Update on Food Allergy Diagnostics

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Case Presentation

- Patient is a 13-month male who presents to your clinic with his parents for evaluation of peanut allergy. In conjunction with their pediatrician, his parents introduced peanut around 9 months of age. He seemed to tolerate peanut on the first day but on the second day he had a red rash around his mouth and was not interested in eating it. They gave him a break and tried again a week later and he developed more rash and vomited when trying to eat peanut. He was prescribed an epinephrine auto-injector and referred to your clinic. While waiting for today's appointment, he has not tried peanut again. He has introduced milk, egg, wheat, and soy products and eats them regularly.

- What testing would you do?

Skin prick testing in food allergy

- Skin prick testing:
  - Commercial extracts – most common food allergens
  - Fresh food (prick-to-prick) – more heat-labile food allergens

- Benefits
  - Results on the day of visit, less invasive, “less-painful”, visual reinforcement
- Drawbacks
  - Requires stopping antihistamines, requires clear skin, operator-dependent results, different pricks may have different results

Skin prick testing extracts are not standardized

FDA Requires Warning about Anaphylaxis Following False Negative Food Allergen Skin Test Results in the Prescribing Information for All Allergenic Extracts for Diagnosis of Food Allergy

FDA Safety Communication - March 3, 2023

Allergenic Extracts for the Diagnosis of Food Allergy

Allergenic extracts for the diagnosis of food allergy are sterile liquids that are manufactured from natural substances (e.g., peanut) known to elicit allergic reactions in susceptible individuals. Among allergenic extracts, some are standardized; for these products there is an established method to determine the potency (or strength) of the product on a lot-by-lot basis. For other allergenic extracts there is no U.S. standard of potency, and these are called "non-standardized." All allergenic extracts for the diagnosis of food allergy currently licensed by FDA for distribution in the United States are non-standardized.

Serum IgE testing in food allergy

- Standardized lab assay available for most common food allergens
  - » ImmunoCAP most commonly used instrument

- Benefits
  - » More reproducible results, allows for comparison across clinics and labs, more accurate for trending
- Drawbacks
  - » Needle-phobia, delayed result requiring follow-up communication, additional lab fee for patient

Interpreting diagnostic testing in food allergy is hard

TABLE E3. Predictive value of IgE testing in positive or negative OFC results[219-222,224-226,228]

	>95% Positive		~50% Negative	
Food	**sIgE**	**SPT**	**sIgE**	**SPT wheal (mm)**
Egg white	≥7 ≥2 if age <2 y	≥7	≤2	≤3
Cow's milk	≥15 ≥5 if age <1 y	≥8	≤2	
Peanut	≥14	≥8	≤2 = history of prior reaction ≤5 = no history of prior reaction	≤3
Fish	≥20			

- Predictive values not available for most foods
- "Positive" values vary by food, and by age, (and by ingestion history)
- In isolation, there is a high risk of false positive results with IgE and also SPT
- Concerns exacerbated by broad availability of panel testing

Sampson. JACI. 2014; doi: 10.1016/j.jaci.2014.05.013

Diagnostic testing in food allergy should confirm the history

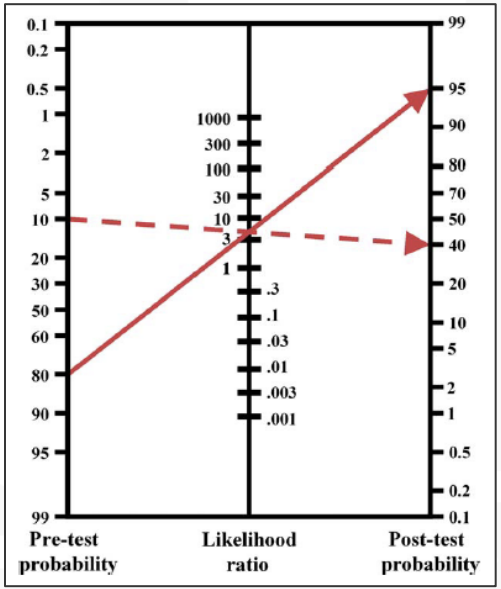
TABLE II. Results of food challenge by skin prick test result*

Skin prick test result (mm)	Challenge result: Positive (%)	Challenge result: Negative (%)	Total number	Likelihood ratio
0	7 (13.2)	46 (86.8)	53	0.15
1	2 (40.0)	3 (60.0)	5	0.68
2	8 (57.1)	6 (42.9)	14	1.35
3	6 (50.0)	6 (50.0)	12	1.01
4	7 (70.0)	3 (30.0)	10	2.37
5-7	20 (87.0)	3 (13.0)	23	6.77
≥8	17 (94.4)	1 (5.6)	18	17.25
Total	67 (49.6)	68 (50.4)	135	—

TABLE IV. Results of food challenge by serum specific IgE result*

Specific IgE result (kU_A/L)	Challenge result: Positive	Challenge result: Negative	Total number	Likelihood ratio
<0.35 (class 0)	15 (27.8%)	39 (72.2%)	54	0.32
0.35-0.69 (class 1)	5 (41.7%)	7 (58.3%)	12	0.60
0.7-3.4 (class 2)	19 (73.1%)	7 (26.9%)	26	2.27
3.5-17.4 (class 3)	16 (69.6%)	7 (30.4%)	23	1.92
17.5-49.9 (class 4)	10 (90.9%)	1 (9.1%)	11	8.38
50-99.9 (class 5)	1 (100.0%)	0 (0.0%)	1	∞
≥100 (class 6)	8 (88.9%)	1 (11.1%)	9	6.70
Total	74 (54.4%)	62 (45.6%)	136	—

Predictive value is highly dependent on pretest probability



Roberts. JACI. 2005; doi: 10.1016/j.jaci.2005.02.038

Component-resolved testing for food allergy

- IgE to whole food includes both allergic and cross-reactive protein components leading to potential for false positives
- Component-resolved testing specifically targets allergic protein components

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REVIEW ARTICLE

Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy

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Systematic review of component-resolved testing

- Available for peanut, milk, egg, hazelnut, cashew, walnut
- Also available for sesame, wheat, shrimp

