Expanding Component Resolved Diagnostic Testing Beyond Food

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Confusion Matrix

<table>
<thead>
<tr>
<th>Index Test outcome</th>
<th>Total population</th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>True positive</td>
<td>False positive  (Type I error)</td>
<td></td>
</tr>
<tr>
<td>Test negative</td>
<td>False negative   (Type II error)</td>
<td>True negative</td>
<td></td>
</tr>
</tbody>
</table>

- **Prevalence** = \( \frac{\Sigma \text{Disease present}}{\Sigma \text{Disease present} + \Sigma \text{Disease absent}} \)
- **Positive predictive value (PPV)** = \( \frac{\Sigma \text{True positive}}{\Sigma \text{Test positive}} \)
- **Negative predictive value (NPV)** = \( \frac{\Sigma \text{True negative}}{\Sigma \text{Test negative}} \)
- **Positive likelihood ratio (LR+)** = \( \frac{\text{TPR}}{\text{FPR}} \)
- **Negative likelihood ratio (LR-)** = \( \frac{\text{FNR}}{\text{TNR}} \)
- **Diagnostic odds ratio (DOR)** = \( \frac{\text{LR+}}{\text{LR-}} \)
- **Sensitivity = TPR**
- **Specificity = TNR**

- **True positive rate (TPR)** = \( \frac{\Sigma \text{True positive}}{\Sigma \text{Disease present}} \)
- **False positive rate (FPR)** = \( \frac{\Sigma \text{False positive}}{\Sigma \text{Disease absent}} \)
- **True negative rate (TNR)** = \( \frac{\Sigma \text{True negative}}{\Sigma \text{Disease absent}} \)
- **False negative rate (FNR)** = \( \frac{\Sigma \text{False negative}}{\Sigma \text{Disease present}} \)
- **Accuracy (ACC)** = \( \frac{\Sigma \text{True positive} + \Sigma \text{True negative}}{\Sigma \text{Total population}} \)
Probability of Disease

Bayesian Approach

Prior = Prevalence

Posterior = Disease Probability

Posttest odds (probability)

Pretest odds x LR = Posttest odds

Diagnostic Testing Strategy

• Pretest odds (probability)
  • History of rxn
  • Prevalence if no history

• Test for specific IgE to get the LR
  • Skin Test
  • Blood test

• Posttest odds (probability)
  • Probability of being allergic to an allergen

• Decide what to do
  • Targeted environmental control
  • Allergy shots
  • Don’t worry about the allergen
The Higher the sIgE, the Greater the Risk for Symptomatic Allergy\textsuperscript{1}

Logistic Regression can help to classify results of a continuous variable


Likelihood Ratio for Peanut-sIgE
How to use Test Results - Likelihood Ratios


COMMON DIAGNOSTIC TESTS
Series Editors: Alan Garber, MD, PhD, and Harold Sox, MD

ACADEMIA AND CLINIC

Evidence-Based Diagnostic Strategies for Evaluating Suspected Allergic Rhinitis

Kama Gendo, MD, and Eric B. Larson, MD, MPH

Allergic rhinitis is an increasingly common disease, with a prevalence of at least 10% to 25% in the United States. Diagnostic allergy tests, such as skin tests and in vitro tests, can assist clinicians in determining whether nasal symptoms are allergic in origin. In addition, safe and effective medications are available to treat allergic rhinitis.

The initial strategy should be to determine whether patients should undergo diagnostic testing or receive empirical treatment. This paper reviews the test characteristics of the history, skin tests, and in vitro tests in diagnosing allergic rhinitis from the perspective of decision thresholds. A combination of pertinent medical history features in a practice with a high baseline prevalence of allergic rhinitis justifies the common practice of empirical treatment since allergy medication has minimal toxicity and side effects.

