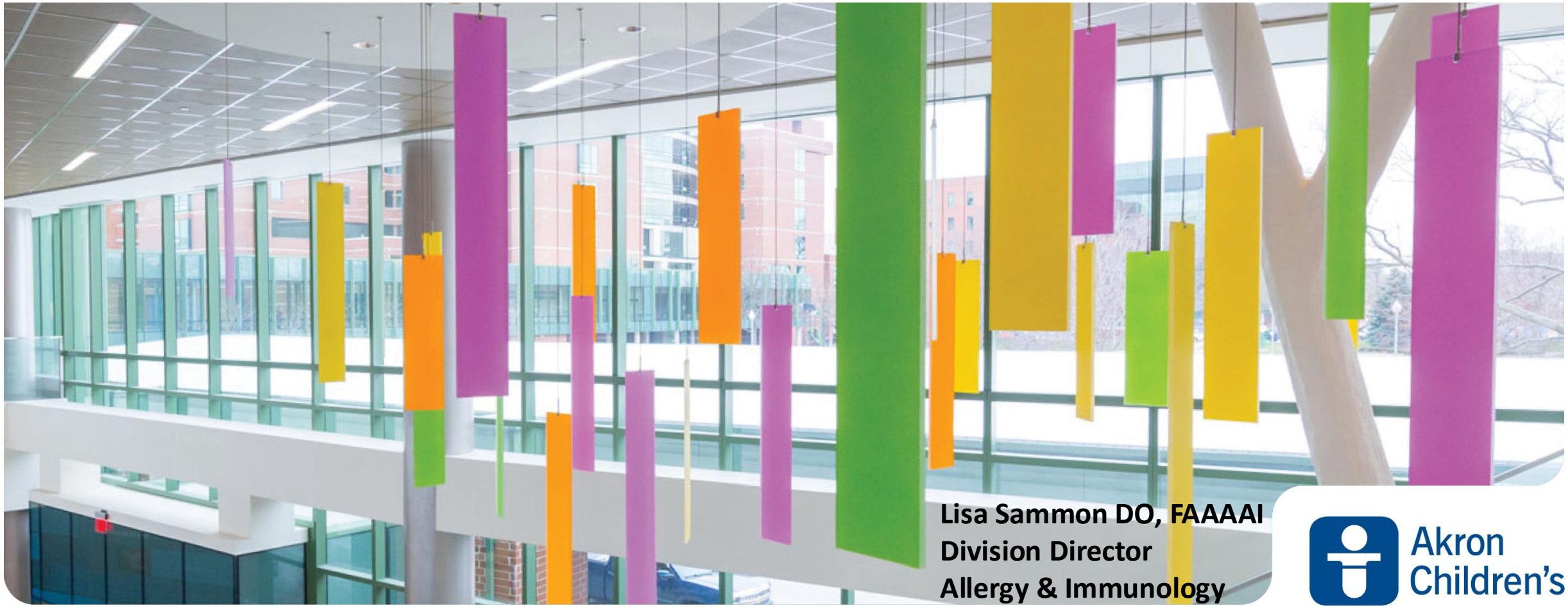
Advancing Treatment for Food Allergy: Oral Immunotherapy in the Modern Era



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Outline

- Food Allergy Pearls
- Oral Immunotherapy
  - Indications
  - Precautions
  - Side Effects
- Evidence-based outcomes
- Alternative options

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Food Allergy Pearls

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Food Allergy

- Diagnosis
  - **CLINICAL HISTORY**
    - Reproducible, **IMMUNE REACTION** usually occurring within 1-2 hours following **INGESTION** with symptoms secondary to histamine release and potentially **LIFE-THREATENING.**
      - Mediated by IgE and other mediators
    - Nonimmune reactions include lactose/fructose intolerance, food poisoning, food aversion, side effects of caffeine (anxiety, palpitations), tyramine (headaches), monosodium glutamate (headaches, nonspecific), etc.

