**Shellfish Allergy Diagnosis – Gaps and Needs**

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**ABSTRACT**
Seafood plays an increasing role in human nutrition worldwide, sustained by international trade of a variety of new seafood products. Increased production and consumption has resulted in more frequent reports of adverse reactions. The most recent prevalence data from Asia highlight seafood as a significant sensitizer in up to 40% of children and 33% of adults. Thousands of different shellfish species are consumed worldwide; however only a few species are utilised in in vitro and in vivo assays to confirm clinical sensitivity. Adding to the diagnostic challenges, over 10 additional seafood allergens have been characterised on a molecular level in the last 10 years alone. Therefore a convincing history and good diagnostic workup is fundamental for the management of adverse and allergic reactions to seafood. This review discusses recent literature in this field.

**INTRODUCTION**
Seafood plays an important role in human nutrition and health. The growing international trade in seafood species and products has added to the popularity and frequency of consumption of a variety of seafood products across many countries. The highest consumption in Europe appears to be in Iceland, where the gross per capita consumption of crustaceans and fish is about 91 kg, followed by Spain (43 kg), UK (19 kg) and Germany (13 kg), as compared with the USA (8 kg) and Australia (11 kg).1,2 This increased production and consumption of seafood has been accompanied by more frequent reporting of allergic health problems among consumers but also among processors of seafood.1,25 Adverse reactions to seafood include reactions mediated by the immune system as well as non-immunological reactions.7 These reactions can result from exposure to the seafood itself or various non-seafood components in the product (Table I). Non-immunological reactions to seafood can be triggered by contaminants such as parasites, bacteria and toxins. Ingredients added during processing and canning of seafood can also cause adverse reactions. Importantly all these substances can trigger clinical symptoms which are similar to true allergic reactions, which are mediated by specific IgE antibodies and produced by the immune system against specific allergens.

**CLASSIFICATION OF IMPORTANT SEAFOOD**
Patients with allergy to seafood may fail to identify the offending seafood species, often as a result of confusion regarding the diversity of seafood consumed and the different common names used to describe seafood. The three most important seafood groupings include the arthropods, molluscs and fish. The two invertebrate phyla of crustaceans and molluscs are generally referred to as ‘shellfish’ in the context of seafood consumption4 (Table II). Most seafood species are edible; more exotic species, such as sea-cucumber, jellyfish and sea urchins, are consumed in small amounts around the world. Names are commonly given in various languages, but even the English names vary from country to country. Scientific names are therefore preferred to assist in the correct choice of diagnostic approach. In addition fraudulent substitution and/or the mislabelling of produce have been demonstrated for various seafood species; e.g. trout has been substituted with salmon. Patients may therefore not be reacting to the seafood they think they have eaten when consuming processed seafood.8,9

**Shellfish allergens**
Crustaceans, perhaps surprisingly, are classified as arthropods together with spiders and insects. Over 30 000 living crustacean species are found worldwide and a large number of varieties are consumed raw or cooked. To date over 40 different shrimp species, but so far only a few allergens, have been studied. In most of the studies, the major allergens responsible for ingestion-related allergic reactions are tropomyosins. In addition, other allergens have been identified and characterised in a few crustacean species, e.g. arginine kinase, myosin light chain and sarcoplasmic calcium-binding protein.3,10-13 The second shellfish group are the molluscs. Molluscs are a large and diverse group, subdivided into the classes bivalve, gastropods and cephalopods (Table II) and comprise over 100 000 different species, including several economically important seafood groups such as mussels, oysters, abalone, snails, and squid (calamari). Molluscs contain, in addition to tropomyosin, other less well characterised allergens.14-19

