Agenda:

Emne Fødevareallergi – både prevalens, diagnose og behandlings muligheder samt aktuelt forskning. Vi har en del voksen fødevareallergi, og der er sket meget på børne området i de sidste år…

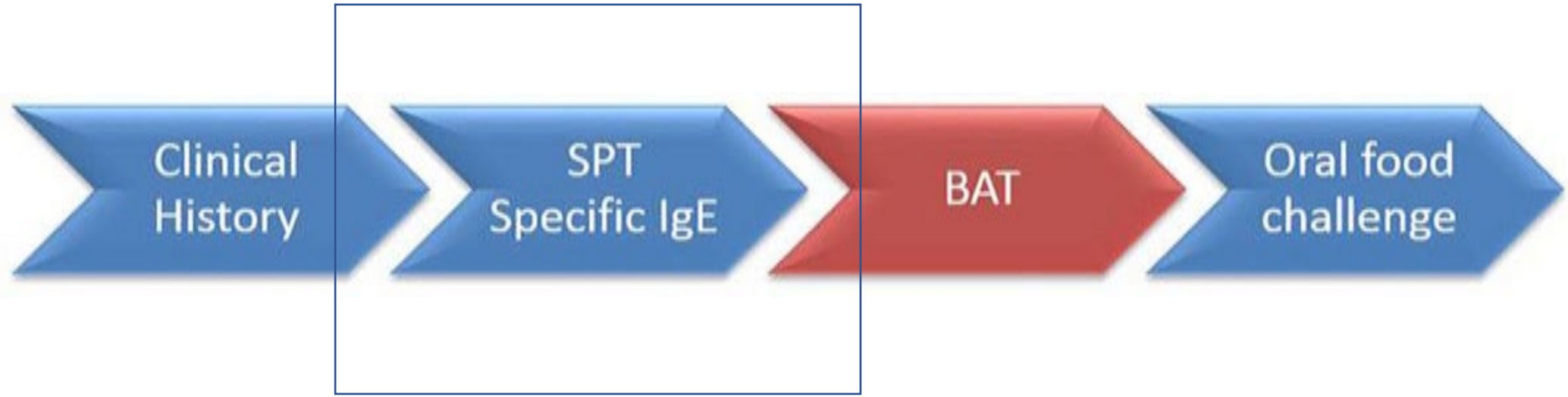
Adult food allergy, Allergy Center AUH and the food industry

- What is food allergy
  - How frequent is food allergy
  - Occupational food allergy
- How is food allergy diagnosed
  - Basophil testing in the diagnosis of food allergy
  - Provocation testing
- Treatment of food allergy, and monitoring of treatment

Research

- BAT – basophil activation test
  - Diagnosis and monitoring of allergic disease and treatment
- activation of Mast cells equipped with recombiant IgE with known specificity and affinity with recombiant allergen to explore how IgE activates mast cells

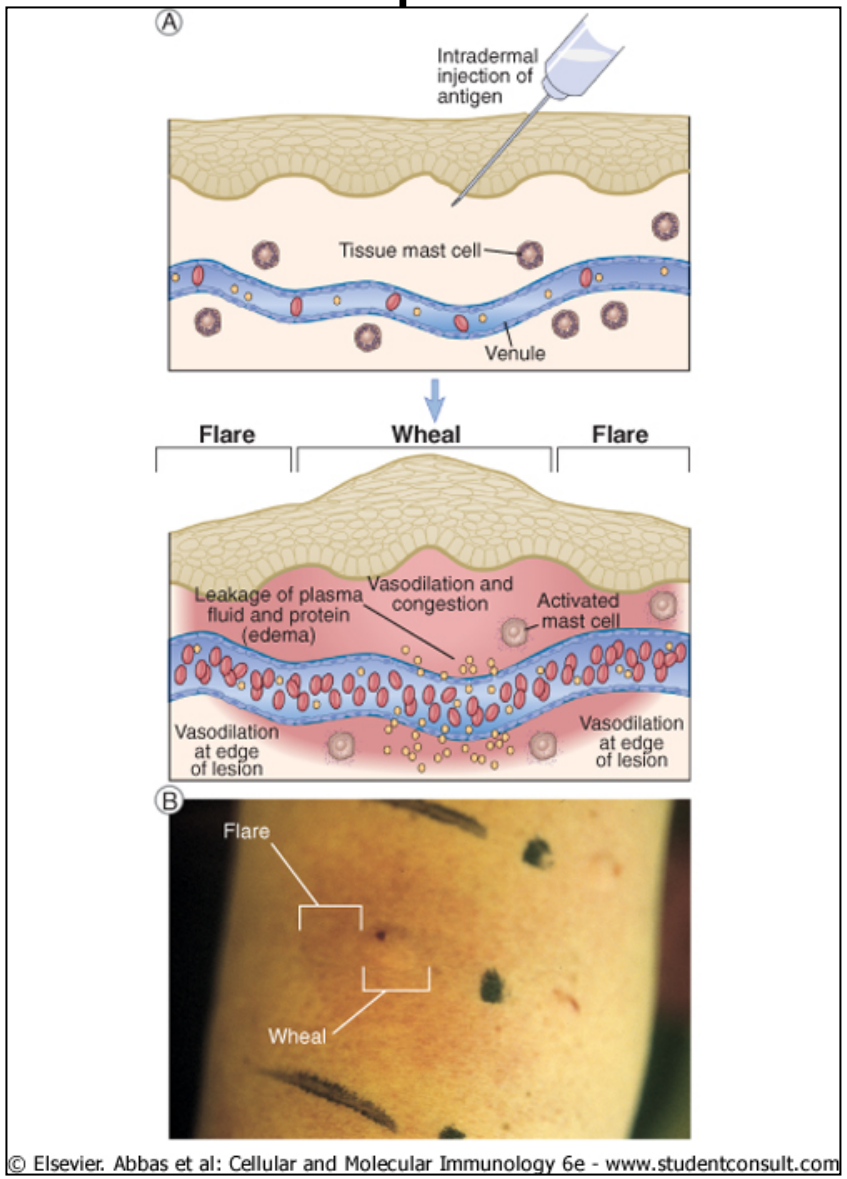
- Intralymphatic Immunotherapy
  - 3 injections of allergen into an inguinal lymph node to achieve at least 3 years of clinically effective treatment
  - We have performed 3 small trials, and are planning a large trial now.
  - We may participate in a trial to explore the usefulness of ILIT in food allergy.