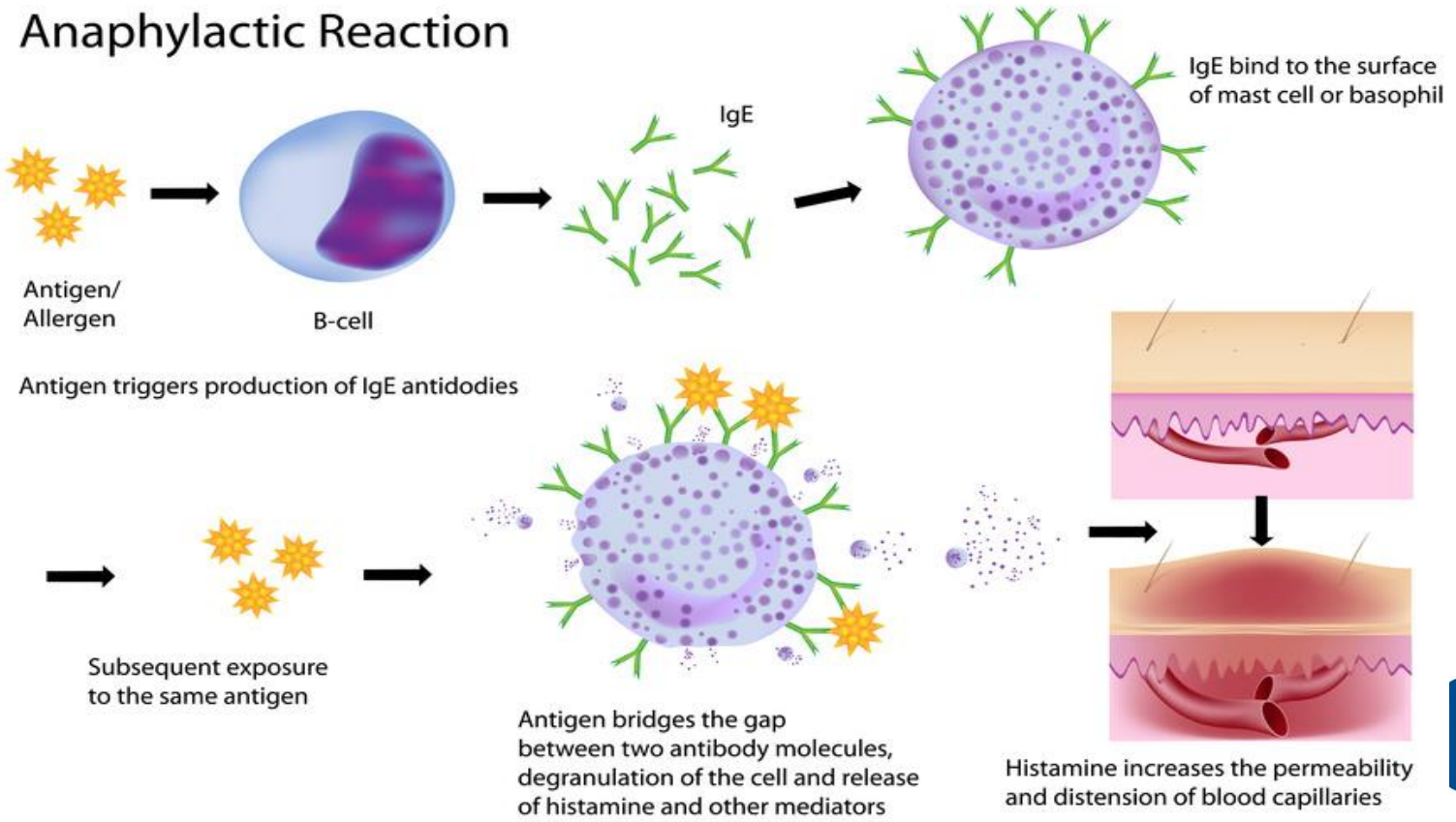
Non-IgE Food Disorders

- **Food protein-induced enterocolitis syndrome (FPIES)**
  - Delayed (1-4 hours) onset of repetitive emesis + **pallor, lethargy or hypotension** with return to baseline several hours later
  - Common foods include milk, soy, egg, rice, oat, sweet potato
  - No current diagnostic marker exists (neutrophilia or increase in left shift following a reaction)
  - Treatment involves avoidance and/or PO rehydration versus IV hydration if a reaction occurs
  - Tolerance usually results by early childhood (1-3 years of age)

- **Food protein-induced proctocolitis of infancy**
  - Symptoms include streaks or specks of blood in the stool
  - Cell-mediated mechanism and colonic biopsies may show eosinophilic infiltration
  - Occurs in early months of life often in breastfed infants
  - Common foods include milk, egg and soy
  - Self-resolves in most by age 10-12 months; no association with atopy

Mechanism

- Immunologic reaction involves cross-linking of IgE antibodies on mast cells and/or basophils following encounter by an allergen.



https://learn.canvas.net/

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Epidemiology

- Foods are the most common cause of anaphylaxis in children
- Prevalence in the United States of food allergy is estimated to be 4% and rising
  - 1 in 13 children have a clinically significant food allergy

- Most common allergens include (top 8):
  - Milk (most common in children)
  - Egg (most commonly associated with atopic dermatitis)
  - Soy
  - Wheat
  - Peanut
  - Tree Nuts
  - Shellfish
  - Fish
  - Sesame* (emerging)

https://www.stmaryshealthcaresystem.org/blog-articles/introduction-food-allergies

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Food Allergy Prevalence

Table 5-17. Prevalence of Food Allergy in North America		
Food	**Infant/Child**	**Adults (%)**
Milk	2.5	0.3
Egg	1.3	0.2
Peanut	0.8	0.6
Tree nuts	0.2	0.5
Fish	0.1	0.4
Shellfish	0.1	2.0
Wheat/soy	0.4	0.3
Sesame	0.1	0.1
Overall	6	3.7

Source: ACAAI Board Review. 2016.

