



ImmunoCAP® Specific IgE test: an objective tool for research and routine allergy diagnosis

SGO Johansson

Immunoglobulin (Ig) E-mediated allergic diseases are increasing rapidly, affecting the quality of life of millions of people and causing enormous costs for society. Accurately identifying the sensitizing allergen and its sources is one of the cornerstones in the clinical management of allergic patients. The original ImmunoCAP® Specific IgE test (Pharmacia Diagnostics) is the only test for IgE antibodies sufficiently documented and recommended in research for advanced diagnosis and risk assessment. It is a reliable diagnostic tool and particularly useful in primary care where the use of *in vivo* tests cannot be recommended if the personnel have insufficient opportunities to get the appropriate experience.

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Immunoglobulin (Ig) E-mediated allergic diseases have increased epidemically in developed countries during the last few decades [1–3]. For example, the European Community Respiratory Health Survey reported a prevalence of 9.5 to 40.9% for allergic rhinitis in different countries [4]. Allergy is rapidly becoming a major health problem that also has severe economic implications for society. In the USA, allergies are the sixth leading cause of chronic disease and cost the healthcare system over US\$18 billion annually [101].

Identifying the substances that cause the allergic symptoms in a patient is of great importance to the physician. An informed decision can then be made to choose the best strategy for managing the disease. The quality of life of the patient can thus be greatly improved by avoiding the allergic substances, but equally important, they may not be burdened with eliminating irrelevant ones.

What is allergy

According to the nomenclature adopted by the European Academy of Allergology and Clinical Immunology [5] and the World Allergy Organization, 'allergy is a hypersensitivity reaction initiated by immunologic mechanisms' [6]. Allergy can be antibody or cell mediated. In most patients with symptoms from the airways,

the gastrointestinal tract or the skin, the antibody typically responsible for an allergic reaction belongs to the IgE isotype, and these patients may be said to suffer from IgE-mediated allergy. Antigens stimulating allergy are called allergens. Common allergen sources include pollens, pets, mites, moulds, foods, drugs and insect venoms. In an IgE-sensitized patient, exposure may result in a wide range of symptoms, for example, rhinitis, conjunctivitis, asthma, atopic eczema/dermatitis syndrome (AEDS), recently proposed to be termed eczema [6], urticaria and, in the worst cases, life-threatening anaphylaxis.

The term atopy refers to the personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, these people can develop typical symptoms of asthma, rhinoconjunctivitis or eczema [6]. Thus, the term is an attempt, in the absence of a genetic marker, to characterize an IgE antibody high responder [6]. The natural course of allergic diseases in an atopic individual, often called atopic diseases, referred to as the allergy march, is characterized by a sequence of sensitization and manifestation of symptoms that appear in relation to age [7,8]. Gastrointestinal and skin symptoms due to

Department of Medicine,
Unit of Clinical Immunology &
Allergy, Karolinska University
Hospital, L2:04 SE-171 76
Stockholm, Sweden
Tel.: +46 851 775 933
Fax: +46 833 5724
s.g.o.johansson@kus.se

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allergy and nonallergic hypersensitivity tend to subside after the age of three. In children of the atopic constitution, however, they are often followed by allergic asthma and rhinitis later in life [9,10]. If not managed adequately, these conditions may develop into a more chronic disease and, in the worst case scenario, may lead to severe handicapping.

The key to managing allergic disease is accurate identification of the causative allergen(s) [11]. An accurate and reproducible test measuring IgE sensitization to a wide range of substances is therefore absolutely essential.

Market profile

The very first IgE test was reported in 1967 [12]. The introduction of Phadebas RAST® (Pharmacia Diagnostics) in the mid-1970s gave physicians access to an accurate and reliable *in vitro* test for the measurement of IgE antibodies to specific allergens [13]. During the past 30 years, these tests and the technology they are based on have continuously been improved [14]. Today, the ImmunoCAP® test (Pharmacia Diagnostics) is considered the *de facto* standard to which other methods are compared [15,16]. It performs excellently for IgE antibody detection but also enables quantitative measurements.

ImmunoCAP systems are validated according to the guidelines of the National Committee on Clinical Laboratory Standards [17]. They have demonstrated a solid, reproducible performance in comparative studies where other *in vitro* test systems have shown substandard overall performance with multiple instances of poor precision and accuracy [18].

