

# Food Allergy Update: To Feed or Not to Feed?

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# Objectives:

- ▶ Prevalence of food allergy, clinical manifestation, diagnosis ,component testing, oral challenges.
- ▶ Discuss LEAP study: impact on peanut allergy prevention.
- ▶ Introduce 2017 NIAID Peanut allergy infant screening guidelines.
- ▶ Discuss future therapies.

# Prevalence of Food Allergy

- ▶ Perception by public: 20-25%
- ▶ Confirmed allergy: Adults: 2-3.5% and infants/young children: 6%
- ▶ Specific Allergens: Geographical and cultural variations
- ▶ Prevalence higher in those with: atopic dermatitis, pollen allergies
- ▶ Prevalence increasing – 18% increase between 1997-2007

# Estimated Prevalence of Food Allergy

Food	Children (%)	Adults (%)
Cow's milk	2.5	0.3
Egg	1.5	0.2
Wheat, Soy	0.4	0.3
Peanut	2.0	0.6
(Israel: 0.17%)		
Sesame	0.1	0.1
Tree nut	0.5	0.6
Crustacean	0.1	2.0
Fish	0.1	0.4
<b>Overall</b>	<b>6</b>	<b>2-3.5</b>

# Immunologic (Allergic) Food Reactions

## IgE-Mediated

- ▶ Systemic (Anaphylaxis)
- ▶ Oral Allergy Syndrome
- ▶ Immediate gastrointestinal allergy
- ▶ Asthma/rhinitis
- ▶ Urticaria

## Mixed IgE/Non IgE

- Eosinophilic esophagitis (EoE)
- Eosinophilic gastroenteritis
- Atopic dermatitis

## Non-IgE Mediated Cell-Mediated

- Allergic Proctocolitis
- Food Protein-Induced Enterocolitis (FPIES)
- Dermatitis herpetiformis
- Celiac disease

Sampson HA. J Allergy Clin Immunol 2004;113:805-9.

Chapman J, et al. Ann Allergy Asthma Immunol 2006;96:S51-68.

# Natural History

80% of milk, soy, egg, wheat allergy remit by teenage years .

Two studies suggest baked egg tolerance hastens overall resolution of the allergy, and this practice has become quite popular, however:

- Systematic review undertaken to evaluate pooled evidence that introducing baked milk or baked egg in the diet truly helps accelerate outgrowing these allergies.

Studies mostly used “similar” but retrospective comparator groups

- ▶ • Only one study used statistical adjustment to control for confounders
- ▶ • All but one study had significant flaws
- ▶ • No evidence to support that addition of baked milk/egg hastens resolution of these allergies.

# Milk Allergy

- ▶ Most common food allergy in children: Prevalence 2-3% of infants
- ▶ Usually develops in the first 6-12 months
- ▶ Symptoms: eczema, hives, wheezing, anaphylaxis, colic, GE reflux (10%)
- ▶ 80% outgrown by teenage years

# Egg Allergy

- ▶ Second most common in children: Prevalence 1.3%
- ▶ Usually develops in the first 6-24 months
- ▶ Present in yellow fever vaccines
- ▶ 80% risk of allergic rhinitis and asthma at age 4 years for infants with egg allergy and eczema<sup>1</sup>
- ▶ Tolerance to baked goods precedes egg tolerance
- ▶ 50%-70% outgrow by teenage years<sup>4</sup>

1 Tariq SM, et al. *Pediatr Allergy Immunol* 2000;11:162-7.

2 Lemon-Mule H, et al. *J Allergy Clin Immunol* 2008;122:977-83.

3 Ando H, et al, *J Allergy Clin Immunol* 2008;122:583-8

4 Savage JH, et al. *J Allergy Clin Immunol* 2007;120:1413-7



# Wheat Allergy

- ▶ Prevalence in children 0.4%<sup>1</sup>
- ▶ Cross-reactivity with other grains (rye, barley, oat, grasses): 20%
- ▶ Associated with exercise-induced anaphylaxis<sup>2</sup>
- ▶ 65% resolution by teenage years

<sup>1</sup>Keet CA, et al. Ann Allergy Asthma Immunol 2009;102:410-15.

<sup>2</sup>Morita E, et al. Allergol Int 2009;58:493-8.

