Identifying Region-Specific Allergy Sensitization Clusters to Optimize Diagnosis and Reduce Costs

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Objective To delineate quantitatively the allergen sensitization patterns in a large pediatric cohort and inform the selection of a region-specific panel of allergen tests for timely and cost-effective in vitro atopy screening.

Study design IgE levels for specific allergens from patients in the Texas Children's Health System were analyzed retrospectively. Statistical and network analyses were conducted to reveal sensitization patterns.

Results Network analysis of 114 distinct allergens among 12 065 patients identified 2 main groups of allergens: environmental and food. Approximately 67.5% of patients were sensitized to environmental allergens, 47.2% to food allergens, and 7.3% to at least 1 allergen from both groups. We identified a novel panel of 13 allergens that could detect sensitization in 95% of patients, whereas panels of 7 allergens within each category effectively identified sensitization in 95% of patients with specific sensitivities. This data-driven approach is estimated to reduce overall testing costs by 52%. In agreement with literature, we observed correlations among allergens within specific categories, such as pollen, shellfish, nuts, and dairy allergens.

Conclusions This study provides insights into allergen sensitization patterns informing an algorithmic testing approach tailored for primary care settings. The use of a region and population-specific test panel can efficiently identify atopy, leading to more targeted testing. This strategy has the potential to refine laboratory testing, reduce costs, and improve the appropriateness of referrals to allergy specialists, ultimately enhancing diagnostic accuracy and resource allocation. *(J Pediatr 2024;270:113999)*.

The efficacy of IgE based serological testing in the diagnosis and treatment of allergies is widely accepted.[1,2] However, there is little guidance toward optimizing a diagnostic workflow that could consist of hundreds of specific IgE tests for a single patient. Empirically chosen panels of tests that were first created when in vitro immunoassays for specific IgE were developed continue to be used unchanged today, with little evaluation of their clinical relevance or efficacy at diagnosis. It is important to acknowledge that, currently, no publicly available studies exist to define an optimal testing panel, particularly for environmental or food allergens. Moreover, there is a dearth of published systematic research on allergen panels suitable for specific regions. Furthermore, the dominance of the same set of allergen tests among major environmental test panel providers limits the available alternatives for testing strategies. To address these gaps, research efforts are warranted to establish evidence-based guidelines for efficient, region-specific, and cost-effective in vitro allergy testing protocols.

A comprehensive cost–benefit evaluation of specific IgE-based testing in various clinical settings remains incomplete. Notably, studies have demonstrated a greater number of specific-IgE "positive" tests in patients with atopic dermatitis compared with skin testing for the same allergens, indicating a potential for a greater false-positive rate.[3] A comparison of epicutaneous, intradermal skin testing, and in vitro IgE-based testing revealed that in vitro testing was nearly 22-fold more expensive than skin testing.[4] Despite this, in vitro testing constitutes a significant portion of allergy diagnosis.[5,6] Although some systematic reviews have attempted cost analyses of multiplex allergen testing via IgE-based serology, firm conclusions for broad atopy surveillance in severely allergic individuals are still lacking.[6] Consequently, there is a critical need for quantitative analysis to optimize the selection of the initial number and type of allergens for evaluation, especially in primary care settings, where patients are being assessed for potential allergies.

Furthermore, the landscape of allergen sensitization patterns among patient populations presents intriguing possibilities for a more targeted testing approach.[7,8] Unique patterns of tree nut sensitization, observed in a Danish cohort, revealed almost all hazelnut-allergic subjects were sensitized to walnut and nearly all cashew-allergic subjects showed allergy to pistachio.[8] Similarly, a German cohort study highlighted common co-sensitization to related grass and tree pollens.[7] These findings suggest that strategic testing, focusing on a subselection of allergens, could help uncover precise sensitization patterns for individual patients. Considering these insights, we believe that there is an opportunity to refine the selection of aeroallergens for in vitro testing, leading to

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optimized diagnostic outcomes and reduced costs, particularly in primary care settings.

Given the aforementioned gaps, we hypothesize that a rigorous understanding of local sensitizations coupled with a data-driven approach may inform a strategy for allergen test panel construction. To test our hypothesis, we leverage aeroallergen and food IgE serology data from a pediatric cohort comprising 12 065 participants from the Greater Houston area in Texas. Our work has implications for enhancing diagnostic accuracy, improving patient care, and for driving cost savings.

