IgE- BASED ALLERGY- DIAGNOSTICS IN CHILDHOOD -

RECENT EAACI RECOMMENDATIONS -

WITH SPECIFIC ATTENTION TO FOOD ALLERGIES

Lajos A. RÉTHY
”OGYEI” - National Institute for Child Health , Budapest

REVIEW ARTICLE

Testing children for allergies: why, how, who and when

An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation

P. A. Eigenmann[1], M. Atanaskovic-Markovic[2,3], J. O'B Hourihane[4], G. Lack[5], S. Lau[6], P. M. Matricardi[6], A. Muraro[7], L. Namazova Baranova[8], A. Nieto[9], N. G. Papadopoulos[10], L. A. Réthy[11], G. Roberts[12,13], O. Rudzeviciene[14], U. Wahn[6], M. Wickman[15] & A. Høst[16]

[1]Department of Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland; [2]University Children's Hospital, Belgrade, Serbia; [3]Medical Faculty, University of Belgrade, Belgrade, Serbia; [4]Paediatrics and Child Health, University College Cork, Cork, Ireland; [5]Guy's and St. Thomas NHS Trust at King's College London, King's Health Partners, MRC Asthma UK Centre in Allergic Mechanisms of Asthma, Department of Paediatric Allergy, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [6]Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany; [7]The Food Allergy Referral Centre, Department of Pediatrics, Veneto Region, Università degli Studi di Padova, Padova, Italy; [8]Scientific Center of Children's Health of Russian Academy of Medical Sciences, Moscow, Russia; [9]Pediatric Pulmonology & Allergy Unit, Children's Hospital La Fe, Valencia, Spain; [10]Allergy Department, 2nd Pediatric Clinic, National & Kapodistrian University of Athens, Athens, Greece; [11]OGYEI National Institute of Child Health, Budapest, Hungary; [12]University of Southampton, Southampton, UK; [13]David Hide Asthma and Allergy Research Centre, Isle of Wight, UK; [14]Clinic of Children's Diseases, Vilnius University, Vilnius, Lithuania; [15]Sachs' Children's Hospital, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [16]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

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Correspondence
Philippe A. Eigenmann, Pediatric Allergy, Department of Child and Adolescent, University Hospitals of Geneva, CH- 1211 Geneva 14, Switzerland.
Tel.: xxxxxxx
Fax: xxxxxxx
E-mail: philippe.eigenmann@hcuge.ch

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Abstract

Allergic diseases are common in childhood and can cause a significant morbidity and impaired quality-of-life of the children and their families. Adequate allergy testing is the prerequisite for optimal care, including allergen avoidance, pharmacotherapy and immunotherapy. Children with persisting or recurrent or severe symptoms suggestive for allergy should undergo an appropriate diagnostic work-up, irrespective of their age. Adequate allergy testing may also allow excluding a possible allergic trigger in common symptoms. We provide here evidence-based guidance on when and how to test for allergy in children based on common presenting symptoms suggestive of allergic diseases.

IgE based tests

Evidence –based recommendations

Table 2 Levels of evidences and grades of recommendation

	Level of evidences
Level I	Systematic reviews, meta-analyses, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One group, non-randomized (e.g. before and after, pre-test and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature reviews and consensus statements
	Grades of recommendation
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies *or* extrapolations from level I studies
Grade C	Level IV studies *or* extrapolations from level II or III studies
Grade D	Level V evidence *or* troublingly inconsistent or inconclusive studies of any level

