

FOOD ALLERGY AND SAFETY ASSESSMENT WORKSHOP
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How is food allergy diagnosed?



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Classification of adverse reactions to foods

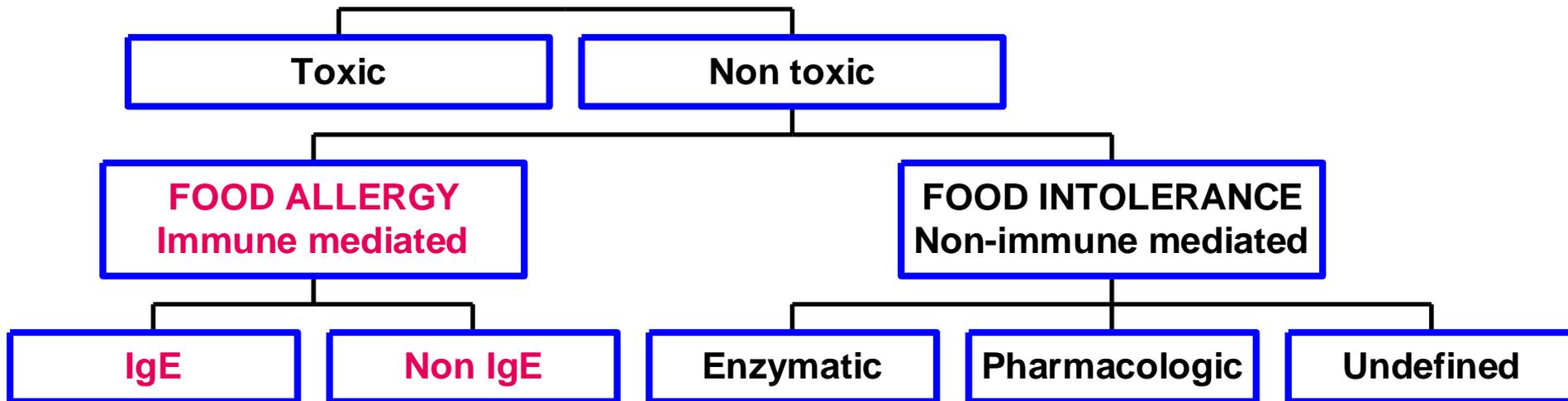


Table 2 Food-induced allergic disorders (classified based on the underlying immunopathology)

Immunopathology	Disorder	Clinical features	Typical age group	Prognosis
IgE mediated	Pollen food allergy syndrome	Pruritus, mild edema confined to oral cavity	Onset after pollen allergy established (adult > young child)	May be persistent and may vary by season
	Urticaria/angioedema Rhinoconjunctivitis/asthma	Triggered by ingestion or direct contact Accompanies food-induced allergic reaction but rarely isolated symptoms May be triggered by the inhalation of aerosolized food protein	Children > adults Infant/child > adult, except for occupational disease	Depends on food Depends on food
	Gastrointestinal symptoms	Symptoms such as nausea, emesis, abdominal pain, and diarrhea triggered by food ingestion	Any age	Depends on food
	Anaphylaxis Food-dependent, exercise-induced anaphylaxis	Rapid progressive, multisystem reaction Food triggers anaphylaxis only if ingestion is followed temporally by exercise	Any age Onset in late childhood/adulthood	Depends on food Presumed persistent
Mixed IgE and cell mediated	Atopic eczema/dermatitis	Associated with food in 30–40% of children with moderate/severe eczema	Infant > child > adult	Usually resolves
	Eosinophilic gastrointestinal disorders	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Any age	Likely persistent
Cell mediated	Dietary protein-induced proctitis/proctocolitis	Mucus-laden, bloody stools in infants	Infancy	Usually resolves
	Food protein-induced enterocolitis syndrome	Chronic exposure: emesis, diarrhea, poor growth, lethargy Re-exposure after restriction: emesis, diarrhea, hypotension a couple of hour after ingestion	Infancy	Usually resolves

Modified from Sicherer and Sampson (86) with permission.

