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American College of Allergy, Asthma & Immunology

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Newborn Screening for TRECs: Looking Beyond SCID

Analysis of T-cell receptor excision circles (TRECs) was added to Michigan's newborn screening panel in 2011. Although used to screen for severe combined immunodeficiency (SCID), abnormal TREC results are also associated with other causes of T-cell lymphopenia. These authors analyzed data for all newborns with abnormal TREC-based screening results in the Michigan Department of Health and Human Services Newborn Screening Program from October 2011 through December 2021.

A total of 949 of 1,116,118 infants screened had abnormal TREC results. The authors further analyzed the 887 infants not diagnosed with SCID, who were matched 1:3 with control infants with normal TREC results.

Male and Black infants were more likely to have abnormal TREC results, as were infants with meconium-stained amniotic fluid (MSAF), suspected chromosomal anomalies, and hypospadias. In the multivariate binary logistic regression analysis, the factors most predictive of abnormal TREC results were male sex (odds ratio [OR], 1.75; 95% CI, 1.49-2.05), MSAF (OR, 1.78; 95% CI, 1.28-2.48), history of transfusion (OR, 1.75; 95% CI, 1.42-2.03), every 1-unit decrease in APGAR scores at 5 minutes (OR, 0.84; 95% CI, 0.81-0.87), and prepregnancy diabetes (OR, 1.75; 95% CI, 1.10-2.72). Factors that were not predictive included maternal alcohol and cigarette use and maternal hypertension before or during pregnancy. The study reported health disparities in infants with abnormal TREC results born in Wayne County (the county with the highest social vulnerability index). These infants had lower mean 5-minute APGAR scores, body weights, and gestational ages and higher rates of prematurity than infants born outside Wayne County.

COMMENT: While TRECs and newborn screening play an essential role in identifying patients with SCID and profound lymphopenia, understanding other factors that may contribute to low TRECs is important. The authors identify higher rates of abnormal TRECs in Black infants and infants of Black mothers. Although the study was limited to infants in Michigan, the article provides valuable information for • • •

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practicing immunologists that may help us in addressing disparities. Further research in different geographic locations is needed to better understand the applicability of these findings to other patient populations.

V.H.T.

Navalpakam A, Hurden I, Lugt MV, et al. Predictors for T cell receptor excision circles in infants without severe combined immunodeficiency or thymic aplasia/hypoplasia. Ann Allergy Asthma Immunol. 2026;137(3):380-386.

Keywords: T-cell receptor antigens, severe combined immunodeficiency

Rural Patients With Inborn Errors of Immunity Face Geographic Barriers to Care

Up to 70% of patients with an inborn error of immunity (IEI) are not properly diagnosed. The median diagnostic lag is estimated at 14 years. After receiving a diagnosis, patients with IEIs need access to clinical immunologists and the means to receive IgG replacement therapy. These challenges are exacerbated in rural communities. This article uses geospatial data to visualize access to expert clinical immunologists and infusion centers throughout the United States. Rurality was defined according to Rural Urban Commuting Area (RUCA) codes and population density by zip code and county. The authors found that patients with IEIs who live in rural areas face geographic barriers to care.

Rural areas had a lower proportion of expert clinical immunologists. Proportions ranged from 0.4% to 23.6% according to how rurality was defined. Washington, DC, had the highest density of expert clinical immunologists (10 per 1 million individuals). Five states had no expert clinical immunologists: Nevada, Oklahoma, South Dakota, Vermont, and Wyoming. New Mexico had 805 federally qualified health centers, ranking first among the states. Figure 1 illustrates the distribution of federally qualified health centers, infusion centers, and expert clinical immunologists throughout the United States. Infusion centers were clustered in California, Texas, Illinois, Virginia, and New York. Figure 2 presents an expert clinical immunologist health care service area desert map. Practice locations and the 2-hour driving radius for each are shown. Large sections of the country fell outside the 2-hour driving radius of all practice locations. One study limitation was that some clinicians who care for patients with IEIs but are not expert clinical immunologists may not have been included in the count.

COMMENT: This analysis offers important insight into a patient population for whom diagnostic delays can have serious consequences. Examining the magnitude of the access gap experienced by rural patients with IEIs is a crucial first step toward addressing these complex, multifactorial disparities. Meaningful progress will require both near- and long-term strategic efforts from multiple stakeholders.

S.W.S.

Blaukovitch JA, Blaukovitch CP, Lawrence MG, et al. Geographic barriers to subspecialty care access for patients with primary immune disorders in the United States. J Allergy Clin Immunol Pract. 2026;14(10):2389-2396.

Keywords: health services accessibility, immune system diseases

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Airway Inflammation and Microbiology Vary by Country

This study addresses a gap in knowledge about asthma characteristics in places other than the usual high-income country research setting. Following up on previously reported differences in asthma phenotypes, the World Asthma Phenotypes (WASP)-biome study assessed characteristics of the airway microbiome in young people with asthma in Brazil, Ecuador, New Zealand, Uganda, and the United Kingdom.

Sputum samples were analyzed from 364 participants with asthma and 124 without. In participants with asthma, 135 bacterial taxa were found, of which *Streptococcus* species were the most prevalent. The composition of the airway microbiome differed by country. α-Diversity and bacterial load were highest in samples from Uganda. In the combined group, microbiota composition differed between participants with asthma and those without. Within countries, microbiota composition differed significantly between participants with asthma and those without in Ecuador and New Zealand. Sputum microbiota differed according to asthma phenotype. In a multivariate analysis, percentages of neutrophils and eosinophils in the airway were significantly associated with microbiota composition, as was age, sex, and country.

These authors previously reported that neutrophilic inflammation is higher in Uganda, whereas eosinophilic inflammation is higher in New Zealand. The present study illustrates how the airway microbiome reflects geographic differences in asthma. To improve asthma diagnosis and treatment, further global studies of asthma pathophysiology are needed.

COMMENT: Asthma in one person is not the same as asthma in another. Phenotypes and endotypes vary by individuals. In this fascinating report by Taylor et al in *Thorax*, the authors demonstrate that asthma may also differ markedly from one country to the next. Inflammatory markers, endotypic biomarkers, microbiome, and the prevalence of neutrophilic asthma varied between countries. Thus, the environment in which you find yourself practicing and treating asthma appears to have an important role in the drama.

C.A.S.