# Tree Nuts, Seeds, Seafood

- ▶ Tree nut allergies usually develop at later ages.
- ▶ Fish: in late childhood and adulthood
- ▶ Shellfish: adulthood in 60%
- ▶ Allergies to tree nuts, seeds, fish and shellfish are typically lifelong.
- ▶ In vitro cross-reactivity between peanut and tree nuts is high (86%).
- ▶ Favorable prognostic factors<sup>2</sup>: decreasing serum Ig E levels over time; resolution of atopic dermatitis; reduction of skin prick test. (wheal diameter)

<sup>1</sup>Fleischer DM. Curr Asthma Reports 2007;7:175-181. <sup>2</sup>Boyce, JA et al. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl ):S1-58

# Peanut Allergy

- ▶ Prevalence has more than tripled, from 0.4% in 1997 to 1.4% in 2008
- ▶ Onset of symptoms usually by age 2 yrs; 75% of reactions may occur with first ingestion ( occult exposure ?contact,inhaled)
- ▶ Peanut: food most commonly associated with anaphylaxis, 150 deaths/ year - associated with Ara-h 2
- ▶ ~20% peanut allergy resolution
- ▶ relapse rate ~ 9% if not incorporated in diet

Skolnick H, et al, J Allergy Clin Immunol 2001;107:367-74. Skripak JM, Wood RA. Pediatr Allergy Immunol 2008;19:368-73. Burks AW. Lancet 2008;371:1538-46. Sicherer SH, Sampson HA. J Allergy Clin Immunol 2007;120:491-503. Fleischer DM, et al. J Allergy Clin Immunol 2004;114:1195-201

# Past Food allergy Prevention Guidance

- ▶ AAP 2000: Delay introducing peanut/tree nuts until age 3.
- ▶ AAP 2008: No evidence for delaying solid food past age 6 mos but no active recommendation of early introduction of any specific food.
- ▶ Observational survey of large cohorts of children in UK vs Israel where kids were fed peanut products at an early age prior to age 1.
- ▶ Rate of peanut allergy 10 times higher in UK.

# The LEAP Study

Du Toit *et al*, NEJM 2015;372:803-813



- ▶ Randomized high risk infants to early peanut introduction or avoidance
- ▶ Primary outcome was clinical peanut allergy at 5 yrs old
- ▶ Main results:
  - u Large reduction in development of peanut allergy in infants randomized to early introduction.

# LEAP Study:

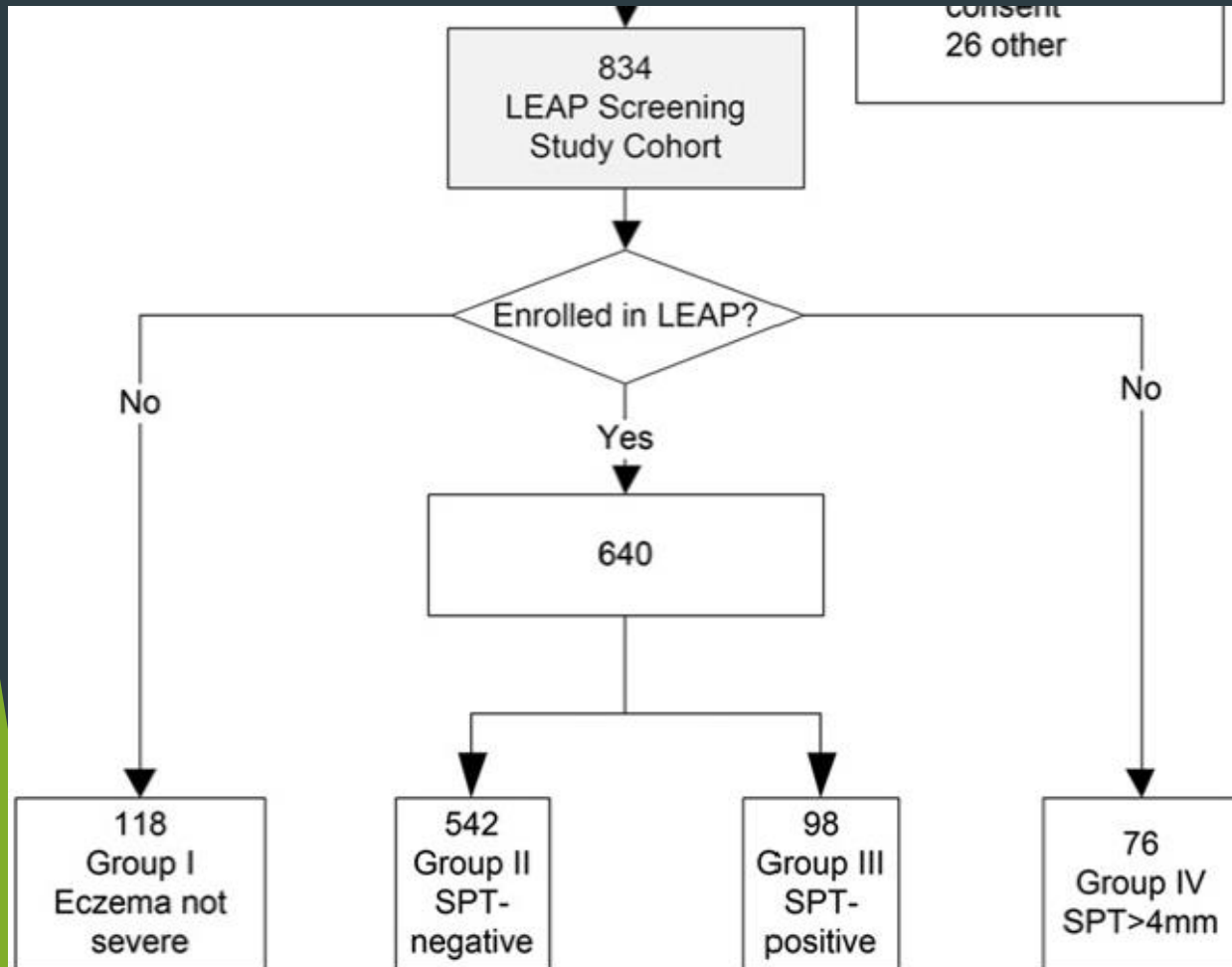
## Enrollment criteria Du Toit et al, JACI 2013

