Oral Immunotherapy: What You Should Know, and What's New

Presented by
Dr. Brian Vickery

April 2020

Today's Presenters

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Associate Professor of Pediatrics

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Medical Advisor for Patient Experience, FARE

The Dawn of the Treatment Era in Food Allergy: Oral Immunotherapy

29 April 2020

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Associate Professor of Pediatrics

Section Chief of Allergy/Immunology

@ATLergist

Disclosures

- Employment: Pediatric Institute of Emory University + Children's
- Consultant/Advisor: Aimmune Therapeutics; AllerGenis, LLC; Food Allergy Research and Education (FARE); Reacta Biosciences
- Grant support: NIH-NIAID; FARE
- Clinical investigator: Aimmune; DBV Technologies; Genentech; Regeneron
- Equity interests/stock ownership: none

- I will discuss the use of unapproved investigational therapy

- I created this talk myself and received no editorial influence or financial compensation from any entity

Acknowledgements

- The entire team at FARE, present and past (FAAN, FAI)
- Clinical trial participants and treated patients
- Research partners and sponsoring organizations
- My mentors, especially Dr. Wesley Burks
- My team at Emory University and Children's Healthcare of Atlanta
- My family

- Essential front-line workers and healthcare providers 👏👏👏

- You, the audience

THE PSYCHOSOCIAL TOLL OF FOOD ALLERGIES: A Patient-Centered Research Target

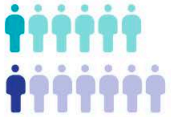
AMONG FOOD ALLERGY CENTERS SURVEYED

MORE THAN 90 PERCENT SERVE PATIENTS & PARENTS WHO HAVE **ANXIETY** RELATED TO FOOD ALLERGY.

OF 500 PATIENTS & CAREGIVERS SURVEYED

TWO-THIRDS REPORT **MENTAL HEALTH CONCERNS** RELATED TO FOOD ALLERGY.

NEARLY 70 PERCENT TREAT PATIENTS WHO SUFFER FOOD ALLERGY-RELATED **PANIC ATTACKS**.

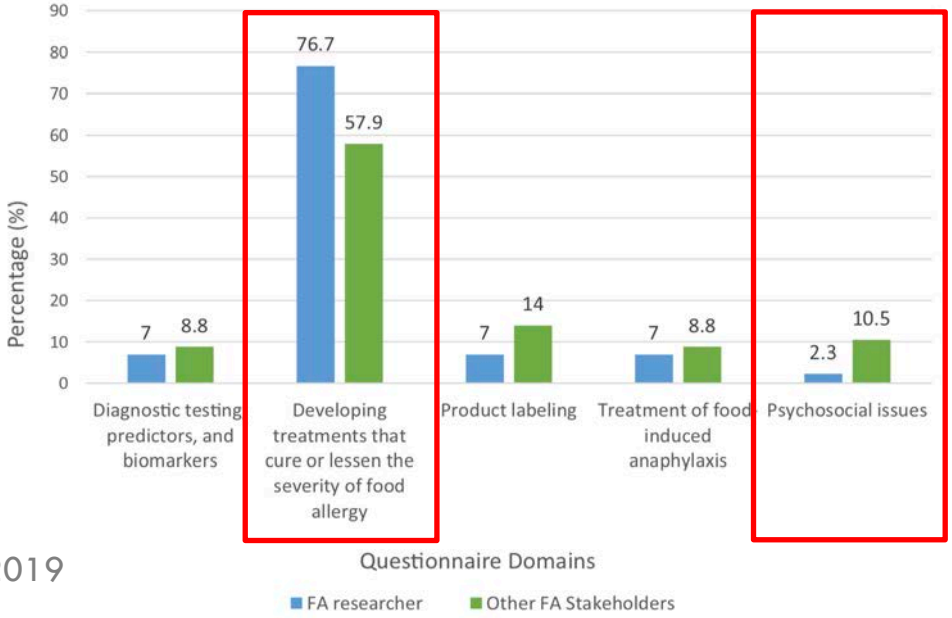


ONLY **1 IN 6** PATIENTS AND **1 IN 7** CAREGIVERS HAD RECEIVED FOOD ALLERGY-RELATED **MENTAL HEALTH SERVICES**.

MORE THAN 70 PERCENT TREAT PATIENTS WHO REPORT FOOD ALLERGY **BULLYING**.

MORE THAN HALF WANT RESOURCES TO HELP THEM COPE WITH FOOD ALLERGY STRESS AND ANXIETY.

Top 5 Research Priorities: FARE ORAB



Bilaver et al JACI 2019

source: Food Allergy Research and Education

Objectives

1. To provide a general overview of what oral immunotherapy (OIT) is, how it works, and in whom it might be most useful.

2. To share some of my perspectives that may help facilitate a conversation with your / your child's allergist.

3. To outline future directions in OIT / food allergy research.

Key Messages

1. Food allergy is at an inflection point, with OIT (especially for peanut allergy) poised to become a much more widely available treatment.
2. Clinical trials and real-world experience show that OIT can produce high rates of desensitization and clinically meaningful improvement.
3. OIT has known risks and tradeoffs, and is not right for all patients.
4. No study has ever convincingly shown that OIT is curative.
5. We have much more to learn about how best to implement OIT in routine care; how to build on it and improve it; and how it will fit in a rapidly changing treatment landscape.

What is OIT?

Is OIT Right For Our Family?

What Does The Future Hold?

Children's[SM]
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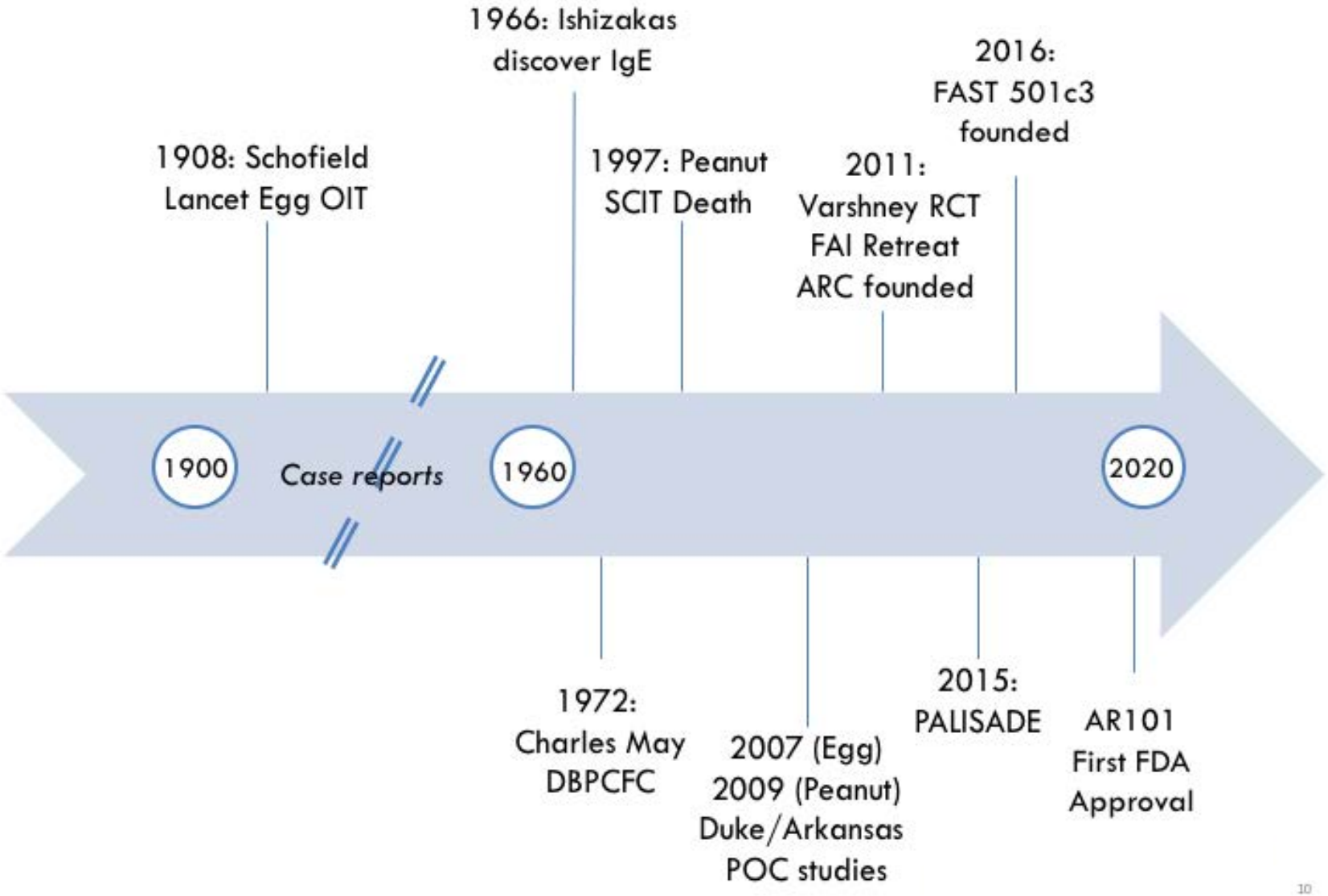
In April 2020, OIT Is:

- An emerging treatment option for certain food allergy/(ies)
  - Data quality: peanut >>> egg, wheat, tree nuts, milk, sesame, others
- A process requiring consistent, controlled ingestion of the allergenic protein(s) to “desensitize” the patient and offer protection from accidents
  - **Must still practice avoidance / carry epi: speed limits and seat belts**
- Associated with known risks, including allergic reactions & anaphylaxis, eosinophilic esophagitis, or “EoE”, and treatment withdrawal
- Not available everywhere and not endorsed for widespread clinical use by stakeholder organizations due to limited data
- Moving into the realm of mainstream allergy practice soon with FDA approval of Palforzia™ for peanut allergy on 31 January

Selected Key Events in the History of OIT



Two Denominations

"Standardized"

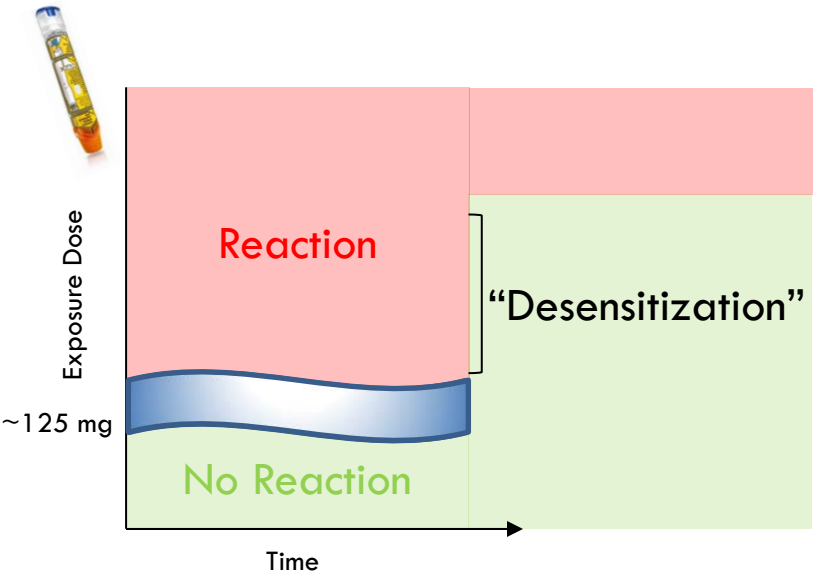
- FDA-approved
- Doses: Precisely manufactured
- Single protocol
- Tested in large randomized trials
- Ease of use / scalable access
- Nationwide safety system
- Cost to patient: 0 - $11K / yr
- Currently available: only AR101 (Palforzia™) for peanut allergy
  - Egg and Tree Nuts in development

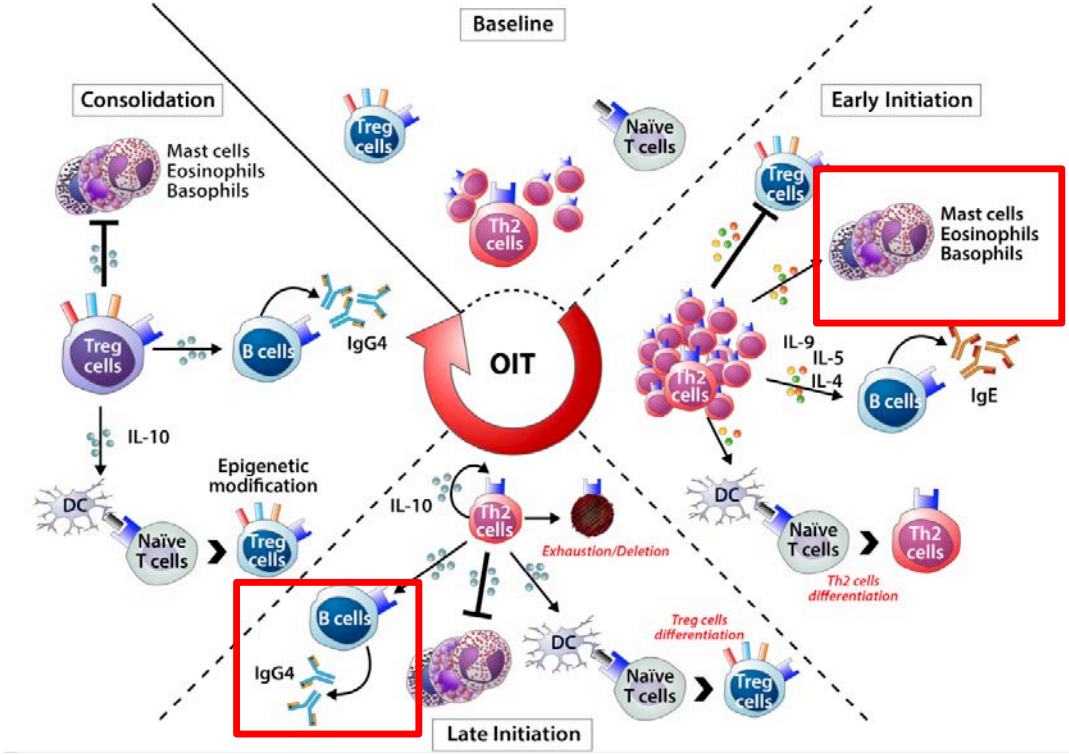
"Non-standardized"

- Not FDA-approved
- Doses: Highly variable
- Protocols vary by office
- No randomized trials
- Offered by ~250/5000 allergists
- Safety mostly unreported
- Cost to patient: varies
- Many / Any / Multiple foods available now

Wasserman et al Annals 2018
Blaiss et al Allergy Asthma Proc 2019
www.aimmune.com

How Does OIT Work?



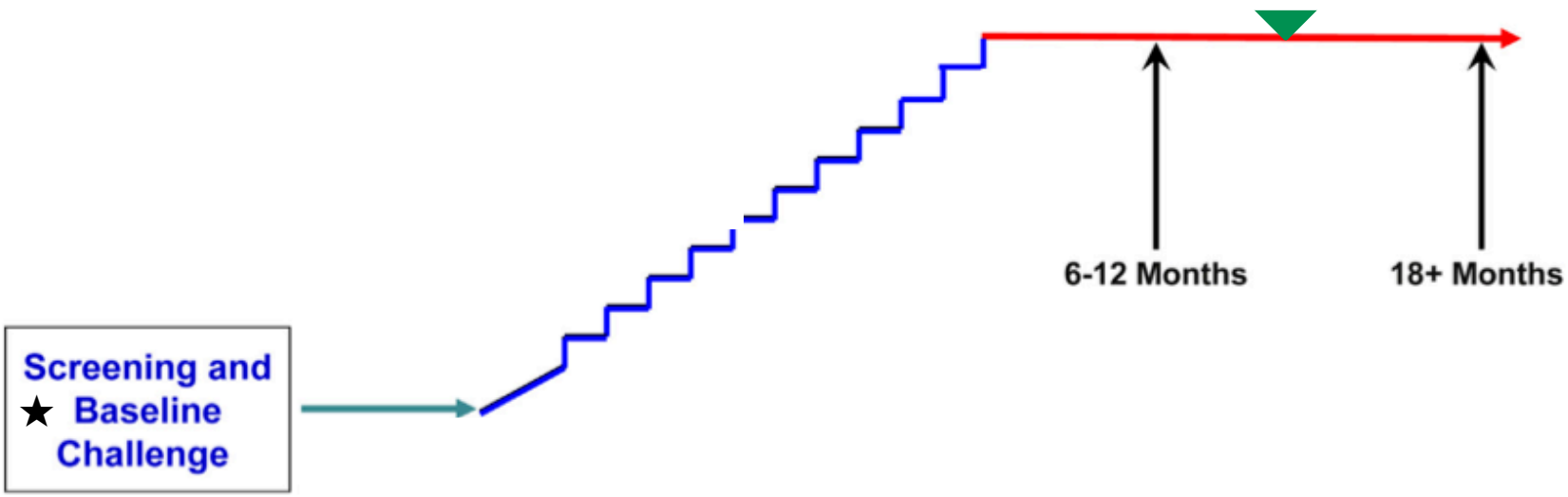


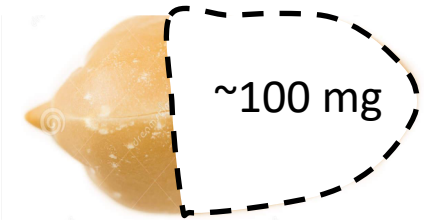
Gradual Allergen Exposures Lessens Reactivity & Changes Immune Response to Treated Allergen

