The “State of the Art” in Food Allergy

Brian P. Vickery, MD
Professor and Chief of Allergy/Immunology
Marcus Professor of Pediatric Immunology

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Children's Healthcare of Atlanta

EMORY UNIVERSITY

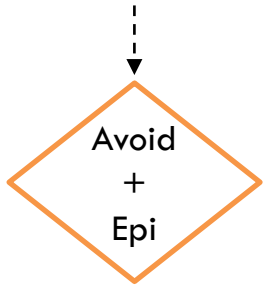
Disclosures

- Employment: Pediatric Institute of Emory University + Children's Healthcare of Atlanta
- Consultant/Advisor: Aimmune Therapeutics; Aravax; DBV; FARE; IgGenix; Novartis; Reacta Biosciences; Regeneron; Revolo; Sanofi; Stallergenes Greer
- Grant support: NIH-NIAID; FARE
- Clinical investigator: Aimmune; Aravax; AstraZeneca; DBV; Genentech; Novartis; Regeneron; Siolta
- Equity interests/stock ownership: Moonlight (stock options)

Considerations for Today's Discussion

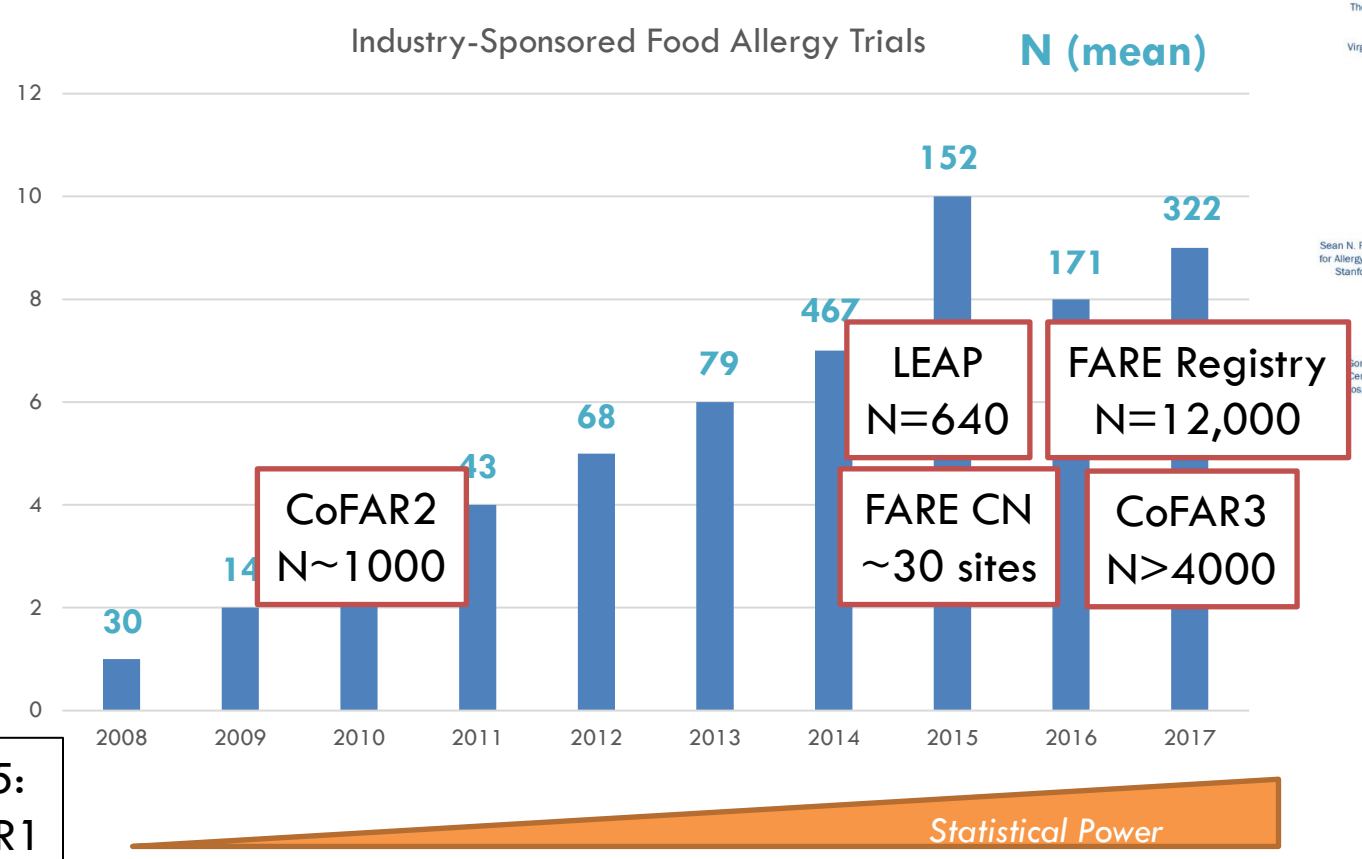
- Food allergy is a young field, recently evolving from small proof-of-concept studies performed at a handful of centers to a global network conducting large-scale pivotal trials.
- This has resulted in the first two (but probably not the last) successful BLAs, ushering in a new era in active food allergy management aimed at allergen desensitization.
- Successful translation of clinical trial data into practice in every disease area is always limited by generalizability, bias, and other issues that require the generation of additional real-world evidence (RWE). Food allergy has unique challenges in translation – lack of daily symptoms, limited understanding of phenotype/risk, proxy endpoints, etc.
- We are only just now poised to encounter these problems in food allergy practice but haven't developed a robust research infrastructure to deal with them.
- Unless these gaps are addressed in a collaborative and patient-centered way, we may have more and more treatments available - a good thing - without really knowing which one(s) work best to improve overall health and quality of care - not a good thing.

Historical Approach to Food Allergy Management

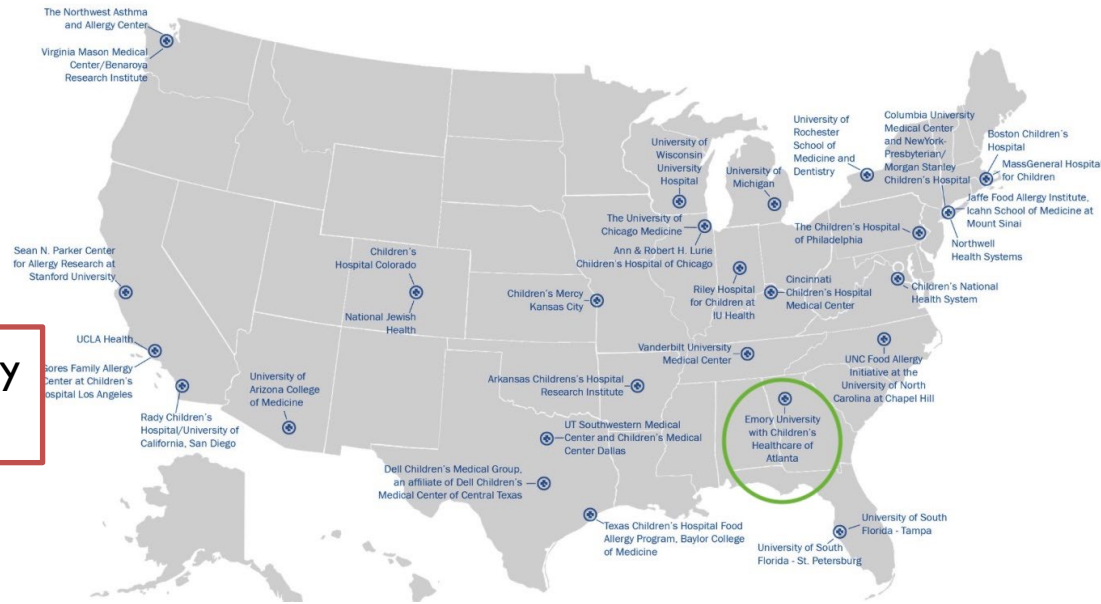


To Improve Care in 2008: Develop New Therapies

The Most Important Food Allergy Technology Over the Past 20 Years



2005:
CoFAR1
Starts
(5 sites)



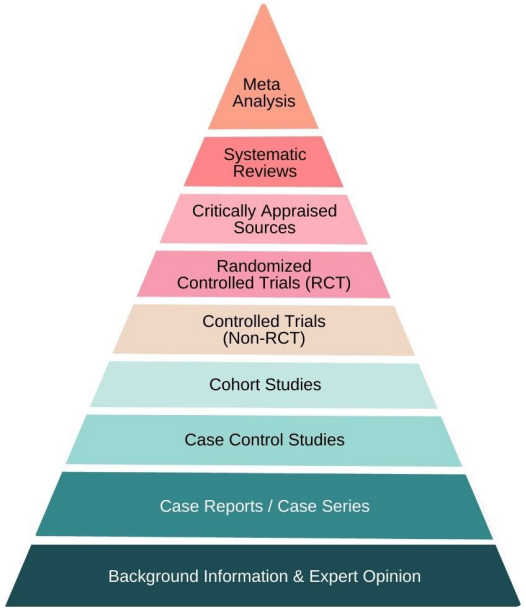
Plus extensively experienced sites / CROs in:

- UK
- Ireland
- France
- Germany
- Spain
- Italy
- Netherlands
- Denmark
- Canada
- Australia

source: clinicaltrials.gov

Evidence From Large RCTs & SR/MA Increasingly Inform Practice

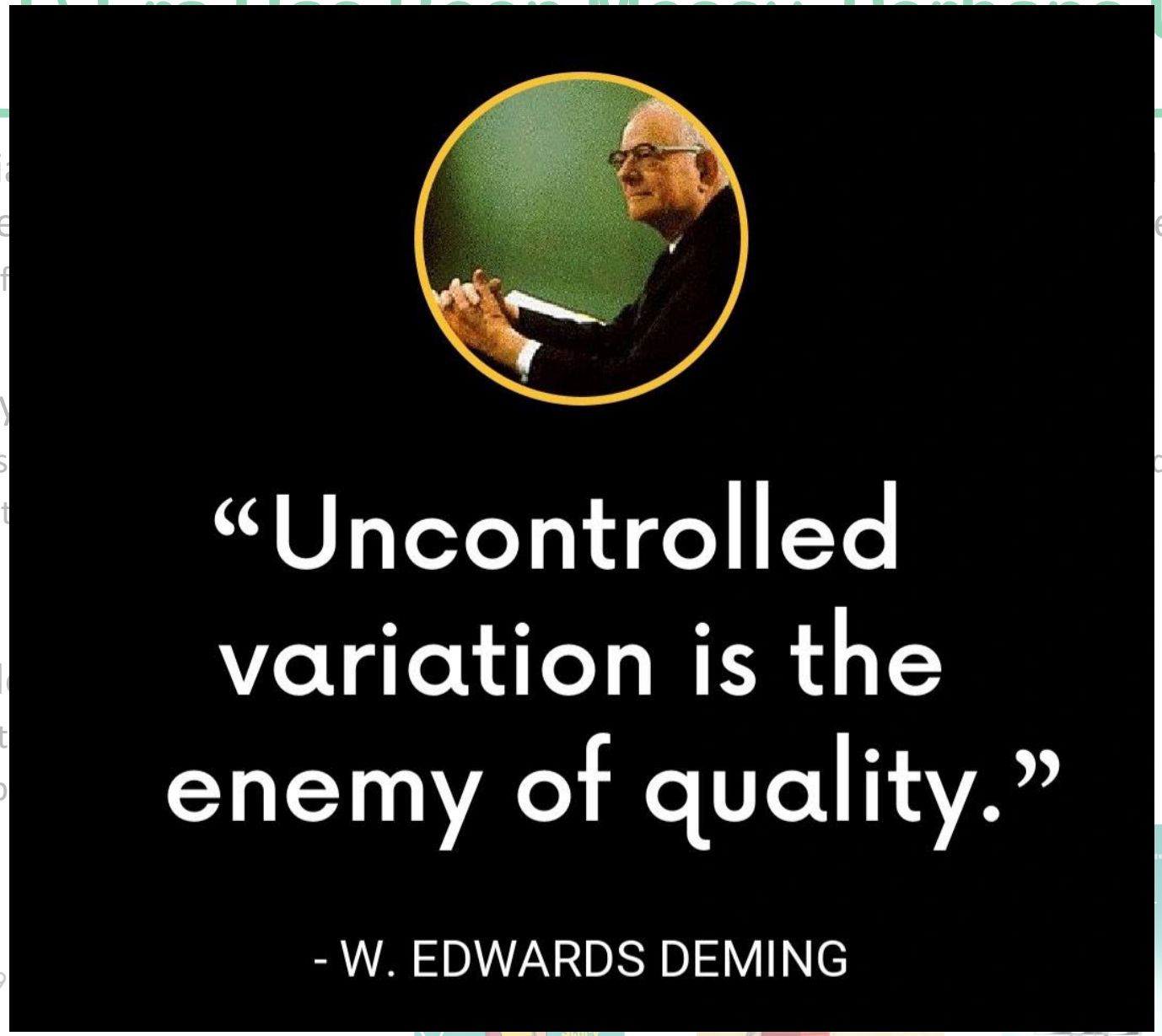
	Sample size	Risk ratio* (95% CI)	Anticipated absolute effects (95% CI) per 1000 individuals			Grades of evidence	Main findings†‡§
			No OIT	OIT	Risk difference		
Anaphylaxis	9 RCTs; 891 participants	3·12 (1·76–5·55)	71¶	222 (125–394)	151 (54–323)	High	Peanut OIT results in large increase in anaphylaxis; NNT_H 7 (3–19); IRR 2·72 (1·57–4·72)
Epinephrine use‡	9 RCTs; 984 participants	2·21 (1·27–3·83)	37	82 (47 to 142)	45 (10–105)	High	Peanut OIT results in large increase in epinephrine use; NNT_H 22 (10–100); IRR 2·87 (1·70–4·85)
Serious adverse events	12 RCTs; 1041 participants	1·92 (1·00–3·66)	62‖	119 (62–227)	57 (0–165)	Moderate**	Peanut OIT probably increases serious adverse events (death, life threatening, disability, or requiring urgent medical intervention or hospitalisation to prevent these events); NNT_H 18 (6–5376)
Vomiting, representative of gastrointestinal reactions††	6 RCTs; 755 participants	1·79 (1·35–2·38)	186	334 (252–444)	147 (65 to 257 more)	High	Peanut OIT results in large increase in vomiting frequency; NNT_H 6 (4–14); IRR 2·11 (1·54–2·89)
Angioedema, representative of mucocutaneous reactions‡‡	5 RCTs; 694 participants	2·25 (1·13–4·47)	39	88 (44–174)	49 (5 to 135 more)	High§§	Peanut OIT increases angioedema; NNT_H 20 (7–200); IRR 2·51 (1·79–3·51)
Nasal congestion or blockage, representative of respiratory reactions§§	6 RCTs; 724 participants	1·36 (1·02–1·81)	178	241 (181–321)	64 (4 to 144 more)	Moderate¶¶	Peanut OIT probably increases nasal congestion or blockage (rhinitis); NNT_H 16 (7–250); IRR 1·48 (1·04–2·10)
Surrogate for exposure to peanut outside of clinic without a reaction: passing a supervised food challenge in-clinic	9 RCTs; 917 participants	12·42 (6·82–22·61)	32	397 (218–723)	365 (186 to 691 more)	High‖‖	Peanut OIT results in large increase in completing a supervised oral food challenge without an allergic reaction, but this does not translate into less reactions outside of clinic; for every gram increase in total cumulative challenge dose, the chance of passing decreases by 26%; NNT 3 (1–5)

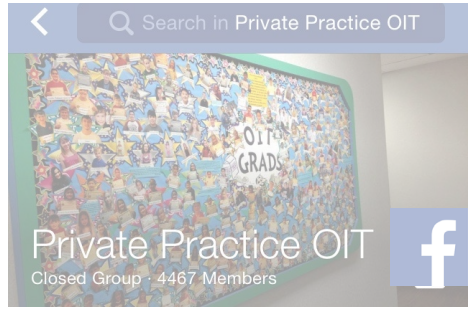


Chu et al Lancet 2019

The AIT (OIT) Era Has Been Messy, Perhaps Uniquely

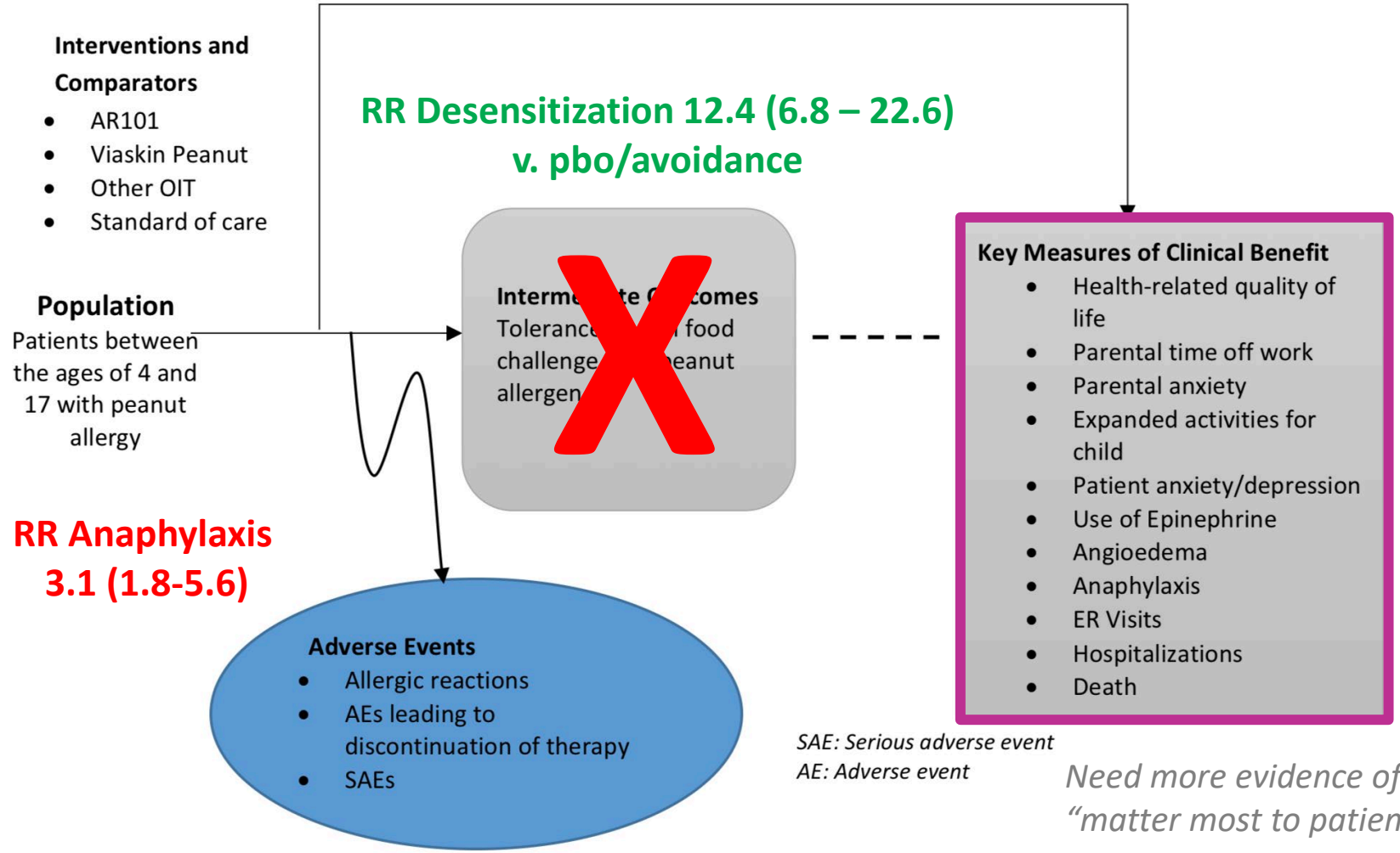
- Outcomes – especia / measured / reporte es
  - No understanding of
- OIT demands lifesty
  - Resource limitations d
  - Baseline impairment with adoption
- OIT can be easily cl
  - A path of least resist
  - Proliferation of besp





Chu et al Lancet 2019
Dunlop and Keet JACI: In Pract 2019
Patrawala et al JACI: In Pract 2021
Leef et al JACI: In Pract 2021

The Effectiveness Gap in FA Research:
We Don't Directly Measure True Benefit to Patients



Need more evidence of outcomes that "matter most to patients"

https://icer.org/wp-content/uploads/2020/10/ICER_PeanutAllergy_Final_Report_071019.pdf
Chu et al Lancet 2019

Special Article

Varying Approaches to Management of IgE-Mediated Food Allergy in Children Around the World

Melanie Lloyd, PhD[a,b], Paxton Loke, MBBS, PhD, FRACP[a,c,d], Douglas P. Mack, MD, MSc, FRCPC[e], Scott H. Sicherer, MD[f], Michael R. Perkin, PhD[g], Robert Boyle, MBChB, PhD[h], Agnes Sze Yin Leung, MBChB[i,j], Bee Wah Lee, MBBS, MMed(Paeds), FRCPChMD[k], Michael Levin, MBChB, PhD[l], Katharina Blumchen, MD[m], Alessandro Fiocchi, MD[n], Motohiro Ebisawa, MD, PhD[o], Lucila Camargo Lopes de Oliveira, MD, PhD[p], and Mimi L.K. Tang, MBBS, PhD[a,d,q] *Parkville, VIC, Australia; Hamilton, ON, Canada; New York, NY; London, United Kingdom; Shatin, Hong Kong; Singapore; Cape Town, South Africa; Frankfurt, Germany; Rome, Italy; Sagamihara, Japan; and São Paulo, Brazil*

Guidelines or Practice Statements Around the World Recommending Food Immunotherapy?

