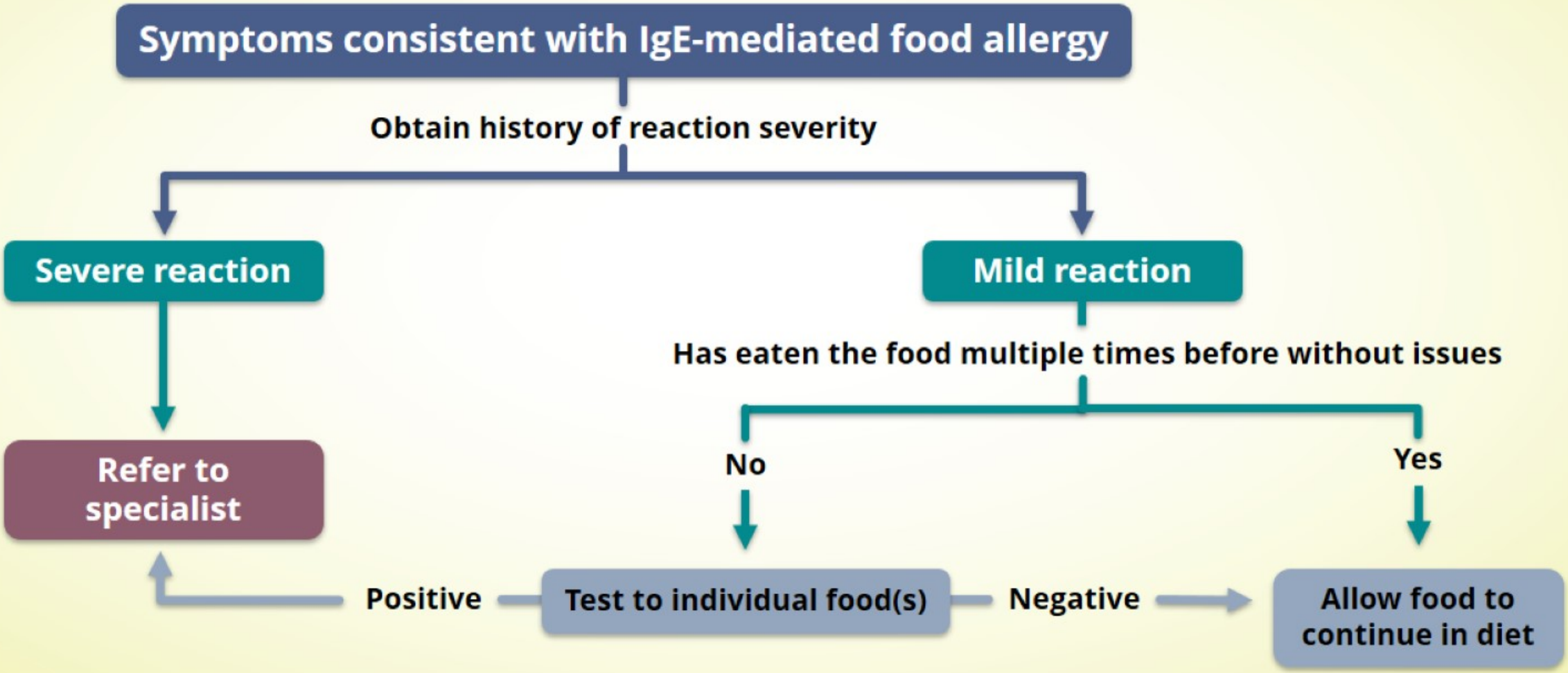
Are there other variables that may influence severity (eg, pollen levels, heat)?

Were any medications ingested around the same time?

MODULE 2:

- IgE-mediated food allergies and testing strategies
- Introduce non-IgE-mediated food allergies and when to test
- Food challenges

Evaluation of Suspected Food Allergy



Boyce et al, *J Allergy Clin Immunol* 2010;126(6):1105-1118.

Differential Diagnosis of Food Allergy

Acute Symptoms	Cutaneous Symptoms	Gastrointestinal Symptoms
Other allergens (eg, medications, insect stings or bites)	Eczematous flares in children with atopic dermatitis	Reflux
Chemical effects or irritant effects of foods (eg, capsaicin in spicy foods)		Infection (eg, parasitic, bacterial)
Gustatory flushing syndrome		Anatomic or metabolic abnormalities
Food poisoning		

Yawn BP, Fenton MJ. *Am Fam Physician*. 2012;86(1):43-50.

