INTRODUCTION

Allergy and severe allergic reactions are increasing worldwide. Many theories exist for this change in global allergy epidemiology, most commonly variants of the “hygiene hypothesis” and “biome depletion” theory. These theories refer to the impact that modern lifestyles have on the normal microbiological flora (the human biome), as well as decreased exposure to environmental allergens. Research has demonstrated that multiple changes (molecular, genetic, epigenetic and manipulation of external environments in which humans exist) impact human microbiological flora. Animal models and human cohort data have demonstrated some associations with decreased exposures to infectious organism and “hyper-clean” environments (increased antibiotic use and caesarean section rates; decreases in helminth loads), leading to changes in human immune tolerance and ultimately allergic or autoimmune disease.

The immunology of these hypotheses and how disease is caused is complex, and the mechanistic processes that lead to disease (either allergy or autoimmunity) are still being elucidated, but the loss of both cellular and humoral immune-regulatory pathways are involved and the outcome similar with these factors. This, in combination with a multifactorial genetic predisposition to allergy in certain individuals (known as atopy), leads to sensitisation of an individual to various environmental allergens which may or may not manifest as clinical symptoms of allergy.

Allergic reactions manifest clinically as anaphylaxis, allergic asthma, urticaria, angioedema, allergic rhinitis, and atopic dermatitis. These reactions are usually mediated by IgE (Type I hypersensitivity reactions, which occur 2 – 4 hours after exposure to the allergen), which differentiates them from non-IgE-mediated (formerly called anaphylactoid) reactions that involve IgE-independent mast cell and basophil degranulation. Such reactions can be caused by iodinated radiocontrast dye, opiates, or vancomycin, and appear similar clinically to urticaria or even anaphylaxis.

Type IV hypersensitivity reactions, which are the immunological reactions implicated in allergic contact dermatitis, are also called delayed hypersensitivity reactions because they require 24 – 48 hours for signs of inflammation to occur. Type IV reactions are inappropriate or excessive immune reactions that are mediated by specific subsets of CD4+ helper T cells (Th-1 and Th-17 cells) or by CD8+ cytotoxic T cells. These reactions form the basis of contact dermatitis (exposure to nickel, latex) and are also implicated in the pathogenesis of some chronic granulomatous diseases.

DIAGNOSING ALLERGIC DISEASE

The crux of diagnosing common allergic conditions in the laboratory lies with measuring IgE sensitisation to a specific allergen or allergens which cause symptoms in an individual. Most patients who experience symptoms upon exposure to an allergen have demonstrable allergen-specific IgE that specifically recognises that allergen, making these tests essential tools in the diagnosis of allergic diseases.

Test systems have been developed, and are increasingly more sophisticated, that allow accurate measurement of IgE levels, but the trick is knowing how to “translate” these IgE levels and whether they are significant in the clinical situation. In essence the question is: “Will a patient with detectable levels of IgE sensitisation to a specific allergen have an allergic reaction when exposed to that allergen?”

Below is a summary of the available methods used in the laboratory to assist in making the diagnosis of an allergy in a patient:

- **Total IgE (T-IgE)**
  - Although this test may provide a rough guide as to whether an individual is atopic (i.e. they have the potential to have an allergic reaction), T-IgE is not a specific diagnostic test for allergic sensitisation. It is a crude indicator with a low sensitivity for allergic conditions, especially in adults (< 60%), meaning that almost 40% of individuals with allergy will be missed if only T-IgE is used as a screening test. Many other conditions can also cause raised T-IgE levels, including helminth infestations, viral infections, bacterial infections, atopic dermatitis and hyper IgE syndromes.

- **Specific IgE (s-IgE)**
  - This is the most common type of allergy test, and is used to detect sensitisation of an individual to specific foods or environmental allergens. s-IgE can be measured in two ways: in vivo using skin prick tests (SPT’s) where the patient is present, or in vitro using a blood sample sent to the laboratory for specific IgE testing. SPT’s and s-IgE testing measure the same thing, but have different advantages and disadvantages (see Table 1 for a comparison). s-IgE tests on blood were previously known as “RAST” tests, which described a particular laboratory method. Nowadays, s-IgE tests are performed on automated immunoassay platforms, and a vast number of food and aero-allergen tests exist to determine s-IgE sensitisation in individuals. The biggest advantage of the laboratory-based s-IgE test versus the SPT to measure IgE sensitisation is that the s-IgE in a laboratory is a standardised, objective measurement.