- ▶ Infants ages 4-11 months old, AND:
- ▶ Severe eczema:
  1. 'Frequent need for treatment with topical corticosteroids or calcineurin inhibitors
  2. Parental description of "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash," or
  3. A severe SCORAD grade (>40) by a clinician before or at the time of screening.'

OR

- ▶ Egg allergy:
  1. An SPT-induced wheal diameter of 6mm or greater with raw hen's egg white and no history of previous egg tolerance or
  2. An SPT-induced wheal diameter of 3 mm or greater with pasteurized hen's egg white with a history of an allergic reaction to egg.

# LEAP Enrollment and Randomization

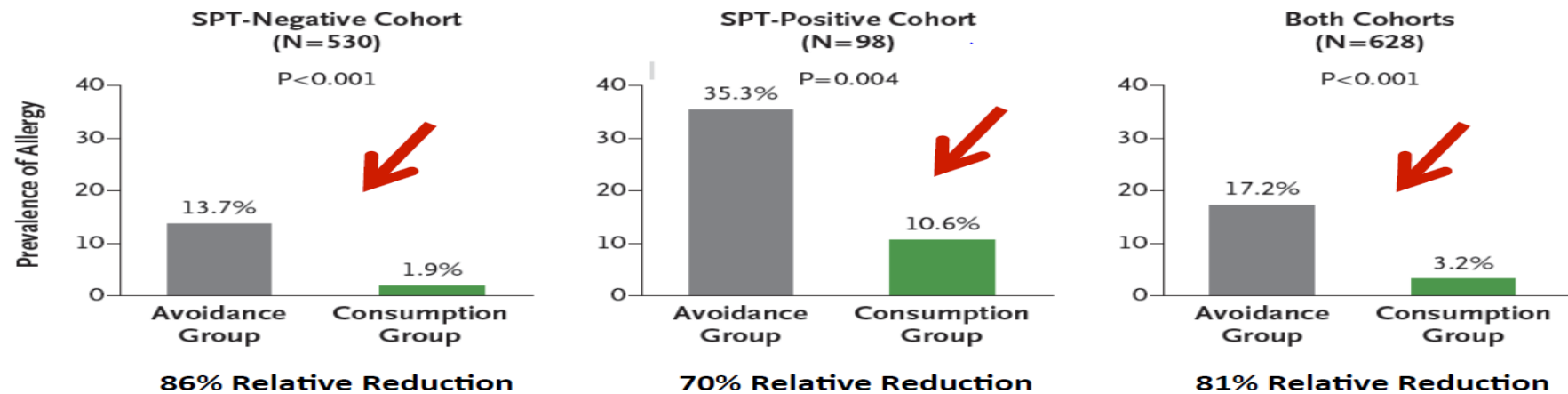


## ★ 834 screened

- 118 excluded because eczema was not severe (all were NEGATIVE on peanut skin test)
- 76 excluded because peanut SPT was >4 mm
  - ★ Considered likely to have clinical peanut allergy
  - ★ Also had median higher SCORAD than other groups