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Testing

- **Skin prick test (SPT):** Suggests sensitization if positive but does not always correlate with clinical reactivity. If negative, allergy highly unlikely and NPV > 95%.
  - High sensitivity; specificity ranges 40-70%

- **Serum IgE test:** Increasing levels suggest increased likelihood of reaction and can support anaphylaxis if reaction has ALREADY OCCURED (no data can predict severity to date).
  - Less sensitive than SPT; specificity ranges 30-60%. High rate of false positives

- **EXTENSIVE IGE FOOD PANELS ARE LOW-YIELD AND CAUSE UNNESSECARY FOOD AVOIDANCE—NOT SCREENING TESTS!**
  - **IgG food panel tests are not validated to correlate with symptomatology**

Skin prick testing

https://www.informedhealth.org/what-kinds-of-allergy-tests-are-there.html

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Laboratory test performance evaluated by Biotrinetix, LLC. This test has not been evaluated by the FDA, and is not intended for diagnosis.
Results are not intended for the diagnosis of Allergies and possible Allergenic Foods.

Food Sensitivity Test (90 panel) – NLRxNutrition

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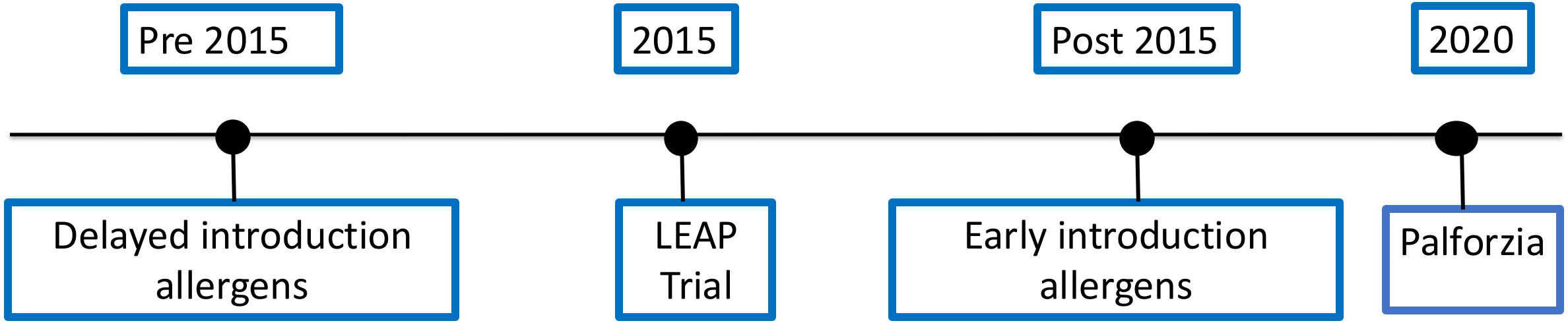
Timeline



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LEAP Study

- Landmark study showing importance of early introduction of peanut in those high-risk to develop food allergy.

- 640 infants (aged 4-11 months) with a history of **SEVERE** eczema, egg allergy or both randomized to two groups (no peanut versus peanut consumption) based on skin prick test size until 60 months of age.
  - Found an **increased prevalence** of peanut allergy in **avoidance** group.

- Implications for screening and food introduction
  - Food introduction is best and has a lower complication rate in infant population irrespective of above risk factors

Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb26;372(9):803-13.