### TABLE 1. Comparison between Skin Prick Tests and Specific IgE Tests

<table>
<thead>
<tr>
<th>Skin Prick Tests (SPT’s)</th>
<th>Specific IgE (s-IgE) Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cheap</td>
<td>- Relatively more expensive</td>
</tr>
<tr>
<td>- Rapid (results within 15 – 20 minutes)</td>
<td>- Larger range of available allergens</td>
</tr>
<tr>
<td>- Patient is involved, but it takes time</td>
<td>- Minimal time commitment for the patient</td>
</tr>
<tr>
<td>- Antihistamines must be withdrawn for 72 hours prior to testing</td>
<td>- No need to withdraw medication prior to testing</td>
</tr>
<tr>
<td>- Requires normal skin, i.e. no severe eczema</td>
<td>- Skin condition irrelevant</td>
</tr>
<tr>
<td>- Technique and reporting must be standardised</td>
<td>- Technique always standardised and traceable</td>
</tr>
<tr>
<td>- Storage and care of allergens</td>
<td>- Performed in quality-controlled laboratories</td>
</tr>
<tr>
<td>- Small risk of anaphylaxis</td>
<td>- Safe, no risk of anaphylaxis</td>
</tr>
<tr>
<td>- Not to be done in very young infants or in pregnant women</td>
<td>- More tests may be added to the same sample after first results</td>
</tr>
<tr>
<td>- Can test for severity with component resolved diagnostics (CRD)</td>
<td></td>
</tr>
</tbody>
</table>

However, whichever method is ultimately chosen to detect s-IgE, both of these are quantitative tests: SPT’s measure a reaction to an allergen in millimetres (mm) and s-IgE measurements in blood give an IgE level against a specific allergen in arbitrary units defined by the test platform used (usually kU/L). The higher the level of s-IgE, either in mm or kU/L, the higher the likelihood that the individual is going to have clinical symptoms of allergy when they are exposed to the specific allergen. This is the positive predictive value (PPV) of the test.

Positive predictive values (PPV’s) for both SPT’s and s-IgE have been determined for various populations for some common food allergens as outlined in Table 2. These clinical decision points must however be used with **CAUTION** as they were derived in specific populations and cannot be directly extrapolated to other groups. Work is in progress to derive similar PPV’s for South African and sub-Saharan African populations.
95% PPV = 95% positive predictive value, i.e. a clinical reaction is likely to occur in 95% of the specified population; SPT = skin prick test, SPT measurements are wheal diameters in mm; s-IgE = specific IgE. If a range is given the lower end of the range is applicable in children < 2 years.

<table>
<thead>
<tr>
<th>FOOD</th>
<th>95% PPV s-IgE (kU/L)</th>
<th>95% PPV SPT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>2 - 7</td>
<td>5 - 6</td>
</tr>
<tr>
<td>Milk</td>
<td>5 - 15</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Soya</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

**TABLE 2. Positive Predictive Values for common allergens**

**Pooled Screening Tests**

It is cost-effective to screen out potential allergy by using pooled screening tests. For example, the paediatric food mix test (also known as FX5) contains egg, milk, fish, peanut, wheat and soya in one immunoassay. If this pooled test is negative, the patient does not have allergic sensitisation to the foods in the pool, and has been effectively “screened out” for allergy to those foods. However, if the pooled test is positive, each of the foods in the pool need to be tested individually.

The pooled Aero-allergen test (also known as "phadiatop") similarly contains common environmental allergens like cat and dog dander, dust mite, moulds and limited grasses and trees. It is advisable to follow the South African consensus approach illustrated in Figure 1 for suspected sensitisation to aero-allergens.

**FIGURE 1. South African Inhalant Allergy Consensus Approach**

*Allergy Diagnostic Working Group (ADWG) panel: Bermuda grass, Rye grass, Dermatophygoideae ptentoryssinus, Blomia tropicalis, Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus, cat, dog.*

**Component Testing**

Component-resolved diagnostics (CRD) is a refinement of s-IgE tests, and is another advantage that blood-based s-IgE testing has over SPT’s. CRD allows testing for specific molecular epitopes of an allergen to which a patient is sensitised. CRD assists in identifying patients who have a higher risk of anaphylaxis, because they have IgE against major “anaphylactogenic” allergens versus patients with IgE directed against allergens that generally do not elicit anaphylaxis.

