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# Preventing Food Allergy: LEAPing Forward, Looking Back

## Pennsylvania Allergy & Asthma Association Annual Meeting

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June 24, 2016



## Disclosures

- 
- Member, Joint Task Force on Allergy Practice Parameters
  - Member of Nutricia specialty advisory board and have received honorarium from Nutricia for lectures
  - Member of the medical advisory team for Kids With Food Allergies Foundation and the International Association for Food Protein Enterocolitis (non-financial)
  - Former member Thermo Fishery Advisory Board regarding Allergen Component Testing and have received honorarium for speaking
  - Have received honorarium from Gerber/Nestle and Adamis Pharmaceuticals
  - Consultant to Canadian Transport Agency, Aimmune, Intromune
  - Receiving support from 1-K08-HS024599-01 (AHRQ, start date 4/15/16)
  - Received support from NIH grants #2KL2TR000434 & UL1RR024986, private foundation (while at U of M)
  - Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food, Health Technologies and Joint Task Force on Quality Improvement Measures Committees
  - Member ACAAI Conferences On-Line Allergy, Abstract, Practice Improvement, and Adverse Reaction to Food committees
  - AAAAI/ACAAI advisor to CDC-ACIP on Egg Allergy/Influenza Vaccine Safety
  - ACAAI representative to consensus statement on interim consensus on early peanut introduction guidelines
  - Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy
  - Associate Editor, Annals of Allergy, Asthma, and Immunology
  - Editorial board: Allergy and Rhinology; Medscape Pediatrics; Infectious Diseases in Children
  - Former officer and legislative advocacy liaison Michigan Allergy and Asthma Society (2010-2015)
  - Have testified to Michigan State Legislature on behalf of Michigan State Medical Society and Michigan Allergy and Asthma Society
  - Member, Scientific Advisory Council, National Peanut Board
  - Former Medical Advisory Chair/member, Food Allergy and Anaphylaxis Connection Team





## Learning Objectives

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- Review the evidence supporting a relationship between timing of peanut introduction and the risk of peanut allergy development
- Review and understand the recent LEAP study data
- Discuss the implications related to making changes to the peanut introduction policy
- Discuss the evidence supporting similar changes for other foods



