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Allergy diagnostics: where are we going?

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The implementation of the EU directive (2001/83/EC) regarding allergens for both in vivo testing and for allergen specific immunotherapy is leading to a worrying deprivation of allergy diagnostics. The directive states that "[..] no medicinal product (including allergens for in vivo tests) may be placed on the market of a Member state unless a marketing authorization has been issued by the competent authorities […]" (1). This is certainly a theoretically correct approach pointing to an increase in quality and safety of marketed products. The dark side of the moon is however that, in view of the stricter quality requirements and of the elevated costs associated with the updating of existing licenses, allergen producing companies do no longer find it convenient to market extracts for in-vivo testing of less common airborne allergens and of foods. In fact, to be economically convenient, these products should be sold at such a high price that most doctors, hospitals or health care systems would not buy them. So, we are left with a dropping number of extracts of most common airborne allergens and with a short list of food extracts for in-vivo diagnostics. Another important point will be the legal status of fresh foods when they are used for in-vivo diagnostic purposes. Should an apple or a fresh shrimp be considered as a medicinal product as soon as they enter a hospital or a medical office to be used for prick-prick testing? Fresh foods represent the simplest, cheapest, most sensitive, and most rapid way to diagnose hypersensitivity to a certain source, and in some cases, they represent inalienable diagnostic means. The interesting study by Scala (2) and co-workers that appears in the present issue of *European Annals of Allergy and Clinical Immunology* compares the ISAC test with the skin prick test and finds discordant results in 20-30% for pollen allergens, 25% for dust mites, between 7-25% animal dander and between 14-33% for foods. Clearly, comparing a multiplex test based on allergen molecules conceived for component-resolved diagnostic with commercial whole allergen extracts may lead inevitably to detect some discrepancies. However, in real life the two methods should be considered more as complementary than as in contraposition. On one hand, limiting allergy diagnostics to the use of currently available allergenic molecules (either as singleplex or as multiplex) may lead to catastrophic mistakes. One example is shrimp allergy. To date, a very limited number of shrimp allergens is available on the marked despite in certain countries shrimps represent the second cause of primary food allergy among adults and contain a large number of allergenic proteins many of whom are still not characterized (3,4). In such a situation, the risk of getting a false negative result from the in-vitro test is quite high and a not experienced doctor might be tempted to consider the patient as "non allergic" despite a clear-cut history of shrimp allergy. Many other examples of this type might be given. On the other hand, extracts and fresh food-based skin tests are poorly standardised and variable in terms of allergens composition, thus leading to diagnostic errors as well. For instance, in the Scala *et al.* paper, ISAC testing identified

from 22% to 26% more cases than skin prick tests in peach and nuts hyper-sensitivity (2).

Progress in molecular biology and in the characterization of allergen molecules has led to the development of potent diagnostic instruments for in-vitro diagnosis. However, these are not perfect as they do not (and, arguably will never) contain all allergenic proteins. As a consequence, these instruments should be complemented by in-vivo tests (either commercial extracts or fresh material) possibly containing all the allergens of that specific source. In this view, allergy specialists are those who should lead this new phase of allergy diagnostics, preserving in vivo tests from too strict legislations on one side and improving diagnostic accuracy and allergens availability of in vitro tests on the other side.

1. Directive 2001/83/EC of the European parliament and of the council of 6 november 2001 on the community code relating to medicinal products for human use. Official Journal of the European Union 311. 28-11-2004:67-128.
2. Scala E, Villalta D, Meneguzzi G, Brusca I, Cecchi L. Comparison of the Performance of Skin Prick and ISAC Tests in the Diagnosis of Allergy. Eur Ann Allergy Clin Immunol 2020;52(6):258-267.
3. Celi G, Brusca I, Scala E, *et al.* House dust mite allergy and shrimp allergy: a complex interaction. Eur Ann Allergy Clin Immunol 2020;52(5):205-209.
4. Asero R, Scala E, Villalta D, *et al.* Shrimp Allergy: Analysis of Commercially Available Extracts for In Vivo Diagnosis. J Investig Allergol Clin Immunol 2017;27:175-182.