Understanding Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

- **Positive predictive value (PPV)** is the probability that patients with a positive screen test are truly positive for allergy

- **Negative predictive value (NPV)** is the probability that patients with a negative screen test are truly negative for allergy

Understanding Sensitivity and Specificity

- **Sensitivity** refers to the proportion of true positive patients that are correctly identified in testing
  - Also known as **true positive rate**

- **Specificity** refers to the proportion of true negative patients that are correctly identified in testing
  - Also known as **true negative rate**

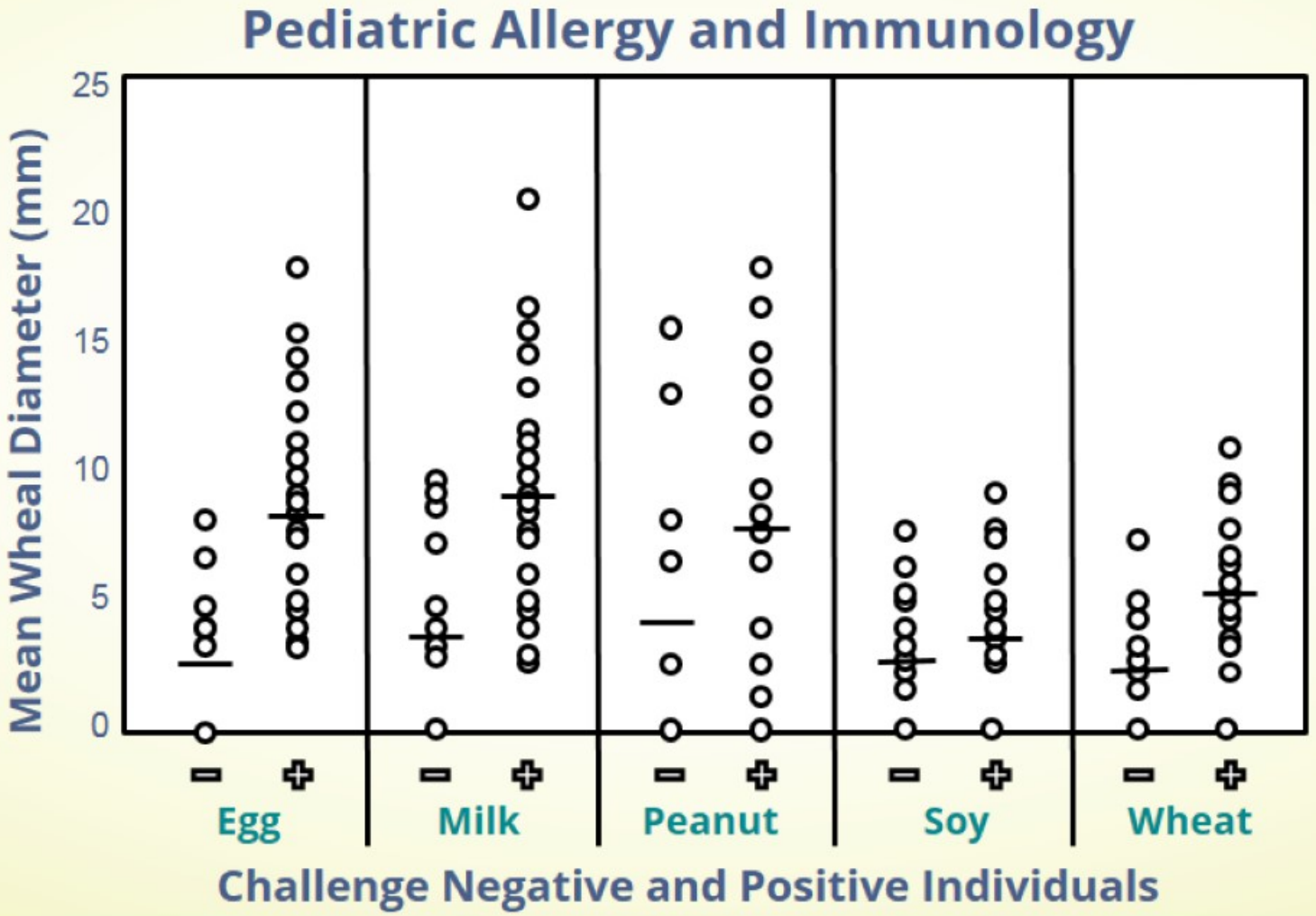
Testing for IgE-Mediated Food Allergy: Skin Prick Testing

- Skin testing options
  - Skin prick
  - Intradermal
  - Atopy patch
- Testing results
  - Wheal size
- Recommended for use in assistance of identification of provoking food, but not as a routine diagnostic[1]

Photo with permission from Allergy Media Kits, 2005

1. Boyce JA, et al. *J Am Acad Dermatol*. 2011;64(1):175-192.

Skin Prick Testing



Eigenmann PA, Sampson HA. *Pediatr Allergy Immunol*. 1998;9(4):186-191.

Skin Prick Testing: Predictive Value

Wheal Diameter (mm)	Likelihood Ratios of Positive Food Challenge		
	Cow's Milk	Egg	Peanut
1	3.1	1.4	2.0
2	3.1	1.7	2.0
3	3.8	2.8	3.4
4	5.8	3.1	6.3
5	7.3	7.3	18.0
6	13.2	12.5	16.7
7	16.2	∞	∞
8	∞	∞	∞

Allergen	Wheal Diameter for 100% PPV	
	Children Aged 0-2 Years	All Children
Milk	≥ 6 mm	≥ 8 mm
Egg	≥ 5 mm	≥ 7 mm
Peanut	≥ 4 mm	≥ 8 mm

Sporik R, et al. *Clin Exp Allergy*. 2000;30(11):1540-1546.