Hoffmann et al, Allergy, 2015

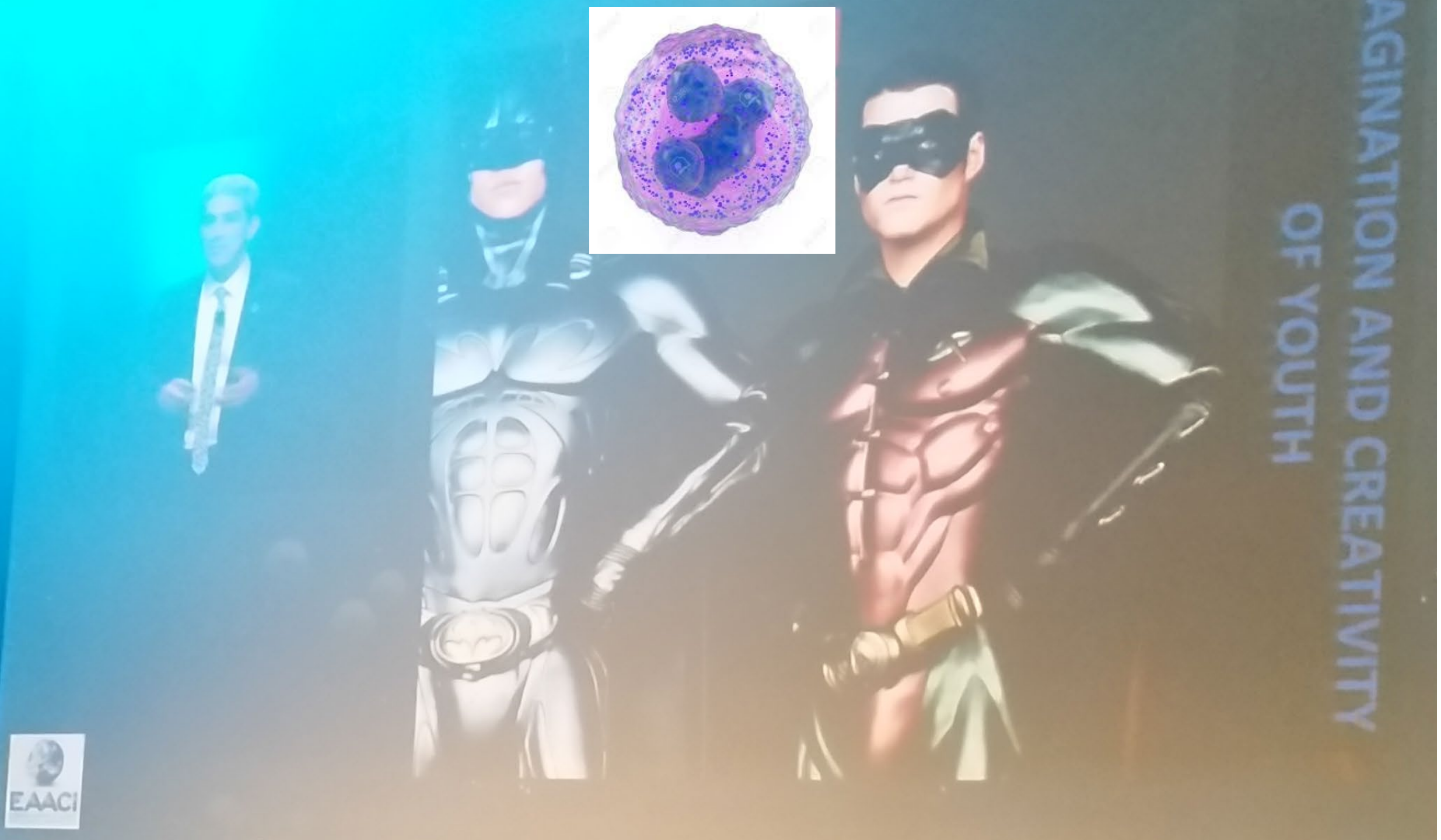
Santos & Lack, 2016, CTA

Den umiddelbare respons – i en hudpriktest



Detection methods for measuring IgE

Kleine-Tebbe et al : J Lab Med 2016; 40(2): 81


AGINATION AND CREATIVITY
OF YOUTH
EAACI

1. Stimulation

Whole blood + Stimulants
- Allergen
- Negative control
- Positive controls

2. Staining

- Stop degranulation
  (EDTA + variation in temperature to 4°C)
- Staining
  (with antibodies conjugated to fluorochromes)

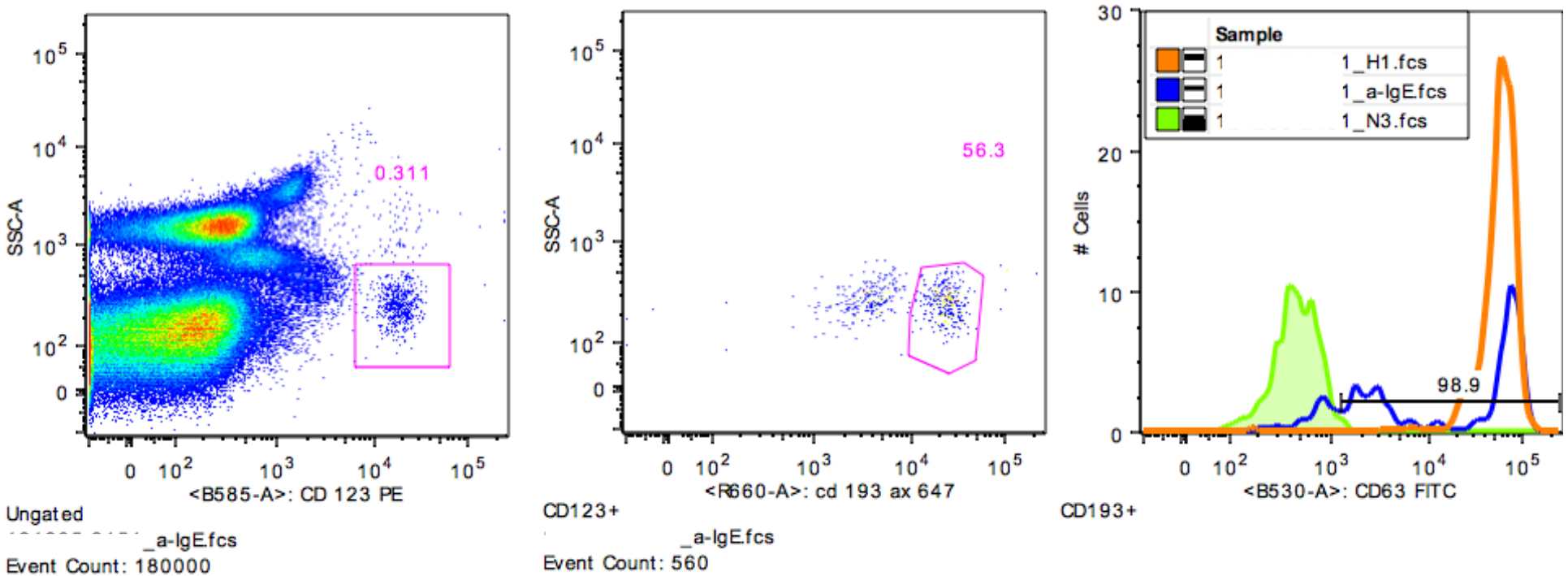
3. Red blood cell lysis

- Red blood cell lysis
- Cell suspension ready for analysis

4. Flow cytometry

Santos and Lack *Clin Transl Allergy (2016) 6:10*

Identifying and classifying activated basophils



Reproducibility of food provocation test and basophil activation test 2 weeks apart

- Double-blind placebo-controlled food challenge, DBPCFC, the gold standard for diagnosing food allergy, is time-consuming and potentially dangerous.
  - 27 children tested (verum 2, placebo 1)
  - 13 negative in DBPCFC
  - 14 positive in both challenges
  - 2 reacted reproducibly

- BAT basophil allergen threshold sensitivity test, CD-sens, has shown promising results as a diagnostic tool in food allergy.
  - 12 of 14 children positive in DBPCFC were positive in BAT
  - 2 non-responders

Glaumann S et al (2012), PLOS1, 8, e53465

Reproducibility of food provocation test and basophil activation test 2 weeks apart

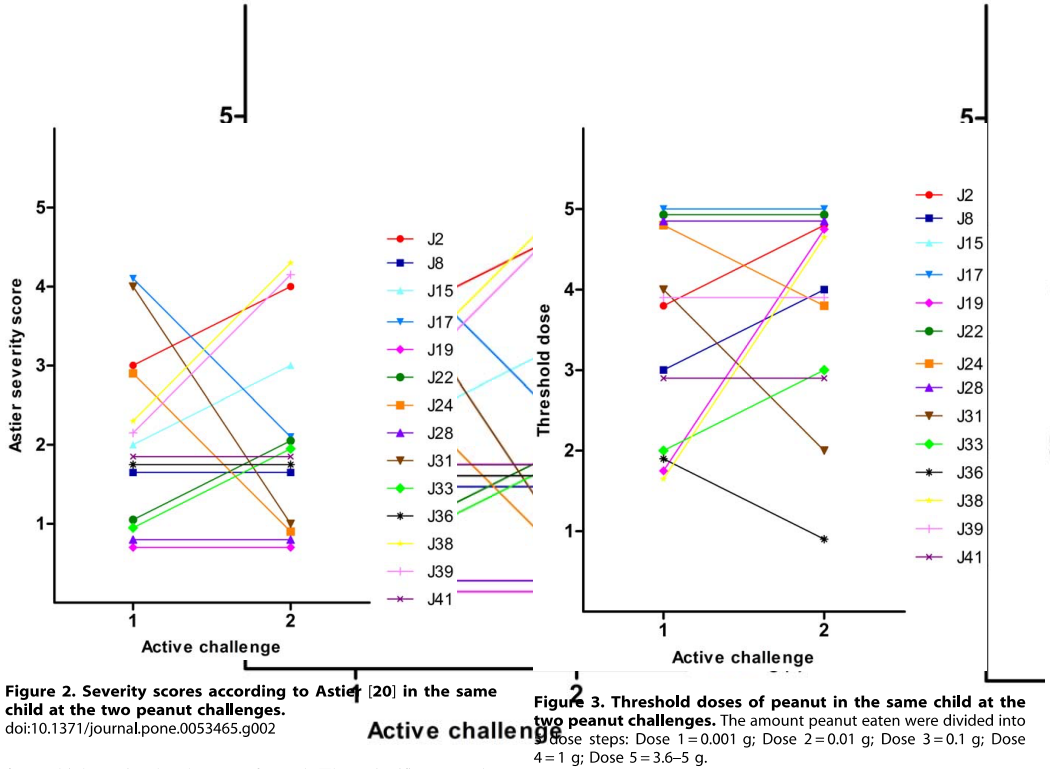


Figure 2. Severity scores according to Astier [20] in the same child at the two peanut challenges.
doi:10.1371/journal.pone.0053465.g002

Figure 3. Threshold doses of peanut in the same child at the two peanut challenges. The amount peanut eaten were divided into 5 dose steps: Dose 1 = 0.001 g; Dose 2 = 0.01 g; Dose 3 = 0.1 g; Dose 4 = 1 g; Dose 5 = 3.6–5 g.