## Guidance to Prevent Food Allergy

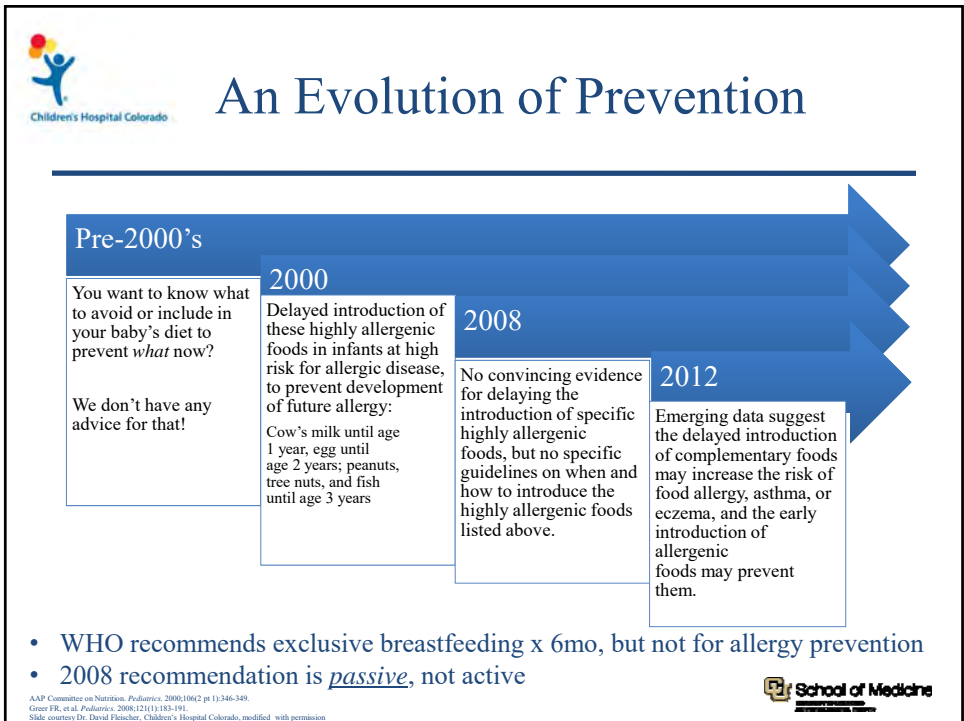
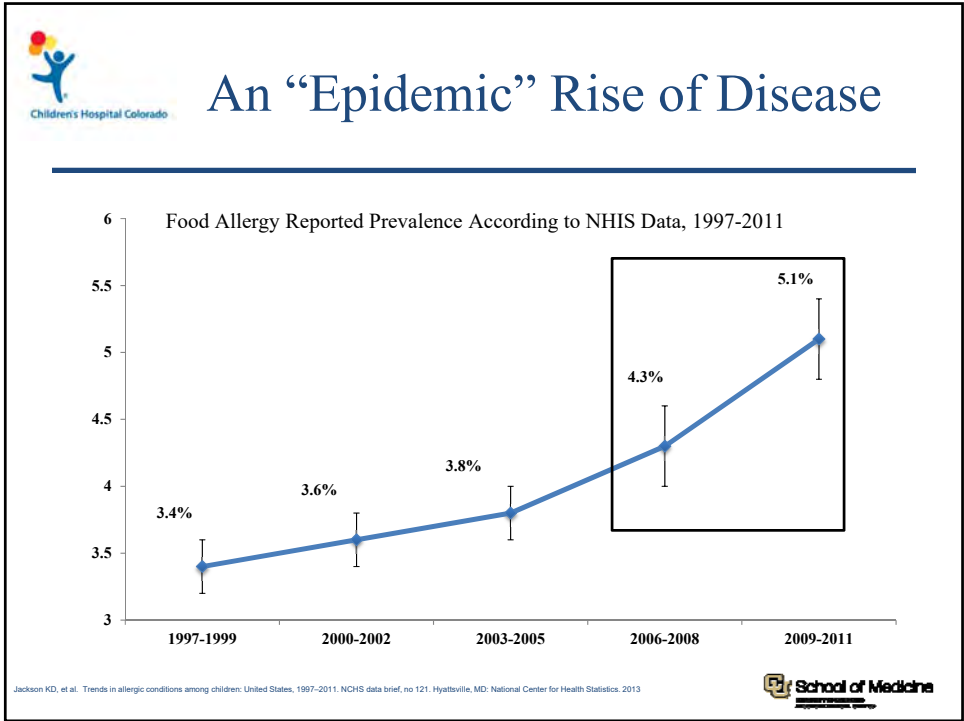
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### **Year 2000 Early Feeding Guidance**

- Dietary avoidance of certain antigens in pregnancy
- Selected avoidance of certain foods while breastfeeding to prevent eczema and asthma
- Use of partially hydrolyzed whey formula
- Delay solid food introduction until 6 months
- Delay introduction of high risk allergens until age 3y

All were felt to reduced risk of food allergy!







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## Can food allergy be prevented?

### The LEAP Study and Peanut Allergy Prevention



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## What Makes Peanut So Special

- Peanut allergy a growing public health problem
- Prevalence between 1-3%, varies by country
  - Milk and egg allergy more prevalent, however
- Prevalence may have doubled in a 10 yr period
- < 20% develop tolerance
- 2000 AAP feeding guidelines suggest delaying introduction of peanut until age 3 to deter risk of developing peanut allergy

De Toir G et al. N Engl J Med 2015;372:803-813



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## A Ray of Light?

- 2008 DuToit et al: UK babies avoiding peanut until age 3 were 10 times more likely to develop peanut allergy than Israeli babies fed Bamba before 9 mo
- Was not an RCT but findings were provocative
  - Could timing of introduction promote primary prevention?
- Learning Early About Peanut Allergy Study started
  - RCT of early vs. delayed peanut introduction in infants at “high-risk” for peanut allergy
  - Use of Bamba or peanut butter as vehicle

Du Toit G et al. N Engl J Med 2015;372:803-813  
Du Toit et al. J Allergy Clin Immunol 2008; 122: 984-91