Testing For IgE-Mediated Food Allergy: In Vitro Testing

- Immunoassays identify food-specific IgE antibodies in blood serum
  - **RAST**: Radioallergosorbent test (not frequently used; term commonly used incorrectly for in vitro testing in general)
  - **FEIA**: Fluorescent enzyme immunoassay (commonly known as ImmunoCAP, or simply CAP)

- Results are reported as **food-specific IgE levels** (kU$_A$/L: kilounits of allergen per liter)

Advantages and Disadvantages of In Vitro Tests

Advantages	Disadvantages
• Widely available to clinicians • Unaffected by antihistamines or other medications in the system • Unaffected by other dermatological conditions which may confound skin prick tests	• Generally less sensitive than skin prick tests[1] • More expensive than skin prick tests • Results are not immediately available • Interpreting results may be difficult for nonspecialists

Hamilton RG, et al. *J Allergy Clin Immunol*. 2004;114(2):213-225.

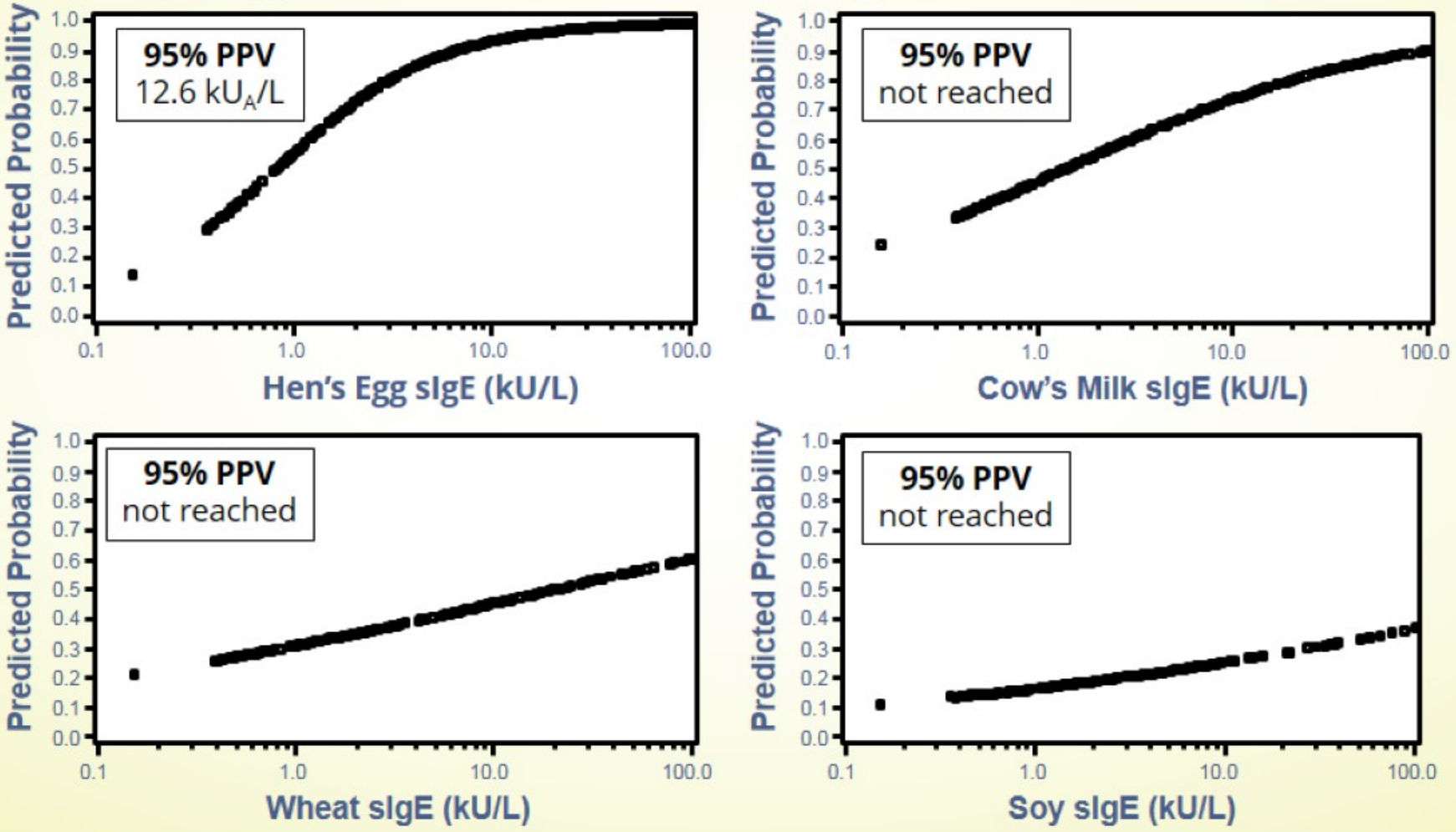
PPV of In Vitro Testing

	Specific IgE Level (kU_A/L)	PPV	Specific IgE Level (kU_A/L)	NPV
Egg	6	95%	<0.6	90%
Egg (<2 yo)	31	90%	0.59	100%
Milk	32	95%	<0.8	95%
Milk (<2 yo)	5	95%	0.35	81%
Peanut	15	95%	<0.35	85%
Fish	20	95%	<0.9	95%
Wheat	100	75%	<5	95%
Soy	65	50%	<2	95%

NPV, negative predictive value; PPV, positive predictive value; yo, years old.