Taylor SL, Brooks CR, Pembrey L, et al. Airway microbiota in young people across four continents differ by country, asthma status and inflammatory phenotype. Thorax. 2026;81(9):903-912.

Keywords: asthma, microbiota

Second-Generation H1-Antihistamines Do Not Alter Dementia Risk

Are second-generation H1-antihistamines associated with dementia risk? A few previous studies identified a potential association between antihistamine use and dementia but had important limitations, such as not adequately controlling for confounding factors and variations in how adverse events were reported. To revisit this question, this study from Germany emulated a target trial by using electronic health record data from the TriNetX clinical database. Included patients were older than 50 years and had allergic rhinitis, chronic sinusitis, or chronic urticaria and no previous diagnosis of dementia. The study outcome was the first diagnosis of dementia.

After propensity score matching, the risk for new-onset dementia did not differ between users of any first- or second-generation H1-antihistamine and users of intranasal or systemic steroids. The authors also found no difference in risk between users of second-generation H1-antihistamines and users of first-generation H1-antihistamines or users of steroids. Dementia risk was slightly higher in people with allergic rhinitis who used second-generation H1-antihistamines than in the comparison group who used intranasal steroids (hazard ratio: 1.239; 95% CI, 1.060-1.447). The authors write that this finding may have been associated with the protective effects of corticosteroids rather than the harmful effects of second-generation H1-antihistamines. No association was found for other conditions such as chronic urticaria, in which second-generation H1-antihistamines are used as first-line therapy in higher dosages.

The findings support continued use of second-generation H1-antihistamines.

COMMENT: Allergists use lots of antihistamines in our patient care. Patients, in turn, do not want to get dementia. Reported associations between first-generation antihistamines and dementia provide additional motivation to avoid these less effective, more toxic older drugs when second-generation antihistamines can get the job done. But the identification of this risk with older antihistamines creates patient uncertainty around all antihistamine use. In that setting, Olbrich et al analyzed patients being treated with nonsedating antihistamines for chronic urticaria, chronic sinusitis, and allergic rhinitis compared with matched participants without second-generation antihistamine exposure. Their findings are reassuring in that no differences were observed in dementia rates among long-term users.

C.A.S.

Olbrich H, Kolkhir P, Zuberbier T, et al. Second-generation H1-antihistamines do not alter dementia risk in type 2 inflammatory diseases: a target trial emulation using real-world data.
J Allergy Clin Immunol Pract. 2026;14(9):2051-2058.

Keywords: dementia, histamine H1 antagonists

First Randomized Trial of Biologic Switching in Severe Asthma

The NIMBLE trial (NCT04718389) was a multicenter, randomized phase 3A noninferiority study of switching • • •

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biologic treatment to depemokimab in patients with severe asthma currently being treated with mepolizumab or benralizumab. Depemokimab is an ultra-long-acting biologic targeting IL-5 that is administered twice yearly.

Participants were randomly assigned to depemokimab 100 mg subcutaneously (SC) every 26 weeks or to continue their previous treatment with either mepolizumab 100 mg SC every 4 weeks or benralizumab 30 mg SC every 8 weeks. The primary end point was the annualized rate of clinically significant exacerbations.

The mean age of the 848 participants in the depemokimab group was 58.3 years; that of the 839 participants in the mepolizumab/benralizumab group was 58.9 years. The baseline rate of exacerbations was low in both groups, corresponding to about one exacerbation every 2 to 3 years. The annualized rate of clinically significant exacerbations was 0.57 in the depemokimab group (95% CI, 0.50-0.64) and 0.49 in the mepolizumab/benralizumab group (95% CI, 0.43-0.55). The rate ratio (1.16; 95% CI, 0.98-1.38) did not meet the statistical criterion for noninferiority. In participants grouped according to the biologic they were receiving at baseline, the annualized rate of exacerbations remained 0.48 in the group switched from mepolizumab to depemokimab and changed from 0.48 to 0.67 in the group switched from benralizumab to depemokimab. Secondary end points remained stable, and adverse events related to the study treatment were similar between groups (9%-10%).

COMMENT: The authors present the first randomized controlled biologic switch study in asthma, which represents a significant milestone as biologic options for severe asthma increase. While depemokimab did not meet the statistical significance threshold for noninferiority, this finding must be nuanced by the low baseline rate of exacerbations. Overall, the depemokimab group experienced a slight increase in the annualized exacerbation rate compared with the mepolizumab/benralizumab groups, which would result in 1 additional exacerbation every 12.5 years. Whether this is clinical meaningful is an important question, and I agree with the authors that this evidence suggests that many patients receiving benralizumab and mepolizumab for severe asthma could safely switch to depemokimab.

T.G.C.

Chupp G, Nagase H, Skowasch D, et al. Switching to twice-yearly depemokimab from mepolizumab/benralizumab in severe asthma: a multicenter, randomized, double-blind, phase 3A clinical trial (NIMBLE).
Am J Respir Crit Care Med. 2026;212(5):921-935.

Keywords: anti-asthmatic agents, asthma

Preliminary Findings on Inhaled Anti-TSLP Antibody Fragment in Asthma

Ecralimab is a neutralizing antibody fragment directed against thymic stromal lymphopoietin (TSLP), a key regulator of type 2 inflammation. This research letter reports the results of a phase 2b clinical trial (NCT04410523) of ecralimab in adults with uncontrolled asthma. Eligible patients had an Asthma Control Questionnaire-5 (ACQ-5) score of 1.5 or greater and prebronchodilator FEV_1 between 40% and 85%. Participants were randomly assigned to ecralimab 0.5, 1, 2, 4, or 8 mg or placebo.

A total of 335 patients were randomly assigned before the trial was ended, and 304 participants completed treatment. Ten patients reported treatment-related adverse events, the most common of which were cough and dry mouth. Study authors reported no dose-response relationship with FEV_1 or fractional exhaled nitric oxide (FeNO). The 0.5-mg dose resulted in the greatest numerical improvement in FEV_1, and the 1-mg dose resulted in the greatest numerical improvement in FeNO. Because of the early study termination, the statistical analysis of study end points was underpowered. The study was funded by Novartis Pharma AG.