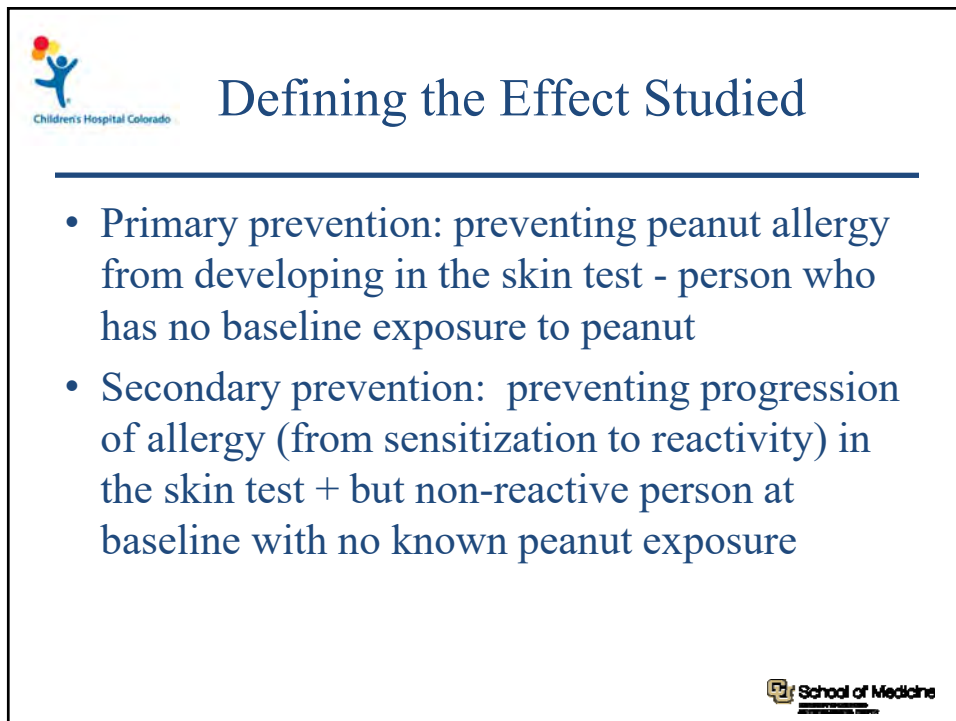
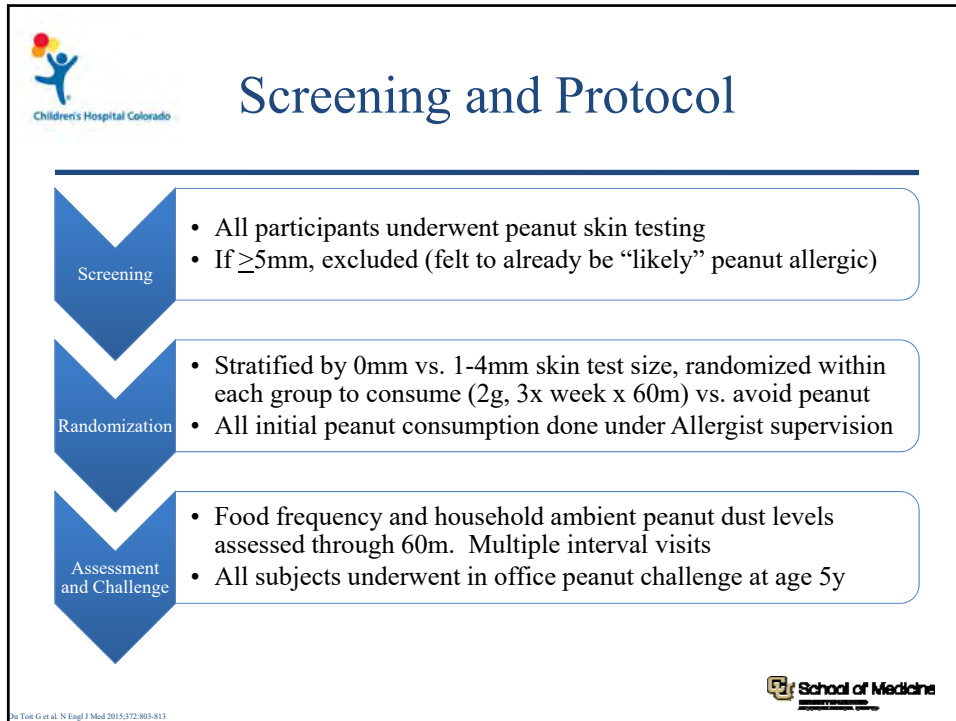
## Learning Early About Peanut Allergy (LEAP)