Methods

Patients and Allergen Tests

We retrieved all IgE allergy test results from the electronic health records of Texas Children's Hospital (TCH) Health System consisting of 870 beds, and 92 ambulatory clinics in the Houston, Texas, metropolitan area, covering a 5-year period from January 2018 to December 2022. Tests were ordered by TCH clinicians for 30 457 children aged between 3 months and 18 years. A total of 758 439 test results were retrieved for 481 individually named specific allergens. To ensure consistency, we consolidated closely related allergens and different synonyms into 204 representative generic names. For example, we combined individual tests for peanut, Ara h 1 (peanut component), Ara h 2 (peanut component), Ara h 3 (peanut component), Ara h 8 (peanut component), Ara h 9 (peanut component), peanut (F13), Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, and Ara h 9 into a single representative allergen named "peanut." The complete list of consolidated names and their originals is available in **Table I** (available online at www.jpeds.com).

In preparation for downstream numerical analysis, we standardized and transformed qualitative test results into numerical values so that correlations and other statistical measures could be calculated. Specifically, we replaced "Negative" and "Positive" with 0.001 and 20.0, respectively. Test results that were reported as "<1," "<0.35," "<2.0," or "0/1" were replaced by "0.1." In addition, test results indicated as ">100.0," ">5000.0," ">15 000.0," or ">50 000.0" were substituted with "150.0," "7500.0," "20 000.0," or "75 000.0," respectively. Further, to eliminate duplicate results, we retained only the highest test result for each patient–allergen pair. For analyses involving clinically relevant specific IgE results, we used published clinically relevant cutoffs[9,10] when available. For all other allergens, we consulted a practicing allergy specialist physician and used specific IgE values greater than the cutoffs of 2.0 kU/L for food and 3.5 kU/L for environmental allergens, respectively.

Network Analysis

Allergen-specific IgE values for each patient were visualized with bipartite patient–allergen networks. In these networks the nodes represented either a patient or an allergen and the edges represented the allergen-specific IgE quantity for the patients. To create the networks, we employed the Edge-weighted Spring Embedded layout algorithm within Cytoscape, version 3.9.1.[11] This approach begins with a random distribution of the nodes in a 2-dimensional plane, followed by iterative node cluster aggregation based on connectivity (topology) and the strength of node edges. We applied a patient degree filter to generate multiple networks. The patient degree was defined as the number of allergen nodes connected to a given patient node.

Allergen Correlations

We used Python, version 3.8.12, to compute Spearman rank-order correlations between allergen pairs using the *spearmanr* function from the Scipy package (version 1.9.3). We calculated the correlations only for allergen pairs that were clinically relevant (greater than the cutoff) for 10 or more patients. To account for multiple comparisons, we adjusted the *P* values for false discovery rate using the Benjamini-Hochberg procedure (q-values). We considered correlations statistically significant only when the q-values were less than 0.05, and generated for these correlations a heatmap of Spearman correlation coefficients (R) using the *clustermap* function from the Seaborn package (version 0.11.2).

Results

Median Number of Specific Allergen IgE Tests

Our initial dataset consisted of 30 457 children and 758 439 test results (**Figure 1**). To evaluate and record the testing load on the patients, we employed these unfiltered datasets to construct histograms, quantifying the number of patients who had undergone allergen testing (illustrated in **Figure 2**, A-C). The distribution of the total number of specific allergen tests per patient is shown in **Figure 2**A, whereas the number of specific food allergens and environmental allergens tested per patient is shown in **Figure 2**, B and C, respectively. We note that the median number of total tests/patient for all allergens was 27, 26 for environmental allergens, and 11 for food allergens. For consistency purposes, total IgE tests were counted only in the all-allergens analysis. We note a common frequency of 15 tests per patient in the all and food allergens histograms, which is associated with a 15-allergen food panel (**Figure 2**, A and B). Other common frequencies of tests/patient (eg, 5 and 6/patient) correspond to heavily used panels at TCH.

Environmental Allergens vs Food Allergens

After removal of the negative and likely clinically irrelevant (eg, very low specific IgE value) test results as described in the Methods section, the final dataset of 52 672 test results from 12 065 children included 144 allergens (**Figure 1**). Of these allergens, 44 were environmental and 88 were food allergens. However, it's worth noting that the count of positive environmental test results (34 698) was approximately twice the count of positive food test results (17 562) (**Table II**; available online at www.jpeds.com).