1. Sampson HA, Ho DG. *J Allergy Clin Immunol*. 1997;100(4):444-451.
2. García-Ara C, et al. *J Allergy Clin Immunol*. 2001;107(1):185-190.
3. Kim J, et al. *Allergy Asthma Immunol Res*. 2015;7(4):332–338.

Predicted Probabilities of Showing a Positive Oral Food Challenge at a Given sIgE Value



Adapted from Celik-Bilgili S, et al. *Clin Exp Allergy*. 2005;35(3):268-273.

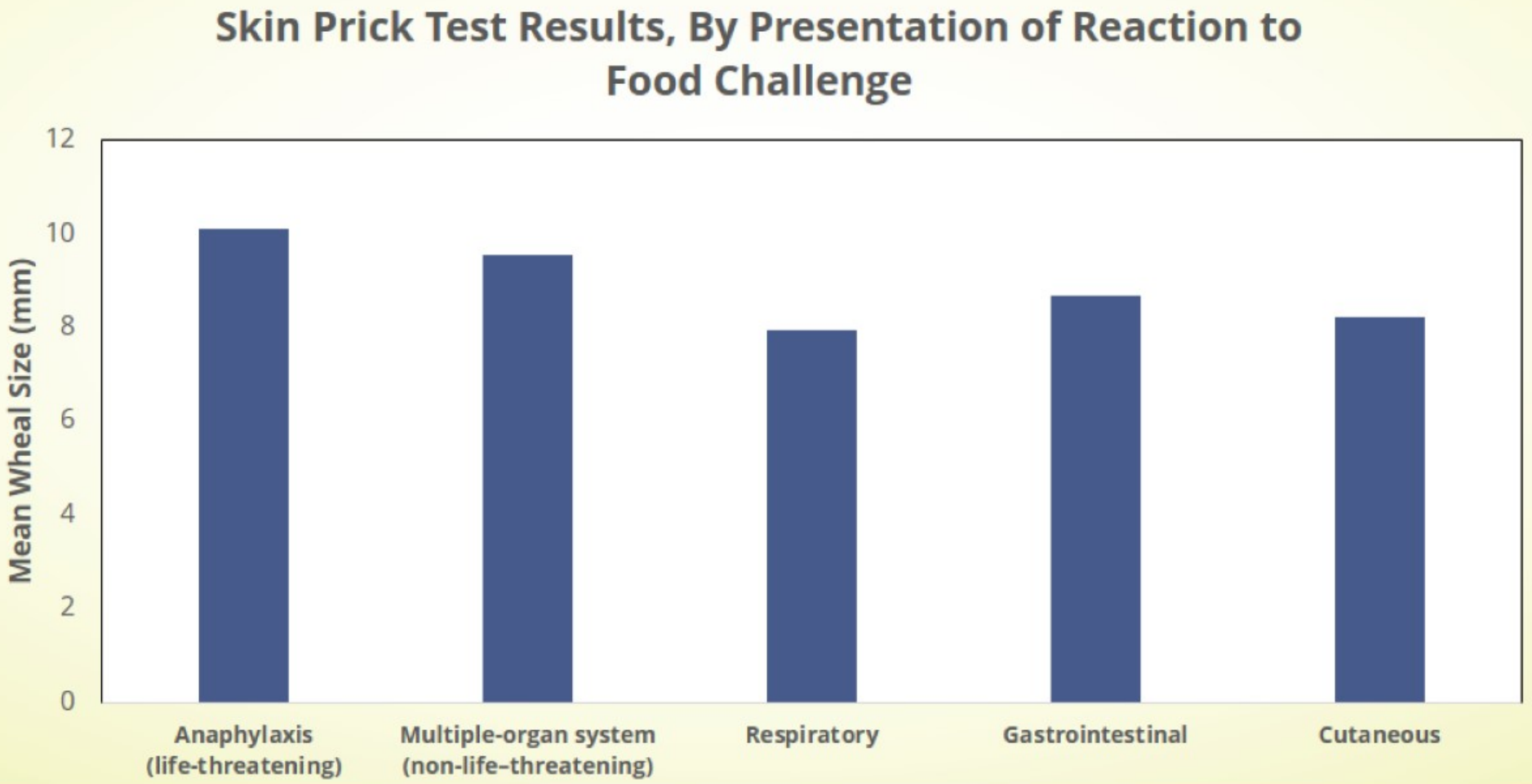
In Vitro Testing: Comparison of RAST Studies

	Sampson (2001)[1]	Boyano-Martinez et al (2001)[2]	Osterballe & Bindslev-Jensen (2003)[3]	Celik-Bilgili et al (2005)[4]
Number of Patients	100	81	56	501
Median Age	3.8 years	16 months	2.2 years	13 months
% Atopic Dermatitis	61%	43%	100%	88%
Egg				
PPV	98%	94%	> 95%	95%
Specific IgE Level (kU_A/L)	7	≥ 0.35	1.5[†]	12.6
Milk				
PPV	95%			90%
Specific IgE Level (kU_A/L)	15			88.8

[†]sIgE level for egg white.
RAST, radioallergosorbent test; PPV, positive predictive value.