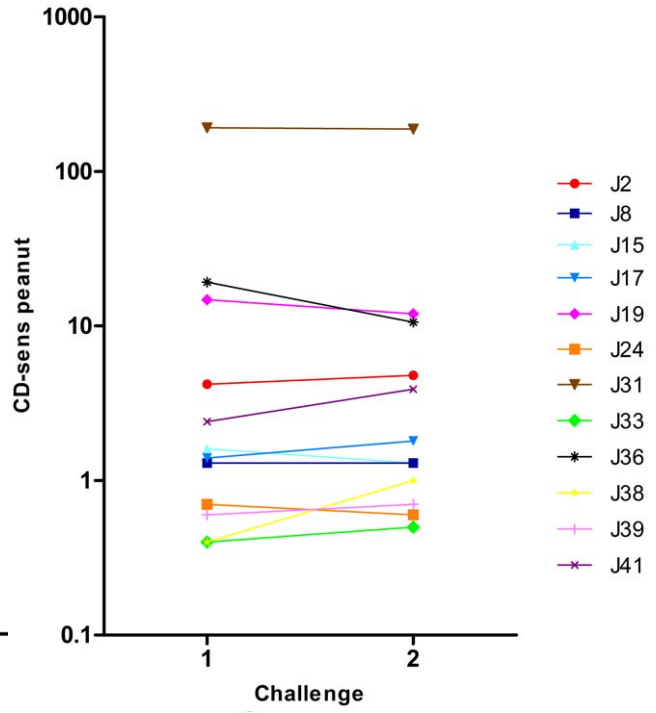


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Figure 6. Peanut CD-sens values in the same child at the two peanut challenges.

Glaumann S et al (2012), PLOS1, 8, e53465

Reproducibility of food provocation test and basophil activation test 2 weeks apart

(rs = 0.11, p = 0.71)

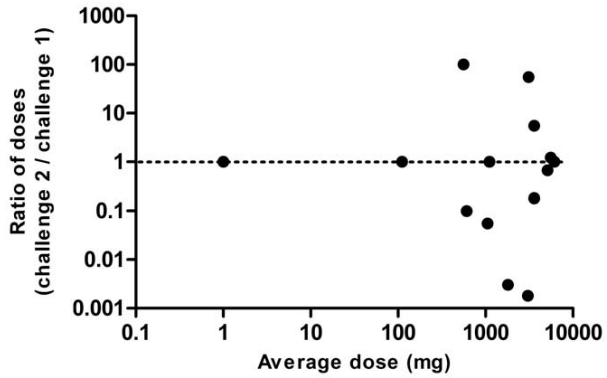


Figure 5. The differences in the ratio of the dose, mg (challenge 2/challenge 1) in each child with positive peanut challenges, presented as a Bland-Altman plot with logarithmically transformed data. The geometric mean of the ratio of the doses was 1.834.
doi:10.1371/journal.pone.0053465.g005

r^2=0.35, p=0.22

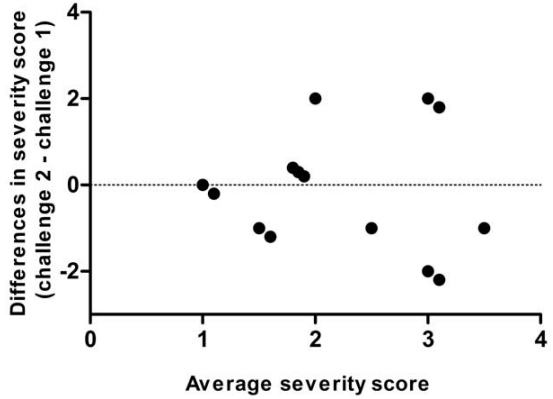


Figure 4. The differences in severity score (challenge 2–challenge 1) in each child with positive peanut challenges, presented as a Bland-Altman plot. The arithmetic mean of the difference between the severity scores was 0.143.
doi:10.1371/journal.pone.0053465.g004

r^2=0.94, p<0.001

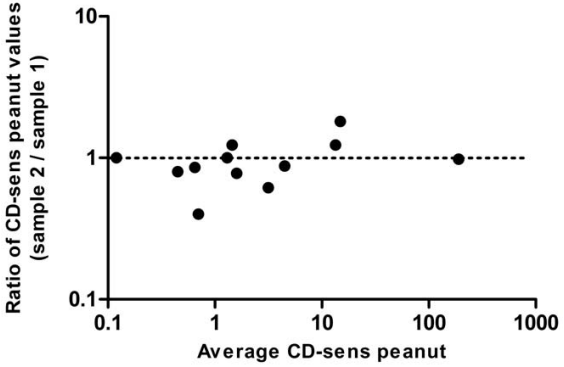
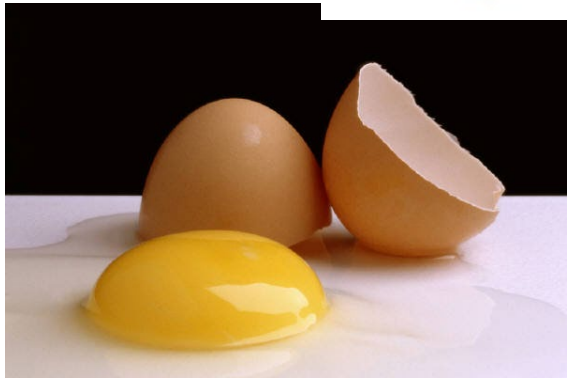
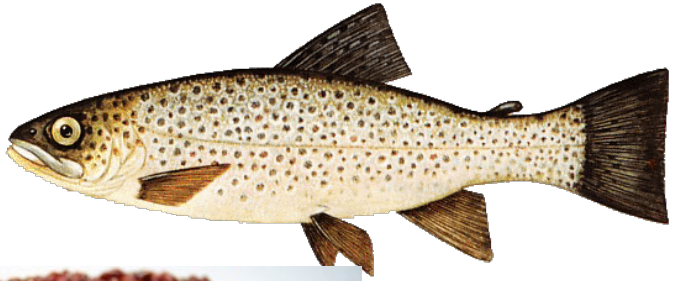


Figure 8. The differences in the ratio for peanut CD-sens values (challenge 2/challenge 1) in each child with positive peanut challenges, presented as a Bland-Altman plot with logarithmically transformed data. Geometric mean of the ratio of CD-sens values was 1.035.
doi:10.1371/journal.pone.0053465.g008

