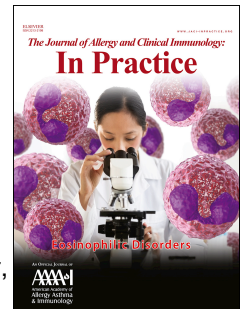


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ABSTRACT

Background: A landmark 2015 trial on early exposure to peanuts led to expert recommendations for screening and early peanut introduction in high-risk (severe eczema and/or egg allergy) infants, but the impact of this paradigm shift on allergy testing and diagnosis is unknown.

Objective: We assessed the effects of the Learning Early About Peanut Allergy (LEAP) trial and guideline publications on allergy testing and food allergy diagnoses in infants.

Methods: In this retrospective cohort study, de-identified administrative health claims from a commercial and Medicare advantage claims database were used. Infants with at least one year of continuous coverage were selected using newborn codes for birth hospitalizations from January 2010 to June 2018. Interrupted time series models were used to compare the prevalence of allergy testing before and after LEAP publication in February 2015 and formal guideline publication in January 2017.

Results: For 487,533 included infants, allergy testing increased after LEAP (risk ratio [RR]: 1.11 [95% CI, 1.07-1.15]) and guidelines (1.21 [1.18-1.23]). This increase of testing was also seen in infants not considered high-risk, both after LEAP (1.12 [1.08-1.17]) and guidelines (1.20 [1.16, 1.23]). For first-time allergy tests, post-guideline median number of allergens tested was 9 for serum tests and 10 for skin tests. Post-guidelines there was a significant increase in diagnosis of peanut (RR: 1.08 [1.00, 1.16]), egg (1.12 [1.05, 1.20]), and other food allergies (excluding milk) (1.22 [1.14, 1.31]).

Conclusion: Allergy testing has increased, including in non-high-risk infants. Multi-allergen testing may be contributing to an increase in the diagnosis of other food allergies.

HIGHLIGHTS BOX:

1. What is already known about this topic?

Current guidelines recommend screening and early peanut introduction in high-risk (severe eczema and/or egg allergy) infants; panel testing is discouraged, as allergy tests have poor positive predictive value when assessing foods never previously ingested.

2. What does this article add to our knowledge?

Within a large national claims database, we show an increase in allergy testing (including in infants not high-risk) after LEAP publication and NIAID guideline publication. Multi-allergen testing is common and food allergy diagnoses are increasing.

3. How does this study impact current management guidelines?

Peanut allergy screening may have additional unintended effects of increased testing to multiple foods, resulting in identification of clinically irrelevant sensitization. Allergy testing may delay introduction of foods if families are awaiting testing (or oral food challenges) before eating.

KEY WORDS: Allergy Testing; Food Allergy; Peanut; Egg; Milk; Food Introduction; Infants; Eczema; Interrupted time series; Practice Guidelines

92 ABBREVIATIONS:

93 CI: Confidence interval

94 CPT: Current Procedural Terminology

95 ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

96 ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification

97 ITS: Interrupted time series

98 LEAP: Learning Early About Peanut Allergy

99 OFC: Oral food challenge

100 NIAID: National Institute of Allergy and Infectious Diseases

101 Q: Quarter

102 RR: Risk ratio

103 US: United States

INTRODUCTION

Food allergy affects around 8% of children in the United States, with the most prevalent allergen being peanut.¹ Peanut allergy is often lifelong and imposes significant social, emotional, and economic burdens on patients and their families.^{2,3} Published in February 2015, the landmark Learning Early About Peanut Allergy (LEAP) clinical trial showed that early exposure to peanut-containing foods can reduce peanut allergy diagnoses at 5 years of age in high-risk infants, defined as a history of egg allergy and/or severe eczema.⁴ The trial prompted interim consensus guidelines in June 2015,⁵ and subsequently formal National Institute of Allergy and Infectious Diseases (NIAID) addendum guidelines in January 2017.⁶

The NIAID addendum guidelines recommend that all infants at high-risk for peanut allergy be evaluated and tested in order to identify infants who are not yet allergic to peanuts and who can be encouraged to regularly consume peanut-containing foods starting as early as 4 to 6 months of life.⁶ This approach contrasts with other food introduction guidelines around the world, as no other guideline recommends screening for peanut allergy before introduction.⁷ The guidelines also specifically recommend against screening for foods other than peanut, given the poor positive predictive value of these tests.⁶

Current assessment of practice patterns following guideline implementation is needed to identify potential targets for improvement efforts. Although insufficient time has elapsed to allow for an assessment of the impact of the new guidelines on the prevalence of peanut allergies at 5 years, the immediate impact on testing and diagnoses in infancy can be analyzed using claims data. To our knowledge, there have been only a few single center studies,⁸⁻¹¹ but no large scale analysis

127 on the impact of guideline implementation in the United States. In addition, there are no studies
128 yet examining whether changes in screening for peanut allergies in infants influence the
129 diagnosis of other food allergies. Because providers may opt to perform allergy panel testing
130 rather than isolated peanut allergy testing, it is possible that changes in testing patterns may
131 influence the diagnosis of other allergies as well. Our investigation aims to assess changes in
132 allergy testing, peanut allergy diagnoses and other food allergy diagnoses after the LEAP study
133 and NIAID addendum guidelines.

METHODS

Data Source

In this retrospective cohort study, we used Optum's de-identified Clinformatics Data Mart Database, which contains administrative health claims for large commercial and Medicare Advantage health plans covering approximately 15-18 million lives annually. The database includes patient demographics, pharmaceutical claims, inpatient and outpatient diagnosis codes, and procedure claims from all 50 states.¹²⁻¹⁴ Diagnoses are recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Allergy testing and food challenges are coded under Current Procedural Terminology (CPT) codes. Medications are identified by their National Drug Code (NDC) and specific therapeutic classifications of medications are assigned within the database using First Databank's classifications. Provider specialty is identified using the National Uniform Claim Committee's provider taxonomy codes.

Approval

The Stanford University institutional review board approved the use of this de-identified database in this study under Stanford's Center for Population Health Sciences (PHS) umbrella protocol.

Selection of Infant Cohort

The index cohort of infants was identified using newborn codes (ICD-9-CM: V30.xx-V39.xx; ICD-10-CM: Z38.xx, Table E1) from birth hospitalizations during January 2010 to June 2018.

Previous studies have used a similar approach with claims data to approximate infant date of birth using date of newborn hospitalization admission.¹⁵⁻¹⁷ Patients were excluded whose year of newborn admission did not equal year of birth, to account for possible coding errors. In order to ensure that we captured testing and food allergy diagnoses in the first year of life, we included only those infants with at least 365 days of continuous coverage from their newborn admission.

A high-risk infant for peanut allergy is defined in the NIAID guidelines as an infant with egg allergy or severe eczema; severe eczema is defined as “persistent or frequently recurring eczema with typical morphology and distribution assessed as severe by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients.”⁶ Others when evaluating the theoretical implications of the guidelines have used “early-onset eczema”, defined as diagnosis of eczema before 6 months of life, and any topical steroid use, as a proxy for severe eczema.^{18,19} We identified a high-risk infant cohort by defining severe eczema as infants with an ICD-9-CM or ICD-10-CM code for eczema in the first 6 months of life (Table E1) and at least 1 filled prescription for a topical steroid, calcineurin inhibitor or crisaborole. In addition, we included infants with an ICD-9-CM or ICD-10-CM code related to egg allergy (Table E1) in our high-risk infant cohort. It cannot be assessed with this dataset if allergy testing was done specifically for egg allergy, screening for peanut allergy, or other reasons.

Outcomes

The primary outcomes of interest were allergy testing within the first 12 months of life among all infants and among non-high-risk infants. Allergy testing was defined by a CPT code for skin

tests (95004) or serum tests (86003, 86005, 86008) (Table E2).

Secondary outcomes included whether or not a diagnosis of peanut, egg, milk, or other food allergies was made within the first 12 months of life. Previously published papers using ICD codes for food allergies were reviewed.²⁰⁻²⁵ We examined food allergy ICD-9-CM and ICD-10-CM codes related specifically to peanut, egg, milk, and other food allergies (Table E1).

Additional exploratory outcomes included age at first allergy testing (if done within the first 12 months of life) and the proportion of allergy testing done before 6 months of life. The median number of allergens tested were assessed. Oral food challenges (OFC) were evaluated, which is the most accurate way to assess the presence or absence of food allergy.²⁶ The two current CPT codes that are used for food challenges (95076 for the first 120 minutes and 95079 for each additional 60 minutes) became effective January 1, 2013.²⁷ We examined these ingestion challenge codes in all infants born in or after 2013.