The situation is more complex when the patient needs a diagnostic test, because reported sensitivities and specificities of skin tests and in vitro tests vary widely. As a result, it is difficult to calculate the post-test probability of allergic rhinitis with any confidence. The decision to initiate diagnostic testing must rely on clinical judgment to select patients who would benefit most from determining their allergic status while minimizing unnecessary testing and medications. Diagnosing allergy to a specific antigen allows patients to avoid the allergen and makes them candidates for allergen immunotherapy, which can decrease the need for medications.

Ann Intern Med. 2004;140:278-289
For author affiliations, see end of text.
### Selected LRs

<table>
<thead>
<tr>
<th>History</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does pollen cause symptoms?</td>
<td>2.52</td>
<td>0.49</td>
</tr>
<tr>
<td>Does mold cause symptoms?</td>
<td>2.09</td>
<td>0.73</td>
</tr>
<tr>
<td>Does dust or mites cause symptoms?</td>
<td>3.34</td>
<td>0.39</td>
</tr>
<tr>
<td>Do you have hayfever?</td>
<td>4.80</td>
<td>0.58</td>
</tr>
<tr>
<td>Family history of allergies?</td>
<td>3.41</td>
<td>0.70</td>
</tr>
<tr>
<td>Are symptoms seasonal?</td>
<td>1.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Itchy, watery eyes?</td>
<td>2.49</td>
<td>0.51</td>
</tr>
<tr>
<td>Are you allergic?</td>
<td>3.12</td>
<td>0.33</td>
</tr>
<tr>
<td>Nasal symptoms (sneezing, runny nose)?</td>
<td>1.33</td>
<td>0.65</td>
</tr>
</tbody>
</table>

### Selected LRs: SPT vs. ICT

<table>
<thead>
<tr>
<th>Percutaneous Test</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>4.93</td>
<td>0.08</td>
</tr>
<tr>
<td>Tree</td>
<td>16.17</td>
<td>0.09</td>
</tr>
<tr>
<td>Grass</td>
<td>3.23</td>
<td>0.04</td>
</tr>
<tr>
<td>Mold</td>
<td>11.75</td>
<td>0.05</td>
</tr>
<tr>
<td>Mite</td>
<td>4.06</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intracutaneous Test</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>2.45</td>
<td>0.28</td>
</tr>
<tr>
<td>Grass</td>
<td>1.05</td>
<td>0.98</td>
</tr>
<tr>
<td>Mold (Alternaria)</td>
<td>8.80</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Selected Likelihood Ratios

<table>
<thead>
<tr>
<th>In-Vitro Test</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>9.38</td>
<td>0.14</td>
</tr>
<tr>
<td>Tree</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Grass</td>
<td>3.13</td>
<td>0.09</td>
</tr>
<tr>
<td>Mold</td>
<td>15.00</td>
<td>0.20</td>
</tr>
<tr>
<td>Mite</td>
<td>6.33</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Reflex testing

- Done when an initial test result meets pre-determined criteria, and the primary test result is inconclusive without the reflex or follow-up test.
- It is performed automatically without the intervention of the ordering physician.
- Reflex testing can avoid unnecessary tests leading to reduced costs.
- Most labs offer reflex testing and can set them up for you on a custom basis.

- Cat IgE = <0.10. No further testing is done.
- Cat IgE > 0.35. Cat component IgE tests are done automatically.

- Posttest odds = Pretest odds x LR (test 1) x LR (test 2)
Process of making a diagnosis leads to determining risk of a reaction


35 Year Old Male

**Presentation**
- Has developed rhinitis symptoms at work and girlfriend's house
- Asthma is persistent but stable

**Past Medical History**
- History of mild persistent asthma on daily ICS

**Social History**
- Works as a school teacher at an elementary school
- Girlfriend has a cat, he is considering a dog

**Questions**
- Is it allergy?
- If yes, to what is he sensitized?
- Is he at risk for worsening of his asthma?
- Personal / employment considerations?
- Allergen exposure reduction?
- Immunotherapy?
Pet Allergy

Allergies to dogs and cats affect 10%–20% of the population worldwide. Approximately 48 Million Americans are sensitized to dog and/or cat allergens. 50% of people with exposure to horse barns report respiratory symptoms such as wheezing, coughing, and shortness of breath.


