

The Health and Economic Outcomes of Peanut Allergy Management Practices



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What is already known on this subject? The health and economic benefits of 2 peanut allergy management strategies, strict avoidance of items with precautionary allergen labeling and administering epinephrine for known allergen ingestion even in the absence of symptoms, are unknown.

What this article adds to our knowledge? Assuming a 10- to 1000-fold risk increase associated with the alternative, routine precautionary allergen labeling (PAL) avoidance and pre-emptive epinephrine use for peanut ingestion without symptoms were not cost-effective. A low-dose supervised peanut threshold challenge was cost-effective to facilitate PAL consumption.

How does this study impact current management guidelines? Single low-dose peanut threshold challenges should be considered to facilitate PAL consumption. Patients should wait for symptom development to administer epinephrine after peanut consumption.

BACKGROUND: Peanut allergy is managed with strict avoidance, epinephrine carriage, and promptly treating reactions.

OBJECTIVE: The objective of this study was to assess the health and economic benefits of pre-emptively injecting epinephrine for peanut ingestion in the absence of any symptoms, and to avoid products with peanut precautionary allergen labeling (PAL).

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METHODS: We used Markov modeling and simulations, assuming a base-case 10-fold fatality risk increase for less conservative management, with sensitivity analysis investigating 100- to 1000-fold increased fatality risk, incorporating risks of accidental exposures, reactions, fatality, and family costs of food allergy. Low-dose threshold challenges were used to exclude subjects highly reactive to PAL items. **RESULTS:** Based on these assumptions, small reductions in per-patient fatality risk resulted from pre-emptive epinephrine injection without symptoms present ($<1 \times 10^{-4}$ fewer per-patient fatalities), with incremental costs of \$1193 per patient, \$11,681,501/life year saved, and \$110,270,820/death prevented versus waiting for symptoms before use, but this was not cost-effective even assuming 1000-fold risk (\$107, 971/quality of life adjusted year) or quality of life (QoL). There were small reductions in per-patient fatality risk ($<1 \times 10^{-4}$ fewer per-patient fatalities) for PAL avoidance versus universal PAL consumption, with incremental costs of \$3342 per patient, \$19,325,994/life year saved, and \$182,434,277/death prevented versus allowing PAL consumption. PAL avoidance was not cost-effective when assuming 1000-fold risk or considering QoL. Incorporating a single, supervised low-dose challenge of 1.5 mg of peanut protein to exclude children reactive to PAL consumption was cost-effective.

CONCLUSIONS: Commonly recommended practices of pre-emptive epinephrine injection in the absence of symptoms, or universal avoidance of PAL, were not cost-effective when compared with administering epinephrine on symptom development or allowing PAL consumption. © 2018 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2018;6:2073-80)

Key words: Quality of life; Food allergy action plan; Precautionary labeling; Eliciting dose; Anaphylaxis; Epinephrine; Epinephrine autoinjector; Emergency medical services; Peanut allergy; Cost-effectiveness; Simulation; Food allergy fatality; Fatal anaphylaxis; Allergic reaction

Abbreviations used

EMS- Emergency medical services
 FAAP- Food allergy action plan
 FAIs- Food-allergic individuals
 FAQLQ-PF- Food Allergy Quality of Life Questionnaire Child Form/Parent Form
 FDA- Food and Drug Administration
 PAL- Precautionary allergen labeling
 QALY- Quality of life adjusted year
 QoL- Quality of life