Independent quality assessment programs, such as the EuroEQAS allergy program, confirm the consistency of results in routine use [19]. The inherent assay precision achieved with ImmunoCAP is in fact comparable to standard clinical chemistry immunoassays, whereas other allergy test methods show considerably higher coefficient of variation [20].

The rapidly increasing incidence of allergy puts a new perspective on the role of the primary care physician [11]. It is quite clear that allergic patients cannot be managed exclusively by allergy specialists; they must, by necessity, also become a concern for the pediatrician and primary care physician. In fact, most allergic patients never see an allergy specialist [21]. Given the predilection for patients to visit primary care physicians, it is imperative that the tests used for this purpose are objective, reliable, reproducible and that the results are unequivocal. The relative inexperience of the physician must not be allowed to influence the interpretation of the test results [22].

Alternatives to *in vitro* allergy testing are available but these methods are less accurate [BOX 1]. Above all, such alternatives also demand considerable experience on the part of the tester, which makes them unsuitable for use in primary care. The most common alternative used is the skin prick test (SPT), where a liquid extract of the substance under investigation is placed on the skin, which is then pierced. If the patient has IgE antibodies, a local allergic reaction develops at the site. SPT is easy to perform but quite tricky to evaluate. The test results are highly dependent on the quality of the allergen extracts used and not

Box 1. Alternative allergy testing approaches.

- Skin prick testing (SPT) – simple to perform but difficult to evaluate. Results are highly dependent on the experience of the tester and the quality of the extracts used. Potentially hazardous to the highly sensitized patient
- Intradermal testing – the same drawbacks as SPT but also too nonspecific, with false-positive results. Even more dangerous to the patient
- Provocation testing – useful in certain types of investigations but complex, expensive and time consuming

least on the experience of the tester. Even in experienced hands, the precision of SPT is, kindly speaking, very poor [23].

The intradermal test, whereby the allergen is injected into the skin, was introduced in the late 19th century and is still used in some countries. It is even more difficult than the SPT to handle and serious side effects have been reported [24]. For many allergens it is nonspecific and for most it is too sensitive. For example, more than 70% of positive cat allergy tests have been reported to lack clinical relevance. Furthermore, for classic inhalant allergens a positive intradermal test, in combination with a negative SPT and no detectable IgE antibodies, has little clinical relevance [25–30].

These methods measure skin reactivity, which is also influenced by a number of external factors such as allergy medication [29,30]. Last but not least, the procedures harbor potential danger to the patient if he or she is highly sensitive to the substance [31].

Provocation-challenge tests for food, drug and occupational allergens, and inhalation tests for nasal or bronchial allergy are used in specialist allergy centers [32]. They are useful in certain types of investigations but are complex, expensive and time-consuming and are therefore only practical for the allergy specialist.

How the test works

ImmunoCAP Specific IgE test is an *in vitro* quantitative assay for the measurement of allergen-specific IgE in human serum or plasma [14,33]. Serum or plasma (EDTA or heparin) samples from venous or capillary blood can be used.

Test principle

The allergen of interest, covalently coupled to the ImmunoCAP cellulose solid phase, reacts with the corresponding IgE antibodies in the patient serum specimen (FIGURE 1). After washing away free IgE, enzyme-labeled antibodies against IgE are added. After incubation, unbound enzyme-anti-IgE is washed away and the ImmunoCAP is then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate is measured. The higher the response value, the more IgE antibodies are present in the specimen. To calculate the test results, the response of the patient samples are transformed to IgE concentrations with the use of a calibration curve based on the