Study Interventions

Two events were assessed. The first event was the publication of the LEAP study results in February 2015 (2/26/15),⁴ which we hypothesized would increase allergy testing based on the wide publicity of the trial, along with subsequent interim guidelines which suggested possible benefit of allergy evaluation in high-risk infants. Given that the interim guidelines were published shortly after the LEAP publication in June 2015, we did not separately evaluate the impact of these. The second event assessed was the publication of the NIAID addendum guidelines in January 2017 (1/5/17),⁶ which we hypothesized would further increase allergy

testing. We defined 3 separate periods: baseline (January 2010 through February 2015), post-LEAP/pre-NIAID guidelines (March 2015 through December 2016), and post-NIAID (January 2017 through June 2019). As infants were assessed only if they had 365 days of continuous coverage, only infants born through June 2018 were analyzed for testing (evaluated for testing through June 2019).

Statistical Analysis

Descriptive statistics summarize the demographics of the cohort overall and by whether allergy testing occurred in the first 12 months of life. Characteristics of first-time allergy testing were summarized overall and across the three study periods. The Kruskal-Wallis rank sum test was used to determine whether the number of allergy tests ordered differed across study periods.

In order to assess additional time points, we converted person-level data to a person-period-level dataset. Each infant observation was expanded into 5 rows, corresponding to their first 12 months of life. For example, an infant born on February 20th, 2013 contributed to 2013 Q1 through 2014 Q1 (only up to February 20th, 2014). Infants born on the first day of a quarter (i.e. January 1, April 1, July 1, or October 1) contributed exactly 4 rows of data. Time from birth to each event of interest was then assessed within each infant's eligible quarter; if an event of interest occurred in a specific quarter, that result was carried forward through the remainder of the infant's observed time. Therefore, each quarter examines prevalence rather than incidence for each event at that particular point in time among all infants up to 12 months of age.

Changes in the rate of allergy testing and other outcomes of interest following each intervention were assessed with an interrupted time series (ITS) analysis. ITS is a quasi-experimental study design that is used to evaluate the causal impact of an intervention on its target population when a true randomized controlled experiment is not feasible.²⁸ ITS estimates the causal effect of the intervention by assuming that the average outcome risk, as well as any temporal trends in outcome risk, in the pre-intervention period would have continued unchanged in the post-intervention period if, in fact, the intervention had never occurred. An ITS model with two change points was fit to assess the effects of the LEAP study publication and of the NIAID addendum guidelines on the prevalence of allergy testing receipt within an infant's first 12 months of life. Data were analyzed using generalized estimating equations (GEE) with the log link function and a first-order autoregressive process correlation structure to account for correlation at the infant level over time. Details regarding the ITS model formulation and sensitivity analyses conducted can be found in the Repository Text.

Estimates were reported as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant. All analyses were conducted using R v 3.2.2.

RESULTS

Study Population

Of the 1,016,209 patients with birth codes from January 2010 to June 2018, 113,006 (11.1%) had a year of birth that did not equal year of birth admission (Figure 1). These patients likely represent coding errors under the parent/subscriber, given that 97.3% of these excluded patients were adults over 18 years old. For the remaining 903,203 infants, 415,670 (46.0%) were not continuously enrolled for the entire year and were excluded. Infants without continuous enrollment had a lower cumulative incidence of allergy testing per month compared to those enrolled with continuous coverage (2.1% vs 2.7% by 12 months, log-rank test $p=0.002$, Figure E1). The remaining 487,533 infants formed our study cohort.

The majority of the cohort was White (58.5%) males (51.4%). Many were from high-income households (41.3%) (Table 1). Eczema was recorded in 18.1% of infants and 5.5% of infants had severe eczema. High-risk infants (defined as patients with a diagnosis of egg allergy or severe eczema) composed 5.9% of the cohort. Of the 28,580 high-risk infants identified, 4,938 (17.2%) were allergy tested within the first 12 months of life.

First-Time Allergy Testing Characteristics

Overall, there were 12,941 infants who were allergy tested in our cohort (Table 2, Table E6, and Table E7). The median age of allergy testing was 8.75 months. Post-guidelines, the median age of testing in infants with a peanut allergy diagnosis was 8.49 months. Post-guidelines, only 16.6% of infants tested were tested by 6 months of age. Of the 4,416 infants who were tested post-guidelines, 387 (8.8%) underwent at least 1 challenge.

First-time testing pre-LEAP was mostly serum testing (59.2%) and post-guidelines it was mostly skin testing (62.0%). The median number of allergens evaluated with serum testing decreased from 11 allergens pre-guidelines to 9 allergens post-guidelines (Kruskal-Wallis $p < 0.001$). The median allergens evaluated with skin testing decreased slightly post-LEAP (11 to 10 allergens) (Kruskal-Wallis $p < 0.001$). Post-guidelines, multiple allergen serum testing was most commonly ordered by pediatricians: 53% by pediatricians, 20% by allergists, 21% by other providers and 6% missing.

Effect of LEAP Trial and NIAID Guidelines on Allergy Testing Rates

Rates of prevalent allergy testing were decreasing slightly prior to the LEAP publication (1.00% in 2011 Q1 to 0.96% in 2014 Q4, $p < 0.001$), but rose during both the post-LEAP / pre-NIAID period (RR: 1.11 [1.07, 1.15]) and post-NIAID period (RR: 1.21 [1.18, 1.23]) (Table 3). These results were consistent among infants not considered high-risk, with a significant increase in rates of allergy testing both after the LEAP publication (RR: 1.12 [1.08, 1.17]) and guideline publication (RR: 1.20 [1.16, 1.23]).

Effect of LEAP Trial and NIAID Guidelines on Food Allergy Diagnosis Rates

Rates of peanut allergy diagnosis remained relatively constant prior to the LEAP publication, while rates of diagnosis of milk and egg allergies were steadily increasing, and rates of other food allergy diagnoses were decreasing (Table 3 and Table E5). Compared to the trend in diagnosis rates prior to LEAP, only rates of other food allergy diagnoses significantly changed during the post-LEAP period (RR: 1.21 [1.09, 1.34]). However, after the final guidelines were published, the trend in rates of diagnosis for peanut allergy (RR: 1.08 [1.00, 1.16]), egg (1.12

[1.05, 1.20]), and other food allergy diagnoses (1.22 [1.14, 1.31]) significantly rose compared to the trend of rates seen in the pre-period.

Overall Prevalence of Food Allergies by 12 Months of Age

The ITS analysis examines prevalence of testing and food allergies in all infants in order to be able to account for the different ages that an infant may be tested and diagnosed with respect to the interventions studied. Table E4 examines overall prevalence of food allergies at 12 months of age. For infants born in 2017, by 12 months age, prevalences for food allergy diagnoses were as follows: peanut allergy, 0.7%; milk allergy, 2.6%; egg allergy, 1.1%; and other food allergies, 2.0%.

DISCUSSION

In this retrospective cohort study of 487,533 US infants, we observed an increase in allergy testing coinciding with publication of the landmark LEAP trial and the NIAID addendum guidelines. The increase in testing post-guidelines was associated with an increase in the diagnosis of peanut allergies, which was an anticipated consequence under the premise that increased screening would lead to earlier identification of high-risk infants who could safely tolerate peanut and thus trigger encouragement of early exposure and prevention of peanut allergy at 5 years. However, because the majority of testing continues to occur after 6 months of age and because testing has increased in non-high risk infants, this evolution in testing trends may not result in the intended effect of the new guidelines. Later testing infers that the window for exposure may be missed, and increased testing of non-high risk infants may yield false positive results that lead to peanut avoidance. We also noted that the increase in testing was not limited to peanut allergies, and that broad testing may have had the unintended consequence of increasing the overall prevalence of food allergy diagnoses in general.

In 2000, the American Academy of Pediatrics recommended that children at risk for allergic disease delay the introduction of potential food allergens until after the first year of life, specifically recommending the avoidance of peanuts until 3 years of age.²⁹ Although these recommendations were rescinded in 2008,³⁰ specific guidance on when to introduce allergenic food was lacking until the early peanut introduction guidelines, which were informed by the LEAP trial. Whether early introduction prevents other food allergies remains unclear, though there is moderate evidence that egg introduction at 4-6 months of age can reduce egg allergy.³¹

The aim of the NIAID guidelines is to help guide health-care providers to encourage early introduction of peanut in infants at risk; testing high-risk infants aims to minimize the possibility of severe reaction on first introduction. Interestingly, high-risk infants only composed 5.9% of our cohort, which is lower than estimates used based on Australian prevalence data that defined high-risk in a similar way (16%).^{18,19} Others have discussed the controversy and difficulties of implementing peanut allergy screening.^{18,19,32,33} Our finding that changes in testing occurred relatively quickly after publication of the LEAP trial findings belies traditional thinking that practice changes often take many years.³⁴ The LEAP trial was widely publicized in the medical community and in traditional media, such that many parents were likely aware of the findings and may have modified their peanut exposure practices and/or pursued testing. Certainly, parents turn to the Internet for advice.^{35,36} It may be that the increase in testing that we are seeing is partially due to parental request and their interpretation of the necessity to test. In contrast to the NIAID guidelines, Australian recommendations suggest early introduction of peanuts without screening prior to the exposure. The impact of these recommendations were immediate and substantial, with almost 9 of 10 infants now consuming peanut by 12 months of age.³⁷

Allergy tests are known generally to have poor positive predictive value when assessing foods never previously ingested.^{38,39} Panel testing is therefore discouraged by the NIAID guidelines which warn that these tests can lead to “misinterpretation, overdiagnosis of food allergy, and unnecessary dietary restriction.”⁶ Food allergy diagnoses can affect the quality of life of the whole family.² There are possible nutritional risks of unnecessary dietary avoidance.⁴⁰ In addition, removing foods that a child is already tolerating based on testing could cause the development of true IgE-mediated allergies.⁴¹⁻⁴³

344
345 Despite an increase in overall allergy testing, the median age of post-NIAID guideline testing
346 remained over 8 months of age (including in infants ultimately diagnosed with a peanut allergy).
347 If the benefit of allergy testing and peanut introduction in high-risk infants is actually greatest at
348 4 to 6 months of age (as the guidelines suggest), then the fact that most infants are not being
349 allergy tested until over 8 months of age could have important clinical implications. Late testing
350 may delay introduction of peanut if families are awaiting testing (and oral food challenges),
351 which could paradoxically increase their risk of developing peanut allergy.