Peanut allergy affects approximately 1.4% to 4.5% of all children,¹⁻³ and is associated with anxiety and diminished quality of life (QoL) in both the caregiver and the child, despite strong caregiver self-efficacy.^{4,5} Peanut allergy can be a lifelong and potentially severe condition, without a present cure or Food and Drug Administration (FDA)-approved treatment beyond strict avoidance of peanut-containing foods and carriage of an epinephrine autoinjector to treat any potential reaction that could develop.⁶⁻⁹ These instructions are part of a written food allergy action plan (FAAP) provided to all patients, which discusses emergency treatment, as well as post-treatment disposition. Multiple FAAPs exist, each with somewhat variable instructions across the available versions.¹⁰ In the United States, all plans advocate epinephrine use for reactions involving 2 organ systems or solitary cardiac or respiratory symptoms, and that if epinephrine is used to immediately call 911 to activate emergency medical services (EMS) and take the child to the nearest emergency department.¹⁰ Particular plans, such as the one from Food Allergy Research and Education, offer an option that medical providers can select for the child to be immediately administered epinephrine if the suspected allergen was “definitely eaten,” even if no symptoms are present, as a pre-emptive treatment.^{11,12} In contrast, the new action plan endorsed by the American Academy of Pediatrics includes an option of early epinephrine for mild symptoms but not pre-emptive use (after known/suspected ingestion but before symptoms emerge). The frequency and variation with which this pre-emptive strategy is recommended is unknown.

Standard food allergy management also advocates strict allergen avoidance, which often constitutes “all forms” including packaging with precautionary allergen labeling (PAL) such as “may contain,” “might contain,” “made in a shared facility,” or “made on shared equipment.”^{9,10} PAL is a voluntary food package labeling declaration of potential allergenic contents, alerting the consumer to the potential allergen contamination of the product, without known verification that the product does contain the allergen.^{13,14} PAL contrasts with declaratory labeling statements of known allergen content that is legally required per the Food Allergen Labeling and Consumer Protection Act for the known presence of one of the 8 common allergens in any packaged food in the United States.¹⁵ Although action plans do not specifically denote PAL avoidance, this is generally understood as part of the instructions, unless the family is instructed otherwise by their provider.⁹ Risks of PAL are poorly understood, given that variable quantities of the allergen may be present, though these are generally on the level of parts per million, and an estimated 95% of the peanut-allergic population may tolerate as much as 1.5 mg peanut protein as noted in multiple allergen threshold studies.^{14,16} However, given that the

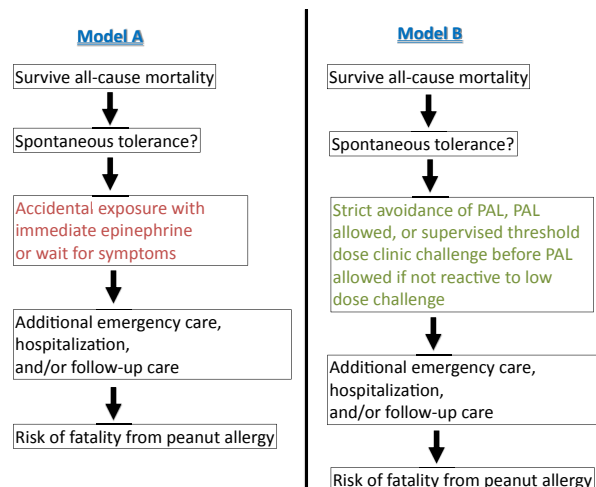


FIGURE 1. Markov transitional health states simulated to evaluate cost-effectiveness of precautionary practices in children with peanut allergy. Two models were constructed. In model A, immediate epinephrine injection for peanut ingestion without symptoms was compared with epinephrine injection for symptoms of anaphylaxis. Model B compared the practice of strict avoidance of foods with precautionary allergen labeling (PAL) to one in which foods with PAL were allowed. Each model assumed a 10-fold increase in fatality risk for less conservative management.

actual quantities of allergen in PAL are unknown and the risks of ingesting PAL products poorly understood, avoidance of products with PAL is often recommended as part of standard avoidance practices.^{14,17-19}

There is a paucity of evidence to direct best practice in regard to PAL avoidance or pre-emptive epinephrine use.¹¹ Given that allergy avoidance advice and reaction treatment instructions on a FAAP may vary considerably, we investigated the health and economic benefits of instructions to pre-emptively use epinephrine after allergen ingestion before any symptoms are present, and to avoid products with PAL, in the context of peanut allergy.