- Canada (CSACI) – yes, broad support across ages and foods
- EU (EAACI) – yes, milk, egg, peanut only; in specialized centers only; not in adults or young children
- Japan – yes but predominantly in research-intensive centers only
- UK, Singapore, Hong Kong, South Africa, Brazil – no guidelines
- Australia (ASCIA) – OIT not recommended
- US (NIAID, JTFPP)….crickets

Although OIT is an increasingly mainstream therapy, there remains considerable uncertainty about its use

Lloyd et al JACI: In Pract 2023

FDA NEWS RELEASE

FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure

More Press Announcements

For Immediate Release: February 16, 2024

Español

Today, the U.S. Food and Drug Administration approved Xolair (omalizumab) injection for immunoglobulin E-mediated food allergy in certain adults and children 1 year or older

Content current as of:
02/16/2024

Regulated Product(s)
Drugs

"Omalizumab is indicated for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy. Omalizumab is to be used in conjunction with food allergen avoidance."

Early Trials of Anti-IgE Monotherapy for Peanut Allergy

- Dose-dependent desensitization seen with 4 monthly doses of TNX-901 (talizumab) in 84 peanut-allergic participants aged 12 – 60y
  - 450 mg superior to placebo ($p<0.001$); **~16x threshold increase**

- 24-week Phase 2 RCT of omalizumab @ 0.016 mg/kg/IgE was planned in 150 peanut-allergic participants aged 6 – 75y but stopped per DSMB recommendation due to severe screening DBPCFC reactions
  - Those already enrolled were allowed to finish and exit:
    - N=14 completed the study: 9 active (**80x threshold increase**) and 5 placebo (4x increase) [p=0.054]

- 6 month single-center study of omalizumab in 14 peanut-allergic participants aged 18 – 50y dosed per package insert, with mechanistic analyses determining subsequent challenges
  - Median **56x threshold increase** (range 3-1000) after 20-77 days of treatment

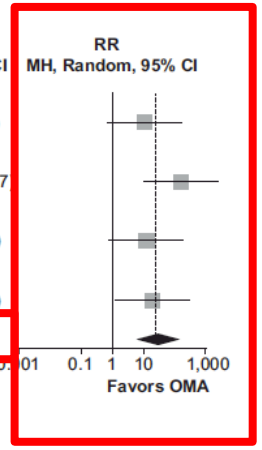
Clinical responses to anti-IgE were variable and were not clearly related to free IgE or other biomarkers

Leung et al NEJM 2003
Sampson et al JACI 2011
Savage et al JACI 2012

Real-World Effectiveness of Omalizumab Monotherapy from Observational Studies

Study or subgroup	Population	Time point	Experimental Events	Experimental Total	Control Events	Control Total	Weight	RR MH, Random, 95% CI
Successfully consumed multiple allergic foods								
Lefevre 2016[50]	Food allergy	22 wk	5	8	0	8	24.9%	11.00 (0.71–169.42)
Highest tolerated dose, ≥1200 mg								
Azzano 2021[58]	Food allergy		76	181	0	181	24.2%	153.00 (9.56–2,449.57)
Restriction free diet								
Alba Jordá 2019[55]	Food allergy		6	6	0	6	26.3%	13.00 (0.91–186.42)
Achieved tolerance to all foods								
Fiocchi 2019[56]	Food allergy	17 wk	9	15	0	15	24.6%	19.00 (1.21–298.79)
Total (95% CI)							**100.0%**	**24.88 (6.35–97.45)**

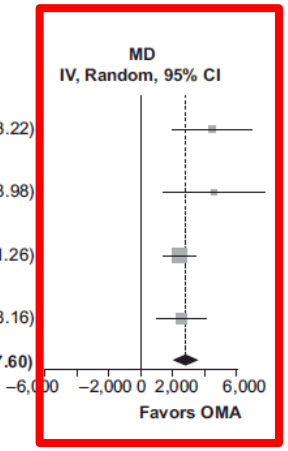
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 2.26$, df = 3 ($P = .52$); $I^2 = 0\%$
Test for overall effect: Z = 4.61 ($P < .001$)



Across different outcome definitions

Study or subgroup	Population	Time point	MD	SE	Weight	MD IV, Random, 95% CI
Food tolerance threshold of egg						
Fiocchi 2019[56]	Food allergy	17 wk	4,470.59	1,246.26	10.4%	4,470.59 (2,027.96–6,913.22)
Food tolerance threshold of wheat						
Fiocchi 2019[56]	Food allergy	17 wk	4,588.23	1,602.45	6.3%	4,588.23 (1,447.48–7,728.98)
Food tolerance threshold of milk						
Fiocchi 2019[56]	Food allergy	17 wk	2,409.09	511.32	57.4%	2,409.09 (1,406.92–3,411.26)
Food tolerance threshold of baked milk						
Fiocchi 2019[56]	Food allergy	17 wk	2,541.66	778.84	26.0%	2,541.66 (1,015.16–4,068.16)
Total (95% CI)					**100.0%**	**2,794.89 (2,002.19–3,587.60)**

Heterogeneity: $\tau^2 = 23{,}716.65$; $\chi^2 = 3.73$, df = 3 ($P = .29$); $I^2 = 20\%$
Test for overall effect: Z = 6.91 ($P < .001$)

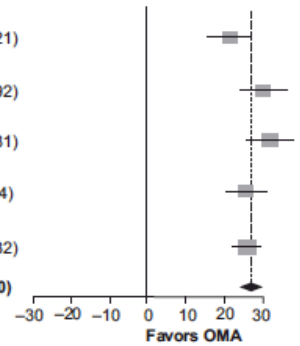


Across different food allergens

Parental judgment of QoL

Study or subgroup	Population	Time point	MD	SE	Weight	MD IV, Random, 95% CI
Cognitive functioning PedSQL, parental judgment						
Fiocchi 2019[56]	Food allergy	17 wk	21.50	2.91	17.6%	21.50 (15.79–27.21)
Emotional functional PedsQL, parental judgment						
Fiocchi 2019[56]	Food allergy	17 wk	30.25	2.89	17.8%	30.25 (24.58–35.92)
Physical functoning PedsQL, parental judgment						
Fiocchi 2019[56]	Food allergy	17 wk	31.90	3.01	16.9%	31.90 (25.99–37.81)
Social functioning PedSQL, parental judgment						
Fiocchi 2019[56]	Food allergy	17 wk	25.75	2.65	19.5%	25.75 (20.56–30.94)
Total score PedsQL, parental judgment						
Fiocchi 2019[56]	Food allergy	17 wk	26.00	1.69	28.2%	26.00 (22.68–29.32)
Total (95% CI)					**100.0%**	**26.91 (23.72–30.10)**

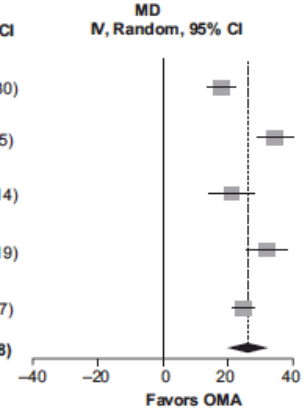
Heterogeneity: $\tau^2 = 6.52$; $\chi^2 = 7.97$, df = 4 ($P = .09$); $I^2 = 50\%$
Test for overall effect: Z = 16.55 ($P < .001$)



Patient's judgment of QoL

Study or subgroup	Population	Time point	MD	SE	Weight	MD IV, Random, 95% CI
Cognitive functioning PedSQL, patient's judgment						
Fiocchi 2019[56]	Food allergy	17 wk	18.25	2.06	21.2%	18.25 (14.20–22.30)
Emotional functional PedsQL, patient's judgment						
Fiocchi 2019[56]	Food allergy	17 wk	34.75	2.70	19.9%	34.75 (29.45–40.05)
Physical functoning PedsQL, patient's judgment						
Fiocchi 2019[56]	Food allergy	17 wk	21.25	3.52	18.0%	21.25 (14.36–28.14)
Social functioning PedSQL, patient's judgment						
Fiocchi 2019[56]	Food allergy	17 wk	32.00	3.16	18.9%	32.00 (25.81–38.19)
Total score PedsQL, patient's judgment						
Fiocchi 2019[56]	Food allergy	17 wk	25.00	1.67	21.9%	25.00 (21.73–28.27)
Total (95% CI)					**100.0%**	**26.15 (20.03–32.28)**

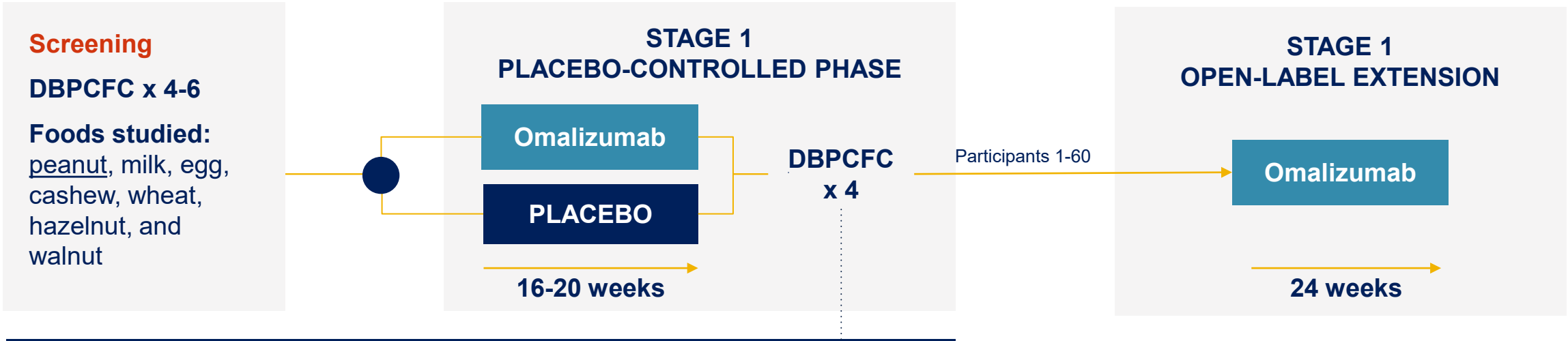
Heterogeneity: $\tau^2 = 41.78$; $\chi^2 = 29.71$, df = 4 ($P < .01$); $I^2 = 87\%$
Test for overall effect: Z = 8.37 ($P < .001$)



Zuberbier et al JACI: In Pract 2023

OUtMATCH Study Design

A multicenter, randomized, double-blind, placebo-controlled Phase 3 collaborative trial between NIAID, CoFAR, and Genentech/Novartis conducted at 10 US sites beginning in August 2019.



Primary Endpoint	Key Secondary Endpoints
Number of patients who successfully consume **≥600 mg peanut protein** without dose-limiting symptoms	Number of patients who successfully consume **≥1000 mg of milk, egg, and/or cashew** protein without dose-limiting symptoms

FDA Breakthrough Therapy Designation

NIH National Institutes of Health

https://clinicaltrials.gov/study/NCT03881696

Wood et al JACI Global 2023

Omalizumab Dosing

Values are milligrams per dose.

Baseline IgE (IU/mL)	Body Weight (kg)												
	≥10-12	> 12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	75	75	75	150	150	150	150	150	300	300
>100-200	75	75	75	150	150	150	300	300	300	300	300	450	600
>200-300	75	75	150	150	150	225	300	300	450	450	450	600	375
>300-400	150	150	150	225	225	300	450	450	450	600	600	450	525
>400-500	150	150	225	225	300	450	450	600	600	375	375	525	600
>500-600	150	150	225	300	300	450	600	600	375	450	450	600	
>600-700	150	150	225	300	225	450	600	375	450	450	525		
>700-800	150	150	150	225	225	300	375	450	450	525	600		
>800-900	150	150	150	225	225	300	375	450	525	600			
>900-1000	150	150	225	225	300	375	450	525	600				
>1000-1100	150	150	225	225	300	375	450	600					
>1100-1200	150	150	225	300	300	450	525	600					
>1200-1300	150	225	225	300	375	450	525						
>1300-1500	150	225	300	300	375	525	600						
>1500-1850		225	300	375	450	600							

DO NOT DOSE

Dosing frequency:

	Dose every 4 weeks
	Dose every 2 weeks
	Do not dose

OUtMATCH Key Eligibility Criteria

Key Inclusion Criteria

- Age 1 to <56
- Body weight and total serum IgE level suitable for omalizumab dosing
- Peanut-allergic
  - SPT ≥ 4 mm AND
  - IgE ≥ 6 kU/L AND
  - Reactive DBPCFC ≤ 100 mg
- Allergic to ≥ 2 of 6 other foods:

  Milk//egg
  - SPT ≥ 4 mm AND
  - IgE ≥ 6 kU/L AND
  - Reactive DBPCFC ≤ 300 mg

  Cashew, wheat, hazelnut, walnut
  - SPT ≥ 4 mm OR
  - IgE ≥ 6 kU/L AND
  - Reactive DBPCFC ≤ 300 mg

Key Exclusion Criteria

- Poorly controlled atopic dermatitis
- Poorly controlled or severe asthma/wheezing at screening
- History of severe anaphylaxis to patient-specific foods used in study
- Dose-limiting symptoms to placebo
- Sensitivity or suspected/known allergy to any of the ingredient (including excipient) of the:
  - Active or placebo OFC material
  - Multi-allergen OIT
  - Drugs related to omalizumab (e.g., monoclonal antibodies)

Baseline Characteristics

	Omalizumab* N = 118	Placebo* N = 59
Age Category (years)		
1-5	45 (38%)	23 (39%)
6-11	46 (39%)	20 (34%)
12-17	27 (23%)	16 (27%)
Race		
White	72 (62%)	37 (63%)
Multiple	23 (20%)	7 (12%)
Asian	12 (10%)	12 (20%)
Black Or African American	10 (8.5%)	3 (5.1%)
Ethnicity		
Not Hispanic Or Latino	108 (92%)	55 (93%)
Hispanic Or Latino	10 (8.5%)	4 (6.8%)
Medical History (Other Atopic Diseases)		
Atopic Dermatitis	94 (80%)	46 (78%)
Allergic Rhinitis	69 (58%)	36 (61%)
History of Asthma	58 (49%)	34 (58%)

*n (%)

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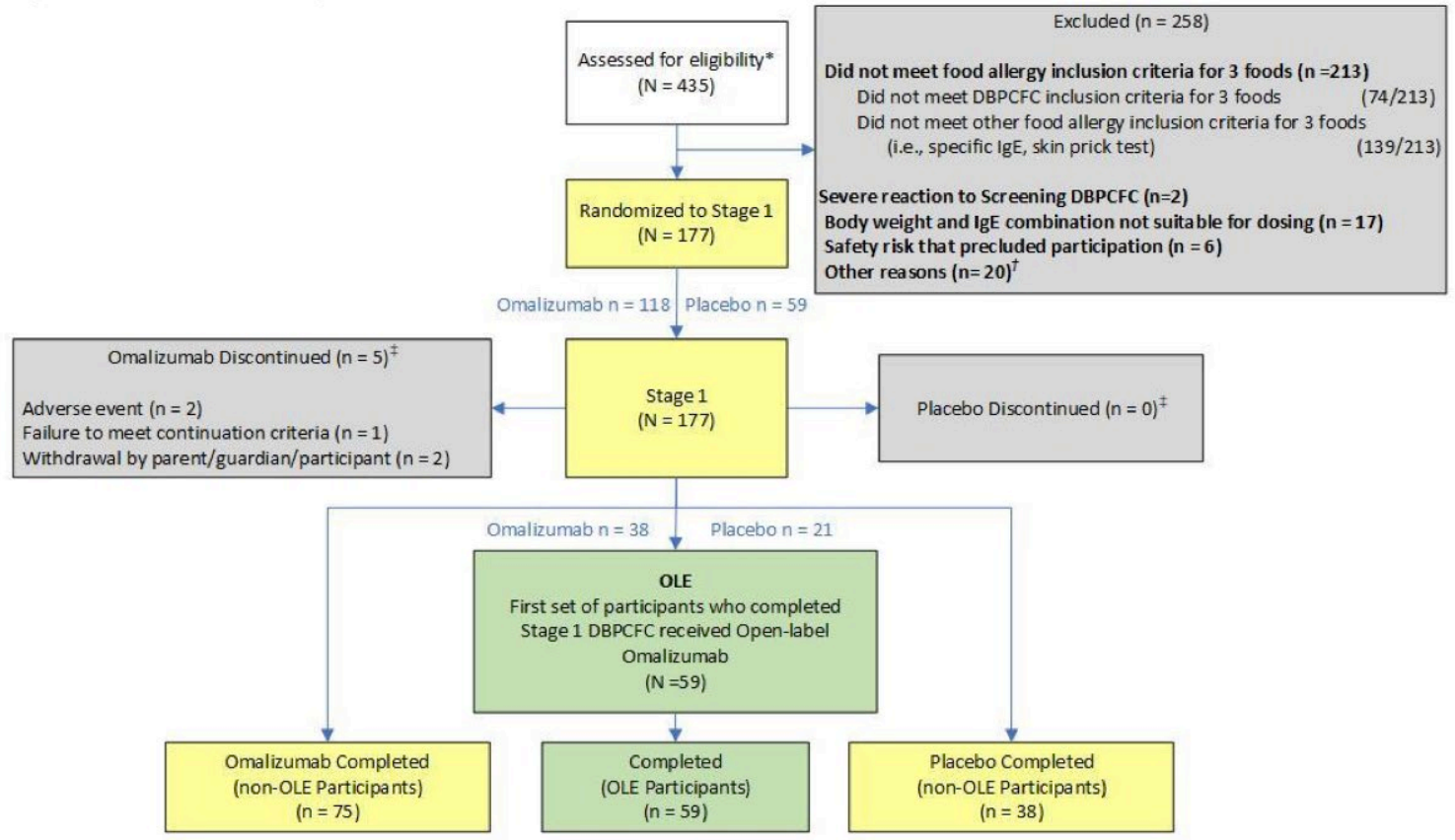
Disposition

Figure S2. CONSORT Diagram



*This diagram includes participants <=17 years of age at the time of consent.
†1 participant was in screening at the time of enrollment closure.
‡For primary and key secondary endpoints, food challenges that did not occur during Stage 1 were considered to be Failures.
Thus all randomized participants had a value for the primary and key secondary endpoints.
DBPCFC=Double-blind placebo-controlled food challenge; OLE=Open-label Extension.

