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A critical analysis of the utility of component tests in the diagnosis of pollen-related peanut and hazelnut allergy in the context of the BSACI guideline

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Running Head:

The diagnostic utility of component tests in pollen-related peanut and hazelnut allergy in relation to the BSACI guideline

Dear Editor,

We congratulate the authors for producing a comprehensive guideline on the diagnosis and management of peanut and tree nut allergy(1) This is likely to improve care *via* standardisation across the UK NHS Allergy services.

Several studies have illustrated the benefit of component resolved diagnostic (CRD) testing by enhancing the accuracy of peanut and hazelnut allergy diagnosis and aiding the process of risk stratification. However, most of these data are derived from studies carried out on children in Europe and USA with little evidence from adults and the British population. The BSACI guideline has highlighted: the possibility of variable performance of CRD across different populations, the need for validation in local populace, interpretation in the context of clinical presentation and pursuance of challenge testing where deemed necessary for a definitive diagnosis.

We recently investigated the utility of CRD in adults presenting with a clinical history suggestive of pollen food syndrome (PFS) to peanut and/or hazelnut in a 'real world' setting in a regional NHS specialist adult Allergy clinic (2). Patients were classified into groups 1 (classical PFS; n=69, reaction to hazelnut = 35, peanut = 34) and 2 (PFS *plus* mild subjective systemic symptoms; n=45, reaction to hazelnut = 12, peanut = 33) and the clinical presentation was correlated to CRD profiles for diagnostic concordance. Ara h1, h2, h3, h8 and h9 and Cor a1, a8, a9 and a14 were included in our panel as per our local laboratory policy with a 'cut off' at ≥ 0.35 KUa/L as per manufacturers recommendation. The concordance between clinical presentation and CRD profile for hazelnut was good (kappa inter-rater agreement = 0.63) with 97% of patients with classical PFS showing sensitisation to the PR10/Bet v1 Cor a1 (at a 'cut-off' of 0.35 KUa/L) (2). However, the concordance between clinical presentation and CRD profile for peanut was poor ($\kappa = -0.12$) (2). We showed that 85% of patients presenting with classical PFS to hazelnut were monosensitised to Cor a1. The other 15% were predominantly co-sensitised to a storage protein and/or Cor a8 (lipid transfer protein) with a small proportion of cases negative to the entire CRD panel. The CRD profile for those with classical PFS to peanut showed monosensitisation to Ara h8 in only 41% of cases with the remaining either co-sensitised or sensitised to storage protein/s (35%) and/or Ara h9 (9%). The CRD profile was negative in 15% of cases (2). Therefore, a confirmatory challenge

procedure is needed to establish an accurate diagnosis in 59% of patients reporting PFS symptoms to peanut thereby determining both the required rigor of avoidance strategies and the need for an adrenaline auto-injector.

To put this into a service perspective, Skypala et al reported that the prevalence of PFS is 2-3% in the British adult population with 23% and 12% reporting symptoms to hazelnut and peanut respectively (3). Extrapolating from these data and our recent experience (2), we estimate (based on 2011 British population census, a total of 63m with 82% adults [≥ 15 years]) that 35,600 and 73,100 patients with symptoms of PFS would require an oral challenge to hazelnut and peanut respectively for a definitive diagnosis. This has significant resource implications given the unmet need for allergy services in the UK (4).

For optimal laboratory quality assurance, it is best practice to produce receiver operating characteristic curves by individual centres. However, the resource implications of performing challenges for each allergen to definitively confirm 'allergic status' and 'clinical tolerance' renders this approach logistically unfeasible. A multi-centre UK study may be the way forward to provide guidance regarding optimal 'cut offs' for CRD in the British population.

In addition, knowledge of the analytical performance of allergy tests should be considered in any such study. Analytical variability can occur within any single laboratory assay, within a certain manufacturers group (on the same analyser/platform or between different analysers/platforms for the same assay) and between manufacturers. This is especially true for specific IgE tests, clearly demonstrated by the UK National External Quality Assurance Scheme (UKNEQAS) reports for the coefficient of variability (CV) for allergens. It is therefore paramount that quantitative specific IgE around any given 'cut-off' for positivity should be interpreted with careful scrutiny in conjunction with the clinical presentation, serum total IgE measurements and skin prick tests.

Therefore, we suggest that CRD tests are interpreted with caution and in conjunction with clinical presentation, and that clinicians be aware of their local laboratory's analytical performance in order to put these guidelines into optimal use.

Declaration:

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