Other Adverse Reactions

"The vet says the cat will be fine."
Pet Allergen Components

**Cat (e1) > 0.1 kU/mL**
- Fel d 1 (Secretoglobin)
- Fel d 2 (Serum albumin)
- Fel d 4 (Lipocalin)
- Fel d 7 (Lipocalin)

**Dog (e5) > 0.1 kU/mL**
- Can f 1 (Lipocalin)
- Can f 2 (Lipocalin)
- Can f 3 (Serum albumin)
- Can f 4 (Lipocalin)
- Can f 5 (Kallikrein)
- Can f 6 (Lipocalin)

**Horse (e3) > 0.1 kU/mL**
- Equ c 1 (Lipocalin)

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**Pet Allergen Components – Proteins**

<table>
<thead>
<tr>
<th>Uteroglobin/Secretoglobin</th>
<th>Kallikrein</th>
<th>Lipocalins</th>
<th>Serum Albumins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitization during childhood can be a predictive marker of cat allergy in adolescence.</td>
<td>Can f 5, a prostatic kallikrein, was isolated from urine of male dogs and is considered a major allergen.</td>
<td>Lipocalins are the most important allergen protein family.</td>
<td>Highly cross-reactive molecules generally considered minor allergens.</td>
</tr>
<tr>
<td>A cat-specific marker of sensitization.</td>
<td>Therefore, patients sensitized only to Can f 5 may tolerate female dogs or castrated male dogs.</td>
<td>Most are major allergens.</td>
<td>Abundant in saliva and dander.</td>
</tr>
<tr>
<td>Fel d 1, a uteroglobin and the major cat allergen.</td>
<td>Patients sensitized to Can f 5 may show allergic reactions to seminal fluid.</td>
<td>Synthesized in salivary glands and dispersed into the environment by saliva and dander.</td>
<td>Respiratory allergens present in animal dander and fluids such as milk, serum, and urine and saliva.</td>
</tr>
<tr>
<td>A uteroglobin expressed in skin and salivary glands, its synthesis is related to sexual hormones.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Measurement of IgE to Components may Provide a More Precise Diagnosis

**Measurement of IgE to Components may Provide a More Precise Diagnosis**

![Image of a diagram showing cross-reactivity of allergen components]

**Help Predict Asthma Severity and Development**

**Help Predict Asthma Severity and Development**

![Image of a graph showing polysensitization and symptoms at age 4]

The risk for and severity of respiratory diseases increase with the number of Pet Allergen Components the patient is sensitized to.

Increasing numbers of positive dog allergen components are correlated with a positive nasal provocation test (NPT).  


**Usefulness for Patient Management**

<table>
<thead>
<tr>
<th>Key questions</th>
<th>1 Is it dog, cat or horse? Or a combination?</th>
<th>2 Which allergen components are involved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant management</td>
<td>1 Exposure reduction</td>
<td>2 Female dog</td>
</tr>
<tr>
<td></td>
<td>• Removal of relevant pet(s)\textsuperscript{1,2}</td>
<td>• Patients monosensitized to Can f 5 may tolerate female dogs or castrated male dogs\textsuperscript{1,2}</td>
</tr>
</tbody>
</table>

According to an evidence-based consensus recommendation, molecular diagnosis is strongly recommended to distinguish between simultaneous sensitization and cross-reactivity (Category B Evidence).\textsuperscript{1}

Example Case:
Patient lives with a dog and cat and has nasal allergies

- **Cat Dander IgE** 36.60 H kU/L 0.00 - 0.34
  - Cat rFel d 1 24.60 H kU/L .00 - .10 uteroglobin
  - Cat rFel d 2 0.16 H kU/L .00 - .10 serum albumin
  - Cat rFel d 7 0.15 H kU/L .00 - .10 lipocalin