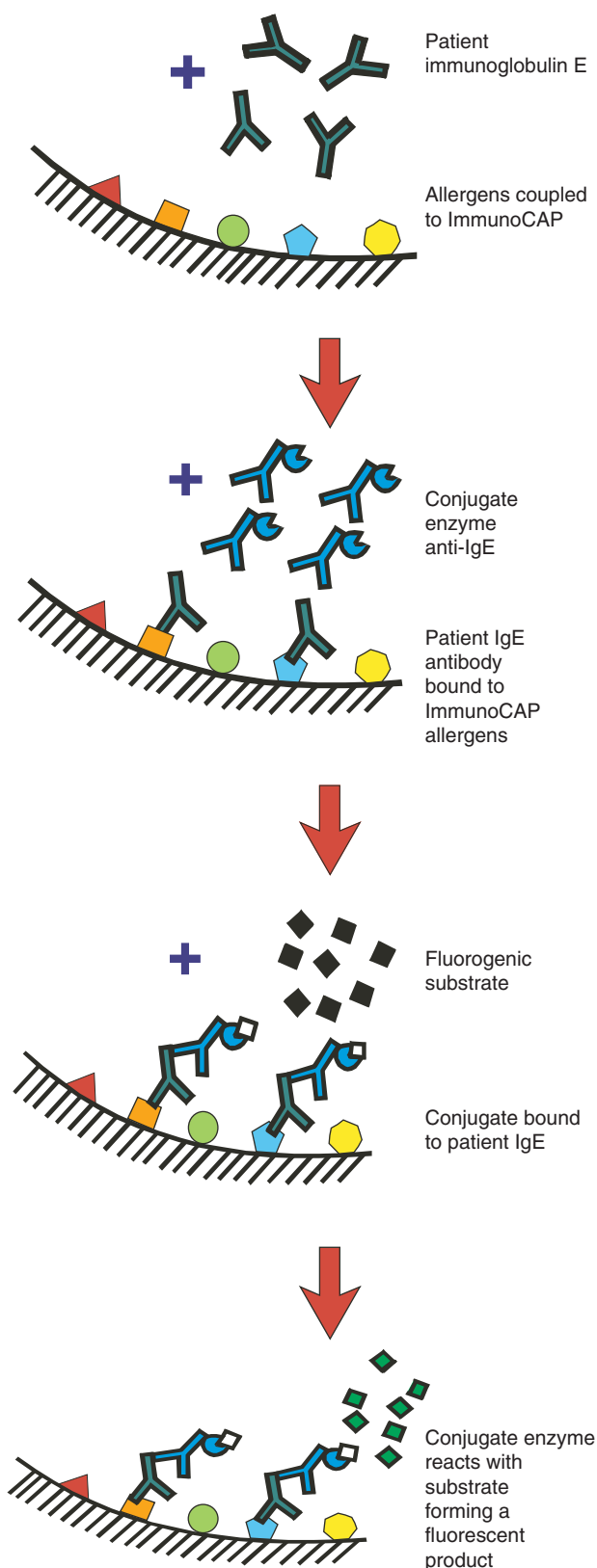


Figure 1. ImmunoCAP® Specific immunoglobulin (Ig) E test.

World Health Organization (WHO) reference preparation 75/502 for IgE [34].

UniCAP instrument platform

The UniCAP® (Pharmacia Diagnostics) instrument platform provides an automated test system incorporating sample and reagent handling, washing, reading, calculation, integrated processing and printing. All tests are performed in a controlled environment kept at a constant temperature. Data are stored and integrated daily calibration is carried out automatically and compared with the stored values. This integral uniformity provides the UniCAP system with high standards of precision and reproducibility as well as fast processing [35–37]. There are various UniCAP models designed for laboratories of different sizes. The instrument with the highest capacity has a throughput of 240 tests/h and a total capacity of 1200 tests/day.

ImmunoCAP solid phase

The key to the quality of the ImmunoCAP results resides in the design of the solid phase. This consists of a 3D cellulose polymer, with the allergens covalently coupled to the polymer. The cellulose structure provides an extremely large surface and high binding capacity, ensuring the coupling of a maximum amount of allergen material [34]. The high allergen excess ensures noncompetitive binding of all antibodies, regardless of antibody isotype, still giving low nonspecific binding. This technology provides high sensitivity and therefore very low concentrations of IgE antibodies can be detected. Excess of allergen is a prerequisite for obtaining serum dilution curves that are parallel to the calibrator curve, thus enabling quantitative measurements [34].

Allergen source material

Another critical factor is the quality of the allergen source material. Most allergen sources are biological materials containing a mixture of allergenic components. Variation in the composition of one and the same species is caused, amongst other factors, by geographic differences and seasonal variations. Standardized high-quality allergen material is therefore a critical factor for an accurate and reproducible test for allergen-specific IgE antibodies.

Sensitivity & specificity

A large number of studies have been performed in which the clinical performance of ImmunoCAP Specific IgE tests in allergy diagnosis has been evaluated. Clinical performance, expressed as sensitivity ranging from 84 to 95% and specificity ranging from 85 to 94%, has been reported from multicenter studies, including several hundred patients tested for a wide range of different allergens [38–41].