3% dropout

60% screen fail

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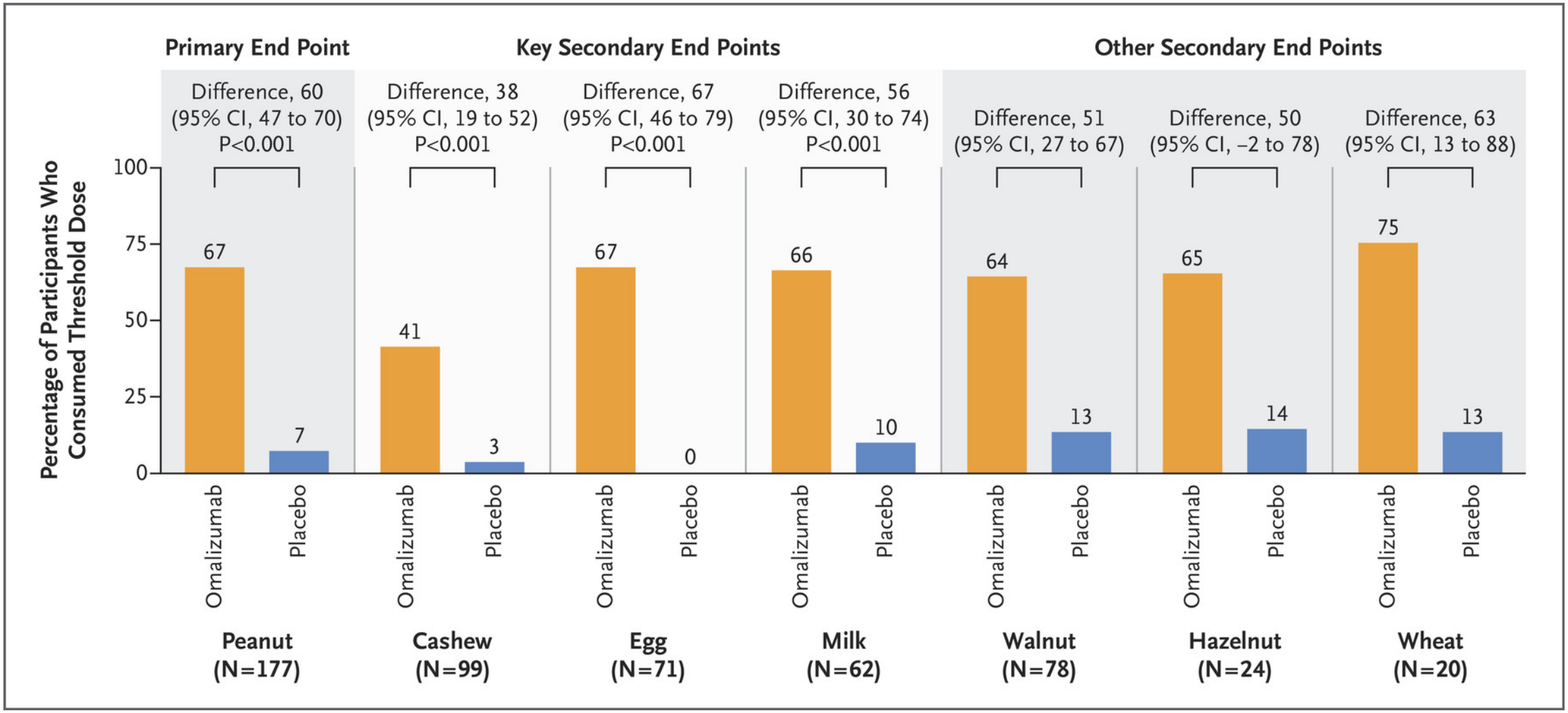
A Brave New World



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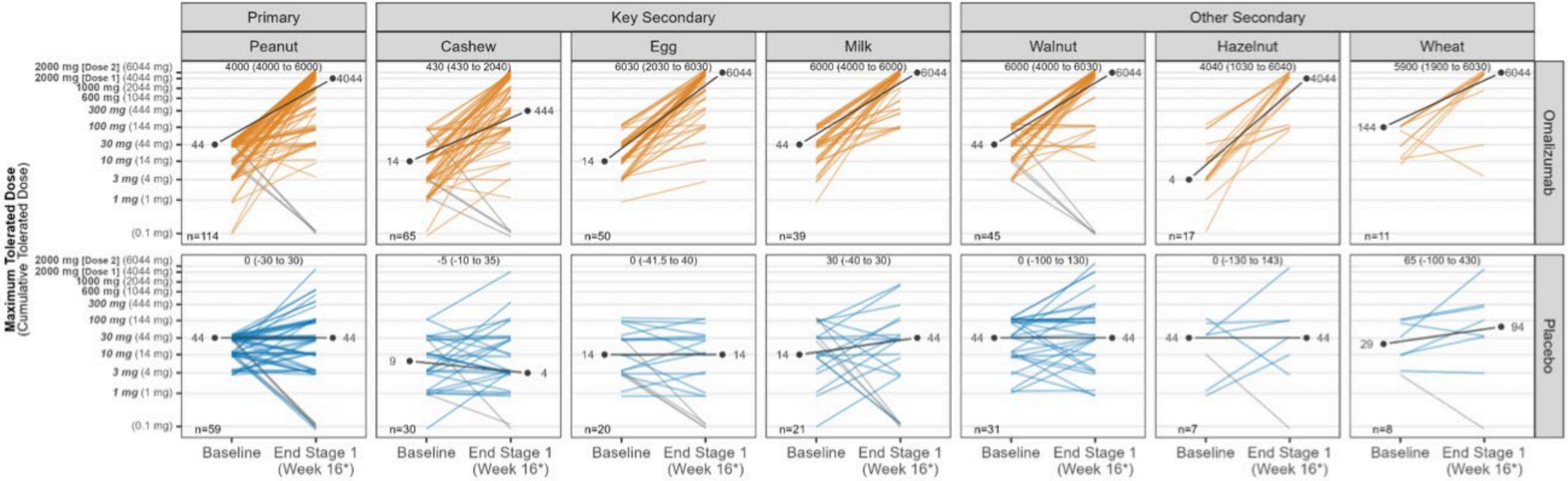

CAVEATS

Grey lines: Participants having dose-limiting symptoms during placebo challenges

Approximately 14% of those receiving omalizumab did not experience a clinically important change

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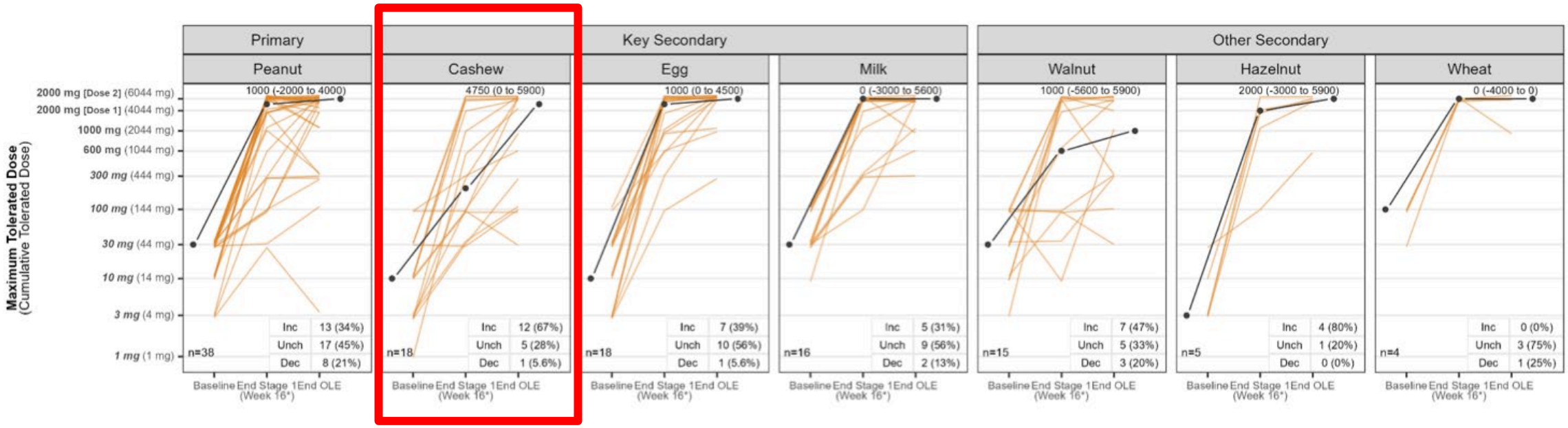
Effect of Longer Treatment – OLE Outcomes



Safety data as expected, consistent with previous omalizumab experience

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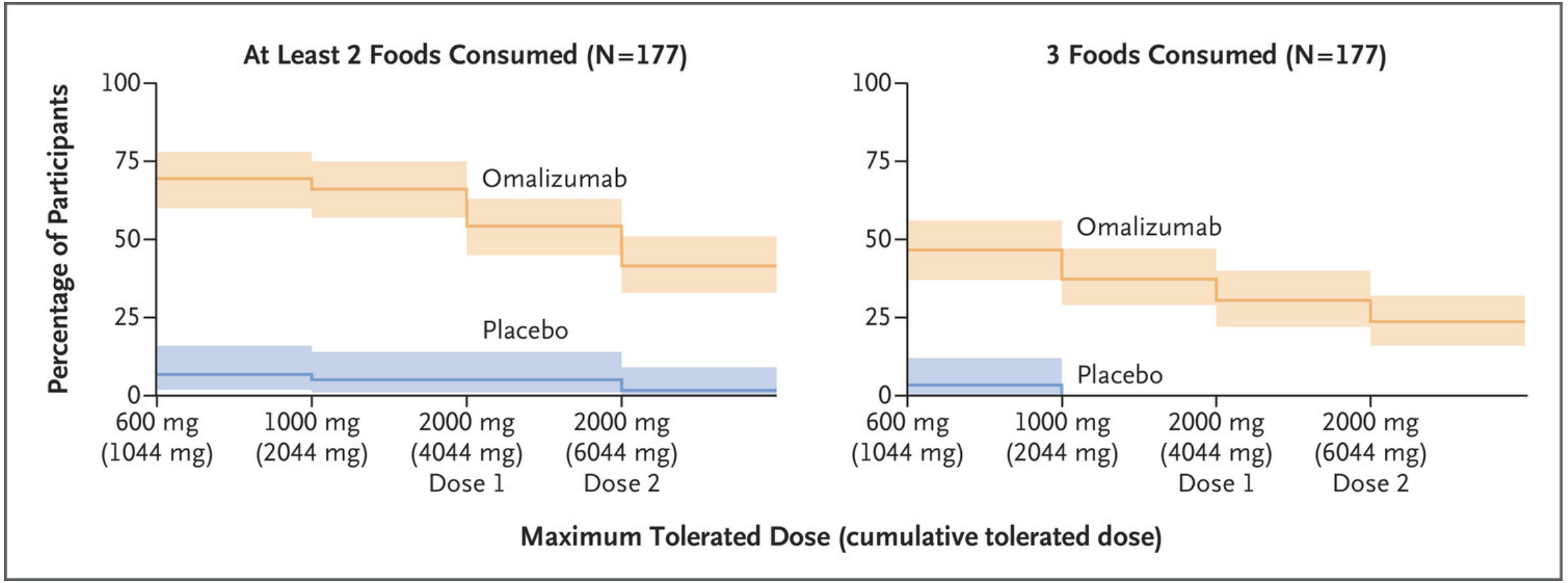
MTD at Week 16 – Protection from Multiple Foods



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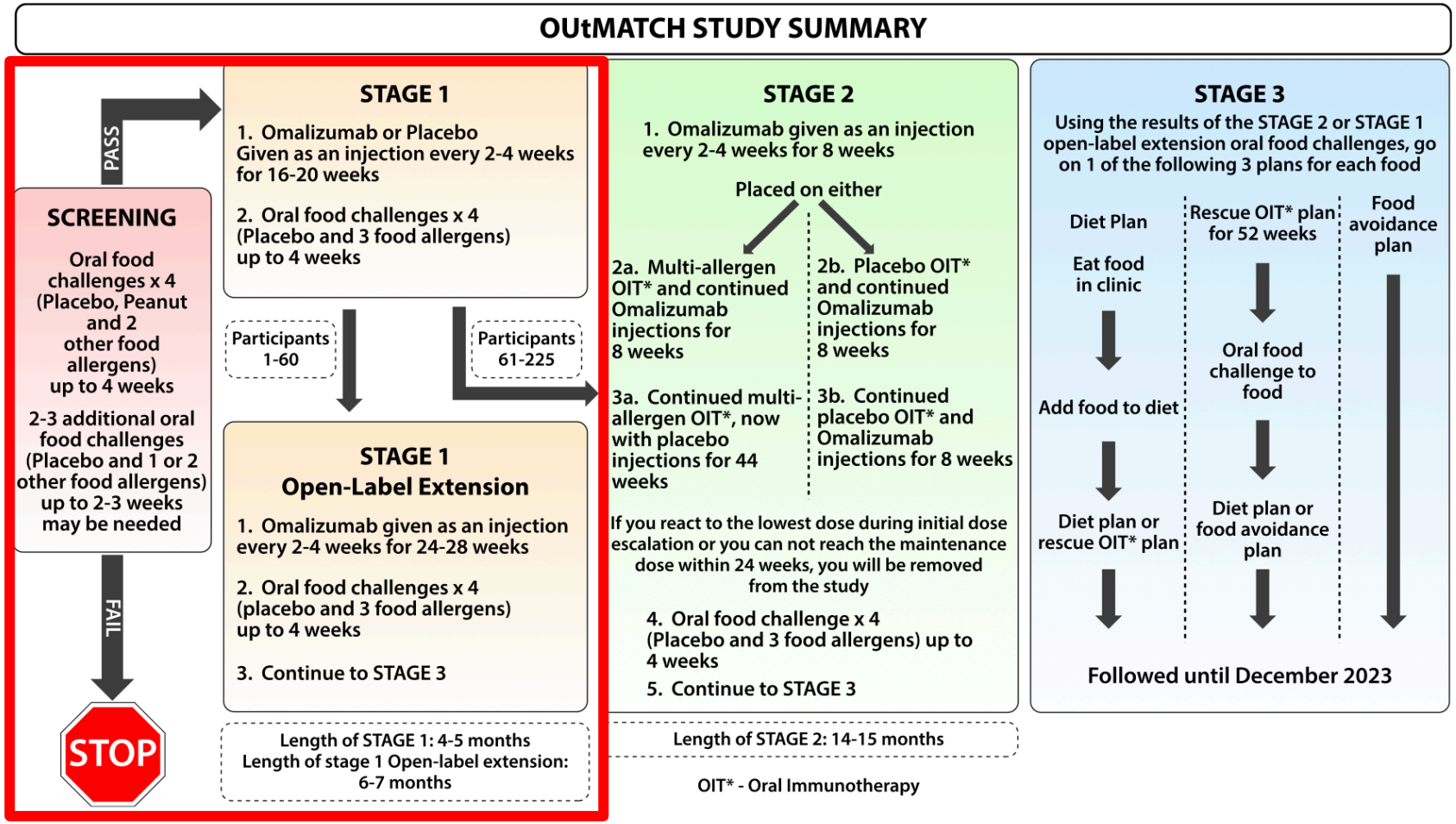
OUtMATCH: Ongoing Stages



Omalizumab's Approval Immediately Raises More Questions Than It Answers. Among Them:

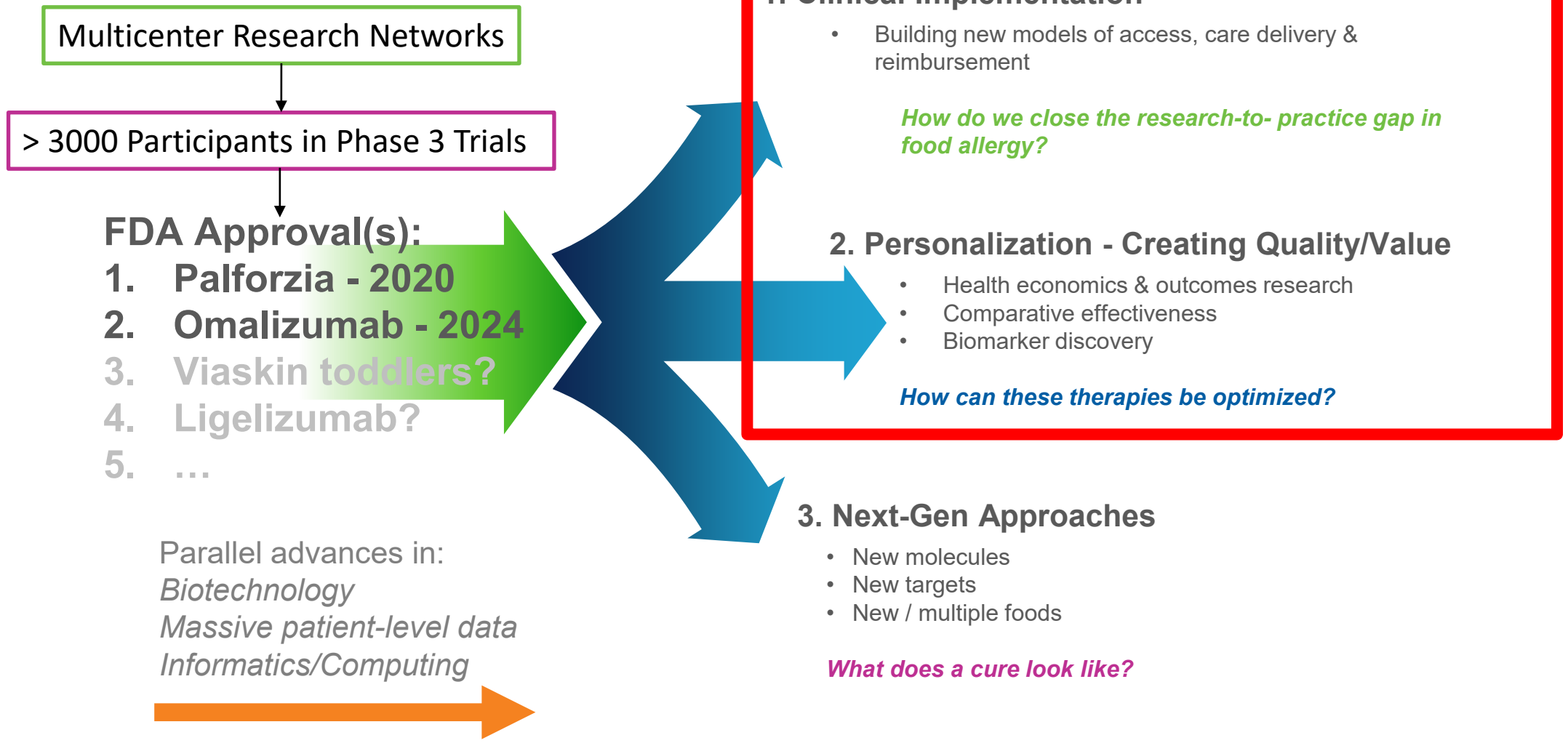
1. If we *can* treat virtually all patients with food allergy(ies)…*should* we?
   - How will we decide?

2. If we do decide to treat someone, how will we know if their condition has improved?
   - What are the right outcomes to measure?
   - Do we even have the measurement tools we need?

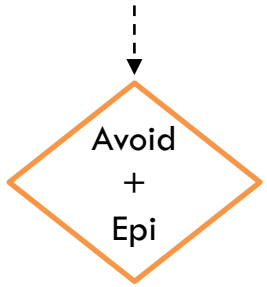
3. How can we personalize the use of omalizumab in a patient-centered way?
   - Monotherapy vs. allergen-plus; age; specific allergen(s); if & when to challenge/stop; etc

4. Is the indefinite use of expensive medications sustainable? How can we approach the concept of value in food allergy?

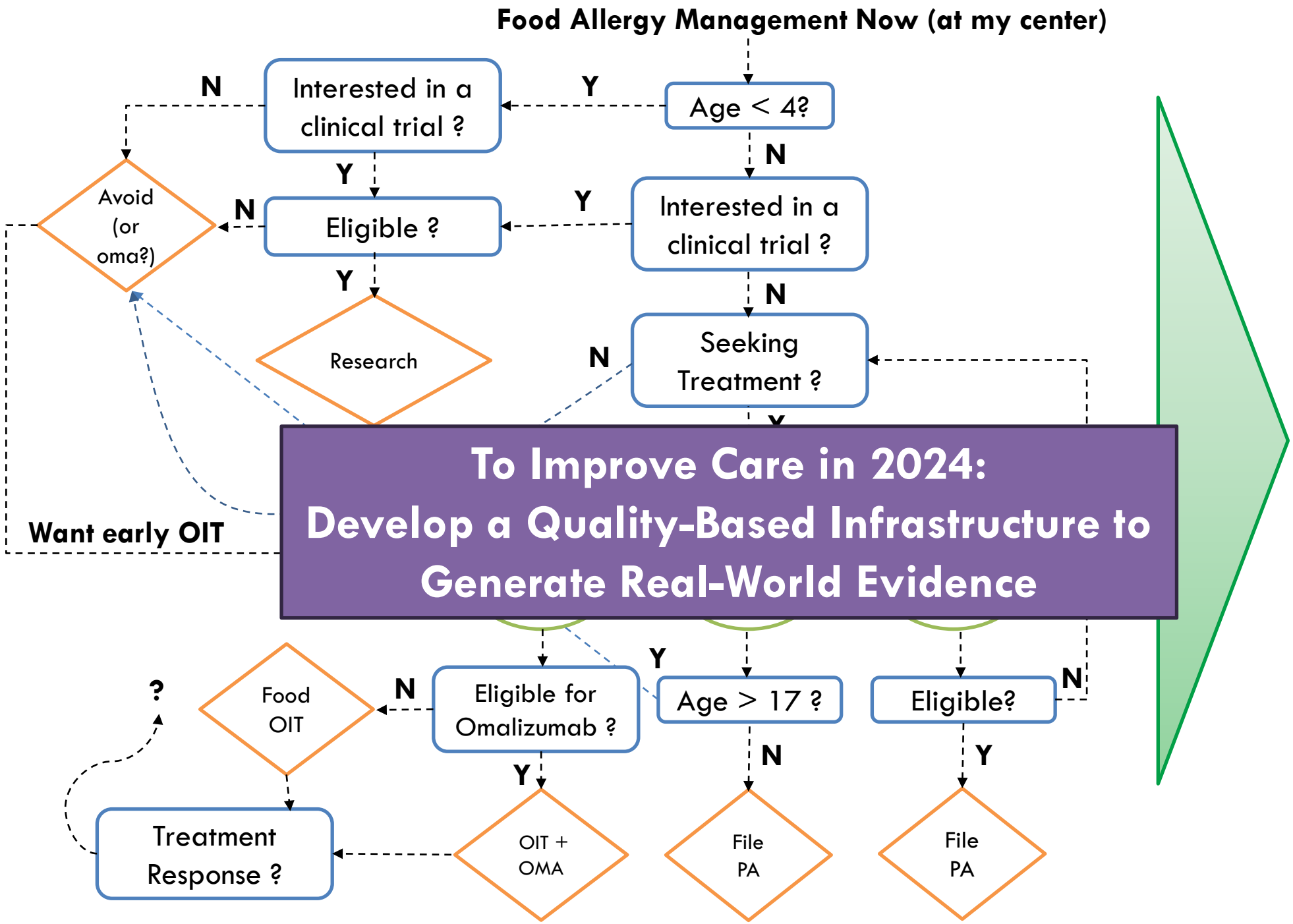
The Field Now Sits at a Major Inflection Point