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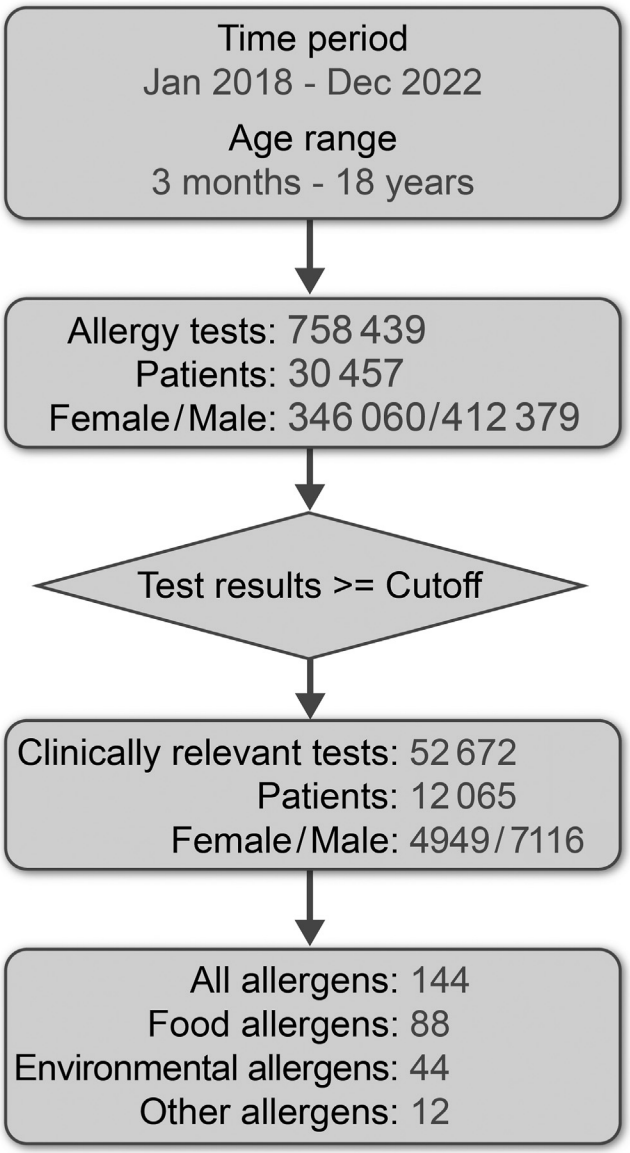

Figure 1. Flowchart for determining the patient cohort and allergen tests analyzed.

The 5 most prevalent environmental allergen sensitizations among all patients were *D farinae* (8.6%), *D pteronyssinus* (8.2%), dog (5.8%), cat (4.7%), and timothy grass (3.3%), whereas the 5 most prevalent food allergen sensitizations were egg (4.7%), peanut (3.8%), walnut (3.2%), hazelnut (3.1%), and shrimp (2.5%).

Detection by Panels with Small Numbers of Allergens

To determine an optimal test panel that could detect at least 1 allergy per patient in the cohort, we first identified the allergen with the greatest frequency of positivity across all patients. Subsequently, we removed these patients who tested positive for the identified allergen and determined the next allergen with the greatest positivity frequency among the remaining patients. We repeated this process until we reached the last patient–allergen pair. We performed this analysis using patient data with sensitizations to all, only food, and only environmental allergens. The complete list of the results is available in **Table III** (available online at www.jpeds.com). Our analysis using all allergen sensitizations revealed that a panel of 13 allergens, which included *D farinae*, *D pteronyssinus*, timothy grass pollen, oak tree pollen, *Alternaria*, dog, cat, egg, peanut, walnut, hazelnut, shrimp, and fire ant, could detect at least 1 sensitization in 11 488 (95%) of our cohort of 12 065 patients (**Figure 2**, D). Furthermore, when we performed the same analysis for food allergens alone (5690 patients), we found that a panel of 7 allergens, including egg, peanut, shrimp, walnut, hazelnut, pistachio, and β-lactoglobulin, could cover 5409 (95%) of the patients with food allergies (**Figure 2**, E). Similarly, the analysis for environmental allergens alone (8140 patients) showed that a panel of 7 allergens, including *D farinae*, dog, timothy grass, *Alternaria*, cat, oak, and cockroach, were sufficient to cover 7808 (95%) of the patients with environmental allergies (**Figure 2**, F).

To emphasize the resilience of our discovery that a limited number of allergens could effectively identify sensitization in 95% of patients, we conducted the same coverage and frequency analyses on 3 subsets of equal-size. These subsets were created by sorting the original dataset by result date and dividing it into 3 equal portions. Detailed frequency and coverage analysis outcomes for each subset, as well as the full dataset, are presented in **Table II** and **Table III** (available online at www.jpeds.com). Remarkably, the frequencies within each subset closely mirrored those of the full dataset analysis. The coverage analysis consistently demonstrated that panels comprising 13, 7, and 7 allergens sufficed to detect at least 1 sensitization in 95% of patients in analyses involving all allergens, exclusive food allergens, and exclusive environmental allergens. Notably, in the analysis focusing solely on environmental allergens, all panels remained unchanged. In the analysis of food allergens, there were small differences: pistachio was substituted with sesame in one subset, and β-lactoglobulin was replaced by α-lactalbumin in another subset. These outcomes underscore the robustness of our findings regarding the efficacy of these compact panels.