- Open label single center RCT
- Trial of early (4-11m) vs. delayed (60m) peanut introduction
- Inclusion Criteria
  - 1) Age 4-11 months at screening
  - 2) Having either or both
    - a) Severe eczema
      - Frequent topical corticosteroids/calcineurin inhibitor use
      - “a very bad rash in joints and creases” or “a very bad itchy, dry, oozing, or crusted rash” reported by parent
      - SCORAD grade ( $\geq 40$ )
    - b) Egg allergy
  - 3) Screening peanut allergy skin test  $< 5$ mm



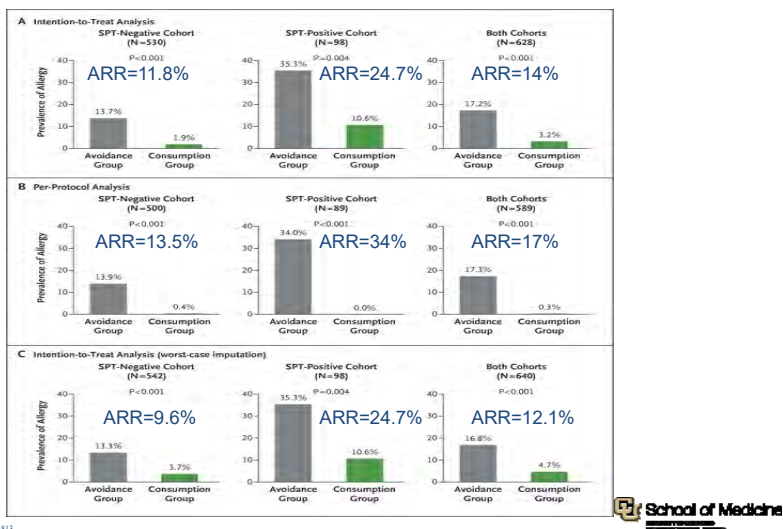
<http://www.seriouscats.com/2012/07/bamba-snacks/>  
Du Toit G et al. N Engl J Med 2015;372:803-813



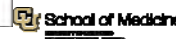




# Results



Yu T et al. N Engl J Med 2015;372:803-813



# LEAP Study: NNT Analysis

	Skin test negative	Skin test positive	Combined
ITT	8.5	4	7.1
Per protocol	7.4	2.9	5.9
Imputed ITT	10.4	4	8.3

- The treatment effect is heterogeneous
- Study showed evidence of both primary and secondary prevention
- Benefit was far greater within the sensitized group
- Unknown effect among the not-at-risk or >4mm sensitized
- How can we assess the health and economic benefits of a single policy with a heterogeneous treatment effect ?



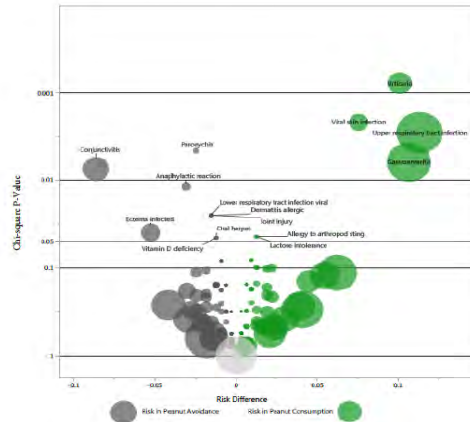
Yu T et al. N Engl J Med 2015;372:803-813



## Adverse Event Plot

Figure S3. Adverse Event Volcano Plot

- No fatalities
- No difference in rates of hospitalization/SAE
- Consumption AE rates higher for URI, skin infection, gastro, urticaria, conjunctivitis
- AE rate not different based on sensitization



De Toit G et al. N Engl J Med 2015;372:803-813



## Challenge Failures

- 7 infants failed challenge at first ingestion
- 57 children failed the 60m challenge
  - 9 consumption vs. 48 avoidance failures
  - 9 required epinephrine, 14 had cardiorespiratory symptoms
- 9 kids in consumption group discontinued due to reported reactions

De Toit G et al. N Engl J Med 2015;372:803-813







## Constructive Criticisms

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- No placebo group or low risk group comparison
- 5mm skin test cut off chosen—arbitrary
- No control group to test necessity of skin testing
- Single center, referral population
- Participation bias? >96% retention at 5yr
- Weak “high risk” criteria
- Dose/duration of exposure not tested
- Unknown effect of partial adherence or long-term outcomes after discontinuation



## What Else Was Learned

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- Challenge and skin test feasible in 4-11mo old
- Rate of significant reactions not very high
- Early sensitization occurs in some without oral exposure
- Skin test negative kids can react
- New model for BAT which predicts reactivity
- Environmental distribution and FLG risk