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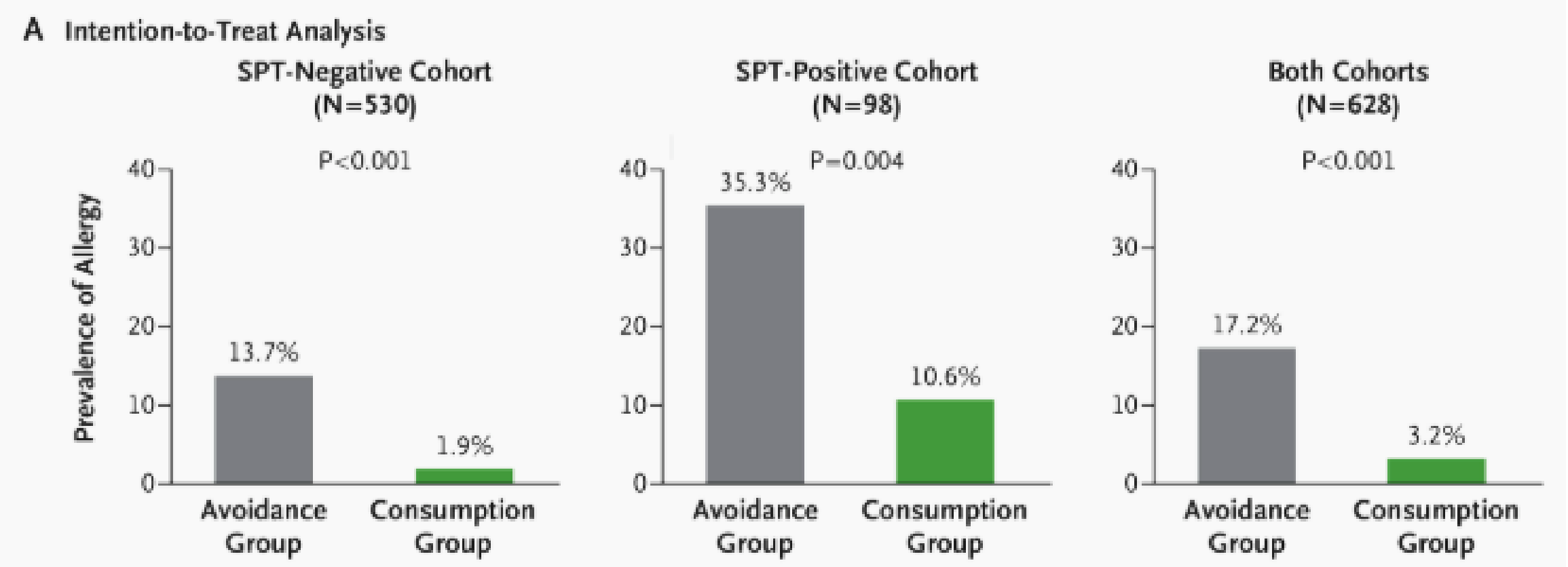
LEAP Study



Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb26;372(9):803-13.

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LEAP Study

- Encouraged clinicians to introduce allergenic foods (peanut) early.
- Screening is not necessarily indicated despite risk factors.
  - Case by case basis if severe eczema or reaction to other food such as egg
  - Anaphylaxis severity less in infants
  - Miss window of opportunity if dependent on testing or referral
- Evidence greatest for peanut introduction in infants.

Du Toit G, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015Feb26;372(9):803-13.

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Palforzia®

Palforzia™
Peanut (*Arachis hypogaea*)
Allergen Powder-dnfp

- Landmark trial showing benefit of peanut oral immunotherapy.
- Participants screened & randomized to consumed 300 mg peanut protein for 24 weeks.
- Primary endpoint: % of patients aged 4-17 years who could ingest ≥ 600 mg peanut protein without dose-limiting symptoms.
  - 67.2% of study drug participants able to reach goal versus 4.0% placebo
  - Side effects common in both treatment groups (> 95% effected)
    - Moderate side effects in active (59.7%) versus placebo (44.4%)
    - Severe side effects in active (4.3%) versus placebo (0.8%)

Palisade Group of Clinical Investigators. AR101 Oral Immunotherapy for Peanut Allergy.