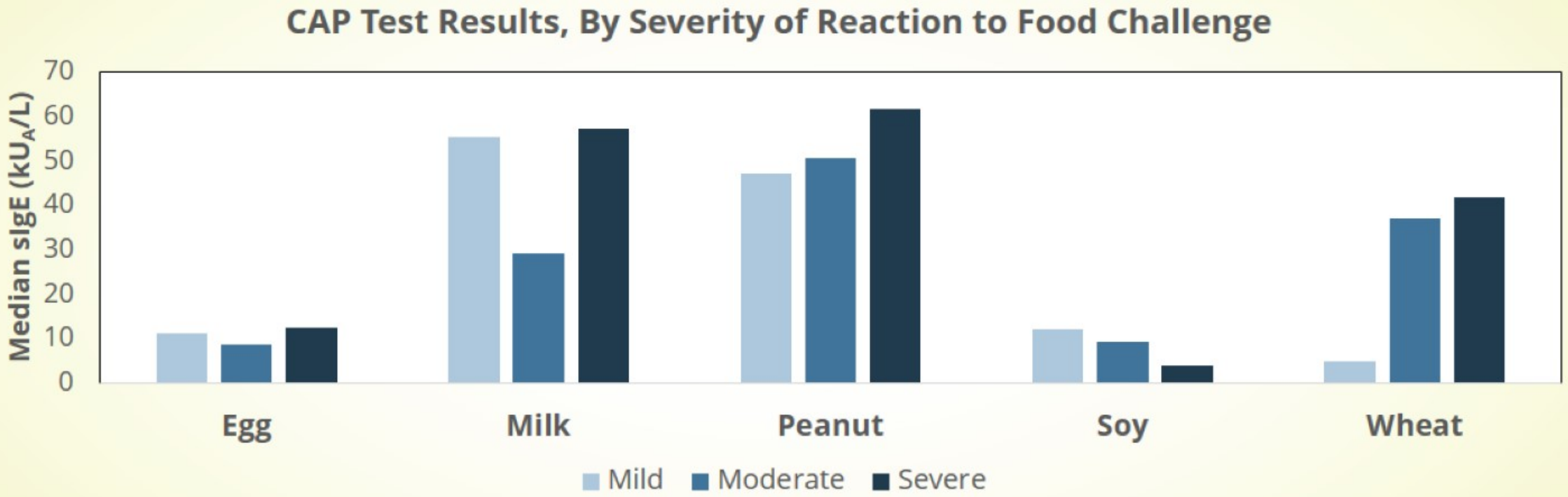
1. Sampson HA. *J Allergy Clin Immunol*. 2001;107(5):891-896.
2. Boyano Martínez, T et al. *Clin Exp Allergy*. 2001;31(9):1464-1469.
3. Osterballe M, Bindslev-Jensen C. *J Allergy Clin Immunol*. 2003;112(1):196-201.
4. Celik-Bilgili S, et al. *Clin Exp Allergy*. 2005;35(3):268-273.

Are Skin Prick Tests or CAP Predictive of Severity?



Spergel JM, et al. *Ann Allergy Immunol*. 2004;92(2):217-224.

Are Skin Prick Tests or CAP Predictive of Severity?



CAP and skin prick tests are **not predictive** of the severity of reaction, though they do play a role in predicting which patients may develop tolerance to a food.

Sampson HA, Ho DG. *J Allergy Clin Immunol*. 1997;100(4):444-451.

Interpretation of Results

- A **positive** skin prick test or CAP indicates the presence of IgE antibody, **not** clinical reactivity
  - 20% to 60% false positive rate, depending on allergen and testing method
- A **negative** skin prick test or CAP essentially excludes the presence of IgE antibody
  - Less than 15% false negative rate

RAST, radioallergosorbent test.

Bernstein IL, et al. *Ann Allergy Asthma Immunol.* 2008;100(3 Suppl 3):S1-148.

Cross-Reactivity

Common glycoproteins between plants and invertebrates can lead to IgE antibody cross-reactivity among vegetable foods, pollen, and—to a lesser extent—insect venoms.