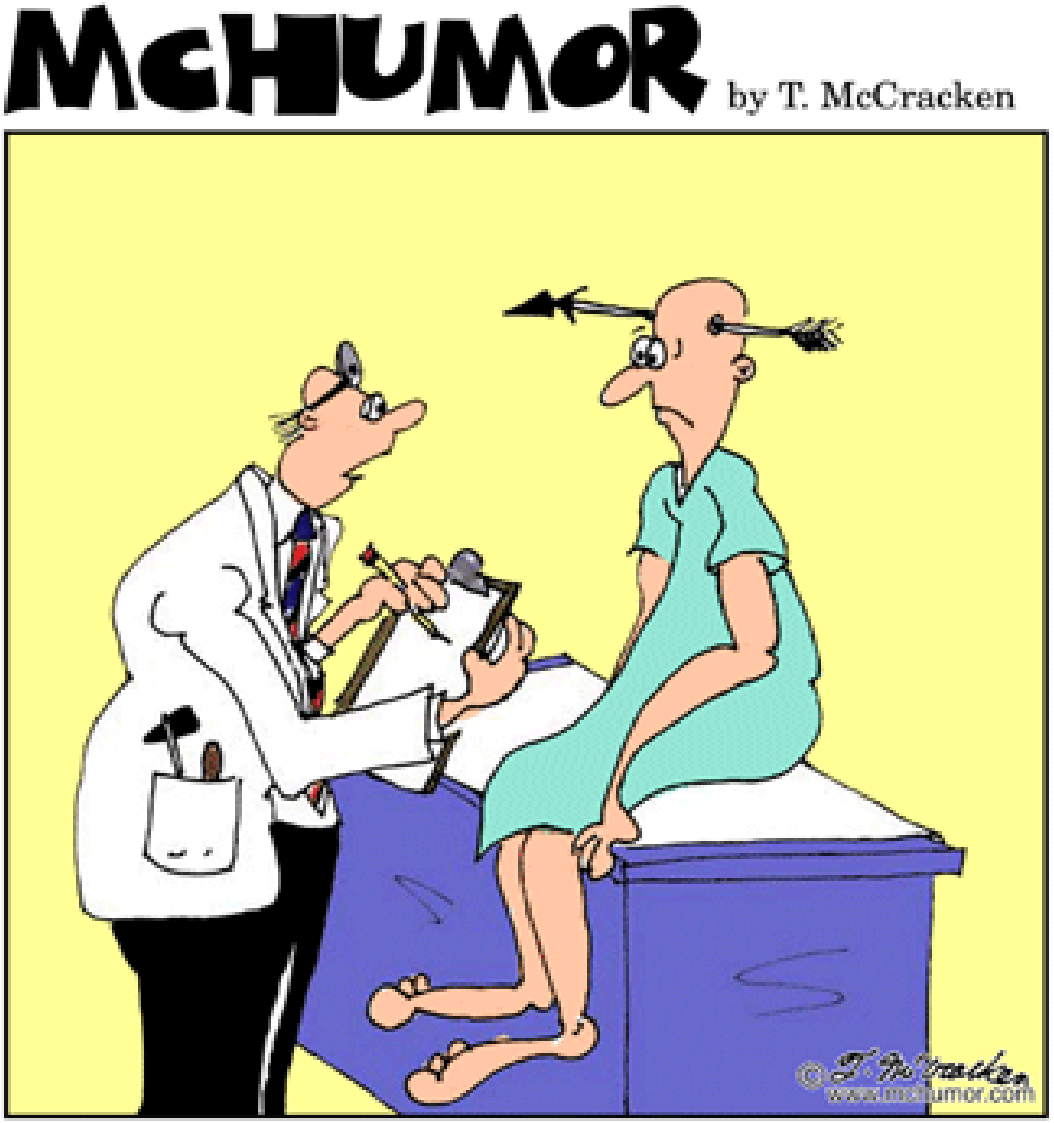
From www.cebm.net.

Total IgE- **has no indication in diagnosing allergic diseases**

But instead, **total IgE plays role as**:

- dosis-determining parameter in omalizumab therapy (B)
- Diagnostic parameter in allergic bronchopulmonary aspergillosis (B)
- algorhytm-parameter in risk calculation for provocation tests (B)

The basics: History & physical examination!



"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."

IgE tests are necessary:

- **To determine the necessity of allergen-free diet**
  - E.g. if food allergies are suspected

- **Immunotherapy-** for clear diagnosis & follow up effectiveness

- **Identification of high risk patients**
  - E.g. **hen's in egg allergy** there is a **20-25% sensibilisation to peanut** – test (B)-*should be offered*..

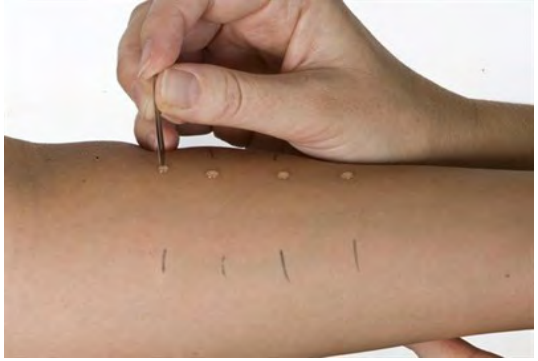
Se sp IgE

- >0,1 ill. 0.35 kU/ml poz. Limit,
  - **Different tests are not interchangable !**
- **Good sensitivity** and NPV / true for SPT as well (C)
- **Lower specificity** (C)
  - Different PPV values for certain allergens .
    - Extracts are not standardized !
    - False positivities eg. Tree pollen/venom CH determinants

CRD-Component Resolved Dg

- **Recombinant allergens**
- Eg. Ara h 2 in peanut allergies – good PPV in children (C)

Prick test: Practical issues



- **Trained staff!**
- Interpretation : ≥ 3mm limit remained
    - **In case of larger wheal reactions : the largest diameter is proposed to be measured**
        - » Constantinou (Papadopoulos),Int Arch Allerg Imm 2010
- **Contraindications** - remained:
    - Activ eczema, local steroid /immunmodulatory treatment antihistamins (**≥3 days)**,
    - **Disturbing effects of local steroids are questionable**
- Wait min. 4-6 weeks after an acute allergic reaction (E)

- No age limit but careful interpretation below 2 years of age (C)

Provocations – mostly in food allergies

Gold standard : DBPCFC

Open provocations : acceptable in most cases (esp. In smaller babies)

If only subjective complaints : hide allergen (vehiculum)

Provocations: Not without risk!