COMMENT: This phase 2b study of ecralimab, an inhaled neutralizing antibody fragment of TSLP, was cut short for "business reasons" after about half of the recruitment goal was met. Apparently, this was before any efficacy analysis, which eventually did not show a dose response for the primary outcome of FEV_1 at weeks 8 and 12. It's unclear why this was chosen as the primary outcome. Interestingly, most patients developed anti-drug antibodies to ecralimab, but it is unknown whether these were neutralizing. It will be important to learn whether the inhaled delivery route of biologics differs from parenteral administration with regard to eliciting a specific immune response, which could affect long-term efficacy.

T.G.C.

Mackay AJ, Gessner C, Budani H, et al. Inhaled anti-thymic stromal lymphopoietin antibody fragment, ecralimab, in severe asthma: A placebo-controlled, multicenter, double-blind, randomized, phase 2b clinical trial.
Am J Respir Crit Care Med. 2026;212(7):1617-1620.

Keywords: anti-asthmatic agents, asthma, human TSLP

Rezpegaldesleukin for Moderate-to-Severe Atopic Dermatitis

Silverberg et al report the final results of the REZOLVE-AD trial (NCT06136741) of rezpegaldesleukin for treatment of moderate-to-severe atopic dermatitis (AD). The normal balance of regulatory T cells (Tregs) to conventional T cells is disrupted in autoimmune diseases like AD. Low-dose IL-2 can rescue Treg function but has a narrow therapeutic window and a short half-life. Rezpegaldesleukin is an IL-2 receptor agonist with preferential activity for Tregs.

The trial was conducted across 10 countries in biologic-naïve adults. Moderate-to-severe AD was defined as a baseline Eczema Area and Severity Index (EASI) score of at least 16, a validated Investigator Global Assessment for Atopic

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Dermatitis (vIGA-AD) score of at least 3, and at least 10% affected body surface area. Study participants were randomly assigned to rezpegaldesleukin 24 μg/kg every 2 weeks (n=104 included in the modified intention-to-treat analysis), rezpegaldesleukin 18 μg/kg every 2 weeks (n=106), rezpegaldesleukin 24 μg/kg every 4 weeks (n=110), or placebo every 2 weeks for 16 weeks (n=73). The primary end point was percentage change from baseline in EASI score.

In the total population, the patients' mean age was 37 years, and 52% were female. Most participants were White and not Hispanic or Latino. Their mean EASI total score at baseline was 26. The primary end point was met in all rezpegaldesleukin groups. Dose-dependent improvements in secondary endpoints including EASI-75 (EASI reduction of at least 75%), vIGA-AD, and itch Numerical Rating Scale score were reported. All treatment groups experienced a greater mean reduction in affected body surface area compared with the placebo group (mean reductions of 43%-54% vs 17%).

The trial was funded by Nektar Therapeutics.

COMMENT: Current systemic therapies for AD suppress cytokines or effector T cells. Rezpegaldesleukin takes the opposite approach: using an IL-2 receptor agonist to expand Tregs. In this phase 2b trial, all 3 dosage groups met the primary end point, with mean EASI reductions of 61%, 58%, and 53% versus 31% for placebo. Injection-site reactions occurred in 70% of patients but were mild. Treg expansion was dose dependent and without an infection signal. This is the first large trial to show that expanding Tregs produces clinical benefit in allergic disease.

K.A.

Silverberg JI, Rosmarin D, Bieber T, et al. Rezpegaldesleukin treatment of moderate-to-severe atopic dermatitis (REZOLVE-AD): final results from the 16-week induction period of an international, double-blind, placebo-controlled, randomised phase 2b study. Lancet. 2026;408(10557):833-846.

Keywords: atopic dermatitis, biological therapy, interleukin-2 receptor agonists

Pooled Safety Data for Remibrutinib in Chronic Spontaneous Urticaria

The authors analyzed pooled safety data for remibrutinib from the REMIX-1 and REMIX-2 clinical trials. Remibrutinib is a Bruton's tyrosine kinase inhibitor approved for the treatment of chronic spontaneous urticaria. The REMIX trials studied the efficacy and safety of remibrutinib 25 mg twice daily as an add-on treatment in patients experiencing symptoms despite treatment with second-generation H1-antihistamines.

The safety analysis included data for 606 participants who received the study drug and 306 who received placebo. The participants' median age was 43 years, and about 67% were female. During the 24-week placebo-controlled study period, about 65% of both groups experienced at least one adverse event. The only adverse event that occurred more frequently in the remibrutinib group was petechiae, which occurred in 3.8% of the remibrutinib group and 0.3% of the placebo group (risk difference estimate, 3.5; 95% CI, 1.5-5.1). Most adverse events were mild or moderate. There were few adverse events leading treatment discontinuation and few serious adverse events. Bleeding events including laboratory abnormalities related to bleeding were reported in 10.6% of the remibrutinib group and 5.2% of the placebo group. Mucocutaneous bleeding was usually reported within the first 12 weeks of treatment. Three patients discontinued treatment because of mucocutaneous bleeding. Bleeding events were not associated with platelet count changes, coagulation abnormalities, or use of antiplatelet medications. The authors write, "the absolute risk of bleeding, serious infections, cytopenias, and hepatic disorders remained low throughout the study period."

COMMENT: The question of when we use remibrutinib in our practices and what we use it for will largely be answered by the safety profile. This pooled analysis is valuable in determining the settings in which remibrutinib might not be as appropriate. Key safety events associated with remibrutinib use that reached significance over placebo included bleeding and petechiae, most often at mucocutaneous sites. The drug was not obviously associated with infections, cytopenias, or liver injury. The safety of remibrutinib in patients who are already at additional risk for bleeding is unknown but should likely be deemphasized.

C.A.S.

Giménez-Arnau AM, Zharkov A, Yang B, et al. Safety of remibrutinib in chronic spontaneous urticaria: a pooled analysis of REMIX-1 and REMIX-2 trials. J Allergy Clin Immunol Pract. 2026;14(8):1901-1913.

Keywords: chronic urticaria, protein kinase inhibitors, pyrimidines

Dupilumab Increases Cutaneous Autoimmune Disease Risk

Using the PEDSnet electronic health record (EHR) database, this retrospective cohort study examined the incidence of new autoimmune or autoinflammatory disease in children with moderate-to-severe atopic dermatitis (AD) and/or persistent asthma prescribed dupilumab. The authors hypothesized, "blockade of T2 allergic inflammation with dupilumab might allow for unopposed non-T2 inflammatory responses."