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy
Peanut allergy				
SPT to peanut	Adults and children with suspected peanut allergy visiting a specialized allergy clinic	0.84 (0.69; 0.92)	0.86 (0.79; 0.91)	Moderate (Potential false negative and false positive results)
sIgE to peanut		0.81 (0.71; 0.88)	0.83 (0.71; 0.90)	Moderate (Potential false negative and false positive results)
Ara h 2-sIgE (ImmunoCAP)		0.82 (0.77; 0.86)	0.92 (0.87; 0.95)	High for ruling in peanut allergy
Ara h 2-sIgE (ISAC)		0.77 (0.64; 0.86)	0.93 (0.66; 0.99)	High for ruling in peanut allergy
Hazelnut allergy				
SPT to hazelnut	Adults and children with suspected hazelnut allergy visiting a specialized allergy clinic	0.82 (0.68; 0.91)	0.78 (0.44; 0.94)	Moderate (Potential false negative and false positive results)
sIgE to hazelnut		0.79 (0.71; 0.85)	0.62 (0.38; 0.81)	Moderate (Potential false negative and false positive results)
Cor a 14-sIgE		0.73 (0.53; 0.87)	0.95 (0.90; 0.98)	High for ruling in hazelnut allergy
Cashew nut allergy				
SPT to cashew	Adults and children with suspected cashew allergy visiting a specialized allergy clinic	0.93 (0.89; 0.96)	0.92 (0.82; 0.96)	High for ruling out and ruling in cashew nut allergy
sIgE to cashew		0.94 (0.89; 0.97)	0.64 (0.54; 0.74)	High for ruling out cashew nut allergy (Potential false positive results)
Ana o 3-sIgE		0.96 (0.91; 0.98)	0.94 (0.88; 0.97)	High for ruling out and ruling in cashew nut allergy

Riggioni. Allergy. 2023; doi: 10.1111/all.15939

Improved accuracy with component testing for nuts

FA	Diagnostic Test	Sens (95% CI)	Rel sens (95% CI)	Spec (95% CI)	Rel Spec (95% CI)
Peanut allergy	SPT peanut	92.0 (83.0; 96.0)	**1.02 (1.00; 1.05)**	78.0 (63.0; 89.0)	**1.19 (1.06; 1.34)**
	*sIgE peanut	90.0 (79.0; 95.0)		66.0 (48.0; 80.0)	
	Ara h 2-sIgE	88.0 (82.0; 93.0)	1.03 (0.98; 1.08)	82.0 (72.0; 89.0)	**1.12 (1.02; 1.22)**
	*SPT peanut	86.0 (78.0; 92.0)		73.0 (60.0; 83.0)	
	Ara h 2-sIgE	87.0 (80.0; 91.0)	1.01 (0.98; 1.04)	84.0 (73.0; 91.0)	**1.37 (1.16; 1.61)**
	*sIgE peanut	86.0 (78.0; 91.0)		62.0 (45.0; 76.0)	
Hazelnut allergy	sIgE hazelnut	79.0 (59.0; 91.0)	**1.23 (1.03; 1.47)**	65.0 (23.0; 92.0)	0.66 (0.36; 1.23)
	*Cor a 14-sIgE	64.0 (41.0; 83.0)		99.0 (91.0; 100)	
	SPT hazelnut	74.0 (58.0; 86.0)	**1.15 (1.01; 1.31)**	74.0 (45.0; 91.0)	0.77 (0.57; 1.02)
	*Cor a 14-sIgE	64.0 (48.0; 78.0)		97.0 (90.0; 99.0)	
	Cor a 14-sIgE	71.0 (44.0; 88.0)	1.15 (0.97; 1.37)	94.0 (89.0; 97.0)	**1.12 (1.04; 1.20)**
	*Cor a 9-sIgE	62.0 (35.0; 83.0)		84.0 (76.0; 90.0)	

Riggioni. Allergy. 2023; doi: 10.1111/all.15939

Some improved accuracy with component testing

FA	Diagnostic Test	Sens (95% CI)	Rel sens (95% CI)	Spec (95% CI)	Rel Spec (95% CI)
Cooked egg allergy	sIgE egg white	81.0 (71.0; 88.0)	**1.30 (1.04; 1.59)**	73.0 (61.0; 82.0)	0.88 (0.78; 1.00)
	*SPT egg white	63.0 (46.0; 77.0)		82.0 (70.0; 90.0)	
	Ovomucoid-sIgE	82.0 (73.0; 89.0)	1.03 (0.97; 1.10)	82.0 (73.0; 88.0)	**1.10 (1.02; 1.19)**
	*sIgE egg white	79.0 (70.0; 86.0)		74.0 (64.0; 82.0)	
	sIgE egg white	82.0 (73.0; 88.0)	**1.19 (1.05; 1.37)**	73.0 (61.0; 82.0)	0.88 (0.77; 1.00)
	*Ovalbumin-sIgE	68.0 (55.0; 80.0)		83.0 (69.0; 91.0)	
	Ovomucoid-sIgE	82.0 (63.0; 92.0)	**1.47 (1.10; 2.00)**	82.0 (63.0; 92.0)	0.94 (0.85; 1.05)
	*Ovalbumin-sIgE	56.0 (31.0; 77.0)		87.0 (69.0; 95.0)	
	sIgE egg white	81.0 (72.0; 88.0)	**1.37 (1.09; 1.72)**	77.0 (64.0; 86.0)	1.03 (0.88; 1.22)
	*SPP raw egg white	59.0 (43.0; 74.0)		74.0 (56.0; 86.0)	
Raw egg allergy	SPT egg white	84.0 (65.0; 94.0)	**1.45 (1.08; 1.94)**	79.0 (59.0; 91.0)	0.97 (0.82; 1.15)
	*Ovomucoid-sIgE	58.0 (37.0; 77.0)		82.0 (64.0; 92.0)	
Cow's milk allergy	Casein-sIgE	72.0 (59.0; 82.0)	**1.18 (1.05; 1.32)**	89.0 (69.0; 97.0)	1.01 (0.94; 1.08)
	*β-Lactoglobulin-sIgE	61.0 (47.0; 73.0)		89.0 (68.0; 96.0)	
	α-Lactoglobulin-sIgE	75.0 (58.0; 86.0)	**1.22 (1.04; 1.43)**	81.0 (58.0; 93.0)	0.93 (0.81; 1.06)
	*sIgE cow's milk	61.0 (42.0; 77.0)		88.0 (72.0; 95.0)	
	sIgE cow's milk	74.0 (59.0; 85.0)	**1.16 (1.02; 1.31)**	88.0 (74.0; 95.0)	1.05 (0.95; 1.17)
	*β-Lactoglobulin-sIgE	64.0 (46.0; 79.0)		83.0 (65.0; 93.0)	
	Casein-sIgE	47.0 (24.0; 71.0)	0.99 (0.79; 1.23)	93.0 (83.0; 97.0)	**1.27 (1.04; 1.54)**
	*SPT cow's milk	47.0 (25.0; 71.0)		73.0 (53.0; 87.0)	
	SPP fresh cow's milk	89.0 (73.0; 96.0)	**1.88 (1.25; 2.84)**	53.0 (24.0; 80.0)	**0.67 (0.47; 0.96)**
	*SPT cow's milk	47.0 (26.0; 70.0)		79.0 (52.0; 93.0)	
	SPP fresh cow's milk	88.0 (79.0; 94.0)	**1.29 (1.09; 1.53)**	61.0 (29.0; 86.0)	0.71 (0.50; 1.00)
	*sIgE cow's milk	68.0 (57.0; 78.0)		86.0 (62.0; 96.0)	