Historical Approach to Food Allergy Management



To Improve Care in 2008: Develop New Therapies



Key Takeaways:

1. Patients have options that didn't exist 3 months ago.
2. Over the next 5-10 years, this landscape will accelerate to multiple competing choices.
3. Endophenotypes could unlock precision medicine but remain unknown in food allergy.
4. Demand for psychosocial & decision support will continue to skyrocket.
5. **No data-driven framework yet exists to determine real-world effectiveness and improved health outcomes.**

It is Past Time to Prioritize Quality in Food Allergy Care

Agency for Healthcare Research and Quality

QUALITY IN HEALTHCARE

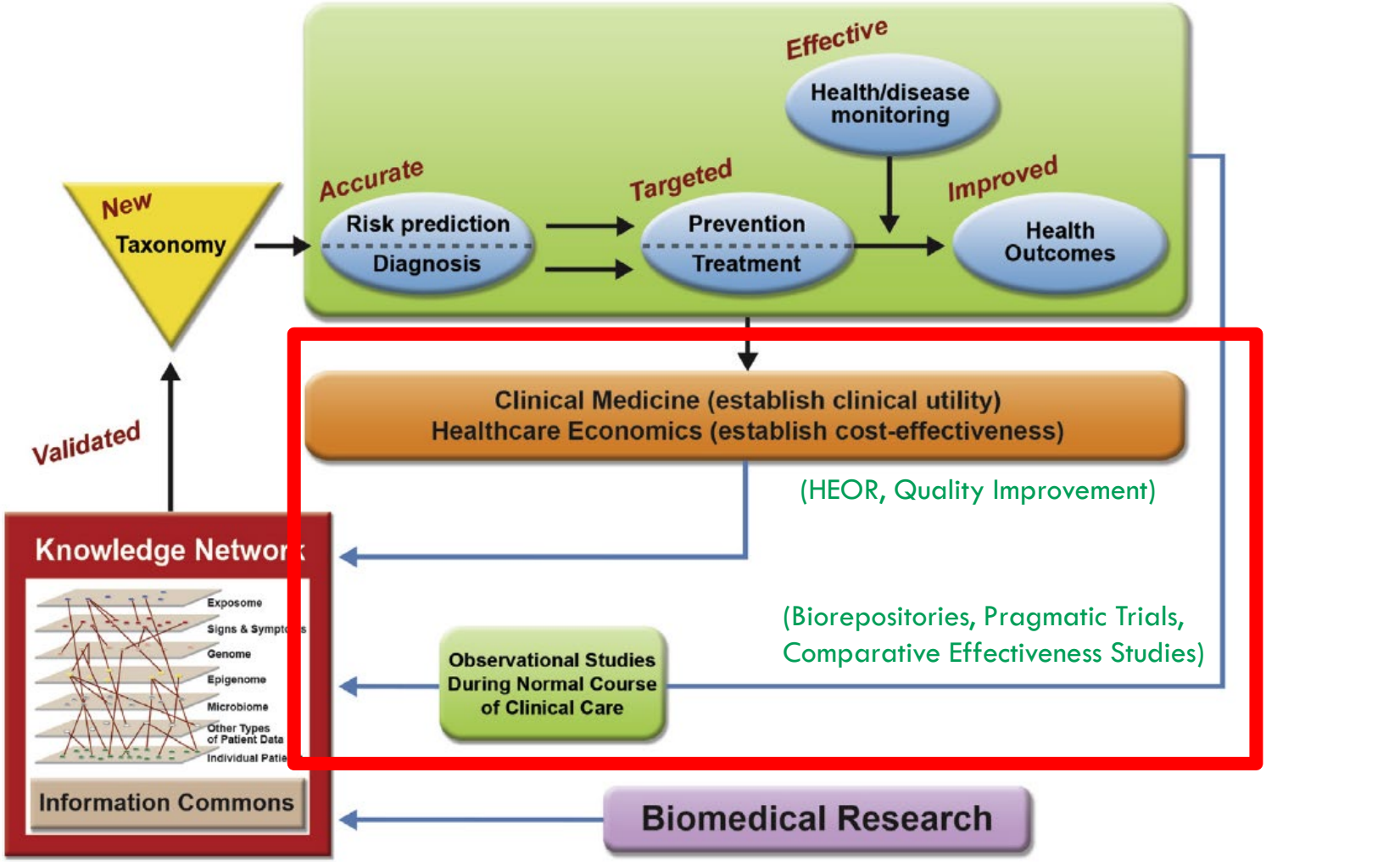
The foundation of quality healthcare is doing the right thing at the right time in the right way for the right person and having the best results possible. Quality healthcare often means striking the right balance in the provision of health services by avoiding overuse (e.g., getting unnecessary tests), underuse (e.g., not being screened for high blood pressure), or misuse (e.g., being prescribed drugs that have dangerous interactions).[1]

- Correctly **diagnosing** patients (avoiding unnecessary IgE testing & using OFCs as appropriate)
- **Preventing** more cases by enhancing implementation of infant oral allergen exposure
- Judiciously **prescribing** epinephrine devices & teaching their appropriate use
- **Recommending** the most appropriate treatment, including nonpharmacologic interventions

"Historically, quality of healthcare has varied based on race, ethnicity, SES, age, sex, disability status, sexual orientation, and residence location."

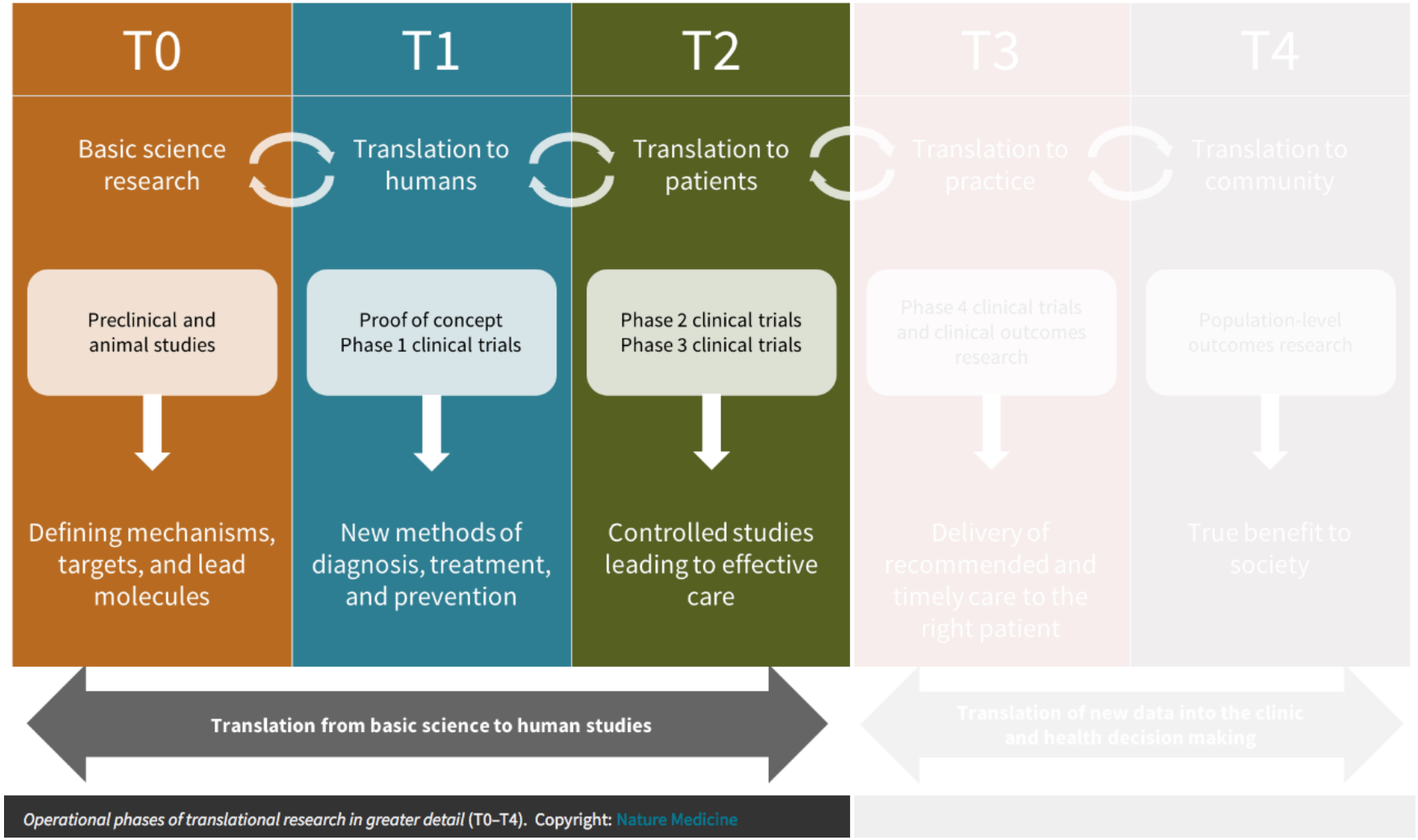
2019 National Healthcare Quality and Disparities Report
https://www.ncbi.nlm.nih.gov/books/NBK579354/

The Goal: A Patient-Driven Quality-Oriented Ecosystem in FA



Adapted from Galli SJ JACI 2016

A Robust T1-T4 Research Infrastructure in FA is Not Yet Built



Operational phases of translational research in greater detail (T0–T4). Copyright: Nature Medicine

Table 1 Differences between efficacy and effectiveness studies

	Efficacy study	Effectiveness study
Question	Does the intervention work under ideal circumstance?	
Setting	Resource-intensive 'ideal setting'	
Study population	Highly selected, homogenous population Several exclusion criteria	
Providers	Highly experienced and trained	
Intervention	Strictly enforced and standardized No concurrent interventions	

3 Key Features Distinguish Effectiveness Studies (Pragmatic or Practical Trials) and Efficacy Studies (Explanatory Trials, Usually RCTs):

1. Population – generalizability
2. Intervention – head-to-head comparisons
3. Outcomes – functional, universal (symptom burden, QOL, impact on ADLs/functioning, life expectancy, healthcare utilization, etc)

    - e.g., in patients with poorly controlled persistent asthma on LABA/ICS, which is the best next step to limit exacerbations – increasing dose of LABA/ICS or adding montelukast?

Singal et al Clin Gastro Hepatol 2014

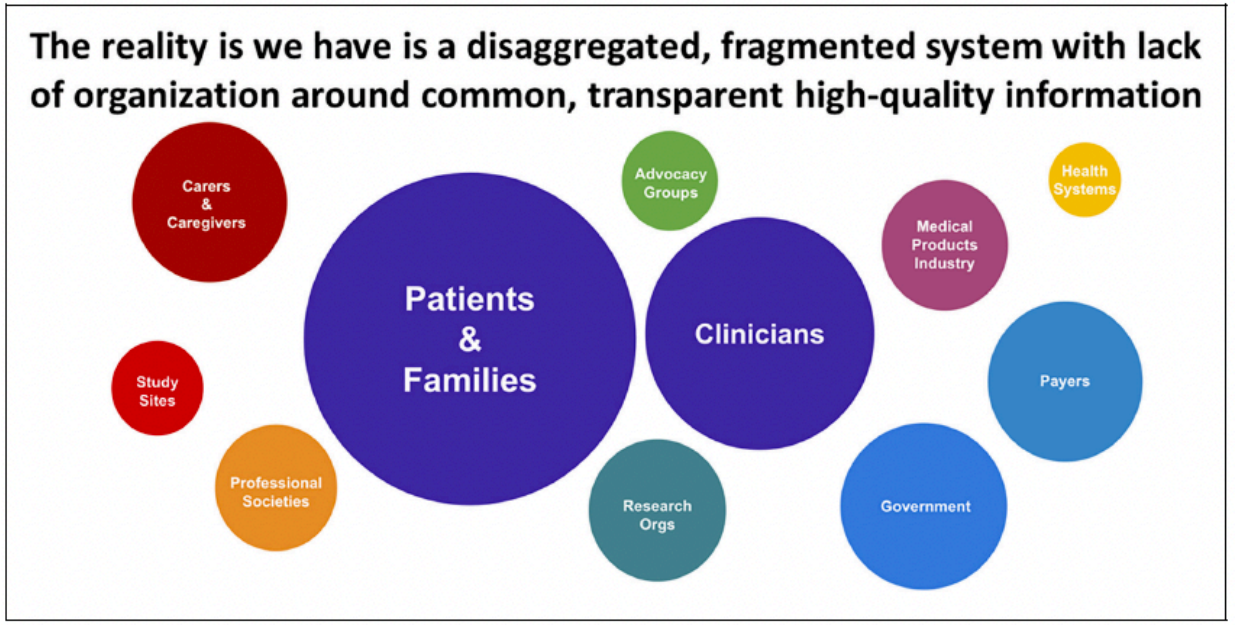
Now is the time to fix the evidence generation system

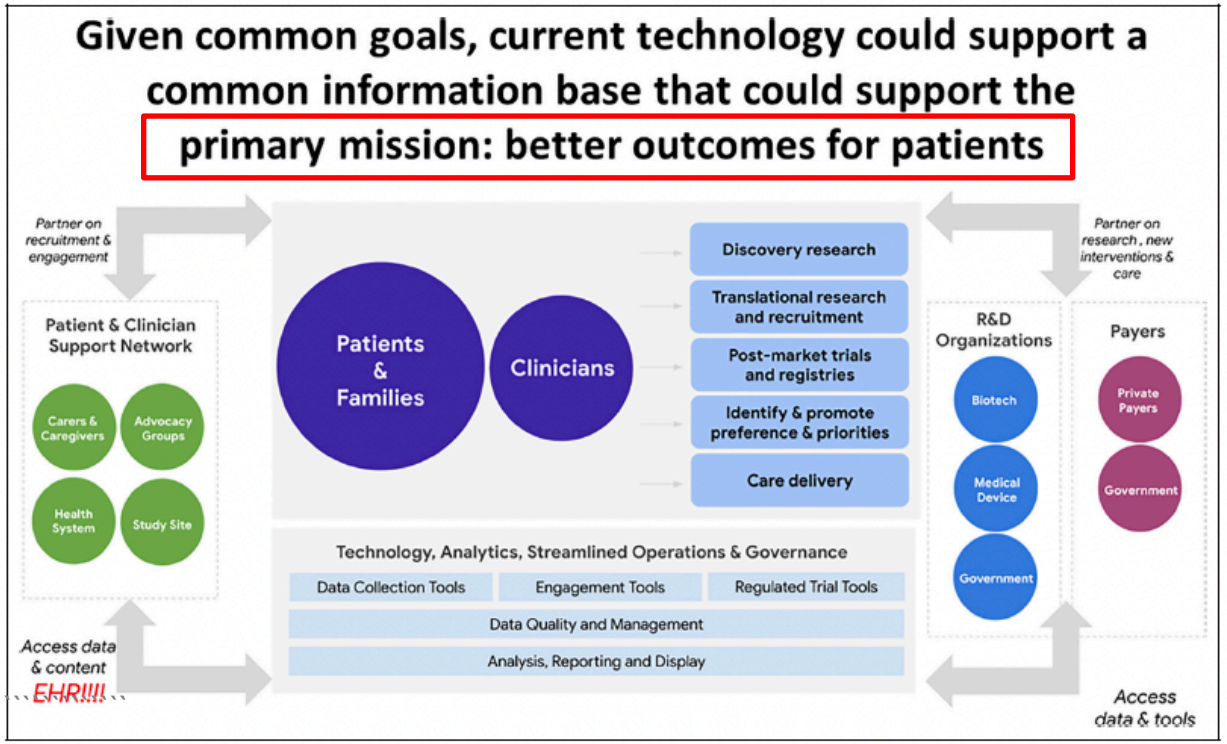
Robert M Califf

Existential Threats to Quality:

- On average, it has taken 17 years for an innovation to make its way into routine practice
- 80% of research spending does not result in a measurable public health impact
- RCTs are long and expensive, and the dissemination of knowledge is archaic
  - Traditional scholarship model & associated incentives
- And now: medical school graduates enter a world with 50X more health data as when they started
- Biomedical knowledge doubles every 73 days

- …yet remember how we innovated around COVID?
  - Rapid trials, pre-prints, social media, WhatsApp, etc





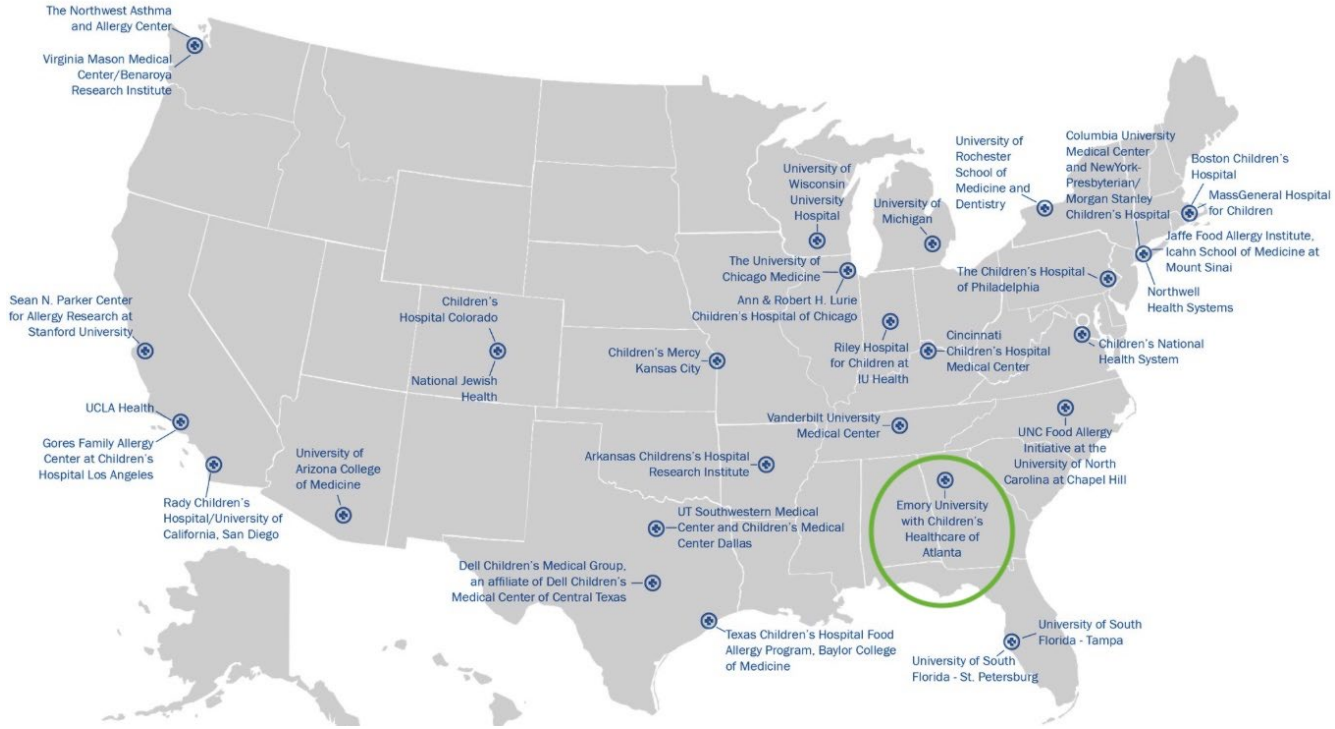
Califf RM Clin Trials 2023
Bauer and Kirchner Psychiatry Res 2020
https://medicine.umich.edu/dept/lhs/service-outreach/learning-health-systems

Learning Health System – An Opportunity in FA?

- A Learning Health System (LHS) is one "in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience" (Institute of Medicine, 2007).