Diagnostic procedure in IgE mediated food allergy

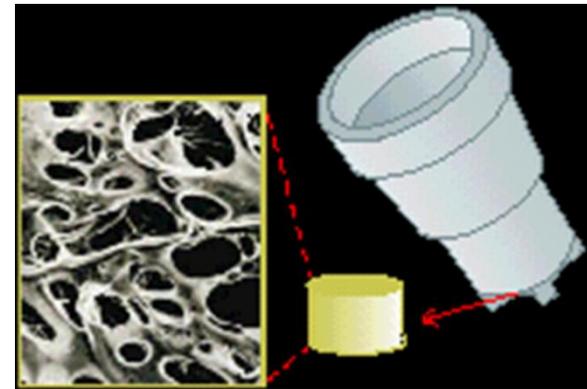
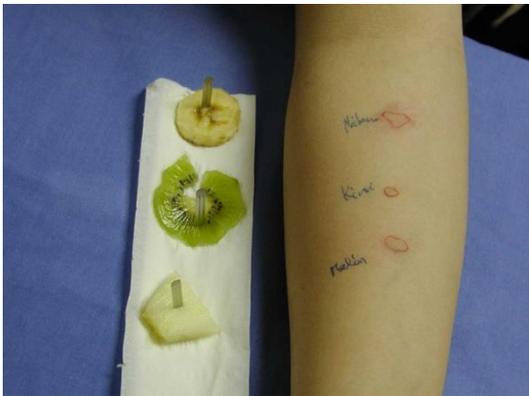
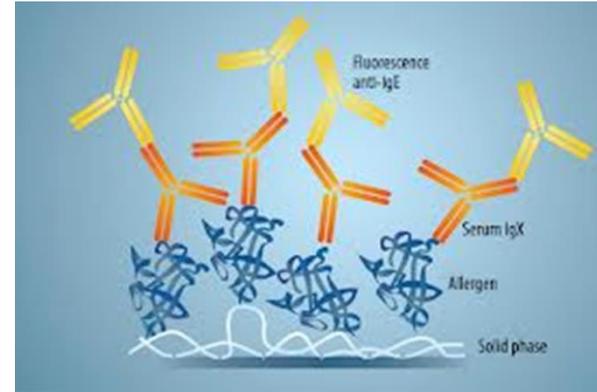
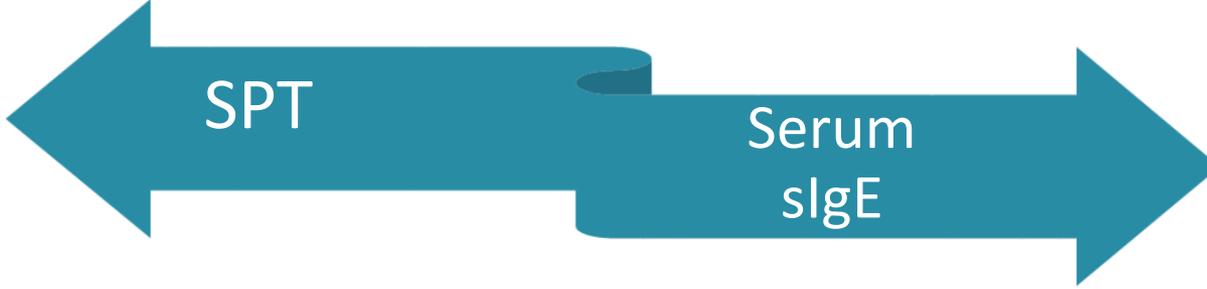
Step	Objective	Tool
1 st	Identify the suspected food Determine if an immune mechanism is likely to be involved	Medical history Physical examination
2 nd	Demonstrate the presence of food specific IgE (sensitisation)	Skin tests Serum sIgE tests
3 rd	Demonstrate the <i>clinical relevance</i> of the sensitisation (the food is responsible of the patient's symptoms)	Oral challenge Medical history Elimination diet

Medical history

- Essential to establish a causal relationship between the food intake and the appearance of symptoms.
 - Temporal relationship between intake and onset of symptoms (minutes-2 h)
 - Clinical reaction experienced by the patient
 - Information on the potential triggering food
- It provides important information to classify patients with adverse reactions to foods into “likely” and “unlikely” allergics.
- It helps to decide on the diagnostic tests to perform and on the diagnostic elimination diet
- The results of the diagnostic tests have to be evaluated in relation to the medical history.