EHR data were from 10 US hospital systems. Eligible children were aged 6 to 17 years and were identified on the basis of diagnosis codes and medication prescriptions. The primary outcome was the incidence of new-onset autoimmune disease. Of the 178,977 children overall, 4189 were treated with dupilumab and 174,788 were not. The children's median age was 11.8 years, and 47% of the study sample was female. About 22% of the children were Hispanic, 32% were non-Hispanic White, and 29% ...

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were non-Hispanic Black. About 32% had asthma only, 54% had AD only, and 14% had both. The authors used weighted cohorts of dupilumab-treated and non-dupilumab-treated children for the analyses.

The incidence rate of all autoimmune disease was 8.78 per 1000 person-years in the dupilumab group vs 6.31 in the comparison group (rate difference: 2.47; 95% CI, 0.82-4.30). For autoimmune cutaneous disease, which included alopecia, dermatomyositis, psoriasis, and vitiligo, the incidence rate difference was 2.18 (95% CI, 0.67-3.66). Differences in noncutaneous autoimmune disease subcategories were not significant. In the fully adjusted Cox proportional hazard model, there was a 1.45-fold increase in risk for any autoimmune disease diagnosis with dupilumab treatment (95% CI, 1.18-1.80) and a 1.57-fold increase in risk for cutaneous autoimmune disease (95% CI, 1.22-2.03). The increase in risk for cutaneous disease was not significant when psoriasis and alopecia were excluded.

The incidence of cutaneous autoimmune disease increased by about 2 cases per 1000 dupilumab-treated children per year, driven by diagnoses of psoriasis and alopecia areata.

COMMENT: A classic paradigm in immunology is the duality between Th1 (and Th17) and Th2 immune responses. This cohort study finds a modest increase in psoriasis and alopecia in children treated with dupilumab, suggesting that blocking T2 inflammation may unmask these conditions. Therefore, the allergist/immunologist should monitor for the development of autoimmune skin diseases in patients receiving dupilumab therapy.

G.B.L.

Gabryszewski SJ, Hirabayashi K, Botdorf M, et al. Incidence of autoimmune diseases in children with atopy treated with dupilumab.
J Allergy Clin Immunol. 2026;158(2):533-541.

Keywords: asthma, atopic dermatitis, autoimmune diseases

Dupilumab Reduces Mucus Burden in Asthma

Adults with asthma who had visible mucus plugs on computed tomography (CT) imaging were followed during dupilumab treatment. Dupilumab, which inhibits IL-13 signaling, has been reported to reduce the total mucus plug burden. The retrospective analysis included 32 adults (mean age, 54 years); 22 were treated with dupilumab every 2 weeks and 10 served as a control group. All participants had evidence of type 2 inflammation and were being treated with high-dose inhaled corticosteroids. All underwent chest CT imaging at baseline and follow-up.

A total of 269 mucus plugs were annotated at baseline: 162 in the dupilumab group and 107 in the control group. At follow-up, individual mucus plugs were classified as being resolved, fixed-location persistent, or new onset. Dupilumab was associated with a reduced mucus score (least-squares mean difference [LSMD], -4.8), reduced total mucus plug count (LSMD, -8.6), and reduced total plug volume (LSMD, -149 μL). More participants treated with dupilumab had complete resolution of mucus plugs (36% vs 10%). The radiodensity of fixed-location persistent plugs was reduced with dupilumab treatment. The dupilumab group also had a lower incidence of new-onset mucus plugs. The reductions in CT-derived mucus plug features after dupilumab treatment were associated with improved airflow as assessed by FEV_1, ratio of FEV_1 to forced vital capacity, and a magnetic resonance imaging–derived measure of ventilation defect percentage. Resolution of mucus plugging was incomplete in 59% of dupilumab-treated patients.

"Dupilumab reduces overall mucus burden in asthma by resolving persistent plugs and decreasing the formation of new plugs," the authors write.

COMMENT: Mucus plugging is a pathologic feature of asthma that is not addressed routinely in most allergists' clinical care. Symptoms reported by patients such as cough and phlegm are also not predictive of radiographic findings of mucus plugging. Nevertheless, mucus plugs can persist for years and are associated with airway obstruction and frequent exacerbations. In this small study, individual plugs were tracked on CT imaging before and after treatment with dupilumab. Although findings may not change clinical practice across the board, the presence of mucus plugs could prompt an additional consideration in the allergists' choice of biologic for severe uncontrolled asthma.

S.Y.J.

Sandhu E, Ragunayakam N, Mappanasingam AA, et al. Changes in mucus radiodensity and new plug formation following dupilumab treatment in asthma. Chest. 2026;170(3):675-688.

Keywords: asthma, dupilumab, mucus

Birch Pollen Allergy Vaccine for Allergen-Specific Immunotherapy

Bet v 1 is the allergen responsible for symptoms in people with birch pollen allergy. This case of a sole causative allergen makes birch pollen allergy especially amenable to treatment with allergen immunotherapy. Using a recombinant fusion protein, this group developed a vaccine for birch pollen allergy called GNR-127 or AB-PreS. The article reports the results of the phase 1 open-label, dose-escalation study and the phase 2 single-blind randomized controlled trial.

Participants eligible for the trials were adults with a history of allergic rhinitis caused by birch pollen allergy. Phase 1 studied the safety of 20, 40, and 80 μg GNR-127 administered as 5 subcutaneous injections every 4 weeks. In phase 2, participants received GNR-127 40 or 80 μg or placebo as 5 injections every 4 weeks. Injections were given before birch pollen season. During the allergy season, participants

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recorded their symptoms and medication use.

Phase 1 involved 6 participants in each of the 3 dose groups. In phase 2, 43 participants received the 40-μg dose, 44 received the 80-μg dose, and 45 received placebo. All 3 doses were well tolerated. Four participants in the 40-μg group and 1 in the 80-μg group experienced anaphylactic reactions, all of which were grade 3. Two participants discontinued treatment because of adverse events and 8 for other reasons. The combined symptom medication score (CSMS) decreased 24% in patients treated with 80 μg compared with placebo. The CSMS decreased nonsignificantly by 17% in the 40-μg dose group. Dose-dependent increases in Bet v 1–specific IgG antibody responses were reported. A phase 3 efficacy study with the 80-μg dose is planned.

The study was funded by Generium.