Wambre, Kulis, Patil, Vickery JACI 2018

How is OIT Administered? – Research Unit/Clinic

✓ at home
★ in clinic





Burks et al JACI 2018

Note: challenges are mostly research tools and will not be universally required in routine OIT practice

How is OIT Administered? – Home Environment

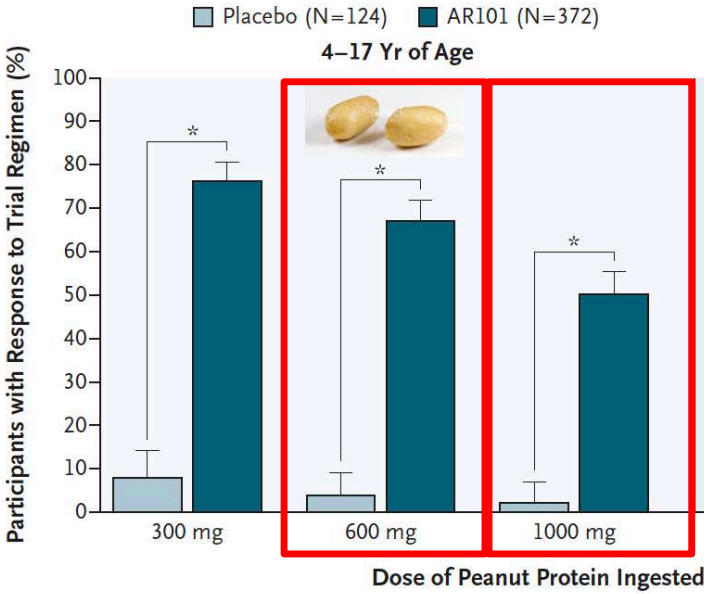
- Remember that 99% of OIT dosing happens at home
- Patient/family must shift mindset from "threat" to "medicine" and:

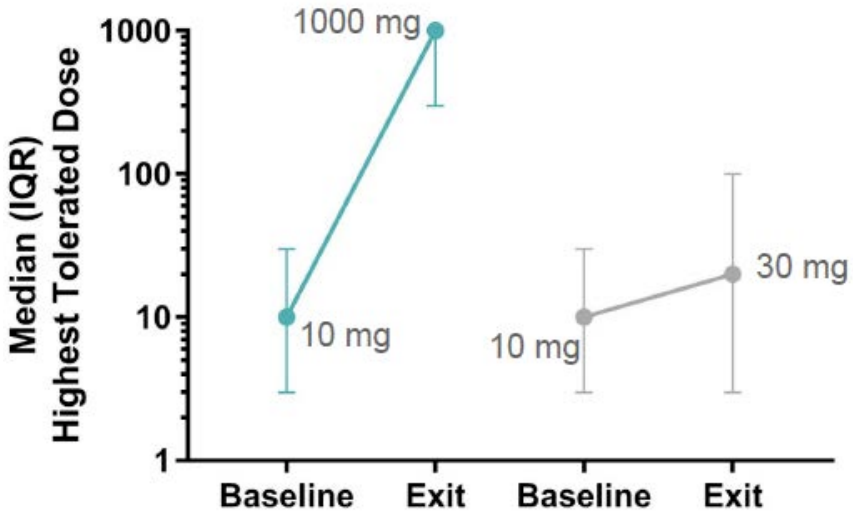
Daily

1. Determine if the child is well enough to dose – **cannot dose when ill**;
2. Prepare the dose properly;
3. Administer the dose - **always on a full stomach**;
4. Assess for any immediate adverse events (AE);
5. If AEs: rescue med? which one? Then what? Call office? ED? EMS?
6. Ensure appropriate post-dosing conditions are maintained - **no vigorous activity / exercise for 2-3hrs; adequate supervision**;
7. Record dose / log adverse events into a data capture system;
8. Take off work / attend regular in-office appointments — Biweekly/ Monthly/ PRN

Indefinitely

Strongest Evidence to Date: PALISADE Trial





- **ITT: 67% (v 4%) tolerated 600 mg**
- **50% tolerated 1000 mg last dose**

Median 100-fold improvement in tolerated dose

Between Subjects

Vickery et al NEJM 2018
Jones et al AAAAI 2018

Other Benefits of OIT

Familiarity

- Easy to understand
- Oral delivery in 5 mins - reassurance of daily dose
- Substantial clinical experience & reproducible trial data

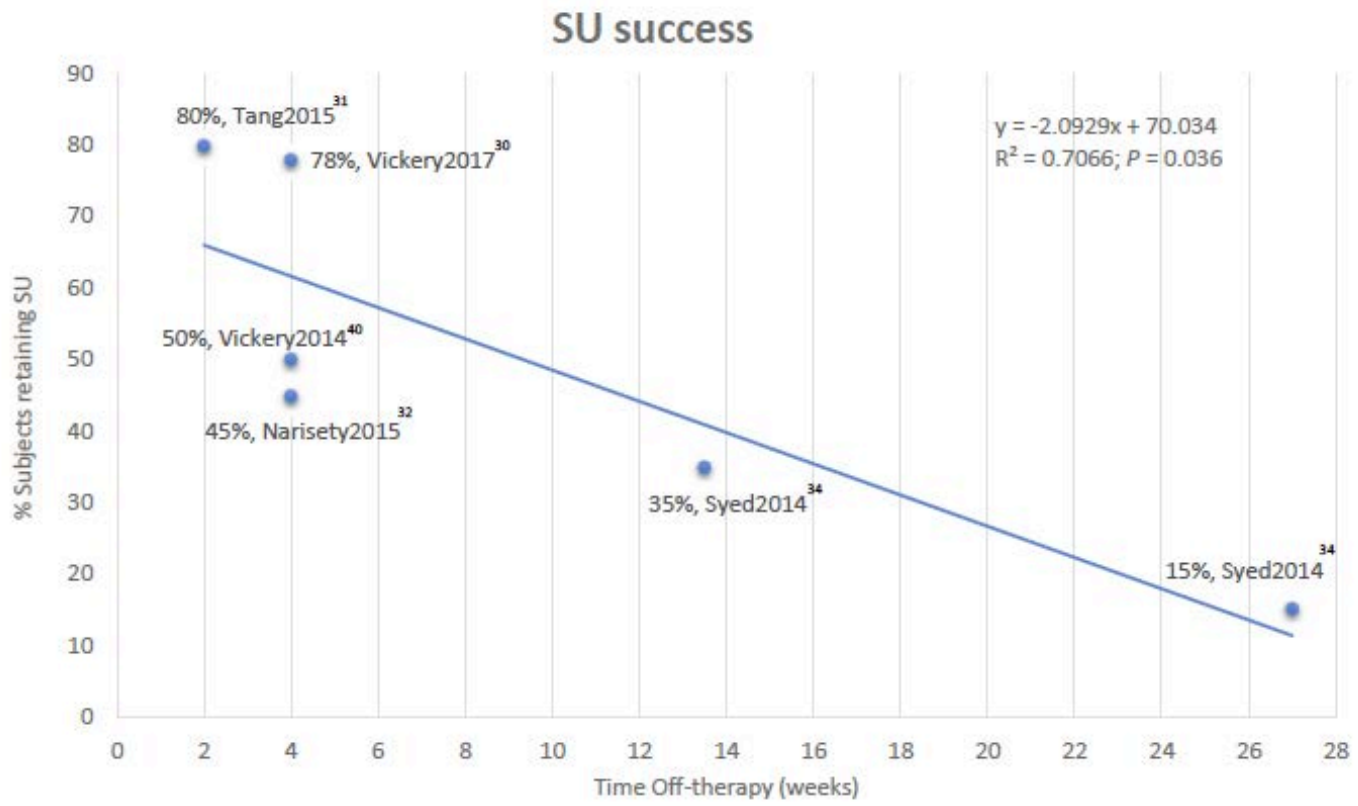
Empowerment

- Taking action
- Facilitating normality – lunch tables, parties, travel – helping "a kid just be a kid"
- Supportive, frequent engagement with OIT team / families

Peace of Mind

- Insurance policy against accidents: mistakes will happen
- Quality of life – complex effects, some do get worse
- Need better tools to measure treatment effects that include value, costs/tradeoffs, burdens, etc

Key Message: OIT is Not Curative



The allergy is always still there in the background. If therapy is interrupted, it can return quickly.

Rodriguez del Rio, Vickery et al JACI 2019
Chinthrajah et al POISED trial Lancet 2019
Many others

THE DAILY BEAST POLITICS ENTERTAINMENT WORLD U.S. NEWS TECH + HEALTH BEASTSTYLE BOOKS

THIS IS NUTS 01.28.15

Researchers Cure Peanut Allergy

"Extraordinary claims require extraordinary evidence."

