

ALLERGY TESTING: INS & OUTS

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Allergy Testing: Ins & Outs

- Why does it matter:
 - Allergic rhinitis – QOL. Rx starts w/ Diagnosis.
 - Asthma/ RAD (reactive airway disease):
 - 4% of the population has asthma, but up to 60% of allergic rhinitis sufferers have asthma.
 - Pet allergy & asthma - #1 predictor not outgrowing it.
 - Pet allergy – no one is allergic to their own pet?!?
 - Predictive of who outgrows asthma & who does not.
 - +allergy 15% outgrow it, (-) allergy 85% outgrow it.
 - Food allergy – 25% of people report a food allergy, reality 3-5% has a food allergy.
 - Eczema – 30-40% of mod-sev worse w/ food allergy

Allergy Testing: Methodologies

Proven Clinical Value

- Prick Skin Testing
- CAP-RAST (serum quantitative IgE)
- Patch Testing
- Direct Challenge (food/environmental)
- Potential Benefit
 - ▣ Limited Intradermal
 - ▣ Basophil activation

No Proven Clinical Value

- Quantitative/ End-point Intradermal titration
- Applied Kinesiology
- Electrodermal Skin Test
- IgG4, IgG, IgA - ELIZA
- Cytotoxic Testing

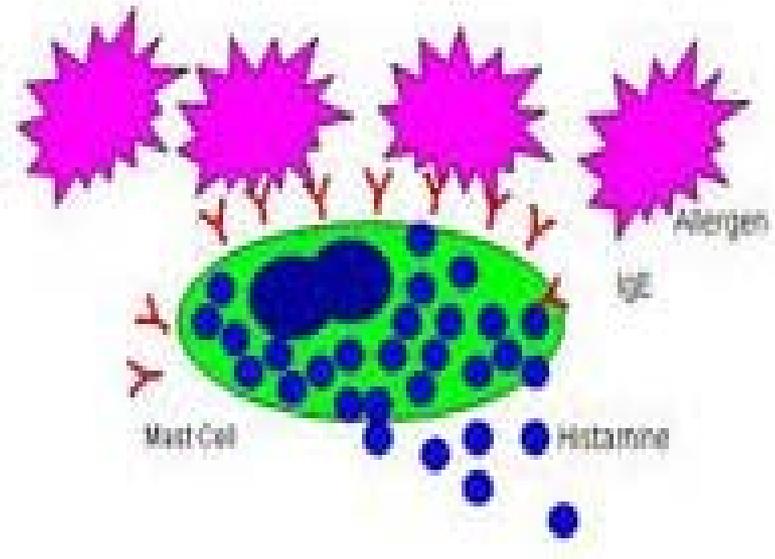
Prick Skin Testing (PST)

Advantages: in vivo, cheap, quick, minimal discomfort, efficient, more accurate than CAP-RAST, visual

Disadvantages: in vivo, false positives/ negatives, cannot test on anti-histamines, less quantifiable, dermagraphism, food intolerances not detected (Celiac).



PST: How it works

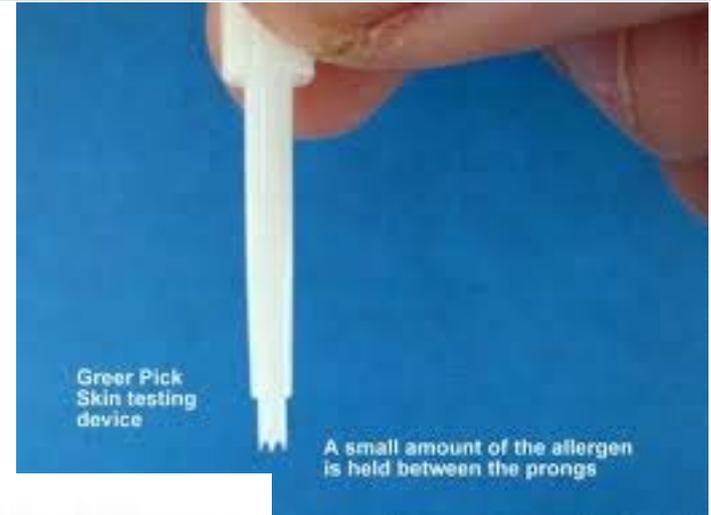
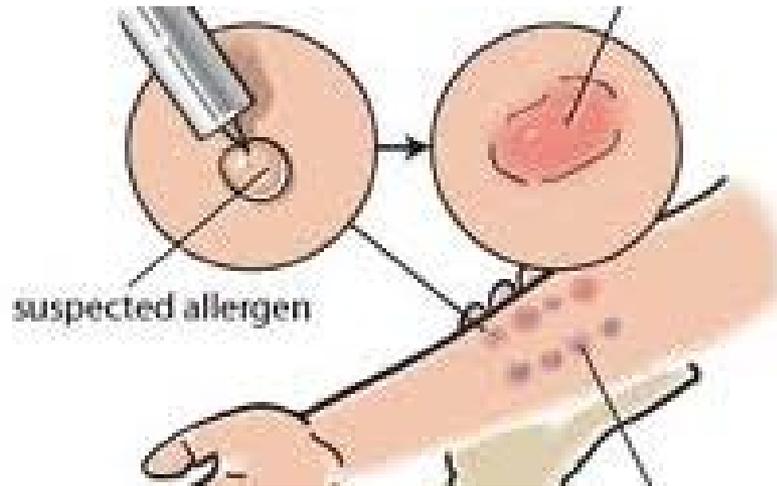