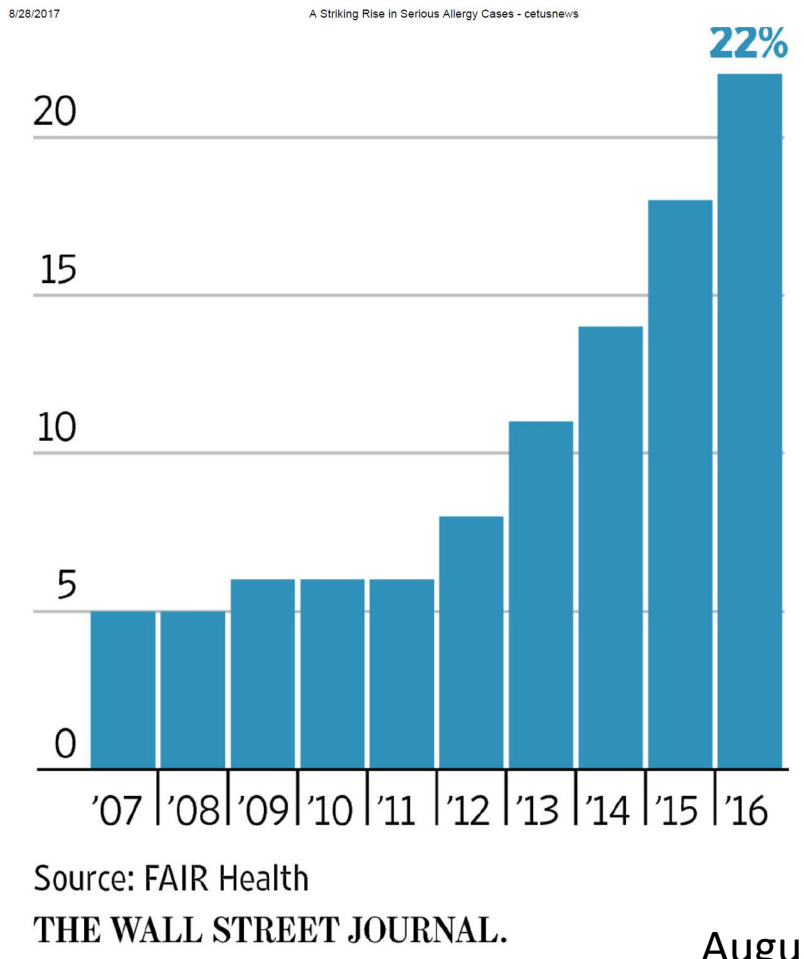
Glaumann S et al (2012), PLOS1, 8, e53465

1 000 000 kg in a life-time





Increase in food allergy?



August 2017

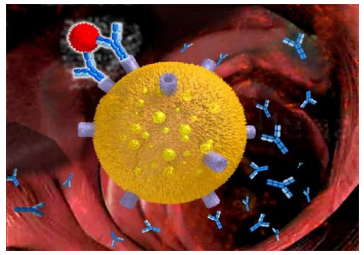
The analysis was conducted by FAIR Health, a New York City-based, independent nonprofit that has a database of 24 billion medical and dental claims from 150 million privately insured people.

- The rate of severe allergic reactions to foods has increased by 377 % the last decade
- Peanut was the most common reason to anaphylaxis, 26 % of the claims
- Tree nuts 18 % followed by egg, shellfish and milk
- 33 % About 33% of claims were due to unknown foods
- 66 % were below 18 years

Food allergy

- Immunological reaction on food proteins
- Incidence: children 8 %, adults 5 %
- No standard curative treatment is aviable and therefore important with a correct diagnosis
- Symptoms vary from mouth-itch to life-threatening reactions
- IgE-mediated food allergy the most common