- **Dog Dander IgE** >100.00 H kU/L 0.00 - 0.34
  - Dog rCan f 1 0.92 H kU/L .00 - .10 lipocalin
  - Dog rCan f 2 16.20 H kU/L .00 - .10 lipocalin
  - Dog rCan f 3 0.34 H kU/L .00 - .10 serum albumin
  - Dog rCan f 4 32.20 H kU/L .00 - .10 lipocalin
  - Dog rCan f 5 <.10 kU/L .00 - .10 prostatic kallikrein
  - Dog rCan f 6 <.10 kU/L .00 - .10 lipocalin

- Consider Purina LiveClear cat food- contains anti Fel d1
- Don’t need AP dog (enriched for Can f1) for allergy shots

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**Past Medical History**
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**Social History**
- Works as a teacher at an elementary school
- Girlfriend has a cat, he is considering a dog

<table>
<thead>
<tr>
<th>Allergen</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat dander</td>
<td>34.37</td>
</tr>
<tr>
<td>Dog dander</td>
<td>6.10</td>
</tr>
<tr>
<td>House dust mite (D. pteronyssinus)</td>
<td>3.22</td>
</tr>
<tr>
<td>Mold (A. alternata)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mold (C. herbarum)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cockroach</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Horse</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Common ragweed</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Saltwort, Russian thistle</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Rough marshelder</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Firebush, Kochia</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Oak</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Elm</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Cottonwood</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Maple, Boxelder</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Redtop, Bentgrass</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Bermuda grass</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td>122</td>
</tr>
</tbody>
</table>
Sensitized to cat, dog, dust mites and mold

What advice should be given regarding animal avoidance/immunotherapy?

Is this true co-sensitization with cats and dogs or is it cross-reactivity?

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>sIgE Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fel d 1 Secretoglobin</td>
<td>18.00 kU/L (nl &lt;0.10)</td>
</tr>
<tr>
<td>Fel d 2 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Fel d 4 Lipocalin</td>
<td>15.00</td>
</tr>
<tr>
<td>Can f 1 Lipocalin</td>
<td>3.00</td>
</tr>
<tr>
<td>Can f 2 Lipocalin</td>
<td>5.40</td>
</tr>
<tr>
<td>Can f 3 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 5 Kallikrein</td>
<td>&lt;0.10</td>
</tr>
</tbody>
</table>

Alternate Test Results

Sensitized to cat, dog, dust mites and mold

What advice should be given regarding animal avoidance/immunotherapy?

Is this true co-sensitization with cats and dogs or is it cross-reactivity?
Another Scenario: 54-year-old female with rhinitis

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy Grass</td>
<td>8.36</td>
</tr>
<tr>
<td>Birch</td>
<td>4.35</td>
</tr>
<tr>
<td>Dog</td>
<td>0.37</td>
</tr>
<tr>
<td>Cat</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Mold (C. herbarum)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Cockroach</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Mold (P. notatum)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Common ragweed</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Rough Pigweed</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Mold (A. fumigatus)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Dust Mite (D. pteronyssinus)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Oak</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Elm</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Cottonwood</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Maple, Boxelder</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Dust Mite (D. farinae)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Bermuda grass</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Total IgE</td>
<td>89</td>
</tr>
</tbody>
</table>

Specific IgE Component Results

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can f 1 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 2 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 3 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 5 Kallikrein</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Specific IgE Component Results

### Allergen Component

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can f 1 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 2 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 3 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 5 Kallikrein</td>
<td>0.31</td>
</tr>
</tbody>
</table>

### Interpretation

- **Patient is monosensitized to Can f 5**, a prostatic kallikrein expressed only by male dogs.
- **She is diagnosed with allergy to male dogs.**
- **She is advised that she possibly could tolerate a female dog.**

**Pet Selection And Human Semen Allergy Relationship**

- **Up to 30% of dog-allergic patients are monosensitized to Can f 5**
- **Patients who are monosensitized may tolerate female dogs or castrated males dogs**

“In women allergic to dog that refer to reactions following contact with human seminal fluid, it would be advisable to determine IgE against Can f 5.”