Quantitative evaluation

The evaluation and presentation of the clinical performance in the studies referred to above has taken into account only the qualitative performance (yes/no discrimination) of the test. In

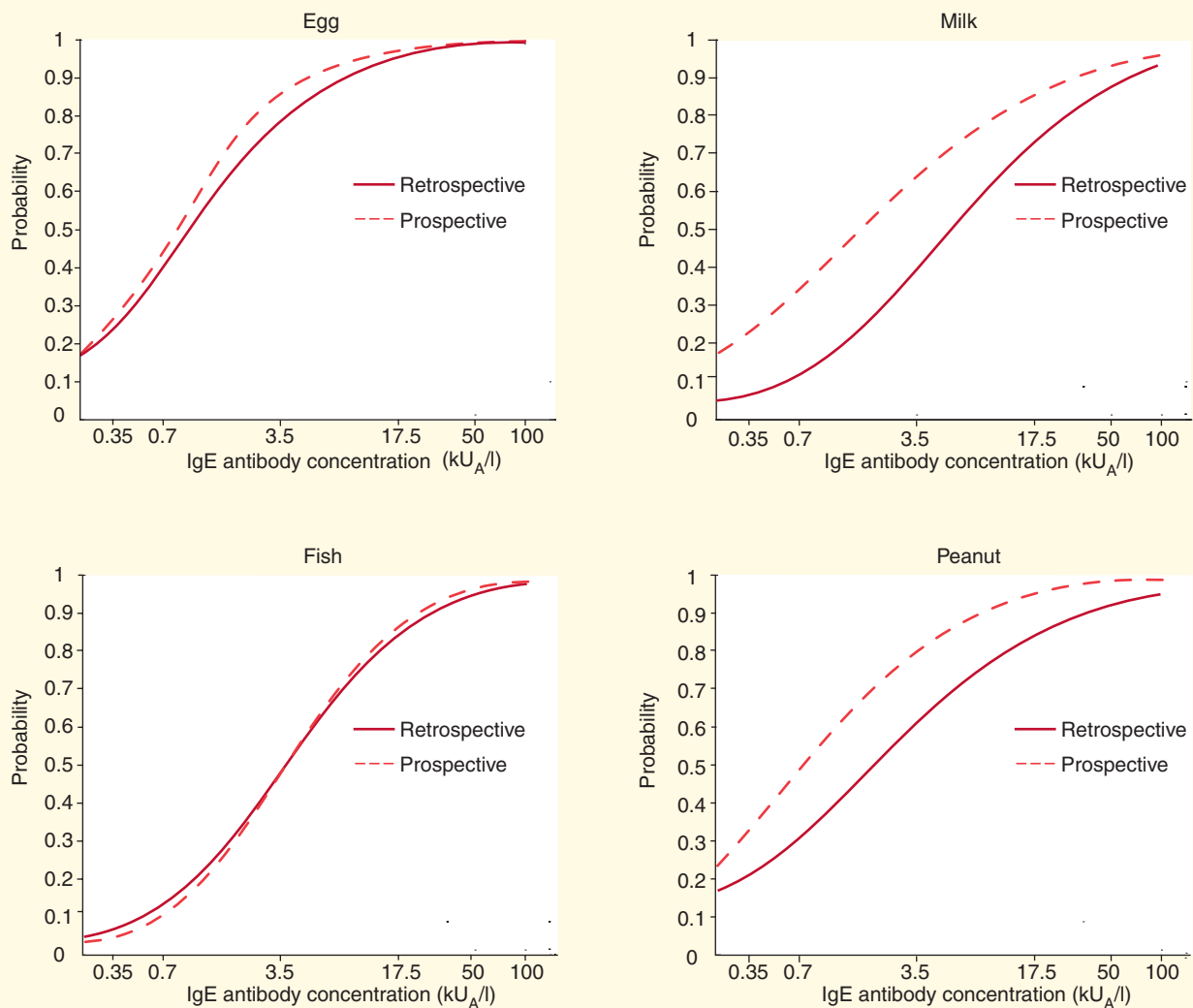


Figure 2. Utility of food-specific immunoglobulin (Ig) E concentrations in predicting symptomatic food allergy [42].

clinical practice, a quantitative evaluation of IgE antibody levels is a more useful tool for diagnosing allergic disease, as has been shown for some foods, for example [42]. Using different techniques such as likelihood ratio and ROC analysis, suggestions of optimal decision levels for IgE antibodies in different populations have been reported [43]. Patient risk assessments based on relationships between IgE antibody levels and the probability of the development of clinical allergic reactions have been published (FIGURE 2) [42,44]. The higher the IgE antibody concentration, the higher the probability for a clinical reaction. However, the presence of IgE antibodies is always a sign of the potential for allergic disease, given the right circumstances.