Food allergy



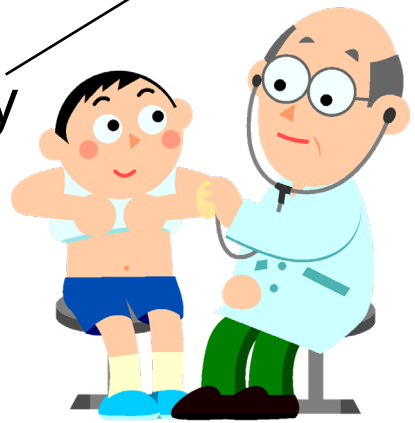
Pathophysiologi

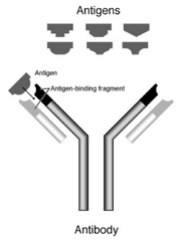
Treatment

Diagnosis

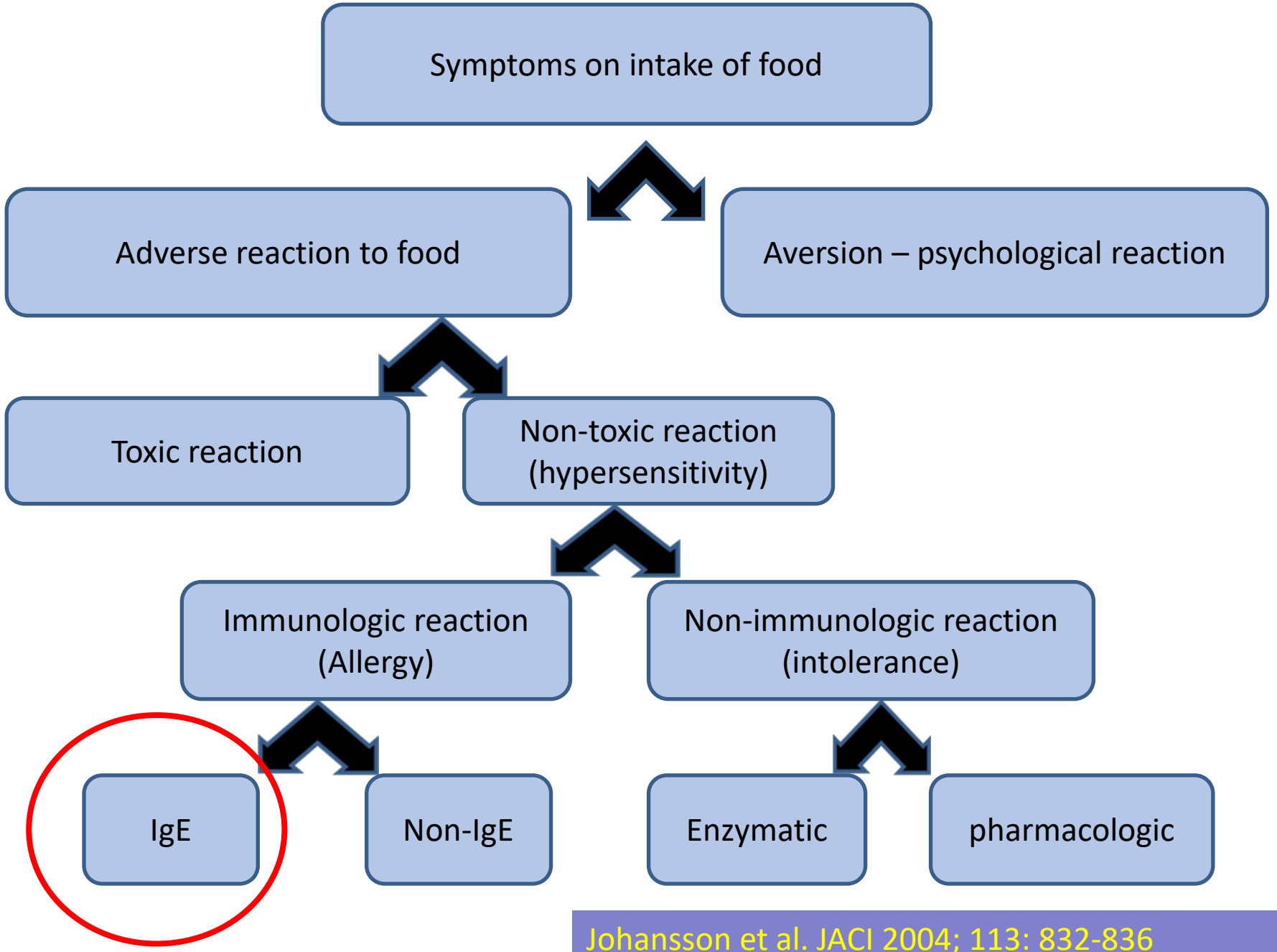
Epidemiologi

Clinical history





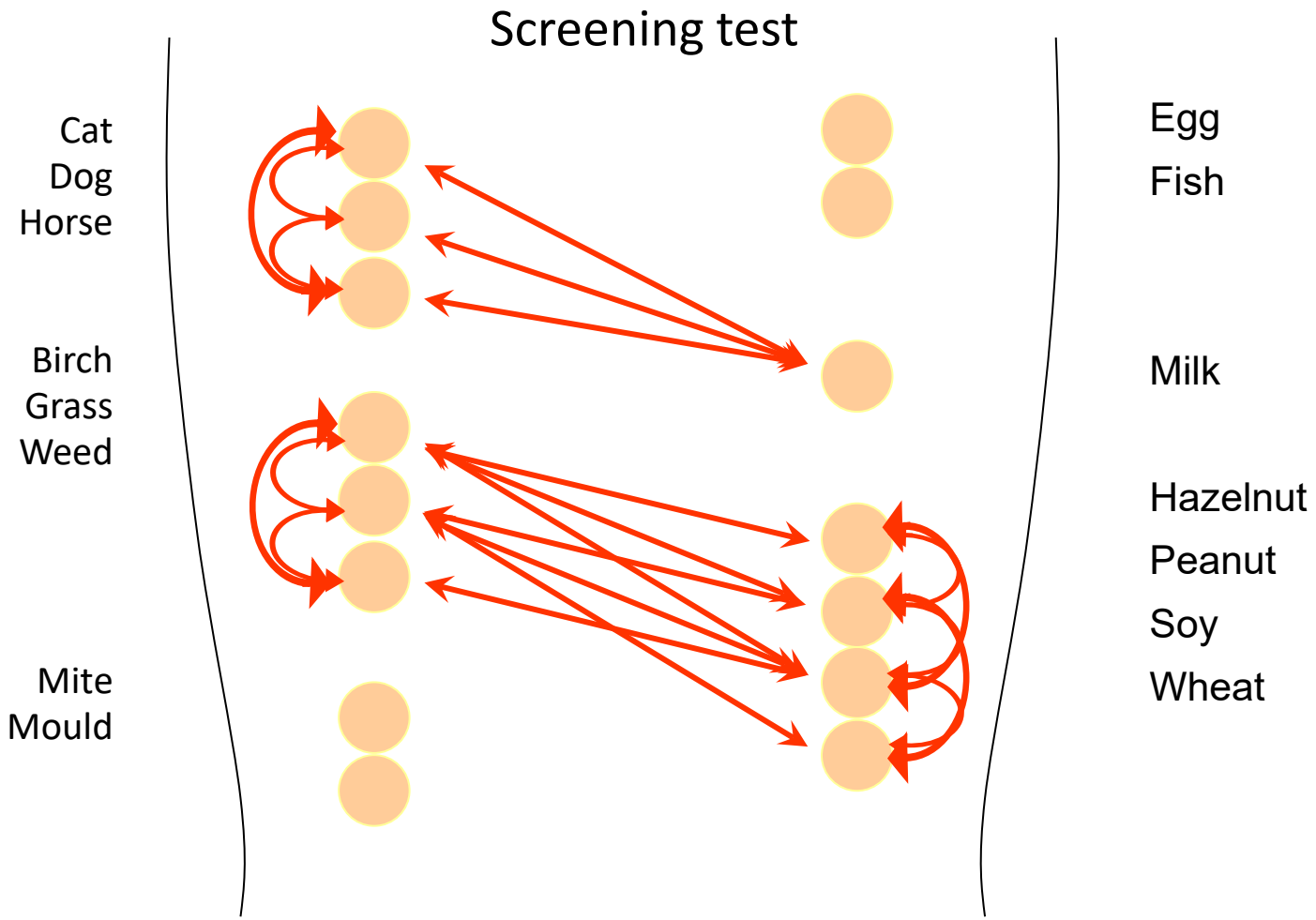
Test results



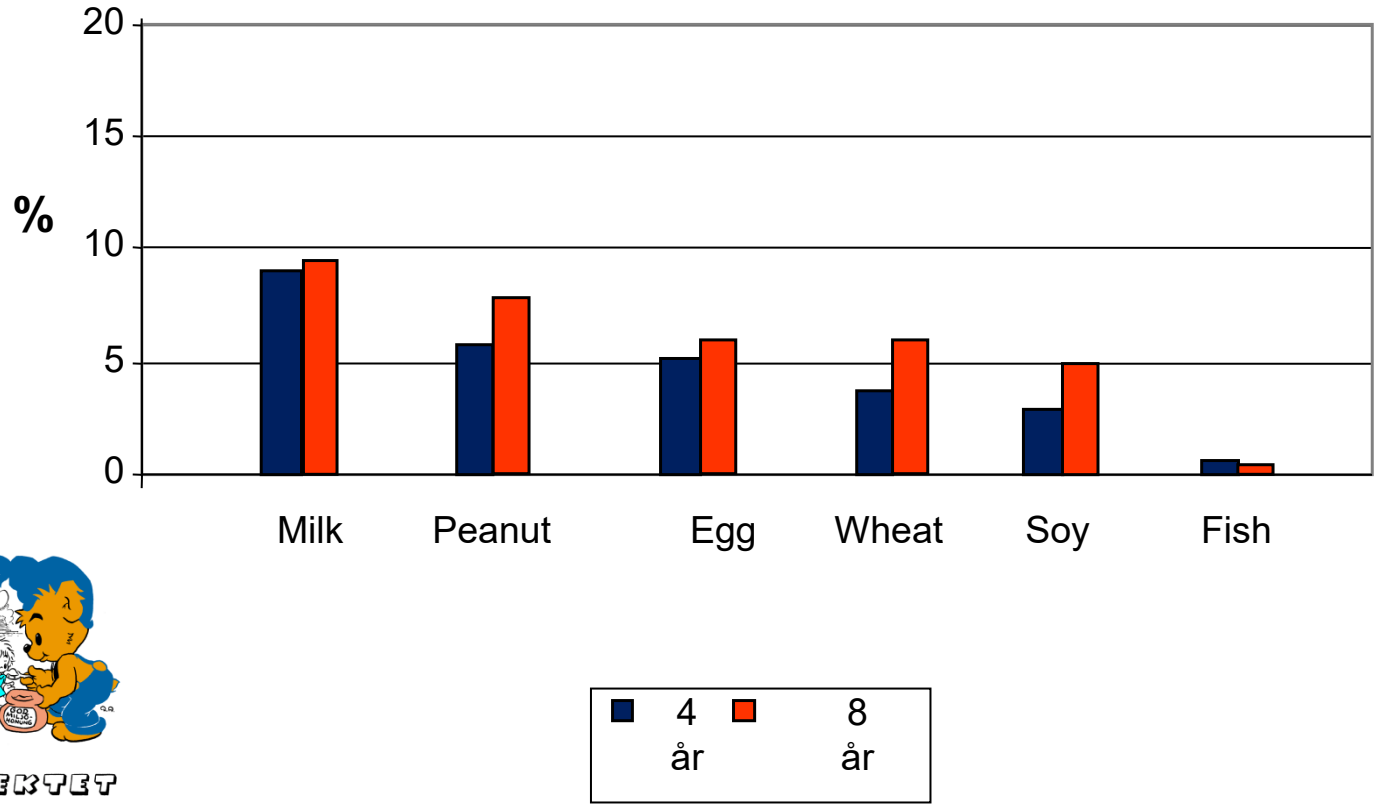
Johansson et al. JACI 2004; 113: 832-836


Milk
Fish
Soybeans
Tree Nuts
TOP 8
FOOD
ALLERGENS
Peanuts
Eggs
Shellfish
Wheat

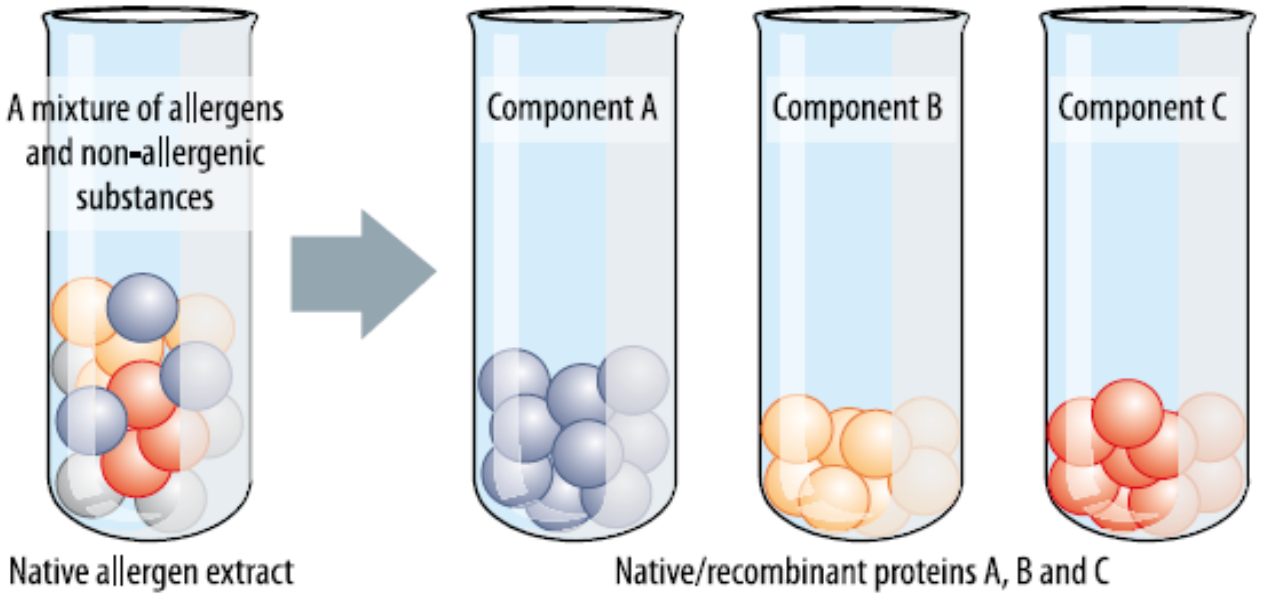
Crossreactions common between food and inhalant allergens