Allergen from the prick device is bound by IgE anti-body bound to the high-affinity IgE receptor on skin-bound basophils. If two IgE anti-bodies bound to two separate IgE receptors on a basophil, the intra-cellular tails cross-link activating a series of events that lead to histamine release by the basophil and local vasodilation and a hive. The more bound allergy-IgE, the more histamine released, the larger the hive.

PST: What we can test



PST: Devices

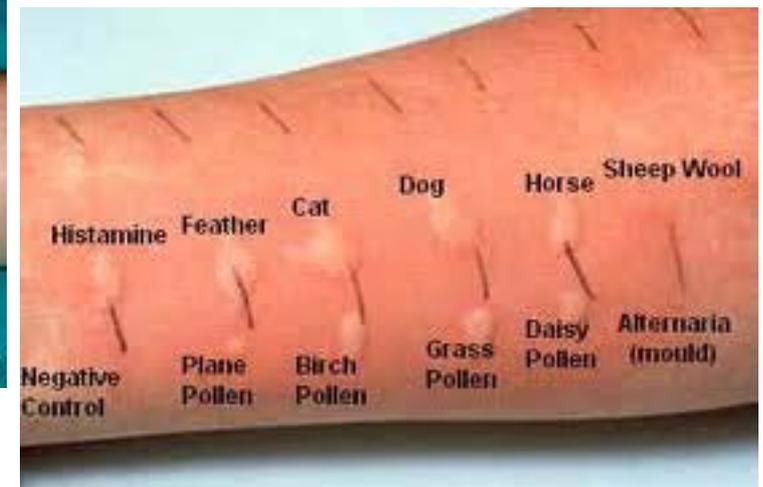


ELSEVIER

PST: what do the results look like



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PST – Sensitivity/ Specificity

Food

- General:
 - ▣ (-) Test 95% negative predictive value
 - ▣ (+) Test 50% positive predictive value
- Larger positives = larger (+) predictive value

Environmental Allergen/ Venom

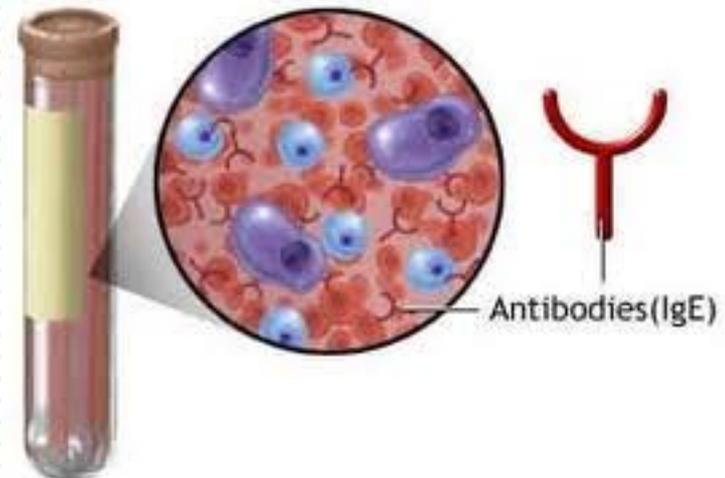
- Environmental
 - ▣ (-) test = likelihood ratio 0.1-0.28
 - ▣ (+) test = likelihood ratio 5-7
- Venom
 - ▣ Only test those with history of systemic rxn.

LR >5.0 or <0.2 has high likelihood of disease probability

CAP-RAST (in vitro serum test)

Advantages: can test on antihistamines, quantifies the amount of free specific IgE anti-body

Disadvantages: expensive, painful, high IgEs skew results, delayed results, difficult to interpret – results printed with blood tests completely wrong



CAP-RAST

- Results reported as allergen-specific IgE concentrations in kU_A/L
- Diagnostic levels indicating 90% and 95% positive and negative predictive values for reactions to egg, milk, peanut and fish
- Results used to identify patients most likely to react on subsequent food exposure
- Findings have been verified and extended to other populations
- Confounders: High total IgE (>3000), Non-IgE mediated disease

UTILITY OF FOOD-SPECIFIC IGE CONCENTRATIONS IN PREDICTING SYMPTOMATIC FOOD ALLERGY

Recommended interpretation of food-allergen specific IgE (kU_A/L) levels in the diagnosis of food allergy

Probability of reaction

	Egg	Milk	Peanut	Fish	Soy	Wheat
No challenge if \geq	7	15	14	20	65	80
Possibly reactive Physician challenge					30	26
Unlikely to react if $<$ And negative skin test And lack of compelling history Home challenge	0.35	0.35	0.35	0.35	0.35	0.35

Even with negative skin test and low CAP RAST challenges are safest under observation.