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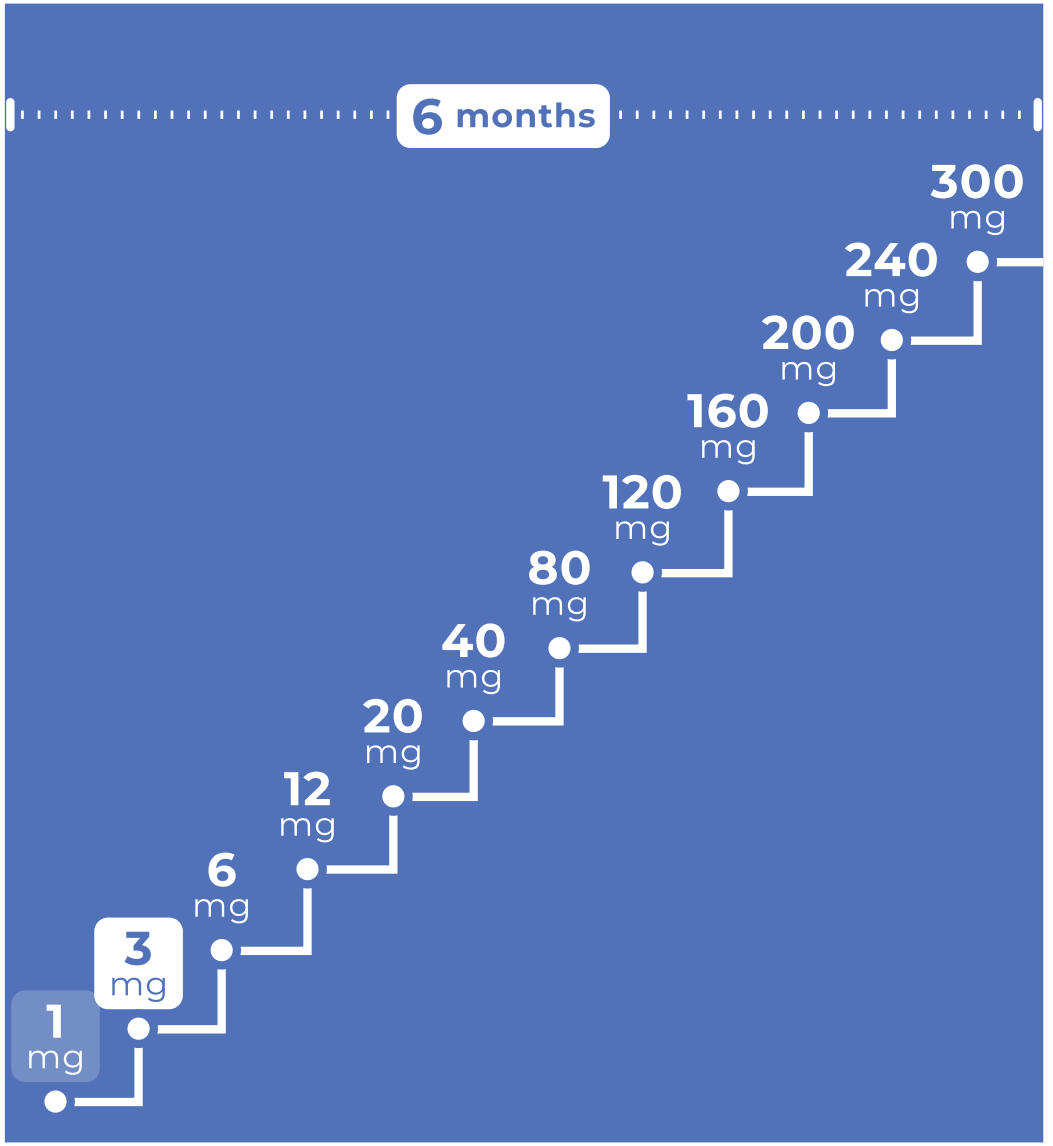
Example of Palforzia® protocol



https://www.palforzia.com/what-is-palforzia/

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Palforzia®

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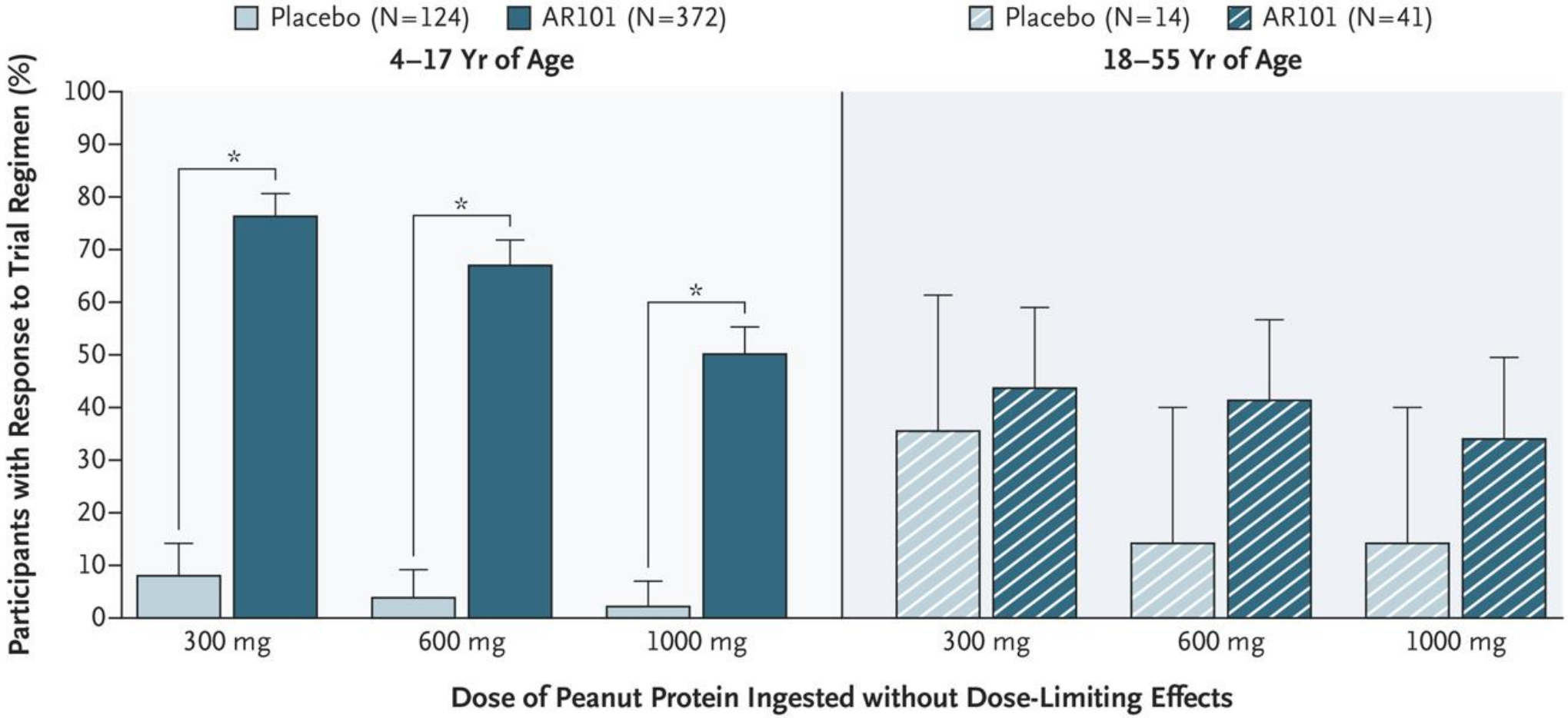
Peanut (*Arachis hypogaea*)
Allergen Powder-dnfp