Elimination diet

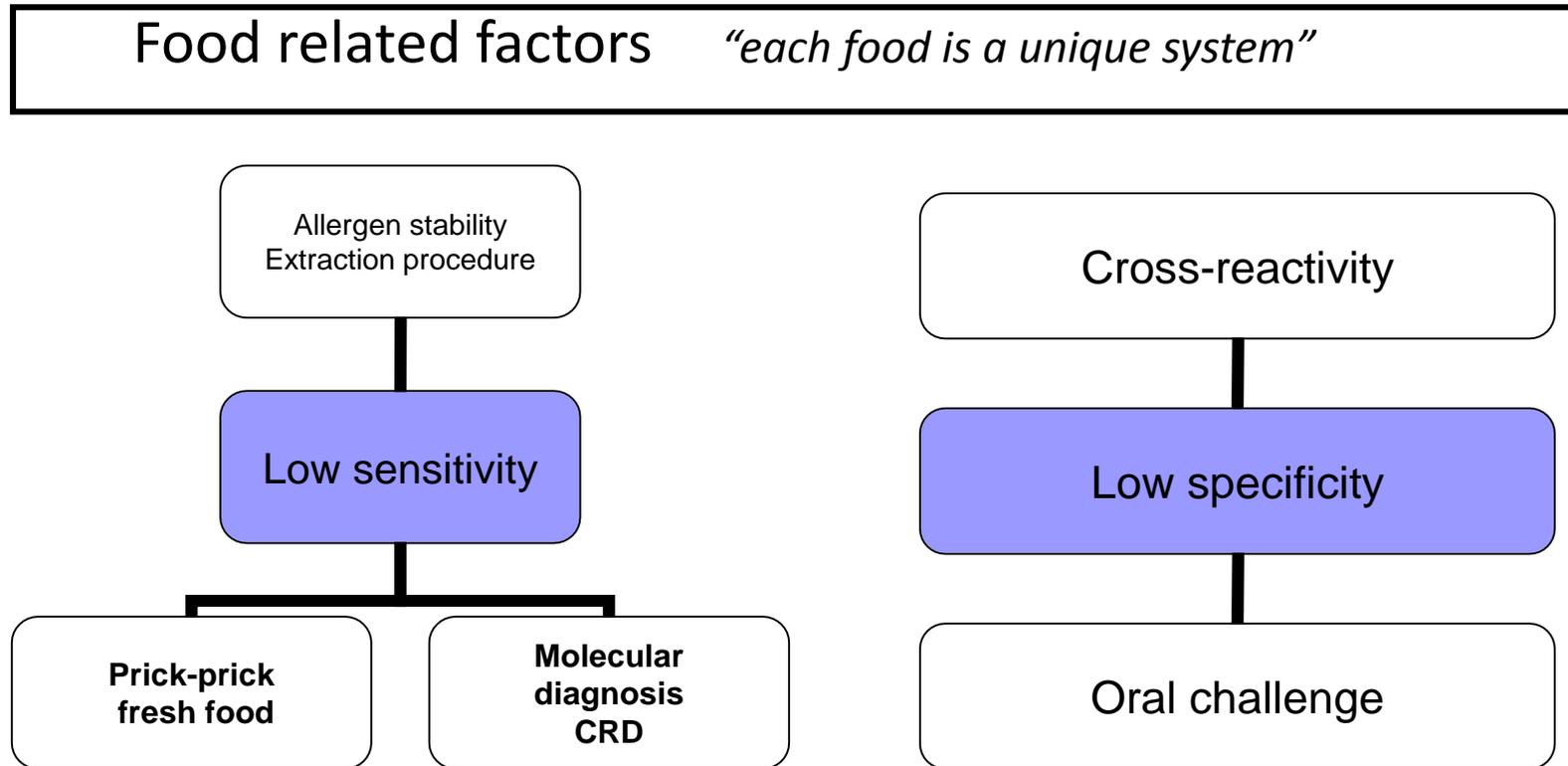
- Avoidance of the suspected “triggering” food based on the medical history and IgE testing
- “Easy” in acute IgE mediated reactions without cofactors involved
- More difficult in late reactions, mixed mechanisms (atopic dermatitis, EoE), or when cofactors involved.
 - 2-4 weeks
 - If no effect, allergy to the eliminated food is unlikely – reintroduction at home/allergy office
 - Oligo allergenic diet



IgE testing

- SPT and serum sIgE determinations are useful to detect a sensitisation to foods and help identifying foods that may provoke allergic reactions, but alone are not diagnostic of FA.

Diagnostic performance of IgE testing



- Food extracts are not standardised
- Different SPT extracts and serum sIgE testing systems are not comparable.
- Negative SPT/sIgE do not rule out FA.

Diagnostic performance of IgE testing

Patient related factors

- Age
 - SPT reactivity lower in < 2 y
- Population prevalence of that food allergy
- Clinical presentation of the FA
- Prevalence of atopic dermatitis
- Time of testing (i.e. avoidance)
- 1st diagnosis- follow-up

Study related factors

- Study design: prospective, retrospective
- Methodology of the oral challenge
- Quality of food extracts utilised

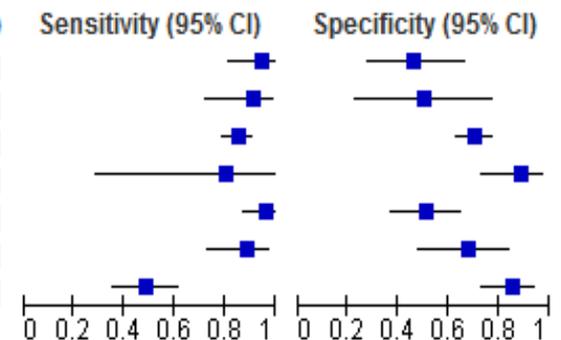
Cut-off values cannot be extrapolated

- From children to adults
- To a different population

Sensitivity and specificity for SPT and sIgE for diagnosis of cow's milk allergy

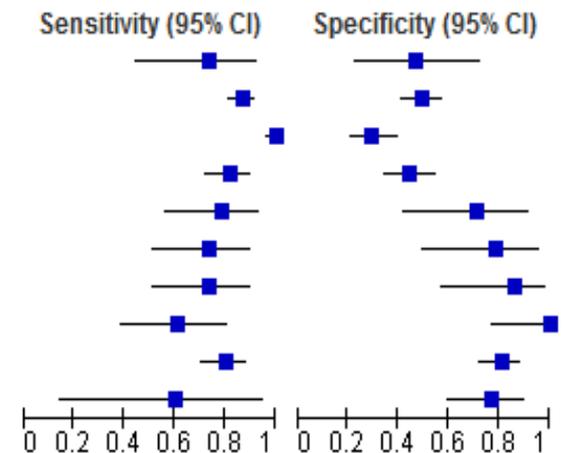
Target food: Cow's milk. Index test: SPT (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998 (A)	33	15	2	13	≥3mm	0.94 [0.81, 0.99]	0.46 [0.28, 0.66]
Keskin 2005	21	7	2	7	≥3mm	0.91 [0.72, 0.99]	0.50 [0.23, 0.77]
Mehl 2006	143	52	25	121	≥3mm	0.85 [0.79, 0.90]	0.70 [0.63, 0.77]
Sampson 1984	4	4	1	31	≥3mm	0.80 [0.28, 0.99]	0.89 [0.73, 0.97]
Sampson 1997	51	26	2	27	≥3mm	0.96 [0.87, 1.00]	0.51 [0.37, 0.65]
Eigenmann 1998 (B)	31	9	4	19	≥5mm	0.89 [0.73, 0.97]	0.68 [0.48, 0.84]
Isolauri 1996	31	8	33	46	1/2 histamine reaction	0.48 [0.36, 0.61]	0.85 [0.73, 0.93]