COMMENT: The CSMS dose-dependent reduction observed in birch pollen–allergic patients receiving the 80-μg dose in this study is comparable to that reported in large studies performed with preseasonal birch pollen allergoid vaccines. Recombinant fusion protein vaccines offer the advantage of reproducible quality at low cost. While molecular allergen-specific immunotherapy trial findings appear promising, more investigation is needed to determine whether this approach will offer superior efficacy or safety over currently available whole allergen extracts.

S.W.S.

Khaitov MR, Byazrova MG, Smolnikov EV, et al. Pre-seasonal treatment with recombinant carrier-based birch vaccine improves birch pollen allergy. Allergy. Published online September 4, 2026.

Keywords: birch pollen allergy, seasonal allergy

Omalizumab vs Multiallergen Oral Immunotherapy in Multifood Allergy

Study findings are reported from a second stage of the OUTMATCH trial in which omalizumab was compared with omalizumab-facilitated multiallergen oral immunotherapy (MOIT). Study participants were allergic to peanuts and at least 2 other foods. They were randomly assigned to MOIT with placebo omalizumab or omalizumab with placebo MOIT. All participants first completed 16 weeks of open-label omalizumab treatment. The primary study end point was a cumulative tolerated dose of 4044 mg or greater of all 3 foods.

The 117 study participants ranged in age from 1 to 29 years. A total of 30 participants (51%) in the active MOIT group and 51 participants (88%) in the active omalizumab group completed the study. In the intention-to-treat analysis, omalizumab was superior to MOIT (36% vs 19% success; odds ratio, 2.6; 95% CI, 1.1-6.3). About 72% of participants in the omalizumab group vs 39% in the MOIT group tolerated 444 mg or more of all 3 allergens, which the authors write is equivalent to protection from small unintentional allergen exposure. No difference in success was found in the per-protocol analysis including all participants who completed stage 2, which reflected the difference in study discontinuations between groups. A total of 18 of 59 participants (31%) in the MOIT treatment group experienced serious adverse events vs. none in the omalizumab group; 22% experienced adverse events leading to study discontinuation.

The higher rate of treatment success in the omalizumab group was likely influenced by the higher number of participants in the MOIT group who discontinued treatment.

COMMENT: The safety signal is striking in this clinical trial: 31% of participants receiving omalizumab-facilitated MOIT had a serious adverse event, 37% required epinephrine, and 22% discontinued because of adverse events, compared with 0%, 7%, and 0% respectively, with omalizumab. It is worth noting that although post hoc analysis of a subgroup of young children aged 1 to 5 was not statistically significant (previously shown in the IMPACT trial as an age subset more likely to experience sustained unresponsiveness), the authors noted a trend in higher OIT success. Patient selection for OIT is key, and this trial is a reminder that for food allergy treatment, treatment success encompasses not only desensitization but also whether patients can realistically and safely undergo the therapy.

S.Y.J.

Wood RA, Togias A, Burk CM, et al. Treatment of multifood allergy with omalizumab or multiallergen oral immunotherapy: a randomized clinical trial. JAMA Pediatr. 2026;180(10):1067-1075.

Keywords: anti-allergic agents, food hypersensitivity, omalizumab

Colic as a Marker of Risk for Food Allergy

Colic during infancy is increasingly being thought of as a disorder of gut–brain interaction and a possible marker of risk for food allergy. These authors followed mother-child pairs recruited in suburban Massachusetts as part of Project Viva. The pairs were followed from the first trimester of pregnancy until the children reached 17 years of age.

According to the mothers' questionnaire responses, the 1263 infants studied were placed in 3 categories: no excessive crying or colic, excessive crying (without signs of abdominal discomfort), and colic (with or without excessive crying). Food allergies were identified by mothers' questionnaire responses when their children were 2 to 3 years of age, in early adolescence, and in mid-adolescence. Measures of total and food-specific IgE were available from 286 plasma samples.

Twenty-five percent of the children had colic, and these children were more likely to be non-Hispanic White. Ten percent of children were categorized as having excessive

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crying, and 65% had neither condition. Food allergies were reported for 10% of children during early childhood, 13% during early adolescence, and 8% during mid-adolescence. The risk for any food allergy during early childhood was 70% greater in children who had colic than in children with neither colic nor excessive crying (odds ratio, 1.7; 95% CI, 1.1-2.7). During early adolescence and mid-adolescence, risks for peanut allergy were 2 or 3 times higher for adolescents who had colic as infants. Children who had colic as infants had 2.5 times the odds of sensitization to peanut as did children with neither colic nor excessive crying.

COMMENT: Colic has been linked to eczema, allergic rhinitis, and asthma, but understanding of its relationship to food allergy has been limited by inconsistent definitions and short follow-up. These authors assessed parent-reported colic and excessive crying at 6 months and followed food allergy outcomes from early childhood through mid-adolescence. Colic was associated with any food allergy in early childhood, peanut allergy in early and mid-adolescence, and peanut sensitization in early childhood. Excessive crying without abdominal discomfort carried no increased risk. Current guidelines identify high-risk infants by severe eczema or egg allergy; colic may be another early marker worth asking about.

K.A.

Switkowski KM, Oken E, Simonin EM, et al. Associations of colic and excessive crying in infancy with food allergy outcomes in childhood and adolescence.
J Pediatr. 2026;294:115111.

Keywords: colic, food hypersensitivity, infants

New EoE Diagnosis Low in Children Undergoing Oral Immunotherapy

With the objective of assessing how often children undergoing oral immunotherapy (OIT) are diagnosed with eosinophilic esophagitis (EoE), these authors performed a retrospective review of 1200 children who underwent single or multiple-food OIT at the Children's Hospital of Philadelphia.

Parents were asked about the following symptoms in their child at intake and each up-dosing visit: nausea, vomiting, abdominal pain, trouble swallowing, drinking more while eating, slower eating, or other changes in eating habits. They were also counseled about EoE.

From 2018 through May 2024, 51 of the 1200 children who underwent OIT were evaluated for EoE. The mean age of the evaluated children was 8.5 years, 53% were male, and 78% had multiple food allergies. Thirty-three children underwent esophagogastroduodenoscopy, and 8 were diagnosed with EoE. Children diagnosed with EoE were more likely to have experienced recurrent gagging, food impaction, weight loss, and persistent nausea than were children with persistent gastrointestinal symptoms but no EoE. Six patients (75%) stopped all OIT.