Palisade Group of Clinical Investigators. AR101 Oral Immunotherapy for Peanut Allergy.

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Oral Immunotherapy

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What is oral immunotherapy (OIT)?

- OIT is a type of allergy treatment that gradually exposes a patient to the source of the allergy to build a tolerance.
  - Desensitization therapy that uses small doses of the allergen to reduce the degree of a severe allergic reaction
  - **THIS IS NOT A CURE**
- OIT must be used in conjunction with strict avoidance of the offending food.
- Patient selection important.

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Indication

- Therapy is available for all ages as recommended per Allergy clinician.
  - OIT therapies are less likely to be pursued in adulthood.
- Patients with asthma must have controlled symptoms before enrollment.
- Commitment to following protocol and adherence to precautions.
  - Includes epinephrine carriage
  - Maintenance of dose in diet following program completion

Treatment phases

- **Initial dosing**
  - Longer visit; often mini-desensitization
  - Other practices may perform threshold dose challenge and reduce dose by 75% or greater for home dosing
- **Up-dosing**
  - Weekly to biweekly visits often 1 hour observation to ensure tolerance of next step
- **Maintenance dosing ie "bite-size" protection**
  - Dose should be given daily to 5-6 times/week
  - High dose challenges may follow depending on patient goals

Side effects

- **Mouth itching and abdominal discomfort** are very common and affect 60-70% of patients.
  - Can consume non-allergy food (i.e. crackers) before dosing to reduce side effects
  - Zyrtec is optional; may take daily to lessen side effects but is not mandatory if symptoms not present
- **Loose stools and/or diarrhea** may occur during early build up doses.
  - Supplementing with probiotics can lessen frequency of loose stools which improve with time
- **Anaphylaxis**
- **Eosinophilic esophagitis (EoE)** in ~4-5% of patients; signs of EoE are difficulty swallowing, abdominal pain, and vomiting. Resolution occurs with discontinuation.
  - A visit with a Gastroenterology provider may be needed for confirmation of EOE

Precautions

- Give daily dose at the same time each day, preferably in the evening
  - Try to avoid taking your dose immediately before bedtime (or after 8 pm)
  - Stay awake for at least 1 h after taking your dose
- Keep epinephrine auto injector out and in clear view during dosing
- Avoid sports/strenuous exercise or hot showers/baths for 60 minutes before the dose AND for two hours after dosing (2 hours)
- Younger children should maintain at baseline activity level
- Follow illness precautions. Call office for questions
- Do not consume more than one dose per day

OIT tips & tricks

To reduce or mask nut flavors:

- Use peppermint/mint products and/or fruit flavors such as flavored yogurts ie grape
- Cinnamon can be added to applesauce