## LEAP Outcome : Intention to treat analysis

### LEAP Outcome: Intention-to-Treat Analysis





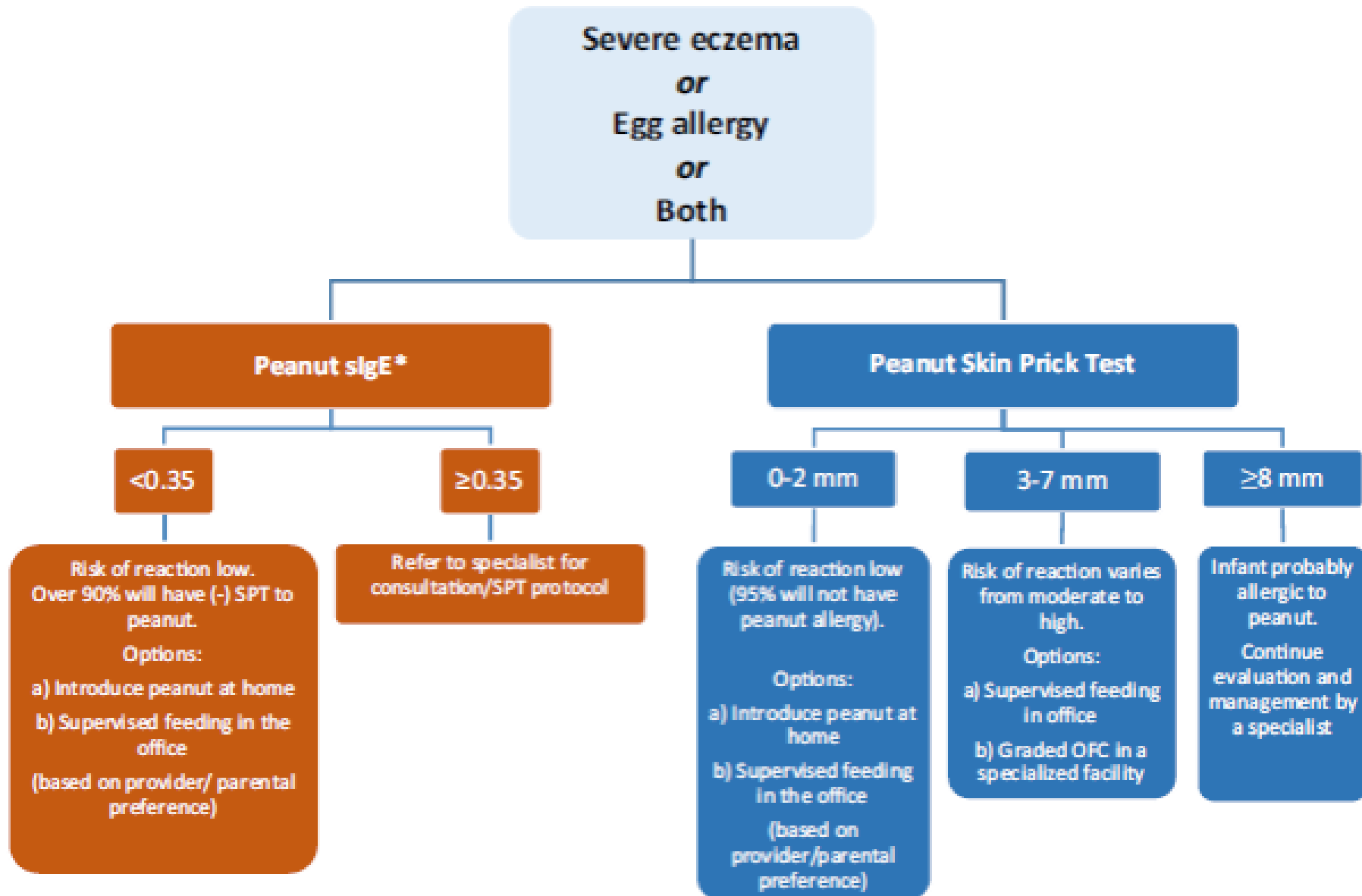
# 2017 NIAID Guideline Update

TABLE I. Summary of addendum guidelines 1, 2, and 3

Addendum guideline	Infant criteria	Recommendations	Earliest age of peanut introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.	4-6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