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Potential cut-off values when using component testing

FA/test	Cut-off values	Sensitivity (95% CI)	I^2sens (%)	Specificity (95% CI)	I^2spec (%)	Subjects included
Peanut allergy						
SPT to peanut	≥8 mm	68.0 (42.0; 86.0)	85.2	**94.0 (85.0; 98.0)**	28.6	1086
sIgE to peanut	≥15 kU_A/L	28.0 (16.0; 45.0)	84.1	**98.0 (96.0; 99.0)**	25.6	872
Ara h 2-sIgE	≥0.35 kU_A/L	83.0 (78.0; 87.0)	54.5	**93.0 (87.0; 96.0)**	58.7	1994
Raw egg allergy						
Ovomucoid-sIgE	≥0.35 kU_A/L	56.0 (37.0; 73.0)	88.8	**91.0 (80.0; 96.0)**	69.5	827
Ovalbumin-sIgE	≥0.35 kU_A/L	76.0 (51.0; 91.0)	84.9	82.0 (62.0; 93.0)	71.9	546
Cooked egg allergy						
SPT to egg white	≥7 mm	45.0 (14.0; 81.0)	84.9	68.0 (55.0; 79.0)	33.7	323
sIgE egg white	≥7 kU_A/L	74.0 (64.0; 82.0)	14.1	70.0 (61.0; 78.0)	6.8	573
Ovomucoid-sIgE	≥0.35 kU_A/L	76.0 (53.0; 90.0)	82.3	**90.0 (85.0; 93.0)**	10.2	827
Cow's milk allergy						
SPT to cow's milk	≥8 mm	28.0 (1.00; 96.0)	18.3	**94.0 (23.0; 100)**	5.0	497
IgE to cow's milk	≥15 kUA/L	Not estimable[a]				
Hazelnut allergy						
Cor a 14-sIgE	≥0.35 kU_A/L	74.0 (51.0; 89.0)	82.1	**95.0 (89.0; 98.0)**	47.8	726

- Component testing may best provide value as part of a sequential testing algorithm
- EAACI recommends use for peanut, hazelnut, and cashew allergies

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Basophil activation testing (BAT)

- Patient basophils isolated from whole blood
  - Incubated with increasing amounts of peanut
  - CD63 measured as proxy for mediator release

- Benefits: tests patient's own effector cells, directly measures response to peanut exposure
- Drawbacks: larger blood volumes needed, must be performed on fresh cells within 48 hours, only available at select labs

Basophil activation test for peanut allergy

Allergen	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
BAT to peanut	42.11	45.83 (31.4-60.8)	97.14 (85.1-99.9)	95.65 (78.1-99.9)	56.67 (43.2-69.4)
	4.717	81.25 (67.4-91.1)	85.7 (69.7-95.2)	88.64 (75.4-96.2)	76.92 (60.7-88.9)
	0.124	93.75 (82.8-98.7)	37.14 (21.5-55.1)	67.16 (54.6-78.2)	81.25 (54.4-96.0)
BAT to Ara h 1	16.02	39.58 (25.8-54.7)	97.14 (85.1-99.9)	95.00 (75.1-99.9)	53.97 (40.9-66.6)
	0.82	64.58 (49.5-77.8)	85.71 (69.7-95.2)	86.11 (70.5-95.3)	63.83 (48.5-77.3)
	0.005	79.17 (65.0-89.5)	60.00 (42.1-76.1)	73.08 (59.0-84.4)	67.74 (48.6-83.3)
BAT to Ara h 2	2.264	79.17 (65.0-89.5)	94.29 (80.8-99.3)	95 (83.1-99.4)	76.74 (61.4-88.2)
	0.57	83.33 (69.8-92.5)	91.43 (76.9-98.2)	93.02 (80.9-98.5)	80 (64.4-91.0)
	0.375	85.42 (72.2-93.9)	85.71 (69.7-95.2)	89.13 (76.4-96.4)	81.08 (64.8-92.0)
BAT to Ara h 6	26.71	43.75 (29.5-58.8)	97.14 (85.1-99.9)	95.45 (77.2-99.9)	55.74 (42.5-68.5)
	0.96	72.92 (58.2-84.7)	88.57 (73.3-96.8)	89.74 (75.8-97.1)	70.45 (54.8-83.2)
	0.325	79.17 (65.0-89.5)	74.29 (56.7-87.5)	80.85 (66.7-90.9)	72.22 (54.8-85.8)

Santos. JACI Pract. 2021; doi: 10.1016/j.jaip.2020.12.039

Basophil activation test for other foods

Allergen	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
BAT to hazelnut	60.98	15.38 (4.4-34.9)	100.00 (93.7-100)	100.00 (39.8-100)	72.15 (60.9-81.7)
	0.924	80.77 (60.7-93.5)	87.72 (76.3-94.9)	75 (55.1-89.3)	90.91 (80.0-97.0)
	0.13	92.31 (74.9-99.1)	66.67 (52.9-78.6)	55.81 (39.9-70.9)	95.00 (83.1-99.4)
BAT to cashew	25.21	42.86 (26.3-60.7)	100 (92.6-100)	100 (78.2-100)	70.6 (58.3-81.0)
	1.79	82.86 (66.4-93.4)	87.5 (74.8-95.3)	82.86 (66.4-93.4)	87.5 (74.8-95.3)
	0.36	88.57 (73.3-96.8)	70.83 (55.9-83.1)	68.89 (53.4-81.8)	89.5 (75.2-97.1)
BAT to sesame	16.11	66.67 (34.9-90.1)	100 (94.9-100)	100 (63.1-100)	94.67 (86.9-98.5)
	8.15	91.67 (61.5-99.8)	98.59 (92.4-100)	91.67 (61.5-99.8)	98.59 (92.4-100)
	14.26	75 (42.8-94.5)	98.59 (92.4-100)	90 (55.6-99.8)	95.89 (88.5-99.1)
BAT to almond	37.57	33.33 (0.8-90.6)	100 (95.5-100)	100 (2.5-100)	97.56 (91.5-99.7)
	0.825	100 (29.2-100)	80 (69.6-88.1)	15.79 (3.4-39.6)	100 (94.4-100)
	18.63	33.33 (0.8-90.6)	93.75 (86.0-97.9)	16.67 (0.4-64.1)	97.4 (90.9-99.7)