IgE sensitisation to food at 4 & 8 years, 2,600 and 2,400 children



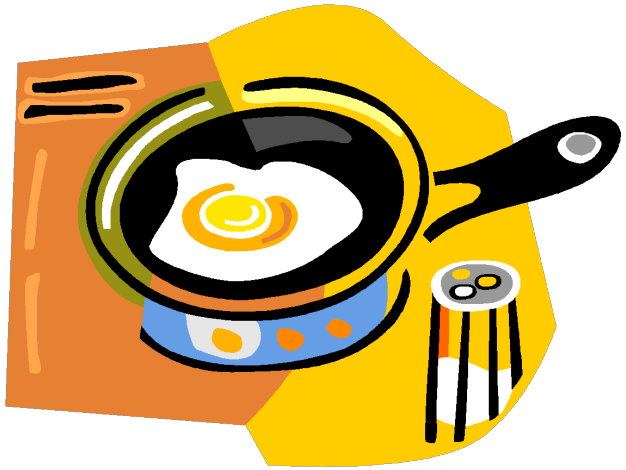
Component resolved diagnostics (CRD) to food



Whole allergen

Allergen components

Egg and milk allergy and components



- Components resolved diagnostics (CRD) in the diagnosis and management of milk and egg allergies is not well established

- Studies do not uniformly find IgE to milk and egg components to outperform standard IgE testing to milk and egg in predicting allergic reactions to egg and milk

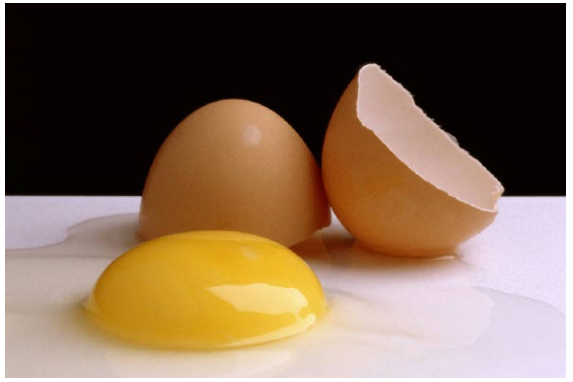
Wang 2016

Cows milk and egg allergy

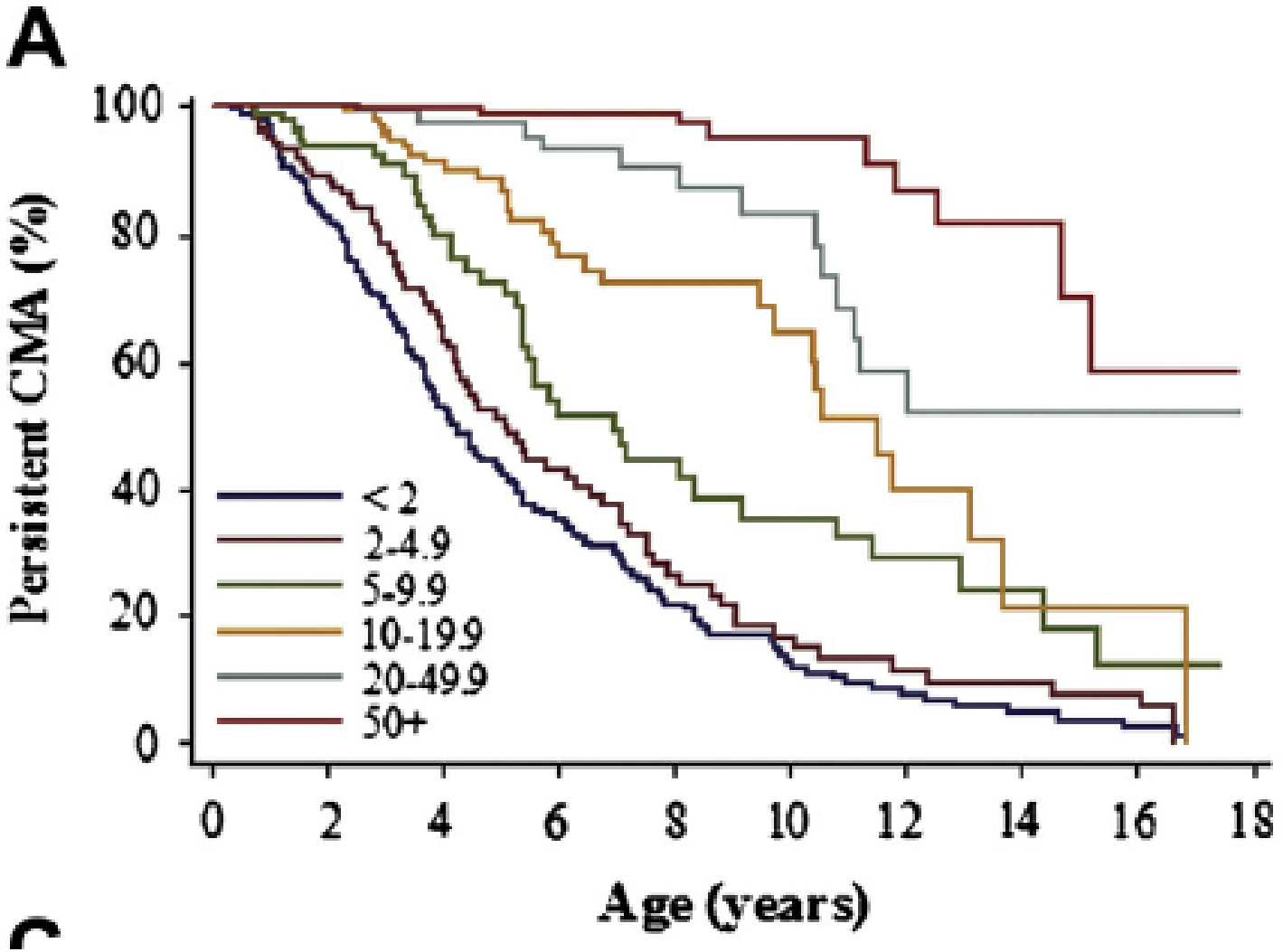
- Milk is the most common allergy among infants, ~ 3-5-8 %