**Severe eczema:** is defined as persistent or frequently recurring *eczema with typical morphology and distribution assessed as severe by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients.*

# Peanut Specific IgE Testing and Peanut Skin Test



Togias et al., J Allergy Clin Immunol 2017 Jan

# Oral Food Challenge

- ▶ Oral food challenge is a diagnostic test to confirm definitively whether peanut allergy is present for infants with borderline test results where PPV is ~20-60%
- ▶ Oral immunotherapy (OIT) is a therapeutic desensitization to attempt to induce a desensitized state or tolerance
  - ▶ Not the standard of practice currently.
  - ▶ Only available through research centers with IRB approval

# Molecular Diagnosis of Food Allergy

Peanut contains:

- Major allergens and cross allergens
- Storage seed proteins: Ara h 1, 2, 3 ,6 in peanut, associated with systemic reactions, recommend strict avoidance, defer challenge.
- Birch cross-reactive allergens: Ara h 8 in peanut

# Supervised Oral Food Challenge

- ▶ Bird et al J Allergy Clin Immunol Pract 2017;5: 301-11.
- ▶ <http://dx.doi.org/10.1016/j.jaip.2016.07.019>

Peanut butter (teaspoon)*	Equivalent weight (g), (Peanut protein content [g]) <sup>†</sup>
1/8	0.67 (0.15)
1/4	1.33 (0.29)
1/2	2.67 (0.59)
1	5.33 (1.17)
1 ½	8 (1.76)

Dose	Bamba dose (sticks)	Equivalent weight (g), (Peanut protein content [g]) <sup>†</sup>
1	1	0.81 (0.1)
2	3	2.43 (0.3)
3	5	4.05 (0.5)
4	10	8.1 (1.0)
5	21	17.01 (2.0)
		<b>Total protein: 3.9 g</b>

# How to feed peanut

How much: 2 gm (protein) servings

= 2/3 bag of Bamba

= 2 teaspoons peanut butter

= 2 teaspoons peanut flour

How often: 2-3 times per week starting right after the test

How long: At least until 18 months old

**Practical advice: Mix the 2 tsp of peanut butter into a pureed fruit/vegetable/grain, or serve diluted with 2 parts water**



Resources:

1) Overview of starting solids, put together up in KPNW (5 min.)

[https://www.youtube.com/watch?v=l-n-dvAfpDQ&feature=em-subtitle\\_digest](https://www.youtube.com/watch?v=l-n-dvAfpDQ&feature=em-subtitle_digest)

2) How-to on peanut introduction, developed by the AAIAP (2 min.)

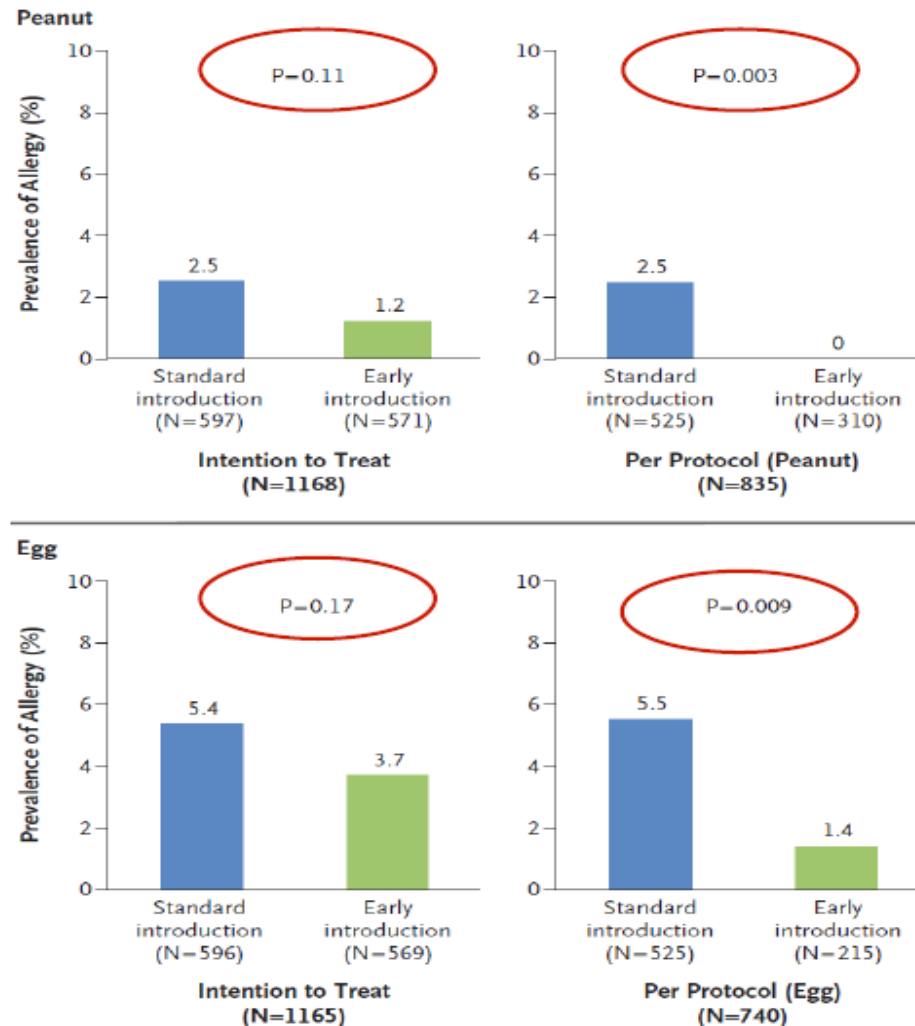
<https://www.youtube.com/watch?v=9pVNFwi0XvU>