Patient Characteristics		Test Results (median [range])			
Peanut Allergy	Pollen Symptoms	Peanut SPT, mm	Food Challenge Threshold, mg	ImmunoCAP Peanut SIgE, kU_A/L	Immunolite Peanut sIgE, kU_A/L
Yes	No	8	100	92 (1.4 to >100)	>100 (1.1 to >100)
Yes	Yes	10	265	49 (3.3 to >100)	>100 (3.1 to >100)
No	No	0	ND	<0.35 (<0.35–0.35)	<0.10 (<0.10–0.91)
No	Yes	0	ND	0.68 (<0.35–53)	0.11 (<0.10–14)

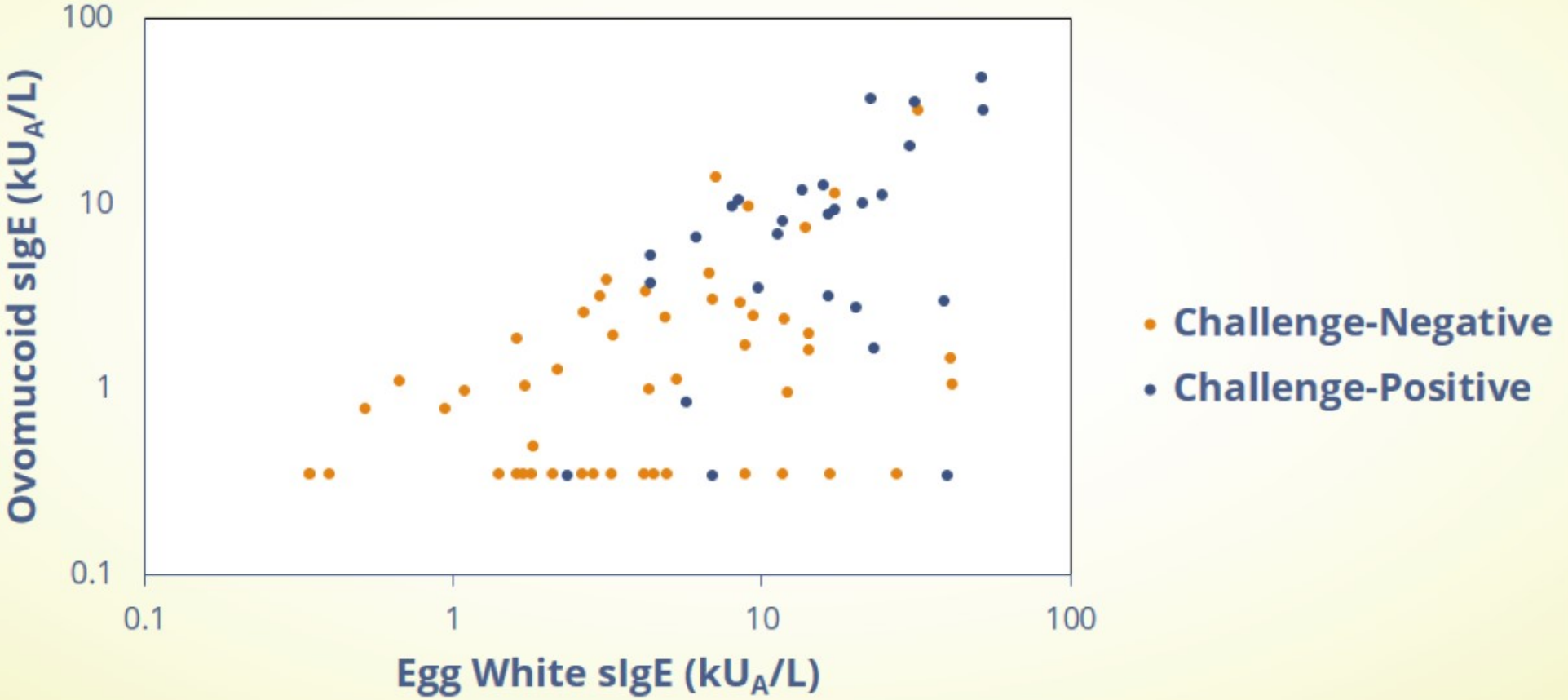
ND, not determined; SPT, skin prick test results.

Guilloux L, et al. *Int Arch Allergy Immunol*. 2009;149(2):91-97.

Testing for IgE-Mediated Food Allergy: Component Testing

- Component testing breaks down traditional extract samples into single proteins such that reactivity to individual components are resolved
- Component testing may help to differentiate between cross-reactivity
- **Example**: Peanut allergy
  - Ara H8 reacts with Bet V1
  - Ara H2/3 is a more sensitive marker for peanut allergy than whole peanut sIgE

Component Testing – Ovomucoid



Adapted from Haneda Y, et al. *J Allergy Clin Immunol*. 2012;129(6):1681-1282.

Peanut Component Testing: Considerations

Factors that make component testing **less** likely to be informative	Factors that make component testing **more** likely to be informative
• A recent convincing clinical reaction	• Mild reactions or no reaction history
• A remote significant clinical reaction in a patient with peanut sIgE ≥ 15 kU_A/L	• Remote clinical reaction with development of birch sensitization over time
• Peanut sIgE > 25 or < 0.35 kU_A/L	• Peanut sIgE 0.35 to 15 kU_A/L
• Lack of birch sensitization	• Birch sensitization
• Younger children	• Older persons

Sicherer SH, Wood RA. *J Allergy Clin Immunol Pract.* 2013;1(1):1-13.