352
353 Some have questioned prioritizing 4 to 6 months of age as too narrow of a time frame.⁴⁴
354 Although, it is thought that there is a window of opportunity to prevent peanut allergy during a
355 child's first year of life, it is unknown exactly how narrow this window is, as the LEAP trial
356 included infants from 4 to 11 months of age. The guidelines do indicate that "if the 4- to 6-month
357 time window is missed for any reason, including developmental delay, infants may still benefit
358 from early peanut introduction."⁶

359
360 Some of the observed testing increase may have been appropriate and driven by reactions of
361 foods at earlier ages. The level of granularity of the data does not allow for distinguishing
362 between screening prior to reaction and testing for reactions. However, the high number of
363 allergens on first-time allergy tests (medians 9-10) suggests that testing was not uniformly driven
364 by prior reactions.

There are several limitations to this study. First, the use of ICD codes to identify diagnoses may lead to misclassification. For example, non-specific general food allergy codes may be used in children with multiple allergies, instead of using a specific allergen code for each allergy. Importantly, an ICD-coded diagnosis of food allergy does not necessarily mean a patient has a true food allergy, and whether an increase in ICD-coded diagnosis in food allergy translates to an increase in true food allergy needs to be further determined. Providers may use an ICD code for peanut allergy to justify billing for a test and later determine the infant is peanut-tolerant; it is also possible that a peanut-tolerant infant is misdiagnosed with a peanut allergy and is avoiding peanut. Despite potential misclassification, compared to a large parent-reported survey analysis done between 2015 and 2016 on the prevalence of food allergy in children,¹ our overall allergy prevalence rates at 12 months of age for infants born in 2015 are similar to the rates they report in infants less than 1 year old (Table E3).

Second, there was an ICD-9-CM to ICD-10-CM coding transition in October 2015. This may have affected the frequency of diagnoses. However, CPT codes for allergy testing, which we used for our primary outcome, were not affected by the ICD transition. Third, the allergy testing codes and the ingestion challenge codes are not allergen specific. We cannot distinguish between particular foods, environmental allergens, and even positive and negative controls in skin testing. The ingestion challenge codes include oral food challenges, but may also include medication challenges, therefore we may have overestimated food challenges; however, medication challenges are rarely done in infancy. Fourth, this database is privately insured patients only and it is unclear whether our results generalize to other pediatric populations. A recent claims-based analysis of Medicaid-enrolled children reported low prevalence of food allergy.⁴⁵ Uninsured or

publicly insured children may receive less allergy testing due to access barriers that result in less care overall.

In addition, because we wanted to capture all testing during the first year of life, we allowed for fallout from patients who lost coverage. Infants without continuous enrollment had a slightly lower cumulative incidence of allergy testing per month compared to those with continuous coverage. However, because our ITS analysis estimates the causal effect based on the discontinuous jump in allergy testing prevalence after versus before each publication, while accounting for secular trends in testing prevalence, this differential attrition would be unlikely to bias the ITS estimate unless attrition itself caused a discontinuous jump in testing prevalence that coincided closely with the publication dates.

Finally, our definition of high-risk may have included infants with mild to moderate eczema whom really have more modest risk. However, this would actually make our ITS analysis for non-high-risk infants include a higher percentage of low-risk infants.

Despite the limitations, our work is the largest cohort to date analyzing how recent guidelines have influenced allergy testing and food allergy diagnoses in infancy. Increased testing in infants not high-risk, possible delayed screening, multi-allergen panel testing, and rate of OFCs in infants will likely have effects on the prevalence of peanut allergy (and other food allergies) at 5 years of age. Potential misdiagnosis and overdiagnosis of food allergies has tremendous public health implications.

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TABLES

Table 1. Baseline characteristics

Characteristic	Overall (N=487,533)	Allergy testing within first 12 months	
		No (N = 474,592)	Yes (N = 12,941)
Sex, n (%)			
Male	250,501 (51.4%)	242,806 (51.2%)	7695 (59.5%)
Female	236,999 (48.6%)	231,754 (48.8%)	5245 (40.5%)
Unknown	33 (<0.1%)	32 (<0.1%)	1 (<0.1%)
Race/ethnicity, n (%)			
White	285,322 (58.5%)	277,926 (58.6%)	7396 (57.2%)
Black	26,059 (5.4%)	25,473 (5.4%)	586 (4.5%)
Asian	33,880 (7.0%)	32,795 (6.9%)	1085 (8.4%)
Hispanic	42,890 (8.8%)	42,066 (8.9%)	824 (6.4%)
Unknown	99,382 (20.4%)	96,332 (20.3%)	3050 (23.6%)
Household income, n (%)			
< \$40K	23,552 (4.8%)	23,162 (4.9%)	390 (3.0%)
\$40K - \$49K	14,312 (2.9%)	14,054 (3.0%)	258 (2.0%)
\$50K - \$59K	17,037 (3.5%)	16,709 (3.5%)	328 (2.5%)
\$60K - \$74K	29,703 (6.1%)	29,110 (6.1%)	593 (4.6%)
\$75K - \$99K	47,759 (9.8%)	46,674 (9.8%)	1085 (8.4%)
\$100K +	201,321 (41.3%)	195,265 (41.1%)	6056 (46.8%)
Unknown	153,849 (31.6%)	149,618 (31.5%)	4231 (32.7%)
Geographic region, n (%)			
East North Central	76,890 (15.8%)	74,976 (15.8%)	1914 (14.8%)
East South Central	13,762 (2.8%)	13,435 (2.8)	327 (2.5%)
Middle Atlantic	43,391 (8.9%)	41,717 (8.8%)	1674 (12.9%)
Mountain	50,990 (10.5%)	49,791 (10.5%)	1199 (9.3%)
New England	13,648 (2.8%)	13,126 (2.8%)	522 (4.0%)
Pacific	46,018 (9.4%)	44,701 (9.4%)	1317 (10.2%)
South Atlantic	104,379 (21.4%)	101,552 (21.4%)	2827 (21.9%)
West North Central	58,667 (12.0%)	57,318 (12.1%)	1350 (10.4%)
West South Central	77,218 (15.8%)	75,458 (15.9%)	1759 (13.6%)
Unknown	2570 (0.5%)	2518 (0.5%)	52 (0.4%)
Eczema cohorts, n (%)			
Any eczema diagnosis	88,008 (18.1%)	80,268 (16.9%)	7740 (59.8%)
Eczema diagnosis + 1 prescription ¹	43,357 (8.9%)	38,198 (8.1%)	5159 (39.9%)
Severe eczema ²	26,996 (5.5%)	23,331 (4.9%)	3665 (28.3%)
At least 2 prescriptions	15,334 (3.1%)	12,584 (2.7%)	2750 (21.3%)

High risk ³	28,580 (5.9%)	23,597 (5.0%)	4983 (38.5%)
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Note: all characteristics were significantly different by allergy testing group (Chi-squared test $p < 0.001$). Percentages in columns 2 and 3 are out of each total column count (474,592 and 12,941, respectively).

¹ Prescription of a topical steroid, topical calcineurin inhibitor, or crisaborole within first year of life.

² Defined as a diagnosis of eczema before 6 months of age and at least 1 prescription within the first year of life.

³ Defined as severe eczema and/or diagnosis of egg allergy in first year of life.

Table 2. Characteristics of first-time allergy testing by time period (in infants who underwent testing).