The study findings suggest that "regular screening before and during OIT is associated with a reduced rate of EoE." A study limitation was the lack of esophagogastroduodenoscopy before children started OIT. The authors note that newer practical and cost-effective testing methods like the string test could benefit the rate of screening for EoE before OIT.

COMMENT: EoE is a known adverse effect of OIT, with rates ranging from 1% to 6%. Of 51 patients evaluated for suspected EoE in this retrospective review, 8 were diagnosed—a rate of 0.7%, which is lower than previous estimates. Rates did not differ between single and multiple-food OIT. Five additional patients were identified by screening before OIT and excluded. The authors attribute the low rate to screening and counseling before and during OIT, which supports building EoE screening into initial and up-dosing visits rather than reacting to symptoms as they arise.

K.A.

Buckey TM, Frangiosa J, Diem L, et al. Eosinophilic esophagitis incidence during single and multiple food oral immunotherapy.
Ann Allergy Asthma Immunol. 2026;136(6):693-698.

Keywords: allergens, eosinophilic esophagitis, food hypersensitivity

Is the Gut Microbiome Important in the Development of FPIES?

Winberg et al studied differences in the gut microbiota profiles between children with food protein–induced enterocolitis syndrome (FPIES) and healthy control children. FPIES is a non-IgE-mediated food allergy that usually appears during an infant's first year of life. The study addressed a gap in evidence for the role of the gut microbiota in FPIES.

Fecal samples were from 56 children with FPIES (mean age, 8.5 months) and 43 age-matched control infants. Children in the FPIES group had a slightly lower mean birth weight and length and a lower percentage of vaginal delivery (82% vs 100% of the control children). The FPIES children were placed into subgroups according to their age at diagnosis: 11 had a mean age at diagnosis of 4.6 months, 20 had a mean age of 6.5 months, and 25 had a mean age of 11.7 months. As analyzed by 16S ribosomal RNA sequencing, α-diversity did not differ between children with FPIES and the control group and increased with age. β-Diversity differed significantly between children with FPIES and the control group. In the combined age group, *Bifidobacterium* species were less abundant and *Bacteroides* species were more abundant in the FPIES group. In the linear regression analysis, age was the strongest determinant of microbiota patterns, followed by FPIES status. Nearly all food triggers studied were associated with lower abundance of Verrucomicrobiota.

COMMENT: The pathogenesis of FPIES is still poorly

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understood, but gut microbiota are known to be important in the development of the mucosal immune system of the gastrointestinal tract. Gut symbionts such as *Bifidobacterium* and Verrucomicrobiota were less abundant in young children with FPIES, which may contribute to defects in the mucosal barrier, inflammatory responses, and overgrowth of pathogenic bacteria. Interventions that promote early life gut microbial composition may play a role in primary prevention of FPIES.

G.B.L.

Winberg A, Simonyté Sjödin K, Öhlund M, et al. Loss of symbiotic gut bacteria in children at diagnosis of food protein-induced enterocolitis syndrome.
J Allergy Clin Immunol. 2026;157(6):1355-1364.

Keywords: dietary protein, food hypersensitivity, microbiome

Updated Guidelines Have Reduced Prevalence of Egg Allergy

Current allergy prevention guidelines recommend introducing egg from around 6 months of age. This cross-sectional study examined whether the population prevalence of egg allergy changed after the guideline update.

Study infants were from 2 previous Australian studies, one conducted in 2007-2011 and one in 2018-1019. Infants were recruited at their 12-month immunization visit. Parents were asked at what age they introduced eggs to their infant's diet: 6 months or younger, 7 to 9 months, 10 to 11 months, or 12 months or older. The primary outcome was the prevalence of egg allergy.

Data for 7209 infants were analyzed (5276 from the 2007-2011 study and 1933 from the 2018-2019 study). Skin-prick test results were available for 97% of the earlier cohort and 73% of the later cohort. The median age of egg introduction was 6 months (IQR, 6-8 months) after introduction of the updated guidelines compared with 8 months (IQR, 6-10 months) in the earlier cohort. The proportion of infants introduced to egg by 6 months more than doubled. The adjusted prevalence of egg allergy decreased from 9.2% to 7.6%, corresponding to a 17.7% relative decline. In infants with eczema, the prevalence of egg allergy decreased from 34.6% to 21.9%.

In these population-based samples, the guideline update was associated with earlier introduction of egg and a reduction in egg allergy.

COMMENT: This large Australian study provides data showing that the updated infant feeding guidelines which recommend earlier introduction of egg did lead to measurable reductions in the prevalence of egg allergy. Unfortunately, the prior guidelines from 2000 that recommended delayed introduction of foods were wrong, but population studies such as this help provide assurance that we are truly making evidenced-based recommendations for our patients.

S.M.F.

Koplin JJ, Shifti DM, Soriano VX, et al. Egg allergy prevalence before and after guidelines for earlier egg introduction.
JAMA Pediatr. 2026;180(9):1015-1023.

Keywords: egg hypersensitivity, practice guidelines

IMPACT of Early Peanut Oral Immunotherapy a Decade Later

Dantzer et al report long-term follow-up data for children with peanut allergy who participated in the IMPACT trial. Their primary outcome of interest was the proportion of children who had received peanut oral immunotherapy (OIT) who could still consume at least 300 mg of peanut protein.

Slightly more than half of the study children (78/146, or 53%) completed follow-up questionnaires. Serologic data and skin-prick testing results were available for 58 and 49 participants, respectively. The children's median age at the time of follow-up was 12 years (range, 9-14 years). Of 40 children treated during the IMPACT trial only, 80% were still eating peanut, most at least weekly. Nine of the 32 children still eating peanut were consuming >4000 mg in a single serving. Allergic reactions were reported by 35%, the most common of which were oral pruritus, hives, and wheezing. Five children were treated with epinephrine. Of 18 children who had participated in another peanut clinical trial or program after IMPACT, 13 (72%) were eating peanut as part of a prescribed regimen. Five reported use of antihistamines and epinephrine for allergic reactions. Of 15 participants who had achieved remission during IMPACT, all were still eating peanut. Nine (60%) were eating 1000 mg or more, although reactions were reported. Compared with children who received placebo during IMPACT, the group treated with peanut OIT had lower levels of peanut-specific IgE, Ara h 2–specific IgE, and ratios of peanut IgE to total IgE.