Environmental and Food Allergen Clusters

Positive specific IgE tests were used to draw patient–allergen bipartite networks (**Figure 3**). Gray circles represent patients, whereas the colored squares represent specific allergen categories: food, environmental, insect related, and other. The networks revealed 2 dominant allergen clusters, food and environmental (**Figure 3**, A). Patients within each cluster shared positive test findings for cluster-specific allergens, whereas patients between clusters were positive for allergens from adjacent clusters. The insect-related allergens separated from both food and environmental clusters with the exception of a small number of patients

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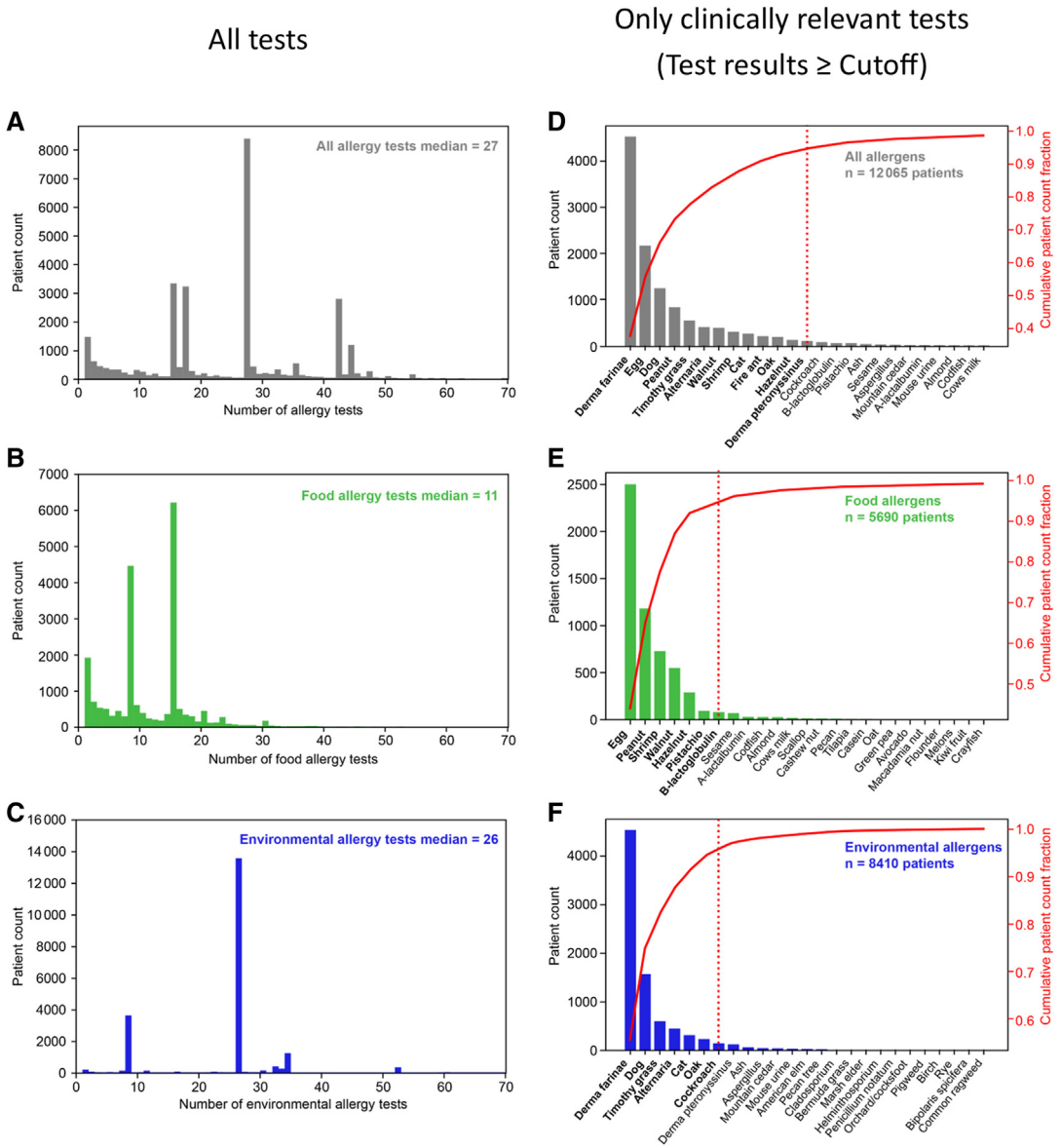