(proper professional- technical background! ICU)

Kruidkoek voor dubbelblinde voedselprovocatie

Veilig en goed

In wetenschappelijke kringen wordt steeds vaker gepleit voor Dubbelblinde Placebo-gecontroleerde Voedselprovocatietests als methode om een allergie voor bepaalde voedingsstoffen veilig en goed te testen. Een van de voordelen van deze manier van testen is dat er minder vaak sprake is van vals positieve uitslagen dan bij open tests.

Pasklaar antwoord

Als pasklaar antwoord op deze ontwikkeling biedt Chef Martin nu een speciale kruidkoek die kan worden ingezet bij het uitvoeren van dubbelblinde tests. De kruidkoek wordt gemaakt op basis van gevalideerde receptuur, ontwikkeld door B.J. Vlieg-Boerstra et al [1].

Vier varianten

De speciale kruidkoek is er in vier varianten, voor het testen van de volgende allergenen:

- Pinda
- Hazelnoot
- Kippenei
- Cashewnoot

Onderscheidende kenmerken

- Hoge einddosering van het allergeen.
- De kruidkoek is direct na bereiding diepgevroren en daardoor bij -18°C minimaal 6 maanden houdbaar.
- Bereid volgens HACCP-normen; positive release (microbiologisch).
- De placebovariant van de kruidkoek is door Chef Martin gecontroleerd op afwezigheid van het betreffende allergeen d.m.v. een sneltest.
- De kruidkoek is onder gecontroleerde omstandigheden bereid en zeer constant van samenstelling, waardoor een vast doseerschema kan worden gehanteerd.
- Door de producten tijdens het bakproces af te dekken, is de Maillardreactie geminimaliseerd.
- Productspecificatiebladen zijn beschikbaar.
- Productiecodes maken verificatie van het type testvoeding achteraf altijd traceerbaar.
- Makkelijk te portioneren.

1. Vlieg-Boerstra et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. Allergy 2011;66:1613-1614

Dát is onze zorg voor lekker eten.

www.chefmartin.nl | Chef Martin is onderdeel van Marlo Food Group
Koperstraat 25 - 31 | 8211 AK Lelystad | 0320 293 800 | info@chefmartin.nl

Likelihood ratios to diagnose allergy

EAACI FA & Anaphyl. Guidelines 2014

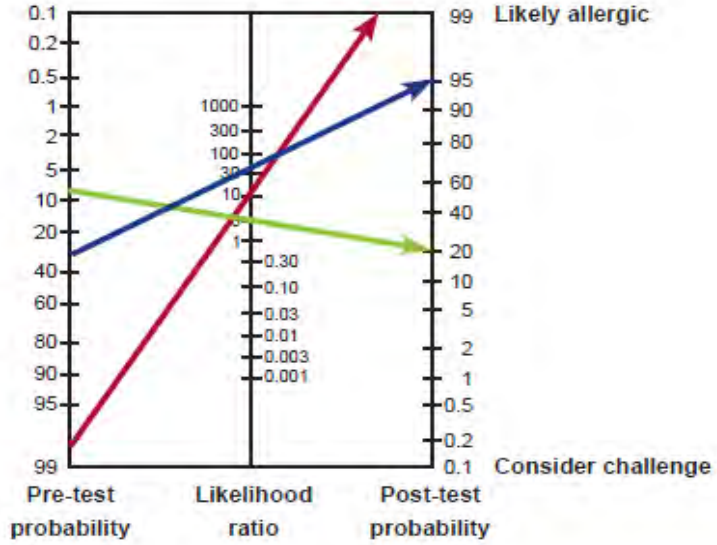


Figure I-C 1 Using likelihood ratios (LR) to diagnose allergy

Figure adapted from: Fagan TJ. (90)

The three arrows are examples of clinical situations described in the Table I-C below (Red arrow refers to scenario A, green to B and blue to C).

		Likelihood of clinical allergy from specific IgE (kU/L) or SPT (mm) results		
		Low (<0.35 or <3)	**Intermediate** (0.35 to <15 or 3 to < 8)	**High** (≥ 15 or ≥ 8)
Likelihood of clinical allergy from history	**High** e.g. Urticaria and wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	Intermediate e.g. Urticaria on a single exposure	Possible allergy	Possible allergy	Probable allergy
	Low e.g. Non-IgE mediated symptoms	No allergy	Possible allergy	Possible allergy

Figure I-C 2 Using likelihood ratios (LR) to diagnose allergy

Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE and SPT values are specific for peanuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk,and fish. Modified from Stiefel and Roberts (91).