Sampson HA, JACI 107:891-6, 2001



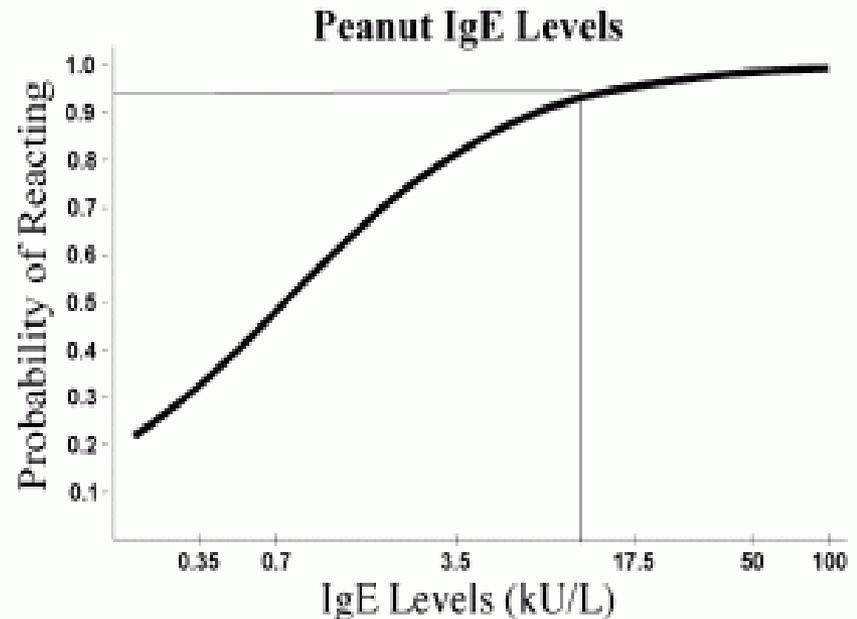
PROBABILITY OF REACTING TO A FOOD AT A GIVEN IGE VALUE

95% Predictive Level

Allergen	[kU _A /L]	PPV
Egg	7	98
- Infants ≤ 2 yrs ⁺	2	95
Milk	15	95
- Infants ≤ 2 yrs ⁺⁺	5	95
Peanut	14	100
Fish	20	100
Tree nuts ⁺⁺⁺	~15	~95
Soybean	30	73
Wheat	26	74

+ Boyano MT, et al. Clin Exp Allergy 2001; 31(9):1464-9.
 ++ Garcia-Ara C, et al. J Allergy Clin Immunol 2001; 107(1):185-90.
 +++ Clark AT, Ewan P. Clin Exp Allergy. 2003; 33(8):1041-5

PPV = Positive predictive value



Increasing probability of clinical reactivity with increasing level of food-antigen specific IgE value; note: values <0.35 do not exclude allergic reactivity

Sampson HA. JACI 113:805-19, 2004

CAP-RAST future

- Specific levels to specific proteins in a food to quantify risk better.
 - ▣ For example: peanut,
 - Positive araH2 high risk of anaphylaxis to peanut
 - Positive ara H1 & H3 – high probability allergy
 - Positive ara H8, likely pollen-food allergy syndrome

DIAGNOSTIC APPROACH TO THE EVALUATION OF FOOD ALLERGY



Epicutaneous skin testing

- Glycerinated commercial extracts 1:10 or 1:20 weight/volume
- Consider freshly prepared extracts for fruits and vegetables or if no commercial extract
- Applied by prick or puncture technique
 - Intradermal technique is not recommended
- Positive predictive accuracy
 - Less than 50% (many “false” positives)
- Negative predictive accuracy
 - Greater than 95% (few “false” negatives)

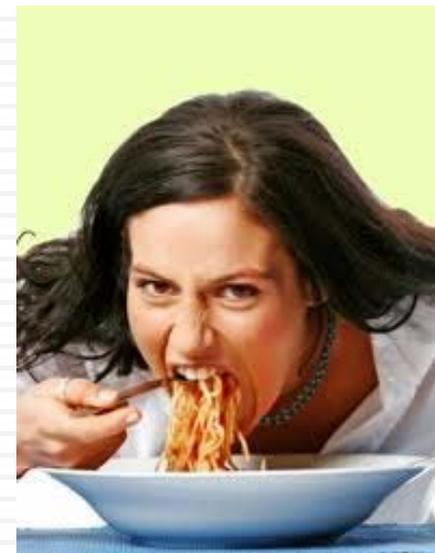
Select skin tests based on history and major foods known to cause symptoms.

Don't ignore a suggestive history, even with a negative skin test or CAP RAST.

