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## Toward a much-needed coming of age

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1 **Toward a much needed coming of age: diagnosis of allergic sensitization to fungi**

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45 Fungal sensitization and allergy are complex topics with many unanswered questions in terms  
46 of pathophysiology and unmet needs in clinical and laboratory practice. In recent years, advances in  
47 taxonomy, exposome science, and fungus – host interactions at the molecular level have been  
48 achieved. Stanley Letovsky and colleagues took advantage of these in order to analyze a vast  
49 database of real-world IgE testing results<sup>1</sup>. The contribution of their findings to clinical practice is  
50 expected to support more accurate diagnosis of fungal sensitization and allergy, thus improving the  
51 management of an array of type 2-related chronic inflammatory diseases. Moreover, their findings  
52 bring undisputable real-world support for the clinical deployment of molecular allergen-assisted  
53 diagnosis of fungal sensitization.

54 Allergic sensitization to fungi, defined as the demonstration of fungi-binding specific  
55 immunoglobulin (Ig) E, is a diagnostic biomarker of fungal allergy in patients with an evocative clinical  
56 history. It is also a pathophysiological contributor to allergic inflammation in asthma, atopic  
57 dermatitis, chronic rhinosinusitis with nasal polyps, allergic bronchopulmonary mycosis, and other  
58 diseases related to chronic type 2 immune responses. Taken together, these diseases span the entire  
59 lifetime, from pediatric to elderly patients, and represent a considerable burden for health systems<sup>2-4</sup>.

60 Conventional diagnosis of allergic sensitization to fungi relies on extracts obtained from  
61 fungal cultures employed for either skin or blood tests. While this strategy might seem  
62 straightforward, the interpretation of its results is hampered in clinical and laboratory practice by a  
63 range of factors:

- 64 (1) the actual species and abundance of fungi to which a subject is actually exposed are unknown;
- 65 (2) diagnostic fungal extracts are only available for a small number of fungal species, among the  
66 hundreds of thousands forming the fungal environmental exposome;
- 67 (3) fungal extracts display notorious variability as a function of culture conditions, harvesting,  
68 extraction and processing time and procedure;
- 69 (4) last but not least, fungal sensitization usually comes as IgE binding to multiple fungal extracts,  
70 leaving open the question of the true pathogenic species<sup>3,5</sup>.

71 The latter two points have been addressed in recent years by the molecular allergen-assisted  
72 approach, taking advantage of commercially available recombinant fungal allergenic proteins  
73 categorized as either “marker” or “cross-reactive” to distinguish between genuine sensitization (one  
74 or more fungal species triggering IgE production) and cross-reactivity (two or more fungal species  
75 recognized by IgE induced by one of them)<sup>6,7</sup>. Two major limitations prevent this approach from a  
76 generalized use: the limited number of commercially available fungal molecular allergens, and  
77 variable degrees of clinical deployment of the method. Thus, fungal allergenic extracts remain the  
78 main diagnostic tool in clinical practice, despite the lack of an unequivocal interpretation.

79 Lotevsky and coworkers sought to combine analysis on novel phylogenetic data on fungi with  
80 the results of a large study on indoor fungi present in US homes, and a vast database of almost 8  
81 million real-world results of IgE tests to fungi in the US. Their major finding was that cross-reactivity,  
82 rather than co-sensitization (i.e., associated genuine sensitization to two or more fungal species),  
83 underlies allergic sensitization to multiple fungi. They also confirmed that allergic sensitization to  
84 multiple fungi is closely related to their phylogenetic distance, rather than to their concomitant  
85 presence in the domestic environment, i.e. co-exposure. Finally, several fungal species that associate  
86 more often than would be expected from phylogenetic data were identified.

87 Although several limitations are present, such as the incomplete overlap between the *in vitro*  
88 and environmental panels of fungal species, the use of unrelated databases of environmental fungi  
89 and allergic sensitization, and the lack of information on the outdoor fungal exposome, Lotevsky and

90 coworkers lift an important barrier in the interpretation of allergic sensitization to fungi. Their results  
91 provide compelling evidence that allergic sensitization to one or more fungal species must be  
92 regarded as widely informative on a group of cross-reacting species, rather than on a single, well-  
93 defined fungal species. Consistently taking into account the cross-reactivity inherent to fungal  
94 extracts should help identify the true culprit species, including those lacking in the assay panel, and  
95 thus assist with the choice of an appropriate allergen immunotherapy. Sampling, characterization and  
96 quantitative assessment of indoor and outdoor fungi in a given subject's domestic, professional, or  
97 leisure environment is available, providing personalized additional clues for the interpretation of  
98 allergic sensitization to fungi <sup>8</sup>.

99 Moreover, it is known from other airborne allergens, such as grass pollen or house dust mites,  
100 that the demonstration of specific IgE binding to an extended panel of cross-reactive extracts usually  
101 implies the existence of a complex sensitization profile, with multiple allergenic molecules and  
102 epitopes involved in specific IgE induction, more severe clinical expression, and suboptimal efficacy of  
103 allergen immunotherapy <sup>6</sup>. Similar mechanisms are apparently at play in the fungal kingdom, since  
104 serum IgE from patients with allergic bronchopulmonary aspergillosis bind to multiple *Aspergillus*  
105 *fumigatus* proteins <sup>9</sup>.

106 The results reported by Letovsky et al are expected to apply also to fungi-specific IgG, which  
107 are important biomarkers for hypersensitivity pneumonitis, infectious fungal diseases, and allergic  
108 bronchopulmonary mycosis. IgG-binding fungal proteins outnumber IgE-binding counterparts<sup>10</sup>,  
109 suggesting that fungal cross-reactivity should be similarly considered in laboratory assays of IgG to  
110 fungi.

111 In conclusion, the study by Letovsky et al marks a major step in the current global effort to  
112 characterize the elusive interaction between fungi and the human host, bringing compelling evidence  
113 for consistent inclusion of fungal cross-reactivity in the diagnostic algorithm, giving clues to do so,  
114 and supporting the much-needed deployment of molecular fungal allergens into clinical practice.

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