Santos AF, James LK, Balmon HT, et al. J Allergy Clin Immunol 2015 (in press).  
 Brough et al. J Allergy Clin Immunol 2013;132:623-9  
 Brough et al. J Allergy Clin Immunol 2013;132:630-8.  
 Brough et al. J Allergy Clin Immunol 2014; 134: 867-75





## Justifying Conclusions

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- “The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.”
- **AGREE, BUT SECONDARY EFFECT MUCH GREATER THAN PRIMARY**
- **UNSURE THEY WERE AS “HIGH RISK” AS BILLED**
- **HOW MANY > 4MM WOULD HAVE HAD BENEFIT?**

De Toit G et al. N Engl J Med 2015;372:803-813



## Looking Before You LEAP:

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Changing policy for early complementary feeding to prevent peanut allergy development





## LEAP NEJM Editorial

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- Recommended “immediate” implementation
- Screen all “high-risk” children 4-8mo
  - if skin test -, start 2g thrice weekly
  - if skin test 1-4mm, challenge in the office
  - if skin test  $\geq$  5mm, do not introduce
- Children considered at “high risk” for peanut allergy not otherwise defined beyond LEAP criteria

Gruichalla RS and Sampson HA. N Engl J Med 2015; 372: 875-877



## Measure Twice, Cut Once

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- Danger in implementing findings from a single study
- Duty to replicate?
- Issue of generalizability to US
  - Referral center vs. population-level
  - Should still work, but with same effect size?
  - Is screening even necessary?
  - What is skin testing cut off point? What was missed benefit?
- Issue of Allergist supply/access and utilization
- Issue of compliance—provider and parent

Are we playing LEAPfrog with a unicorn?





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## Current Early Feeding Policy

- 2008 AAP and 2013 AAAAI guidance *already advises* against delayed introduction of foods beyond 4-6 mo if standard risk
- Recommendation is passive, not active
- Reversed guidelines urging delay issued in 2000
- Both AAP and AAAAI recommend allergist evaluation prior to highly allergenic food introduction in patients with hx food allergy or moderate-to-severe atopic dermatitis
- Guidance is based on available data from observational studies suggesting favorable benefit for early introduction of food, and the promise of several RCTs investigating these questions

Fleischer DM et al. J Allergy Clin Immunol Pract 2013; 1: 29-36.  
Greer F. Pediatrics 2008; 121: 183-91.



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## Mission Impossible?

~4,000,000 US children under the age of 1

20% have eczema, and 2% have egg allergy

Only 10% of the 5,500 US allergists perform >1 challenge per week

- Between 20,000-800,000 infants to be seen in 5mo window
- Is this reimbursable or cost effective?
- What would happen to access for other diagnoses?
- How many providers or parents would comply?

Martin PE, et al. Clin Exp Allergy 2013; 43:642-51.  
<http://dx.doi.org/10.1111/cea.12405>, February 24, 2015.  
Fleischer DM et al. J Allergy Clin Immunol Pract 2013; 1: 29-36.  
<http://dx.doi.org/10.1186/2169-0045-1-29>, February 24, 2013.  
Kongpin JN, Book SA, Siskind SR. J Allergy Clin Immunol 2012; 129:564-6.





## Long Term Unknowns

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- Are duration and doses the right targets?
- What is outcome after discontinuing?
- What about partial compliance?
- What about other foods, other evidence?
- Has the “high-risk” child really been identified?
- Have the variable costs of the procedure been determined?

Should we really be altering policy yet?



## “Official” Policy

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- Interim guidelines formulated by an international consortium (US, Canada, Europe, Japan, Israel, and World Allergy Organization as well as AAP and Society for Pediatric Dermatology)
- Restricted to peanut only
- Expert panel met at NIAID on June 16 to start process for a “final” document (GRADE analysis)
- Official addendum to 2010 NIAID food allergy guidelines anticipated Summer/Fall 2016

D. Rottrosen, H. Sampson, personal communication





## Interim Consensus

- There is now strong scientific supporting early introduction of peanut-containing products into the diet of “high-risk” infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent, since delaying may be associated with an increased risk of developing peanut allergy.
- Infants with early-onset atopic disease, such as severe eczema or egg allergy in the first 4-6 months of life may benefit from evaluation by an allergist or physician trained in management of allergic diseases to assist in implementing these suggestions regarding the appropriateness of early peanut introduction.
- Evaluation of such patients may consist of performing peanut skin testing and/or in-office observed peanut ingestion, as they deem appropriate after discussion with the family, especially for those with evidence of a positive peanut skin test
- The study does not address use of alternative doses of peanut protein, minimal length of treatment necessary to induce the tolerogenic effect, or potential risks of prematurely stopping or sporadic feeding of peanut.



Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants. 2015. In press.



## Revising the NIAID Guidelines

- Expert panel recommending 3 addendum
- Addendum 1: infants with severe eczema, egg allergy or both have introduction of age-appropriate peanut-containing food as early as 4-6 months of age to reduce the risk of peanut allergy.
- Addendum 2: infants with mild to moderate eczema should have introduction of age-appropriate peanut-containing food as early as 4-6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy.
- Addendum 3: infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet as early as 4 to 6 months of age, together with other solid foods, and in accordance with family preferences and cultural practices.



NIAID 2016 Early Feeding Guideline Addendum Draft Copy



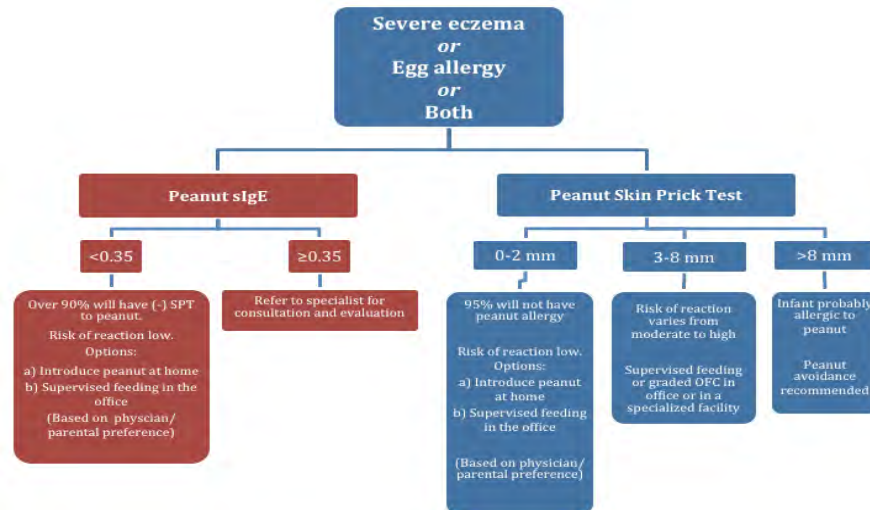
## Redefined Risk Criteria

- **Severe eczema** is defined as persistent or frequently recurring eczema covering  $\geq 10\%$  of body surface area with typical morphology and distribution as assessed 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.
- **Egg allergy** is defined as a skin prick test wheal diameter of 3 mm or greater with egg white extract in an infant with a history of an allergic reaction to egg or who has failed an egg oral food challenge.
- A **specialist** is defined as a health care provider with the training and experience to perform and interpret skin prick testing and oral food challenges; and know and manage their risks.

NIAID 2016 Early Feeding Guideline Addendum Draft Copy



## NIAID Guideline Algorithm





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## Medicinal Peanut Introduction?

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- Are data strong enough to suggest a policy?
- Have all stakeholders “bought in” & who benefits?
- How will the knowledge translate?
- What are the health and economic benefits?
- Should expectations for success be tempered?
  - TIPS Study: 7% introduce solids by 4mo, 13% by 6 mo
  - Wheat (8.7m), egg (11.2m), fish (13.4m), peanut/tree nut (20-22m)
  - Asian race, maternal hx food allergy associated w/delay

McKinn et al. Clin Pediatrics 2015; 54: 745-51



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## Latest Data







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## LEAP ON—Does this Help?