Non-IgE-Mediated Food Allergy and Gastrointestinal Syndromes

- Pediatric gastrointestinal syndromes are non-IgE-mediated and are typically induced by **milk** or **soy**

	Enterocolitis	Enteropathy	Proctitis
Age of Onset	Infant	Infant/Toddler	Newborn
Duration	3–5 years	12–24 months	9–12 months
Characteristics	Vomiting, diarrhea, failure to thrive, shock, lethargy	Malabsorption, villous atrophy, diarrhea	Bloody stools, no systemic symptoms, eosinophilic

Cianferoni A, Spergel JM. *Allergol Int*. 2009;58(4):457-466.

Food Protein-Induced Enterocolitis (FPIES)

- Age of onset is usually less than 12 months with a 0.5% prevalence rate
- **Milk** and **soy** are most common triggers, but rice, chicken, oat, egg, beef, vegetables, grains, or peanuts may be causative as well
  - Patients often react to more than one food
- FPIES will test **negative** on skin prick tests and blood tests

For more information on FPIES, see
Guidelines for Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome
with Anna Nowak-Wegrzyn, MD, PhD.

Eosinophilic Esophagitis (EoE)

- Prevalence of 1 in 2000 children, most commonly in boys (3:1 ratio)
- Symptoms vary with age
  - **Infants and toddlers** – reflux symptoms (vomiting, regurgitation, heartburn, epigastric pain, growth concerns)
  - **School-age children** – abdominal pain
  - **Adolescents and adults** – dysphagia (symptoms are often intermittent)

For more information on EoE, see
Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients with EoE
with Mirna Chehade MD, MPH.

Testing for Non-IgE-Mediated Food Allergy

- Skin prick testing and in vitro testing for non-IgE-mediated food allergies is **not recommended**

- Testing for non-IgE-mediated food allergies may be done in conjunction with a gastroenterologist
  - Endoscopy
  - Colonoscopy
  - Gastrointestinal biopsy

Elimination Diets and Food Challenges

- Elimination diets typically last 1–6 weeks
  - Suspected foods should be eliminated from the diet, or physicians can prescribe a limited "eat only diet" or elemental diet
- Oral food challenges should be done only under direct supervision of a medical doctor with emergency medications available
  - Oral food challenges should be preceded by an elimination diet to ensure the suspected allergen is removed from the system
  - Challenges can be **open**, **single-blind**, or **double-blind, placebo-controlled (DBPCFC)**

Yawn BP, Fenton MJ. *Am Fam Physician*. 2012;86(1):43-50.

Indications for Food Challenge

- **Reactivity to a food**
  - Reaction with multiple positive foods and the cause is unclear
  - History is unconvincing but a positive skin test is observed
  - Patients with a history of atopic dermatitis and a positive skin test
- **If tolerance has developed**
  - History of previous reaction in the past
  - Evaluate tolerance to baked form of a food
- **Level of reactivity**
  - Food challenge is not indicated if there has been a recent, severe anaphylactic IgE-mediated reaction

Food Challenge Guidelines

Medical factors to consider	Patient factors to consider
• Risk and safety of reaction to food challenge • Nutritional importance of the implicated food • Physiological factors	• Quality of life associated with avoidance of the food • Ability and willingness of patient to cooperate with challenge procedures

! Oral food challenges should always be completed under the supervision of a specialist.

Outcomes of Food Challenge

- **Negative challenge** – Food can be eaten ad lib
  - Patients should be counseled to avoid potential cross-contamination with other allergens that may cause reaction
- **Positive challenge** – Depends on level of sensitivity
  - Consider dose and severity
  - Future reactions may be unpredictable

Role of the Allergist

- Patients should be referred to an allergy specialist in cases of suspected IgE-mediated food allergy
  - Instruct patients to avoid suspected food until further evaluation, but take care not to impose restrictions that put patients at nutritional risk
  - If anaphylaxis is **not a risk**, antihistamines can be used to treat symptoms
- If non-IgE-mediated allergy is expected, a gastroenterologist, in combination with an allergist, should be consulted

> ! **Skin testing is the preferred method of allergy diagnosis and should be performed by an allergist.**

Evaluating Resolution of Allergy

- Strict avoidance is recommended for children with food allergies, but is not associated with increased acquisition of tolerance[1]
  - Strict avoidance is recommended to prevent accidental over-exposure to allergen
- Current evidence suggests that low-level exposure to an allergen has no effect on allergy resolution[2]
- Oral food challenges are required to demonstrate resolution of reactivity to a given food
  - Skin prick tests and in vitro tests are not reliable for assessing resolution[3,4]

1. Allen CW, et al. *Pediatr Allergy Immunol*. 2009;20(3):213-218.
2. Sicherer SH, et al. *J Allergy Clin Immunol Pract*. 2016;4(2):239-245.e4.
3. Hill DJ, et al. *Clin Exp Allergy*. 1993;23(2):124-131.
4. Perry TT, et al. *J Allergy Clin Immunol*. 2004;114(1):144-149.