Cost effectiveness

The cost effectiveness of the ImmunoCAP tests is best seen in relation to the alternative, which, unfortunately, is still the most common used in primary care. Such tests rely solely on

case history, a physical examination and nonspecific medication trials, without the support of any diagnostic test [22].

The value of a correct diagnosis is immense, in health economic terms as well as in terms of the clinical status of the patient. The costs for testing, on the other hand, represent a very minor part in relation to the total healthcare costs (FIGURE 3) [45].

Prescribing symptomatic allergy treatment to all patients with a runny nose means that cases involving upper respiratory tract diseases will not receive the right treatment, despite being prescribed costly medication. Similarly, antibiotics might cure an infection but will not help the patient with allergic disease.

Often the most effective ways to manage allergy is to make the allergic patient aware of the offending allergen source, which is based on the specificity of the diagnostic test, thus enabling him or her to avoid exposure [46,47]. In some cases,

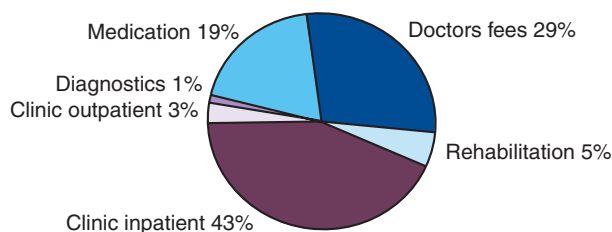


Figure 3. Asthma cost structure. Costs per disease year. (n = 76 children) [45].

such as sensitization to peanut or bee or wasp venom, it may literally be a question of life or death. A somewhat low test sensitivity is not a threat but will actually save the patient and society unnecessary worries and expenses, as a false-positive test result may lead to major decisions affecting the patient's quality of life.

The allergy march, that is, the development of different allergic diseases in an atopic individual following a given age-related pathway, is a strong argument for monitoring the possible sensitization to new allergens in patients that have been diagnosed as allergic at an early age [11]. Early detection of sensitization to new allergens enables the physician to prescribe the best strategy for managing the disease and avoiding development into a severe and costly chronic condition.

The recent German multicenter allergy study clearly indicated the need for early diagnosis and the institution of effective prophylaxis in order to reduce healthcare costs [45].

Expert opinion

The only objective method of measuring IgE antibodies is using an immunodiagnostic test calibrated against an established reference preparation. The ImmunoCAP tests use a calibrator directly traceable to the WHO reference preparation 75/502 for IgE. ImmunoCAP is also the only test giving precise, quantitative results reported in $\text{kU}_\text{A}/\text{l}$, as opposed to yes/no answers or results reported in broad classes. ImmunoCAP is by far the most frequently used *in vitro* test for IgE antibodies, which is the *de facto* standard that has been documented in thousands of scientific publications since it was launched in 1989.

Other *in vitro* tests are available but many methods fail to give an adequate dose–response curve (i.e., not being able to recognize different concentrations of IgE antibodies to the allergen in question) [18]. Others claim to measure IgE antibodies to substances that are generally recognized as not inducing IgE response, such as aspirin, and thus cannot be recommended.

In the author's opinion, ImmunoCAP is the only test accurate and reliable enough to be used in scientific studies and for advanced investigations of patients with IgE-mediated allergy. In experienced hands and using appropriate controls, it is possible to take advantage of the sensitivity potential of the test and objectively quantitate IgE antibodies down to $0.1 \text{ kU}_\text{A}/\text{l}$ [48]. The very large panel of ImmunoCAP allergens available, today

about 500, each documented in a publication, allows the allergy specialist to investigate almost every case of suspected allergy. In addition, quantitative results are obtained, which is a prerequisite for following the development of the sensitization in a patient and for making an accurate assessment of the risk of the patient to further development of allergic disease.