- The next most common food allergy among infants, ~ 2 – 4 %

- The prognosis is good. Most children outgrow their milk and egg allergy



Prognosis of milk allergy and milk IgE



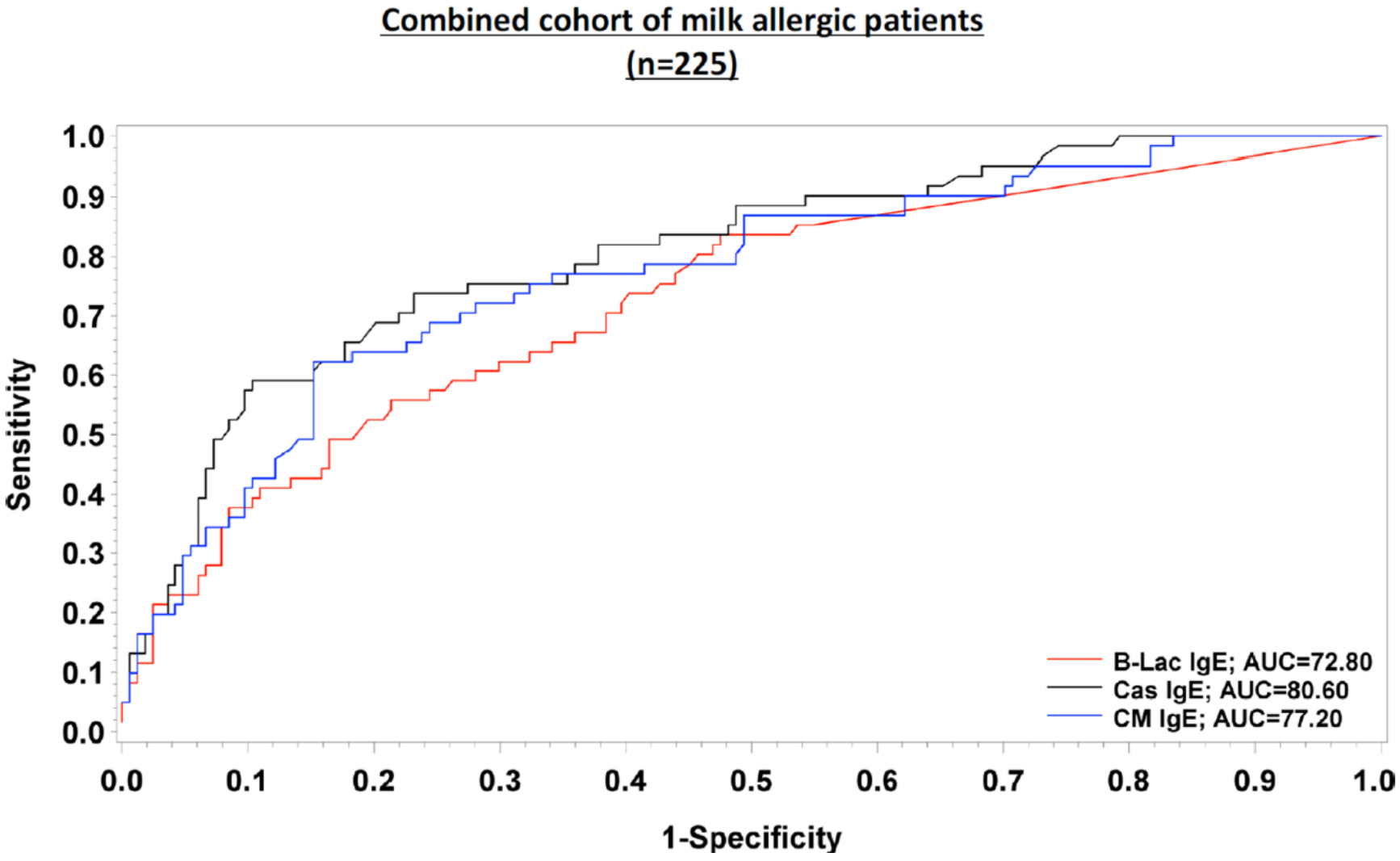
Savage, JACI in Pract, 2016

Milk - Bos domesticus

Allergen components

- Bos d 4 - α lactalbumin
- Bos d 5 - β lactglobulin
- Bos d 6 - serumalbumin
- Bos d 8 – casein, the most common allergen in milk
- Bos d lactoferrin – transferrin

Milk allergy and components

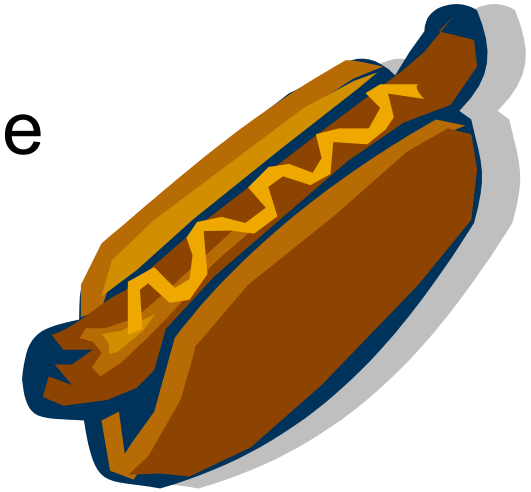


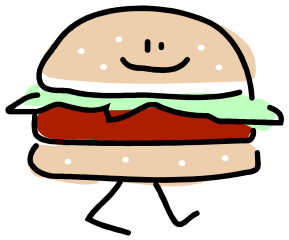
- Oral food challenge with baked milk
- IgE to casein slightly better than IgE to whole milk

Caubet JACI 2013

Red meat allergy

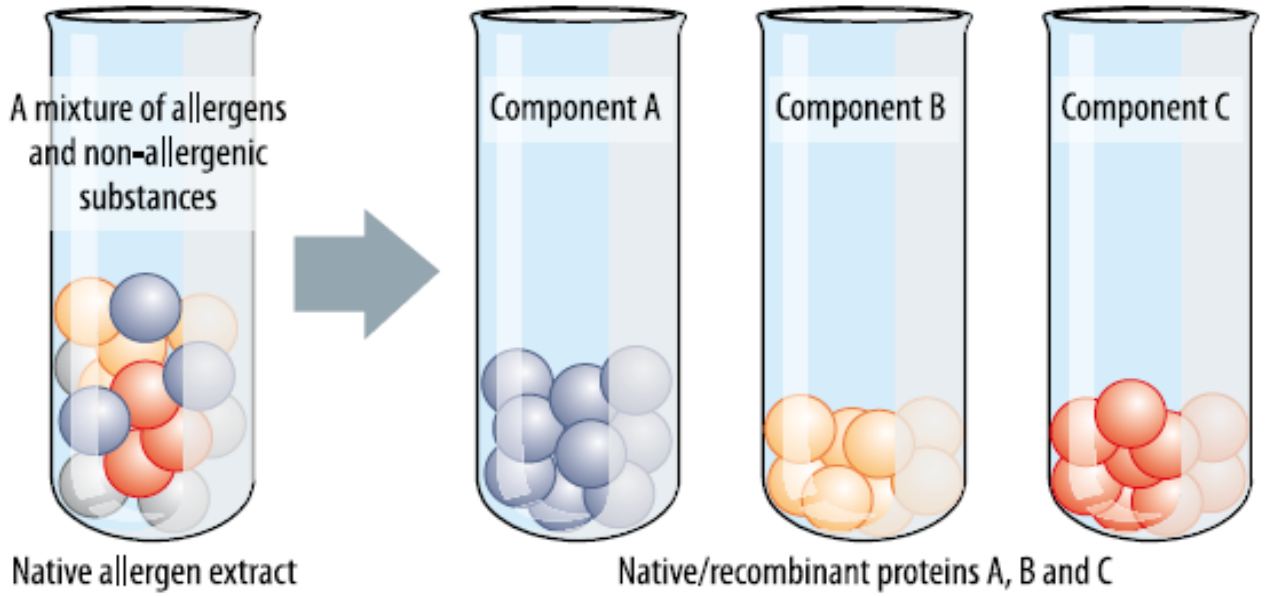
- Adults and adolescents – more common than reported?
- Individuals at risk of being sensitized are those living in areas with high exposure to ticks
- IgE to carbohydrate alpha-galactose,
- Most reactions are delayed for 2–5 hours
- Symptoms are often; urticaria, angioedema or anaphylaxis after 6:00 pm





Villalta D, 2016

Component resolved diagnostics (CRD) to food of plant origin

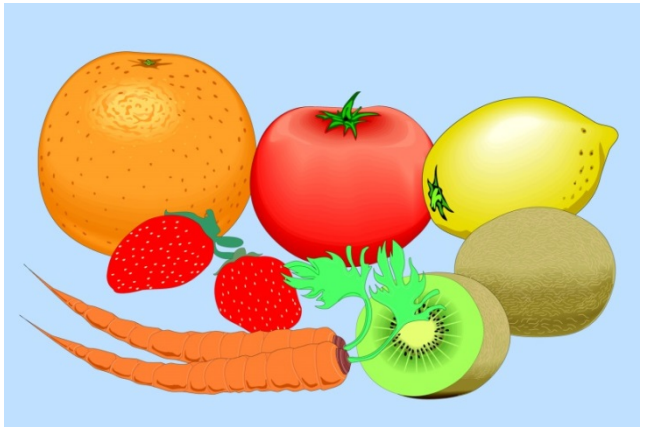


Whole allergen Allergen components

Unstabile proteins

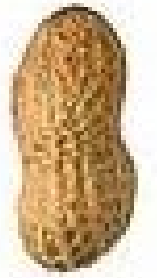
- PR-10 protein (birch)