Target food: Cow's milk. Index test: Specific IgE (all cutoffs)

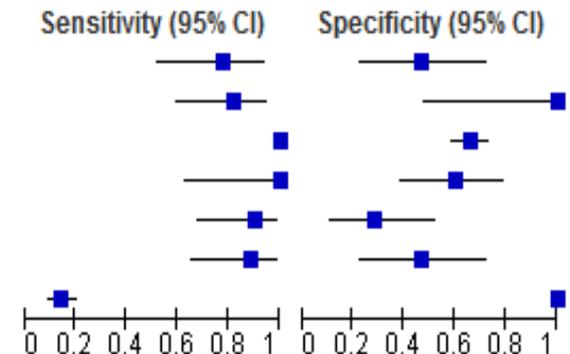
Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Breuer 2004	11	9	4	8	>0.35 kU/L	0.73 [0.45, 0.92]	0.47 [0.23, 0.72]
Mehl 2006	146	88	22	85	>0.35 kU/L	0.87 [0.81, 0.92]	0.49 [0.41, 0.57]
Sampson 1997 (A)	95	71	0	30	>0.35 kU/L	1.00 [0.96, 1.00]	0.30 [0.21, 0.40]
van den 2012	69	56	15	45	>0.35 kU/L	0.82 [0.72, 0.90]	0.45 [0.35, 0.55]
Keskin 2005 (A)	18	4	5	10	>0.59 kU/L	0.78 [0.56, 0.93]	0.71 [0.42, 0.92]
Keskin 2005 (B)	17	3	6	11	>0.70 kU/L	0.74 [0.52, 0.90]	0.79 [0.49, 0.95]
Keskin 2005 (C)	17	2	6	12	≥0.84 kU/L	0.74 [0.52, 0.90]	0.86 [0.57, 0.98]
Keskin 2005 (D)	14	0	9	14	≥4.18 kU/L	0.61 [0.39, 0.80]	1.00 [0.77, 1.00]
Sampson 1997 (B)	76	19	19	82	≥4.18 kU/L	0.80 [0.71, 0.88]	0.81 [0.72, 0.88]
Sampson 1984	3	8	2	27	NR	0.60 [0.15, 0.95]	0.77 [0.60, 0.90]



Sensitivity and specificity for SPT and sIgE for diagnosis of peanut allergy

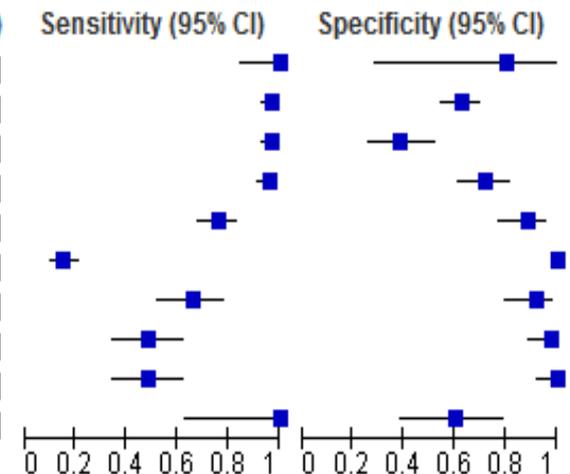
Target food: Peanut. Index test: SPT (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998 (A)	14	9	4	8	≥3mm	0.78 [0.52, 0.94]	0.47 [0.23, 0.72]
Flinterman 2006	18	0	4	5	≥3mm	0.82 [0.60, 0.95]	1.00 [0.48, 1.00]
Rance 2002 (A)	177	63	0	123	≥3mm	1.00 [0.98, 1.00]	0.66 [0.59, 0.73]
Sampson 1984	8	10	0	15	≥3mm	1.00 [0.63, 1.00]	0.60 [0.39, 0.79]
Sampson 1997	18	15	2	6	≥3mm	0.90 [0.68, 0.99]	0.29 [0.11, 0.52]
Eigenmann 1998 (B)	16	9	2	8	≥6mm	0.89 [0.65, 0.99]	0.47 [0.23, 0.72]
Rance 2002 (B)	26	0	151	186	≥16mm	0.15 [0.10, 0.21]	1.00 [0.98, 1.00]



