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Food Allergy Testing

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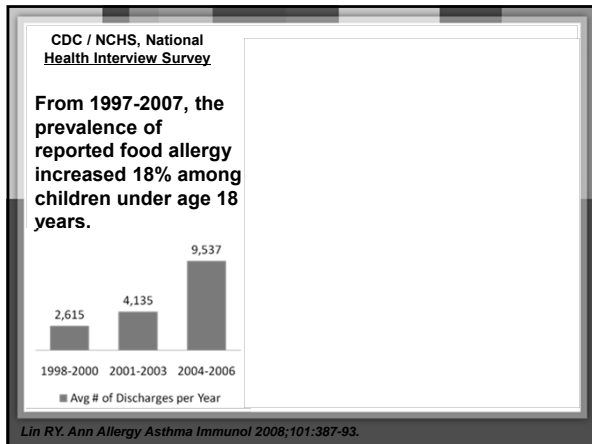
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- I do not intend to discuss an unapproved / investigative use of a commercial product / device in my presentation.


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Learning Objectives

After completion of this activity, participants will be able to:

- Recognize the importance of accurate food allergy testing in children
- List the variables that influence the interpretation of food allergy blood tests
- Recognize unproven methods for food allergy testing



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Overestimation of Food Allergies

- **Perceived:**
 - 12-30% of parents believe their children have at least one food allergy
 - 13-33% of adults believe they have food allergies
- **Actual:**
 - 3 - 8% of children <3 - 6 years have verifiable food allergies
 - 2 - 4% of general population have verifiable food allergies
 - May be higher in selected groups
 - + Atopic dermatitis (eczema) -30-50+

Rona R.J. *J Allergy Clin Immunol.* 2007;120:638-46; Sicherer SH. *J Allergy Clin Immunol.* 2010;125:s116-s125

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Quality of Life in Families with Food Allergy


- **Children** with food allergies report worse QOL scores compared to those with irritable bowel synd., rheumatologic diseases, & diabetes
 - In general, the most affected scores are in social (especially social interaction), emotional (e.g. fear) and psychosocial (e.g. anxiety) scales
 - But also "bodily pain", "general health" & "vitality"
- **Parents** of food-allergic children also report worse scores on QOL surveys

Primeau MN. *Clin Exp Allergy*;2000;30:113-43; Flokstra de Blok BMJ. *Allergy* 2010;65:238-44; Cummings A.J. *Ped Allergy Immunol.* 2010;21:586-94; Lieberman JA. *Curr Opin Allergy Clin Immunol* 2011;11:236-42.

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Bullying Due to Food Allergies




- Of 353 respondents (parents and kids) 24% reported being bullied, teased or harassed due to their food allergies
 - Verbal
 - Physical: allergen thrown at them, their food purposely contaminated with allergen

Lieberman JA. *Ann Allergy Asthma Immunol.* 2010;105:282-6.

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Costs of Food Allergies



- 2007: Economic burden of allergic reactions cause by foods ~ \$½ billion
 - \$307 million direct costs
 - \$203 million indirect costs
- Amazon.com (per oz of powder ~2014)
 - Milk / soy intact protein formula ~\$1.08/oz
 - Extensively hydrolyzed formula ~\$1.80/oz
 - Amino acid formula ~\$2.60/oz

Patel D. *J Allergy Clin Immunol.* 2011;128:110-5.


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Nutritional Consequences


- Failure to thrive
- Macronutrient deficiencies
 - Protein (kwashiorkor)
- Micronutrient deficiencies
 - Calcium with rickets & hypocalcemic sz's
 - Iron deficiency with anemia, zinc
 - Multiple vitamins- D, B-complex, E
- Electrolyte abnormalities

Alvares M. *Pediatrics.* 2013;132:e229-32; Nolmark L. *Ped Allergy Immunol.* 2008;19:188-95; Kirby M. *Ped Clin N Am.* 2009;56:1085-1103; Isolauri E. *J Pediatr* 1998;132:1004-9; Christie L. *J Am Diet Assoc.* 2002;102:1648-51