**Table I. Adverse reactions to shellfish produced by various substances**

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Seafood implicated</th>
<th>Clinical symptoms</th>
<th>Time of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella, Vibrio, Aeromonas, Listeria</td>
<td>Crustacean, mollusc</td>
<td>Dermatological</td>
<td>Minutes to several hours</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A, rota-astrovirus, small round viruses, etc.</td>
<td>Crustacean, mollusc</td>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td><strong>Toxins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algae toxins</td>
<td>Fish, crustacean, mollusc</td>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td><strong>Allergens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The tropomyosin protein demonstrates high amino acid homologies among the different crustacean groups but low homology between crustaceans and molluscs. These various protein homologies are most likely the reason for low immunological and allergenic cross-reactivity between crustaceans and shellfish. Importantly, the allergen tropomyosin, a common protein found in muscle tissue, is commonly found in allergen sources related to crustaceans, such as insects and house-dust mites. This cross-reactive allergen has been implicated in clinical cross-reactivity in patients with shellfish and mite allergy and should be considered during the diagnostic evaluation of the patient.

**PATHOGENESIS OF SHELLFISH ALLERGY**

The pattern of allergic symptoms after ingestion of shellfish appears similar to those which occur during allergic reactions to other foods. Most reactions are immediate, and reported within 2 hours; however, late-phase reactions have been reported up to 8 hours after ingestion of molluscs such as squid and abalone. Patients may have a single symptom but often there is multi-organ involvement. Particularly after ingestion of crustaceans, symptoms occur within minutes and include itching and angio-oedema of the lips, mouth and pharynx (oral involvement). Particularly after ingestion of crustaceans, symptoms occur within minutes and include itching and angio-oedema of the lips, mouth and pharynx (oral involvement). After ingestion of molluscs such as squid and abalone, patients may experience the oral allergy syndrome, while crustacean-sensitive subjects very frequently experience the oral allergy syndrome, while mollusc-sensitive subjects often experience gastrointestinal symptoms; however, respiratory symptoms such as rhinitis and asthma are common among all sensitised subjects. Prawns have also been implicated in food-dependent exercise-induced anaphylaxis.

It seems that atopic individuals are at greater risk of developing anaphylactic reactions. The appearance of allergic symptoms results not only from ingestion of seafood, but can also be triggered from inhaling cooking vapours and handling seafood. Importantly, patients with shellfish allergy, similarly to those with peanut allergy, will mostly remain clinically reactive throughout their lives and are at increased risk for wheezing illness and hyperreactive airways at school age.

**OCCUPATIONAL SHELLFISH ALLERGIES AND EXPOSURE**

Allergic reactions to shellfish at the workplace are the result of exposure to seafood itself or to various non-seafood components present in the product. The composition of aerosols generated by snow crab and king crab processing has been found to contain not only allergenic muscle proteins, but also crab exoskeleton, gills, kanimiso (internal organs) as well as background material such as sodium chloride crystals, cellulose, synthetic fibres, silicate, pigment constituent particles, and inorganic particles (silicon, aluminium, iron). Storage conditions can generate degradation compounds such as digestive enzymes and histamine and thereby influence the allergenic nature of seafood. In addition, biochemical sensitisers such as garlic, spices and preservatives added to shellfish can also cause delayed allergic contact dermatitis and general sensitisation. Limited evidence from dose-response relation studies indicates that development of symptoms is related to duration and intensity of exposure.

**DEMOGRAPHICS**

As with all food allergies, accurate epidemiological data on the prevalence of seafood allergy are limited by the lack of controlled population-based studies incorporating the gold standard of double-blind placebo-controlled oral food challenge (DBPCFC). While the consumption of seafood is steadily increasing worldwide, shellfish and fish are generally considered to be among the four foods that most commonly provoke severe food anaphylaxis. A recent telephone survey in the USA established perhaps surprisingly that individuals identified ‘seafood allergy’ as a major source of health concern, affecting an estimated 6.5 million people in the USA — more than twice as common as reported peanut allergy. About 2% reported seafood allergy, which was almost 5 times more common among adults than children. Only 14% reacted to both shellfish groups, suggesting low clinical cross-reactivity between the crustacean and mollusc groups. These observations are supported by a study conducted in South Africa on 105 seafood-allergic individuals where few patients had multiple sensitivity and crustacean allergy was much more common than fish allergy.