Target food: Peanut. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Flinterman 2006	22	1	0	4	>0.35 kU/L	1.00 [0.85, 1.00]	0.80 [0.28, 0.99]
Rance 2002 (A)	171	70	6	116	>0.35 kU/L	0.97 [0.93, 0.99]	0.62 [0.55, 0.69]
Sampson 1997 (A)	132	37	4	23	>0.35 kU/L	0.97 [0.93, 0.99]	0.38 [0.26, 0.52]
van den 2012	105	25	4	64	>0.35 kU/L	0.96 [0.91, 0.99]	0.72 [0.61, 0.81]
Sampson 1997 (B)	103	7	33	53	≥10.7 kU/L	0.76 [0.68, 0.83]	0.88 [0.77, 0.95]
Rance 2002 (B)	27	0	150	186	≥57 kU/L	0.15 [0.10, 0.21]	1.00 [0.98, 1.00]
van Nieuwaal 2010 (A)	37	4	19	43	10.4 kU/L	0.66 [0.52, 0.78]	0.91 [0.80, 0.98]
van Nieuwaal 2010 (B)	27	1	29	46	24.1 kU/L	0.48 [0.35, 0.62]	0.98 [0.89, 1.00]
van Nieuwaal 2010 (C)	27	0	29	47	26.5 kU/L	0.48 [0.35, 0.62]	1.00 [0.92, 1.00]
Sampson 1984	8	10	0	15	NR	1.00 [0.63, 1.00]	0.60 [0.39, 0.79]



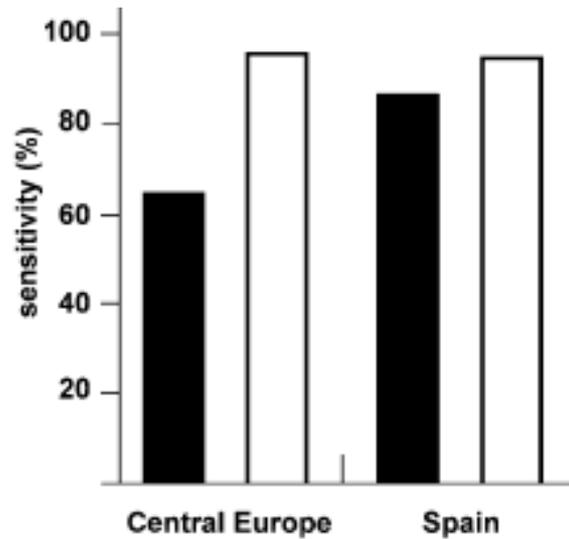
SPT and sIgE for diagnosis of milk, egg and peanut allergies

MILK	Studies	Participants	Cases	Sensitivity % (95% CI)	Specificity % (95% CI)
SPT (≥3mm)	5	587	284	87.9 (75.6, 94.4)	67.5 (56.0, 77.2)
Specific IgE (mixed cutoffs)	6	831	390	87.3 (75.2, 93.9)	47.7 (36.4, 59.2)

EGG	Studies	Participants	Cases	Sensitivity % (95% CI)	Specificity % (95% CI)
SPT (mixed cutoffs)	5	448	287	92.4 (79.9, 97.4)	58.1 (49.1, 66.6)
Specific IgE (mixed cutoffs)	5	572	346	93.4 (82.1, 97.8)	49.2 (40.2, 58.1)

PEANUT	Studies	Participants	Cases	Sensitivity % (95% CI)	Specificity % (95% CI)
SPT (≥3mm)	5	499	245	94.7 (87.9, 97.8)	61.0 (46.6, 73.6)
Specific IgE (mixed cutoffs)	5	817	452	96.3 (91.6, 98.4)	59.3 (45.4, 72.0)

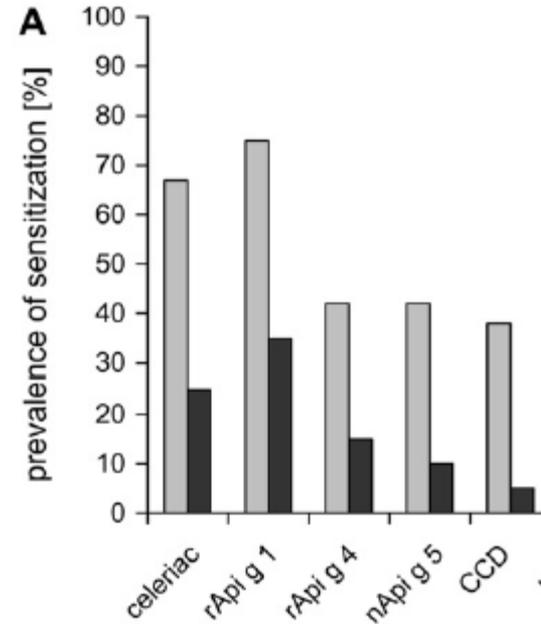
CRD – higher sensitivity in plant food allergies