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Importance of Accurate Food Allergy Testing in Children

- The frequency and severity of food allergic reactions is truly increasing
 - But...the frequency of food allergies are also over-estimated by patients
- Food allergies have a significant negative impact on children / families
- Food allergies have significant economic costs for individuals and the system
- May have significant nutritional consequences


Accurate Food Allergy Testing in Children

- Impact of false positive diagnosis:
 - Unnecessary negative psychosocial, financial & nutritional consequences
- Impact of false negative diagnosis:
 - Ongoing risk for exposure to food and potential serious allergic reactions or worsening chronic disease

Boyce JA. NIAID-Sponsored Panel. Guidelines for the Diagnosis and Management of Food Allergy. J Allergy Clin Immunol. 2010;126:s1-s58.


How To Diagnose Food Allergies

- History and physical exam
- Specific food tests
 - Blood tests (IgE and non-IgE)
 - Skin testing (prick and patch)
- Food challenges
- Unproven testing methods

Boyce JA. NIAID-Sponsored Panel. Guidelines for the Diagnosis and Management of Food Allergy. J Allergy Clin Immunol. 2010;126:s1-s58.

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Know Your Foods

Eight foods account for 90% of all food allergic reactions

Egg Milk Soy Wheat Peanut Tree Nuts Seafood Shellfish

↑ More common in children More common in adults ↓

- Rarely necessary to tests for other foods
- Tests have highest predictive value for these foods

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Know Your Diseases

Often Associated With Food Allergies

- Urticaria - *acute*
- Anaphylaxis
- Atopic dermatitis
- Eosinophilic esophagitis and gastroenteritis
- FPIE
- Oral allergy syndrome

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History Suggestive of Food Allergy

- Immediate onset of symptoms
 - Usually minutes, occasionally hours
 - Rarely sev. hours-days (certain GI, eczema)
- Multiple systems (resp., skin, GI)
 - Isolated single system can occur
- Happens each time food is eaten in same form
- Does not occur if food is not eaten
- Very small amounts can trigger symptoms
- Responsive to allergy therapy

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History Not Suggestive of Food Allergy

- Delayed onset of symptoms
 - Day or days
- Prolonged duration (days to weeks)
- Only occurs with large quantities of food, or “cumulative” effect over days
- Occurs even when food is not eaten
- Doesn't occur each time food is eaten
 - In same “form” (low-heat vs high-heat)
- Atypical symptoms ('hyper', bruising, fever, etc)

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How Common are Delayed Onset of Symptoms?

Very Rare

Respiratory

- Rhinitis
- Conjunctivitis
- Wheeze/cough

Cutaneous

- Eczema**
- Flush*
- Itch*
- Angioedema*
- Urticaria

Gastrointestinal

- N/V/D
- Pain
- Hematochezia*
- Irritability**
- Food refusal**
- Weight loss**

Very Common

* = more likely than others in group to present later, but still more common overall to present early

With few exceptions, most food allergy symptoms present quickly after food is eaten

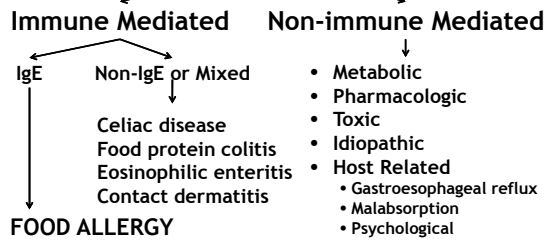
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Benefits of a Comprehensive Food Allergy History

- Can be “diagnostic” in some cases
 - Symptom + food diary
- Guide specific food tests
- Confirm the validity of food tests

Not all *adverse* reactions to foods are *allergic* reactions

ADVERSE REACTIONS TO FOODS



Boyce JA. NIAID-Sponsored Panel. Guidelines for the Diagnosis and Management of Food Allergy. J Allergy Clin Immunol. 2010;126:s1-s58.