METHODS

Using Markov modeling with TreeAge Pro (TreeAge, Williamstown, Mass), we evaluated the cost-effectiveness of advice regarding reaction treatment and food avoidance practices provided to peanut-allergic patients. The model simulated recurrent probabilistic risk and health state transitions through childhood with each model concluding after 20 years of simulation.²⁰ Models were constructed to evaluate 2 discrete practice recommendations. Model A evaluated the practice of pre-emptive epinephrine use before symptom development in peanut-allergic children after known peanut consumption, compared with epinephrine use only after onset of a moderate-to-severe reaction. This pre-emptive epinephrine-use practice is an optional recommendation on a very commonly used FAAP in the United States (“give epinephrine immediately if the allergen was DEFINITELY eaten, even if no symptoms are apparent”).¹² Model B evaluated the practice of strict peanut avoidance, including PAL avoidance, compared with more permissive avoidance allowing foods with peanut PAL but otherwise strictly avoiding peanut (Figure 1). Each model assumed a base-case 10-fold increase in fatality risk for

TABLE I. Model inputs

Variable	Model reference	Source
US Life Table	National Vital Statistics Reports, April 2017	Arias et al ²¹
Probabilities		
Fatality from peanut-allergic reaction	5.77×10^{-7}	Shaker ²²
Accidental peanut exposure if allergic (strict avoidance)	11.7% per year	Vander Leek et al ²⁴
Incremental risk of consuming eliciting dose of foods with precautionary allergen labeling (PAL)	1% per food with PAL	Ford et al ²⁵
Moderate-to-severe reaction after peanut ingestion	52%	Vander Leek et al ²⁴
Hospitalization after severe food-allergic reaction	0.18% per year after reaction	Shaker ²²
Outpatient visits for food allergy after reaction	20.4% per year after allergic reaction	Shaker ²²
Spontaneous peanut tolerance	1.1% per year	Skolnick et al ²⁶
Probability of low-dose peanut tolerance	95%	Hourihane et al ¹⁶
Costs		
Epinephrine autoinjector (annual cost per twin pack)	\$635	Shaker et al ²⁷
Cost low-dose peanut challenge	\$196	Dartmouth Hitchcock ²⁸
Hospitalization	\$5638	Patel et al ²⁹ US Department of Labor, Bureau of Labor Statistics ²³
Emergency department visit	\$661	Patel et al ²⁹ US Department of Labor, Bureau of Labor Statistics ²³
Outpatient visit for food-allergic reactions	\$231	Patel et al ²⁹ US Department of Labor, Bureau of Labor Statistics ²³
Ambulance transport for allergic reactions	\$561	Patel et al ²⁹ US Department of Labor, Bureau of Labor Statistics ²³
Pediatrician visits for food allergy (annual) (mean incremental annual cost for food allergy diagnosis)	\$98	Gupta et al ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Allergist visits for food allergy (annual)	\$146	Gupta et al, ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Nutritionist visits for food allergy (annual)	\$17	Gupta et al ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Alternative provider visits for food allergy (annual)	\$24	Gupta et al ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Incremental grocery costs (annual)*	\$304	Gupta et al ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Job-related opportunity costs from food allergy (annual)	\$2544	Gupta et al ³⁰ US Department of Labor, Bureau of Labor Statistics ²³
Additional assumptions		
Annual discount rate	0.03	US Department of Labor, Bureau of Labor Statistics ²³
Negative health state influence for food allergy	−0.09	Carroll and Downs ³¹ Mittmann et al ³²
Risk from waiting for symptoms before epinephrine use (or from consuming foods with PAL)	10×	Baseline case assumption
“May contain snack food”	2 per day	1% risk per food, 1% of allergic children reactive, incremental annual risk 7.3% ³³
Quality of life health state utility improvement when foods with PAL allowed	13%	Based on incremental improvement in FAQL-PF applied to base health state utility ¹⁶
Disutility of unnecessary epinephrine use	8%	Ward and Greenhawt ³⁴

FAQLQ-PF, Food Allergy Quality of Life Questionnaire Child Form/Parent Form.

*excluded for subjects allowed to eat foods with precautionary labeling.