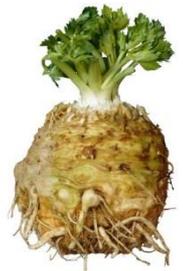
 Se CAP cherry
 Se CAP rPru av 1 +3 + 4



Reuter et al. CEA 2006



Se CAP celeriac: 67%
 Se CRD: 88%



Bauermeister et al. JACI 2009

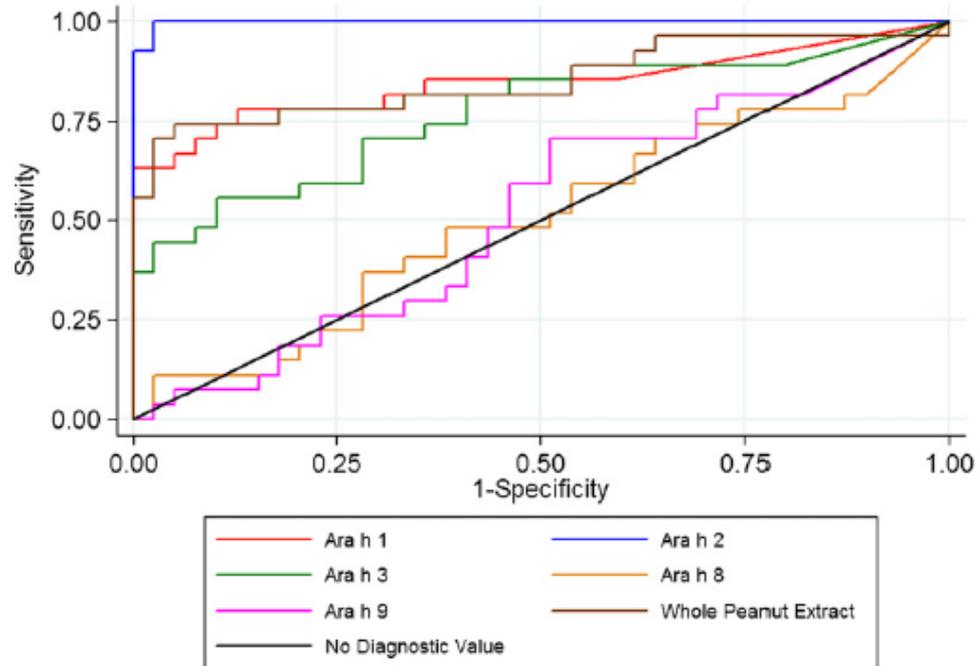
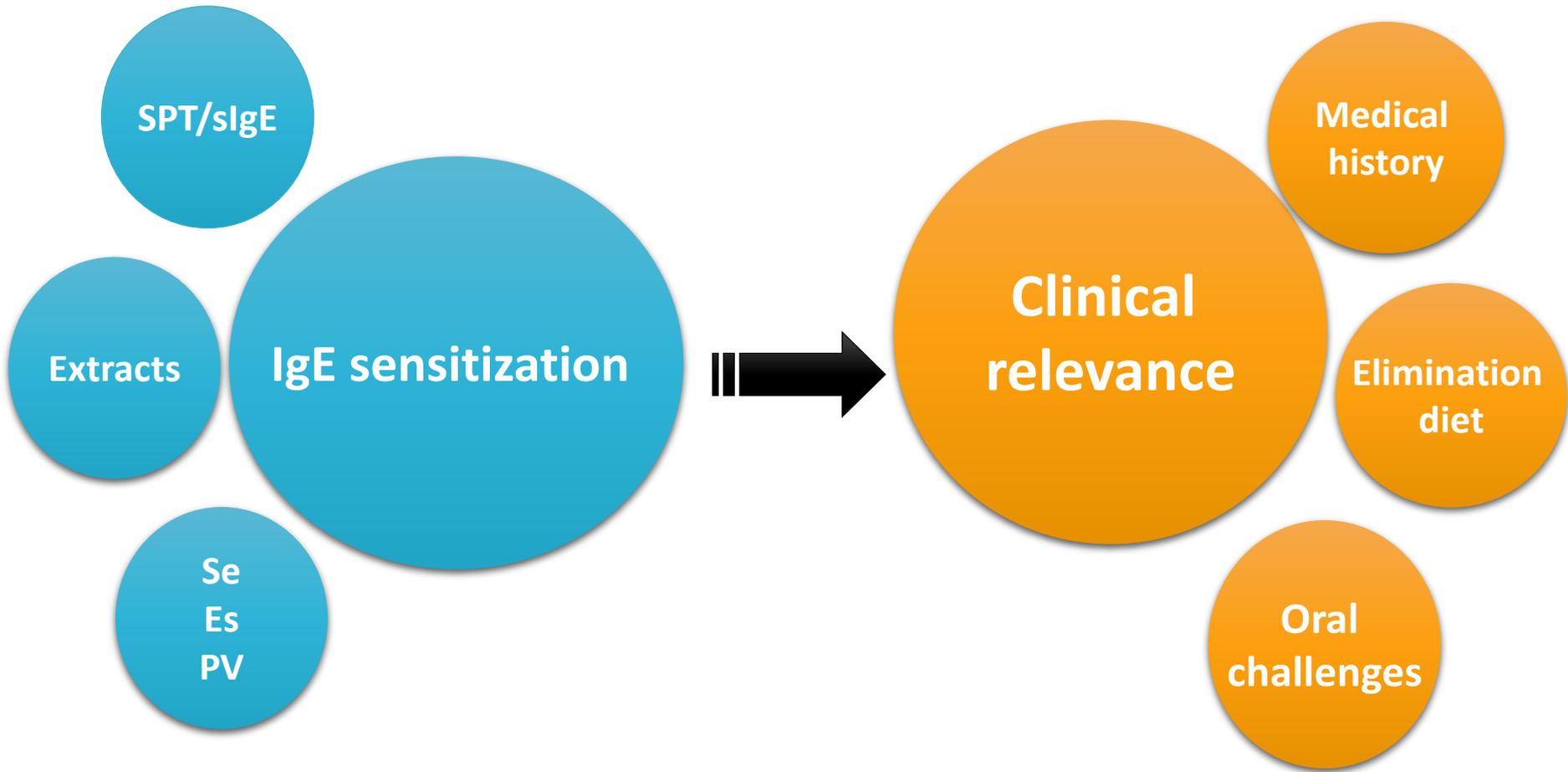
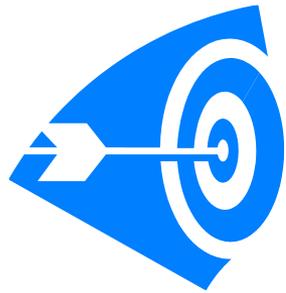