Food Allergy Physical Exam

- No specific physical findings
 - Except for non-specific acute allergic (urticaria, angioedema, eczema, etc)
- Mostly used to assess for signs of underlying non-allergic disease
 - Overall nutritional status

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Diagnostic Tests

MCHUMOR.com by T. McCracken




"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."
Theresa McCracken, used with permission.

- **IgE testing**
 - Skin prick testing
 - Blood food-specific IgE
- **Oral Challenge**
- **Non-IgE testing**
 - Patch testing
 - Basophil release
- **Unproven Techniques**

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Skin Testing

- **Rapid and safe assessment of food-specific IgE**
- **Skin prick testing (SPT)**
 - “Scratch” tests → antiquated method
 - Intradermal (ID) food tests not recommended
 - ID tests are still performed selectively for aeroallergens, medications and venoms, but not for foods
 - Scoring: size (mm) of wheal (less so flare)
- **“Prick-Prick” testing useful for fresh food testing (especially fruits and vegetables)**
 - Prick food - then prick patient
- **Blocked by H1-antagonists**

Blood IgE Testing

- “RAST” often used as “generic” name of blood allergy test for specific IgE
- Many proprietary tests available
 - ImmunoCAP® - has most clinical studies correlating with oral food challenges
 - Immulite®
 - Turbo RAST®
- Score (ImmunoCAP): <0.35 kU/L ↔ >100 kU/L
 - Other scales for different brands
- Not affected by H1-blockers

Food-Specific IgE Testing

(not a very good test)

- Positive test indicates “sensitivity” (presence of IgE against food), but not necessarily “reactivity” (clinical reaction to food)
 - Many people have detectable IgE to foods, but have absolutely no symptoms
 - Seen with all other antigens (venom, medications, aeroallergens....)
- Can NOT make the diagnosis of food allergy based solely on an elevated IgE

Pastorella EA. J Allergy Clin Immunol. 1995;96:580-7; Golden DBK. J Allergy Clin Immunol. 2011;128:852-4 (e1-e23).

Food-Specific IgE Testing

(not a very good test)

- Sensitivity of IgE tests is generally high
 - Very good at showing what patient is NOT allergic to (high negative predictive value (NPV))
 - Skin test NPV (>90%) > blood IgE NPV (~75-90%)
- Specificity for “random” screen IgE tests is low
 - Low positive predictive value (PPV) ~<50%
- Specificity & PPV of test improves when using “targeted” testing guided by clinical history.
 - Dependent on level of IgE, specific food, clinical hx
 - PPV may be as high as >95%

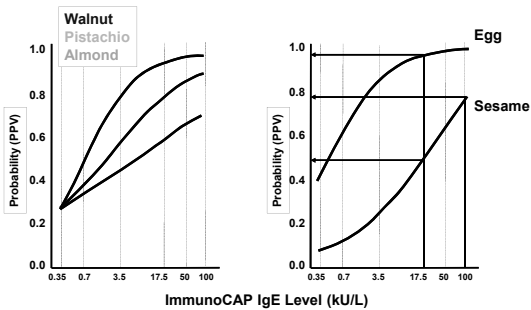
General Interpretation of Food Tests

- General perception
 - The more positive the test (bigger size skin test, high value of blood IgE) → the more severe the food allergy
- More accurate perception
 - The more positive the test (bigger size skin test, high value of blood IgE) → the more likely the patient is allergic to the food

Interpretation of Food-Specific IgE Blood Tests

- Level of IgE
- Specific food
- Age of child
- Underlying disease
- Clinical history
- Preparation of the food (milk, egg)

Predicting Clinical Reactivity Based on Specific IgE Level



Maloney JM. J Allergy Clin Immunol 2008;122:1457

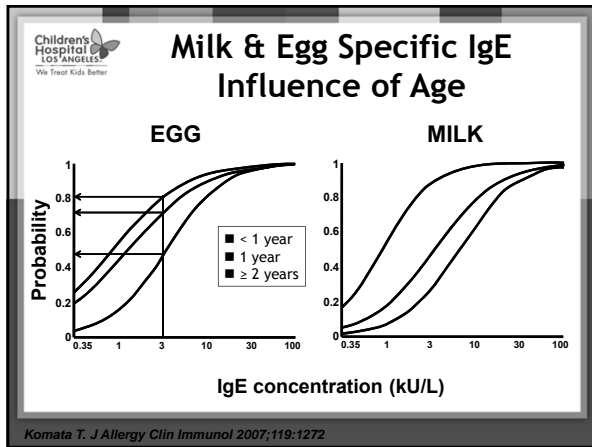
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Predictive Values for CAP RAST for Children with Suspected Food Allergy