Figure 2. Analyses in panels **A-C** (*left half*) represent all IgE test results, whereas panels **E-F** (*right-hand side*) excluded results below the specified cutoffs, detailed in the Methods section. Histograms (**A-C**) display test frequency per patient for **A,** all **B,** food; and **C,** environmental allergens. Pareto-plots (**D-F**) show patient coverage by allergen, with *red lines* indicating cumulative counts. The allergens that cumulatively produce reactive test results in at least 95% of all patients are denoted by *boldface characters* (located to the *left* of the *dotted vertical lines*). **D, E,** and **F** present analyses for all, food, and environmental allergens (*gray*, *green*, *blue bars*).

who had co-occurring environmental allergen sensitization. Rare allergen sensitizations, such as *Ascaris* and *Mucor racemosus*, were detected in only 3 patients and thus located in the periphery of the network. The same network topology of 2 major, food and environmental, clusters and a separated insect-related group was observed in networks that included only patients with ≥2, ≥3, ≥5, and ≥10 positive allergen tests (**Figure 3**, B-E). Therefore, this overall trend indicated that a large fraction of patients was either sensitive to environmental or food allergens with a relatively small fraction of patients sensitive to allergens from both clusters.

Correlations of Allergen Groups

To identify statistically significant allergen–allergen correlations, we analyzed pairs of allergens that tested positive for at least 10 patients. There were 1929 such allergen pairs. We calculated for these pairs Spearman correlation coefficients R and false discovery rate corrected q-values to reduce the statistical effects of multiple testing. We chose the

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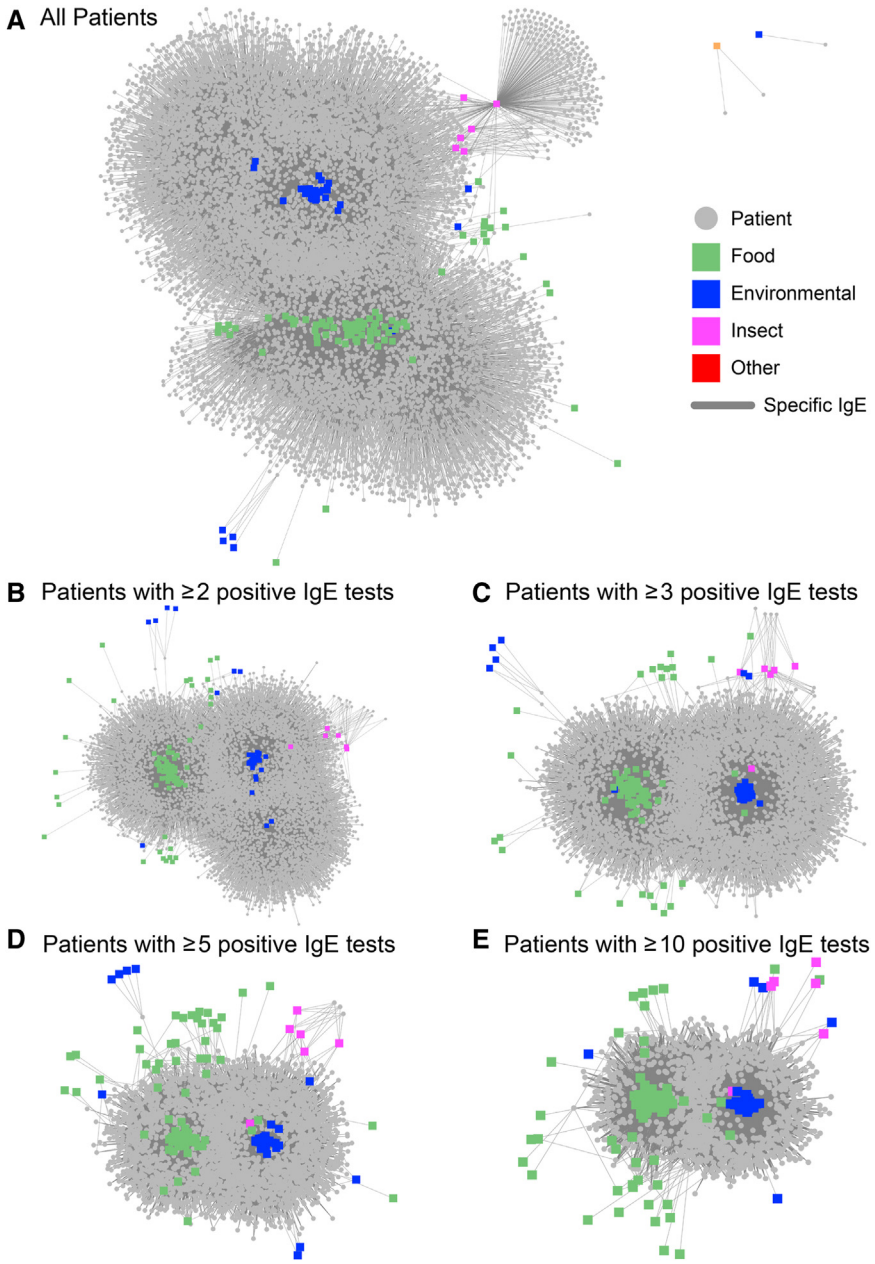