Predictive values of algorhytms in food challenge outcomes

PPV- s of clinical algorhytms based on calculations using available parameters :

spIgE, total IgE, clinical signs/score , gender & age for risk predictions

Still in testing phase - may make provocation tests unnecessary…

(Dunn-Galvin, Hourihane, JACI 2011)

Unproven tests

IgG tests - not recommended for (IgE based) allergy diagnosis

IgG4 :

role in tolerance? -

Immunotherapy- marker for follow up ? (Sverremark-Ekström 2012)

Non validated tests – not recommended :

- Elektromagnetic conductance ,
- kinesiology,
- hair analysis,
- iris-diagnostics,
- face-thermography,
- gastric fluid analysis
- **Etc..- not recommended !**

Molecular diagnostics (CRD) offers:

- Increasing diagnostic accuracy,
- Better evaluation for the efficacy of immunotherapies
- More effective prediction of cross-reactions .
- Less false diagnoses, less unnecessary diets
- Better quality of life


Allergen source
Allergen extract
Specific allergen components
Cross-reactive allergen components

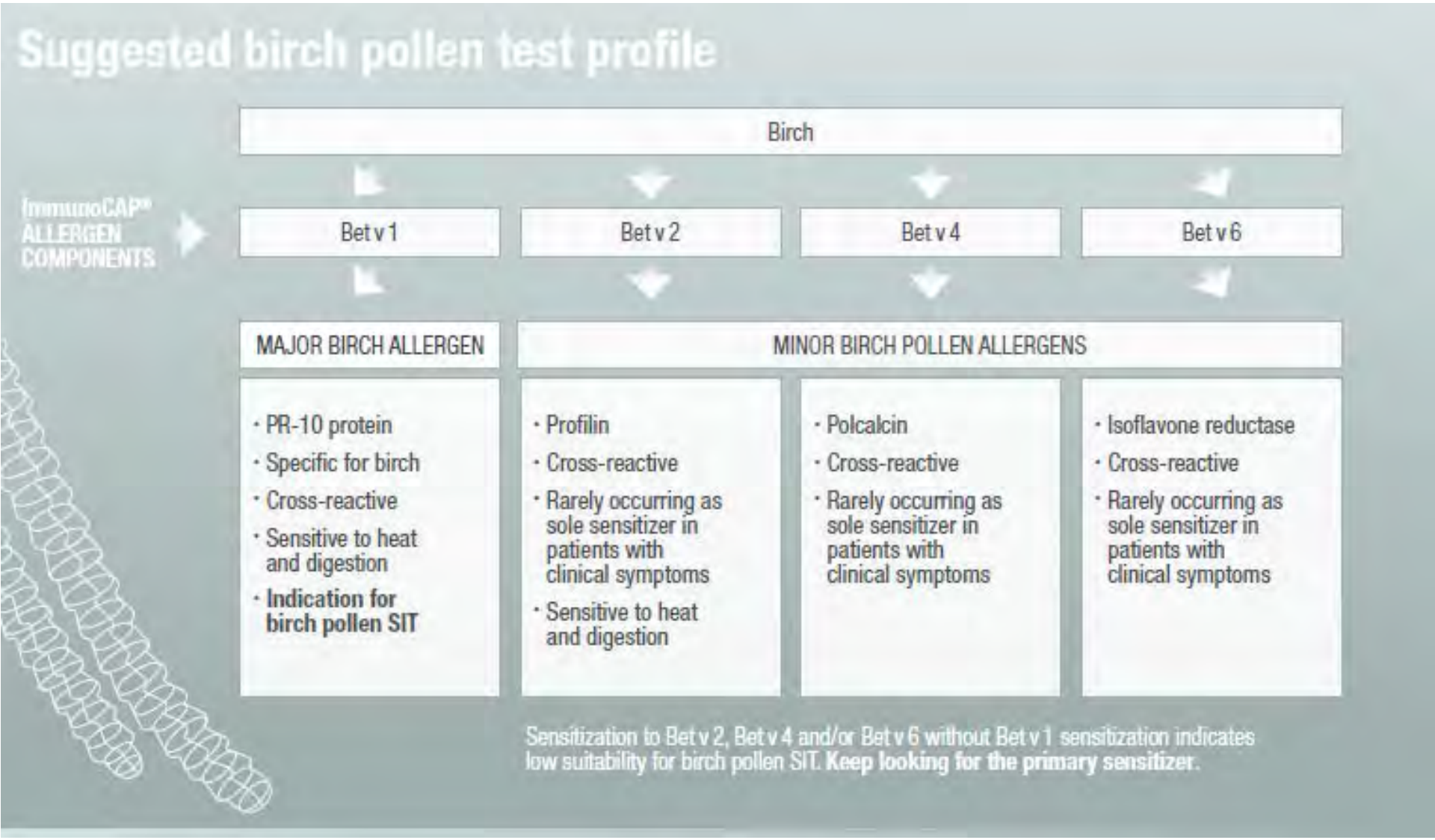
Molecular diagnostics (CRD) Food allergens- risk of anaphylaxis/high vs. low