TABLE I. Sensitivity and specificity* for Ara h 2 and whole peanut extract

Test	Cutoff point (kU _A /L)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Ara h 2	0.30	100.00	90.20	93.75
	0.32	100.00	94.12	95.00
	0.35	100.00	96.08	97.50
	0.38	96.55	96.08	96.25
	0.40	93.10	98.04	96.25
	0.55	93.10	100.00	97.50
	0.87	89.66	100.00	96.25
Whole extract	0.35	96.55	26.92	51.85
	3.91	79.31	84.62	82.72
	5.00	75.86	90.38	85.19
	5.30	75.86	94.23	87.65
	5.96	72.41	94.23	86.42
	7.81	72.41	96.15	87.65
	15.00	55.17	96.15	81.48
	43.86	34.85	98.08	75.31





The oral challenge is the only conclusive evidence of a food allergy

When to perform oral food challenges

WITH a previous adverse reaction to the food

To establish or exclude FA

To assess the development of tolerance

Before starting food immunotherapy

For determination of the threshold value

For scientific reasons

WITHOUT a previous adverse reaction to the food

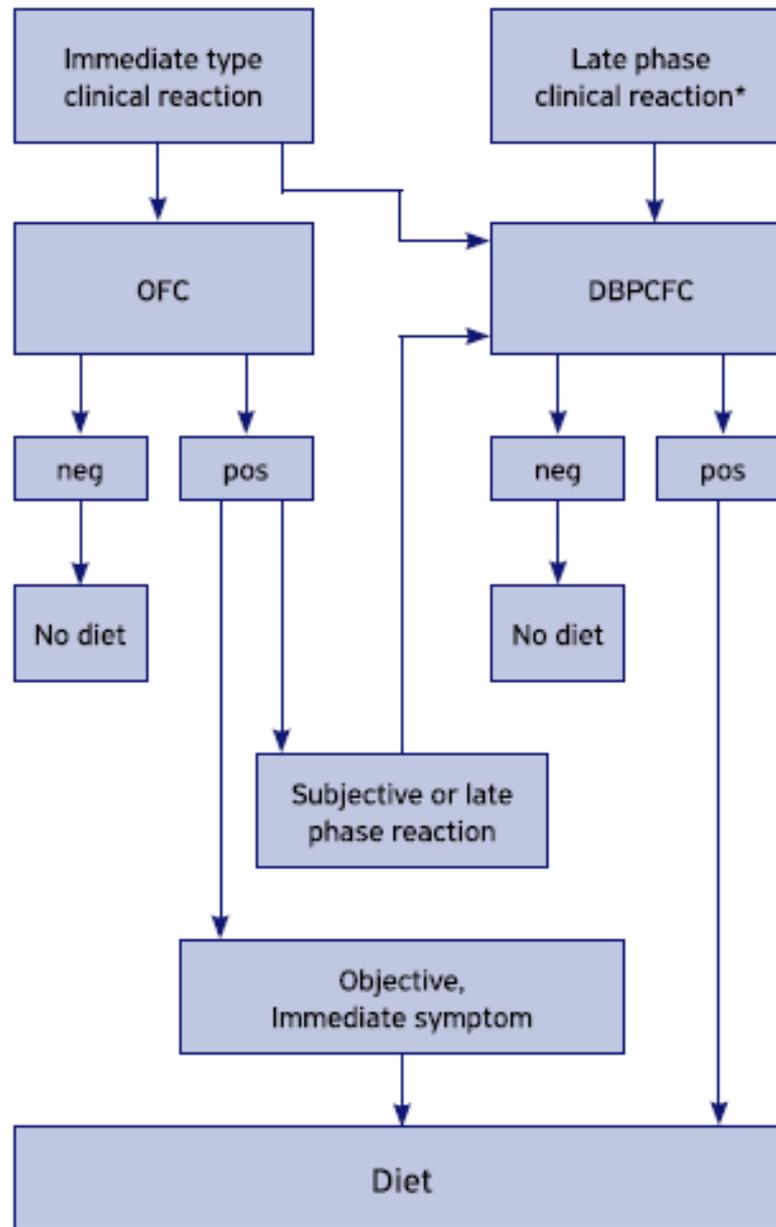
A chronic symptom suspected by the patient/physician to be food-related (after elimination diet)