# Further Recommendations from the 2017 NIAID Guidelines:

- ▶ To minimize a delay in peanut introduction for children who may test negative, testing for peanut specific IgE may be the preferred initial approach in certain health care settings.
- ▶ Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value (false positive results)

# Clinical Reactivity – EAT Trial

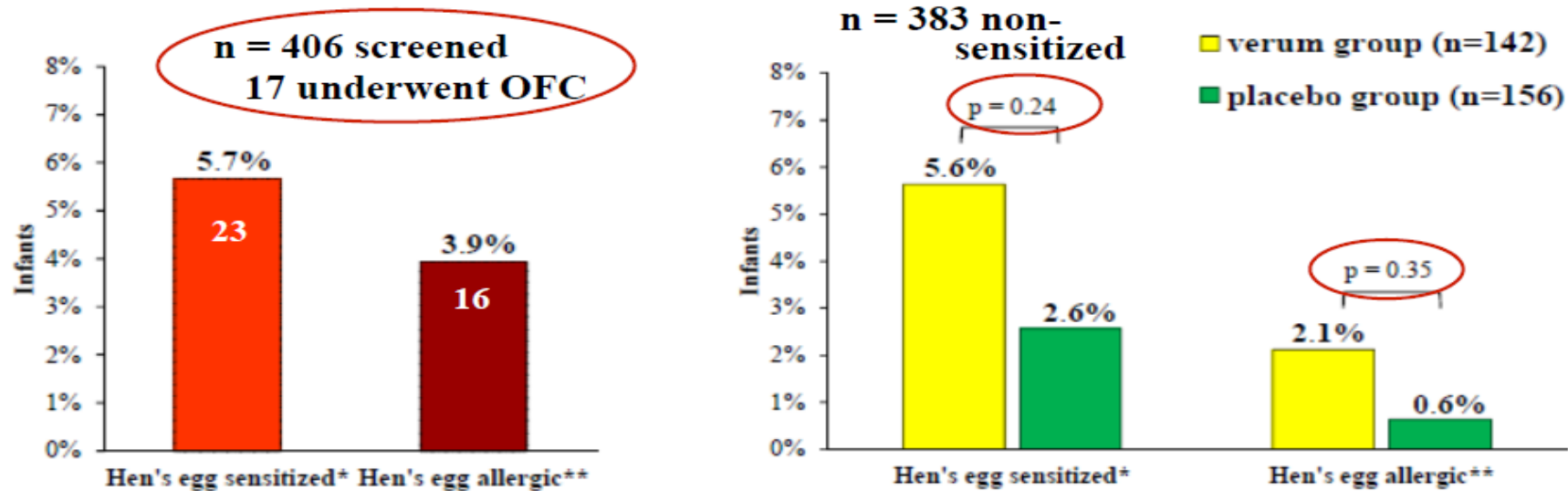
- 1,162 infants enrolled in the trial (median age = 3.4 months)
- Randomized to early introduction of milk, egg, peanut, fish, wheat & sesame (567) or standard feeding (595)
- Overall, by ITT analysis, there was no significant difference in food allergy or SPTs between groups
- Adherence – Early feeding: 42.8%; Standard: 92.9%