High- versus low-risk molecules from foods giving rise to anaphylaxis

Source	High risk	Low risk
Peanut	Ara h 1, 2, 3, 9	Ara h 8, profilin, CCD
Hazelnut	Cor a 8, 9, 14	Profilin, CCD
Walnut	Jug r 1, 2, 3	Profilin, CCD
Soy	Gly m 5, 6, (4)	Profilin, CCD
Rosacea fruits	Pru p 3, Mal d 3	Pru p 1, Mal d 1, profilin, CCD
Wheat	Tri a 14, Tri a 19	Profilin, CCD

KEY: CCD = Cross-reactive Carbohydrate Determinant

Test profile, birch allergy



Canonica et al. World Allergy Organization Journal 2013, 6:17
http://www.waojournal.org/content/6/1/17

WAO journal
WORLD ALLERGY ORGANIZATION

CONSENSUS DOCUMENT Open Access

A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnostics

Giorgio Walter Canonica[1*], Ignacio J Ansotegui[2], Ruby Pawankar[3], Peter Schmid-Grendelmeier[4], Marianne van Hage[5], Carlos E Baena-Cagnani[6], Giovanni Melioli[7], Carlos Nunes[8], Giovanni Passalacqua[9], Lanny Rosenwasser[10], Hugh Sampson[11], Joaquin Sastre[12], Jean Bousquet[13], Torsten Zuberbier[14] and WAO-ARIA-GA2LEN Task Force: Katrina Allen, Riccardo Asero, Barbara Bohle, Linda Cox, Frederic de Blay, Motohiro Ebisawa, Rene Maximiliano-Gomez, Sandra Gonzalez-Diaz, Tari Haahtela, Stephen Holgate, Thilo Jakob, Mark Larche, Paolo Maria Matricardi, John Oppenheimer, Lars K Poulsen, Harald E Renz, Nelson Rosario, Marc Rothenberg, Mario Sanchez-Borges, Enrico Scala, Rudolf Valenta

Abstract

Molecular-based allergy (MA) diagnostics is an approach used to map the allergen sensitization of a patient at a molecular level, using purified natural or recombinant allergenic molecules (allergen components) instead of allergen extracts. Since its introduction, MA diagnostics has increasingly entered routine care, with currently more than 130 allergenic molecules commercially available for *in vitro* specific IgE (sIgE) testing.

MA diagnostics allows for an increased accuracy in allergy diagnosis and prognosis and plays an important role in three key aspects of allergy diagnosis: (1) resolving genuine versus cross-reactive sensitization in poly-sensitized patients, thereby improving the understanding of triggering allergens; (2) assessing, in selected cases, the risk of severe, systemic versus mild, local reactions in food allergy, thereby reducing unnecessary anxiety for the patient and the need for food challenge testing; and (3) identifying patients and triggering allergens for specific immunotherapy (SIT).

Singleplex and multiplex measurement platforms are available for MA diagnostics. The Immuno-Solid phase Allergen Chip (ISAC) is the most comprehensive platform currently available, which involves a biochip technology to measure sIgE antibodies against more than one hundred allergenic molecules in a single assay. As the field of MA diagnostics advances, future work needs to focus on large-scale, population-based studies involving practical applications, elucidation and expansion of additional allergenic molecules, and support for appropriate test interpretation. With the rapidly expanding evidence-base for MA diagnosis, there is a need for allergists to keep abreast of the latest information. The aim of this consensus document is to provide a practical guide for the indications, determination, and interpretation of MA diagnostics for clinicians trained in allergology.