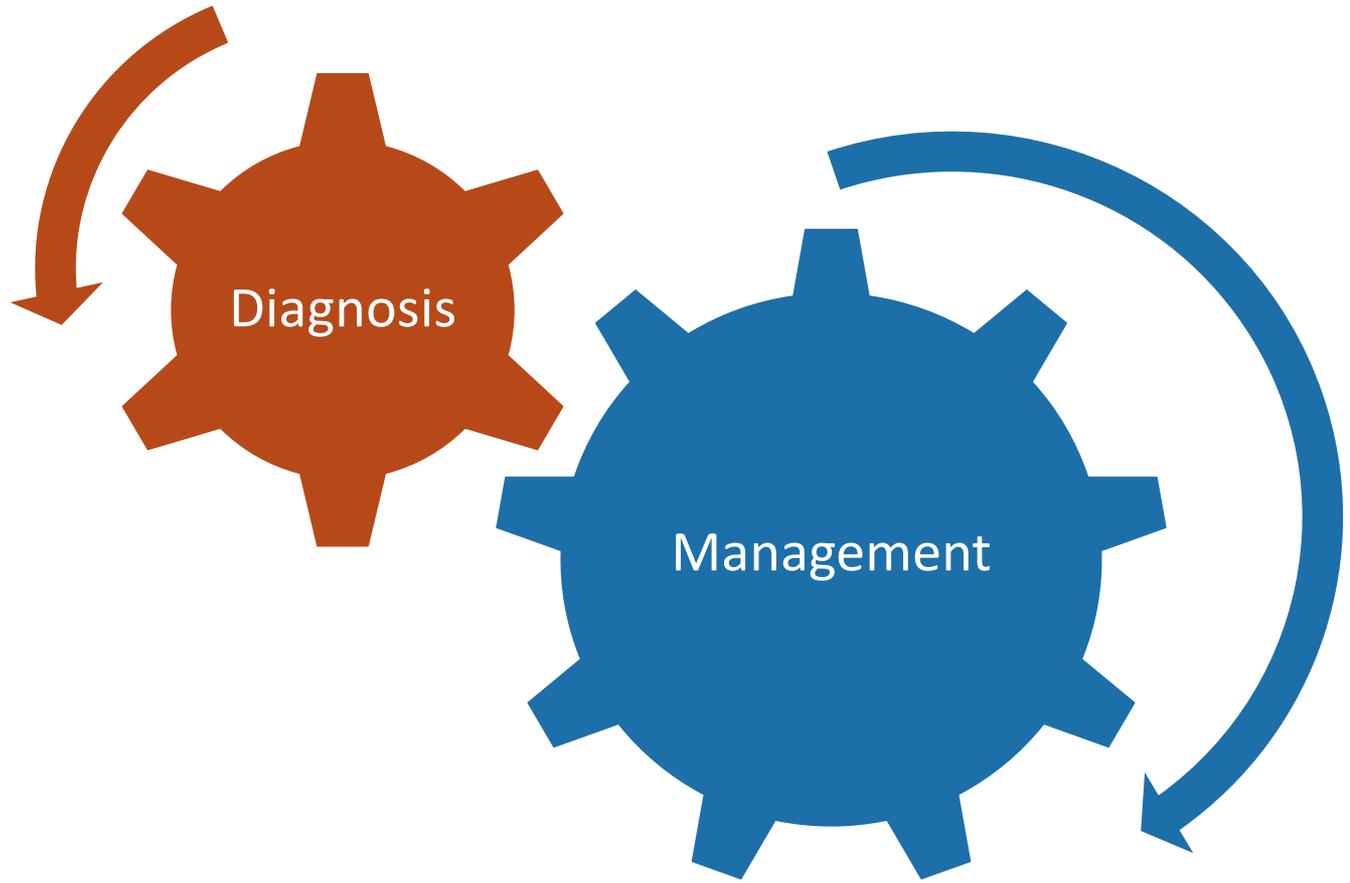
Improper elimination diet: food has to be reintroduced and there are reasons for suspecting that an adverse reaction is possible.

Sensitisation to a food diagnosed and tolerance is not known

Procedure

Safety	<p>Close monitoring of vital signs</p> <p>Trained staff in management of allergic reactions, including anaphylaxis</p> <p>Specialist setting with emergency support immediately available</p>
Design	<p>Open / Blinded (SB-DB) placebo controlled</p> <p>DBPCFC is the gold standard for the objective diagnosis of food allergy</p> <p>DBPCFC: subjective symptoms; delayed or atypical symptoms; anxiety of patients and/or relatives research.</p> <p>OFC with an objective unequivocal reaction is sufficient for diagnosis.</p> <p>A negative OFC may be useful as 1st step in ruling out food allergy</p>
Dosing	<p>Titrated doses at set intervals (15-30 min) up to an age appropriate portion.</p> <p>A negative DBPCFC should be followed by an open challenge.</p>
Stopping criteria	<p>Objective reaction</p>





References

- EAACI Food Allergy and Anaphylaxis Guidelines:
 - Soares-Weiser et al. The diagnosis of food allergy: a systematic review and meta-analysis. Allergy 2014
 - Muraro A, et al. Diagnosis and management of food allergy. Allergy 2014
- AAAAI & EAACI. PRACTALL consensus report.
 - Sampson HA et al. Standardizing double-blind placebo-controlled oral food challenges. JACI 2012.