- Carl Sagan

When doing your OIT homework:

- Be judicious consumers of information
- Question everything you read
- Rely upon basic fundamentals in evaluating claims

h/t Dr. David Stukus @allergykidsdoc

A team of Australian researchers seem to have basically cured the peanut aller
children. The kids were given a daily dose of peanut protein and an increasing

Key Message: OIT Has Known Risks

1. Most participants experience adverse events during OIT
   - GI tract, skin, and respiratory system
2. These are usually mild-moderate & manageable, but can be severe
   - Anaphylaxis: 15-20% of patients or more
   - Eosinophilic esophagitis (EoE): 2-5%, likely underestimate
     - Unclear yet how to predict these more significant events
3. Symptoms lead to withdrawal in 10-20%: usually GI, & within 6-8 wks
4. Importance of "augmentation," or "co-" factors, even in maintenance
   - Infections; post-dose activity/exercise; NSAIDs; empty stomach; menses; sleep deprivation/stress; likely others – e.g. still "unexplained" cases
5. Dose may be important
   - No evidence that high-dose OIT leads to true tolerance but could cause more AEs!

Virkud et al JACI 2016
Vickery et al NEJM 2018
Blumchen et al JACI:Pract 2019
Many others

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Virkud et al JACI 2016
Vickery et al NEJM 2018
Blumchen et al JACI:Pract 2019
Many others

OIT and EoE

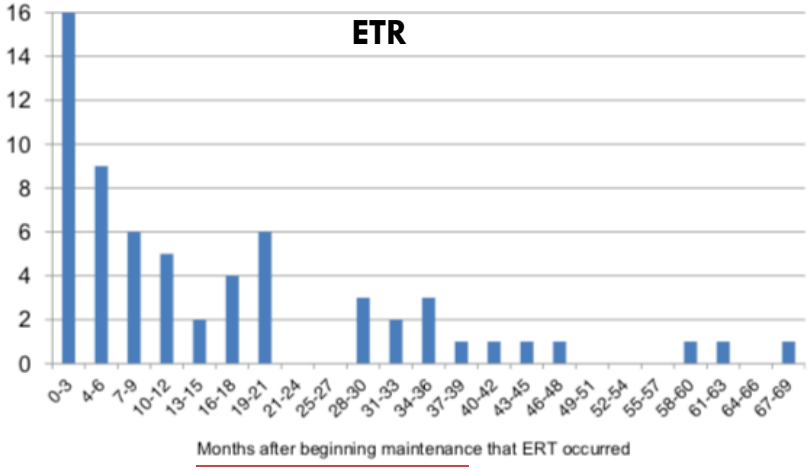
- Repetitive oral administration of allergens to atopic individuals mimics exposures thought to trigger EoE
- Typical rates of "new-onset" EoE diagnosed during OIT range from 2-5%
- But OIT-associated EoE is problematic for at least two reasons:
  1. Many patients drop out of OIT with GI symptoms before being referred for endoscopy, so rates of OIT-associated EoE may be underestimated
  2. Study participants / patients not routinely scoped prior to treatment, and rarely during treatment

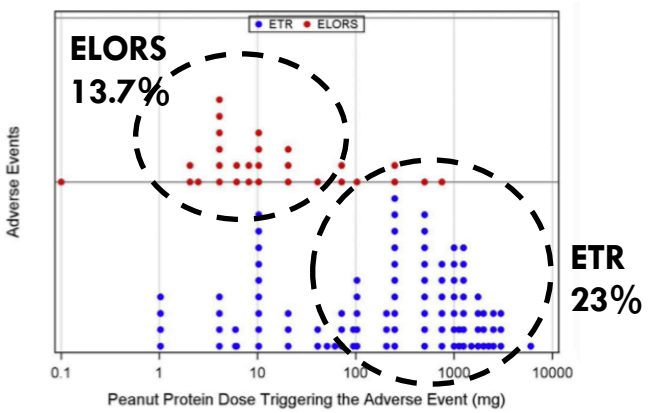
- Remains unknown whether OIT-associated EoE is specifically caused by the OIT allergen, becomes unmasked during OIT, or develops concurrently
- Some groups have tried to "treat through it" by reducing dose
- Discuss with your doctor how you will handle GI events

Lucendo AJ et al . Ann Allergy Asthma Immunol 2014;113:624-9.
Semancik E et al. Pediatr Allergy Immunol 2016;27:539-41.
Many others

Risks May Be Linked to Dosing Regimen: Critical Need for Optimization

- A private practice group reported on 3 years of maintenance OIT @ **2000 mg/d** :
  - 114/270 (42%) stopped, transferred care, or were lost to follow-up (27% in maintenance period)
  - Overall, 23% required epinephrine and 13.7% developed an EoE-like syndrome:



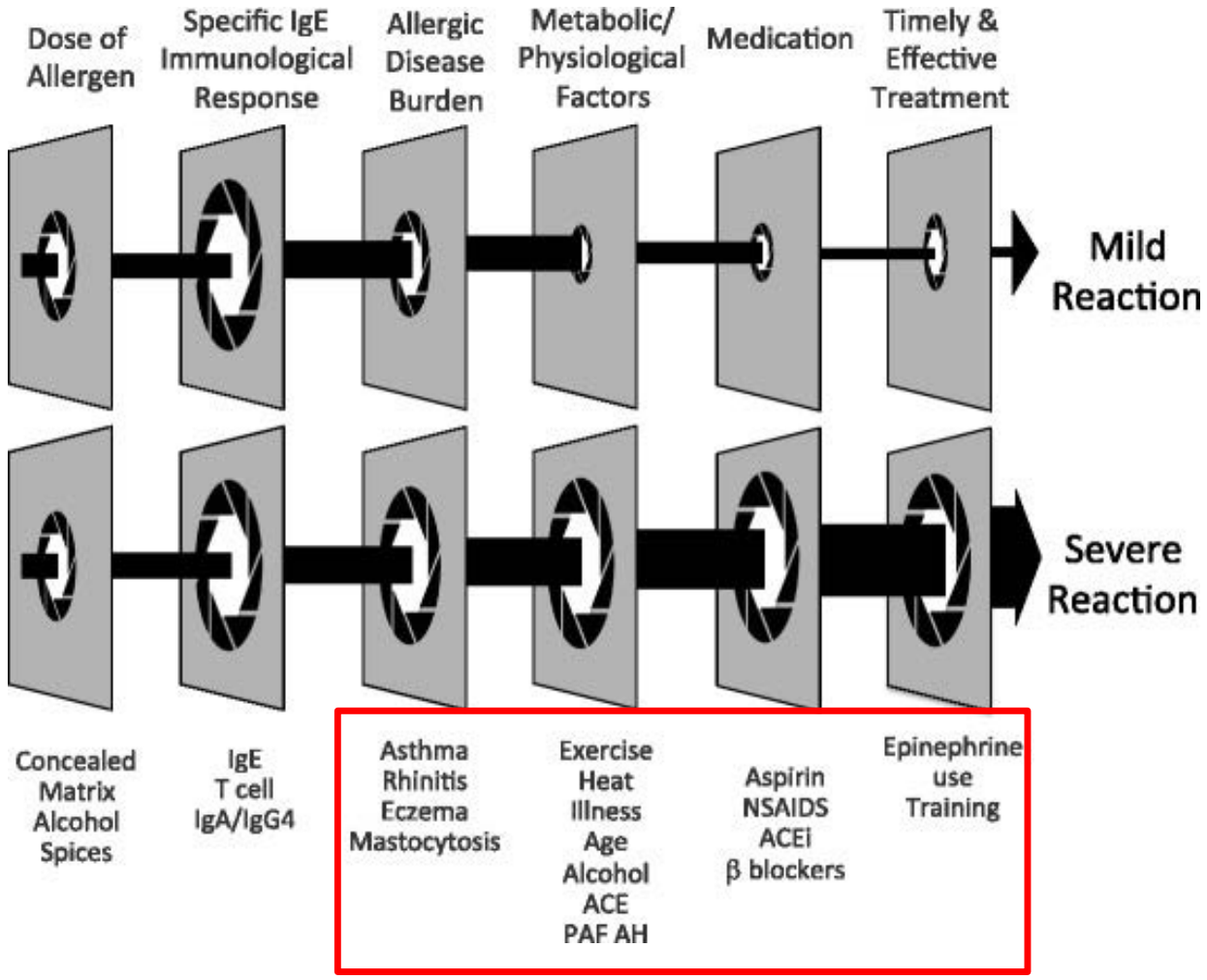


ETR, epinephrine-treated reaction
ELORS, EoE-Like OIT-Related Syndrome

- With very slow up-dosing (~13 mo) and a **125 mg/d** target maintenance dose, 74% of actively-treated patients in Germany achieved desensitization to ≥ 300 mg:
  - Withdrawal rates, SAEs, & objective, OIT-related AEs were low & equal between active & placebo
  - No epinephrine use related to OIT; and no EoE

Blumchen et al JACI:Pract 2019
Wasserman et al JACI:Pract 2019

Risks Clearly Linked to Environmental Factors: Importance of Adhering to Dosing Instructions



★

Smith PK et al WAOJ 2015

What is OIT?