Santos. JACI Pract. 2021; doi: 10.1016/j.jaip.2020.12.039

Overview of available food allergy testing options

TABLE 7 Summary of diagnostic performance of various tests for specific foods based on the results of recent meta-analyses[11].

Diagnostic test	Cow's milk	Egg	Peanut	Hazelnut	Cashew	Sesame	Wheat	Shrimp
Skin prick test								
Cut-offs (mm)	4 (3; 8)	5 (3; 8)	4 (3–8)	5 (3–7)	5 (4–6)	8 (4–10)	3 (3–5)	3 (3–5)
Sensitivity	0.52 (0.24- 0.79)	0.68 (0.37- 0.88)	0.84 (0.69- 0.92)	0.82 (0.68- 0.91)	0.93 (0.89- 0.96)	0.70 (0.55- 0.82)	0.53 (0.23;0.81)	0.62 (0.44 0.77)
Specificity	0.80 (0.65- 0.90)	0.77 (0.64- 0.86)	0.86 (0.79- 0.91)	0.78 (0.44; 0.94)	0.92 (0.82; 0.96)	0.89 (0.76- 0.95)	0.72 (0.57; 0.84)	0.90 (0.31; 0.99)
Specific IgE to allergen extracts								
Cut-offs (KU/L)	3.5 (0.9–10.5)	3.5 (1.7–5.5)	4.3 (0.35–10)	2.34 (0.6–6.3)	1.1 (0.6–3.1)	7.5 (0.9–50)	0.6 (0.35–5.6)	1.2 (0.5–3.1)
Sensitivity	0.82 (0.59; 0.94)	0.85 (0.77; 0.90)	0.81 (0.71- 0.88)	0.79 (0.71- 0.85)	0.94 (0.89- 0.97)	0.70 (0.23- 0.95)	0.72 (0.54; 0.84)	0.96 (0.42; 1.00)
Specificity	0.92 (0.80; 0.97)	0.73 (0.63- 0.80)	0.83 (0.71- 0.90)	0.62 (0.38- 0.81)	0.64 (0.54- 0.74)	0.83 (0.26- 0.99)	0.79 (0.68; 0.86)	0.63 (0.46- 0.78)
Specific IgE to allergen-components								
Cut-offs (KU/L)	Casein 2.6 (1.0–5.3)	Ovomucoid 0.8 (0.35–3.7)	Ara h 2 0.44 (0.3–1.3)	Cor a 14 0.64 (0.35–3.5)	Ana o 3 0.4 (0.2; 0.6)	Ses i 1 2.0 (0.3-4.0)	Omega-5-gliadin 0.3 (0.1–0.6)	Pen a 1 1.1 (0.6; 4.4)
Sensitivity	0.67 (0.53- 0.78)	0.74 (0.54; 0.87)	0.82 (0.77- 0.86)	0.73 (0.53- 0.87)	0.96 (0.91- 0.98)	0.77 (0.64-0.86)	0.79 (0.68- 0.88)	0.62 (0.45- 0.76)
Specificity	0.93 (0.85- 0.97)	0.91 (0.87- 0.93)	0.92 (0.87- 0.95)	0.95 (0.90- 0.98)	0.94 (0.88- 0.97)	0.87 (0.77-0.92)	0.78 (0.66- 0.86)	0.89 (0.75- 0.95)
Basophil activation test								
Cut-offs (%CD63+ Basophils)			5.0 (4.7–7.1)			10.9 (8.2–11. 6)		
Sensitivity			0.84 (0.76- 0.90)			0.89 (0.80- 0.94)		
Specificity			0.90 (0.83- 0.94)			0.93 (0.76- 0.98)		

Santos. Allergy. 2023; doi: 10.1111/all.15902

EAACI recommendations for diagnosis of food allergy

TABLE 4 Recommendations about the diagnosis of IgE-mediated food allergy.

Topic	Recommendations	Certainty of evidence	Strength of recommendation
Clinical history	1. In patients with suspected IgE-mediated food allergy, a detailed allergy-focused clinical history is recommended as the first step in the diagnostic work-up for food allergy	Low	Strong
Diagnostic tests	2. In patients with a history of suspected IgE-mediated food allergy, skin prick test and/or measurement of serum specific IgE are recommended as first-line test to support diagnosis	High	Strong
	3. In patients with a history of suspected IgE-mediated allergy to peanut, hazelnut or cashew nut, specific IgE to Ara h 2, Cor a 14 or Ana o 3, respectively, are recommended, where available, in addition to skin prick test and/or IgE to extracts, to further support diagnosis	High	Strong
	4. In patients with an equivocal diagnosis of IgE-mediated allergy to peanut or sesame, BAT to peanut or sesame, respectively, are suggested, where available, to further support diagnosis	High	Conditional
	5. In patients with suspected IgE-mediated food allergy, the isolated use of IgG and IgG subclass tests and the other tests listed on Table S2 is recommended against to support the diagnosis of IgE-mediated food allergy	Very low	Strong
	6. Reassessment of food allergic children, at regular intervals, depending on age, food and patient's history, is suggested for possible development of spontaneous tolerance	Moderate	Conditional

Santos. Allergy. 2023; doi: 10.1111/all.15902

Diagnostic oral food challenges (OFC)

- Considered the gold standard

- When to do them
  - » Equivocal or discrepant test results
  - » Avoidance based on testing alone
  - » Assess for natural resolution

- Risk-Benefit considerations
  - » Nutritional/cultural value of food
  - » Burden of the food allergy, effects on quality of life
  - » Will the patient reintroduce the food

When should OFCs be considered

TABLE 8 Indications for oral food challenge.