	Overall (N=12,941)	Pre-LEAP (N=5942)	<u>Time period</u> ¹ Post-LEAP & Pre-NIAID (N=2583)	Post-NIAID (N=4416)
Allergy testing event				
Allergy testing				
Age in months, median (IQR)	8.75 (3.77)	8.72 (4.03)	8.75 (3.75)	8.75 (3.48)
First 6 months of age, n (%)	2565 (19.8%)	1354 (22.8%)	480 (18.6%)	731 (16.6%)
With peanut allergy diagnosis first year of life, n (%)	1486 (11.5%)	335 (5.6%)	335 (13.0%)	816 (18.5%)
Age in months, median (IQR)	8.72 (3.51)	8.98 (4.26)	8.92 (3.64)	8.49 (3.30)
Test type				
Oral food challenge, n (%) ²	537 (6.0%)	32 (1.8%)	118 (4.6%)	387 (8.8%)
Serum testing ^{3*}	6673 (51.6%)	3515 (59.2%)	1261 (48.8%)	1897 (43.0%)
Number of allergens, median (IQR)	11 (11)	11 (11)	11 (12)	9 (13)
Single allergen serum ^{4*}	624 (4.8%)	272 (4.6%)	115 (4.5%)	237 (5.4%)
Multiple allergen serum	6049 (46.7%)	3243 (54.6%)	1146 (44.4%)	1660 (37.6%)
Skin testing ^{5*}	6790 (52.5%)	2613 (44.0%)	1437 (55.6%)	2740 (62.0%)
Number of allergens, median (IQR)	10 (11)	11 (12)	10 (9)	10 (10)
< 4 tests ⁶	561 (4.3%)	166 (2.8%)	118 (4.6%)	277 (6.3%)
4 or more skin tests	6229 (48.1%)	2447 (41.2%)	1319 (51.1%)	2463 (55.8%)

IQR = inner quartile range.

¹ Pre-LEAP spans January 1, 2010 – February 25, 2015; Post-LEAP & Pre-NIAID spans February 26, 2015 – January 4, 2017; Post-NIAID spans January 5, 2017 – June 30, 2019.² based on CPT 95076 or 95079, codes effective starting 2013, therefore only infants tested starting in 2013 counted towards OFC % pre-LEAP (32 of 1740)³ based on CPT 86003, 86005, or 86008; Individual component testing (86008) was coded under 86003 until Jan 2018. CPT 86005 was not included when looking at median number of allergens in serum testing as it is a qualitative multiallergen panel.⁴ where only one allergen was tested under CPT 86003 or 86008.⁵ based on CPT 95004.⁶ allows for possibility that individual charges can be incurred for positive and negative controls with single allergen tests.

* Some infants had multiple CPT codes billed on the first day of testing.

557 **Table 3.** Parameter estimates of primary interrupted time series models

Section of time series	Risk ratio (95% CI)		
	Allergy testing	Non-high risk allergy testing	Peanut allergy diagnosis
Pre-LEAP slope ¹	0.96*** (0.94, 0.97)	0.95*** (0.93, 0.97)	1.03 (0.96, 1.09)
Slope change for LEAP ²	1.11*** (1.07, 1.15)	1.12*** (1.08, 1.17)	1.12 (0.99, 1.26)
Slope change for NIAID ³	1.21*** (1.18, 1.23)	1.20*** (1.16, 1.23)	1.08* (1.00, 1.16)

558 ***p < 0.001, **p < 0.01, *p < 0.05. CI = confidence interval. All models additionally included terms for quadratic
 559 time and indicators for each quarter and adjusted for sex, race/ethnicity, and categorical household income.

560 ¹Represents the per-quarter rate of change (slope) in diagnosis during the pre-LEAP period. ²Represents the trend
 561 change in the rate of testing per quarter after the LEAP publication, compared with the quarterly rate prior to the
 562 publication. The product of the estimates for the pre-LEAP slope and slope change for LEAP represent the post-
 563 LEAP slope. ³Represents the trend change in the rate of testing per quarter after the NIAID guidelines publication,
 564 compared with the quarterly rate prior to the publication of the NIAID guidelines.

FIGURE LEGENDS

Figure 1. Patient flowchart

Footnote: *2018 includes only infants born through 6/30/18

Figure 2. Observed rates of allergy testing in (a) non-high risk infants and (b) all infants by quarter year intervals

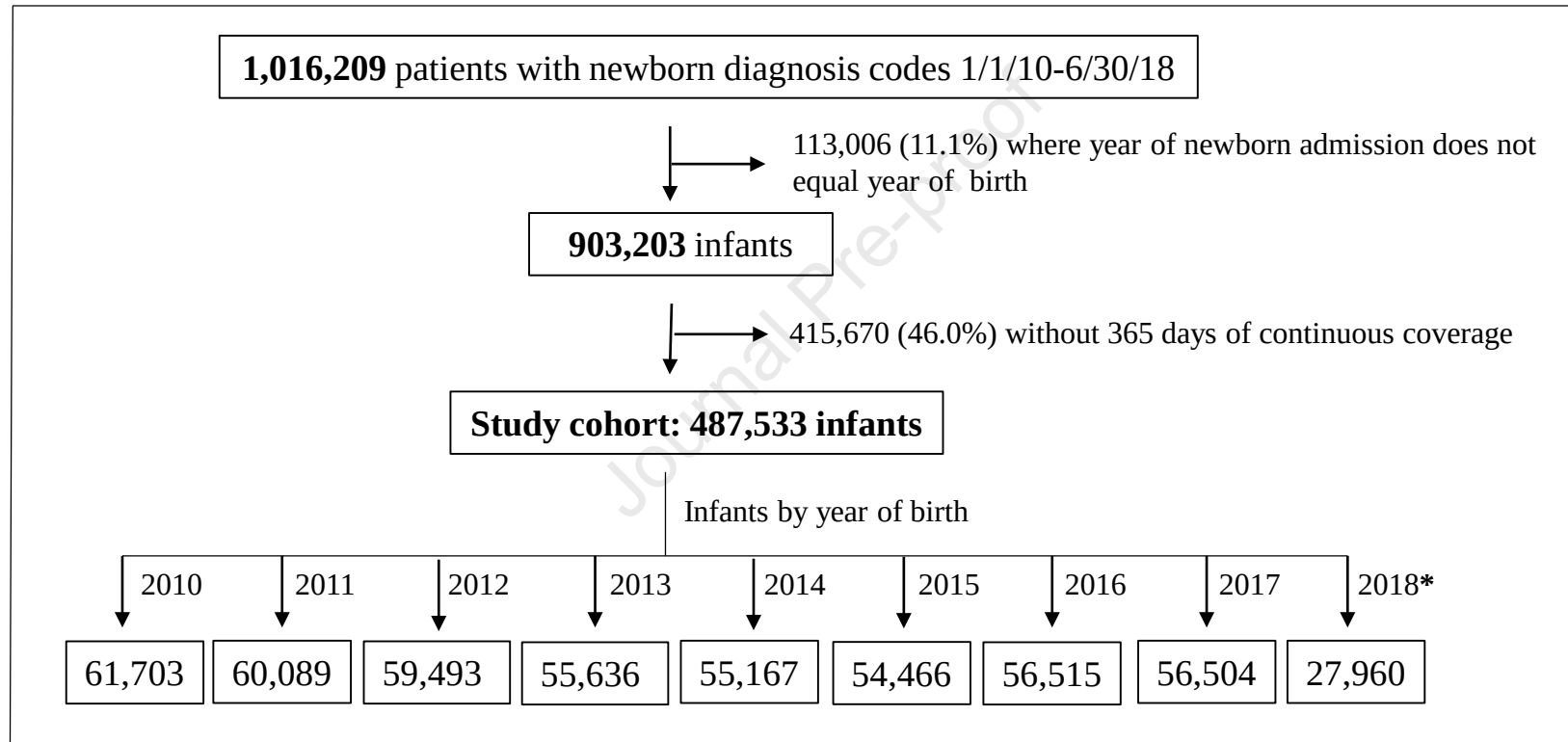
Caption: Dots connected by solid lines represent the prevalence of allergy testing in a given quarter. Vertical red lines represent the LEAP publication (2015 Q1) and the NIAID guideline release (2017 Q1). Dashed lines represent predicted trends in allergy testing rates based on a de-seasonalized interrupted time series analysis with two change points (LEAP and NIAID) and 95% pointwise confidence bands.