Challenge – Primarily Food

Advantages: gold standard for food allergy, in vivo

Disadvantages: Time, cost, inconvenient, risk - SCARY



FOOD CHALLENGE - experiences

- Why – gold standard in food allergy & testing is not perfect.
 - ▣ 6 yo female, h/o tolerating cashew, PST negative, CAP-RAST 0.99 (most severe anaphylaxis to date)
 - ▣ 17 yo male, h/o tolerating peanut, PST positive, CAP-RAST 18, passed with flying colors, not allergic
 - ▣ 12 yo female, no peanut exposures in life, PST positive, CAP-RAST 10, passed peanut challenge, not allergic
 - ▣ 2 yo female, no walnut hx, PST positive, CAP-RAST 0.24, anaphylaxis to walnut
 - ▣ 58 yo female, hx anaphylaxis to shrimp 2 hrs after eating, PST positive, CAP-RAST <0.10, challenge ????

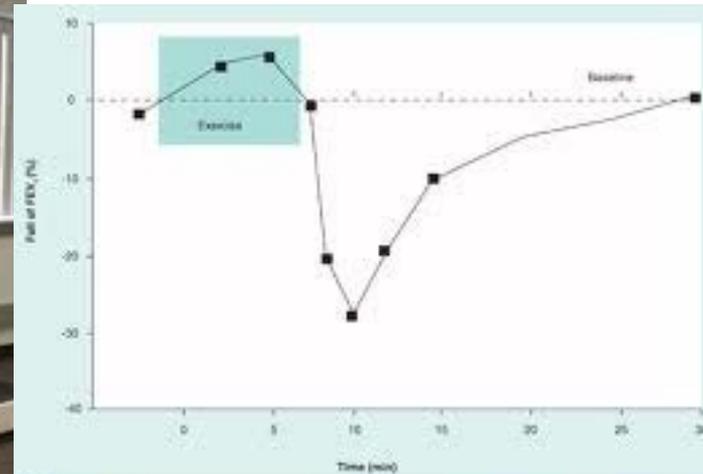
Challenges – What else?

- Perfumes
- Glade plug-in
- Cleaners
- Roof glue
- Exercise challenge
- Food + exercise challenge
- Medications
- Supplements

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"An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger."



Patch testing – dermatitis

For contact/ atopic dermatitis – Nickel most common

Tests: leather, cosmetics, formaldehyde, rubbers, cleaning products, meds & controversial: foods (eosinophilic esophagitis, accuracy for food testing questionable)



Patch tests

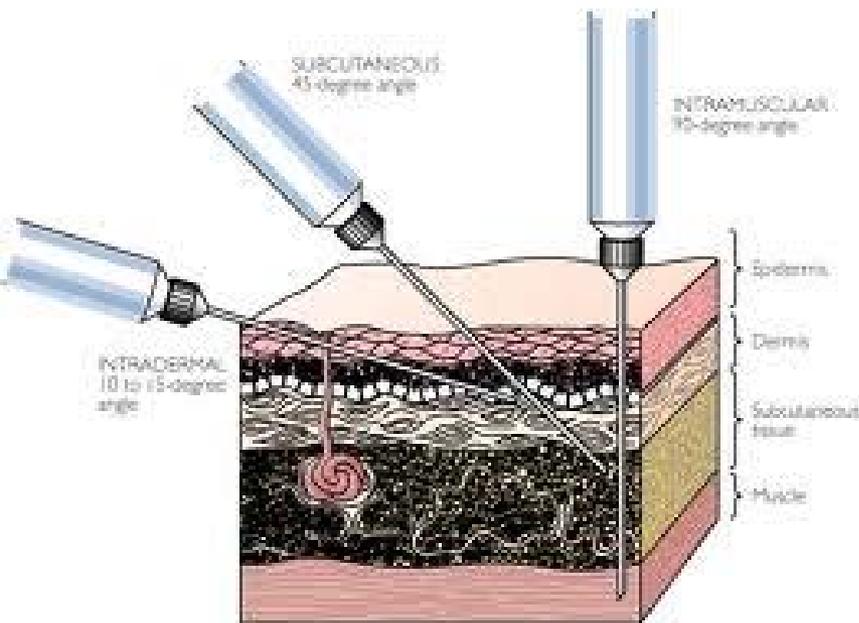
- Primarily for contact/ atopic dermatitis
 - ▣ TRUE test most common form
 - ▣ 72 hr test, needs to be placed Mon, Tue, Fri
 - ▣ Cannot shower for 72 hours.
 - ▣ Not as helpful as one would like.
- Food allergy patch testing for eosinophilic esophagitis (EoE)
 - ▣ Some promising results but questionable sensitivity
 - ▣ This author has not seen a positive test yet for this despite a year of research on it during fellowship.

Basophil activation (BAT)

Still being studied, basically evaluates the number of basophils that release histamine – not ready for prime-time

Intradermal Testing (IDT) - controversial

Similar to PST but small amount of allergen injected into dermis.



PST vs IDT

Quantitative Intradermal

- Prick skin testing (PST) followed by quantitative intradermal testing (qIDT) ~30/ pt.

Prick skin testing

- Prick skin testing (PST) w/ rare use of 1:1000 IDT (IDT) for pets (~1 in 20pts).

GOAL: Highly sensitive with low false negatives/ false positives, minimal pain/ cost

PST vs quantitative IDT

Why IDT is done, the myth.