In pediatrics alone: 558 teams in 286 orgs across 44 states and 5 countries are currently working in the following areas:

- Cardiac surgery
- Autism
- CF
- Epilepsy
- Perinatal health
- Rheumatology
- Hospital safety
- IBD (ImproveCareNow): "steal shamelessly and share seamlessly"

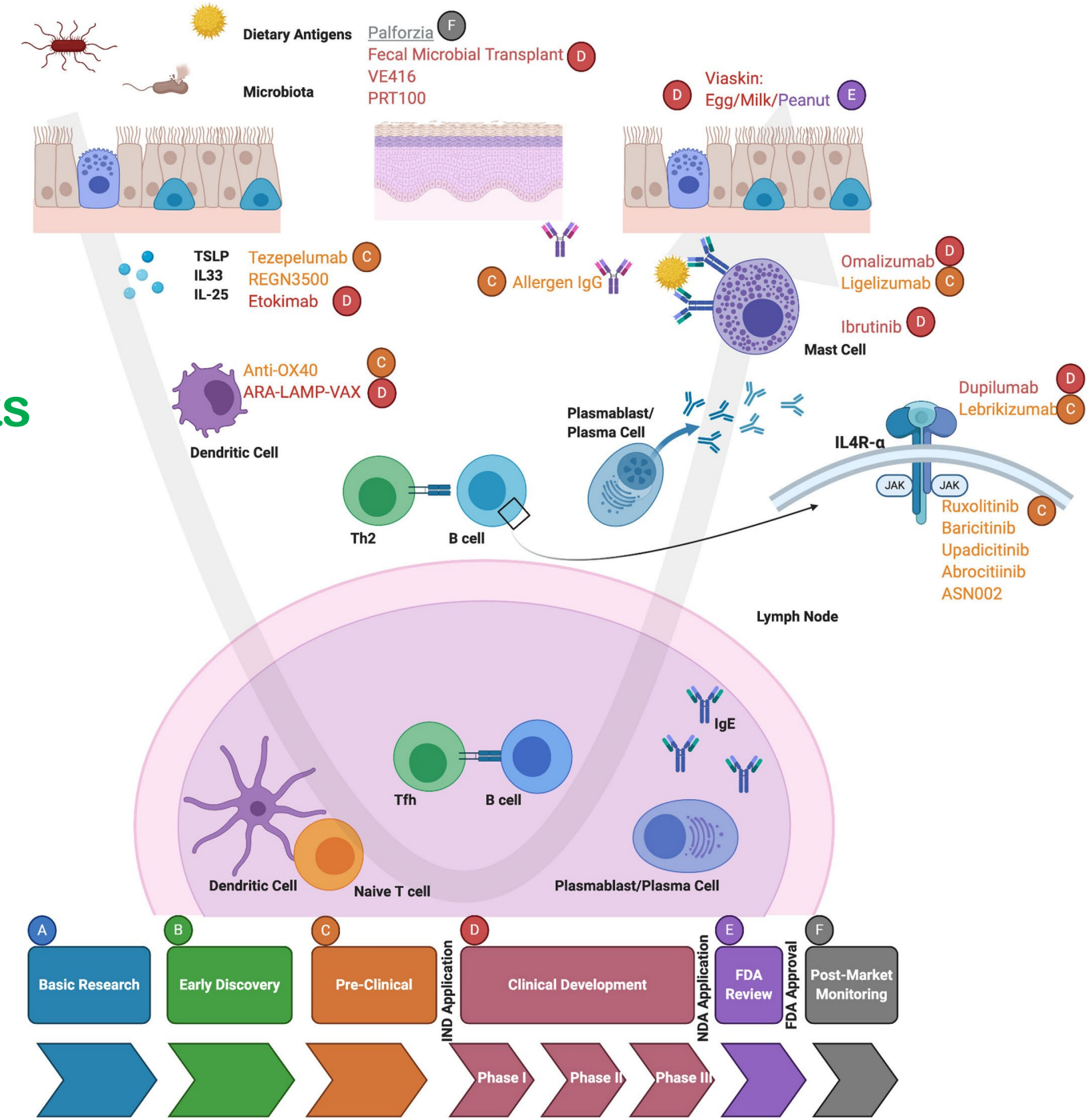


https://www.cincinnatichildrens.org/research/divisions/j/anderson-center/learning-networks/active-emerging

Treatment Options Will Very Likely Expand & Offer Patients Even More Choice

(combinations?)
(progressions?)

Others not shown:
- *CNP-201*
- *IGNX001*
- *UB221*
- *AIMab 7195*
- *Abatacept*
- *Talizumab*
- *Quilizumab*
- *More?*



Ramsey and Berin Pediatr Allergy Immunol 2021

5 Key Messages

1. Foundational multicenter research networks are now generating Level 1, Grade A evidence supporting the landmark international regulatory approvals for PTAH (Palforzia) and omalizumab – major accomplishments.

2. However, in reality, practice with OIT, oma, and oma+OIT is moving forward in a fragmented, haphazard way.

3. New approaches – other immunotherapies, biologics, & small molecules – are very likely to enter the clinic in the coming years, vastly increasing complexity.

4. None of these products are being developed uniformly, which will lead to further confusion and misunderstanding of their true effects. Up to half of *bona fide* (correctly diagnosed) food allergy patients may not even "need" them.

5. For the first era of food allergy research to improve outcomes, stakeholders must call for:
   - Harmonization of research methods in trials, and;
   - Adoption of methods, such as learning health systems, to facilitate real-world evidence generation & outcomes research; and
   - New ways of thinking, collaborating, and funding.

Acknowledgements

ACAAI American College of Allergy, Asthma & Immunology
Follow the Leader Into the Future

FARE Food Allergy Research & Education

National Peanut Board AMERICA'S PEANUT FARMERS

Ansley Atlanta
Hammill Family Foundation
Marshall Family
McMillen Family
Reynolds Family
Steve Goodman

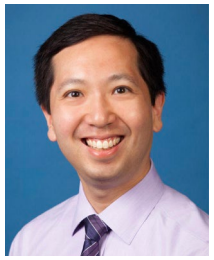
Thrasher Research Fund

CoFAR CONSORTIUM FOR FOOD ALLERGY RESEARCH

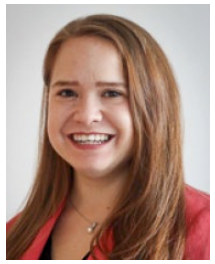
Immune Tolerance Network

Pediatric Institute Faculty

B. Vickery



G. Lee



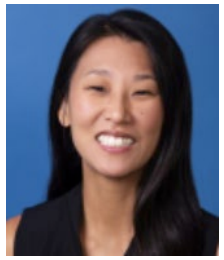
I. Ezhuthachan

M. Rathkopf

K. Proctor
PhD Psych

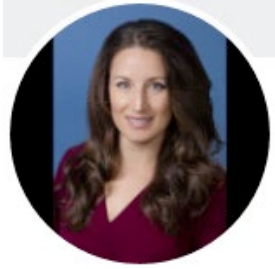
LTD

L. Kobrynski



T. Lee
PRN

Children's Providers



C. Horton, CPNP

C. Leef, DNP

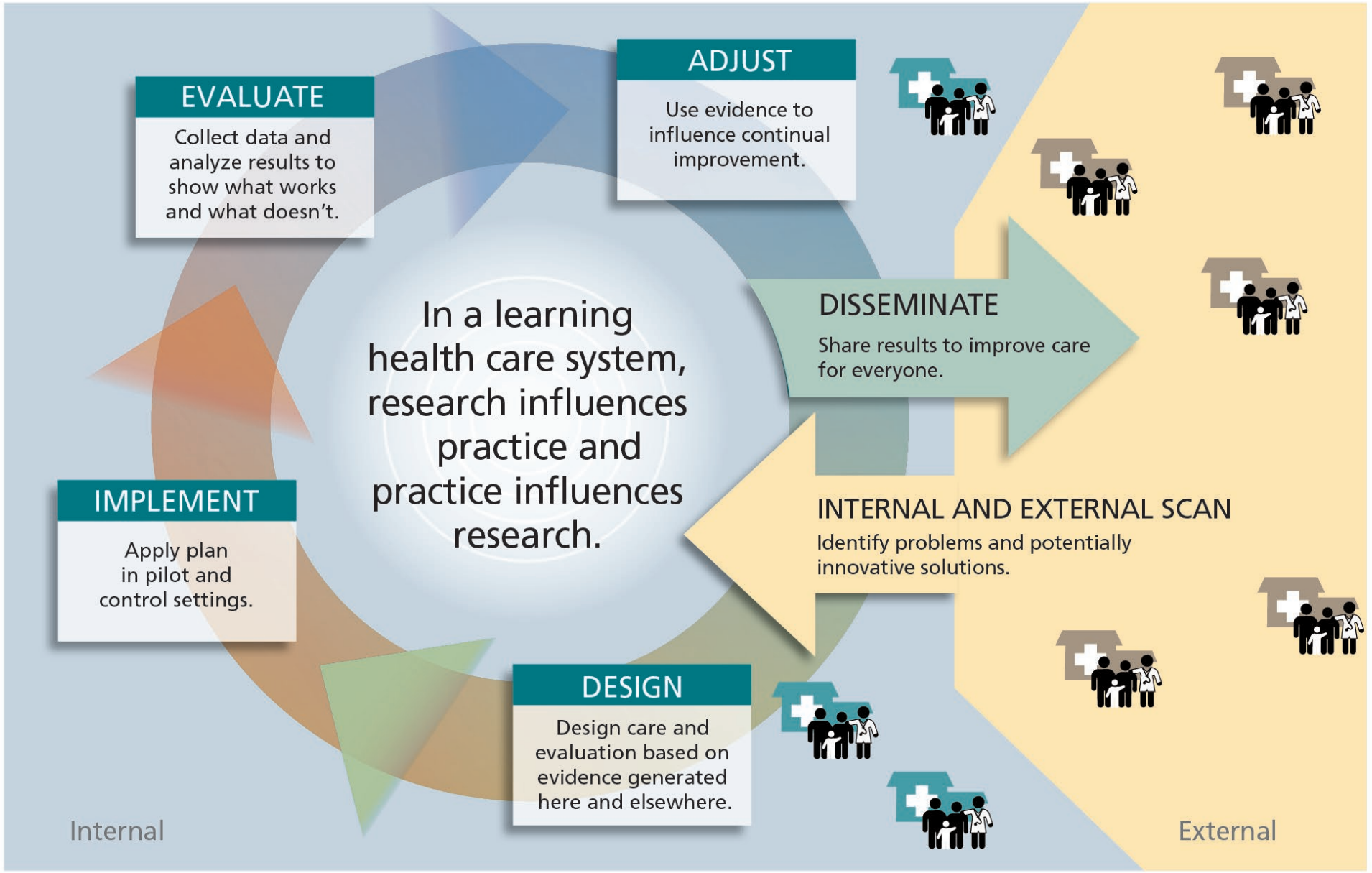
<u>Other Contributors:</u>

- Dr. Jennifer Xu, 2nd year fellow
- Dr. Jessica Feng, 1st year fellow
- Dr. Kiran Patel PRN (2 clinics/mo)
- Dr. Merin Kalangara PRN (2 clinics/mo)

<u>CADRE Research Team:</u>

- Ashley Dulson, BS, CCRP
- Mary Vess, RN, MSN, CCRP
- Dhondup Tso King, MPH
- Jessica Stafford
- Cherish Foxworth, RN
- Carrie Mason, BS, RRT
- Jalicae Norwood
- *Not pictured: Rebecca Cleeton, MPH, CCRP*
- *Not pictured: Anne Fitzpatrick, PhD, RN*
- *Not pictured: PRU team & Cheryl Stone*

NIH NIAID



https://medicalxpress.com/news/2012-08-health-idea-action.html

OUtMATCH Study Status

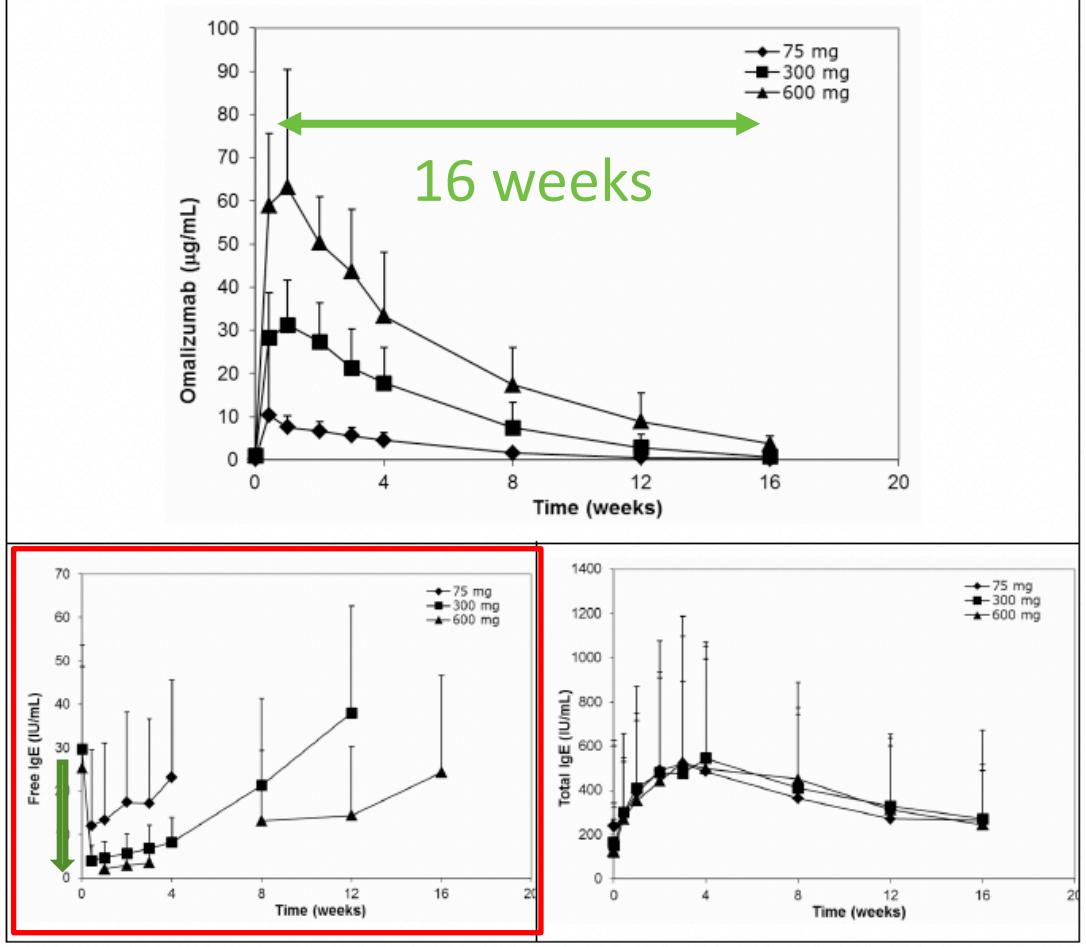
- Enrolled 462 across 10 sites, randomized N=180
  - Overall screen failure rate of 60%
  - 68 participants aged 1 to 5 years: minimum weight 10 kg

- Over 1500 screening OFCs were performed (peanut, placebo, 2+ allergens)
  - Participants also completed > 1500 post-treatment OFCs
  - Stage 1 completed in 4Q 2023; Stages 2 and 3 ongoing

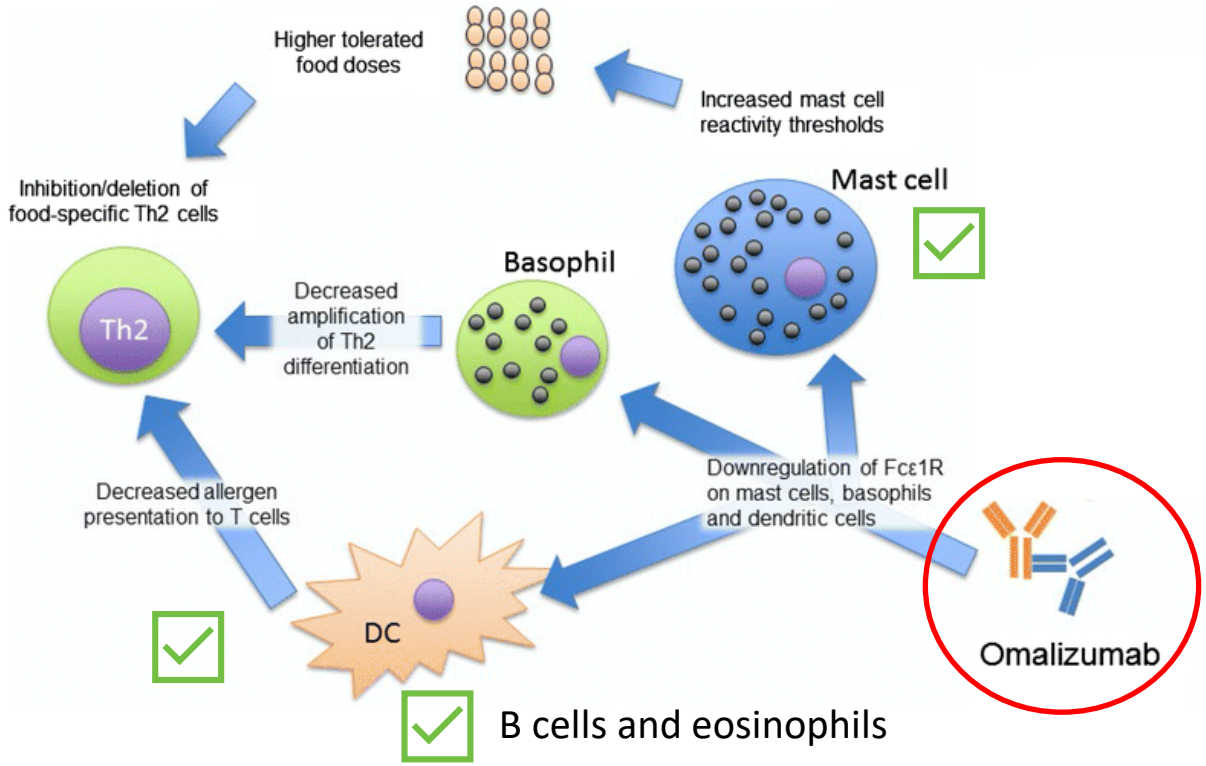
- Managed through COVID with zero pandemic-related withdrawals

Personal communication, Drs. Wood, Togias, Wheatley
Slide courtesy of Dr. Wood

Figure 3. Mean (SD) serum concentration–time profiles of omalizumab (upper panel), free IgE (left lower panel) and total IgE (left right panel) following a single dose of 75, 300, or 600 mg omalizumab



Source: Source: sponsor's clinical study report for Q4577.

