WHERE WE STAND.

Does anyone really think they can find an answer to this?

The analysis of Mr Callaghan's allergy profile using the ALEX^2 molecular allergy test reveals a comprehensive absence of IgE-mediated sensitization to all major milk proteins. Every component of cow's milk, including α-Lactalbumin, β-Lactoglobulin and Casein, as well as milks from goat, sheep, camel and mare, shows IgE levels below 0.10 kUA/L, indicating no current IgE-mediated milk allergy. This suggests that any previous IgE-mediated milk allergy has completely resolved, yet the patient continues to experience reactions, pointing towards a non-IgE mediated persistent reactivity.

Regarding non-specific lipid transfer proteins (nsLTPs), the test shows only minimal sensitization. The patient has low-level positive IgE to Par j 2 (wall pellitory) at 0.36 kUA/L and borderline to Api g 2 (celery) at 0.27 kUA/L, but all major food nsLTPs, including Pru p 3 (peach), Mal d 3 (apple), Ara h 9 (peanut) and others, are negative. This minimal nsLTP signal does not align with the classical nsLTP syndrome, which is typically driven by Pru p 3 sensitization. Consequently, Mr Callaghan's reactions to fruits such as citrus, avocado and tamarind, which also show negative specific IgE, are likely non-IgE mediated.

The ALEX^2 test highlights significant IgE-mediated sensitizations elsewhere, notably to grass pollen allergens Phl p 5 and Lol p 1, with high IgE levels of 7.95 and 6.90 kUA/L respectively, confirming genuine grass pollen allergy. Additionally, there is strong IgE

reactivity to tropomyosin-containing organisms, including shellfish, dust mites, cockroaches and parasites, with elevated IgE to Ani s 3, Blo t 10, Der p 10, Per a 7 and Pen m 1. The patient also shows high IgE to Alternaria mold (Alt a 1 at 7.68) and insect proteins such as migratory locust, mealworm and house cricket. Total IgE is massively elevated at over 2,500 kU/L, far exceeding the normal reference of less than 100.

This pattern indicates that while the patient has clear IgE-mediated allergies to environmental allergens and certain invertebrates, the foods causing the most clinical issues—dairy, citrus, avocado and tamarind—do not show IgE sensitization. This discrepancy suggests that these food reactions are driven by non-IgE mechanisms, such as food protein-induced enterocolitis syndrome (FPIES) or other cell-mediated hypersensitivity pathways not detected by current IgE-based diagnostics.

The minimal nsLTP sensitization may contribute to lowering the reaction threshold but does not fully explain the severe reactions to these foods. The diagnostic frameworks currently in use rely heavily on textbook presentations and specific IgE patterns, which may not capture the complexity of cases like this. The immune system does not conform to rigid diagnostic criteria; it can manifest overlapping mechanisms and atypical presentations that defy simple categorization.

Mr Callaghan's history of 54 years of documented reactivity starting in infancy, combined with multiple co-existing immune pathways, challenges the conventional approach that assumes one patient equals one mechanism. The current diagnostic system, with its discrete categories and mandatory criteria, often fails to accommodate patients with complex, multi-mechanistic allergic profiles. Negative test results for specific IgE do not equate to absence of disease but rather indicate absence of that particular mechanism.

Molecular allergy testing, including ALEX^2, is a powerful tool but remains limited to detecting IgE binding. It does not assess T-cell mediated responses, mast cell activation through non-IgE pathways, epithelial barrier function, or gut mucosal immune responses. Thus, it only illuminates a fraction of the immune landscape involved in food hypersensitivity.

For patients with complex allergy profiles like this, a more comprehensive approach is needed. Functional immunological profiling, such as T-cell activation assays and basophil activation testing, could detect non-IgE mechanisms directly. Clinicians should focus on treating the clinical phenotype rather than forcing it to fit established consensus criteria. Recognizing that overlapping immune mechanisms in a highly atopic individual constitute a distinct clinical entity is crucial, even if it lacks a formal name.

In summary, Mr Callaghan's case exemplifies the limitations of current allergy diagnostic frameworks and the need for a broader understanding of immune responses beyond IgE. The science has yet to catch up with the complexity of such cases and while existing tools help the majority of patients, those with atypical or multi-mechanistic allergies require more nuanced evaluation and management strategies.