IgE sensitization, but…	No IgE sensitization, but…
… the food has never been consumed or previously tolerated but avoided for a significant period of time. This might occur for example when an allergy is diagnosed to an allied food group (e.g. peanut allergy diagnosed and also advised to avoid tree nuts), or because allergy tests were positive but without any symptoms to the food tested, or not introduced as a weaning food so far.	… reactions have been attributed to the food.
… the test result is below a validated cut-off point for that food.	… it is necessary to confirm that the allergy is outgrown.
… the history is not consistent with this result, despite a test result above the validated cut-off point.	… the individual and/or parents are highly anxious and/or avoiding multiple foods.
… co-sensitization to house dust mite or pollens may mean that positive tests to some foods (shellfish, fruits, tree nuts or peanuts) are not clinically relevant due to cross-reactivity.	… there is high clinical suspicion.
… the eliciting dose of the allergen needs to be determined. This may be useful when determining therapeutic dosing regimens.	…severe reactions have been reported to the trigger food.
… the development of tolerance is expected due to the natural history of allergy to a specific food.	… a non-IgE-mediated food allergy is suspected.
… the food might be tolerated in an alternative form, for example baked milk or egg, cooked or processed fruits/vegetables/nuts.	

Santos. Allergy. 2023; doi: 10.1111/all.15902

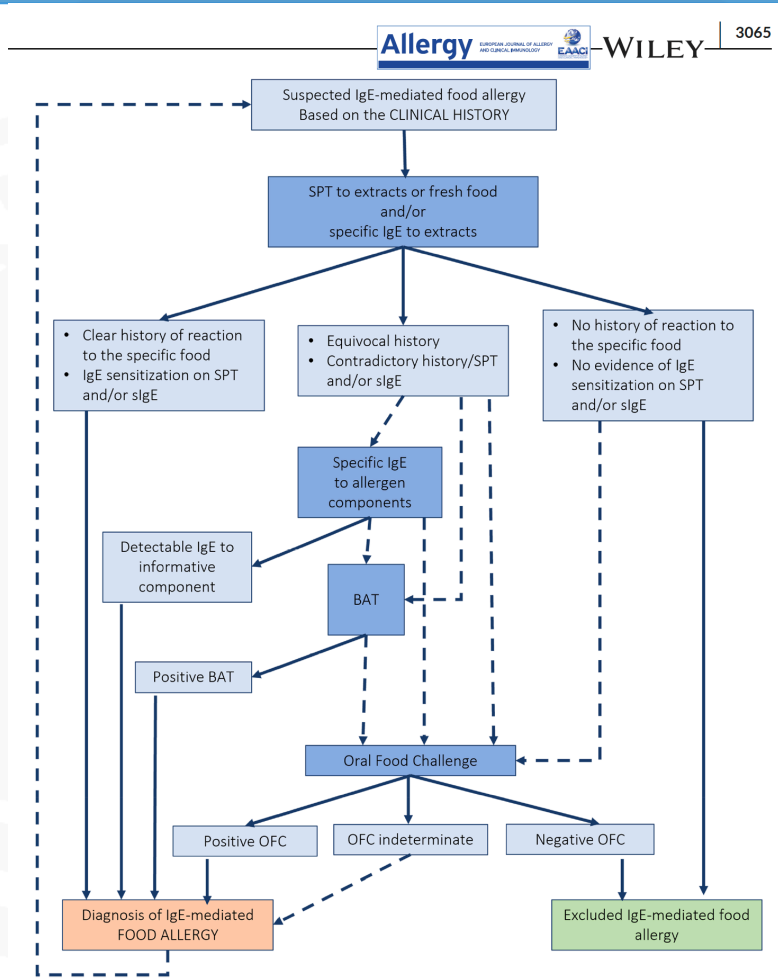
Oral food challenges are difficult

- Requires ingesting multiple doses of the allergenic food
  - Total amount estimates a serving size
- Multi-hour procedure day
  - 15-30 minutes between doses
  - 1-2 hour observation after completion
- Risk of allergic reaction and anaphylaxis
  - Direct exposure to the allergen, and potentially in large amounts
- Could non-injection epinephrine change the perception of OFCs?