COMMENT: The IMPACT study created a paradigm shift for the treatment of peanut allergy in children under 4 by demonstrating that peanut OIT could induce remission and facilitate reintroduction of peanut into the diet if started early. This follow-up report 8 to 11 years later found that most of these children are still tolerating peanut. One child who achieved remission tolerated peanut after a 9-month gap in dosing! Reactions and epinephrine use were still reported, which reminds allergists to remind their patients—even those in remission—about augmenting factors for anaphylaxis.

G.B.L.

Dantzer JA, Virkud YV, Cox AL, et al. Early-life peanut oral immunotherapy associated with long-term ingestion and immunologic changes.
J Allergy Clin Immunol. 2026;158(2):482-491.

Keywords: allergens, peanut hypersensitivity

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Precautionary Allergy Labeling: What Patients Think

Although widely used, precautionary allergy labeling is not regulated in the United States. This type of labeling includes "may contain" statements added voluntarily by food manufacturers. Madireddy et al interviewed 20 participants of the 2024 Food Allergy Research and Education Food Allergy Summit about precautionary allergy labeling and their preferences. Interviewees were 6 adults with food allergy and 14 caregivers; 85% were female and 75% were White.

Participants were educated about population thresholds, such as the eliciting dose 5%, the amount of allergen estimated to trigger an allergic reaction in 5% of people with a specific food allergy. They were then asked their preferences about 2 options for incorporating population thresholds into precautionary labeling. Through thematic analysis of the interviews, the investigators identified 4 main themes in the participants' responses. Participants wanted precautionary labeling to be standardized, such as with the use of consistent language or bold and consistent labeling. They felt that using objective measures like population thresholds for these statements could make them easier to understand because these measures are number based. Participants preferred a labeling model in which products with detectable allergen levels less than the eliciting dose threshold of 5% would not be labeled or would be given a "low risk" label. Patients and caregivers were often unfamiliar with terms like *eliciting dose* and *population threshold*.

COMMENT: Patients with food allergy and their families experience frustration regarding precautionary labeling. The variability and lack of standardization can present challenges for patients who are already limited in terms of their diets. This article presents information on the levels of labeling that caregivers prefer. For products containing allergen levels below the 5% eliciting dose threshold, caregivers preferred that the product not require labeling or be listed as low risk. As the authors suggest, many stakeholders will need to agree to changes in precautionary labeling. Standardization remains an unmet need for our patients with food allergy.

V.H.T.

Madireddy S, Milliron C, Wong S, et al. Patient and caregiver perspectives on threshold-based precautionary allergen labeling.
Ann Allergy Asthma Immunol. 2026;137(3):362-367.

Keywords: food hypersensitivity, food labeling

Investigating GDF15 as a Biomarker in Common Variable Immunodeficiency

These authors studied whether serum levels of the cytokine growth differentiation factor 15 (GDF15) could serve as a biomarker in common variable immunodeficiency (CVID). Because of the autoimmune complications associated with CVID, early detection is essential. The retrospective, cross-sectional study was conducted in Turkey with 80 patients with CVID and 40 matched control participants. Patients with CVID were placed into subgroups according to whether they had autoimmune disease. The most frequent autoimmune diseases in the patients with CVID were leukopenia (36%), thrombocytopenia (33%), and immune thrombocytopenic purpura (19%).

CVID patients with autoimmunity had higher serum values of C-reactive protein, erythrocyte sedimentation rate, aspartate aminotransferase, and GDF15 than did patients without autoimmune disease or control participants. They had lower platelet and albumin values. Median GDF15 concentrations were 2205 pg/mL in CVID patients with autoimmunity, 1526 pg/mL in CVID patients without autoimmunity, and 1083 pg/mL in control participants. GDF15 levels were negatively correlated with IgG, IgM, and IgA concentrations.

For diagnosing CVID, a GDF15 cutoff 1651 pg/mL had 53% sensitivity, 87% specificity, 89% positive predictive value, and 52% negative predictive value. For predicting the presence of autoimmune disease in patients with CVID, a GDF15 cutoff of 1564 pg/mL had 68% sensitivity and 64% specificity. As shown by multivariable logistic regression, patients with GDF15 levels higher than 1564 pg/mL had a 5.1-fold increased risk for developing autoimmunity. GDF15 has potential as a biomarker in CVID and can predict autoimmunity in patients with CVID.

COMMENT: Patients with inborn errors of immunity often have comorbid autoimmune disease. Having biomarkers to predict those who may be at risk for these conditions would be useful. This article provides some insight into GDF15 as a possible biomarker that may be helpful in identifying patients who may develop autoimmune disease.

V.H.T.

Karatopuk G, Colkesen F, Ugrakli S, et al. Growth differentiation factor 15 in common variable immunodeficiency patients: Diagnostic value and prediction of autoimmunity risk. Allergy Asthma Proc. 2026;47(5):e81-e88.

Keywords: autoimmune diseases, common variable immunodeficiency

Consider Deep Sequencing for Mosaicism in Inborn Errors of Immunity

For patients with inborn errors of immunity (IEIs), receiving a molecular diagnosis improves the management of their disease and allows for genetic counseling in families. However, most genetic sequencing strategies have limitations when identifying mosaic variants as a cause of disease. These authors developed a targeted deep sequencing assay to screen for mosaic variants and tested it in 452 patients with immune dysregulation and 154 healthy control

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participants. The platform could identify variant allele fractions as low as 1%, compared with the typically reported value of >5% for other exome and genome sequencing methods.

The patients' mean age was 19.4 years; that of the control participants was 17.3 years. All patients had symptoms; the most common was fever. Targeted sequencing was performed of genes known or suspected to be involved in dominant immune dysregulation. One panel covered 71 genes, and an expanded panel covered 101 genes. Sequencing identified 48 mosaic variants in 43 patients without a molecular diagnosis (9.6% of the undiagnosed affected population) and in 12 healthy participants. Slightly more than half of the variants identified in patients were predicted to alter the translated protein sequence and thus potentially cell function.

The authors also developed scoring criteria for mosaic variants in the context of genetic errors of immunity. The criteria differentiate 4 categories of mosaic variants according to how likely it is that the variant contributes to the patient's disease presentation: likely mosaic benign, likely mosaic pathogenic, mosaic pathogenic, and uncertain mosaic significance. About one-third of the mosaic variants in patients without a molecular diagnosis were scored as mosaic pathogenic or likely mosaic pathogenic. None of the mosaic variants identified in the control participants were predicted to be pathogenic or likely pathogenic. One limitation of the approach is that causative variants in untargeted genes will be missed.