- Danaturation from heating, hydrochloric acid and enzymes in saliva
- Sensitisation to PR-10 proteins through pollen
- Symptoms – locally in mouth and throat



Oral allergy syndrom

Ara h 8
(Bet v 1
homolog)



Ara h 5
(profilin)

Dau c 1 (Bet v 1 homolog)
Dau c 4 (profilin)

Gly m 4 (Bet v 1 homolog)

Cor a 1 (Bet v 1 homolog)
Cor a 2 (profilin)

Mal d 1 (bet v 1 h
Mal d 4 (profilin)

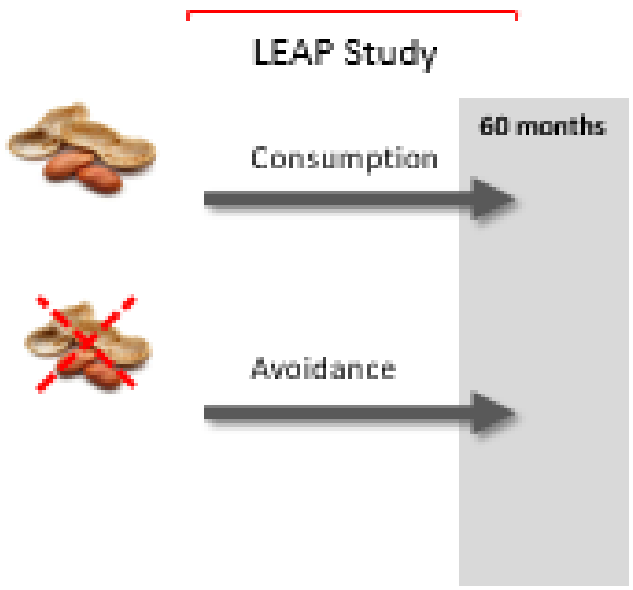
Resistant proteins - Storage proteins

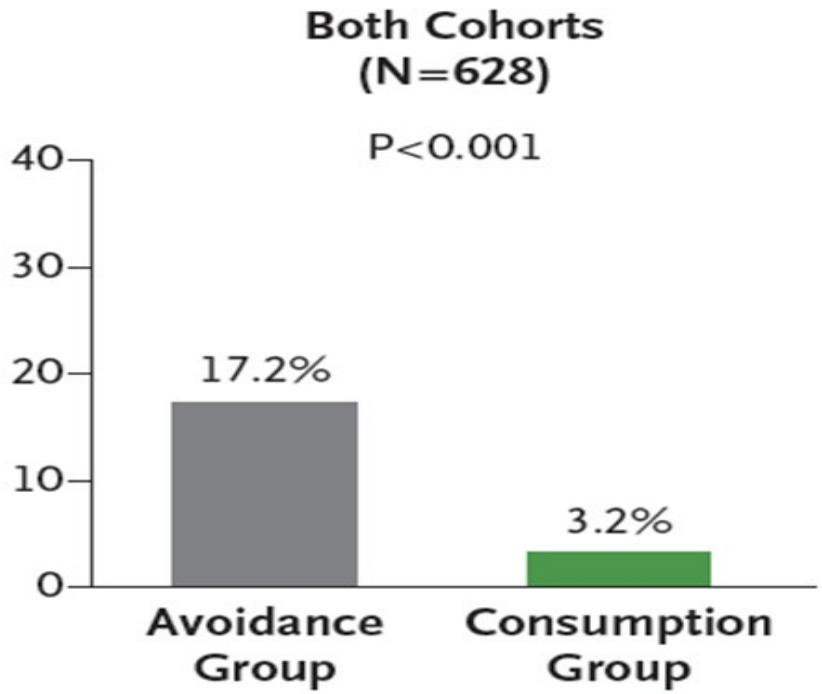
- Proteins mainly in nuts/peanut/seeds, stable to heating, hydrochloric acid and enzymes in saliva
- IgE to storage proteins a risk factor for systemic allergic reactions


Milk
Fish
Soybeans
Tree Nuts
TOP 8
FOOD
ALLERGENS
Peanuts
Eggs
Shellfish
Wheat

LEAP Study

Frequency of developing allergy to peanut





81% Relative Reduction

LEAP-On Summary

Peanut Allergy

- Benefits of early peanut introduction persisted after 12 months of cessation of peanut consumption:

  LEAP avoiders **(18.6%)** > LEAP Consumers **(4.8%)**

- Non-significant increase in PA in **LEAP consumers** after 12 months of avoidance; **3.6% at 60 months** to **4.8% at 72 months** (p=0.250)

Immunology:

- LEAP **consumers** continued to have **higher levels of peanut-specific IgG4** and **peanut-specific IgG4:IgE ratios and a high ratio was associated with tolerance.**
- Both **peanut-specific IgE and IgE to Ara h2 declined** for the first time in LEAP consumers after 60 months of age despite coinciding with 12 months of peanut avoidance

The LEAP and LEAP-On studies together demonstrate that the **early introduction of peanut** induces unresponsiveness to peanut that **persists** following 12 months of avoidance.

This gives rise to further questions:

- Is an intervention that prevents peanut allergy in a **high-risk population** also an effective prevention strategy in the **general population**?
- Is such an intervention effective to prevent allergies to **other foods**?

These questions gave rise to

EAT
Enquiring About Tolerance

The EAT Study Hypothesis

The EAT Study tested the hypothesis that the **introduction of 6 allergenic foods** from **3 months of age**, alongside **continued breastfeeding**, would result in a **reduced prevalence of IgE-mediated food allergy** by 3 years of age.

EAT
Enquiring About Tolerance

EAT Study per-protocol analysis

Per-protocol (PP): All ITT participants who have complied to EAT criteria below.

Both Groups:

- **Exclusive breastfeeding** for **three** months
- **Continued breastfeeding** up to **five** months

Standard Introduction Group compliance is defined as:

- **No consumption** of peanut, egg, sesame, wheat or fish **before five months**
- **Cow's milk (or goat's milk) consumption** of less than 300mls/day **between three and six months**

Early Introduction Group compliance is defined as:

- **Consumption** of **at least 5** of the allergenic foods in **at least 75% of the recommended amount** (i.e. at least 3g allergen protein), on **at least 5 weeks** between three and six months of age

Introduction Schedule

WEEK 1

MON	TUES	WED	THURS	FRI	SAT	SUN
						

WEEK 2

MON	TUES	WED	THURS	FRI	SAT	SUN
						

WEEK 3

MON	TUES	WED	THURS	FRI	SAT	SUN
						

WEEK 4

MON	TUES	WED	THURS	FRI	SAT	SUN
						

WEEK 5 and Onwards

MON	TUES	WED	THURS	FRI	SAT	SUN
						

1st: Cow's milk | Randomized to [Egg, Peanut, Sesame, Fish] | 6th : Wheat

EAT Study Summary

- Early introduction of allergenic foods **was safe.**
- **Adherence:**
  - Standard Introduction Group **(92.9%)** > Early Introduction Group **(42.8%)**
- **Overall Allergy:**
  - **reduction (non-significant) in Allergy** in the **ITT group.**
- **Peanut allergy:**
  - in the Early Introduction **Per-protocol group** was **0% vs. 2.5%** in the Standard Introduction Group, **p<0.003**.
- **Egg allergy:**
  - in the Early Introduction **Per-protocol Group** was **1.4% vs. 5.5%** in the Standard Introduction Group, **p<0.009**.

No statistically significant effect for sesame, fish, milk or wheat

EAT
Enquiring About Tolerance

Conclusion

- Food allergy is an overlooked entitiy for adult more than pediatric populations
- Food allergy may be prevented by early introduction of allergenic foods

- Allergicenter Vest (ACV) offers allergy diagnosis, advice and treatment
- We take careful history, do diagnostic tests and can treat some food allergies
- We do research to improve diagnostic tests and therapy of food allergy

Hans Jürgen Hoffmann hjh@clin.au.dk