Is OIT Right For Our Family?

What Does The Future Hold?

Children's℠ Healthcare of Atlanta

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Five Key Questions – I

1. Is the diagnosis correct?
   - High false-positive test rate in food allergy; some may need oral challenge first

2. Are there any other allergic diseases & how well-controlled are they?
   - Confirmed or suspected EoE should be disqualifying; also severe and/or poorly-controlled asthma
   - Even mild asthma / atopic dermatitis can flare and should be optimally managed
   - Allergic rhinitis may be a risk factor and starting injections may be difficult

3. Do we have the time? Can we make the lifestyle adjustments?
   - Updosing visit schedules
   - Parent / caregiver transition to “nursing” role
   - Guidelines around dosing administration

Five Key Questions – II

4. Are our expectations realistic? In tune with child's desires?
   - Not curative: sustainable long-term plan for treatment
   - Risks of allergic symptoms: comfort giving doses of OIT/epinephrine

5. How comfortable are we with the practice environment?
   - Experience/familiarity with food allergy & OIT
   - Intended treatment plan: material, dose, regimen – huge variations across practices
   - Support & communications infrastructure
   - Ease of access to a provider, associated costs
   - Might be good to get a couple of different opinions

Patient Selection: Fundamentals

- Two main goals of patient selection: to identify good candidates with *actual food allergy* while minimizing dependence on OFCs.

- The history of reaction to the allergenic food is critical in this selection:
  - Scenario 1: Recent history with unequivocal, objective signs of anaphylaxis
  - Scenario 2: Distant history of objective allergic reaction
  - Scenario 3: Vague / subjective / no signs or symptoms

- In Scenario 1, any positive test result (SPT, specific- or component-IgE test) is essentially diagnostic.
  - These individuals could be considered candidates for therapy without an OFC
  - Warnings: severe/life-threatening anaphylaxis, severe/poorly controlled asthma, and EGID

- **In the other scenarios, further evaluation is warranted before determining whether therapy can be recommended.**
  - A reliable biomarker that accurately predicts allergy would be immensely helpful

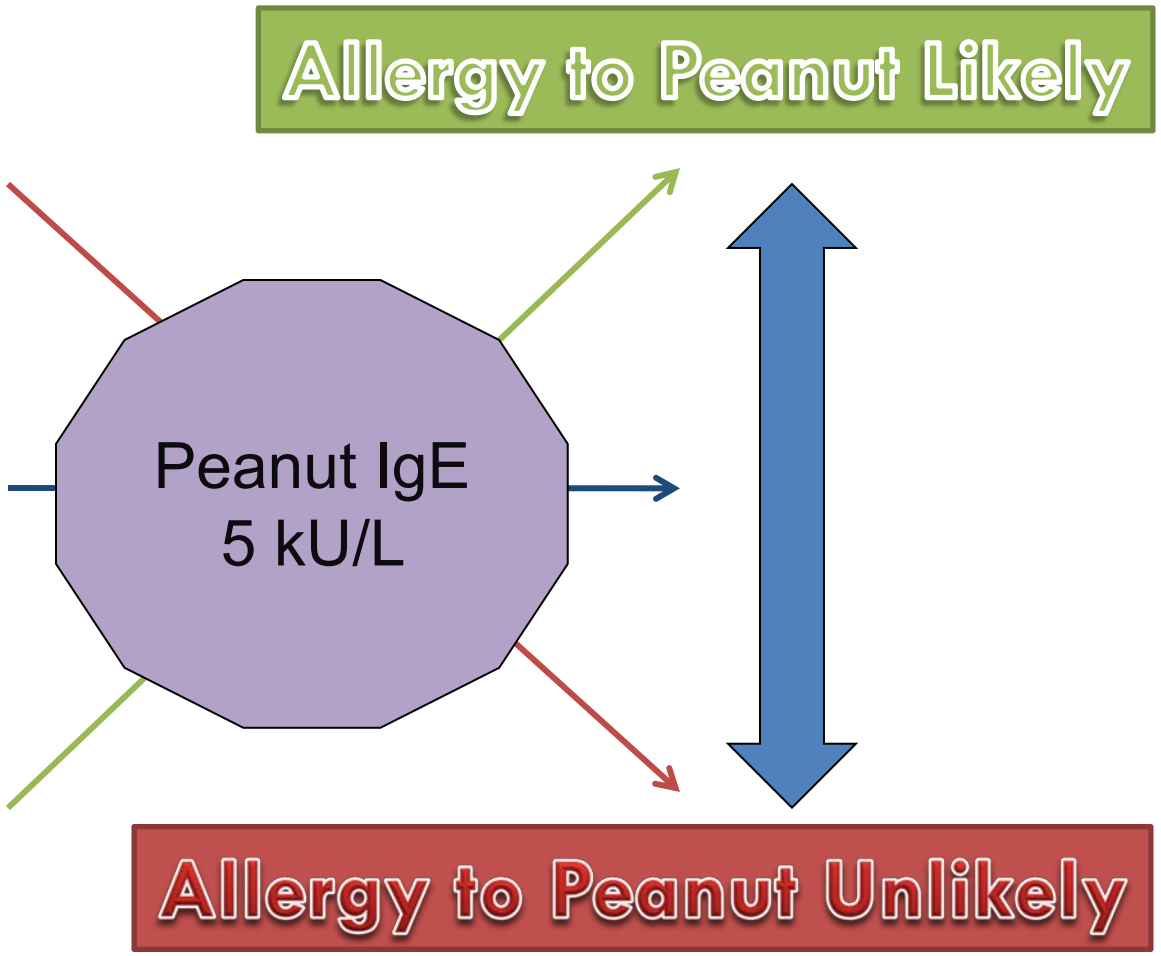
Sicherer and Wood, J Allergy Clin Immunol Pract 2017
Roberts and Lack, JACI 2005

Diagnosis Depends Critically on History:
Treat the patient, not the number!

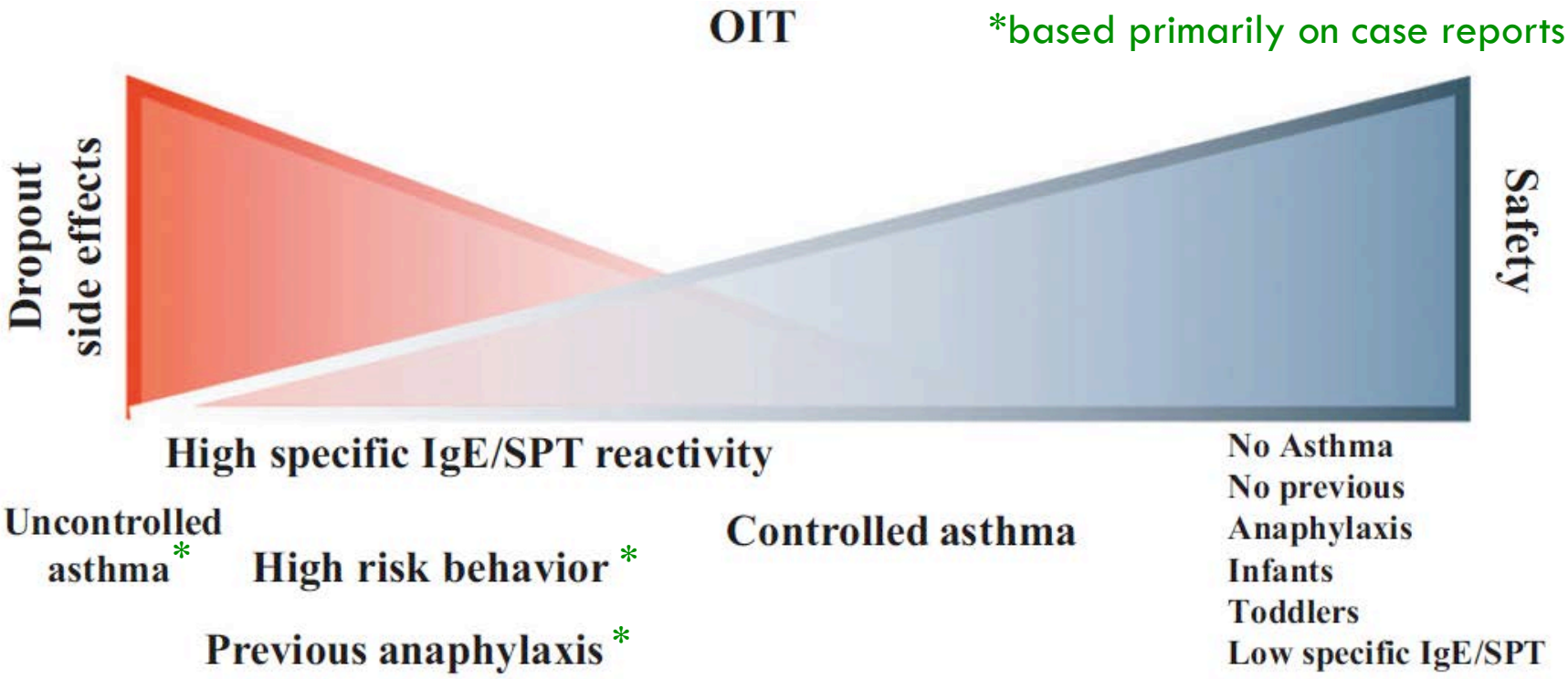
Pt 1: Allergic to shrimp; loves to eat peanut butter

Pt 2: Flare of atopic dermatitis after peanut exposure

Pt 3: Hives, vomiting, and wheeze with peanut



Can We Predict Response to OIT? Still Early Days



Anticipate Forthcoming Guidance from FARE Summit, AAAAI/ACAAI, and Other Organizations

Blumchen & Eiwegger Allergy 2019

Speak With Your Doctor!