ImmunoCAP is well suited for use in primary care, where there is an additional focus on ease of use and on unambiguously interpreted results. As previously noted, skin tests tend to be too sensitive and nonspecific, which may lead to incorrect treatment decisions, especially if the physician is inexperienced in the use and interpretation of allergy skin tests.

However, the large number of allergens available for ImmunoCAP testing also puts a certain pressure on the inexperienced user: never ask a question if you are not prepared to take responsibility for the answer. One way of simplifying the selection of allergens is to use symptom-based allergen panels consisting of common allergens, predefined by local allergists.

Five-year view

The immunodiagnostic laboratory test will most likely remain the predominant type of test for IgE-mediated allergy. However, new types of tests are also evolving that might offer interesting complements. Doctor's office tests are being developed that are targeted at the primary care segment. These may constitute a quick and useful tool in the initial assessment of patients with suspected allergy, but will not offer sufficient information for actual patient management and follow-up of the allergic individual. Increased scientific knowledge about the inflammatory process may make it possible to find new ways of studying allergic reactions at the cytokine and cellular level. Information on the presence and concentration (absolute and relative to total IgE) of the clinically relevant IgE antibodies will be useful information for selection and therapy monitoring of patients for immunomodulatory treatments such as anti-IgE injections.

Recombinant allergens (i.e., individual allergens produced as recombinant proteins) offer interesting possibilities to fine-tune the tests to ensure that individuals with rare sensitization patterns are captured. Testing only with individual allergenic components is not a likely prospect because of the enormous complexity of common allergens, for example, house dust mite is in fact today known to comprise as many as 20 different allergenic components.

There are no signs that the need for IgE testing will decrease in the coming years; quite the contrary. Reliable, specific and reproducible *in vitro* tests, such as ImmunoCAP, will in all likelihood remain the first choice. Their use is likely to increase considerably with the increasing prevalence of allergy and as primary care physicians become increasingly aware of the necessity to support their diagnoses by reliable tests.

Information resources

- Journal of Allergy and Clinical Immunology
www.aaaai.org/members/jaci.stm
 (Viewed April 2004)

- Allergy Clinical and Experimental Allergy
www.ingenta.com/journals/browse/bsc/cea
(Viewed April 2004)
- Annals of Allergy, Asthma and Immunology
http://allergy.edoc.com
(Viewed April 2004)
- World Allergy Organization
www.worldallergy.org
(Viewed April 2004)
- European Academy of Allergology and Clinical Immunology
www.eaaci.net
(Viewed April 2004)
- American Academy of Allergy, Asthma and Immunology
www.aaaai.org
(Viewed April 2004)
- American College of Allergy, Asthma & Immunology
www.acaaai.org
(Viewed April 2004)

Key issues

- The incidence of allergy has been increasing rapidly over the last 100 years and today represents a severe health problem with great financial implications for society.
- Today the prevalence of allergy in industrialized countries is in the range of 30 to 40% and is still increasing.
- The increasing number of patients means that most must, by necessity, be managed in primary care. Primary care physicians need a good diagnostic tool.
- ImmunoCAP® is the best test for use in primary care where there is an additional focus on ease of use and on unambiguously interpreted results.
- ImmunoCAP is an accurate and reproducible *in vitro* test for measuring immunoglobulin E antibodies, the key factor initializing allergic inflammation.
- ImmunoCAP is the *de facto* standard, documented in more than 2000 peer-reviewed scientific publications.
- The very large panel of allergens available for ImmunoCAP allows the specialist to detect almost any case of suspected allergy.
- ImmunoCAP is the only test accurate and reliable enough to be used in scientific studies.
- Alternative *in vivo* methods, for example skin prick testing and intradermal testing, are heavily dependent on the knowledge and experience of the tester, and are not without danger to the patient. Provocation testing, to be used only by specialists, is very complex and expensive.
- The value of a correct diagnosis is great - in health economic terms as well as for the quality of life of the patient.

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Website

- 101 Allergies
www.aafa.org/public/pdfs/npcallergy.pdf
 (Viewed April 2004)

Affiliation

- SGO Johansson
 Department of Medicine, Unit of Clinical Immunology and Allergy,
 Karolinska University Hospital, L2:04
 SE-171 76 Stockholm, Sweden
 Tel.: +46 851 775 933
 Fax: +46 833 5724
s.g.o.johansson@kus.se