**DIAGNOSIS OF SHELLFISH ALLERGY**

Diagnostic methods of establishing a true seafood allergy include various in vivo and in vitro tests to demonstrate the presence of specific IgE antibodies. Owing to the possible unavailability of the exact species, using skin-prick tests (SPTs) and blood IgE assays, posi-
tive and negative test results should be supported by a clinical history from the patient and/or oral challenge where possible. An accurate evaluation of shellfish allergy using the best in vivo and in vitro tests will result in a less restricted dietary curtailment than is currently recommended. Below some common methods and approaches are detailed. A possible diagnostic algorithm for seafood allergy is shown in Fig. 1.

**History**

A precise and detailed history is very important to gain information regarding the seafood species under suspicion, nature of the symptoms and the atopic status of the patient. In addition, the identification of the implicated seafood species using specific diagnostic procedures is of importance, particularly if mislabelling of a seafood product is a possibility. An atypical clinical history or an inconsistent history always suggests a non-atopic aetiology, such as contamination with toxins or parasites or intolerance to seafood (see below).

**Skin-prick tests**

The use of commercial SPTs is often considered and two different providers of shellfish SPT solutions are

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**Fig. 1. Diagnostic algorithm for shellfish allergy (RAST – radio-allergosorbent test, DBPCFC – double-blind, placebo-controlled food challenge).**

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| Table III. Some commercial skin-prick tests available for crustacean and mollusc antigens* |
|-----------------------------------------------|-----------------------------------|-------------------------------|---------------------------------|-----------------------------------|
| Commercial skin-prick tests       | Crustacean specific (test code) | Source | Mollusc specific (test code) | Source |
| Soluprick (Spain)                 | Crab (Cancer pagurus) (6.9)     | Fresh meat | None                        |        |
|                                 | Shrimp (Pandalus borealis) (6.89)|        |                               |        |
| ALK-Abello                       | Crab (Paralithodes camtschatica) | Fresh meat | Oyster (Ostrea spp.) (OYST)  | Fresh meat |
|                                 | (CRAB)                           |        |                               |        |
|                                 | Lobster (Panulirus spp.) (LOBs)  |        |                               |        |
|                                 | Shrimp (Penaeus spp.) (SHRS)     |        |                               |        |
|                                 | Shellfish, mixed (crab, shrimp, lobster, oyster) (MISH) |        |                               |        |
|                                 | Shellfish Mix 4 (crab, clam, lobster, shrimp) (SHM4) |        |                               |        |
| Stallergenes                     | * Shrimp (120)                   |        | * Mussel (139)                |        |
|                                 | * Spiny lobster (131)            |        | * Oyster (131)                |        |

*Bold letters/numbers indicate the test code.
highlighted as examples in Table III. In some cases the species name is not provided for single allergens or for mixed tests. In addition fewer SPT solutions seem to be available for the mollusc group as compared with the crustacean group. If specific extracts are not available, so called in-house prepared SPT extracts can be utilised, if they are confirmed to be safe for testing (no toxins) and contain the appropriate allergens. Despite the drawbacks of possible false-positive/negative results obtained with skin-prick testing, if performed properly and with the appropriate shellfish extracts, it is a quick and sensitive test.

**Blood IgE tests**

A precise and reliable in vitro assay to quantify the amount of allergen specific IgE antibodies is a valuable tool to support the clinician in confirming or refuting an allergic reaction to seafood, prescribing medication, following up treatment and predicting disease development. Detecting and quantifying IgE antibodies is considerably more complicated than performing many other immune-assays.

A number of complicating factors need to be considered:

- The concentration of IgE antibodies in blood is extremely low (several thousand times lower than IgG), even in highly sensitised individuals.
- Each main allergen contains a large number of different allergenic components (mostly proteins). The assay must therefore be sensitive enough to capture antibodies to all relevant allergens, even if these are present only in very minute amounts.
- The assay must have high enough capacity to bind all IgE antibodies to an allergen in competition with other antibodies with the same specificity from other immunoglobulin classes present in higher concentrations (e.g. IgG).
- To achieve a precise and reproducible test system, total control of the allergen source material is necessary, both in content and in allergenic activity, thus reassuring reproducibility when comparing different patients.