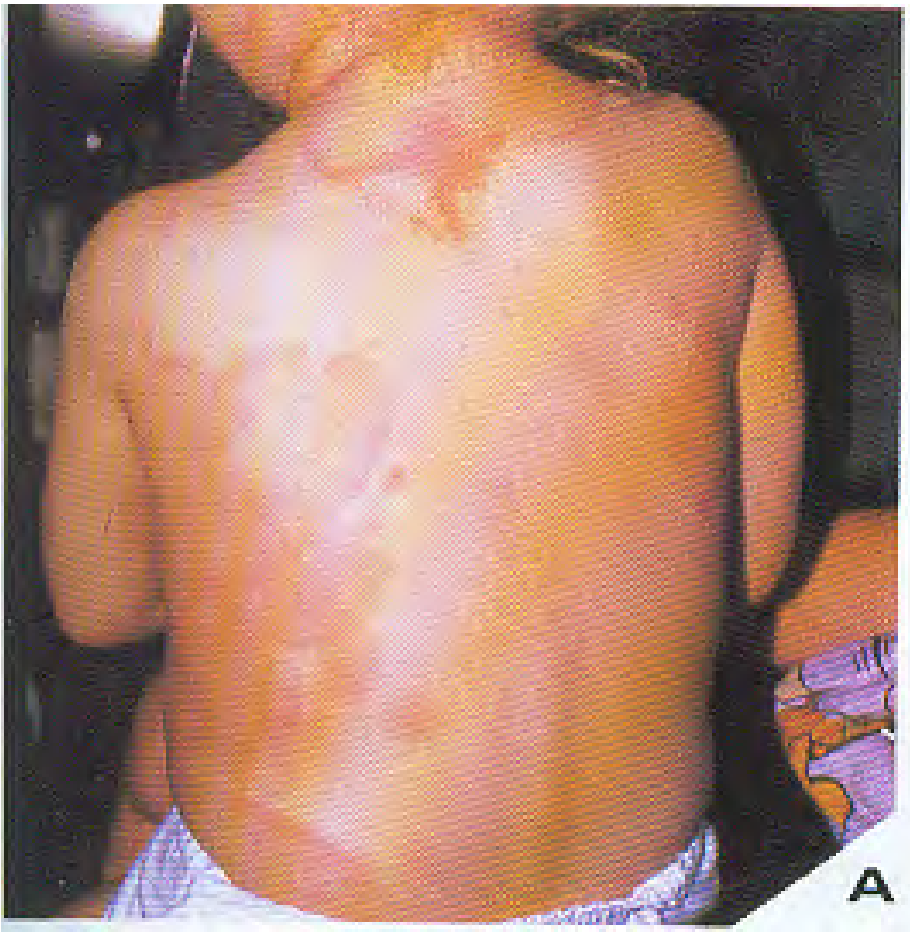
Organ symptoms, related issues

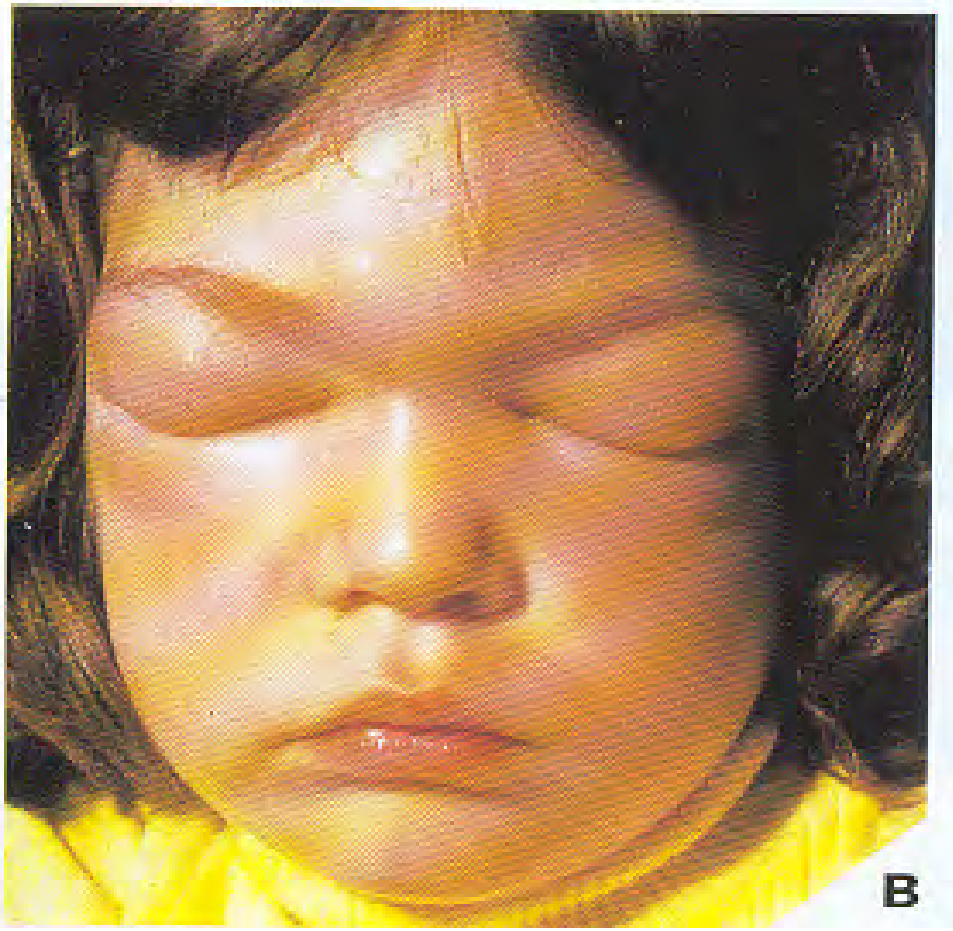
***Atopic eczema* – if early onset and medium/strong signes**

Higher risk for food allergies – to be excluded!