- More accurate
- Safer, decreases risk of anaphylaxis with allergy shots.
- Cuts costs, shortens build up time.

Why it is not done, the reality.

- Not, true, see slides below for accuracy data.
- If large local reactions (LLR) do not predict systemic reactions, IDT does not.
- PST clinic - 80% pts at maintenance 6 months after starting vs. 20% in qIDT clinic.

JACI 2009;124:739-44
Ann All 1986: 56:331-4
JACI 2000;106:840-3
Ann All 2004;92:225-7

(Author's data)

PST vs qIDT - Accuracy

□ What does the data show:

1. +IDT vs -IDT showed no difference in prevalence in patients with AR/ asthma and those without.

Brown, JACI 1979; 63-328-335.

2. Pts w/ SAR Hx & negative PST to grass

- Compared above with +IDT vs -IDT to nasal challenge & sx's during season, no difference in the 2 groups.

Nelson, JACI 1996;1997:1193-1201

3. Pts w/ SAR Hx got PST, those neg got IDT follow up. If ID positive then nasal challenge:

- 17% of positive IDT tests correlated with history, 0% correlated with nasal challenge.

Schwindt. Ann All & Immun 2005;94:627-633

PST vs IDT - Accuracy

Test	Allergen	+ Likelihood	- Likelihood
PST	Cat	4.93	0.08
IDT	Cat	0.89	1.24
PST	Grass	6.82	0.28
IDT	Grass	1.05	0.98

- LR >5.0 or <0.2 has high likelihood of disease probability
- 1.0 to 2.0 and 0.5 to 1.0 small likelihood of disease and likely clinically insignificant.

PST vs qIDT - cost

Community Data

Mean	PST primarily	qIDT
#IDT	0.2	33
#PST	43	33
Total Cost	\$345	\$591 (71% more)

Select Health - Insurance data

Mean cost	IHC All	PST primarily	qIDT
IDT - \$	\$1.75	\$12	\$150
PST - \$	\$211	\$260	\$238
Total Cost	\$213	\$272 (28% More)	\$388 (82% more)

****Total direct cost of IDT to Select Health \$90,845 (2009) up from \$48,699 (2005).**

PST vs qIDT – additional costs

How many false positives are there?

	AR	NAR	Both
IHC Allergy	215 79.6%	55 20.4%	0 (0%)
Allergy – ID	1441 88.4%	190 11.6%	0 (0%)
qIDT	1290 93.5%	92 6.5%	0 (0%)

How many patients of each are on allergy immunotherapy - 2009?

	Total	# potential false positive
Allergy - ID	1557	137 (8.8%)
qIDT	542	75 (13.9%)

Assuming that all IHC-All pts are not false positives then **at least 13.9% of qIDT pts diagnosed with allergic rhinitis actually have non-allergic rhinitis and 13.9% of qIDT pts on shots probably should not be on shots.

PST vs qIDT – Total Cost 2009

Item	Cost
Direct costs of paying for Dx code 95024	\$90,845
Assuming 10.9% & 7.4% false positives, cost for shot administration (95117/95115) in patients on allergy shots.	\$73,410
Assuming 10.9% & 7.4% false positives, cost for extract prep (95165).	\$142,781
Total costs for intradermal testing to Select Health in 2009	\$307,036

****IDT added \$307,036 in costs to Select Health 2009 (2005 it added \$147,766).**

****If trend continues the likely cost to Select Health in 2021 is \$2,755,027.**

PST vs qIDT – costs to Utah & U.S.

- Select Health covers 535,224 (19.2%) people in Utah.
- Utah has 2,783,885 people and U.S. has 308,745,538 (US Census 2010).
- Total estimated **Utah costs \$1.6 million in 2009** and estimated **\$14 million in 2021.**
- Total estimated **U.S. costs \$177 million in 2009** and estimated **\$1.6 billion in 2021.**

PST vs qIDT: Why it matters

- IDT in addition to PST:
 - ▣ Increases cost (additional \$307,036 to IHC in 2009)
 - ▣ Increases patient discomfort
 - ▣ Is inferior to PST in accuracy
 - ▣ Fails to deliver on stated promises, i.e. time to maintenance (qIDT \$341 /year, All/Imm \$223/yr).
 - ▣ Over-diagnoses allergic rhinitis leading to ineffective therapies/ poor outcomes (13.9% false positives).

Electrodermal skin testing & Laser

Unproven methodology: Frequently used by chiropractors to evaluate & treat imbalances in energy

Key: Diagnose allergy that does not exist & then treat/ cure that allergy.

Electrodermal testing & Laser allergy therapy



Applied kinesiology

Unproven methodology: Naturopaths/ chiropractors/ etc evaluate for the effect of allergies/ intolerances on your bodies energy by evaluating your strength while holding the allergen.