There are several commercial tests available to quantify specific IgE antibodies; however, the most prominent system is ImmunoCAP (Phadia) which is shown below as a model system to demonstrate the gaps and needs in the context of seafood allergy diagnosis. The ImmunoCAP test (previously known as CAP-RAST) is an in vitro diagnostic test to measure the amount of specific IgE antibodies to a given allergen. The accuracy of this assay is dependent on the selection of the correct seafood species and is restricted to the panel of commercially available species.

Tables IV and V list the names of some important crustacean and mollusc species, as well as the available commercial tests for quantifying specific IgE antibodies:

### Table IV. Serum based assay to quantify specific IgE. Commonly consumed allergenic crustacean species including their scientific names and list of all currently available ImmunoCAP tests and the crustacean species utilised*

<table>
<thead>
<tr>
<th>Group</th>
<th>Commonly consumed species</th>
<th>Species used for ImmunoCAP tests (test code)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crustacea</strong></td>
<td><strong>Shrimps, prawns</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Black tiger prawn (Penaeus monodon)</td>
<td>Shrimps (f24)</td>
<td>Fresh or boiled frozen meat</td>
</tr>
<tr>
<td></td>
<td>- Vannamei prawn (Litopenaeus vannamei)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Brown shrimp (Penaeus aztecus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Crabs</strong></td>
<td>Crab (f23)</td>
<td>Boiled meat</td>
</tr>
<tr>
<td></td>
<td>- Mud crab (Scylla serrata)</td>
<td>Edible crab (Cancer pagurus)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Snow crab (Chionoecetes opilio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- King crab (Parathodes camtschaticus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Lobsters</strong></td>
<td>Lobster (f80)</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>- Southern rock lobster (Jasus edwardsii)</td>
<td>European lobster (Homarus gammarus)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Spiny lobster (Panulirus stimpsoni)</td>
<td>Common spiny lobster (Palinurus vulgaris)</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>* Crayfish, yabby (EU; Australia) (Astacus spp; Cherax spp.)</td>
<td>Crayfish (f320)</td>
<td>Boiled meat and shell</td>
</tr>
<tr>
<td></td>
<td>* Crawfish (USA) (Procambarus spp.)</td>
<td>Crayfish (Astacus astacus)</td>
<td></td>
</tr>
<tr>
<td><strong>Crustacean allergen component</strong></td>
<td><strong>Shrimp (Penaeus aztecus)</strong></td>
<td>Recombinant tropomyosin, rPen a1 (f351)</td>
<td></td>
</tr>
</tbody>
</table>

*Bold numbers indicate test codes.
Commercial ImmunoCAP tests. The repertoire of species is limited in particular with regard to molluscs. The correct choice of test presents a problem to the clinician as the common names often cause confusion. One example is the analysis of allergic reactions to ‘crayfish’. The correct application of this species name is for a freshwater crustacean species (e.g. crayfish, red claw, yabby). However, commonly rock lobster is also called ‘crayfish’, adding to the confusion as the former is actually a spiny lobster. The most appropriate test species in this case would be the ImmunoCAP for Spiny Lobster/Langoustine, Rf304 (see Table IV). Owing to the vast number of different shrimp/prawn species available worldwide, an improved ImmunoCAP has been developed (f24) which includes four different species. Many patients with seafood allergy have simultaneous sensitivity to other seafood species, but some patients are truly monosensitive to a particular species. In addition, the use of allergens derived from raw or heat-treated sources must be considered, as differential allergic responses have been documented.40,41 Some of the allergens used for example in the ImmunoCAPs are identified as being derived from heated extracts (e.g. crab and some prawns), whereas this information is not known for the majority of shellfish and mollusc allergens.