Figure 3. Bipartite patients (*circles*) and allergens (*squares*) networks for clinically relevant positive allergen test results. Patient nodes are shaded in *gray*, whereas allergen nodes are color-coded based on their broad classification into food (*green*), environmental (*blue*), insect-related (*pink*), and other (*orange*) allergens. Edges denote positive tests for allergen-patient pairs. **A,** All patients; **B, C, D,** and **E,** subsets of patients who had of ≥2, ≥3, ≥5, and ≥10 positive allergen tests, respectively.

nonparametric Spearman rank order correlations over parametric linear Pearson correlations, because the IgE test results were not normally distributed. There were 739 statistically significant allergen pair correlations with $q < 0.05$. **Figure 4** shows a heatmap plot of the correlation coefficients R for these highly significant correlations.

The heatmap plot, combined with hierarchical clustering, revealed a distinct pattern where highly correlated allergens were positioned near the diagonal. We detected known allergen correlations; for example, nut allergens clustered together. The clustering algorithm placed these groups together. Therefore, correlations between members of these groups were placed on the diagonal. Within the upper left corner of the heatmap (box 1), there was a prominent cluster of highly correlated tree and weed pollen allergens. Further along the diagonal is a cluster of shellfish allergens: crayfish, shrimp, lobster, crab, scallop, clam, blue mussel, and oyster. Not surprisingly, shellfish allergens also correlated with cockroach, a known cross-reactivity among proteins from phylogenetically related organisms (box 2). Next along the

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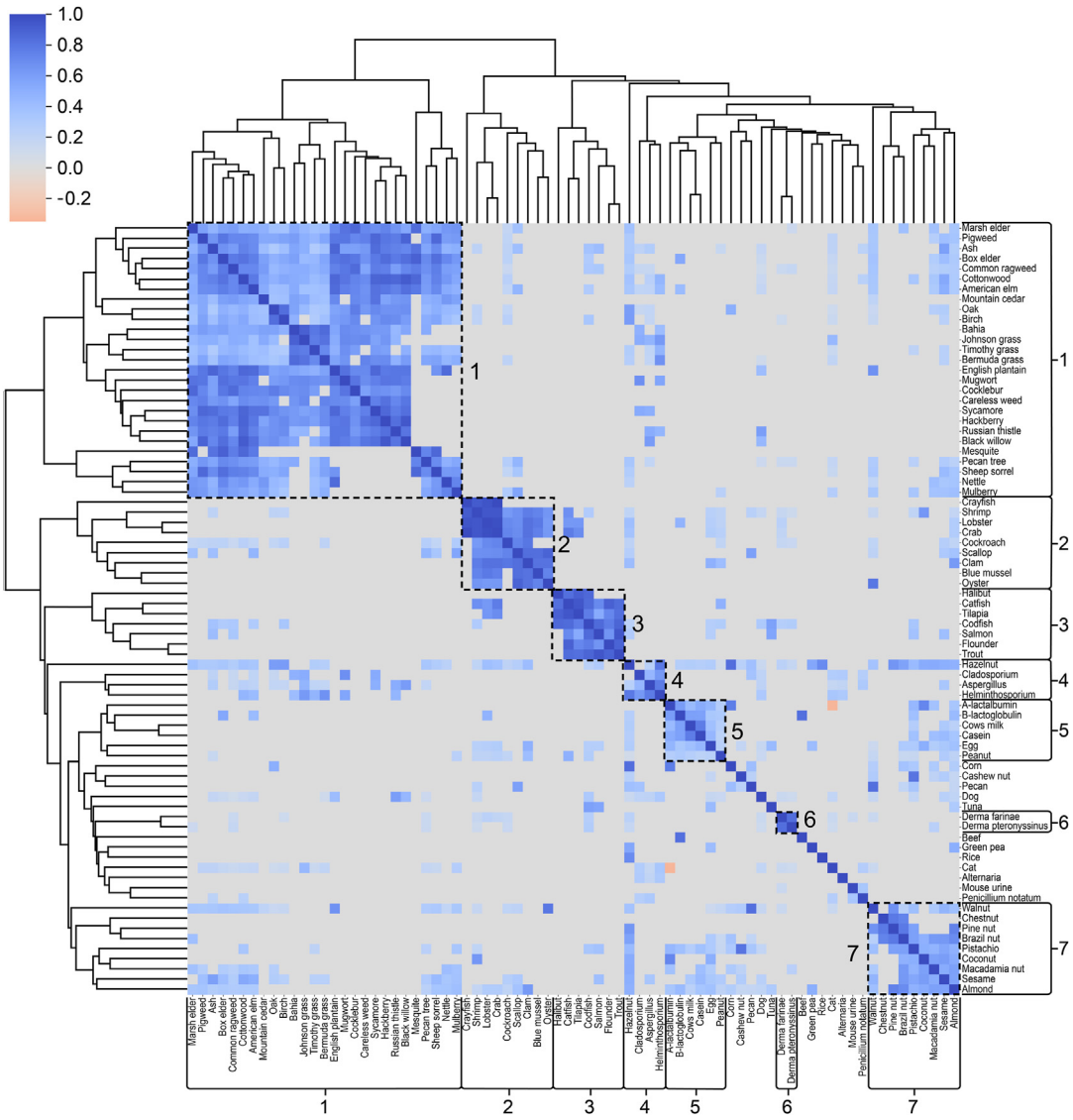