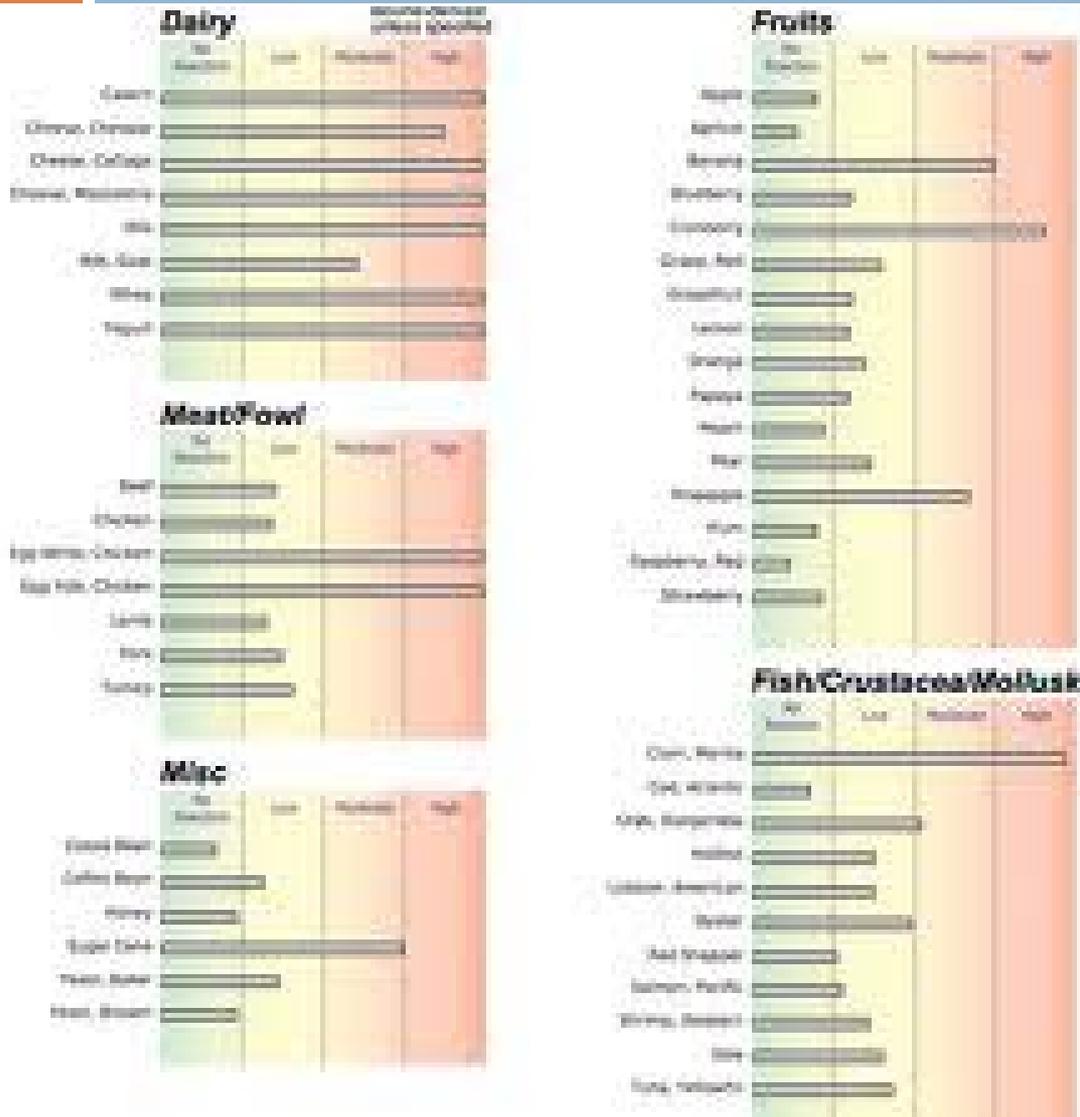
Applied Kinesiology



IgG, IgA & IgG₄ testing

Unproven testing method: Quantify specific IgG, IgA and/ or IgG₄ to specific foods, popular with naturopaths/ chiropractors.

IgG testing results



- Popular with naturopaths and argue it better tests delayed food allergy.
- No corroborating science.
- Pts with IgE mediated food allergy show increased IgG to those foods as people become tolerant.

Cytotoxic testing

Unproven methodology: As previous, another method reportedly to evaluate for delayed food allergy.

Key: Evaluates how WBCs proliferate around when in contact with the food or not.

Why does this all matter?

At least with food allergy???