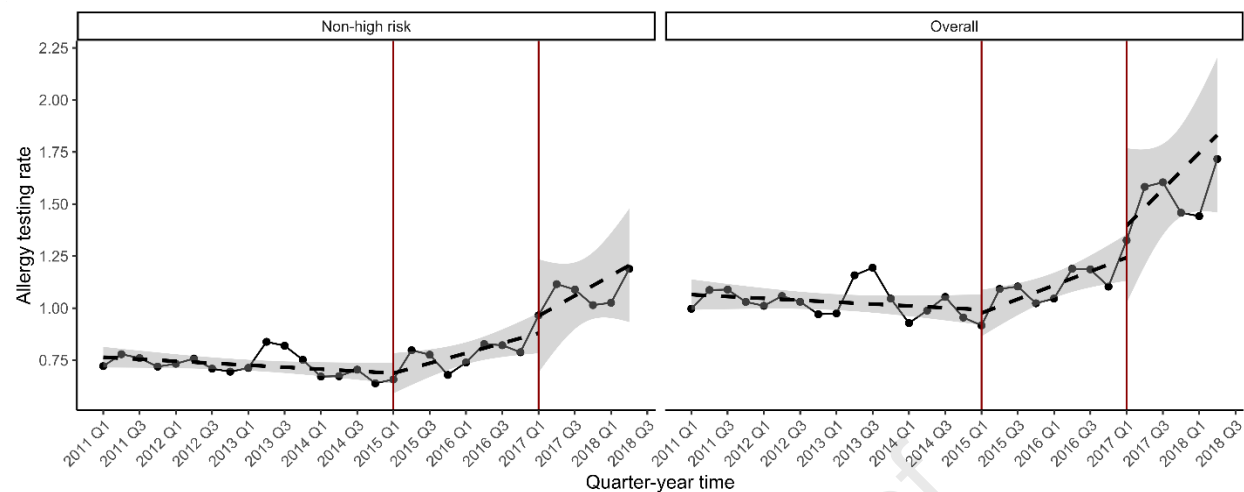
Figure 3. Observed prevalence of food allergy diagnoses of infants by quarter year intervals

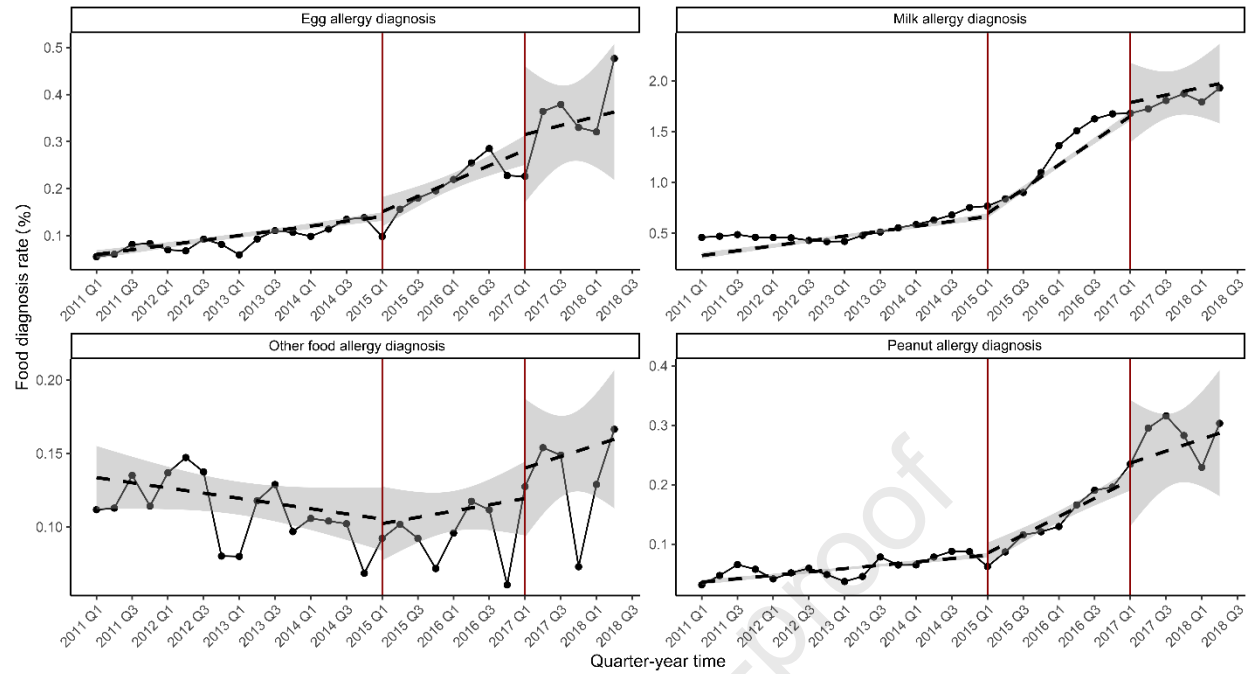
Caption: Dots represent the prevalence of each event of interest in a given quarter. Vertical red lines represent the LEAP publication (2015 Q1) and the NIAID guideline release (2017 Q1). Dashed lines represent predicted trends in allergy testing rates based on a de-seasonalized interrupted time series analysis with two change points (LEAP and NIAID) and 95% pointwise confidence bands. Note that Y-axis is a different scale for each allergen.

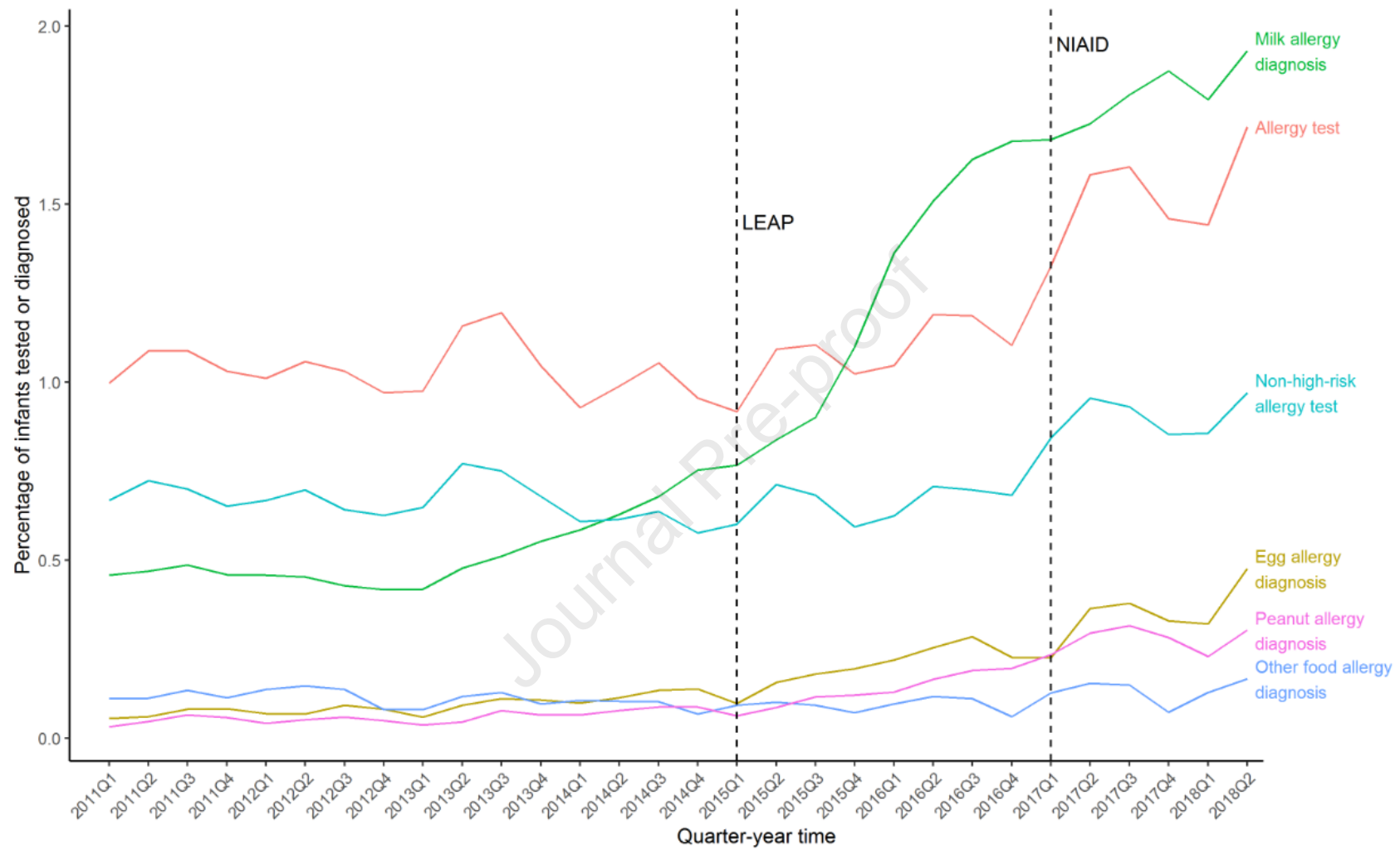
Figure 4. Summary of allergy testing and food allergy diagnoses in ITS analyses