TABLE II. Simulation outcomes with sensitivity analyses

Strategy	Sensitivity analyses	Cost*	QALY*	Fatality*	Cost per QALY	Incremental cost per life year saved†	Incremental cost per death prevented
Model A: epinephrine for peanut ingestion without symptoms							
						Incremental cost of pre-emptive use	
Start age 1 y							
Pre-emptive epinephrine for any exposure before symptoms	Base case	\$54,025.04	18.2497162471	0.0000012021	\$2,960.32		
	Unnecessary epinephrine disutility (−8%)	\$54,025.04	18.2424160660		\$2,961.51		
Epinephrine for symptoms	Base case	\$52,832.02	18.2496141181	0.0000120211	\$2,894.97	\$11,681,501	\$110,270,820
	Unnecessary epinephrine disutility					Dominated	
Fatality risk							
	100×	\$52,829.24	18.2485928678	0.0001202040	\$2,894.98	\$1,064,467	\$10,048,579
	500×	\$52,816.93	18.2440548664	0.0006008718	\$2,895.02	\$213,395	\$2,014,626
	1000×	\$52,801.53	18.2383844046	0.0012013736	\$2,895.08	\$107,971	\$1,019,446
Start age 6 y							
Epinephrine for any exposure before symptoms	Base case	\$54,014.56	18.2423407058	0.0000012016	\$2,960.94		
	Unnecessary epinephrine disutility (−8%)	\$54,014.56	18.2350434618		\$2,962.13		
Epinephrine for symptoms	Base case	\$52,821.82	18.2422386734	0.0000120162	\$2,895.58	\$11,689,816	\$110,289,793
	Unnecessary epinephrine disutility					Dominated	
Fatality risk							
	100×	\$52,819.05	18.2412183899	0.0001201556	\$2,895.59	\$1,065,217	\$10,050,187
	500×	\$52,806.74	18.2366846839	0.0006006302	\$2,895.63	\$213,546	\$2,014,952
	1000×	\$52,791.36	18.2310195885	0.0012008907	\$2,895.69	\$108,046	\$1,019,597
Model B: avoidance of foods with precautionary allergen labeling (PAL)							
						Incremental cost of PAL avoidance	
Start age 1 y							
PAL avoided	Base case	\$52,832.29	18.2497162471	0.0000012021	\$2,894.97		
PAL allowed	Base case	\$49,490.24	18.2495433168	0.0000195213	\$2,711.86	\$19,325,994	\$182,434,277
	PAL benefit (QoL), 13%	\$49,490.24	18.4644376529		\$2,680.30	Dominated	
Fatality risk							
	100×	\$49,486.03	18.2478849216	0.0001951956	\$2,711.88	\$1,827,234	\$17,249,341
	500×	\$49,467.32	18.2405166201	0.0009755873	\$2,711.95	\$365,772	\$3,453,429
	1000×	\$49,443.93	18.2313116213	0.0019501990	\$2,712.03	\$184,104	\$1,738,515

Low-dose challenge PAL allowed if tolerated	Base case	\$49,254.29	18.2497157398	0.0000012306	\$2,698.91	\$7,053,025,807	\$125,543,869,649
	PAL benefit (QoL), 13%	\$49,254.29	18.4481673803		\$2,669.87	Dominated	
	Base case	\$52,822.10	18.2423407058	0.0000012016	\$2,895.58		
	PAL benefit (QoL), 13%	\$49,480.65	18.2421679392	0.0000195135	\$2,712.43	\$19,340,833	\$182,474,238
Start age 6 y PAL avoided PAL allowed	Base case	\$49,480.65	18.4569876735		\$2,680.86	Dominated	
	Fatality risk						
	100×	\$49,476.44	18.2405111139	0.0001951170	\$2,712.45	\$1,828,637	\$17,253,194
	500×	\$49,457.74	18.2331497862	0.0009751951	\$2,711.42	\$366,053	\$3,454,191
Low-dose challenge PAL allowed if tolerated	1000×	\$49,434.38	18.2239534974	0.0019494156	\$2,712.60	\$184,243	\$1,738,885
	Base case	\$49,244.92	18.2423401987	0.0000012302	\$2,699.48	\$7,054,190,480	\$125,076,233,776
	PAL benefit (QoL), 13%	\$49,244.92	18.4407209655		\$2,670.44	Dominated	

Base case assumes a 10-fold fatality risk increase for deferring epinephrine until symptoms occur or allowing PALs.