- <3 y, CM, hen's egg allergens (B)
- >3 é: house dust mite ! + local prevalent allergens (B)

Allergic urticaria, angioedema





Acute urticaria, angioedema

- Urtic: Starts within 2 hours , symptoms disappear within 24 hours
  - >24 hrs: **virus, drugs** (NSAID), histamin liberation, physical effect (eg. Cold, vasculitis: Schonlein-Henoch) more likely
  - HANO-, ACE inhibitors : angioedema without (!) urticaria
- IgE: based on history, targeted tests
- **Panel –screens may increase false positivities – not recommended !**
- Mostly: Cow milk, nuts, other food allergens, sometimes indoor allergens – or
- To rule out other triggers if necessary

Chr. urticaria

- Recurrent >6 weeks laesion
- Rare in childhood,
- **Allergy test: extreem rarely diagnostic!**

- Backgound: parasites, chronic infection, autoimmunity, (coeliak disease too!) drug, mastocytosis, C1inh deficiency

- **Drug induced skin rashes:**
  - **Diagnostics recommended in specialized centers for drug allergies:** lactams, makrolides, sulfonamids, NSAID, anaesthesia-related drugs, latex, hypnotics, opoids, Anticonvulsives , contrast media

Anaphylaxis, childhood

Mostly food IgE

- During acute episodes: store serum (spec IgE , tryptase)
- **Tryptase** : Measurement within 1-3. hours (sometimes even normal)
- Later: Prick or Prick to Prick to be considered (more sensitive)
- **SpIgE tests may be negative – if within 4-6 week anergic state -** (E)
- recombinant allergens may increase sensitivity .
- Provocation test: Only if there is no correlation btw. Signs and allergy tests

Gastrointestinal signs – role of history !

IgE test if other allergic sign/s is/are present - (even anaphylaxis)

Mostly non-IgE origin, if: vomiting, diarrhoea, reflux, colic , irritability , delayed growth

Chronic signs –extreme rare IgE type backgound ! –extensive diff dg, Consultation- GI specialist !

Exclude : FPIES, eosinophil GI diseases, - coeliakia

colic : Exclude fatigue air-swallowing, **reflux**

- **If atopic signs present at a child with** excessive, inconsolable crying**:**
  - **Exclude CMA & other food allergies**

Delay in growth:

- Primary : Optimize food intake and follow up weight charts ,
- Coeliakia, CF, immunodeficiencies –to be excluded
- (Rare: seroius atop. Dermatitis : oedema,hypalbuminaemia etc)

Acute vomiting, diarrhoea: think about infections, esp. in younger children!

Child with a sibling with food allergies

- Relatives: Higher risks –
- Child with a sibling with food allergies- when to test?
  - In case of moderate/ severe eczema
  - Symptomless sibling- testing depends on actual situation

Some other points:

- Extreme high sp IgE results- always check total IgE – maybe this is the reason
- IgE and activity of allergies: still to be discovered

Take home message:

Neither spIgE nor SPT can reflect the seriousness of the allergic reaction! It reflects the probability of an allergic reaction. (C)

Thank you for your attention !

Insect sting reactions

- **Allergy diagnostics: only if the sting resulted in a systemic reaction!**
- **Local reactions do not indicate allergy testing** ! (B)
  - Biló, Allegy 2005, Valentine NEJM 1990, Golden NEJM 2004

- Allergy testing may establish
  - Immunotherapy / prevention

- Additional tests if necessary: basophil activation, recombinant allergens, basal se tryptase (to rule out mastocytosis)

Respiratory symptoms I.

- **Rhinitis:** asthma should be ruled out always!
- **Caugh, IgE tests if:**
  - Persistent (weeks or more),
  - Recurrent (>2 /year)
  - Dry / nocturnal
  - Induced
  - + if allergy- risk is higher (e.g. familial or individual)
  - If asthma medication can help …

- In other cases it is primary to rule out other possible causes

Table 6 Potentially serious disorders that are associated with chronic coughing in children

- Cystic fibrosis
- Immunodeficiency
- Primary ciliary disorders
- Persistent bacterial bronchitis
- Bronchiectasis
- Recurrent aspiration, gastro-oesophageal reflux, laryngeal cleft, H-type tracheoesophageal fistula, swallowing incoordination with or without neurodevelopmental or neuromuscular disorder
- Retained inhaled foreign body
- Tuberculosis
- Anatomical abnormality, tracheomalacia, bronchomalacia, congenital lung malformation
- Interstitial lung disease or obliterative bronchiolitis
- Cardiac disease