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5-year-old with suspected allergic rhinitis: Whole Allergen Specific IgE Results

<table>
<thead>
<tr>
<th>Allergen</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat dander</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Dog dander</td>
<td>9.00</td>
</tr>
<tr>
<td>House dust mite (D. pteronyssinus)</td>
<td>3.20</td>
</tr>
<tr>
<td>Silver Birch</td>
<td>1.26</td>
</tr>
<tr>
<td>Common ragweed</td>
<td>0.86</td>
</tr>
<tr>
<td>Cockroach</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Horse</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Saltwort, Russian thistle</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Mold (C. herbarum)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Mold (A. alternata)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Oak</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Elm</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Cottonwood</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Maple, Boxelder</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Redtop, Bentgrass</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Bermuda grass</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Total IgE</td>
<td>239</td>
</tr>
</tbody>
</table>

Results - Continued

- Sensitized to cat, dog, dust mites, trees, and ragweed
- What advice should be given regarding animal avoidance/immunotherapy?
- Is this true co-sensitization with cats and dogs or is it cross-reactivity?

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>kU/L (nl &lt;0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fel d 1 Secretoglobin</td>
<td>51.30</td>
</tr>
<tr>
<td>Fel d 2 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Fel d 4 Lipocalin</td>
<td>49.60</td>
</tr>
<tr>
<td>Can f 1 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 2 Lipocalin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 3 Serum Albumin</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 5 Kallikrein</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Can f 6 Lipocalin</td>
<td>18.20</td>
</tr>
</tbody>
</table>

Species-Specific Primary Sensitization
Cross-reactivity (Fel d 4, Equ c 1)

Cross-reactivity (Fel d 6, Equ c 1)
5 Year Old Female - Continued

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>She is diagnosed with allergy to cat</td>
<td>Targeted exposure reduction: Cat, dust mite, pollens</td>
</tr>
<tr>
<td>Dogs may be tolerated</td>
<td>Daily prn antihistamine for allergic rhinitis symptoms</td>
</tr>
<tr>
<td>She may be at greater risk of developing asthma or severe allergic rhinitis later in life because she is positive to 3 pet allergen components. (≥ 3 Increases Risk)</td>
<td>Seasonal use of inhaled nasal steroid (INS) during pollen seasons</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>As Fel d 1 is a primary allergen component and at higher levels, especially given her potential exposure, cat immunotherapy may be considered</td>
</tr>
</tbody>
</table>

Further Reading: Molecular Allergology User’s Guide
Podium to Practice Takeaways

- Diagnostic tests are used to update your pretest credence of the diagnosis to a posttest credence.
- The likelihood ratio can be used to determine how much more (or less) probable a diagnosis is than you thought it was before doing the test.
- A reflex test (e.g., components) can be used when a primary test (e.g., whole extract IgE) is indeterminant.
- Pet component testing can help to determine whether there is primary sensitization to a pet or cross-reactivity.

Enjoy Testing with Components and stay safe

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Unproven Diagnostic Tests for Adverse Reactions to Foods

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Faculty Disclosure Information

• I have not had a financial interest or other relationship with the manufacturers of the products that will be discussed in my presentation.

• This presentation will include discussion of devices that have not been approved by the FDA.
Objective

• Communicate the lack of validity and clinical applicability of non-IgE testing in the evaluation of food allergy or sensitivity

Unproven Diagnostic Tests for Adverse Reactions to Foods

Kelso JM.
(No relevant disclosures)

Unproven food tests

BACKGROUND

• Patients often seek opinions from allergists regarding unconventional testing for adverse reactions to foods, either before or after the fact.
• By understanding the methodology of these tests and the lack of evidence supporting their utility, allergists can provide knowledgeable, evidence-based information to patients who inquire about them.
THE ALCAT TEST: HOW IT WORKS

• Incubate patient’s WBC with foods to identify those that may trigger “potentially harmful immune system reactions”
• Uses flow cytometry to measure the % change in the distribution of cell sizes from baseline to after the food incubations

• % change in a healthy control group reported to be <9% and consider a change of >13% to be positive and 9-13% to be equivocal
• Results used to customize an elimination or rotation diet to eliminate the “specific triggers of chronic immune system activation”
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THE ALCAT TEST: CLAIMS

• Diet will alleviate “gastrointestinal complaints, skin diseases, neurological and mental disorders, respiratory diseases, metabolic diseases, endocrine disorders, musculoskeletal and joint disorders, immune system, and other comorbidities.”