QALY, Quality of life adjusted year; QoL, quality of life.

*Cost, QALY, fatality per patient over model horizon.

†Incremental cost per life year saved over model time horizon.

less conservative management (waiting for symptoms to emerge before using epinephrine; permissive inclusion of products with PAL in the diet), with sensitivity analysis investigating 100-fold, 500-fold, and 1000-fold risk increases.

The simulations incorporated all-cause age-adjusted mortality using the 2013 life table.²¹ Each decision analysis included simulations of children entering the models at 1 and 6 years of age, and incorporated risks of accidental exposures, reactions, and food-allergic fatalities together with costs associated with treatment and of living with a peanut allergy, as previously described.²² A 3% per annum discount rate was used to reflect the average consumer price index for all goods and services.²³ Base-case model assumptions are shown in Table I.

Model inputs for the risk of accidental peanut exposures and reactions were taken from available published data.²⁶ Vander Leek et al²⁴ reported that 31 of 53 subjects with peanut allergy experienced accidental reactions over a 5-year period, 31 of 60 involving potentially life-threatening symptoms (throat tightness and angioedema, laryngeal angioedema, angioedema in the mouth, cough, wheeze, chest tightness, shortness of breath, noisy breathing, tachypnea, or voice changes). Based on these data, model A assumed an annual risk of accidental ingestion despite strict avoidance of 11.7% (with 52% experiencing a moderate-to-severe reaction with accidental ingestion).^{1,24} In model A, all subjects using epinephrine subsequently had EMS activation, with ambulance transport and emergency department evaluation (per common instructions on emergency action plans), and assumed probabilities associated with subsequent hospitalization and care.^{27,29,30}

Model B focused on comparing advice to avoid foods with peanut PAL versus a more permissive strategy in which consumption of these foods was allowed. Comparison of avoidance of foods with PAL versus not avoiding foods with PAL also took into account the potential for increased costs associated with reactions requiring epinephrine treatment occurring as a result of peanut contamination of foods with PAL. In this model, we explored the use of epinephrine only for symptoms developing after ingestion related to a product with precautionary labeling for peanut, and as in model A, if epinephrine was used EMS was activated, with ambulance transport and emergency department evaluation. Inputs included risks of symptomatic allergic reactions from ingestion of foods with peanut PAL.²⁵ In a convenience sample of supermarket products in New York and New Jersey, Ford et al²⁵ reported that 4.5% of products with PAL had detectable peanut. Data reported by Taylor et al calculated that less than 1% of products with peanut PAL would contain a sufficient eliciting dose of allergen to cause symptoms.^{17,18,33} Our simulation assumed that each subject with more permissive avoidance consumed 2 snacks per day containing peanut PAL expected to elicit a reaction in only 1% of peanut-allergic subjects, translating to a 7.3% incremental annual risk for accidental peanut-associated allergic reactions. Incremental grocery costs of living with peanut allergy were excluded for subjects allowed to eat foods with peanut PAL.

We added an additional model B analysis to compare a strategy of front-end supervised single, low-dose threshold peanut challenges to exclude highly reactive patients. For this strategy, challenge reactive patients avoided PAL foods, but the 95% of peanut-allergic patients who tolerated an eliciting dose of 1.5 mg of peanut protein¹⁶ were allowed to have PAL-containing foods but did not assume any increase in reaction risk or fatality from this approach. Costs of this approach were modeled using a single dose challenge (1.5 mg of peanut protein).

