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, dermatographism, food intolerances not detected (Celiac).
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

suspected allergen

Greer Pick Skin testing device
A small amount of the allergen is held between the prongs

Skin Testing
PST: what do the results look like
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
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 kUa/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

Sampson HA & Ho DG. JACI 100:144, 1998
### Utility of Food-Specific IgE Concentrations in Predicting Symptomatic Food Allergy

Recommended interpretation of food-allergen specific IgE (kU\textsubscript{A}/L) levels in the diagnosis of food allergy

<table>
<thead>
<tr>
<th></th>
<th>Egg</th>
<th>Milk</th>
<th>Peanut</th>
<th>Fish</th>
<th>Soy</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>No challenge if $&gt;$</td>
<td>7</td>
<td>15</td>
<td>14</td>
<td>20</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Possibly reactive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely to react if $&lt; 0.35$</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>And negative skin test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>And lack of compelling history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Allergen</th>
<th>[kU (_A)/L]</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>- Infants ≤ 2 yrs(^+)</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>- Infants ≤ 2 yrs(^++)</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Tree nuts(^+++)</td>
<td>~15</td>
<td>~95</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
</tr>
</tbody>
</table>

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

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**Sampson HA. JACI 113:805-19, 2004**
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

Sampson HA JACI 103:981-9, 1999

**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
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.
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

<table>
<thead>
<tr>
<th>Quantitative Intradermal</th>
<th>Prick skin testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Prick skin testing (PST) followed by quantitative intradermal testing (qIDT) ~30/ pt.</td>
<td>□ Prick skin testing (PST) w/ rare use of 1:1000 IDT (IDT) for pets (~1 in 20pts).</td>
</tr>
</tbody>
</table>

**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.

(Author’s data)

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


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

<table>
<thead>
<tr>
<th>Test</th>
<th>Allergen</th>
<th>+ Likelihood</th>
<th>- Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>PST</td>
<td>Cat</td>
<td>4.93</td>
<td>0.08</td>
</tr>
<tr>
<td>IDT</td>
<td>Cat</td>
<td>0.89</td>
<td>1.24</td>
</tr>
<tr>
<td>PST</td>
<td>Grass</td>
<td>6.82</td>
<td>0.28</td>
</tr>
<tr>
<td>IDT</td>
<td>Grass</td>
<td>1.05</td>
<td>0.98</td>
</tr>
</tbody>
</table>

- 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.

Gendo Ann Int Med 2004; 140:278-89
## PST vs qIDT - cost

### Community Data

<table>
<thead>
<tr>
<th>Mean</th>
<th>PST primarily</th>
<th>qIDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>#IDT</td>
<td>0.2</td>
<td>33</td>
</tr>
<tr>
<td>#PST</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$345</td>
<td>$591 (71% more)</td>
</tr>
</tbody>
</table>

### Select Health - Insurance data

<table>
<thead>
<tr>
<th>Mean cost</th>
<th>IHC All</th>
<th>PST primarily</th>
<th>qIDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDT - $</td>
<td>$1.75</td>
<td>$12</td>
<td>$150</td>
</tr>
<tr>
<td>PST - $</td>
<td>$211</td>
<td>$260</td>
<td>$238</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$213</td>
<td>$272 (28% More)</td>
<td>$388 (82% more)</td>
</tr>
</tbody>
</table>

**Total direct cost of IDT to Select Health $90,845 (2009) up from $48,699 (2005).**
<table>
<thead>
<tr>
<th></th>
<th>AR</th>
<th>NAR</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC Allergy - Allergy</td>
<td>215</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>79.6%</td>
<td>20.4%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Allergy - Allergy - ID</td>
<td>1441</td>
<td>190</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>88.4%</td>
<td>11.6%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>qIDT</td>
<td>1290</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>93.5%</td>
<td>6.5%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**How many false positives are there?**

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

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th># potential false positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy - ID</td>
<td>1557</td>
<td>137 (8.8%)</td>
</tr>
<tr>
<td>qIDT</td>
<td>542</td>
<td>75 (13.9%)</td>
</tr>
</tbody>
</table>

**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

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

**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.**
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).
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