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THE ALCAT TEST: PLAUSIBILITY

• The laboratory instrument may accurately measure WBC volumes, but unclear whether or not any change in response to food exposure would be physiologic or pathologic or how they would lead to the long and disparate list of maladies being investigated
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THE ALCAT TEST: EVIDENCE

• No studies published in peer reviewed journals using the test and diet for treatment
IgG FOOD TESTING: HOW IT WORKS

- Immunoassay to measure IgG or IgG4 antibodies to foods
- Just like serum specific IgE assays (“RAST”) but measuring IgG or IgG4 instead of IgE

IgG FOOD TESTING: CLAIMS

- Diagnose “food sensitivities” that might manifest as acne, eczema, dry and itchy skin, food intolerance, bloated after eating, fatigue, irritable bowel syndrome (IBS), joint pain, migraines, respiratory issues, weight gain and/or difficulty losing weight, ear infections, sinusitis, or urticaria
- Reactions described as delayed or chronic
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IgG FOOD TESTING: PLAUSIBILITY

• Theories advanced on how IgG food antibodies lead to these conditions include chronic inflammation perhaps through the formation of immune complexes
• However, IgG antibodies to foods are found in virtually all healthy individuals are associated with food desensitization or tolerance

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IgG FOOD TESTING: EVIDENCE

• Retrospective review of 55 patients placed on elimination of diets based on this testing because they had “complained of symptoms suggestive of adverse food reactions” and had shown elevated IgG titers to foods.

Marinkovich V. Specific IgG antibodies as markers of adverse reactions to foods. Monogr Allergy 1996;32:221-5.
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IgG FOOD TESTING: EVIDENCE

• The symptoms could include “malaise, prostration, fever, rash, arthritis, gastrointestinal symptoms, neurological symptoms, lymphadenopathy, myocardial ischemia, or transient renal disease.”

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IgG FOOD TESTING: EVIDENCE

• 31 patients who chose to follow the diet were compared with 24 who did not
• Based on clinical interviews, 28/31 who followed the diet improved compared with 7/24 who did not
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IgG FOOD TESTING: EVIDENCE
• Demonstrates the flaws found in most studies of unproven tests for food intolerance
  – Evaluated broad array of symptoms and conditions unlikely to have a common pathophysiology
  – Used ill-defined and subjective measures of improvement
  – Retrospective, not randomized or blinded

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IgG FOOD TESTING: REVIEWS
• “Food-specific IgG4 does not indicate food allergy or intolerance, but rather a physiological response of the immune system after exposition to food”
• “Testing of IgG4 to foods is irrelevant for the laboratory work-up of food allergy or intolerance and should not be performed”

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PROVOCATION-NEUTRALIZATION TESTING: HOW IT WORKS

• Food sensitivities identified by intradermal injection of extracts of suspected foods in an attempt to provoke previously reported food-related symptoms

• A different dose (higher or lower) of the offending allergen is then injected to “neutralize” the reaction
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PROVOCATION-NEUTRALIZATION TESTING: CLAIMS

• Use the "neutralizing" dose to administer to the patient to prevent or treat symptoms when the patient eats that food

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PROVOCATION-NEUTRALIZATION TESTING: EVIDENCE

• Double-blind study of 18 patients who reported reactions to specific foods
• Evaluated by physicians experienced with the technique by injection of either the suspect food or saline in random order