Both more restrictive dietary avoidance and unnecessary epinephrine use may impair overall QoL. To investigate these additional QoL impairments, additional sensitivity analyses were performed that were not incorporated in the base-case analysis. Relative QoL changes reported in the literature were applied to health state utilities associated with peanut allergy.^{31,32} In model A, QoL sensitivity analysis, unnecessary epinephrine disutility was applied as a transient nonbaseline health state utility for those patients who received epinephrine without symptoms. In an online survey administered to 3451 caregivers of food-allergic individuals (FAIs), those reporting FAIs receiving epinephrine had worse QoL (higher scores) than those who did not (Food Allergy Quality of Life—Parental burden questionnaire, mean score 3.07 vs 2.84, $P < .001$).³⁴ An interaction was noted between reported epinephrine use and reported anaphylaxis, such that those using epinephrine without reporting anaphylaxis had worse QoL, but epinephrine use with reported anaphylaxis had better QoL. This relative QoL difference was used to derive a transient disutility assumed by patients receiving epinephrine outside of a context of moderate-to-severe symptoms.

In the model B sensitivity analysis, QoL benefit associated with tolerating products with PAL was extrapolated from data from Hourihane et al¹⁶ by applying relative QoL adjustment for children permitted to eat and tolerant of PAL foods to the baseline peanut allergy health state utilities. This study demonstrated QoL improvements (Food Allergy Quality of Life Questionnaire Child Form/Parent Form [FAQLQ-PF] improvement 0.24, $P = .014$ on baseline FAQLQ-PF of nonreactive children of 1.8, standard deviation 1.3) in children who tolerated exposure to a cookie with 1.5 mg peanut protein, a level hypothesized at which 95% of peanut-allergic children would tolerate (eliciting dose for 5%). Change and impact on QoL in the analysis was reported in terms of quality of life adjusted years (QALYs).

RESULTS

Model A showed a very small reduction in per-patient fatality risk resulting from the pre-emptive approach of injecting epinephrine after ingestion of a peanut-containing product but before symptoms actually emerged ($<1 \times 10^{-4}$ fewer per-patient fatalities over the model horizon), for subjects entering the simulation at 1 year of age. For this group, pre-emptive epinephrine use, with reflex emergency medical services activation and care (per instructions on a food allergy action plan), cost an additional \$1193 per patient over the model horizon. The cost of living with peanut allergy following this strict advice was \$54,025 compared with \$52,832 if the patient waits for moderate-to-severe symptoms to emerge before using epinephrine. The incremental cost per life year saved in this simulation was \$11,681,501 for early precautionary epinephrine use without symptoms (\$110,270,820 per death prevented). Costs of pre-emptive epinephrine use were lower as the risks of fatal allergic reactions from waiting increased, but even at assumed 100-, 500-, and 1000-fold increased risk over waiting to use epinephrine when symptoms emerged, pre-emptive epinephrine use cost greater than \$100,000 per QALY saved (\$1,064,467, \$213,395, \$107,971 per QALY), the threshold for a treatment to be considered cost-effective.³⁵ When QoL impairments associated with unnecessary epinephrine use were modeled for additional sensitivity, the strategy of pre-emptive epinephrine use was dominated by an approach in which epinephrine was used

only after symptoms emerged. Similar economic outcomes were identified for subjects entering the simulation at 6 years of age (Table II).

In model B (avoidance of foods with peanut PAL), subjects entering the simulation at 1 year of age also experienced a minimal reduction in peanut-associated fatality over the model horizon ($<1 \times 10^{-4}$ fewer per-patient fatalities). Incremental model-horizon cost for strict avoidance of PAL was \$3342 per patient. The incremental cost per life year saved with strict avoidance of PAL was \$19,325,994 (\$182,434,277 per death prevented). The base-case model assumed a 1% population risk of reactivity to PAL, but further sensitivity analysis to a 5% rate of reactivity continued to show universal PAL avoidance to be cost-ineffective (incremental cost-effectiveness ratio of \$204,672 per QALY). In sensitivity analyses, similar costs were demonstrated for children entering the simulation at 6 years of age. When QoL associated with allowing PALs was modeled for additional sensitivity, strict avoidance of PAL was dominated by a strategy in which PALs were allowed. However, when a strategy of supervised low-dose threshold challenge was used to exclude the most allergic patients who would react to PAL, this strategy dominated one that allowed all patients to consume PAL, with lower peanut allergy costs, higher QALYs, and lower peanut allergy fatality rates (Table II).