Food Protein	90% Spec. (kU _A /L)	PPV %	95% NPV (kU _A /L)	90% NPV (kU _A /L)
Egg	7 (2*)	98	-	0.6
Milk	15 (5*)	95	0.8	1
Peanut	14	95	Best NPV = 85% @ 0.35	Best NPV = 85% @ 0.35
Fish	20	100	0.9	5
Soy	30	73	2	5
Wheat	26	74	5	9

* = ≤ 2 year old

Sampson HA. J Allergy Clin Immunol. 2001;107:891-6; Sicherer SH. J Allergy Clin Immunol. 2010;125:a116-s125



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Predictive Values for CAP RAST for Children with Atopic Dermatitis

Food Protein	95% PPV (kU _A /L)	90% PPV (kU _A /L)	95% NPV (kU _A /L)	90% NPV (kU _A /L)
Egg	6	2	-	0.6
Milk	32	23	0.8	1
Peanut	15	9	Best NPV = 85% @ 0.35	Best NPV = 85% @ 0.35
Fish	20	9.5	0.9	5
Soy	Best PPV = 50% @ 65	-	2	5
Wheat	Best PPV = 75% @ 100	-	5	79

Sampson HA. J Allergy Clin Immunol. 2001;107:891-6; Sicherer SH. J Allergy Clin Immunol. 2010;125:a116-s125

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Influence of Clinical History

History of past reaction to peanut		
IgE (kU/L)	Total	Failed Challenge
<0.35	38	24%
0.36 – 1.9	38	56%
2 – 4.9	27	60%
>5	7	100%

Perry TT. J Allergy Clin Immunol 2004;114:144.

You Can't Un-Fry an Egg

← Heated Milk Or Heated Egg →

- 100 children (2.1-17.3 yrs) with milk allergy
- Challenged with extensively heated milk products
 - ≥350°F for ≥ 30 minutes
- 75% tolerated heated milk
- 117 children (1.6-18.6 yrs) with egg allergy
- Challenged with extensively heated egg products
 - Baked products
- 54% tolerated heated egg

Nowak-Węgrzyn A. J Allergy Clin Immunol 2008;122:342; Lemon-Mule H. J Allergy Clin Immunol 2008;122:977.

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Which is Better Skin Test or Blood Test?

Summary ROC Curves for the Diagnosis of All Food Allergies, Cow's Milk Allergy, and Hen's Egg Allergy Comparing SPT With sIgE Testing

- In most cases, when properly chosen and interpreted, they have similar validity

Schneider Chafen JJ. JAMA. 2010;303:1848-56.

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What Foods?

- Should generally avoid testing for large “random” food panels
 - Should be driven by medical history
- Should generally avoid testing for foods that are currently being tolerated
- 90% of childhood food allergies
 - Milk, eggs, peanut, wheat, soy
- 90% of adult food allergies
 - Shellfish, peanuts, tree nuts, seafood

ALLERGY TO:	RELATED FOOD	APPROXIMATE RATE OF SENSITIVITY	APPROXIMATE CLINICAL REACTION RATE
Peanut	Other legumes (beans + soybean)	19-79%	3-5%
A Tree Nut	Other tree nuts	92%	12-37% , higher for: walnut-pecan almond-hazelnut cashew-pistachio
A Tree Nut	Peanut	59-86%	33%
Codfish	Another fish	5-100%	30-85%
Shrimp	Other crustacea	50-100%	38%
Crustacea	Mollusk	47%	14%
A mollusk	Other mullusks		49%
Wheat	Another grain	47-85%	20% (eczema)
Cow's milk	Goat / sheep milk Mare's milk	20-100%	>90% 5%
Hen's egg	Other eggs		Common (90%)

Sicherer S. J Allergy Clin Immunol. 2010;125:S116-S125; NIAID Panel. Guidelines for the Diagnosis and Management of Food Allergy. J Allergy Clin Immunol. 2010;126:s1-s58.