Figure 4. The figure displays a heatmap of Spearman rank-order correlations that are statistically significant between allergen pairs. The correlations were computed for allergen pairs that tested positive for at least 10 patients. To ensure robustness, only correlations that remained significant after Benjamini-Hochberg false discovery rate corrections ($q < 0.05$) were included. The heatmap was generated based on the Spearman R correlation coefficient.

diagonal is a cluster of fish allergens (box 3): halibut, catfish, tilapia, codfish, salmon, flounder, and trout. In Box 4, hazelnut was highly correlated with the molds *Cladosporium*, *Aspergillus*, and *Helminthosporium*. Dairy allergens α-lactalbumin, β-lactoglobulin, casein, and cow's milk were in Box 5, along with egg and peanut. Notably, egg and peanut also exhibited high correlations with several other off-diagonal allergens. The mite allergens *D pteronyssinus* and *D farinae* (box 6) demonstrated a strong correlation with each other and were the most frequently detected allergens in our cohort, together testing positive in 4655 of 12 065 children (39% of all children). The lower right corner (box 7) contained a cluster of nuts: walnut, chestnut, Brazil nut, pine nut, pistachio, and almond, accompanied by sesame, a seed.

We investigated the only one negative correlation between cat and α-lactalbumin in the heatmap and found that it was an artifact caused by a data-cleaning step. This allergen–pair was highly affected by the data-cleaning step where we replaced original qualitative values of ">100" by the numerical value of "150.0" for 16 patients so that correlations could be calculated (**Figure 5**; available online at www.jpeds.com).

Algorithmic Approach to Allergy Testing in Primary Care

For primary care facilities lacking access to allergy specialists, we recommend employing our allergen panels for food, environmental, or general allergen testing consisting of 7, 7, and 13 allergens. These panels can effectively detect positive sensitizations in

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95% of patients. They can be particularly valuable when providers suspect allergies based on patient symptoms, whether related to environmental or food allergens, or when a comprehensive assessment of all allergens is required. Subsequently, the correlation data presented in **Figure 4** can guide targeted and personalized follow-up testing, reducing the number of tests and related expenses. For instance, in cases in which follow-up tests are not required, the median cost savings for environmental, food, and all allergen testing would amount to (26 − 7)/26 = 73%, (11 − 7)/11 = 36%, and (27 − 13)/27 = 52%, respectively. Based on the 2023 third-quarter release of the Clinical Laboratory Fee Schedule for multiallergen screen reimbursement, this approach could result in savings for only environmental, only food, or all allergen testing of $151.43, $31.88, or $111.58 per patient, respectively. Thus, adopting this data-driven strategy can lead to improved and personalized patient care and optimized resource use in primary care settings.