DISCUSSION

In this analysis of precautionary management advice to families of peanut-allergic children, based on our models and assumptions, the absolute protective effect of pre-emptive epinephrine in the absence of symptoms was low, even assuming a 10- to 1000-fold increase in fatality rates for these practices. Food-allergic patients and their caregivers are offered a variety of advice in terms of allergen avoidance and reaction management. FAAPs are an essential tool for patient self-management, but uncharacterized practice variation exists in how these plans are used, and with various FAAPs available.^{10,12,36} Anaphylaxis research is heavily reliant on expert opinion and observational data, given the ethical limitations of conducting randomized controlled trials regarding management.⁹ As such, it is unlikely that a clinical study will ever be performed comparing pre-emptive epinephrine in the absence of symptoms with an approach where epinephrine is given immediately after symptoms develop after peanut ingestion. This is what makes simulation an invaluable tool to explore such scenarios.

Although early epinephrine is critical in treating anaphylaxis,¹¹ there may be uncertainty as to how early is too early for when to use epinephrine. It is of interest that no mechanistic evidence to date has demonstrated that pre-emptive epinephrine administered after ingestion of an allergen (but before symptoms emerge) prevents a reaction from occurring. It is possible that due to its short half-life, pharmacologic concentrations of epinephrine could theoretically begin to wane before digested food allergen triggers a reaction if used before symptoms occur.^{11,37} Furthermore, food allergy reaction severity is unpredictable and timing of onset of a reaction is variable.⁸ The very best pharmacokinetic data supporting intramuscular epinephrine injection (in the vastus lateralis muscle) derive from a very small case series of healthy controls who were not undergoing anaphylaxis at the time of study, and note a peak absorption at 8 minutes.^{38,39} Anaphylaxis-related hospital admissions are more likely if

epinephrine is delayed, and fatality is associated with either no administration of epinephrine, or a significant delay in epinephrine use.^{9,40,41} However, it is unclear if either outcome would change from pre-emptive epinephrine use when compared with recommending epinephrine use immediately after symptoms develop. Complicating this uncertainty is the confounding effect of suboptimal patient adherence to action plan recommendations, and the dangerous tendency of some to delay epinephrine use while instead using an antihistamine or traveling to an emergency department for a provider to initiate treatment.

Regarding advice on the degree to how strictly PAL must be avoided, this is a poorly understood area.^{14,18} The core issue is the nature of the variability in what the PAL may represent—the product may contain relevant allergen, or it may not and just be labeled as such out of an abundance of caution. Such uncertainty does not benefit patients or providers in trying to provide clear advice.¹³ There are emerging data regarding allergen thresholds and what someone may be able to tolerate in terms of exposure before objective symptoms develop. With peanut, 3 separate studies have suggested that 95% of the peanut-allergic population level will tolerate 1.5 mg of peanut protein (6 mg peanut by package weight) and may be able to tolerate as much as 1.95 mg peanut protein.^{16,42,43} Although data on both threshold doses and peanut content in packages with PAL continue to emerge, there are enough data at present to be able to make a reasonable assessment as to the risk involved in consuming these for the average individual.^{17,19} The recent Peanut Allergy Threshold Study noted a significant improvement in QoL associated with a 1.5 mg peanut protein threshold, which shows the power that such liberation of the diet can hold in terms of making a meaningful change.¹⁶ There are no data that have definitively shown that consumption of PAL products is dangerous, or that their avoidance is associated with superior outcomes.³³ However, avoidance of such products is very common advice, in line with not taking any unnecessary risks, despite a lack of evidence demonstrating benefit. We found the optimal approach in regard to PAL avoidance appeared to be one in which the most highly reactive peanut-allergic subjects avoided PAL foods but all others were allowed PAL-containing foods. Based on our models and assumptions, such a strategy would involve a one-time, low-dose threshold challenge to identify the 95% of peanut-allergic children nonreactive to 1.5 mg of peanut protein,¹⁶ who would then be allowed to consume PAL-containing foods without incremental risk.