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Oral Food Challenge

- Gold standard for diagnosis of food allergy
 - Double blind placebo controlled (DBPCFC)
 - Open challenge, single blind
- When history and testing are inconclusive
 - Test for “outgrowing” of certain food allergies
- In properly selected patients, risk is low
 - Should be done under adequate supervision
 - Home “challenge -- de-challenge” diets, for very low risk

ANA

- A 10 year old boy presents with a fever
- Chemistry panel: ANA 1:80
 - Normal lab cut-off = <1:40
- You make the diagnosis of lupus and prescribe methotrexate

- 5-20% of the general population have a positive ANA
- Need more than a test result alone to make the diagnosis of lupus

Kavanaugh A. Arch Pathol Lab Med. 2000;24:71-81

IgG4

- 10 year old boy presents with abdominal pain
- IgG4 to milk, wheat, egg, beef, soy and chicken are elevated
- You advise elimination of all these foods from his diet

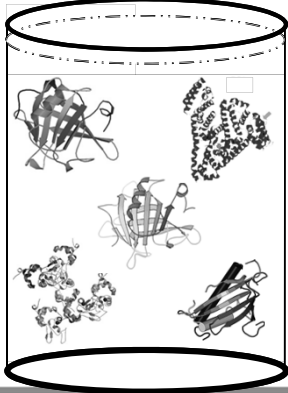
- Can detect IgG to foods in up to >80% of the population (increases with exposure)
- Most studies show IgG4 increases as children begin to outgrow allergy

Savilahti EM. J Allergy Clin Immunol. 2010;125:1315-21; Cerecedo I. J Allergy Clin Immunol. 2008;122:589-94.

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Unproven Methods for Food Allergy Testing

- “Valid” test, but not to diagnose allergy
 - IgG (especially IgG4) tests
 - Basophil histamine release (research)
- Non-standardized or unproven
 - Lymphocyte stimulation / cytotoxic tests
 - Mediator release assay (LEAP)
 - Electrodermal testing (Vega)
 - Provocation/neutralization
 - Facial thermography
 - Applied kinesiology
 - Reagenic pulse
 - Iridology
 - Hair analysis



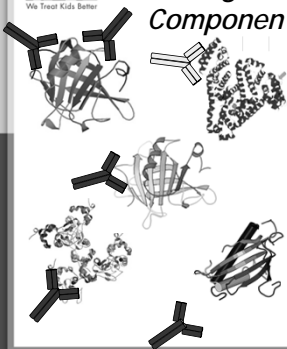
Milk

- Not a homogenous liquid
- Proteins, fats & carbohydrates
- Collection of several proteins
 - α -lactalbumin
 - β -lactoglobulin
 - Caseins (α -s1, α -s2, β , κ)
 - Serum albumin
 - Transferrin
 - Lactoferrin
 - others