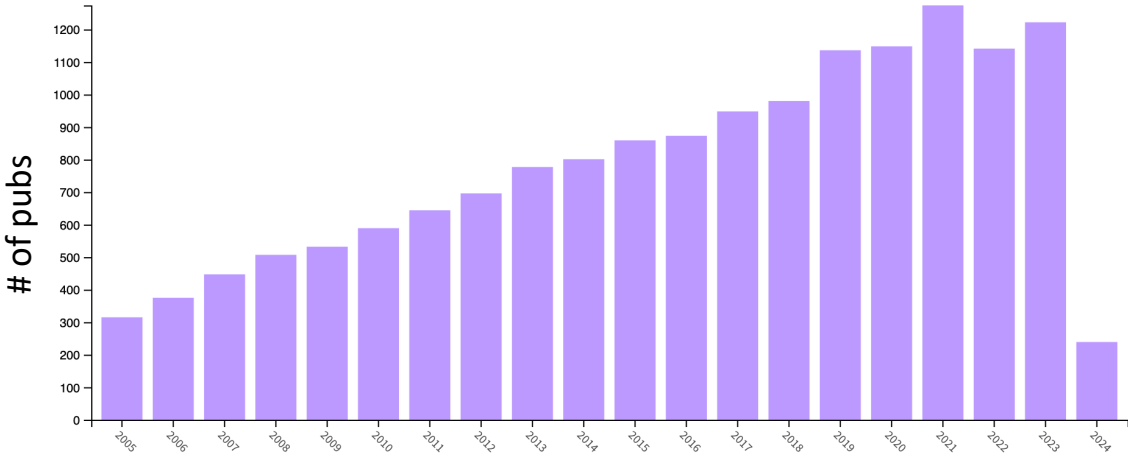


Year Approved	Indication
2003	Moderate to severe asthma
2014	Chronic spontaneous urticaria
2016	Allergic asthma in children ≥ 6y
2020	Adults with nasal polyps

https://www.accessdata.fda.gov

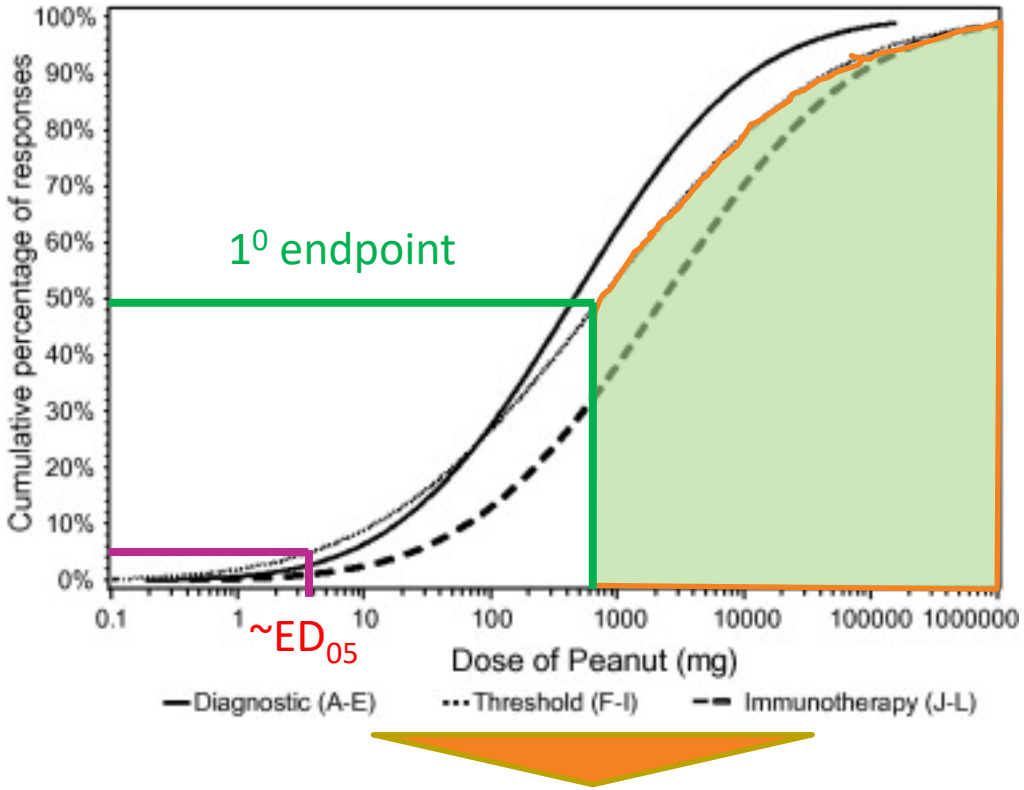
Labrosse, Des Roches, Begin *Arch Immunol Ther Exp* 2017

Foundational Thought Leadership



Web of Science, search term “food allergy” 2004-2024, accessed 10 April 2024

Key Problem: Phenotypic Variation is Not Readily Known



Half the population already lives at a sensitivity level at or above "desensitized. "They:

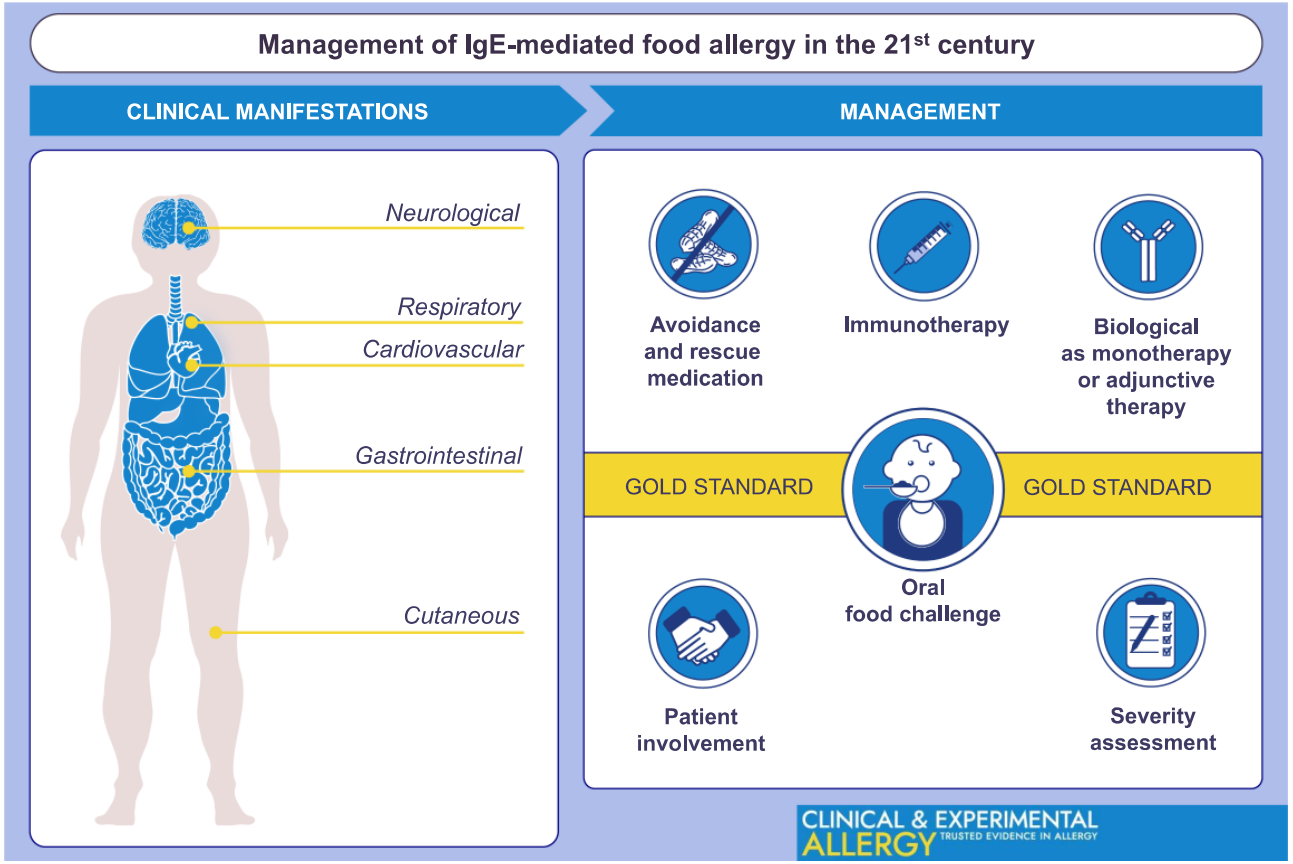
- Certainly shouldn't worry about PAL "may contain"
- Likely don't need AIT (but might still have severe reactions)
- Might even start sub-threshold consumption

1. **Patients do not have daily / frequent symptoms but instead only when they are exposed to supra-threshold allergen doses**
2. **Because we don't routinely determine differences in threshold sensitivity, all patients are given the same general advice**
3. **This may create unnecessary stress, and could limit options, for less sensitive patients who might live more freely**
4. **Therapies are only tested in the most sensitive half of the distribution – creating bias and limiting generalizability**

Allen et al JACI 2014

Future Directions

1. Continued focus on living well with food allergies
   - Improving diagnosis, mental health, threshold-based management strategies
2. Health services research / Phase 4 RWE trials
3. New approaches with existing molecules
   - Interrupting disease progression?
   - Optimal approach to AIT combination?
4. Precision medicine & endotyping
   - Severity classification / risk-stratification
5. Continued development focused on curing disease



Cafarotti et al Clin Exp Allergy 2022

Should we pursue OIT?

Which doctor?

What are the long-term consequences / harms?

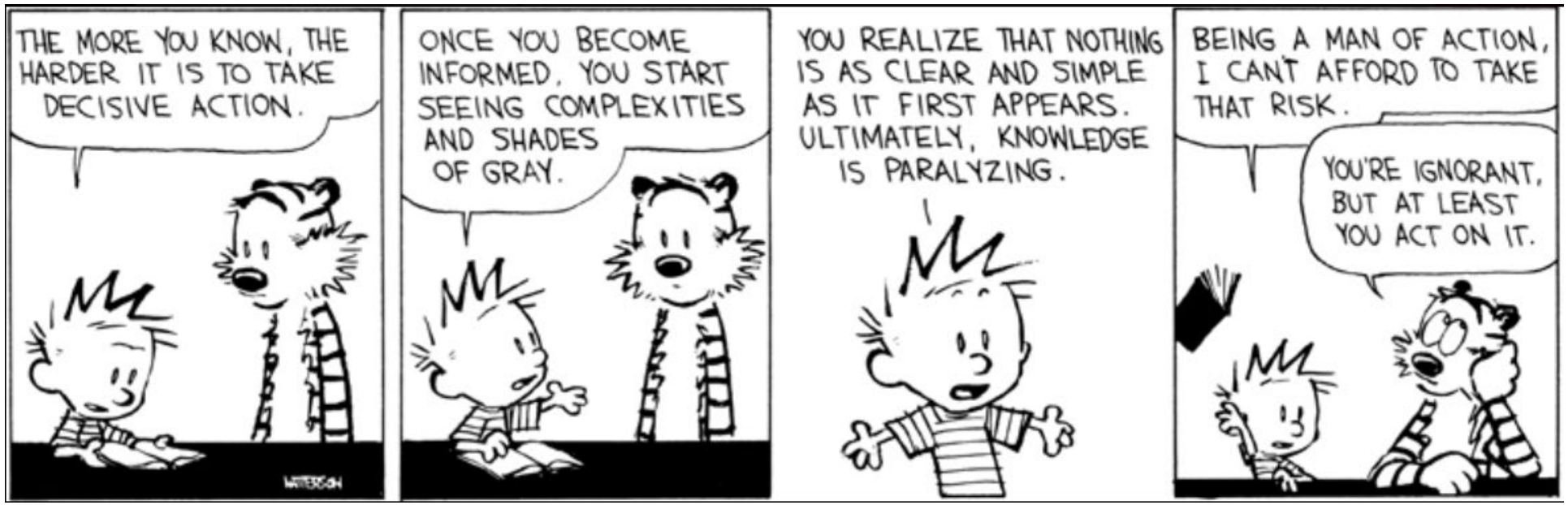
What does my child want?

Which protocol?

Which food(s)?

Should we wait?

The Expanding Decisional Dilemma in Food Allergy



What about this clinic in Southern California?

What other treatments will become available? When?

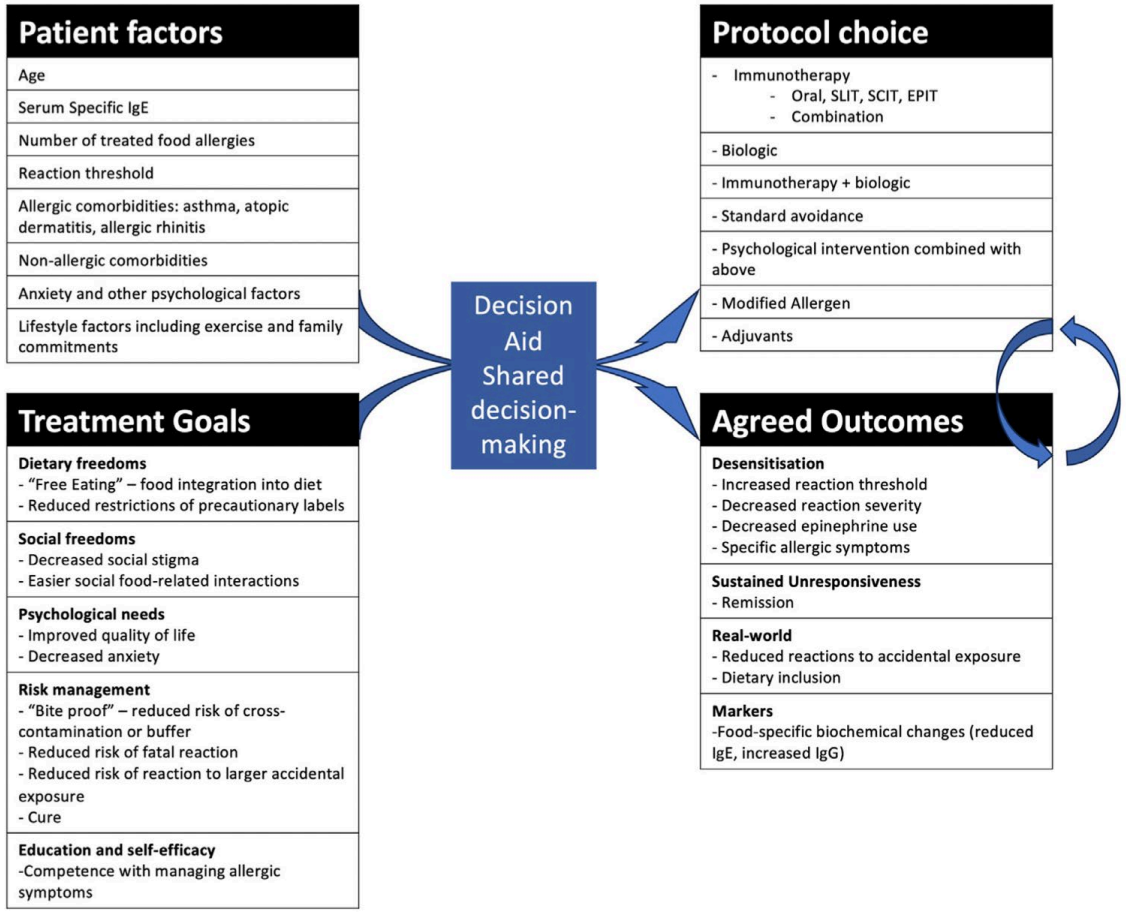
Do we have the time or resources to commit to this?

Can we afford it?

Rostrum

Flex-IT! Applying "Platform Trials" Methodology to Immunotherapy for Food Allergy in Research and Clinical Practice

Douglas P. Mack, MD[a], Julia Upton, MD[b,c], Nandinee Patel, MD, PhD[d], and Paul J. Turner, FRCPCH, PhD[d] *Hamilton and Toronto, Ontario, Canada; and London, United Kingdom*



Mack et al JACI: In Pract 2024

What are we currently focusing on in Atlanta?

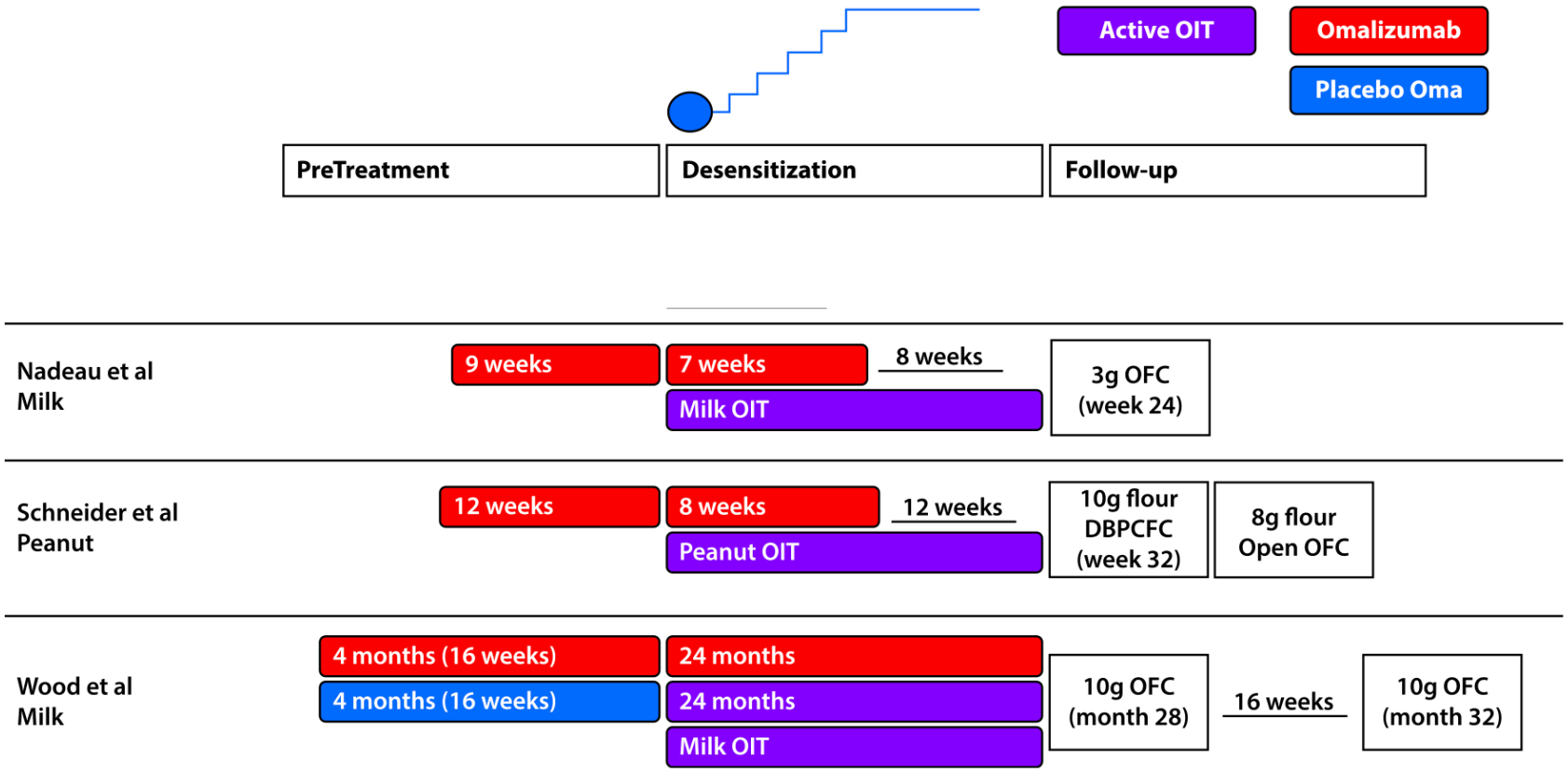
- Optimize usual care: OFCs, psychology, nutrition
  - Filling information gaps identified by families
  - Threshold-guided feeding in some high-threshold challenge reactors
  - Ladders/DAT in a small subset of milk & egg patients
- Limit misdiagnosis: QI project involving > 1500 PCPs (Gerry Lee)
- Equity / Access: working on it!
- OIT: currently peanut only, from **< 1y** to 21, “puffs” & PTAH
- Research: 9 clinical trials & soon, real-world clinic-based studies

PARKING LOT

Children's℠
Healthcare of Atlanta

EMORY
UNIVERSITY

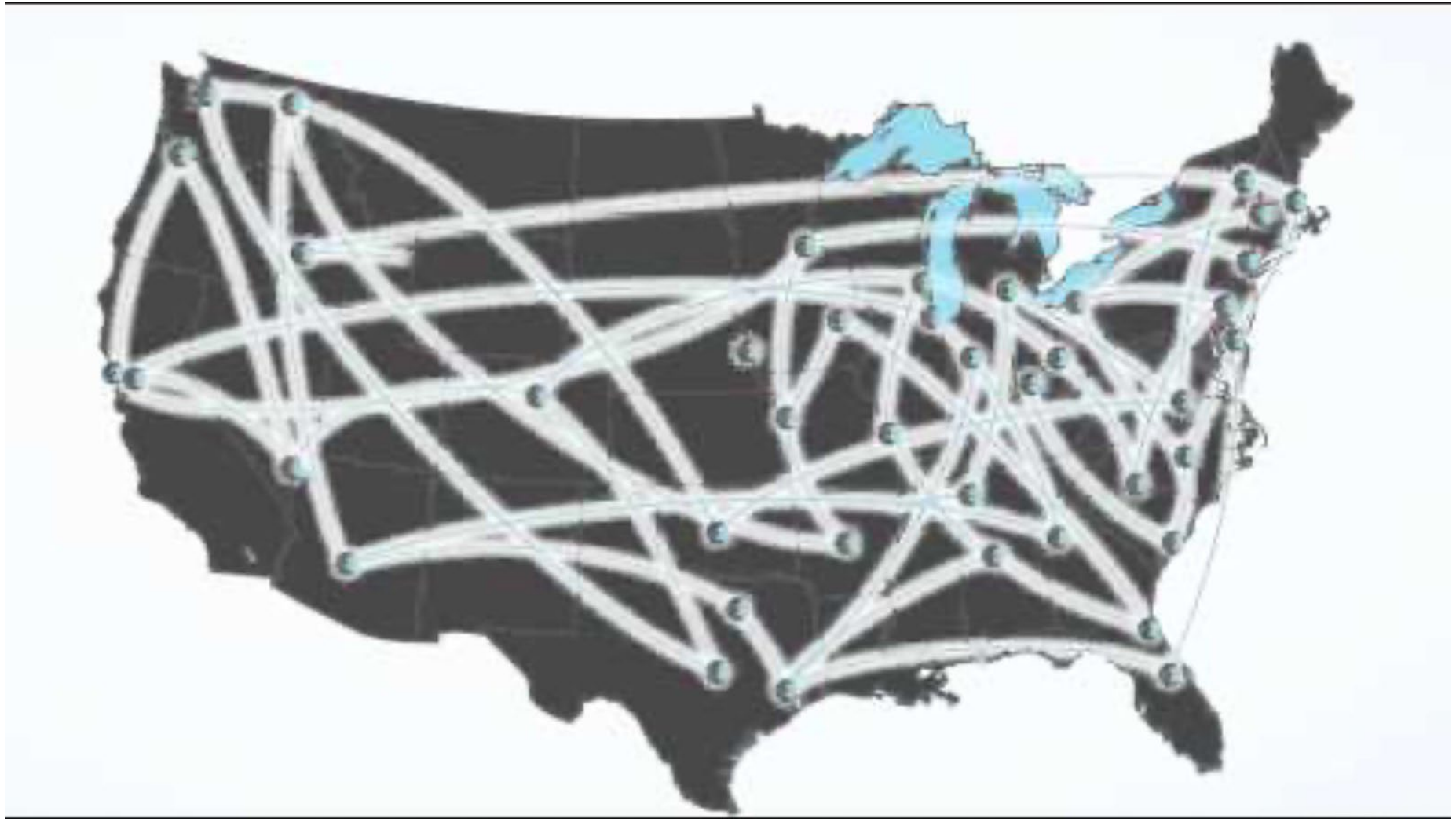
Omalizumab: as Adjunct to Oral Immunotherapy



A SR/MA of 36 interventional clinical trials showed OMA+OIT significantly improved desensitization, QoL, & IgG4 levels across multiple foods treated

Dantzer and Wood Annals 2023
Zuberbier et al JACI: In Pract 2023

An Example of a LHS: ImproveCareNow



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 5, 2011 VOL. 364 NO. 18

Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

Design: Two parallel, pragmatic trials to evaluate effectiveness of LTRA

Study 1: LTRA vs inhaled glucocorticoid for first-line asthma-controller therapy

Study 2: LTRA vs a long-acting beta2- agonist as add-on therapy in patients already receiving inhaled glucocorticoid therapy.