Discussion

Diagnosing atopy requires clinicians to meld a careful clinical history and IgE-based diagnostic testing to precisely identify symptom triggers for individual patients.[12] Importantly, the identification of allergen triggers can guide management for patients with allergen-induced respiratory and skin diseases, which are common reasons for patients to seek emergency care when suboptimally controlled.[13] Achieving optimal clinical outcomes also will lead to attenuated costs for care.[14] Finally, practice guidelines advocate for precisely identifying environmental and food allergen triggers so that patient-specific treatment planning can ensue.[15,16]

One approach for improving in vitro allergy diagnosis involves the reimagining of health care systems that drive toward quality and value in care delivery.[17-19] Our approach is aligned with said approaches through the design of optimal in vitro allergy diagnostic testing strategies via population-level sensitization assessments. Mapping associations between similar allergens quantifies their relevance with sensitization clusters. These clusters can be used as a basis for developing a systematic, algorithmic, and cost-effective testing strategy tailored to specific geographic regions. By carefully selecting and strategically administering tests in primary care settings, health care providers can effectively employ allergy testing strategies and therapies or further refer patients to specialists.

Currently, there is a dearth of published systematic research on allergen panels appropriate for specific regions. Commercially available panels are created based upon regional prevalence without accounting for likelihood of sensitization (https://www.questdiagnostics.com/content/dam/corporate/restricted/documents/hcp/about-our-tests/TL3930_Allergy%20Test%20list%202017.pdf, last accessed on January 24, 2024). Notably, environmental allergen panels performed by the 4 largest commercial laboratories in the US are nearly identical, because they all source their tests from a single vendor (**Table IV**; available online at www.jpeds.com). Such conforming panels are likely to be insufficient for some patients but excessive for others. In our study, we conducted a comprehensive analysis of the prevalence of all positively tested allergens within our cohort. We emphasize the importance of avoiding indiscriminate initial testing and instead adopting a more targeted approach based on a combination of regional allergen occurrences and population sensitization patterns. This data-driven approach could identify a core set of geographically relevant allergens with prevalent sensitizations. Using this strategy, we envision a more precise initial evaluation that can be further refined, as needed, with longitudinal clinical allergy evaluations and therapeutic interventions. In this way, additional testing can be done via skin testing or expanded IgE-based serological testing.

Our results suggest that an initial test panel comprising a small number of allergens is suitable as a starting point for assessment of atopy in the primary care setting. This approach not only reduces the burden on patients but may prove to be economically advantageous. For example, in our analyzed cohort, the median number of allergy tests was 27. Using our 13-allergen panel, that would constitute a reduction of up to 52% in test numbers and costs. The savings would increase to 73% in cases in which only environmental allergen testing is necessary. In cases in which a positive test result is obtained using the limited panel, the analysis of allergen correlations can guide the testing for additional missed correlated allergens. However, allergens that are not correlated to any panel, or are rare, will be missed with this approach. If the latter is suspected, referral to an allergy specialist for personalized testing and treatment is appropriate.

We would also like to point out that this approach revealed novel associations between allergens. Alternatively, it is possible that these associations are of no biological relevance and reflect sensitization bias in this single cohort. For example, the association between hazelnut and mold is not explained by our analysis, but it may reflect contamination of mycotoxin and other mold-associated proteins in hazelnuts, as has been previously reported.[20] A finding that suggests that our approach holds value for mining previously unrecognized associations is the coupling of crustacean and dust mite sensitization which is known but represents an "internal control," bolstering the validity of our approach. Along these lines, an important point of clinical relevance worth mentioning is that we do not advocate for indiscriminate food allergy testing. Testing for food sensitizations must be born out of a rigorous clinical history. However, it is possible that future network analyses like this, from different or larger populations, may uncover previously unrecognized food sensitization patterns.

It is important to acknowledge certain limitations of this analysis. Our study cohort is specific to a single center in Houston, Texas, and the prevalence of certain allergens in our region may differ from others. For example, fire ant allergies are prevalent in our region but nonexistent in some northern regions. In addition, our proposed approach may miss approximately 5% of patients with rare allergies that are not covered by the selected allergens in our panel.

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In conclusion, we provide a systematic analysis of allergen prevalence and correlations that can serve as a foundation for implementing algorithmic testing approaches in primary care settings. Although our findings are specific to Southeast Texas, this approach can be generalized and can serve as a valuable framework for other regions to develop their own specialized panels. Further research and collaboration among experts are necessary to establish region-specific allergen panels and stepwise algorithms to optimize patient care. ■

Declaration of Generative AI

During the preparation of this work the authors used ChatGPT4 (https://chat.openai.com) in order to reformulate parts of the text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT Authorship Contribution Statement

Numan Oezguen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nicholas L. Rider:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Michael Dowlin:** Data curation, Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Ila Singh:** Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors declare no conflict of interest.

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