EAACI suggested diagnostic algorithm for food allergy

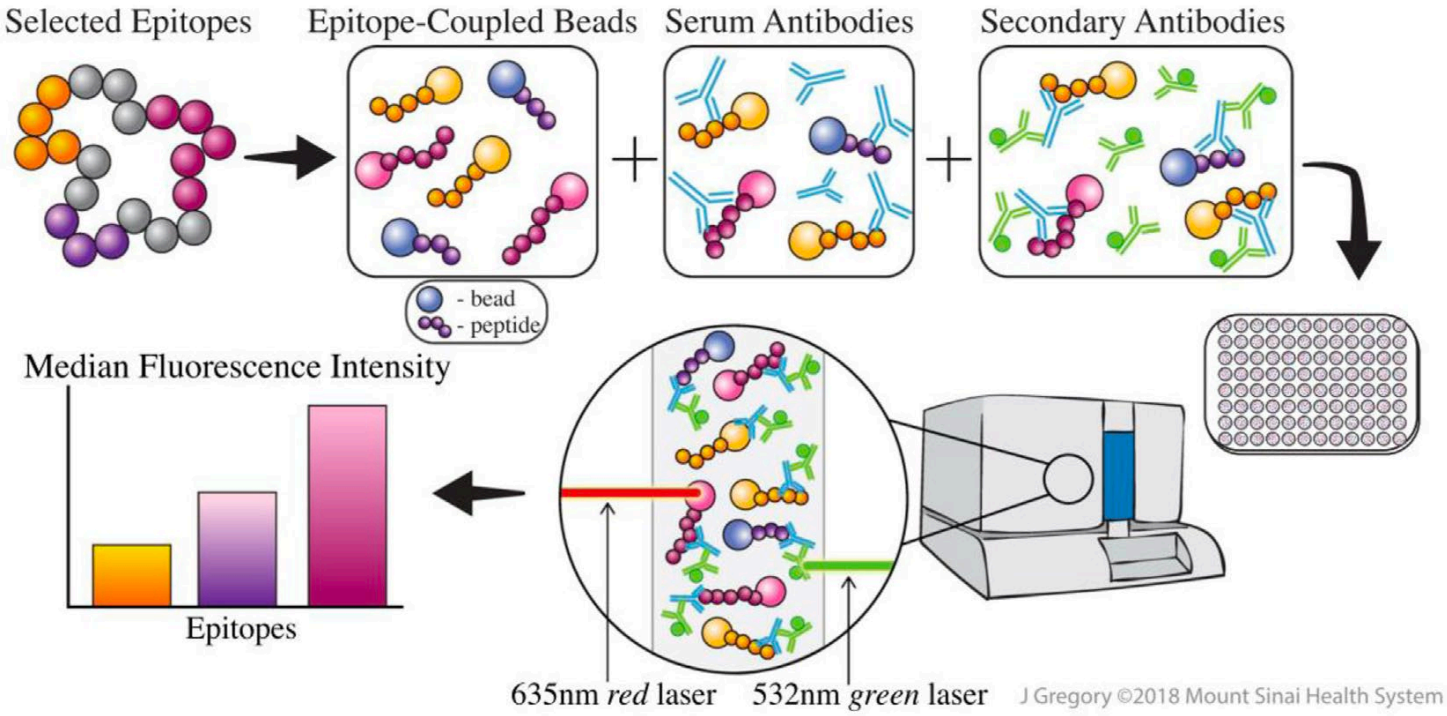
- Clinical history
- SPT/specific IgE

- Component IgE
- Basophil activation testing
- Oral food challenge



Santos. Allergy. 2023; doi: 10.1111/all.15902

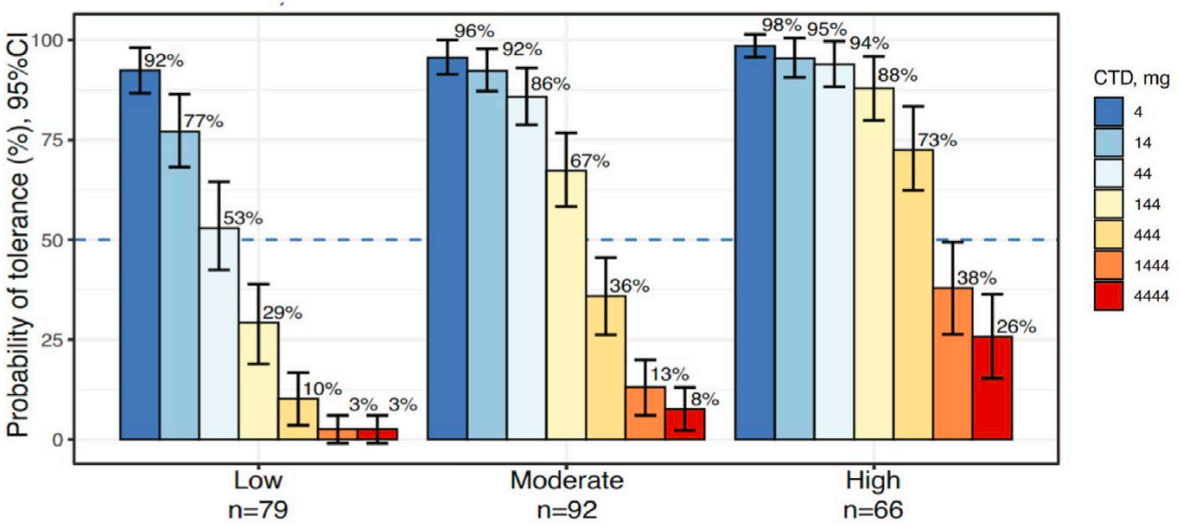
Bead-based epitope assay (BBEA)



Lee. JACI Pract. 2023; doi: 10.1016/j.jaip.2023.06.043

Bead-based epitope assay in peanut allergy

- Diagnosis: two immunodominant epitopes on Ara h2
  - » Accuracy of 93%-95%
- Threshold: immunodominant epitope on Ara h2 and on Ara h3
  - » May be able to separate patients into low, medium, high thresholds on OFC



Lee. JACI Pract. 2023; doi: 10.1016/j.jaip.2023.06.043

Bead-based epitope assay in other foods

- Baked egg reactivity
  - » Ovalbumin IgE plus immunodominant ovomucoid epitope IgE and ovalbumin epitope IgE may be predictive
- Milk allergy
  - » Baseline epitope specific IgE may predict outcomes with milk OIT
- Wheat allergy: 4 immunodominant epitopes on ω-5-gliadin and γ-gliadin
  - » AUC 0.908
  - » May also have role in predicting anaphylaxis and exercise-induced phenotype

Suprun. Int Arch Allergy Immunol. 2022; doi: 10.1159/000519618
Suarez-Farinas. JACI. 2019; doi: 10.1016/j.jaci.2018.10.028
Srisuwatchari. JACI. 2024; doi: 10.1016/j.jaci.2024.08.003

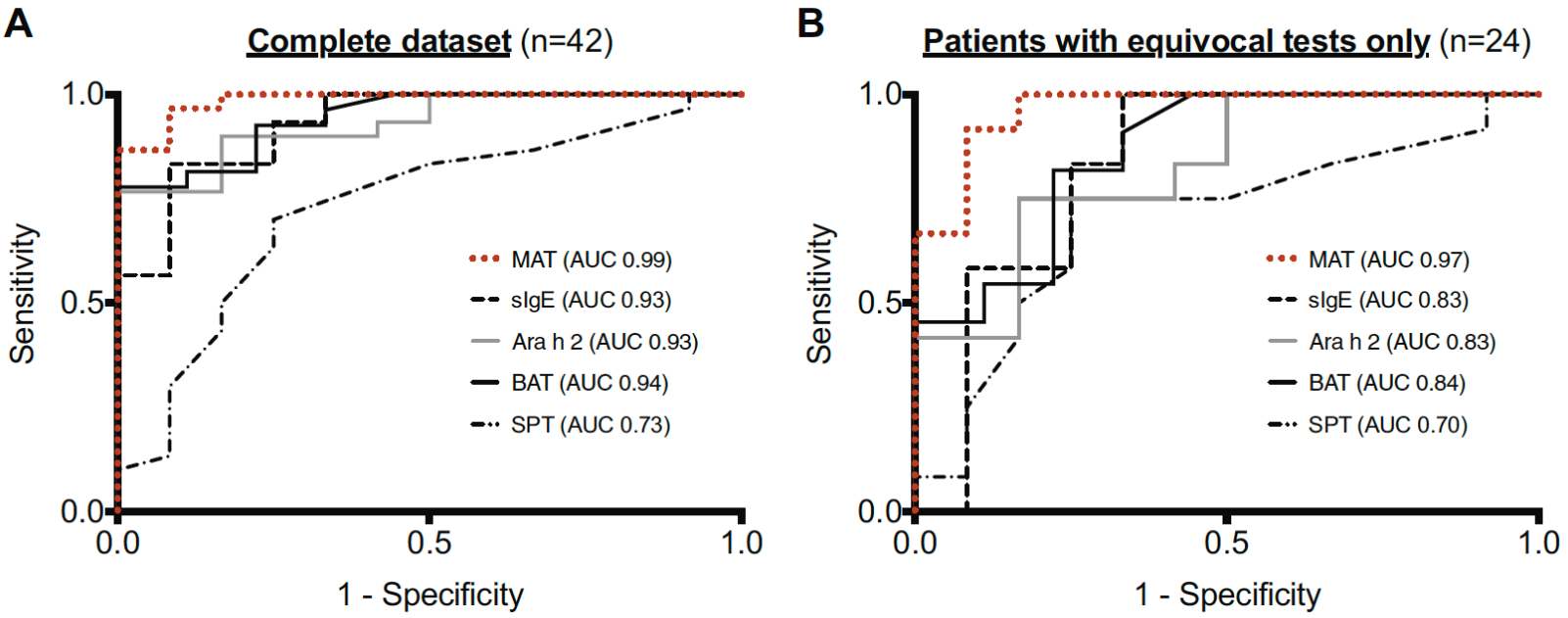
Mast cell activation test (MAT)