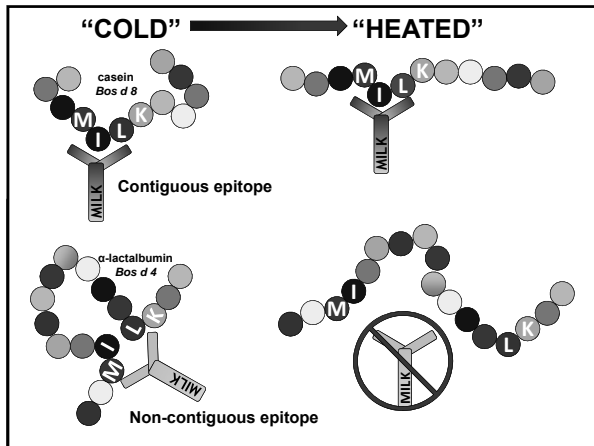
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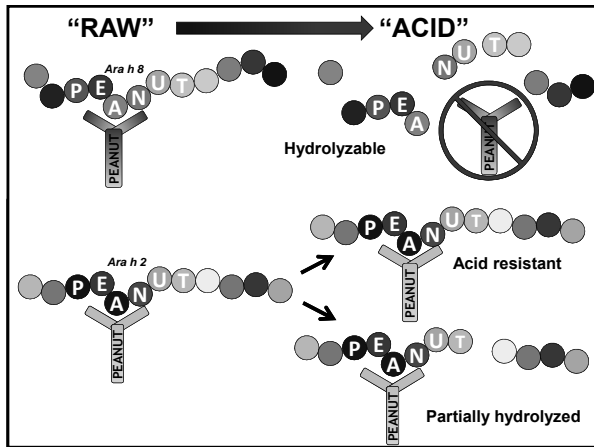
Building a Better Allergy Test

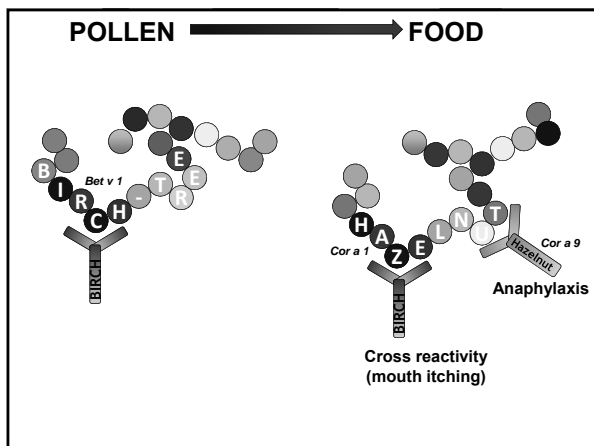
Component-Resolved Testing



- Most allergens have more than one epitope
- Some may bind IgE, others may bind IgG
- Some bind with very high avidity, others with low
- Some are resistant to acid hydrolysis, others not
- Some are resistant to heating, others not
- Some may cross react with other allergens, others not







Conventional vs Component Testing

- Conventional 'RAST' (or skin test)
 - Extract - mixture of multiple proteins, some allergenic and some not
- Component-resolved diagnostics (CRD)
 - Multiple individual proteins (chosen for clinical relevance) either isolated from natural source or produced recombinantly
 - Microarray chip



Conventional RAST

Positive if:

IgE 1

OR

IgE 2

OR

IgE 3

OR

IgE 4

detected

Component-Resolved

Sensitized
No clinical reaction
("false positive")

Allergic
High risk anaphylaxis
Cross react with other foods

Allergic
Likely to outgrow

Allergic
Likely to tolerate heated food

Overview of the allergic proteins in peanut (Arachis hypogea)

Name	Type protein
Ara h 1	Vicilin family of storage proteins
Ara h 2	Conglutin family, 2S albumin seed storage protein
Ara h 3/4	Glycinin
Ara h 5	Profilin
Ara h 6	Like Ara h 2
Ara h 7	Conglutin family, 2S albumin seed storage protein
Ara h 8	PR10 (Bet v 1) family
Ara h 9	Lipid transfer protein
Ara h 10	Oleosin
Ara h 11	Oleosin

Khal EF. Application of multiplexed immunoglobulin E determination on a chip in component-resolved diagnostics in allergy. Clin Exp Allergy. 2010;40:190-2.

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Nicolaou N. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol. 2010;125:191-7,e1-e13.

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Food Testing Summary

- There is a significant impact on many levels for families with true food allergies, as well as with falsely identified or missed food allergies
- Food allergy testing should be guided by history
 - Should generally not test for random panel of foods, or for foods that are being tolerated
- Tests for food-specific IgE (skin or blood) are the only validated test in the majority of clinical contexts
- Food allergy-specific IgE blood tests should be interpreted in context of validated predictive values and clinical scenarios
- Multiple non-IgE food “allergy” tests are available which have unproven and disproven validity