In general a negative test result excludes sensitisation to these constituents whereas a positive result could be followed up with a specific ImmunoCAP for the individual component allergen. However a positive history of shellfish allergy and negative ImmunoCAP result need further investigation and must be followed up by additional investigations (see below).

**Micro-array technology**

A novel antibody detection system, the allergen micro-array has emerged as a promising approach to high-throughput large-scale profiling of allergen interactions for simultaneous monitoring of IgE and IgG antibodies directed against a variety of allergy-eliciting molecules.42-45 A number of allergens are micro-arrayed onto a solid phase (e.g. modified glass slides or nitrocellulose membranes) and subsequently used to bind antibodies from the serum of allergic patients. Detection of allergen-specific antibody binding is accomplished by the addition of specific secondary antibodies that carry an appropriate label for the quantification using laser technology and are quantified in terms of g/l or IU/ml. The major benefit of this technology lies in its ability to screen for several hundred allergen molecules simultaneously while employing only minute amounts of the patient’s serum (usually 20 µl). The capturing agents that can be used are crude or partially purified allergen extracts, highly purified recombinant or natural allergenic components. Subsequently this will result in an optimal profiling of the patient’s IgE response (in one analytical step), identifying major/minor allergens and pan-allergens, as well as possible cross-reactive carbohydrate determinants (CCDs).

**Western blot**

Sometimes patients present with a clear history of allergenic sensitisation to shellfish but commercially available assays do not detect elevated specific antibodies. In this case when sensitisation to an unknown allergen source is suspected, Western blotting (immunoblotting) can be conducted. Protein extracts of the offending allergen source are separated by gel-electrophoresis (in an electrical field) according to molecular size; the allergens are then transferred to a membrane (blotting) and detected with serum IgE antibodies from sensitised patients.46,47 This method can be very sensitive and allows the direct identification of specific allergens (major and minor) for individual patients. In addition this method allows comparison of IgE reactivity to raw and heated allergen sources, which might be of clinical importance.

Food is subjected to a large variety of processing conditions to prolong storage or improve sensory qualities. Many different processes are used, often in combination, but can be generally categorised into thermal and non-thermal procedures.48 A recent workshop evaluated the effects of food processing on the allergenicity of food allergens.49 Various food processes have been implemented to reduce the allergenicity of certain foods, but very few studies focused on seafood.

**Basophil stimulation assay**

The results of immuno-assays for the detection of specific IgE antibodies are potentially susceptible to the presence of IgG antibodies of the same specificity, can

### Table V. Serum based assay to quantify specific IgE antibody. Commonly consumed allergenic molluscs; commercially available ImmunoCAP tests and the molluscs species utilised*

<table>
<thead>
<tr>
<th>Group</th>
<th>Commonly consumed species</th>
<th>Species used for ImmunoCAP tests (Test code)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastropoda</strong></td>
<td>• Abalone (Haliotis midae) • Snail (Helix aspersa) • Penwinkle (Oxytelus spp.)</td>
<td>• Abalone (Haliotis spp.) (f346)</td>
<td>?</td>
</tr>
<tr>
<td><strong>Bivalvia</strong></td>
<td>• Black mussel (Chromomytilus meridionalis) • Red oyster (Ostrea atherostronei) • White mussel (Donax serra)</td>
<td>• Blue mussel (Mytilus edulis) (f37)</td>
<td>Canned meat</td>
</tr>
<tr>
<td><strong>Mollusca</strong></td>
<td>• Clam (Ruditapes spp.) (f207)</td>
<td>• Oyster (Ostrea edulis) (f290)</td>
<td>Fresh meat</td>
</tr>
<tr>
<td></td>
<td>• Scallop (Pecten spp.) (f338)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td><strong>Cephalopoda</strong></td>
<td>• White squid (Loligo vulgaris reynaudii) • Red squid (Todarodes angolensis) • Octopus (Octopus vulgaris)</td>
<td>• Squid (Loligo edulis, Loligo) vulgaris (f258)</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>• Pacific squid (Todarodes pacificus) (f58)</td>
<td>• Pacific squid (Todarodes pacificus) (f58)</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>• Octopus (Octopus vulgaris) (f59)</td>
<td></td>
<td>Fresh frozen meat</td>
</tr>
</tbody>
</table>