- 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**

<table>
<thead>
<tr>
<th></th>
<th>Heated milk-reactive (I)</th>
<th>Heated milk-tolerant (II)</th>
<th>Milk-tolerant (III)</th>
<th>P value* (I vs II)</th>
<th>P value* (I vs III)</th>
<th>P value* (II vs III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk SPT, wheal size (mm), median (range)</td>
<td>9.5 (5-24)</td>
<td>7 (2.5-19)</td>
<td>6 (0-8)</td>
<td>.009</td>
<td>.001</td>
<td>.083</td>
</tr>
<tr>
<td>Milk IgE (kU/L), median (range)</td>
<td>11.6 (0.69-101)</td>
<td>2.43 (0-79.1)</td>
<td>0.925 (0.001-6.06)</td>
<td>&lt;.001</td>
<td>.003</td>
<td>.854</td>
</tr>
<tr>
<td>Casein IgE (mg/L), median (range)</td>
<td>14.15 (0.71-101)</td>
<td>1.41 (0-101)</td>
<td>1.475 (0.48-3.69)</td>
<td>&lt;.001</td>
<td>.013</td>
<td>.850</td>
</tr>
<tr>
<td>β-Lactoglobulin IgE (mg/L), median (range)</td>
<td>4.48 (0-101)</td>
<td>0.43 (0-63.7)</td>
<td>0.001 (0.001-2.32)</td>
<td>.002</td>
<td>.057</td>
<td>.960</td>
</tr>
<tr>
<td>Casein IgG₄ (mg/L), median (range)</td>
<td>1.53 (0.04-6.73)</td>
<td>0.64 (0-23.8)</td>
<td>1.35 (0.09-31)</td>
<td>.999</td>
<td>.173</td>
<td>.113</td>
</tr>
<tr>
<td>β-Lactoglobulin IgG₄ (mg/L), median (range)</td>
<td>0.57 (0-8.38)</td>
<td>0.36 (0-31)</td>
<td>1.23 (0.06-31)</td>
<td>.896</td>
<td>.326</td>
<td>.146</td>
</tr>
<tr>
<td>Casein IgE/IgG₄ ratio, median (range)</td>
<td>10.58 (0-69.25)</td>
<td>1.69 (0-131.2)</td>
<td>1.327 (0.3667)</td>
<td>.079</td>
<td>.068</td>
<td>.588</td>
</tr>
<tr>
<td>β-Lactoglobulin IgE/IgG₄ ratio, median (range)</td>
<td>4.259 (0-54.74)</td>
<td>0.496 (0-1120)</td>
<td>0.0008 (0-2.417)</td>
<td>.868</td>
<td>.971</td>
<td>.82</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline median (range)</th>
<th>3-Month median (range)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk SPT, wheal size (mm)</td>
<td>8 (2.5-19)</td>
<td>7 (2-10.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Milk IgE (kU/L)</td>
<td>2.5 (0-79.1)</td>
<td>1.99 (0-76)</td>
<td>.493</td>
</tr>
<tr>
<td>Casein IgE (mg/L)</td>
<td>1.29 (0-101)</td>
<td>1.6 (0-84)</td>
<td>.769</td>
</tr>
<tr>
<td>β-Lactoglobulin IgE (mg/L)</td>
<td>0.15 (0-63.7)</td>
<td>0.49 (0-18.7)</td>
<td>.758</td>
</tr>
<tr>
<td>Casein IgG₄ (mg/L)</td>
<td>0.54 (0-8.1)</td>
<td>1.02 (0.05-14.7)</td>
<td>.005</td>
</tr>
<tr>
<td>β-Lactoglobulin IgG₄ (mg/L)</td>
<td>0.29 (0-11.3)</td>
<td>0.49 (0-31)</td>
<td>.528</td>
</tr>
<tr>
<td>Undetectable casein IgG₄ (%)</td>
<td>6 (12)</td>
<td>0 (0)</td>
<td>.027†</td>
</tr>
<tr>
<td>Undetectable β-lactoglobulin</td>
<td>7 (14.3)</td>
<td>6 (12)</td>
<td>1.0‡</td>
</tr>
<tr>
<td>IgG₄ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casein IgE/IgG₄ ratio</td>
<td>1.43 (0-131.2)</td>
<td>1.38 (0-55.4)</td>
<td>.148</td>
</tr>
<tr>
<td>β-Lactoglobulin IgE/IgG₄ ratio</td>
<td>0.23 (0-235.9)</td>
<td>0.49 (0-17.4)</td>
<td>.319</td>
</tr>
</tbody>
</table>

• 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

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

Milk-specific IgE ≥15 kU/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