Tolerance to extensively heated milk in children with cow's milk allergy

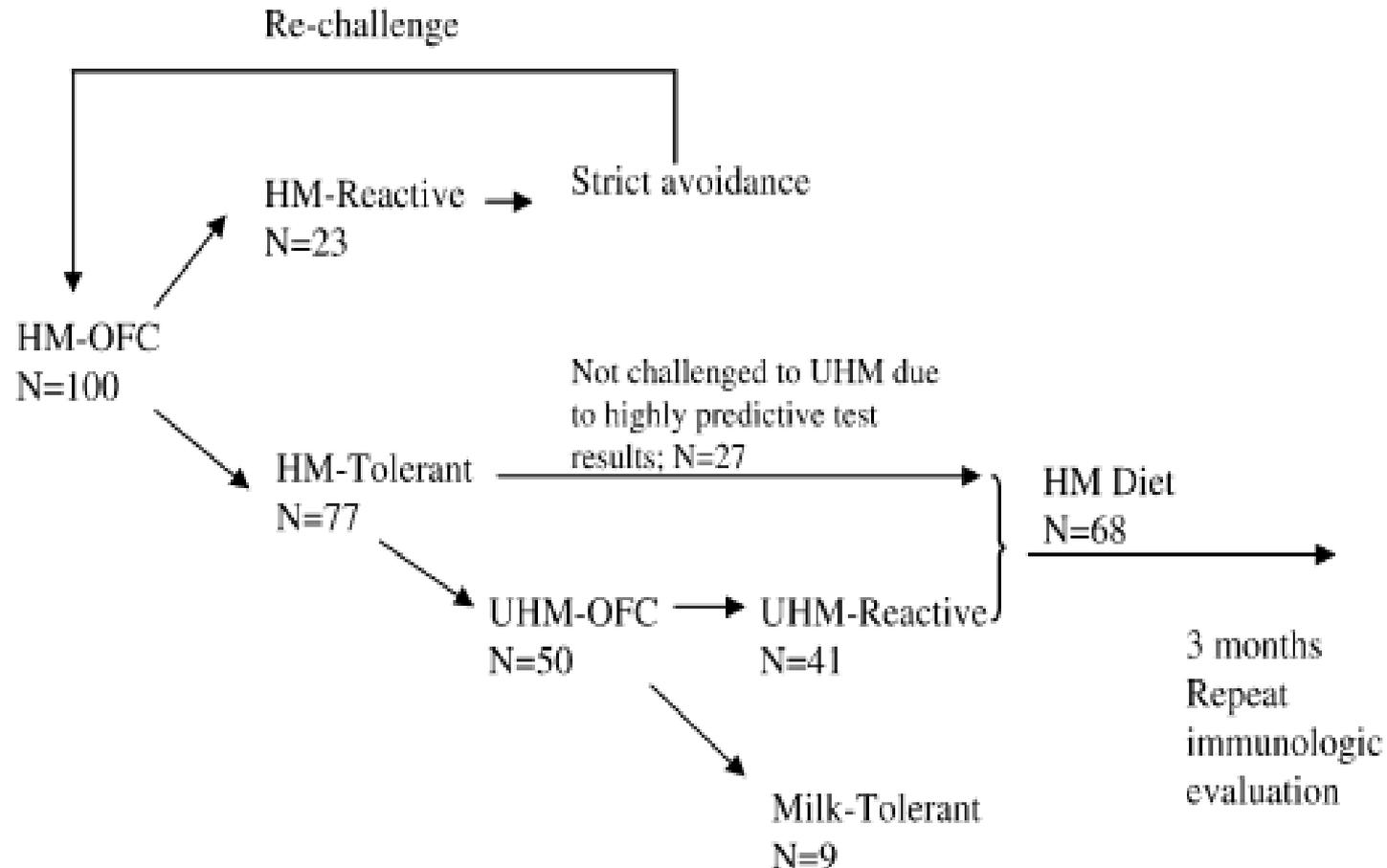


FIG 1. Study design and enrollment. *HM*, Heated milk; *OFC*, oral food challenge; *UHM*, unheated milk.

•75% of people with allergy tolerate milk cooked into baked goods.

Tolerance to extensively heated milk in children with cow's milk allergy

TABLE I. Baseline immunologic responses to milk proteins

	Heated milk-reactive (I)	Heated milk-tolerant (II)	Milk-tolerant (III)	P value* (I vs II)	P value* (I vs III)	P value* (II vs III)
Milk SPT, wheal size (mm), median (range)	9.5 (5-24)	7 (2.5-19)	6 (0-8)	.009	.001	.083
Milk IgE (kU _A /L), median (range)	11.6 (0.69-101)	2.43 (0-79.1)	0.925 (0.001-6.06)	<.001	.003	.854
Casein IgE (mg _A /L), median (range)	14.15 (0.71-101)	1.41 (0-101)	1.475 (0.48-3.69)	<.001	.013	.850
β-Lactoglobulin IgE (mg _A /L), median (range)	4.48 (0-101)	0.43 (0-63.7)	0.001 (0.001-2.32)	.002	.057	.960
Casein IgG ₄ (mg _A /L), median (range)	1.53 (0.04-6.73)	0.64 (0-23.8)	1.35 (0.09-31)	.999	.173	.113
β-Lactoglobulin IgG ₄ (mg _A /L), median (range)	0.57 (0-8.38)	0.36 (0-31)	1.23 (0.06-31)	.896	.326	.146
Casein IgE/IgG ₄ ratio, median (range)	10.58 (0-69.25)	1.69 (0-131.2)	1.327 (0-3.667)	.079	.068	.588
β-Lactoglobulin IgE/IgG ₄ ratio, median (range)	4.259 (0-54.74)	0.496 (0-1120)	0.0008 (0-2.417)	.868	.971	.82

TABLE II. Comparison of baseline and 3-month immunologic parameters in heated milk-tolerant subjects