- Aim to test effect of discontinuation
  - 1 year follow-up at the end of the original 5 year LEAP study
  - Both consumption and avoidance group avoided peanut
- 3 new cases of peanut allergy in each arm
- Shows effect was not transient desensitization
- Question of applicability
  - Does not address partial adherence/discontinuation at younger ages*
  - Does not address long term outcomes of shorter periods of adherence*

DuToit et al NEJM 2016; 10.1056/NEJMa1514209



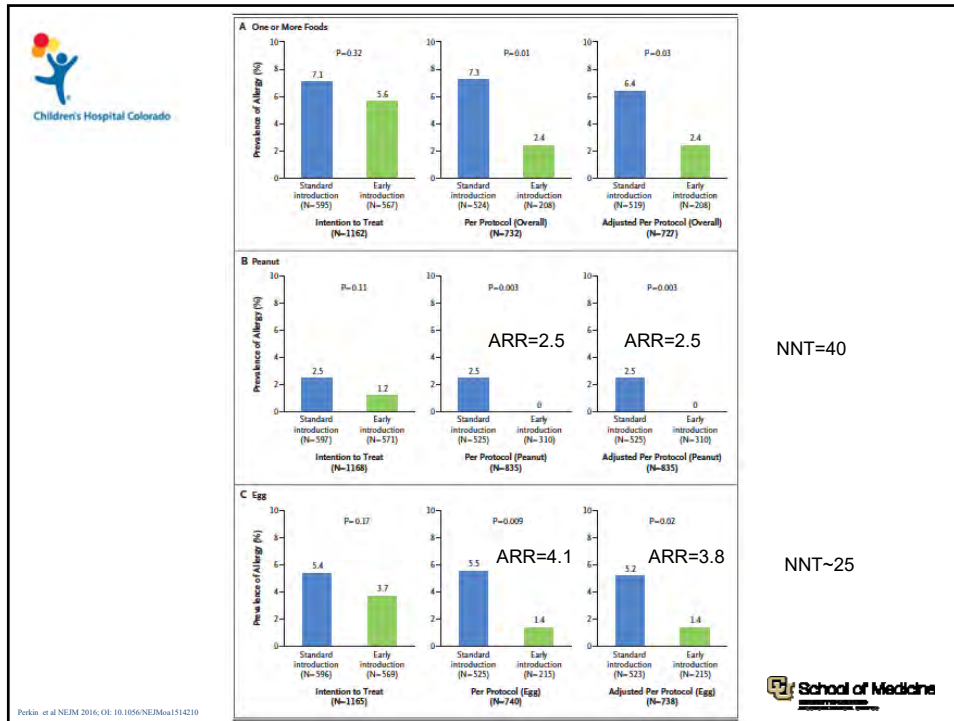
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## EAT: Evidence in Low Risk Kids?

- Enquiring About Tolerance study
  - Early introduction of allergens in breastfed infants at 3mo vs 6 mo
  - Infants were not considered “high-risk” as in LEAP study
  - Milk 1<sup>st</sup>, then egg, fish, sesame, wheat, peanut in random order
  - Assessed rates of allergy development between 1-3 years in 1303 children
- 68% unable to follow protocol in the early intro group
  - Influenced by perceived sx, nonwhite race, poor caregiver QoL, eczema
  - Adherence: milk 85%, peanut 62%, fish 60%, sesame 51%, egg 43%
- No significant differences between groups
  - Concern for limited power, drop out
  - Best case scenario shows approaches non-inferior

Perkin et al NEJM 2016; 01.10.1056/NEJMa1514210





## Conclusions

- Early introduction of peanut may have distinct protective effects
- Unclear if this has been definitively proven
- Policy change is coming, but unclear how to best implement such change
- Trade-offs associated with these changes need to be better defined
- More data for other foods forthcoming

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# Food Allergy: Is there an Answer?

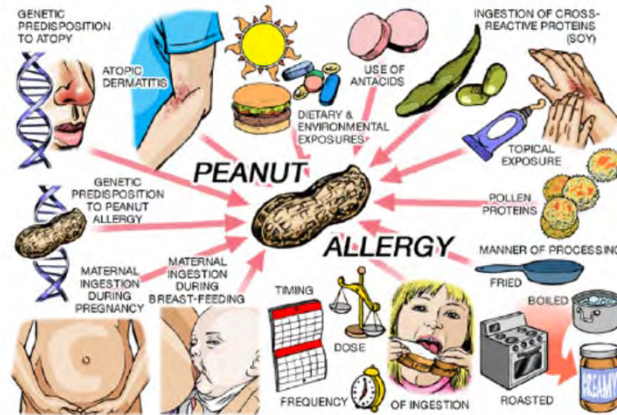


FIG 1. Possible genetic, immunologic, and environmental risk factors for food allergy.

Sampson and Sicherer J Allergy Clin Immunol 2007; 120: 491-503



# Thanks!



The view from the Food Challenge Unit, Children's Hospital Colorado