Suggestions to Continue Moving Forward For Patients

- Data harmonization "package" – with consensus standards for all studies
  - Endpoint definitions and reporting conventions (e.g. MTD, CRD, severity of resulting reaction)
  - Uniform challenge schedules & stopping rules
  - Case report forms built for these purposes
  - Raw data available wherever possible for re-analysis by journals, regulators, academic groups
- Commitment towards developing low-cost methods to characterize allergens and study them with rigorous research methods
- Continued progress towards "less invasive"/challenge-alternative endpoints – AI/machine learning? Composite scores?
- RWE/Phase 4 networked research using standardized materials, dosing, CRFs embedded within EHRs
- Accelerating tolerance approaches to move beyond desensitization
- More funding - $78M of $33B total NIH budget (0.2%) went to food allergy in 2017
- Other ideas???

Coordinated, global effort among diverse stakeholders – this is an international field

Regulators, patient advocates, clinical scientists, data scientists, journal editors, society leaders

Defining Severe Phenotypes – DEFASE

Domains	Mild (1 point for each domain)	Moderate (2 points for each domain)	Severe(3 points for each domain)
(A) Symptoms / signs with the most severe previous reaction	• Only cutaneous (e.g. generalized pruritus, flushing, urticaria, angioedema) and/or mild gastrointestinal (e.g. oral pruritus, oral tingling, mild lip swelling, nausea or 1-3 emesis, mild abdominal pain) and/or rhinoconjunctivitis symptoms	• Lower respiratory and/or laryngeal and/or gastrointestinal (e.g. persistent crampy, abdominal pain, ≥4 vomiting and/or diarrhoea) and/or cardiovascular symptoms or signs	• Respiratory and/or circulatory failure
(B) Minimum therapy to treat the most severe previous reaction[α]	• No previous need for adrenaline (epinephrine). Only symptomatic therapy (e.g. local and systemic antihistamines)	• Reaction(s) have always visibly responded to a maximum of two doses of i.m. adrenaline (epinephrine)*	At least one of the following therapies was administered to treat a previous reaction: • More than 2 doses of i.m. adrenaline (epinephrine) needed* • Intensive care treatment (e.g. positive pressure ventilation, intubation, intravenous vasopressors, extracorporeal membrane oxygenation)*
(C) Individual minimal eliciting dose [α] Based on datasets reviewed and used by WHO/UN FAO Codex Expert Panel	• > ED20 exposure	• ED05 <exposure≤ ED20	• ≤ED05 exposure
(D) Current food allergy-related - quality of life (FA-QoL)	• No/minimal impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0 to 6 (6-0/3) =2, 0-1.99 = no - minimal impact]	• Moderate impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0 to 6 (6-0/3) =2, 2-3.99 = moderate impact]	• Severe impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0 to 6 (6-0/3) =2, ≥4: severe impact]
(E) Current health-economic impact **Items: direct medical costs, direct costs to other sectors of the economy, and indirect costs (see DEFASE economic score at Table 1B.**	• No or minimal impact (ES ≤ 30)	• Moderate impact (ES: 31 to 60)	• Severe impact (ES ≥ 61)

≤ 6: Mild FA ; 7 – 12 Moderate FA ; ≥ 13 Severe FA
Still in development, requiring validation

Arasi et al WAOJ 2023

Lesson 3: We Still Have Major Data Gaps to Address

A. How do we even know if these treatments work? (Outcomes)

- Standardized endpoints: challenge schedules & stopping rules
- Universal reporting conventions
- Patient Reported Outcomes

B. What approaches yield the best outcomes? (Optimization)

- Target maintenance dose and buildup schedule

(*note: can't really be done without at least some allergen standardization/controls*)

C. Who is the right patient? (Phenotype)

- Threshold sensitivity and risk

Five Key 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 are focused on?
   - 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

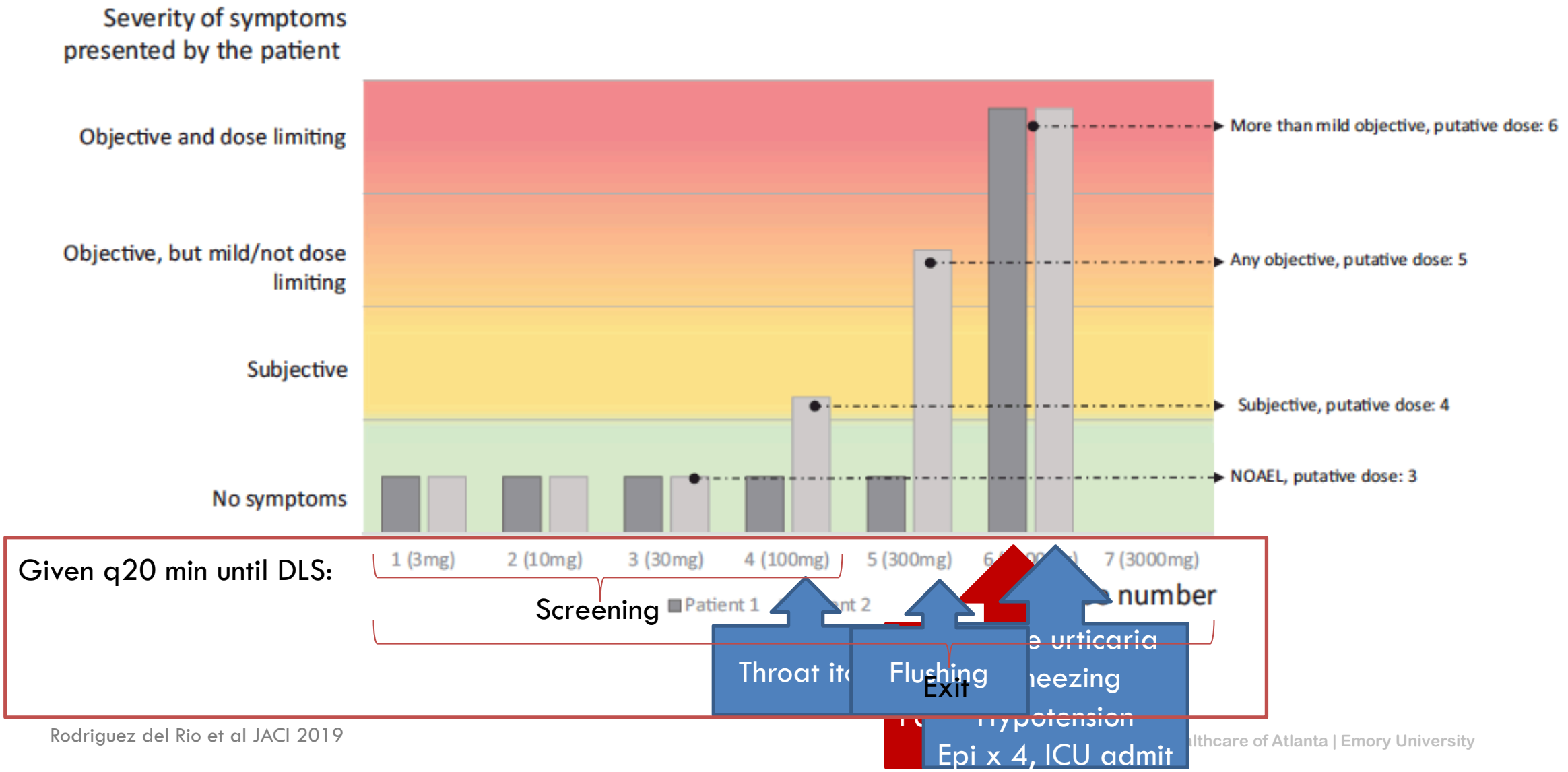
4. For whom (and for which treatment(s)) is the risk/benefit equation acceptable and for whom is it not?

5. Will treatment be cost-effective? How do we define value?

DEFASE Economic Scoring

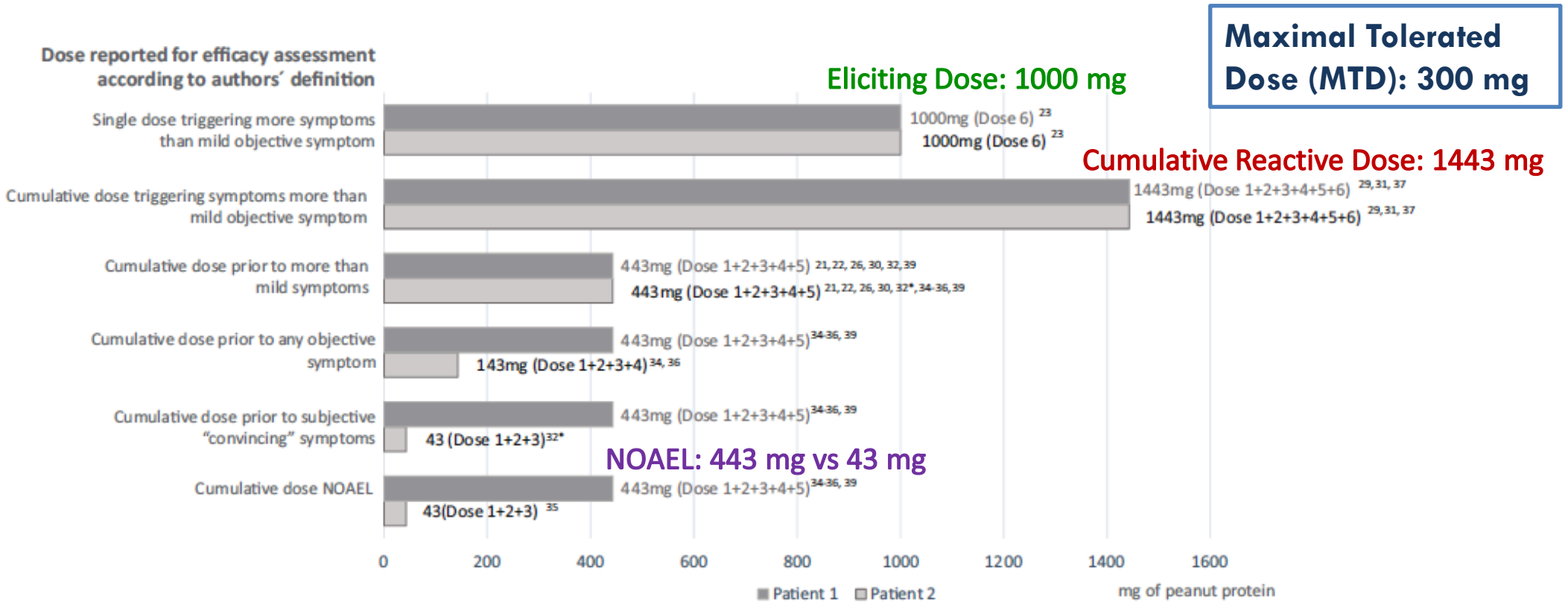
ITEMS*	Unit value	Number of events	Final value
N° of outpatient visit(s) to the allergy specialist(s) in the last year	2.5		
N° of other outpatient visits due to FA in the last year (eg. dietician, psychologist [non-MD])	1		
N° of community visits due to FA in the last year (eg. GPs, general pediatrician)	1.2		
N° of serum test panels (extracts) in the last year	1.5		
N° of molecular diagnostic tests in the last year	3		
N° of cutaneous tests in the last year	1		
N° of in vivo tests (oral food challenges) in the last year	6.5		
N° emergency department visit(s) in the last year because of FA	8.5		
N° emergency department admission(s) in the last year because of FA	20		
N° emergency ambulance call(s) because of FA in the last year	5		
N° day(s) spent in ICU because of FA in the entire patient's life	33		
N° adrenaline(/epinephrine) auto-injector prescription in the last year because of FA	2.5		

Within-Study: 2 Participants Reacting at the Same Challenge Dose



Rodriguez del Rio et al JACI 2019

The Reporting Convention Influences the Perception of Effect



Note: The severity of the challenge reaction symptoms are generally not part of the outcome description!

Rodriguez del Rio et al JACI 2018

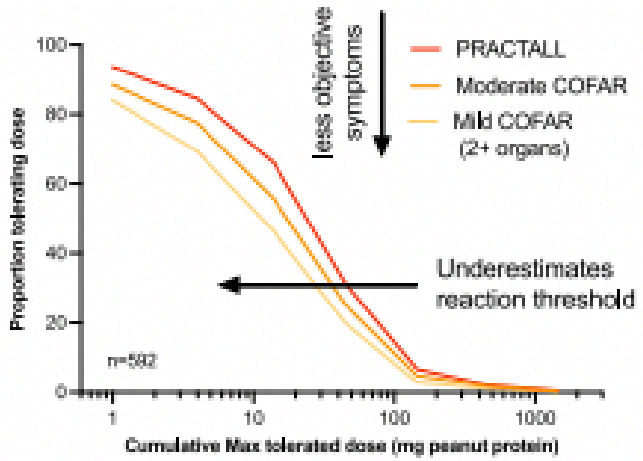
Also see: Chipps et al JACI:Pract 2019

Between-Studies: Subjectivity in Stopping Rules

GRAPHICAL ABSTRACT

Impact of using less objective symptoms to define tolerated dose during food challenges: a data-driven approach

Underestimates maximum tolerated dose at baseline by around 1 dosing interval

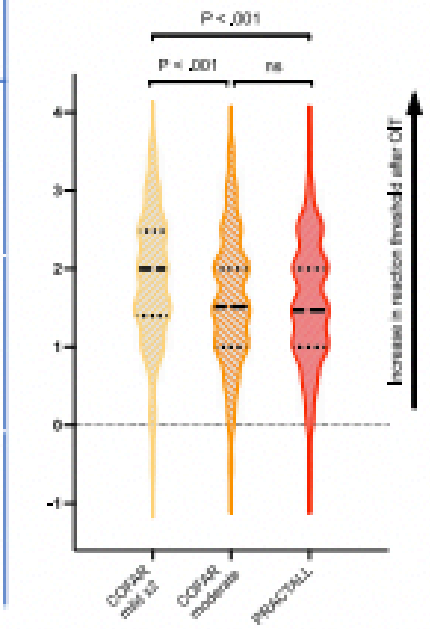


...and increases rate of placebo reactions

Challenge threshold less reproducible

	% reacting to ±1 dosing interval
Mild COFAR symptoms (2+ organs)	51%
Moderate COFAR symptoms	61%
PRACTALL criteria	71%

15% overestimate in efficacy of oral immunotherapy (OIT)



For Reference:

Lower bound of 95%CI ≥ 12.5% is considered evidence of superiority

Turner et al JACI 2023

We Have Ignored the Patient Voice For Too Long

1. The (increasingly available) choice of allergen immunotherapy requires a major shift in mindset & responsibility: from avoidance to home-based daily exposure by a caregiver-provider.

+

2. Why & how patients and caregivers make this choice and how it affects outcomes that they, not their physicians, prioritize are major knowledge gaps.

+

3. Currently this framework is relatively simple but complexity will only continue to increase.

=

There is an Urgent Need to Address These Gaps Through Patient-Centered Research and Other Means

Potentially vulnerable individuals are left to navigate this landscape without adequate mental health & other support

Limitations With Current Efficacy Endpoints

Areas of alignment or adherence to precedent

- Use of DBPCFC for efficacy outcomes
  - Rejection of field studies for registration
- Semi-log DBPCFC dosing based on PRACTALL
- Qualifying sensitivity at baseline
  - When ≤ 100 mg, efficacy met @ ≥ 600 mg
  - When ≤ 300 mg, may need ≥ 1000 mg

Note: we may not be as aligned as we thought! Stakeholder groups are increasingly seeking to refine or even replace these methods.

Areas not yet aligned

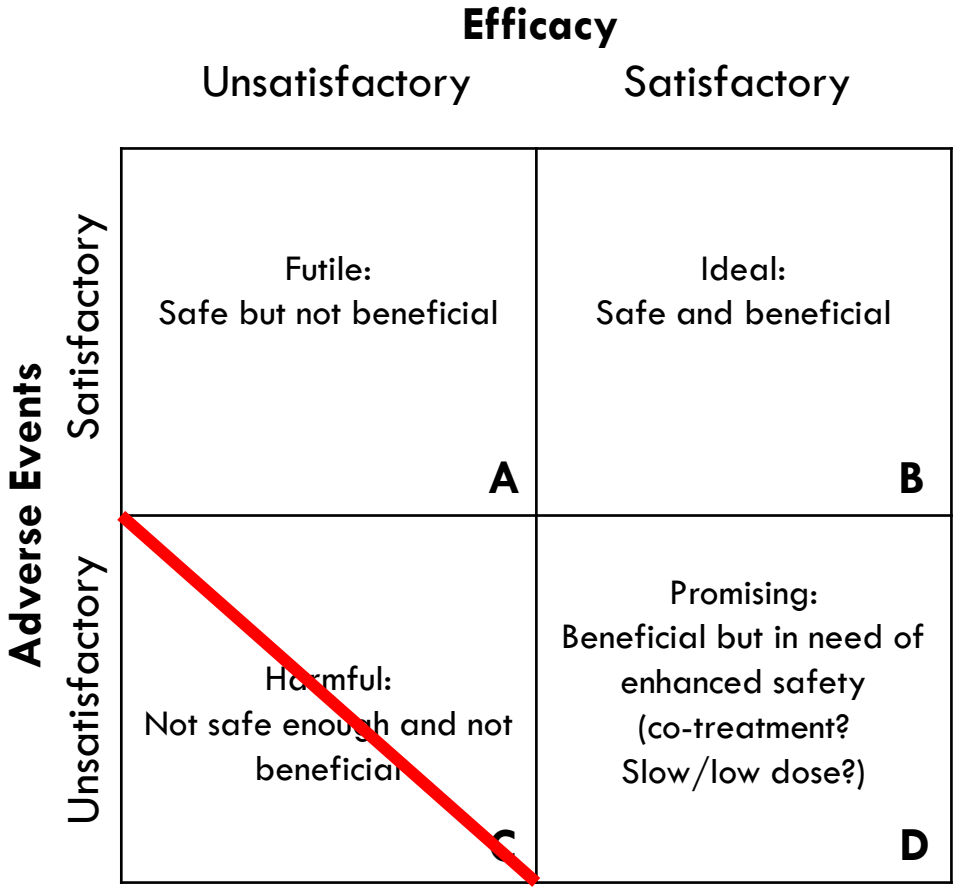
- Challenge stopping rules – CoFAR/PRACTALL/etc
- Deviation from PRACTALL dose schedule
- How to report the threshold measurement
  - Absolute or relative to baseline
  - Single dose or cumulative
  - Highest tolerated or reactive
- How to factor severity into endpoint measure
  - "no more than mild" symptoms vs. any symptoms
- Methods to protect the blind
  - Of the IMP in an RCT
  - Of the challenge material itself
- Which statistical analysis to use
- How to measure patient-important outcomes

Generally speaking, no two sponsors or studies measure and analyze the primary outcome the exact same way

Hise and Rabin Curr Allergy Asthma Rep 2021

Until a Cure is Developed, Food Allergy is a Threshold Game

Endotypes Likely Influence Outcomes (and eventually, treatment decisions)