# Hen's Egg Allergy Prevention

- Screened 406 unselected infants 4 – 6 mos of age
  - Blinded RCT: egg or placebo to 12 mo of age
  - Outcome: egg sensitization or allergic reactivity at 1 yr
  - 11 anaphylactic reactions during screening OFC



**Conclusion:** early introduction not protective

Bellach et al. JACI 2016 e-Pub

# Future Therapies for Food Allergy

## In clinical trials:

- ▶ Oral immunotherapy (OIT) for milk, egg, peanut, multiple food combinations
- ▶ OIT in combination with anti-IgE
- ▶ Sublingual immunotherapy (SLIT)
- ▶ Epicutaneous (patch) immunotherapy for milk, peanut
- ▶ OIT with baked milk, egg for milk and egg allergy
- ▶ Anti-IL5 for treatment of eosinophilic esophagitis

Nowak-Wegrzyn A, Sampson HA. JACI 2011;127:558-73. Lieberman JA, Nowak-Wegrzyn. Curr Allergy Asthma Rep 2012;12:55-63. Berin MC. Curr Pediatr Rep 2014;2:119-26.

# Summary of Immunotherapy in Ongoing Trials

- Baked-milk & egg for majority of milk- & egg-allergic children will accelerate “tolerance”
- OIT → most robust desensitization to food allergens, but high adverse reaction rate & ? sustainability
  - omalizumab → ↓ adverse reaction rate
- SLIT → modest desensitization, but low adverse reaction rate & poor compliance; ? sustainability
- EPIT (PN Viaskin ) → modest desensitization in 1<sup>st</sup> year, substantially better after 2<sup>nd</sup> year; low adverse reaction rate & possibly more sustainable

# Managing Food Allergy & Food-induced Anaphylaxis

- Appropriate diagnosis of specific food allergy
- Education
  - strict avoidance of food allergen
  - learn to read food labels & recognize high risk situations
  - early signs of an allergic / anaphylactic reaction
- Provide emergency treatment plans in writing
  - FARE website: [www.foodallergy.org](http://www.foodallergy.org)
- Provide self-Injectable epinephrine & liquid antihistamine
- Instructions to go to a medical facility



EpiPen® Auto-Injector,  
0.3 mg Epinephrine  
EpiPen® Jr. Auto-Injector,  
0.15 mg Epinephrine



# Reasons for Allergy Referral

- ▶ Infants with moderate to severe eczema and/or egg allergy
- ▶ Atopic infants with eczema requiring topical steroid/calcineurin inhibitors
- ▶ Infants with peanut allergic sibling (7% increased risk)
- ▶ Evaluation of possible food allergies in eosinophilic esophagitis.

# Conclusions:

- ▶ Both under-diagnosis and over diagnosis of food allergy are significant problems.
- ▶ Skin testing and specific Ig E tests can't distinguish sensitization vs. allergy, Can't determine significance of cross-reactivity or severity of reactivity.
- ▶ Oral challenges leads to more accurate diagnoses.
- ▶ Early peanuts introduction to infants at risks lead to reduction of peanut allergy.

What challenge dose of peanuts would indicate a negative challenge?

a. 1 gram

b. 2 grams

c. 4 grams

d. 8 grams (2 grams peanut protein, 2/3 bag of Bamba)

e. 16 grams

# What is the per patient per year accidental ingestion rate of peanuts for peanut allergic patients?

- ▶ 6%
- ▶ **12%**
- ▶ 25%
- ▶ 50%

In *Pediatr Allergy Immunol*. 2011 Dec 4, Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, St-Pierre Y, Clarke A. published Inadvertent exposures in children with peanut allergy.



# Negative Food Challenge with Positive Testing to Peanut

*-933 normal population based cohort (age 8)*

*-110 (11.8%) were peanut-sensitized, 79 children underwent peanut challenge.*

*-7 children had a positive challenge (22%)*

Nicolaou N. et al have a publication called Allergy or tolerance in children sensitized to peanut: Prevalence and differentiation using component- resolved diagnostics. *:J Allergy Clin Immunol.* 2010 Jan;125(1):191- 197.e13.