Cost-effectiveness analysis can be useful to compare medical therapies and strategies, and care costing less than \$100,000 per quality-adjusted life year is considered cost-effective.³⁵ A health care delivery strategy is considered “dominated” if it costs more and results in lower health care QoL, meaning it has limited effect compared with alternative approaches. One could consider if low-dose threshold challenges could be used to stratify high-risk children for pre-emptive epinephrine use as well. Indeed, although in our sensitivity analysis, even assuming a 1000-fold increased fatality risk associated with non-pre-emptive epinephrine use, such a practice was still not cost-effective (\$107,971 per QALY), although a 1000-fold risk was the estimate that was closest to the threshold of cost-effective care. It is unknown if a child reactive to 1.5 mg of peanut protein would assume to have this high a risk from non-pre-emptive epinephrine use after peanut ingestion (which we think is unlikely), but it is highly unlikely that a clinical study could or would ever be performed to

better inform pre-emptive treatment decision for these highly reactive children. If a clinician felt that such a highly reactive child is assumed to potentially have a fatality risk above this threshold, then pre-emptive epinephrine use could be a reasonable consideration. However, if a fatality risk increase is assumed to be below this level, the pre-emptive use of epinephrine is not a cost-effective practice.

This study has limitations. Foremost, we assume a 10-fold base-case level of risk of fatality, which could be inaccurate. There are poor data to understand the nature of the potential increase risk between strategies, but we felt that a 10-fold increased risk was a reasonable base case that would be easy to understand and represent a level that would be conservative enough to incorporate most cases where a clinician would be weighing a decision. For comparison, the FDA accepted just under a 3-fold risk of fatality from the use of long-acting beta-agonists in combination with inhaled steroids for the removal of the black-box warning for fatality, which may better underscore the magnitude of a 10-fold risk.^{44,45} To account for additional scenarios that could additionally escalate risk even over a 10-fold baseline, we modeled sensitivity of assuming 100-, 500-, and 1000-fold fatality risk increases as well. Again, the true level of risk is unknown, and could also be under 10-fold, which we did not model (though the cost-effectiveness data would still not improve at any lower risk assumption). We only modeled peanut as a provoking source. Foods are the most common cause of anaphylaxis in children, and peanut is commonly believed to be associated with potential fatal anaphylaxis and severe reactions.⁶ This was a pediatric analysis and did not include peanut allergic adults who may have different considerations based on comorbidities more common in adults. Rates of severe reactions to peanut and related reaction sequelae were taken from published studies, but there are limited data that are available. We did not account for opportunity costs of the ambulance, emergency facility time, and resources being used for other health care services in this model.

This is the first known study of the health and economic benefits of this particular food allergy management advice regarding avoidance and treatment. In 2 simulations of precautionary advice given to caregivers of peanut-allergic children, based on our models and assumptions, pre-emptive epinephrine use for peanut ingestion before symptoms occur and routine advice to avoid foods with PAL statements were cost-ineffective therapies. Both pieces of advice may be preference-sensitive, and patient engagement may enhance self-efficacy. Importantly, the true frequency with which providers instruct families to use pre-emptive epinephrine is unexplored. Practice variation in how providers complete FAAPs also requires further evaluation. In addition, a specific study of family and contextual factors and the development of a decision aid may lead to better optimization of specific advice. There may be situations where contextual factors influence advice, such as in patients who have previously experienced reactions to PAL-containing foods or those patients with prior intubations or near-fatal anaphylaxis. Consistent with these patient-factor specific situations, our analysis found that the optimal approach to PAL avoidance would involve a one-time low-dose threshold challenge of 1.5 mg of peanut protein to exclude highly reactive children from PAL consumption. However, as a matter of routine, neither pre-emptive epinephrine nor strict PAL avoidance is associated with favorable health or economic benefits.

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