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PROVOCATION-NEUTRALIZATION TESTING : EVIDENCE

• Patients asked to say whether the injection was the food to which they were sensitive or saline
  – Responded positively to 27% of the food injections and to 24% of the saline injections
• When neutralizing doses administered, just as likely to be “effective” whether the food or saline was injected
HAIR ANALYSIS: HOW IT WORKS

• Laboratory methodology is not described
• Hair samples are checked against a “database” and “those displaying an intolerance of 85% and over typically trigger intolerance symptoms within the body”

HAIR ANALYSIS: CLAIMS

• The “intolerance” could lead to “headaches, nausea, bloating, stomach cramps, diarrhea, constipation, fatigue, skin disorders, brain fog, lethargy or constant tiredness.”
• Changing one’s diet based on the results can alleviate these symptoms
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HAIR ANALYSIS: EVIDENCE

• Hair samples from 9 nonallergic subjects who “were not aware of any sensitivity reactions to food or any other substances” were sent in duplicate to 3 different laboratories offering hair analysis for food intolerances


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HAIR ANALYSIS: EVIDENCE

• Frequent positive test results
• Discrepancies between matched samples
• Authors’ conclusion: “The results gave clear evidence of diagnostic failure, lack of reproducibility, and a remarkably high number of reports suggesting that unsuspected allergies were present in [the controls]”
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ELECTRODERMAL TESTING: HOW IT WORKS

• Patients hold an electrode in one hand and another electrode is placed somewhere else on the patient’s body

• An electrical circuit exists between the 2 electrodes to which a small voltage is applied
ELECTRODERMAL TESTING: HOW IT WORKS

- Also within the electrical circuit, but not touching the patient, are glass vials containing test substances, and skin impedance is measured in arbitrary units.

ELECTRODERMAL TESTING: CLAIMS

- In addition to assessing for food “sensitivities,” some practitioners promote this testing as a substitute for IgE testing, which could pose a danger if truly allergenic foods are reintroduced into the diet.
ELECTRODERMAL TESTING: EVIDENCE

- No reproducibility of observations with the same test substance in the same individual and no relationship between the skin conductivity measurements and the substance in the vial.
APPLIED KINESIOLOGY: HOW IT WORKS

• Food sensitivities or intolerances are evaluated by having the patient hold a vial containing the test food in one hand while the contralateral arm is extended.
• The practitioner then applies downward pressure to the extended arm and evaluates for weakness, which would demonstrate a sensitivity.

APPLIED KINESIOLOGY: CLAIMS

• “Muscle testing foods can help you find out what it is that is holding you back from radiant health”
• “Kinesiology Food Testing takes some of the guesswork out of balancing the diet”
• “So valuable because it can really be the difference between debilitating problems vs vibrant health”
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APPLIED KINESIOLOGY: REVIEWS

• Literature review of applied kinesiology: “There is insufficient evidence for diagnostic accuracy with kinesiology, the validity of muscle response and the effectiveness of kinesiology for any condition.”


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APPROACH TO PATIENTS

• Many patients suffer from physical, psychological, and psychosomatic conditions for which conventional medicine cannot provide diagnosis or treatment

• Such patients understandably turn to practitioners who tell them that these ailments are the result of ingestion of certain foods that can be identified by unconventional testing
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APPROACH TO PATIENTS

• Many patients feel better:
  – They feel like they have an explanation for their illness
  – The placebo effect is very powerful
  – Dietary changes may improve symptoms for reasons unrelated to their test results

• Be sympathetic
• Gently explain that these tests have not been validated by science
  – Rather than “That’s quackery”
  – Try, “Well, as it turns out, studies of these tests have shown…”
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APPROACH TO PATIENTS

• Potential detriments to the use of such tests
  – Nutritional deficiencies if certain foods are avoided
  – Dangerous reactions if foods to which the patient has a true hypersensitivity response are consumed

• If, despite our explanations to the contrary, a patient believes strongly in such testing and it will not result in an adverse financial or health outcome, it may be best to simply acknowledge that there are many things in medicine we do not fully understand
• All we can do is firmly state our case and respect the patient’s autonomy