*Bold numbers indicate the specific test codes.
vary between the different assay systems and often do not correlate with data obtained by skin testing. With these issues in mind more sensitive and specific functional in vitro tests have been developed to investigate the cause of allergic reactions. These functional in vitro assays focus on basophil mediator release assays such as histamine and leukotriene release tests and recently on the utilisation of flow cytometry.26

Human basophils express a variety of cytokine receptors including receptors for the IgE antibody (FceRI). The basophil can be activated by cross-linking of these IgE-binding receptors with the specific allergen, resulting in the release of vesicles containing mediators such as histamine and leukotrienes. Recently new specific marker proteins, known as CD63 and CD203c were discovered on basophils and it was observed that these proteins were associated with secreted granules and up-regulated concomitantly with basophilic degranulation. These two marker proteins are now used to demonstrate activation of basophils using flow cytometry. This assay is relatively fast (within 2-8 hours) and needs about 2-5 ml of whole blood. Protein allergens can easily be tested; however, healthy control subjects have to be included and assessed for each allergen.

**Double-blind placebo-controlled food challenge (DBPCFC)**

The "gold standard" for diagnosis of food allergy and for the identification of the offending agent is the DBPCFC. Various studies indicate a range of minimal seafood concentrations to elicit clinical reactions. Wu and Williams reported that fatal anaphylaxis occurred after ingestion of three shafts.38 A different study using DBPCFC reported the accumulated amount of as little as 120 mg of dried snail causing a significant decrease in forced expiratory volume in 1 second (FEV1).20 For crustaceans Bernstein et al. reported that patients in a DBPCFC reacted to 14 g of shrimp.52 Similar results were confirmed by Daul et al. who reported that the equivalent dose of about four medium-sized shrimps (16 g) caused reactions in DBPCFC.54 However, this technique does not distinguish between allergic (IgE-mediated) and non-allergic hypersensitivity involving different antibody types, cellular immune mechanisms and reactions based on intolerance or toxins (see below).

**NATURAL VERSUS RECOMBINANT ALLERGENS**

Naturally occurring allergens are nowadays routinely used in in vitro and in vivo diagnostics, but vary significantly in their composition and allergenicity. Most patients do not raise specific IgE to all but only some allergenic components in an allergen source. This is of special importance for the correct diagnosis and composition of allergen vaccines for specific immunotherapy (SIT). To address this, recombinant allergens have recently been introduced into conventional testing, a strategy termed component resolved diagnosis (CRD).55,56 Recombinant allergens are biologically produced pure allergen proteins using *Escherichia coli* or yeast expression systems. Hundreds of food allergens are characterised and many of these have been produced as recombinant allergens (see http://www.allergome.org). One major allergen of the brown shrimp is also available as recombinant allergen and used in the ImmunoCAP assay (see Table IV).

**CONCLUSIONS**

While immunological cross-reactivity between crustaceans and molluscs is observed frequently, clinical cross-reactivity is not well studied. The often poor correlation of clinical symptoms with IgE-based assays calls for improved in vitro assays. The increased repertoire of newly identified allergens using proteomics techniques and biotechnological production of allergens will improve the CRD of seafood allergy. Improved reagent compositions will optimise the diagnosis for both clinical sensitivity and species specificity, as well as accommodate geographical differences between populations.

Whereas specific IgE assays have so far been mostly designed for single allergens, the increasing availability of specific recombinant seafood allergens facilitates the possibilities for new applications. Recent developments in protein array technologies allow the simultaneous measurement of IgE reactivity to large numbers of allergens. While these areas of technological development are still in their infancy, it is likely they will have significant impact on more precise clinical implications for correct diagnosis and management of shellfish allergy.

**Declaration of conflict of interest**

The authors declare no conflict of interest.

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