Management of food allergy in the 21st century

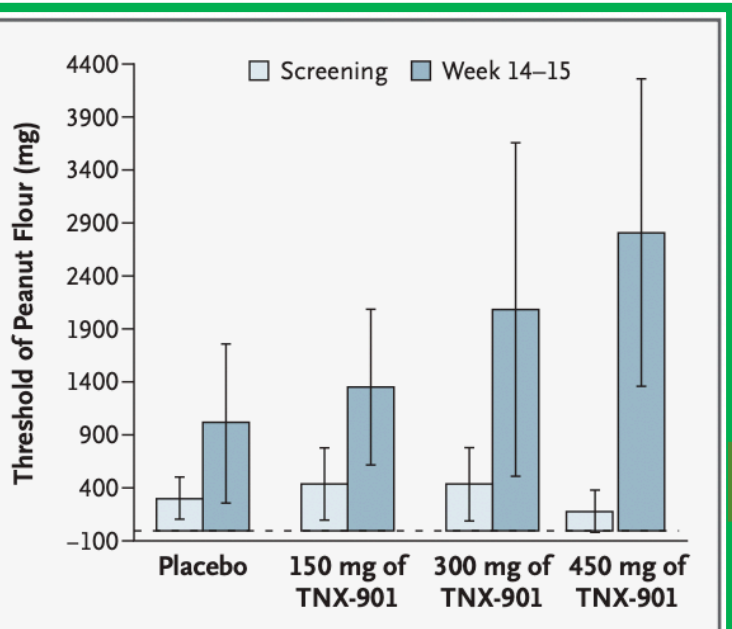
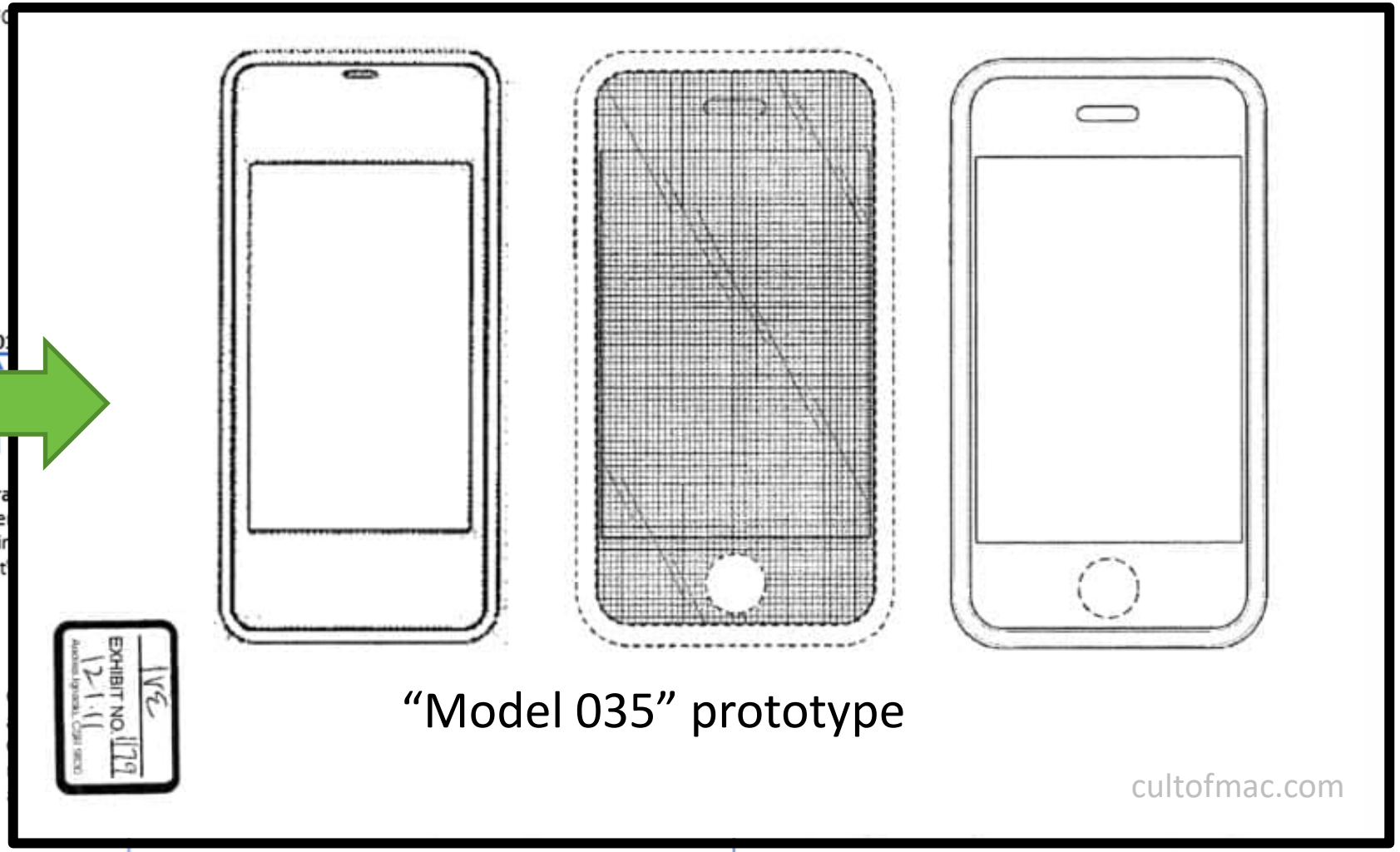


Figure 1. Mean Threshold Dose of Peanut Flour Eliciting Symptoms in Patients Receiving TNX-901 or Placebo.

The mean increase in the threshold of sensitivity, as compared with that in the placebo group, reached significance only in the 450-mg group (P<0.001); however, results of the test for trend with increasing doses were significant (P<0.001). I bars are 95 percent confidence intervals.



"Model 035" prototype

cultofmac.com

TNX 901 identified as potential therapy in FA patients[85]

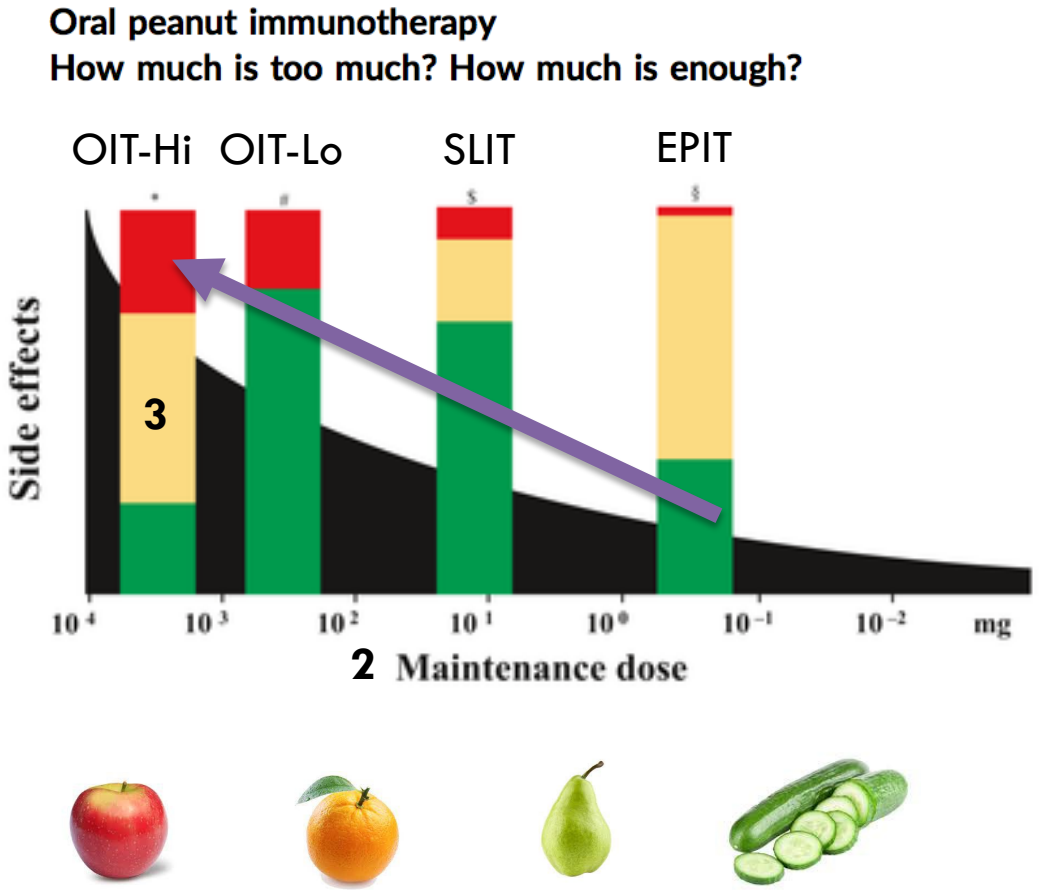
OMA tested as monotherapy in peanut allergic adolescents and adults[86]

FAQLQ developed, validated and recommended as gold standard tools by the EAACI to assess FA-HRQL[121]

PANAS adapted for a population of individuals with FA[118]

Cafarotti et al Clin Exp Allergy 2022
Leung et al NEJM 2003

Fundamental Challenges in Food Allergy Clinical Development



No way to measure exposure vs. outcome / dose-response

- No consensus definition of "desensitization" or "remission"
- Poor understanding of what patients truly want
- Different doses/routes under study; PK/PD impossible
- No reliable biomarkers (yet?)

Food AIT clinical development is not traditional

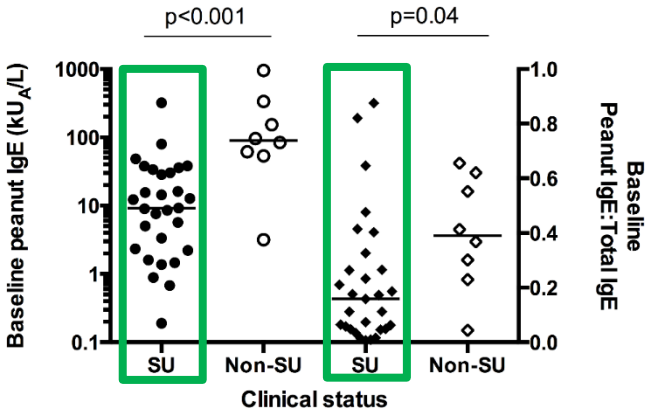
- Tox studies generally not required & some sponsors have bypassed Phase 1
- Dose-finding trials rare; to my knowledge not required or urged by regulators
- Few programs have performed > 1 Phase 2 trial

Efficacy-effectiveness are tenuously related

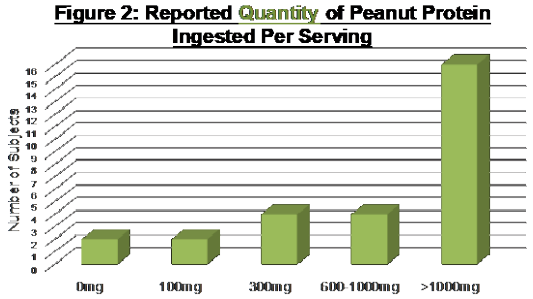
- No MCID estimates
- Trial outcomes reliant on DBPCFCs (not used in practice – introduces bias and limits generalizability)
- Variation in endpoint assessments as already discussed
- No accepted way to define phenotypes

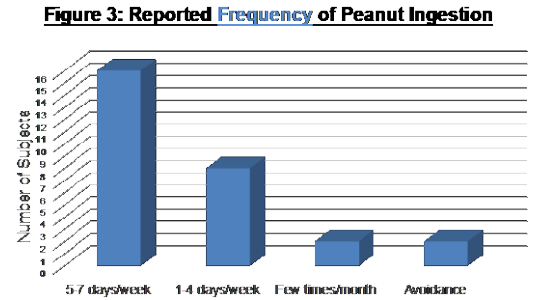
Blumchen & Eiwegger Allergy 2019

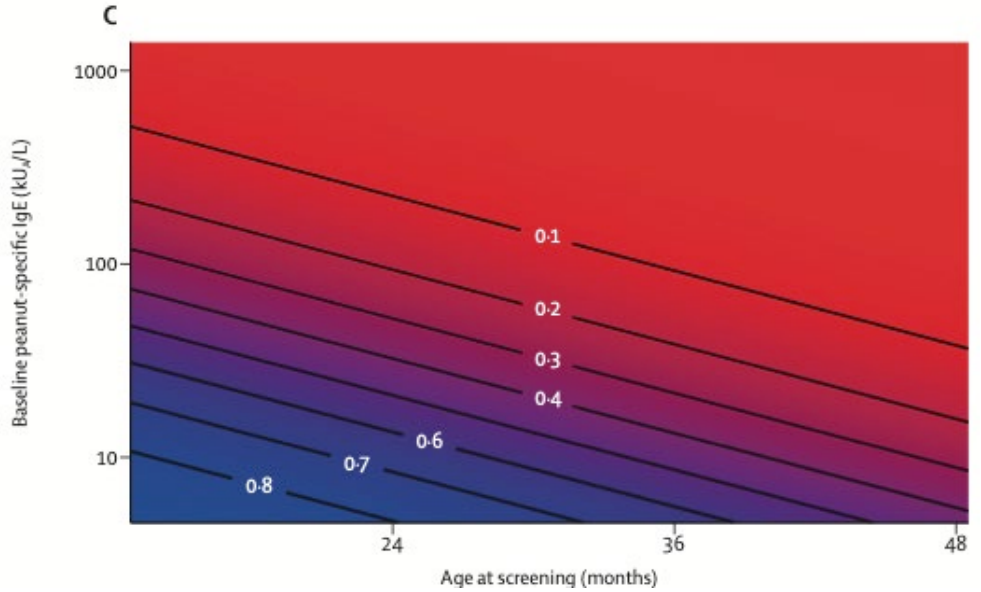
Early OIT May Be Disease-Modifying & is Arguably Best Use



Overall: 78% SU (aka remission)
Low dose (300 mg) = high dose (3000 mg)





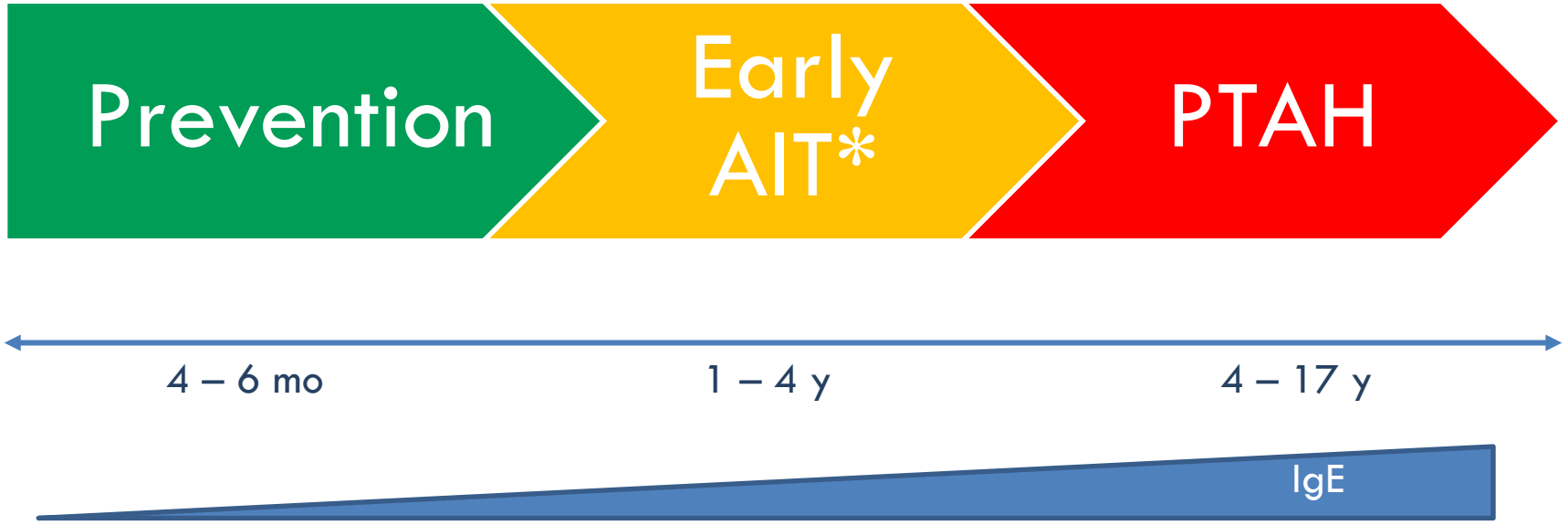


DEVIL
Single-Center
Randomized, Open label
N=40

IMPACT
5 Centers
Randomized, DBPC Trial
N=146

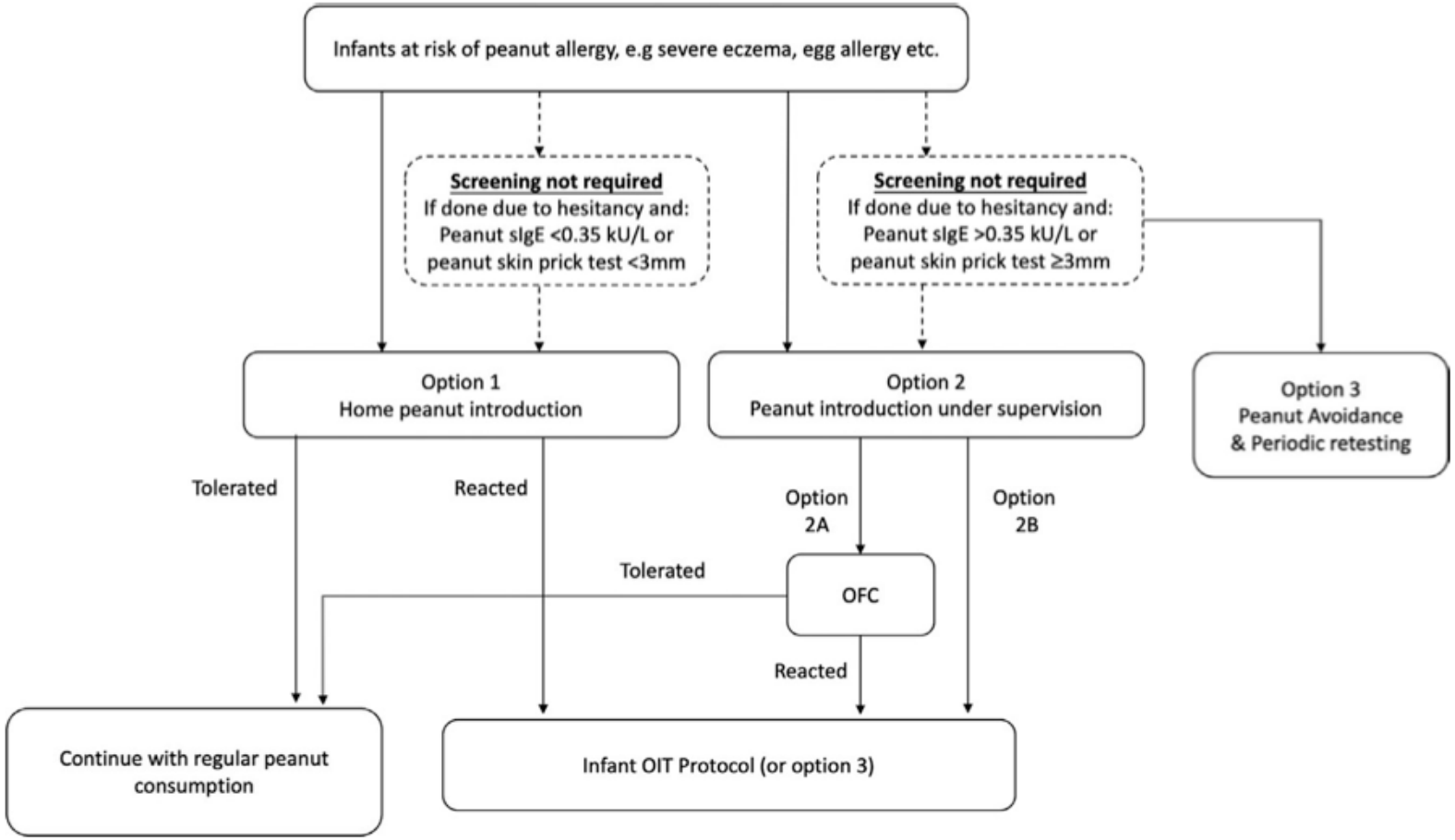
Vickery et al JACI 2017
Herlihy et al JACI:In Pract 2020
Jones et al Lancet 2022

Managing Peanut Allergy Through Exposure: High-Quality Data Support A New "Continuum" Approach



***Positive Phase 3 results from EPITOPE EPIT trial and POSEIDON OIT trial in 1 to 4 year olds: commercial potential in this age group?**

Prevent or "Salvage"



Chua et al JACI: In Pract 2022

Table 1 Differences between efficacy and effectiveness studies

	Efficacy study	Effectiveness study
Question	Does the intervention work under ideal circumstance?	
Setting	Resource-intensive 'ideal setting'	
Study population	Highly selected, homogenous population Several exclusion criteria	
Providers	Highly experienced and trained	
Intervention	Strictly enforced and standardized No concurrent interventions	

3 Key Features Distinguish Effectiveness Studies (Pragmatic or Practical Trials) and Efficacy Studies (Explanatory Trials, Usually RCTs):

1. Population – generalizability
2. Intervention – head to head comparisons
3. Outcomes – functional, universal (symptom burden, QOL, impact on ADLs/functioning, life expectancy, healthcare utilization, etc)

Singal et al Clin Gastro Hepatol 2014

Was Palforzia's Market Failure Related To These Difficulties? And Where Do We Go From Here?

Bloomberg

US Ec

● Live Now Markets Economics Industries Tech AI Politics Wealth Pursuits Opinion **Businessweek** Equality G

Businessweek
Business

Nestlé's $6,000 Peanut Allergy Pill Has Been a Dud

It spent $2.6 billion developing Palforzia, but the treatment regimen proved too cumbersome for many prospective patients.