- Dose can be added to salty or savory foods (dip, refried beans, taco, chips, mashed potatoes, ground meat, tomato sauce, ketchup)
- Ok to consume food such as candy, cookie, ice cream or flavored milk/yogurt immediately following to “chase” dose for taste tolerance
  - Cold foods such as ice cream can reduce mouth itching/taste after dose
- Of note, chocolate/sweets can enhance nut or seed flavors

Evidence-based outcomes

Efficacy

- Infancy & toddler years excellent time to initiate OIT.
  - 73.5% participants in treatment group (n=98) tolerated ≥ 600 mg peanut protein in exit DBPCFC after 12 months consumption 300 mg peanut protein vs 6.3% in placebo (n=98).
    - 72.7% of patients aged between 1 to ≤2 years of age tolerated 2 grams peanut protein compared to 56.7% children aged 3 to ≤4 years of age
  - While majority experienced side effects they were primarily mild to moderate; none graded as severe.

Du Toit G et al. Oral Immunotherapy for Peanut Allergy in Children 1 to Less Than 4 Years of Age.NEJM Evid. 2023 Nov;2(11):EVIDoa2300145.

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Efficacy contd.

- OIT initiated before age 4 results in greater likelihood of desensitization & remission
  - Peanut-allergic participants aged 2-12 years recruited to consume 2 grams peanut protein for 134 weeks then avoid peanut for 26 weeks (remission)
    - 71% (68/96) participants desensitized to 5 grams peanut protein
    - Median dose tolerated 5005 mg for treatment versus 5 mg (placebo) at week 134
      - At week 160, median dose in treatment group decreased to 755 mg versus 0 mg for placebo

Jones S et al. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. The Lancet, 399, 359-371.

Probiotics?

- In one study, participants (aged 1-10) randomized to receive OIT (2 g peanut protein), probiotic (PPOIT) + OIT & placebo for 18 months.
  - Probiotic consisted of daily dose 2 x 10^{10} CFU *Lactobacillus rhamnosus*
  - 36/79 (43%) PPOIT & 42/83 (51%) OIT group able to achieve sustained unresponsiveness; efficacy not statistically significant between groups
  - Lower adverse event rate seen in PPOIT group notably in regards to GI symptoms in those aged 1-5

Loke P et al. PPOIT-003 study group; Tang MLK. Two-year post-treatment outcomes following peanut oral immunotherapy in the Probiotic and Peanut Oral Immunotherapy-003 Long-Term (PPOIT-003LT) study. Allergy. 2024 Oct;79(10):2759-2774.

Safety

- More data suggests OIT reactions tend to be low grade and well tolerated in younger patients.
- 52 participants ≤2 years of age initiated on OIT with commercially available food products; 15.4% on multi-food OIT
  - 51.9% participants experienced ZERO side effects
  - Reactions were cutaneous (88%) in majority of cases and 3% experienced GI symptoms ie vomiting
  - No reaction required treatment with epinephrine

Huang J et al. Safety and Feasibility of Peanut, Tree Nut, and Sesame Oral Immunotherapy in Infants and Toddlers in a Real-World Setting. J Allergy Clin Immunol Pract. 2025 Jan;13(1):185-191.e3.