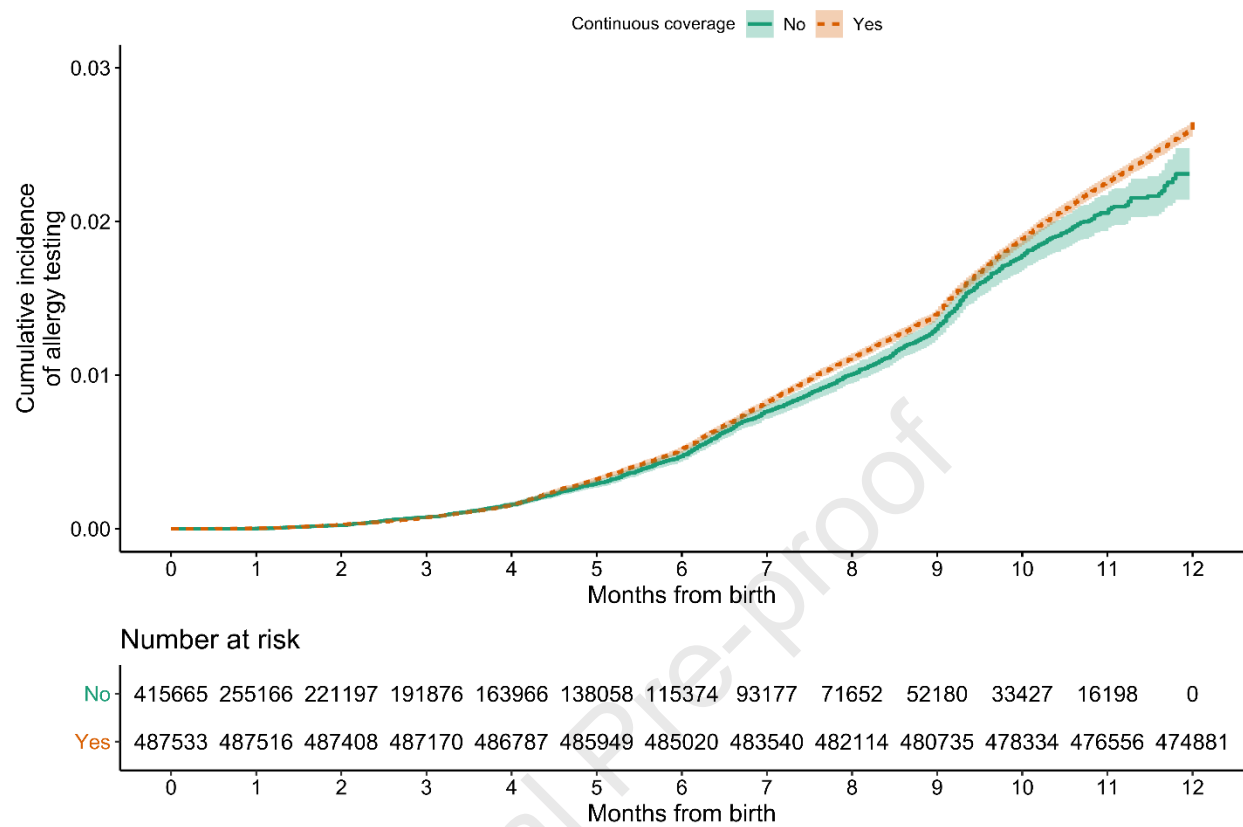
Caption: Line plot of percentage of infants tested or diagnosed within the first year of life over time by test/diagnosis.











Repository E-Tables

Table E1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. ICD-CM codes are based on the World Health Organization's ICD codes, and are updated by the National Center for Health Statistics (NCHS) for utilization in the United States. ICD-CM codes were looked up through their classification of diseases website: <https://www.cdc.gov/nchs/icd/index.htm>. Codes reviewed in the look-up tables through Optum's de-Identified Clinformatics Data Mart Database.

E1a. Newborn Codes:

ICD-9-CM: V30.xx-V39.xx	ICD-10-CM: Z38.xx
V30 Single liveborn	Z38 Liveborn infants according to place of birth and type of delivery
V30.0 Single liveborn, born in hospital	Z38.0 Single liveborn infant, born in hospital
V30.00 Single liveborn, born in hospital, without mention of cesarean delivery	Z38.00 Single liveborn infant, delivered vaginally
V30.01 Single liveborn, born in hospital, delivered by cesarean	Z38.01 Single liveborn infant, delivered by cesarean
V30.1 Single liveborn, born outside hospital, hospitalized	Z38.1 Single liveborn infant, born outside hospital
V30.2 Single liveborn, born outside hospital, not hospitalized	Z38.2 Single liveborn infant, unspecified as to place of birth
V31 Twin, mate liveborn	Z38.3 Twin liveborn infant, born in hospital
V31.0 Twin, mate liveborn, born in hospital	Z38.30 Twin liveborn infant, delivered vaginally
V31.00 Twin, mate liveborn, born in hospital, without mention of cesarean delivery	Z38.31 Twin liveborn infant, delivered by cesarean
V31.01 Twin, mate liveborn, born in hospital, delivered by cesarean	Z38.4 Twin liveborn infant, born outside hospital
V31.1 Twin, mate liveborn, born outside hospital, hospitalized	Z38.5 Twin liveborn infant, unspecified as to place of birth
V31.2 Twin, mate liveborn, born outside hospital, not hospitalized	Z38.6 Other multiple liveborn infant, born in hospital
V32 Twin, mate stillborn	Z38.61 Triplet liveborn infant, delivered vaginally
V32.0 Twin, mate stillborn, born in hospital	Z38.62 Triplet liveborn infant, delivered by cesarean
V32.00 Twin, mate stillborn, born in hospital, without mention of cesarean delivery	Z38.63 Quadruplet liveborn infant, delivered vaginally
V32.01 Twin, mate stillborn, born in hospital, delivered by cesarean	Z38.64 Quadruplet liveborn infant, delivered by cesarean
V32.1 Twin, mate stillborn, born outside hospital, hospitalized	Z38.65 Quintuplet liveborn infant, delivered vaginally
V32.2 Twin, mate stillborn, born outside hospital, not hospitalized	Z38.66 Quintuplet liveborn infant, delivered by cesarean
V33 Twin, unspecified	Z38.68 Other multiple liveborn infant, delivered vaginally
V33.0 Twin, unspecified, born in hospital	Z38.69 Other multiple liveborn infant, delivered by cesarean
V33.00 Twin, unspecified, born in hospital, without mention of cesarean delivery	Z38.7 Other multiple liveborn infant, born outside hospital
V33.01 Twin, unspecified, born in hospital, delivered by cesarean	Z38.8 Other multiple liveborn infant, unspecified as to place of birth
V33.1 Twin, unspecified, born outside hospital, hospitalized	
V33.2 Twin, unspecified, born outside hospital, not hospitalized	
V34 Other multiple, mates all liveborn	
V34.0 Other multiple, mates all liveborn, born in hospital	
V34.00 Other multiple, mates all liveborn, born in hospital, without mention of cesarean delivery	
V34.01 Other multiple, mates all liveborn, born in hospital, delivered by cesarean	
V34.1 Other multiple, mates all liveborn, born outside hospital, hospitalized	
V34.2 Other multiple, mates all liveborn, born outside hospital, not hospitalized	
V35 Other multiple, mates all stillborn	
V35.0 Other multiple, mates all stillborn, born in hospital	
V35.00 Other multiple, mates all stillborn, born in hospital, without mention of cesarean delivery	
V35.01 Other multiple, mates all stillborn, born in hospital, delivered by cesarean	
V35.1 Other multiple, mates all stillborn, born outside hospital, hospitalized	
V35.2 Other multiple, mates all stillborn, born outside hospital, not hospitalized	
V36 Other multiple, mates live- and still born	
V36.0 Other multiple, mates live- and still born, born in hospital	
V36.00 Other multiple, mates live- and still born, born in hospital, without mention of cesarean delivery	
V36.01 Other multiple, mates live- and still born, born in hospital, delivered by cesarean	
V36.1 Other multiple, mates live- and still born, born outside hospital, hospitalized	
V36.2 Other multiple, mates live- and still born, born outside hospital, not hospitalized	
V37 Other multiple, unspecified	
V37.0 Other multiple, unspecified, born in hospital	
V37.00 Other multiple, unspecified, born in hospital, without mention of cesarean delivery	
V37.01 Other multiple, unspecified, born in hospital, delivered by cesarean	
V37.1 Other multiple, unspecified, born outside hospital, hospitalized	
V37.2 Other multiple, unspecified, born outside hospital, not hospitalized	
V39 Unspecified as to single or multiple birth	
V39.0 Unspecified as to single or multiple birth, born in hospital	
V39.00 Unspecified as to single or multiple birth, born in hospital, without mention of cesarean delivery	
V39.01 Unspecified as to single or multiple birth, born in hospital, delivered by cesarean	
V39.1 Unspecified as to single or multiple birth, unspecified, born outside hospital, hospitalized	
V39.2 Unspecified as to single or multiple birth, born outside hospital, not hospitalized	

E1b. Eczema codes:

ICD-9-CM 691 Atopic dermatitis and related conditions 691.8 Other atopic dermatitis and related conditions 692.9 Contact dermatitis and other eczema, unspecified cause	ICD-10-CM L20 Atopic dermatitis L20.0 Besnier's prurigo L20.8 Other atopic dermatitis L20.81 Atopic neurodermatitis L20.82 Flexural eczema L20.83 Infantile eczema L20.84 Intrinsic eczema L20.89 Other atopic dermatitis L20.9 Atopic dermatitis, unspecified L30.9 Dermatitis, unspecified. Eczema NOS.
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E1c. Food allergy codes:

Peanut allergy ICD-9-CM codes: V15.01 Allergy to peanuts 995.61 Anaphylactic reaction due to peanuts	Peanut allergy ICD-10-CM codes: Z91.010 Allergy to peanuts T78.01 Anaphylactic reaction due to peanuts T78.01XA Anaphylactic reaction due to peanuts, initial encounter T78.01XD Anaphylactic reaction due to peanuts, subsequent encounter T78.01XS Anaphylactic reaction due to peanuts, sequela
Egg allergy ICD-9-CM codes: V15.03 Allergy to eggs 995.68 Anaphylactic reaction due to eggs	Egg allergy ICD-10-CM codes: Z91.012 Allergy to eggs T78.08 Anaphylactic reaction due to eggs T78.08XA Anaphylactic reaction due to eggs, initial encounter T78.08XD Anaphylactic reaction due to eggs, subsequent encounter T78.08XS Anaphylactic reaction due to eggs, sequela
Milk allergy ICD-9-CM codes: V15.02 Allergy to milk products 995.67 Anaphylactic reaction due to milk product	Milk allergy ICD-10-CM codes: Z91.011 Allergy to milk products T78.07 Anaphylactic reaction due to milk and dairy products T78.07XA Anaphylactic reaction due to milk and dairy products, initial encounter T78.07XD Anaphylactic reaction due to milk and dairy products, subsequent encounter T78.07XS Anaphylactic reaction due to milk and dairy products, sequela
Other food allergy ICD-9-CM codes: V15.04 Allergy to seafood V15.05 Allergy to other foods 477.1 Allergic rhinitis due to food 693.1 Dermatitis due to food taken internally 995.6 Anaphylactic reaction due to food 995.60 Anaphylactic reaction due to unspecified food 995.62 Anaphylactic reaction due to crustaceans 995.63 Anaphylactic reaction due to fruits and vegetables 995.64 Anaphylactic reaction due to tree nuts and seeds 995.65 Anaphylactic reaction due to fish 995.66 Anaphylactic reaction due to food additives 995.69 Anaphylactic reaction due to other specified food	Other food allergy ICD-10-CM codes: Z91.01 Food allergy Status Z91.013 Allergy to seafood Z91.018 Allergy to other foods Z91.02 Food additives allergy status J30.5 Allergic rhinitis due to a food L27.2 Dermatitis due to ingested food T78.0 Anaphylactic reaction due to a food T78.00 Anaphylactic reaction due to unspecified food T78.00XA Anaphylactic reaction due to unspecified food, initial encounter T78.00XD Anaphylactic reaction due to unspecified food, subsequent encounter T78.00XS Anaphylactic reaction due to unspecified food, sequela T78.02 Anaphylactic reaction due to shellfish T78.02XA Anaphylactic reaction due to shellfish (crustaceans), initial encounter T78.02XD Anaphylactic reaction due to shellfish (crustaceans), subsequent encounter T78.02XS Anaphylactic reaction due to shellfish (crustaceans), sequela T78.03 Anaphylactic reaction due to other fish T78.03XA Anaphylactic reaction due to other fish, initial encounter T78.03XD Anaphylactic reaction due to other fish, subsequent encounter T78.03XS Anaphylactic reaction due to other fish, sequela T78.04 Anaphylactic reaction due to fruits and vegetables T78.04XA Anaphylactic reaction due to fruits and vegetables, initial encounter T78.04XD Anaphylactic reaction due to fruits and vegetables, subsequent encounter T78.04XS Anaphylactic reaction due to fruits and vegetables, sequela T78.05 Anaphylactic reaction due to tree nuts and seeds T78.05XA Anaphylactic reaction due to tree nuts and seeds, initial encounter T78.05XD Anaphylactic reaction due to tree nuts and seeds, subsequent encounter T78.05XS Anaphylactic reaction due to tree nuts and seeds, sequela T78.06 Anaphylactic reaction due to food additives T78.06XA Anaphylactic reaction due to food additives, initial encounter T78.06XD Anaphylactic reaction due to food additives, subsequent encounter T78.06XS Anaphylactic reaction due to food additives, sequela T78.09 Anaphylactic reaction due to other food products T78.09XA Anaphylactic reaction due to other food products, initial encounter T78.09XD Anaphylactic reaction due to other food products, subsequent encounter T78.09XS Anaphylactic reaction due to other food products, sequela

E1d. Excluded codes which may be related to IgE mediated food allergy. Other studies have included the following ICD-9-CM codes, however, we felt these to be less likely related to purely IgE mediated food allergy. Including these codes would have increased our prevalence of other food allergies.

ICD-9-CM excluded codes: 558.3 Allergic gastroenteritis and colitis 692.5 Contact dermatitis and other eczema due to food in contact with skin 995.7 Other adverse food reactions, not elsewhere classified	ICD-10-CM excluded codes: K52.2 Allergic and dietetic gastroenteritis and colitis K52.21 Food protein-induced enterocolitis syndrome K52.22 Food protein-induced enteropathy K52.29 Other allergic and dietetic gastroenteritis and colitis
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988.0 Toxic effect of noxious substances eaten as food, fish and shellfish	L23.6 Allergic contact dermatitis due to a food in contact with the skin L24.6 Irritant contact dermatitis due to food in contact with skin L25.4 Unspecified contact dermatitis due to food in contact with skin T78.1XX Other adverse food reactions, not elsewhere classified T78.1XXA Other adverse food reactions, not elsewhere classified, initial encounter T78.1XXD Other adverse food reactions, not elsewhere classified, subsequent encounter T78.1XXS Other adverse food reactions, not elsewhere classified, sequela T61.XX Codes related to fish or seafood poisoning
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Table E2. Current Procedural Terminology (CPT) codes used in allergy tests and oral food challenges. CPT® is a registered trademark of the American Medical Association.

Test/Procedure	CPT	Description*
Allergy Skin Test	95004	Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests
Allergy Serum Tests	86003	Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each
	86005	Allergen specific IgE; qualitative, multiallergen screen (e.g., disk, sponge, card)
	86008	Allergen specific IgE; quantitative or semiquantitative, recombinant or purified component, each (new code in Jan 2018)
Oral Food Challenge	95076	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); initial 120 minutes of testing (new code in Jan 2013)
	95079	Ingestion challenge test, each additional 60 minutes of testing (new code in Jan 2013)

*Reference: American Medical Association. CPT Professional 2019: Vol. [Fifth edition, revised]. [Chicago, Ill.]: American Medical Association; 2018.

Table E3. Comparison of prevalence of food allergy diagnoses at 12 months of age for infants born in 2015 in our dataset with another study (Gupta et al, 2018)¹ which did a large survey-based analysis on parental reported food allergies in children (included infants under 1); survey done from Oct 2015-Sept 2016.

Allergy	Prevalence at 12 months of age (infants born in 2015 in our data)	Prevalence (95% CI) in study by Gupta et al, 2018. Infants <1 year old
Peanut	0.4%	0.6% (0.3-0.9%)
Milk	1.9%	1.5% (0.9 -2.3%)
Egg	0.6%	0.4% (0.2-0.7%)
Any food allergy	3.3%	2.8% (2.1-3.7%)

Table E4. Prevalence of food allergies and eczema at 12 months of age, by year of birth.

		Year of birth								
		2010	2011	2012	2013	2014	2015	2016	2017	2018 (½)
Event	Number of infants	61,703	60,089	59,493	55,636	55,167	54,466	56,515	56,504	27,960
Food allergy diagnosis										
Peanut		80 (0.1%)	76 (0.1%)	82 (0.1%)	120 (0.2%)	132 (0.2%)	224 (0.4%)	360 (0.6%)	413 (0.7%)	189 (0.7%)
Milk		412 (0.7%)	414 (0.7%)	396 (0.7%)	499 (0.9%)	627 (1.1%)	1045 (1.9%)	1359 (2.4%)	1453 (2.6%)	706 (2.5%)
Egg		112 (0.2%)	113 (0.2%)	131 (0.2%)	176 (0.3%)	212 (0.4%)	340 (0.6%)	426 (0.8%)	614 (1.1%)	292 (1.0%)
Other		829 (1.3%)	819 (1.2%)	735 (1.2%)	669 (1.2%)	732 (1.3%)	722 (1.3%)	898 (1.6%)	1105 (2.0%)	492 (1.8%)
Eczema diagnosis		11,339 (18.4)	11,111 (18.0%)	10,829 (18.2%)	10,102 (18.2%)	9906 (18.0%)	9214 (16.9%)	9965 (17.6%)	10507 (18.6%)	5035 (18.0%)
Severe eczema diagnosis		3707 (6.0%)	3508 (5.6%)	3341 (5.6%)	3170 (5.7%)	3062 (5.6%)	2811 (5.1%)	3060 (5.4%)	3142 (5.6%)	1195 (4.3%)

Table E5. Parameter estimates of secondary interrupted time series models

Section of time series	Risk ratio (95% CI)		
	Milk diagnosis	Egg diagnosis	Other food diagnosis
Pre-LEAP slope ¹	1.06*** (1.04, 1.09)	1.05* (1.00, 1.11)	0.91** (0.86, 0.95)
Slope change for LEAP ²	1.04 (1.00, 1.09)	1.03 (0.94, 1.14)	1.21*** (1.09, 1.34)
Slope change for NIAID ³	1.00 (0.98, 1.03)	1.12*** (1.05, 1.20)	1.22*** (1.14, 1.31)

***p < 0.001, **p < 0.01, *p < 0.05. CI = confidence interval. All models additionally included terms for quadratic time and indicators for each quarter and adjusted for sex, race/ethnicity, and categorical household income.