American College of Allergy, Asthma & Immunology | allergist

AllergyAndAsthmaRelief.org

Should My Child Try Peanut Allergy Treatment?

Use this discussion guide to help decide if the treatment is right for your child

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Children's[SM] Healthcare of Atlanta

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The Next Decade

"There's a cure—but it's light-years away."

The New Yorker

Moving Forward: Clinical Translation

PHASE 3

FDA Approval of First Peanut Allergy Treatments

1. Changing Practice

- Building new models of access, care delivery & reimbursement
- Implementation, patient selection, etc.

How do we close the research-to-practice gap in food allergy?

2. New T3/T4 Research Questions

- Health economics & outcomes research
- Comparative effectiveness
- Biomarker discovery - "precision"

How can these therapies be optimized?

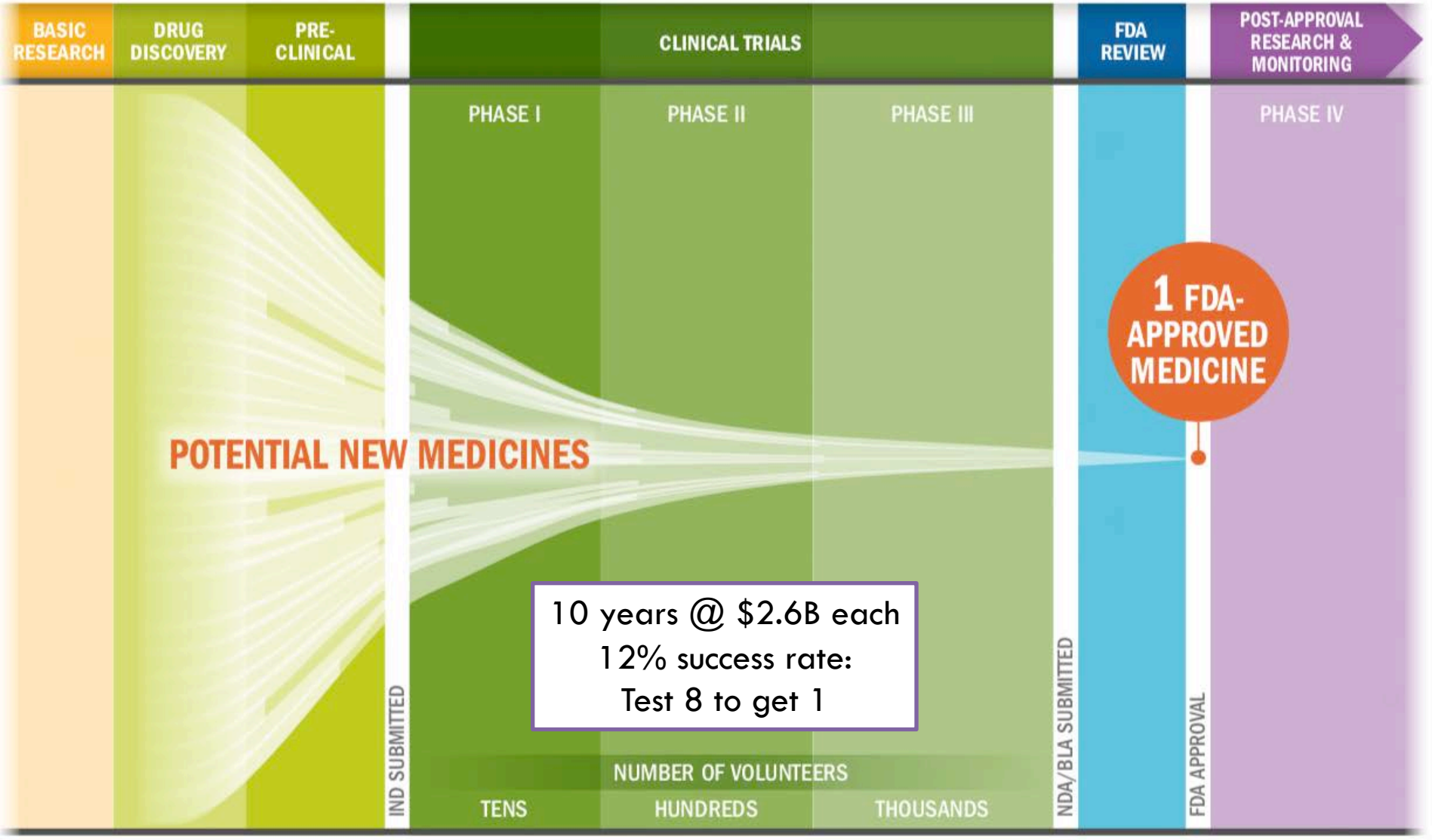
3. Next-gen Clinical Trials

- New molecules
- New targets
- New / multiple foods

What does a cure look like?

Parallel advances in:
Multicenter Networks
Biotechnology
Massive patient-level data
Informatics/Computing

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

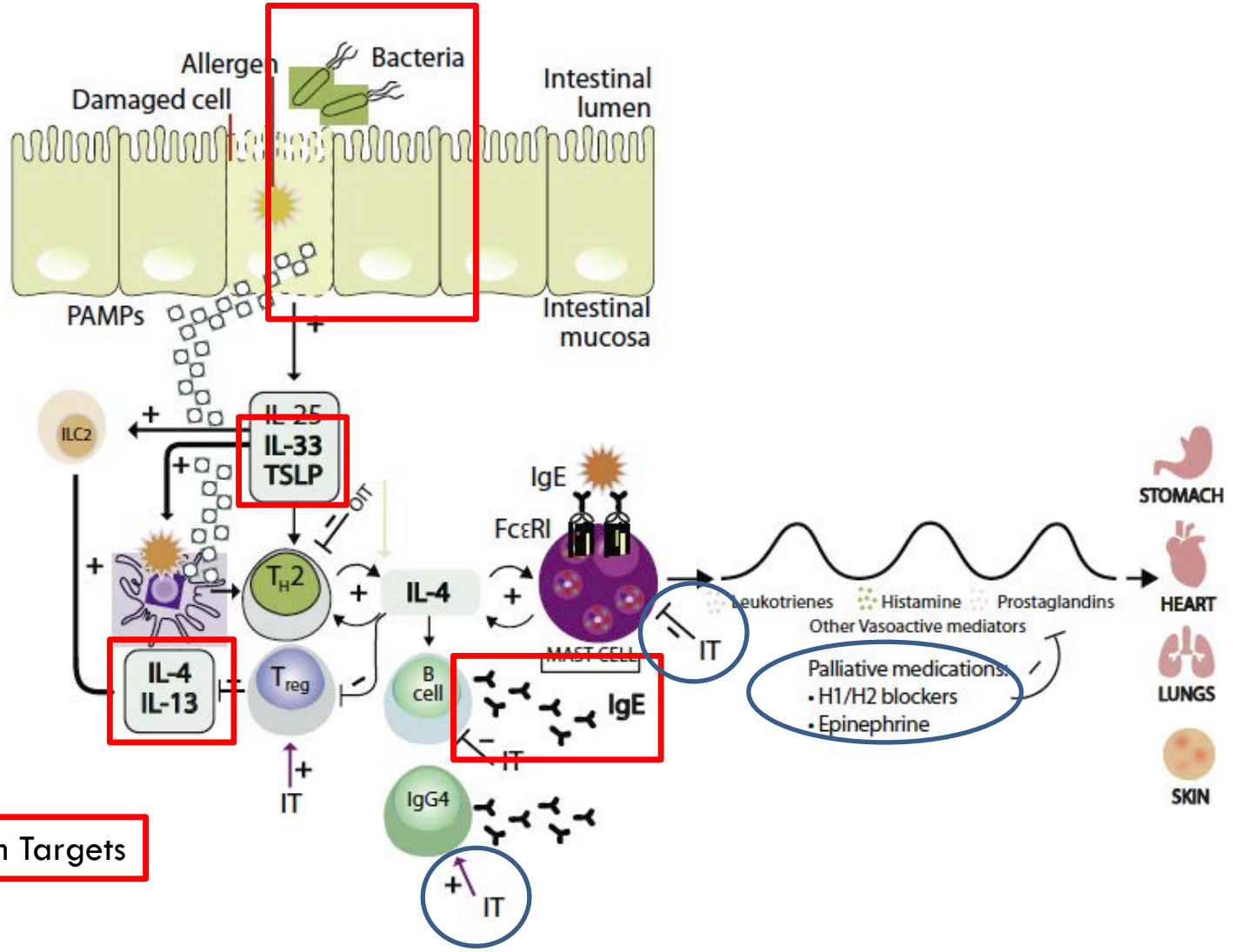


10 years @ $2.6B each
12% success rate:
Test 8 to get 1

Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

phrma.org

Current Focus on "Allergen-Plus:" Combining OIT With An Improved Understanding of Disease