Alternative Options

Alternative Options

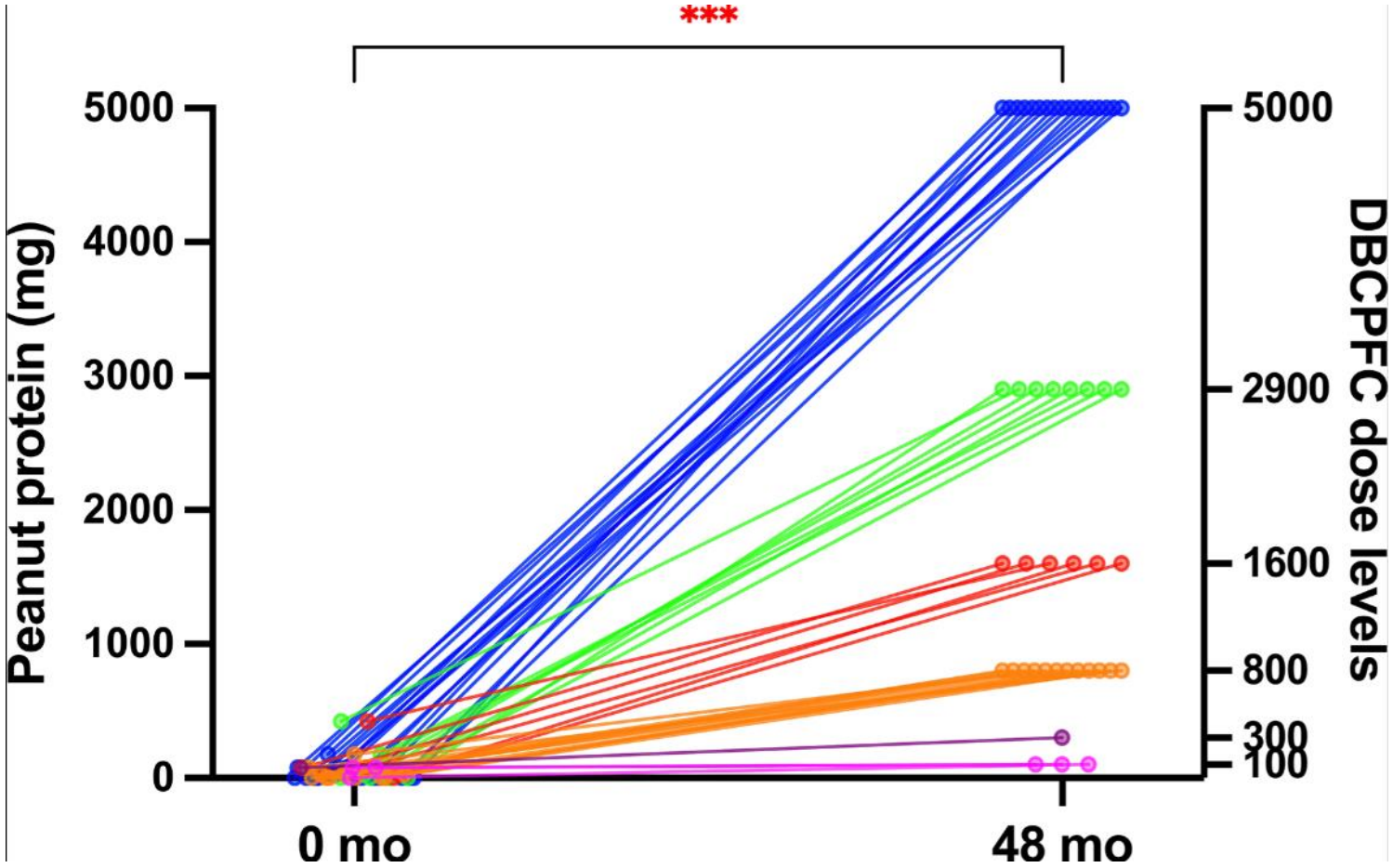
- For patients that do not tolerate standard OIT doses, sublingual (SLIT) or droplet therapy may be applicable.
  - SLIT is available for certain foods and has less adverse effects compared to standard OIT. May also be more tolerable in adolescents with less exercise restrictions.
    - Doses are held under the tongue for 1-2 minutes then swallowed
    - Maintenance doses range from 2-10 mg
  - SLIT is a home therapy that requires regular preparation of solutions and purchase of syringes and/or small bottles for long term maintenance.
  - SLIT requires a training visit on mixing of solutions and observation of dose for safety.

Sublingual Immunotherapy

- A randomized trial recruited 54 patients ages 1-11 with history peanut allergy.
- Participants consumed 4 mg peanut protein via SLIT for 48 months.
- Mean amount consumed ~2723 mg of peanut protein and 70% able to consume > 800 mg peanut protein.
  - 36% participants able to consume > 5000 mg peanut protein
  - Reaction rate low (median reaction rate/dose 0.5% with oral itching the most common SE). No participants required epinephrine

J Allergy Clin Immunol. 2023 Jun;151(6):1558-1565.e6.

Sublingual Immunotherapy



J Allergy Clin Immunol. 2023 Jun;151(6):1558-1565.e6.

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Sublingual Immunotherapy contd.

	SLIT	OIT
Number of in office dose visits	4	12+
Overall Dose Given	Lower	Higher
Level of risk/side effect profile	Lower	Higher
Level of protection offered	Lower	Higher
Treat more than one allergen simultaneously?	Yes	No
Time to see a response	1+ Year	4-6 Months
Activity restrictions	15-30 minutes after dose	2 hours after dose
Dose adjustments for illness	No	Yes

https://www.msaac.com/sublingual-immunotherapy-1

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Omalizumab

- Omalizumab (Xolair) now an added tool for Allergists' to utilize for patients with severe food allergy reactions or refractory to OIT therapies in patients 1 year and older to raise reaction threshold.
- OUTMATCH trial involved participants receiving Xolair every 2-4 weeks for 16-20 weeks.
  - 79/118 or 77% participants could tolerate ≥ 600 mg peanut protein compared to placebo
  - Secondary endpoints included data for (milk: 66% vs. 10%); (egg: 67% vs. 0%) and (cashew: 41% vs. 3%) that could tolerate ≥ 1000 mg food protein
  - Safety profile similar between groups

N Engl J Med 2024;390:889-899.

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