	Baseline median (range)	3-Month median (range)	P value*
Milk SPT, wheal size (mm)	8 (2.5-19)	7 (2-10.5)	.001
Milk IgE (kU _A /L)	2.5 (0-79.1)	1.99 (0-76)	.493
Casein IgE (mg _A /L)	1.29 (0-101)	1.6 (0-84)	.769
β-Lactoglobulin IgE (mg _A /L)	0.15 (0-63.7)	0.49 (0-18.7)	.758
Casein IgG ₄ (mg _A /L)	0.54 (0-8.1)	1.02 (0.05-14.7)	.005
β-Lactoglobulin IgG ₄ (mg _A /L)	0.29 (0-11.3)	0.49 (0-31)	.328
Undetectable casein IgG ₄ (%)	6 (12)	0 (0)	.027†
Undetectable β-lactoglobulin IgG ₄ (%)	7 (14.3)	6 (12)	1.0‡
Casein IgE/IgG ₄ ratio	1.43 (0-131.2)	1.38 (0-55.4)	.148
β-Lactoglobulin IgE/IgG ₄ ratio	0.23 (0-235.9)	0.49 (0-17.4)	.319

- Some potential lab differences between MA patients with tolerance of extensively heated milk.
- Some evidence of immunological changes associated with ingesting extensively heated milk consistent with tolerance.

Tolerance to extensively heated milk in children with cow's milk allergy

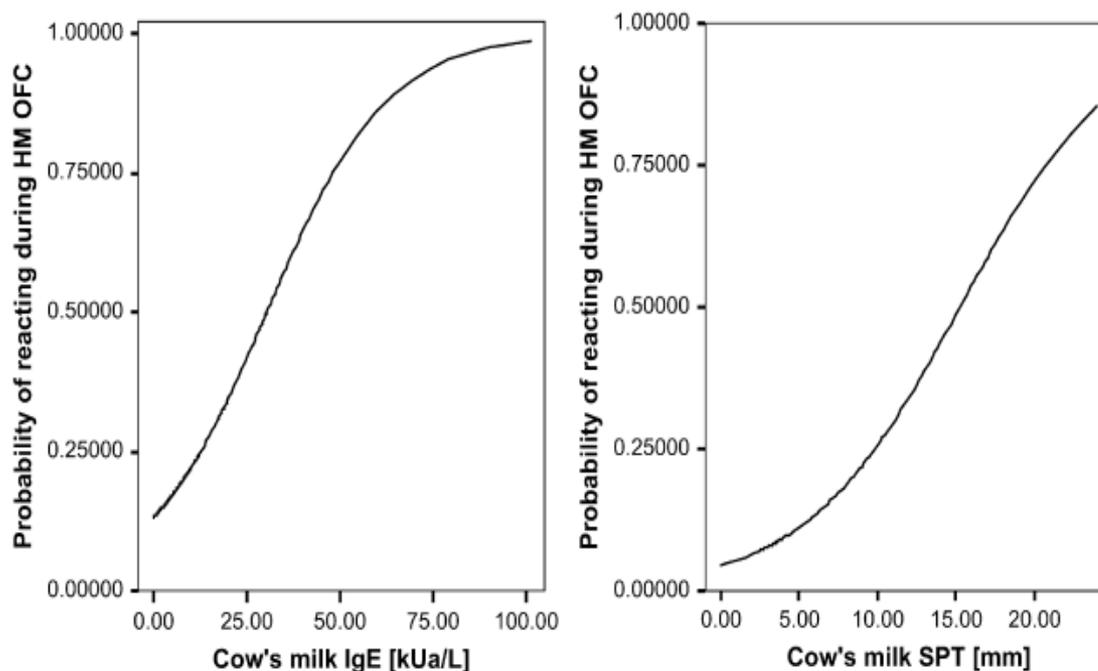


FIG 2. Predicted probabilities of the heated milk challenge outcome in regard to milk-specific IgE and SPT. Logistic regression was used to calculate the probability of reacting during heated milk (HM) oral food challenge (OFC) in regard to serum milk-specific IgE antibody concentration and SPT wheal size.

TABLE III. Percent tolerating heated milk oral food challenge in comparison with milk-specific IgE and SPT

Milk IgE (kU _A /L)	<0.35	0.35 to <5	5 to <20	20-100	<35	>15	>35
Tolerant	6/6 (100%)	51/57 (89.5%)	12/18 (66.7%)	4/14 (28.6%)	72/89 (80.9%)	6/17 (35.3%)	1/7 (14.3%)
Milk SPT wheal (mm)	0 to <3	3 to <5	5 to <8	<10	≥8	≥10	>14
Tolerant	2/2 (100%)	7/7 (100%)	32/39 (82.1%)	58/68 (85.3%)	31/45 (68.9%)	15/25 (60%)	2/6 (33.3)

Milk-specific IgE ≥15 kU_A/L and milk SPT wheal ≥8 mm have a 95% predictive value for acute reactions during an oral challenge with nonheated milk.^{15,16}



Thanks to my wife for her patience