5 Hard Questions We Must Answer To Move Forward

1. How do patients and families define success? What are their goals and what are they willing to give to achieve these goals?
   - "bite-proof" protection? High-threshold/free eating? Remission? Cure?
2. Is that really aligned with what doctors and researchers want?
   - How can we measure these outcomes in a rigorous, standardized way?
3. What do these treatments really offer?
   - Degree of protection
   - Duration of protection
   - Food-specific or more generalized protection
   - Long-term acceptability and adherence
4. For whom is the risk / benefit equation acceptable?
5. Will treatment be cost-effective? How do we define value?

From here, we can start to identify which treatment (if any) is best for which patient…

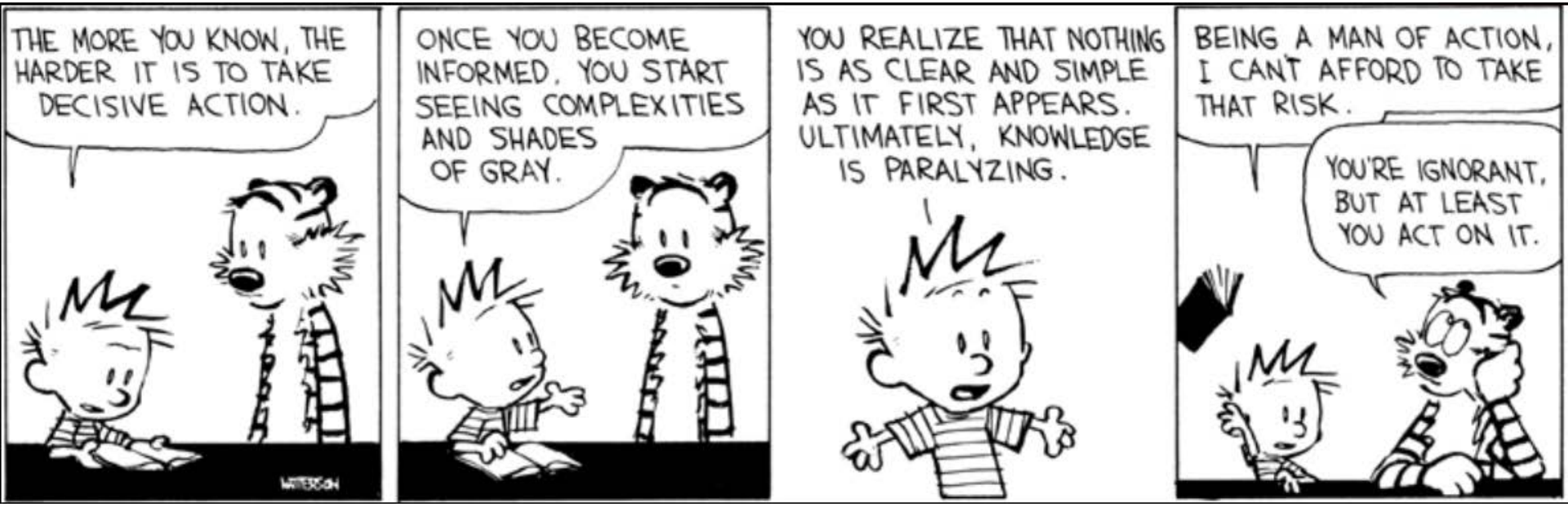
Credit: Dr. Bob Wood

Should we pursue OIT?

Will other treatments be available? When?

The Coming Decisional Dilemma in Food Allergy

Should we wait?



What are the long-term consequences?

What does my child want?

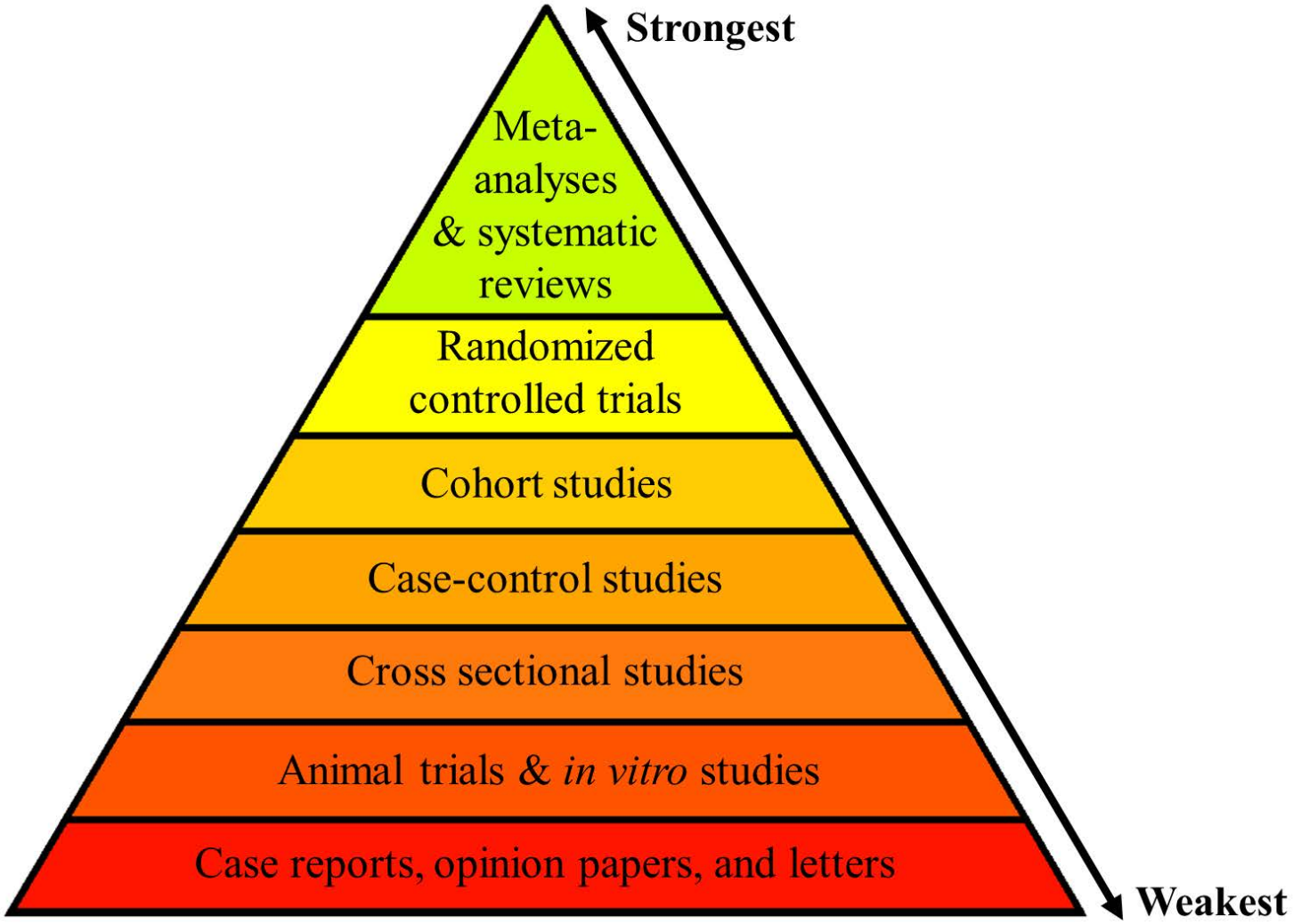
Which doctor?

Which protocol?

Which food(s)?

Can we afford it?