Chronic/recurrent wheeze

All children with

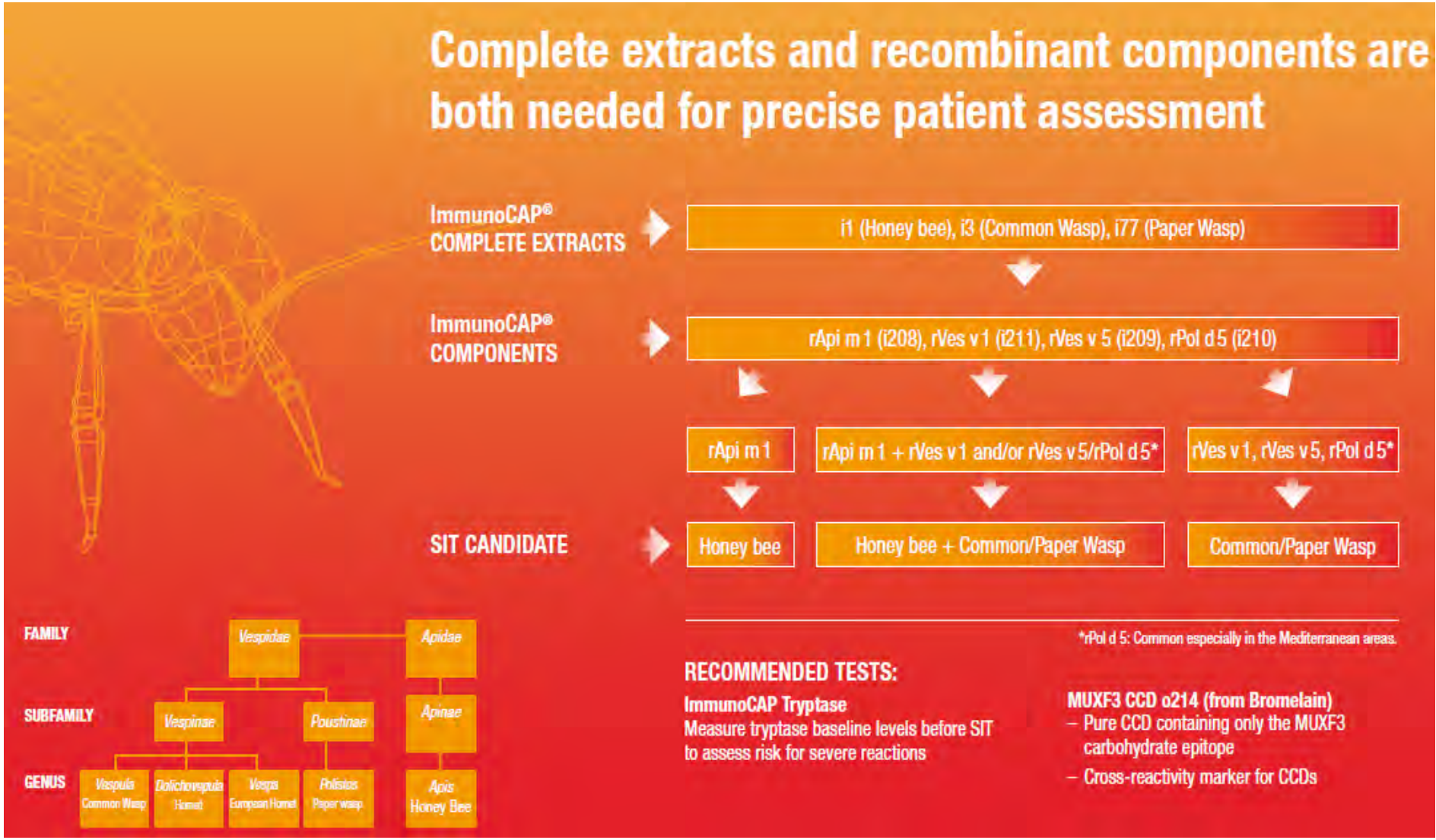
- Chronic or recurrent (>3 times) wheeze, not triggered by upper airway infections,
- or possible asthma diagnosis

should be tested for IgE sensitizations [A].

Need for test is increasing by :

Increasing age, positive family history, the presence of additional allergic symptoms.

Bee/wasps- Venom diagnostics



Suggested profiles for SIT decision

Phleum pratense

ImmunoCAP® Allergen Components

Phl p 1, Phl p 5b | Phl p 2, Phl p 4, Phl p 6, Phl p 11 | Phl p 7, Phl p 12

- Specific components for grass
- **Indication for grass pollen SIT**

- Specific components for grass
- Data on SIT outcome are not available in literature

- Cross-reactive allergen components
- Often minor allergens which may not be available in sufficient amount in the SIT extract
- **IgE to Phl p 7 and 12 alone indicate low suitability for grass pollen SIT. Keep on looking for the real cause.**

Timothy components are suitable markers for many grass due to high degree of similarity between species

POACEAE (Gramineae)

- **ARUNDINOIDEAE**: *Phragmites* (Common reed)
- **CHLORIDOIDEAE**: *Cynodon* (Bermuda grass)
- **PANICOIDEAE**: *Paspalum* (Bahia grass); *Zea* (Maize), *Sorghum* (Johnson grass)
- **POOIDEAE**: *Elymus* (Wild rye grass), *Triticum* (Cultivated wheat), *Hordeum* (Barley); *Holcus* (Velvet grass), *Arrhenatherum* (False oat-grass), *Anthoxanthum* (Sweet vernal grass), *Avena* (Cultivated oat), *Phalaris* (Canary grass); *Phleum* (Timothy), *Alopecurus* (Meadow foxtail), *Agrostis* (Redtop); *Distichlis* (Salt grass), *Lolium* (Rye grass), *Dactylis* (Cocksfoot), *Poa* (Meadow grass), *Festuca* (Meadow fescue); *Secale* (Cultivated rye); *Bromus* (Brome grass)

Grasses and their botanical relations, adapted from L Yman (24)