MODULE 3:

- Unproven or disproven allergen tests
- Future diagnostic tools

Unproven and Disproven Tests for Food Allergy

- **Provocation-neutralization testing** – Food extracts are injected intradermally in increasing concentrations until symptoms are induced, followed by re-exposure to relieve the symptoms
  - Intradermal testing is **not recommended** due to risk of systemic reactions
  - These testing methods have been shown to be no more likely to induce or alleviate symptoms than saline solution[1,2]
- **Cytotoxic testing** – White blood cells from a patient are placed on a slide containing samples of the suspected allergen and monitored for morphological changes
  - More advanced imaging techniques are needed to visualize cytotoxic response to allergen exposure

1. Jewett DL, et al. *N Engl J Med*. 1990;323(7):429-433.
2. Fox RA, et al. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):907-911.

Unproven and Disproven Tests for Food Allergy *(continued)*

- **Applied kinesiology** – Patients hold a glass vial of suspected food allergen in one hand while muscle strength is measured in the opposite arm
  - Multiple studies have failed to demonstrate reproducible or reliable results[1,2]
- **Hair analysis** – Hair samples are submitted to a laboratory and tested against as many as 600 food and non-food allergens using unspecified diagnostic methods
  - A study of multiple asymptomatic patients who sent in samples found lack of reproducibility in results and a high rate of false-positives[3]

1. Garrow JS. *Br Med J (Clin Res Ed).* 1988;296(6636):1573-1574.
2. Schwartz SA, et al. *Explore (NY).* 2014;10(2):99-108.
3. Sethi TJ, et al. *Lancet*. 1987;1(8524):92-94.

Unproven and Disproven Tests for Food Allergy *(continued)*

IgG and IgG4 testing – Using similar in vitro methods as those that quantify IgE antibodies, the amount of immunoglobulin G (IgG) and IgG subclass 4 (IgG4) antibodies is quantified in the blood

- Assay methodology is standardized and reliable
- Utility of results is questionable

"[The] presence of specific IgG to food is a marker of exposure and tolerance to food… Hence, positive test results for food-specific IgG are to be expected in normal, healthy adults and children."

– Canadian Society of Allergy and Clinical Immunology†

†Carr S, et al. *Allergy Asthma Clin Immunol*. 2012;8(1):12.

New Research in Improved Diagnostic Tools

Recombinant allergens – Allergens are generated using genetic engineering to represent pure components of traditionally used whole allergen extracts

- Similar to highly purified allergen samples
- Results appear to vary depending on allergen source

Accuracy of Recombinant Allergen Results Compared With Traditional Diagnostic Methods		
Improved Accuracy	**Comparable Accuracy**	**Insufficient Accuracy**
Anisakis simplex (Caballero et al. 2012)[1]	Birch pollen (Smoldovskaya et al. 2016)[3]	Timothy grass (Smoldovskaya et al. 2016)[3]
Sesame seeds (Maruyama et al. 2015)[2]	Cat dander (Smoldovskaya et al. 2016)[3]	

1. Caballero ML, et al. *Int Arch Allergy Immunol*. 2012;158(3):232-240.
2. Maruyama N, et al. *Clin Exp Allergy*. 2016;46(1):163-171.
3. Smoldovskaya O, et al. *Allergy Asthma Clin Immunol*. 2016;12:9.

New Research in Improved Diagnostic Tools

- **Determination of IgE-binding epitopes** – Identification of clinically relevant IgE-binding epitopes can aid in identification of patients with allergy as well as severity of reaction
  - Recombinant allergens can aid in the identification of IgE-binding epitopes
- Linear epitopes are identified using overlapping peptides tested for antibody reaction using nitrocellulose membranes or glass slides
- Conformational epitopes are formed by spatial arrangement of amino acids and require more sophisticated techniques for identification (eg, X-ray crystallography, nuclear magnetic resonance)

Matsuo H, et al. *Allergol Int*. 2015;64(4):332-343.

New Research in Improved Diagnostic Tools

Atopy patch testing – A solution containing food allergen is topically applied to the skin and assessed for reaction

- Currently no standardized testing or interpretation of results

Results of Atopy Patch Testing	Sensitivity			Specificity		
	Cow's Milk	Wheat	Soy	Cow's Milk	Wheat	Soy
Atopic Dermatitis						
Mansouri et al (2018)[1]	91.7%	100%	87.5%	72.7%	75%	-
Visitsunthern et al (2016)[2]	42.9%	33.3%	44.4%	95.8%	92.3%	82.4%
Niggemann et al (2008)[3]	31%	27%	23%	95%	89%	86%
Eosinophilic Esophagitis						
Spergel et al (2012)[4]	29.9%	57.1%	52.5%	87%	81.8%	86.7%

1. Mansouri M, et al. *Int Arch Allergy Immunol*. 2018;175(1-2):85-90.
2. Visitsunthorn N, et al. *Ann Allergy Asthma Immunol*. 2016;117(6):668-673.
3. Niggemann B, et al. *Allergy*. 2000;55(3):281-285.
4. Spergel JM, et al. *J Allergy Clin Immunol*. 2012;130(2):461-467.e5.

Key Takeaways

- A thorough clinical history and physical exam are key for diagnosing potential food allergies
- Initial testing for suspected IgE-mediated allergies can be completed by clinicians, but serious reactions and suspected non-IgE-mediated allergies should be referred to a specialist
- Food challenges should always be performed under direct supervision of a specialist