Editorial

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Lateral Flow Tests for Allergy Diagnosis: Point-of-Care or Point of Contention?

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Lateral flow technology, or 'point-of-care' (POC) testing, has been a staple of the in vitro diagnostics and medical device industry since the 1980s. Originally, developed for use in pregnancy tests, the technology is widely used not only in pregnancy tests, but in tests for drugs of abuse, tuberculosis, HIV, cardiac markers, infectious diseases and food testing, in what is now a multi-billion Euro market. Lateral flow tests (LFT) enable small chemicals, hormones, drugs, antigens, haptens and antibodies to be measured rapidly, with high sensitivity and specificity. Typically, they involve antibody coupled to nitrocellulose membrane as a line on an immuno-chromatographic strip. Analytes diffuse from a well along the strip and release a detector antibody (labeled with colloidal gold or latex particles). The soluble analyte/antibody complexes diffuse to the capture antibody line where they are deposited (if analyte is present) and form a red (gold) or blue (latex) line which indicates a positive test. Modifications of this format – including use of magnetic beads, nanoparticle-based signal amplification techniques, DNA barcodes and digital-style readouts for multiplexed analyte detection – are being developed for use in a wide range of POC tests [1]. The POC tests are designed for use in doctors' offices, hospital clinics, healthcare centers, pharmacies and consumers and provide a quick, accurate and inexpensive diagnostic test.

In the 1990s, lateral flow technology was first applied in the allergy field for the detection of dust mite and other allergens in environmental samples [2–5]. It was clear at the time that with various modifications, LFT could be developed for detection of allergen-specific IgE and could have utility for allergy diagnosis. However, it is only recently that an allergy diagnostic LFT has been introduced to practice.

In this issue, Sanchez-Bahillo et al. [6] compare the performance of an allergy diagnostic LFT (ImmunoCAP Rapid, Phadia, Sweden) with skin prick testing in a cohort of allergic children from Cartagena (Spain) who were recruited as part of the ISAAC Phase II study. The IgE LFT is a plastic device with a well where serum, plasma or whole blood can be applied. The serum diffuses along 2 parallel strips where different allergen extracts have been applied and specific IgE is detected using gold-labeled anti-IgE incorporated in the test strip. The IgE LFT measures IgE to cat, dog, birch, olive, mugwort, wall pellitory, dust mite, timothy, egg white and cow milk on lines that appear as 2 parallel 'barcodes' contained within the plastic housing. Plasma samples from 270 children (aged 9–12) who had been skin tested using the ISAAC phase II protocol were compared in the IgE LFT using a 4-point scoring system (from value 1 indicating a lightly visible line to value 4 indicating a line with greater intensity than that of the positive control).

By skin prick test, only 4–7% of patients were sensitized to birch, timothy grass or pellitory, which was insufficient for comparison with IgE LFT. The data was analyzed based on results from patients with positive skin tests to *D. pteronyssinus* (n = 123), olive (n = 62) and cat (n = 48) using Cohen's κ statistic and the Z statistic. Considering an IgE LFT score of 1 to be positive, there was ~90%

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agreement between the results of skin prick testing and LFT, which was reduced to 84% if the LFT score 1 was considered negative. The results were significantly correlated ($p < 0.0001$) in both cases. Moreover, there was a good correlation between LFT scores and the mean wheal diameter of skin prick tests, with LFT scores of 2–4 corresponding to skin tests of >3mm diameter and a score of 1 showing borderline positive skin tests. The results indicate that, at least for these 3 allergens, the IgE LFT is a sufficiently sensitive and accurate screening test for allergy diagnosis.

The limitations of the study are that only 3 of the 10 allergens included in the test could be compared with skin tests and that plasma samples (and not whole blood) were used for the testing. The latter point is important if the test is to be used in doctors' offices, outpatient facilities and clinics, or for field use in epidemiologic studies. The IgE LFT described here is marketed with separate allergen panels for 'child' and 'adult'. In the 'adult' test, egg and milk allergens are substituted with cockroach and 'mould' (the origin of which is unclear). It is important not to over-interpret the results of LFT. These tests are designed to show the presence or absence of an analyte and are at best semi-quantitative. It would be a mistake to equate IgE LFT scores with specific wheal diameters on skin testing. While further validation of the IgE LFT for other allergens is needed, the Sanchez-Bahillo study strongly suggests that IgE LFT will be a useful screening test for allergy diagnosis. The authors point to the use of IgE LFT for assessing sensitization in epidemiologic studies among schoolchildren (as an alternative to skin testing or laboratory-based in vitro tests), which is but one example of how this technology could be used.

The key advantages of IgE LFT are that they can be performed in less time than a panel of skin tests and they can be performed by non-specialists. It opens the door to allergy diagnosis by primary care physicians, ENT specialists, pediatricians and respiratory physicians to a much greater extent than laboratory-based in vitro IgE tests, which are time consuming, require expensive equipment and trained laboratory personnel. This threatens the primacy of allergists in the diagnostic arena and is, of course, a point of contention. Add to this the likely use of such tests by consumers, and these concerns are accentuated. In an era of personalized medicine and increasing health care costs, POC tests offer consumers choice, convenience and the opportunity to see for themselves whether or not they are at risk for a particular disease. Given the lack of adequate allergy testing services in many developed and developing countries, validated POC tests, such as the IgE LFT, could be a useful first step in allergy testing. This is especially the case in developing countries with limited clinical resources.

There is ongoing debate about the marketing of in vitro IgE testing to consumers via pharmacies. In the United Kingdom, the non-profit Allergy UK offers in vitro allergy testing services in conjunction with the British Pharmaceutical Association. Although training and guidelines have been established for this testing, the approach is not supported by the British Society for Allergy and Immunology, on the grounds that in vitro testing has a high false positive rate, will increase patient demand for testing, and will deter the government from making adequate investment in allergy services.

The advent of allergy POC tests will spur further debate. It would be a mistake for allergists to become defensive about in vitro testing and POC tests. Wider dissemination of less invasive IgE testing will encourage patients to seek specialist care. Allergists have the opportunity to incorporate properly validated IgE tests into their clinics and practices and should embrace new technologies. The aim of POC testing is not to encourage self-diagnosis, but to educate patients so that they will seek appropriate medical care. The results of IgE LFT should be interpreted within the context of the patient's clinical history, symptoms and relevant allergen exposures [6]. This is the realm of the allergist and one can foresee that allergy POC tests may well increase the number of referrals to allergists for further diagnosis and treatment. The era of personalized medicine is upon us.

Conflict of Interest

The author is founder and an owner of Indoor Biotechnologies, a biotechnology company that markets lateral flow tests for environmental exposure testing.

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