¹ Represents the per-quarter rate of change (slope) in diagnosis during the pre-LEAP period. ² Represents the trend change in the rate of testing per quarter after the LEAP publication, compared with the quarterly rate prior to the publication. The sum of the estimates for the pre-LEAP slope and slope change for LEAP represent the post-LEAP slope. ³ Represents the trend change in the rate of testing per quarter after the NIAID guidelines publication, compared with the quarterly rate prior to the publication of the NIAID guidelines.

Table E6. Characteristics of first-time allergy testing by time period (in infants who underwent testing and were high-risk at time of testing)

	Overall (N=4650)	Pre-LEAP (N=1943)	<u>Time period¹</u> Post-LEAP & Pre-NIAID (N=950)	Post-NIAID (N=1757)
Allergy testing event				
Allergy testing				
Age in months, median (IQR)	8.1 (4.1)	7.5 (4.6)	8.2 (4.1)	8.4 (3.5)
First 6 months of age, n (%)	1278 (27.5%)	676 (34.8%)	249 (26.2%)	353 (20.1%)
With peanut allergy diagnosis first year of life, n (%)	842 (18.1%)	201 (10.3%)	184 (19.4%)	457 (26.0%)
Age in months, median (IQR)	8.4 (3.7)	8.5 (4.2)	8.3 (4.0)	8.4 (3.4)
Test type				
Oral food challenge, n (%) ²	290 (8.0%)	10 (1.1%)	69 (7.3%)	211 (12.0%)
Serum testing ^{3*} , n (%)	2142 (46.1%)	1081 (55.6%)	410 (43.2%)	651 (37.1%)
Number of allergens, median (IQR)	9 (12)	10 (11)	9 (12)	9 (13)
Single allergen serum ^{4*} , n (%)	166 (3.6%)	65 (3.3%)	29 (3.1%)	72 (4.1%)
Non-single allergen serum, n (%)	1976 (42.5%)	1016 (52.3%)	381 (40.1%)	579 (33.0%)
Skin testing ^{5*} , n (%)	2780 (59.8%)	949 (48.8%)	597 (62.8%)	1234 (70.2%)
Number of allergens, median (IQR)	10.5 (10)	11 (11)	11 (10)	10 (10)
< 4 tests ⁶ , n (%)	195 (4.2%)	57 (2.9%)	36 (3.8%)	102 (5.8%)
4 or more skin tests, n (%)	2585 (55.6%)	892 (45.9%)	561 (59.1%)	1132 (64.4%)

IQR = inner quartile range.

¹ Pre-LEAP spans January 1, 2010 – February 25, 2015; Post-LEAP & Pre-NIAID spans February 26, 2015 – January 4, 2017; Post-NIAID spans January 5, 2017 – June 30, 2019.² based on CPT 95076 or 95079, codes effective starting 2013, therefore only infants tested starting in 2013 counted towards OFC % pre-LEAP (10 of 925)³ based on CPT 86003, 86005, or 86008; Individual component testing (86008) was coded under 86003 until Jan 2018. CPT 86005 was not included when looking at median number of allergens in serum testing as it is a qualitative multiallergen panel.⁴ where only one allergen was tested under CPT 86003 or 86008.⁵ based on CPT 95004.⁶ allows for possibility that individual charges can be incurred for positive and negative controls with single allergen tests.

* Some infants had multiple CPT codes billed on the first day of testing.

Table E7. Characteristics of first-time allergy testing by time period (in infants who underwent testing and were not high-risk at time of testing)

	Time period¹			
	Overall (N=8291)	Pre-LEAP (N=3999)	Post-LEAP & Pre-NIAID (N=1633)	Post-NIAID (N=2659)
Allergy testing event				
Allergy testing				
Age in months, median (IQR)	9.0 (3.5)	9.0 (3.6)	9.0 (3.6)	9.0 (3.4)
First 6 months of age, n (%)	1287 (15.5%)	678 (17.0%)	231 (14.1%)	378 (14.2%)
With peanut allergy diagnosis first year of life, n (%)	644 (7.8%)	134 (3.4%)	151 (9.2%)	359 (13.5%)
Age in months, median (IQR)	9.0 (3.2)	9.5 (3.2)	9.1 (3.2)	8.6 (3.2)
Test type				
Oral food challenge, n (%) ²	247 (4.0%)	22 (1.2%)	49 (3.0%)	176 (6.6%)
Serum testing ^{3*}	4531 (54.6%)	2434 (60.9%)	851 (52.1%)	1246 (46.9%)
Number of allergens, median (IQR)	10 (13)	10 (12)	11 (13)	9 (12)
Single allergen serum ^{4*}	458	207 (5.2%)	86 (5.2%)	165 (6.2%)
Non-single allergen serum	4073	2227 (55.7%)	765 (46.8%)	1081 (40.7%)
Skin testing ^{5*}	4010 (48.4%)	1664 (41.6%)	840 (51.4%)	1506 (56.6%)
Number of allergens, median (IQR)	10 (11)	11 (12)	10 (10)	10 (11)
< 4 tests ⁶	366	109 (2.7%)	82 (5.0%)	175 (6.6%)
4 or more skin tests	3644	1555 (38.9%)	758 (46.4%)	1331 (50.1%)

IQR = inner quartile range.

¹ Pre-LEAP spans January 1, 2010 – February 25, 2015; Post-LEAP & Pre-NIAID spans February 26, 2015 – January 4, 2017; Post-NIAID spans January 5, 2017 – June 30, 2019.² based on CPT 95076 or 95079, codes effective starting 2013, therefore only infants tested starting in 2013 counted towards OFC % pre-LEAP (22 of 1854)³ based on CPT 86003, 86005, or 86008; Individual component testing (86008) was coded under 86003 until Jan 2018. CPT 86005 was not included when looking at median number of allergens in serum testing as it is a qualitative multiallergen panel.⁴ where only one allergen was tested under CPT 86003 or 86008.⁵ based on CPT 95004.⁶ allows for possibility that individual charges can be incurred for positive and negative controls with single allergen tests.

* Some infants had multiple CPT codes billed on the first day of testing.

Repository Text

Statistical analysis

Graphical illustrations of various ITS models have been previously published.²⁸

The following slope change interrupted time series model formulation was used:

$$\log(\mu_t) = \beta_0 + \beta_1 time + \beta_2 time^2 + \beta_3 quarter + \beta_4 postslopeLEAP + \beta_5 postslopeNIAID + e_t$$

Where μ_t is the mean of the event of interest at time t , $time$ is a continuous variable representing quarter-years at time t (1-30) from the beginning until the end of the observation period. As the data exhibited non-linear trends, additional nuisance parameters to account for non-linearity time were included. Specially, $time^2$ as a quadratic function of $time$ and $quarter$ as a categorical variable numbered 1-4 to account for seasonality. Both $time$ and $time^2$ were centered prior to model inclusion to reduce the inherent correlation. The variables $postslopeLEAP$ and $postslopeNIAID$ were coded as 0 up to the last point prior to the intervention and sequential time since intervention (1-14 and 1-6, respectively) after the intervention; e_t is the error term at time t which represents the random variability not explained by the model. Similarly, β_1 represents the change in prevalent testing rate associated with a quarter-year of elapsed time (representing the underlying baseline trend), β_2 and β_3 represent estimates for the nuisance time parameters, β_4 represents the slope change in rate following the LEAP publication, and β_5 represents the slope change in rate following the NIAID guidelines. This model was fit to each of the events of interest described in the Outcomes section, and additionally adjusted for sex, race/ethnicity, and categorical household income; therefore, a total of 6 models were fit.

Due to the high number of excluded infants having non-continuous enrollment, a sensitivity analysis was conducted to determine whether infants with less than 12 months of continuous enrollment were inherently different in terms of rates of allergy testing compared to those with a full year of coverage. The cumulative incidence of allergy testing over the observation period was reported by infants with and without a full year of continuous coverage, and the time until allergy testing was compared between the two coverage groups using the log-rank test.⁴⁶

Figure E1. Cumulative incidence of allergy testing by medical coverage group

Caption: Cumulative incidence of allergy testing within the first year of life by whether or not an infant had at least 12 months of continuous medical coverage with 95% confidence bands. Rates of allergy testing were significantly different between coverage groups (logrank test $p=0.002$).