- Mast cells sensitized with human sera
  - » Initial studies used donor peripheral blood precursors
  - » More recent studies use immortalized mouse mast cell progenitors

- Incubated with increasing levels of peanut allergen and components
  - » Like with BAT, CD63 measured as well as CD107a as proxy for mediator release
  - » Also measured PGD2 and β-hexaminidase as functional assays

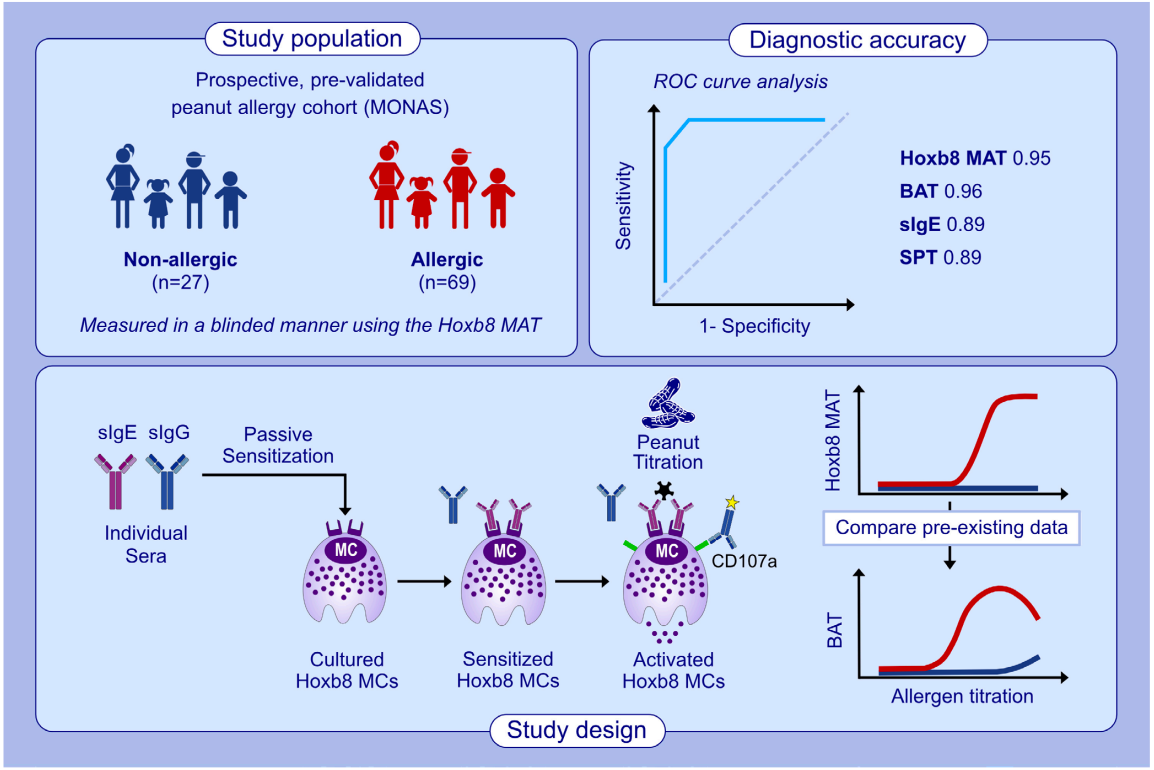
Bahri. JACI. 2018; doi: 10.1016/j.jaci.2018.01.043