In the case of plant foods, CRD testing may help to clarify which food-allergic patients are likely to experience “oral allergy syndrome” (OAS), and which are at risk for more serious systemic reactions to foods. Such discrimination is not possible using only allergen skin prick testing or conventional allergen-specific IgE assays. For example, in peanut allergy, patients sensitised to pollen-related components, such as the peanut allergen Ara h 8 (which is related to some birch pollen allergens), usually experience no or very mild oral symptoms. In comparison, those who are sensitised to more stable components, such as seed storage proteins (e.g. Ara h 2), are more likely to experience systemic reactions to peanut in any form. CRD for foods in addition to peanut include tree nuts, wheat, vegetables, fruits, milk, and hen’s egg. Table 3 outlines some of the most clinically important component tests in allergy.
**Table 4. Allergy Patch Test Series currently available**

**Metal/Implant APT**
Includes most prosthetic metals, bone cements and glues used in orthopaedic, dental and IUD devices. Iron, Potassium dichromate, Manganese, Platinum, Diethyltoluidine, Gentamicin bone cement, Cadmium, Titanium, Cobalt, Molybdenum, Polysilicone, Tungsten, Niobium, Tantalum, Gold, Zirconium, Zinc, Nickel.

**Standard Series**
Extensive series includes some metals (nickel, cobalt), local anaesthetics, fragrances, cosmetics, hair dyes, resins and leather preservatives.

**Cosmetic Series**
Contains allergens associated with cosmetics applied to the face and body.

**Acrylate Nails Series**
For artificial nails.

**Mast Cell Trypsinase (MCT)**
Granules in activated mast cells secrete the enzyme trypsin during anaphylactic reactions. This test is a definitive marker of anaphylaxis. MCT levels peak at 45 - 60 minutes and may remain elevated for several hours (up to 24 hours). Three serial measurements are recommended: the first as soon as possible after the reaction, the second a few hours later, and a final sample after 24 - 48 hours to establish a baseline trypsin level. MCT is also indicated in patients with the complex clinical condition of mastocytosis, reflecting pathological levels in mast cell burden.
Figure 3. General Approach to Allergy Diagnostic Testing

SPT = skin prick test; sIgE = specific IgE; CRD = component resolved diagnostics; CAST/BAT = cellular antigen stimulation test/basophil activation test; DBPC = double-blind placebo-controlled challenge.

IN CONCLUSION
Because of the range of tests available for allergy and what they measure exactly, approaching a patient with symptoms suggestive of allergy may be confusing. The general approach is outlined in Figure 3. Invariably the starting point is a good clinical history, followed by a specific IgE test (SPT or laboratory-based immunoassay) and only then resorting to more specialised tests like CAST/BAT testing and APT’s. If the symptoms and signs direct to these specialised tests. However, CAST/BAT testing is usually the first line allergy test in suspected drug allergy (including non-steroidal anti-inflammatory drugs, anaesthetics and antibiotics), and APT’s the first line in allergic contact dermatitis or dental/orthopaedic implants.

SUMMARY – take away 10 Points
1. There has been an increase in the prevalence of allergic conditions globally.
2. Allergic sensitisation occurs either as Type I (IgE mediated or non-IgE mediated) OR Type IV hypersensitivity reactions.
3. Clinical history must direct allergy testing.
4. Laboratory methods measure sensitisation, the relevance of which has to be determined clinically before restricting patients to them for allergy.
5. Component resolved diagnostics are useful to determine prognosis and severity of certain allergies.
6. CAST/BAT testing is indicated in complicated allergy cases, and as first line tests for drug allergies.
7. Allergy patch tests should be used for allergic contact dermatitis or sensitivity to orthopaedic and dental implants.
8. Mast cell tryptase is a test for anaphylaxis or mastocytosis syndromes.
9. Specific IgG4 is used to determine tolerance in patients on allergen immunotherapy.
10. IgG testing (also known as “ALCAT”) is not supported by allergy societies globally, and patients should be discouraged from using this expensive test which has no clinical relevance.

REFERENCES