Hierarchy of Scientific Evidence



thelogicofscience.com

Reasonable Expectations for the Next 5-10 Years

1. Widespread utilization of real-world OIT with Palforzia™ and also other non-FDA-approved food-based approaches
   - Improvement/alignment in outcome measures, dosing regimens, patient selection, availability of biomarkers
2. Additional FDA / EMA approvals and label expansions for standardized IT products
   - New peanut products, age groups
   - Egg, tree nut(s), milk (?)
   - Multi-allergen?
3. Continued development & clinical use of “allergen-plus” strategies
4. Other therapeutic strategies move into late stage development
   - New specific immune-modulating approaches: modified allergens; nanotech
   - New non-specific approaches: biologics; microbiome manipulation

Where We Are Now

- "Educated guess" dosing strategy
- Poorly defined endpoints
- "All comers" → heterogeneity
- Physician voice > patient voice

Where We Need to Go

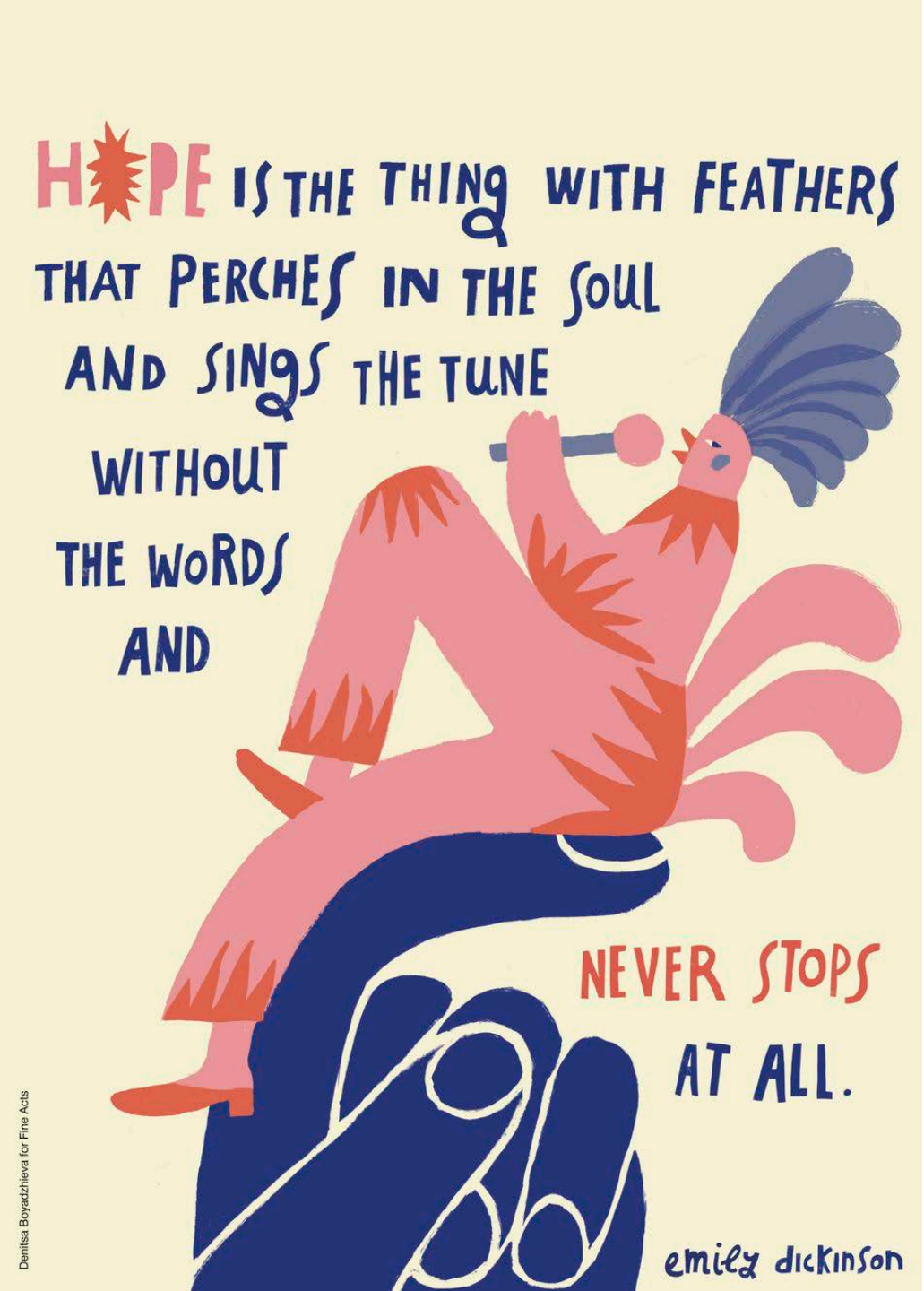
- "Educated guess" dosing strategy
- Poorly defined endpoints
- "All comers" → heterogeneity
- Physician voice > patient voice

- Rational dosing strategy
  1. Evidence-based
  2. Driven by biology
- Clear, reproducible endpoints
- Precision patient selection
- Patient voice ≥ physician voice

Key Messages

1. Food allergy is at an inflection point, with OIT (especially for peanut allergy) poised to become a much more widely available treatment.
2. Clinical trials and real-world experience show that OIT can produce high rates of desensitization and clinically meaningful improvement.
3. OIT has known risks and tradeoffs, and is not right for all patients.
4. No study has ever convincingly shown that OIT is curative.
5. We have much more to learn about how best to implement OIT in routine care; how to build on it and improve it; and how it will fit in a rapidly changing treatment landscape.

We are now at the dawn of the treatment era in food allergy: the future is bright!

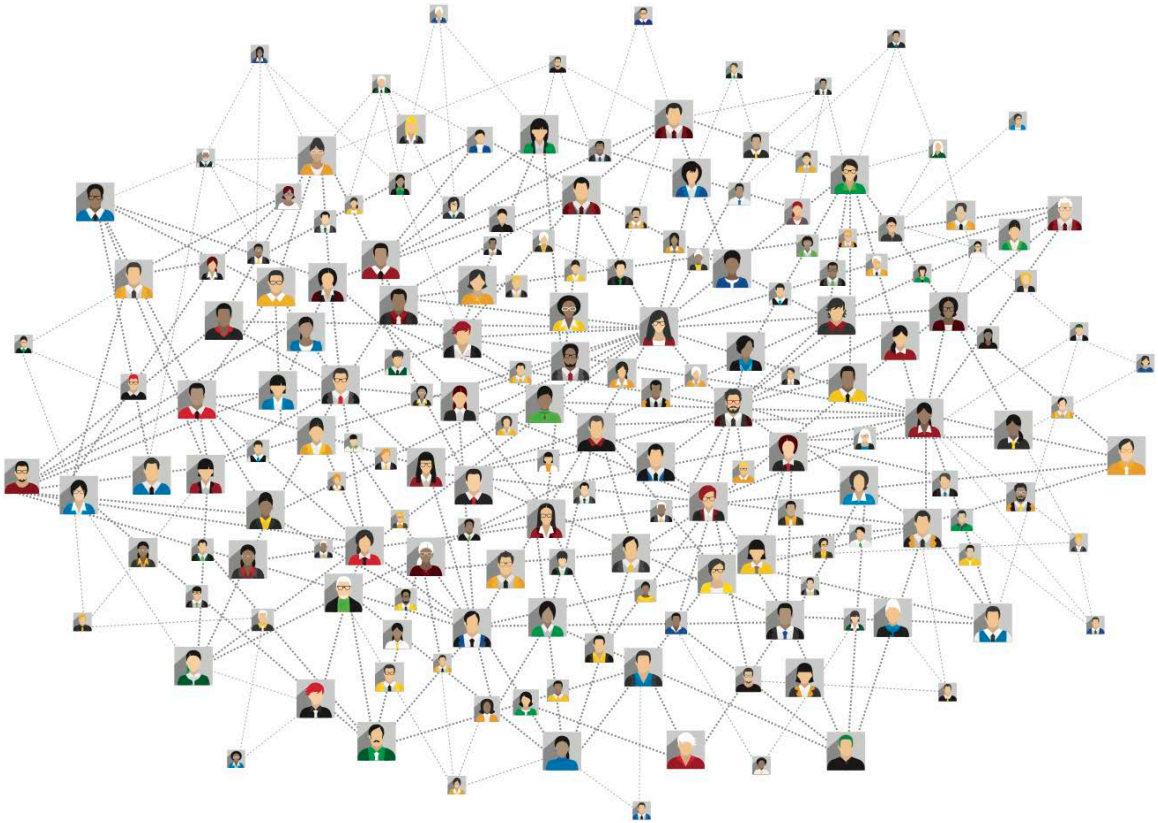


#WashYourHands
#BeKind
#StayStrong
#ThankYou

@ATLergist

YOUR Food Allergy Story Drives Research Forward

FARE Patient Registry®



The FARE Patient Registry connects people living with food allergies to researchers seeking answers.

Join in 3 easy steps:

1. Enroll for free
2. Create your confidential patient profile
3. Take our surveys

JOIN TODAY at FAREregistry.org

Thank you!