Donor cell MAT in peanut allergy



Bahri. JACI. 2018; doi: 10.1016/j.jaci.2018.01.043

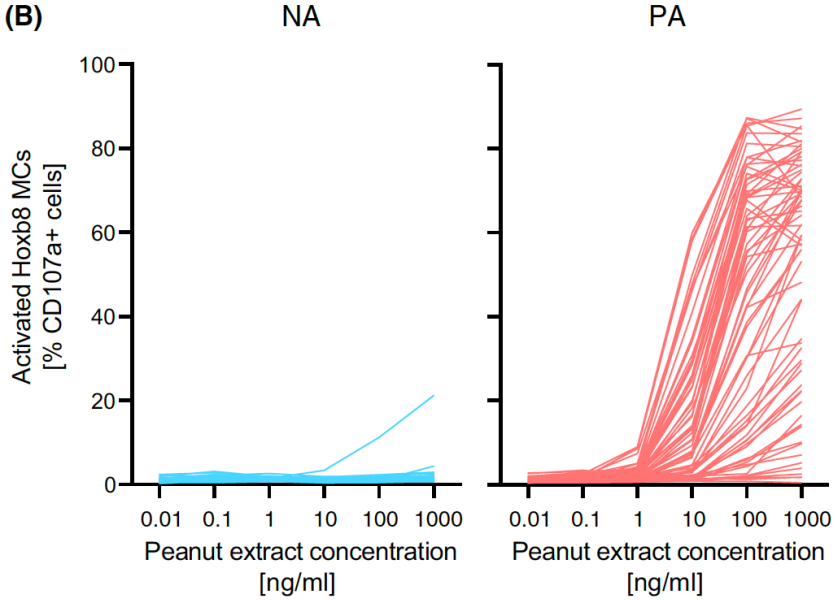
Hox b8 MAT in peanut allergy



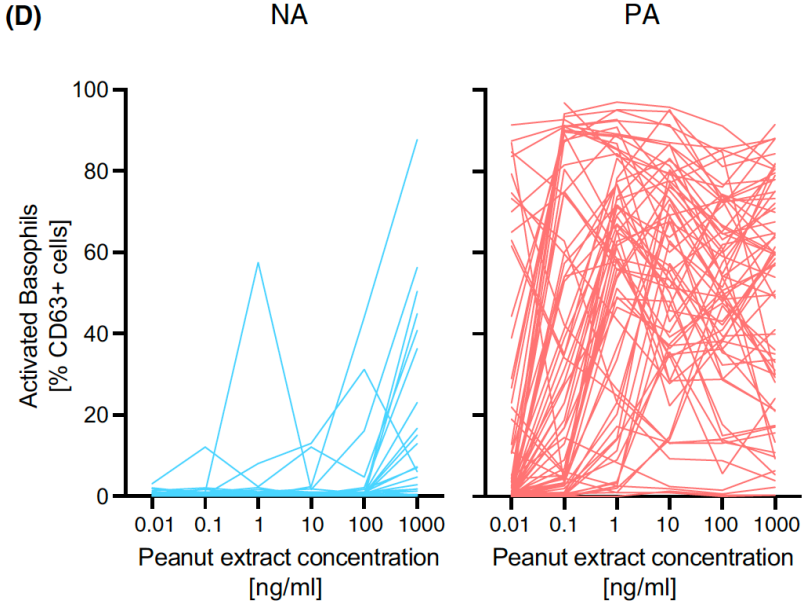
- Mouse mast cell progenitors
- Immortalized with 4-OHT inducible Hoxb8 gene expression system
- Removing 4-OHT leads to mast cell differentiation
- Sensitize with patient sera (IgE and IgG)
- Incubate with increasing peanut
- Diagnostic AUC 0.95

Bachmeier-Zbaren. Allergy. 2024; doi: 10.1111/all.16341

MAT may improve on BAT results for peanut allergy



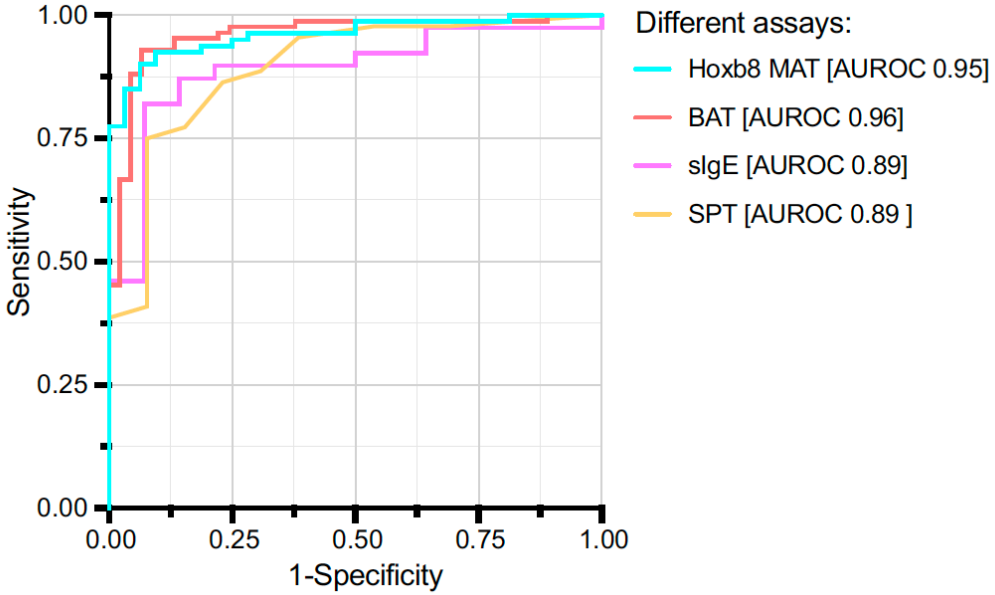
MAT

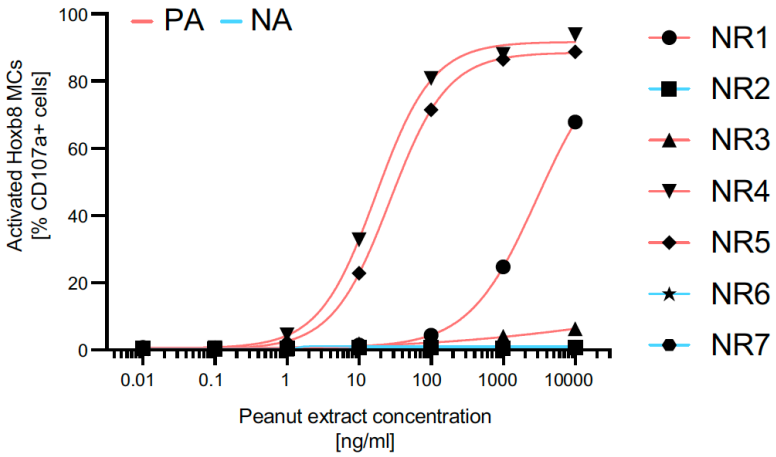


BAT

Bachmeier-Zbaren. Allergy. 2024; doi: 10.1111/all.16341

MAT has high AUC and may differentiate equivocal BAT results





Bachmeier-Zbaren. Allergy. 2024; doi: 10.1111/all.16341

Point-of-service IgE testing

- Finger stick whole blood instruments in development
  - ImmunoCAP Rapid
    - Single-use disposable device
    - Colored band demonstrating presence of antibodies
    - Focused on common asthma and rhinitis allergens
  - Kenota 1 Total IgE
    - Tabletop device
    - Quantitative result for total IgE levels
    - Food allergens in development

Conclusions

- The continued increase in food allergy and the growing number of therapeutics have made diagnostics more important than ever
- Clinical history remains the cornerstone
- SPT and IgE show the presence of IgE, but not reactivity. Can be confirmatory but have a risk of false positives
- Component testing and BAT may provide improved accuracy when used as part of an algorithm with history, SPT, and IgE
- OFCs are still the most accurate test but the risk, logistical burden, and limited access make it imperfect

- MAT might perform as good as BAT and would be easier to use in clinical practice
- Point-of-service IgE testing may be an option although clinical value needs to be determined