COMMENT: Pathogenic variants that are present in only a subset of cells, or mosaicism, can be missed by standard whole-exome or whole-genome analysis pipelines. This study uses a targeted deep sequencing assay that can detect variant allele fractions of 1% and finds previously undiscovered mosaic variants in nearly 10% of patients with undiagnosed immune dysregulation. Mosaic variants were also detected in healthy control participants, so it is important to have robust pathogenicity scoring systems and functional validation testing available to distinguish benign versus pathogenic variants.

G.B.L.

Schmitz EG, Paul AJ, Ghosh R, et al. Targeted deep sequencing identifies mosaicism in patients with immune dysregulation.
J Allergy Clin Immunol. 2026;157(5):1179-1194.

Keywords: genetics, high-throughput nucleotide sequencing

Risk Stratification Tools for Cephalosporin Allergy Testing

Because many patients with cephalosporin allergy labels in their medical record are not actually allergic to these drugs, verifying these labels is important for antimicrobial stewardship. In this research letter, Belmont et al report on their external validation of 3 risk stratification tools: CEPH-FAST, Urticaria 1-1-1, and the Vanderbilt criteria. The retrospective review included adults with cephalosporin allergy labels who were evaluated at a Yale University–affiliated allergy and immunology clinic from December 2014 to July 2025. Patients who were considered to have had a "complete" evaluation had undergone skin testing with drug challenge (for patients with negative test results) or direct cephalosporin challenge.

The 121 eligible patients had a median age of 49 years; 86% were female and 88% were White. Cephalexin was the most commonly implicated cephalosporin (37% of patients). About 83% of the patients had multiple drug allergy labels. A total of 23 patients (19%) had a verified cephalosporin allergy. CEPH-FAST had 84% specificity and 94% negative predictive value. The Vanderbilt criteria had 88% specificity and 96% negative predictive value. The sensitivity of both tools was lower when intravenous cephalosporin allergy labels were excluded. Few patients had Urticaria 1-1-1 documentation sufficient for scoring. Study limitations included the retrospective design and single site setting.

The authors found that the CEPH-FAST and Vanderbilt criteria performed similarly to the original studies. They note the importance of "using these tools alongside a comprehensive allergy history," and write, "these tools are best at identifying patients with low-risk histories for direct challenge."

COMMENT: The authors sought to externally validate cephalosporin allergy decision aids. The tools included CEPH-FAST (adapted from PEN-FAST to identify low-risk patients by Cox et al, 2025), Urticaria 1-1-1 (appearance within 1 hour after the first dose and regression within 1 day and occurrence within 1 year suggests high likelihood of skin-test positivity), and the Vanderbilt criteria for cephalosporin allergy label risk stratification (history-based approach with stratification criteria). Their high negative predictive value in their adult patients is clinically useful. The drop in sensitivity when intravenous cephalosporin allergy labels are excluded highlights the importance of history taking and, ultimately, clinical judgment.

S.Y.J.

Belmont AP, Valente M, Workineh A, et al. Performance of risk stratification tools for cephalosporin allergy testing.
JAMA Netw Open. 2026;9(9):e2634079.

Keywords: cephalosporin allergy, risk stratification

Persistent Eosinophil Deficiency Associated With Lower Cardiovascular Disease Risk

This retrospective matched cohort study reports that people with chronically low eosinophil counts in the absence of identifiable causes have a lower incidence of ischemic heart disease, myocardial infarction, coronary revascularization, cerebrovascular events, and peripheral vascular disease

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than people with normal eosinophil counts. Eosinopenia was defined as having at least 3 consecutive eosinophil counts less than or equal to 0.05 x10^9 cells/L within 2 years; control participants had at least 3 eosinophil counts greater than 0.05 x10^9 cells/L within 2 years.

Electronic health record data were from Leumit Health Services, a nationwide integrated health care organization in Israel. The participants had undergone complete blood count lab work between 2005 and 2017. The final dataset for analysis included 11,754 individuals with chronic eosinopenia and 23,508 matched control participants.

The age and sex distributions of the case and control groups were similar (mean age, 41 years; 78% female), but participants with eosinopenia had slightly lower systolic and diastolic blood pressures and lower body mass index. They also had lower glucose, HbA1c, and LDL cholesterol values. After a mean follow-up of 15 years, the adjusted hazard ratio (HR) for ischemic heart disease in the eosinopenia group was 0.81 (95% CI, 0.72-0.91). The adjusted HR for myocardial infarction was 0.75 (95% CI, 0.65-0.86) and that for peripheral vascular disease was 0.60 (95% CI, 0.47-0.79). The risk for pericarditis was higher in the eosinopenia group (adjusted HR, 1.43; 95% CI, 1.10-1.86).

In this large population-based cohort, chronic idiopathic eosinopenia was associated with lower risk for several cardiovascular outcomes. The findings "provide reassurance regarding the long-term cardiovascular safety of therapies that reduce eosinophil levels." The study design did not allow for conclusions related to causality.

COMMENT: The effects and activities of eosinophils are still becoming understood. Whether they are simply the brightest-staining cell in a high-powered field or contributing to pathophysiology is not always clear. Magen et al looked at a cohort of patients with idiopathic eosinopenia and noted that compared with matched control participants, they had a lower rate of cardiovascular, cerebrovascular, and peripheral vascular events. This research is hypothesis generating but suggestive that eosinophils may be playing an important role in cardiovascular disease outcomes. In this case, the evidence of an absence may be helping with our absence of evidence.

C.A.S.

Magen E, Merzon E, Magen I, et al. Chronic idiopathic eosinopenia and long-term cardiovascular outcomes: a population-based cohort study.
Am J Med. 2026;139(9):1200-1209.

Keywords: cardiovascular diseases, eosinophilia

REVIEW OF NOTE

COMMENT: This succinct review outlines the changes in the 2025 Inborn Errors of Immunity Practice Parameter.

G.B.L.

Chinen J, Horner CC, Orange JS. Practice parameter for inborn errors of immunity: what is new in the 2025 update.
J Allergy Clin Immunol. 2026;158(2):368-373.

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