

genomic DNA confirmed the presence of the mutation in all probands (see Fig E3 in this article's Online Repository at www.jacionline.org). The parents of P1 were heterozygous for the mutation. The frameshift mutation results in substitution of the Cys³⁰⁶ residue with valine, followed by 2 novel residues and a premature stop codon (Fig 1, C). The patient fibroblasts had significantly lower *NIK* mRNA levels than those of controls (Fig 1, D). Because endogenous *NIK* protein level is extremely low due to continuous degradation by TNF Receptor Associated Factor 3,² expression of an N-terminal Myc-tagged mutant *NIK* was examined in transfected HEK293T cells. Immunoblotting revealed an approximately 130-kDa band in wild-type *NIK*-transfected cells and an approximately 34-kDa band in *NIK*^{Cys306Valfs*2}-transfected cells, corresponding to the expected sizes of wild-type and mutant *NIK* (Fig 1, E). Fibroblasts from P1 stimulated with α -LT β R for 48 hours had absent p100 phosphorylation and processing (Fig 1, F). P1 fibroblasts also failed to upregulate *VCAM1* and chemokine (C-C motif) ligand 20 expression after α -LT β R stimulation but did so normally after TNF- α stimulation (Fig 1, G).

Lymphotoxin α can drive the formation of mesenteric and cervical LNs, and splenic PNA⁺ B-cell clusters independently from LT β R signaling in *LT β ^{-/-}* mice.⁸ Increased TNF- α levels can drive mesenteric LNs and organized spleen formation in the absence of LT β R.⁹ Intact lymphotoxin α and TNF- α production and signaling, which depend on the classical NF- κ B pathway, may have permitted residual lymphoid structures to form in our patient, also reflected in his lack of lymphocytosis and near-normal antigen-specific T-cell proliferation studies. Residual secondary lymphoid organs (SLOs) may have enabled donor hematopoietic cells to mount a robust adaptive immune response in our patient. As in our patient, HSCT corrects low serum IgG levels in *aly/aly* mice.³ In contrast, in patients and mice with missense mutations in *I κ B α* , disruption of both classical and noncanonical NF- κ B signaling results in both impaired TNF- α production and defective LT β R signaling, which may not allow the formation of sufficient SLOs for the development of an adaptive immune response, resulting in failure of HSCT to achieve immune reconstitution. HSCT may be useful in treating patients with *NIK* deficiency, or other deficiencies that selectively disrupt the noncanonical NF- κ B pathway, who have residual SLOs.

Khaoula Ben Farhat, PhD^{a,*}
Mohammed F. Alosaimi, MD^{a,b,*}
Hiba Shendi, MBBS^c
Suleiman Al-Hammadi, MBBS^d
Jennifer Jones, BA^a
Klaus Schwarz, MD^e
Ansgar Schulz, MD^f
Laila S. Alawdah, MBBS^g
Sandra Burchett, MD, MSc^h
Sultan Albuhairei, MDⁱ
Jennifer Whangbo, MD, PhD^h
Neha Kwatra, MBBS^j
Hanan E. Shamseldin, MSc^k
Fowzan S. Alkuraya, MD^l
Janet Chou, MD^{a,†}
Raif S. Geha, MD^{a,†}

From ^athe Division of Immunology, Boston Children's Hospital and Harvard Medical School, Boston, Mass; ^bthe Department of Pediatrics, King Saud University, Riyadh, Saudi Arabia; ^cthe Department of Allergy/Immunology, Tawam Hospital, Al Ain, United Arab Emirates; ^dthe Department of Pediatrics, College of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates; ^ethe Institute for

Transfusion Medicine, Ulm University and Institute for Clinical Transfusion Medicine and Immunogenetics Ulm, German Red Cross Blood Service Baden-Württemberg – Hessen, Ulm, Germany; ^fthe Department of Pediatrics and Adolescent Medicine, University Medical Center, Ulm, Germany; ^gthe Division of Infectious Diseases, Boston Children's Hospital, Harvard Medical School, Boston, Mass; ^hthe Division of Pediatric Hematology-Oncology, Boston Children's Hospital and the Dana Farber Cancer Institute, Boston, Mass; ⁱthe Division of Nuclear Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Mass; and ^jthe Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. E-mail: Mohammed.Alosaimi@childrens.harvard.edu.

*Equal contributing first authors.

†Equal contributing last authors.

Supported by National Institutes of Health grant 1R01AI139633-01 (R.S.G.) and 5K08AI116979-04 (J.C.) as well Perkin Fund (R.S.G.).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Sun SC. The non-canonical NF-kappaB pathway in immunity and inflammation. *Nat Rev Immunol* 2017;17:545-58.
2. van de Pavert SA, Mebius RE. New insights into the development of lymphoid tissues. *Nat Rev Immunol* 2010;10:664-74.
3. Miyawaki S, Nakamura Y, Suzuka H, Koba M, Yasumizu R, Ikehara S, et al. A new mutation, *aly*, that induces a generalized lack of lymph nodes accompanied by immunodeficiency in mice. *Eur J Immunol* 1994;24:429-34.
4. Yin L, Wu L, Wesche H, Arthur CD, White JM, Goeddel DV, et al. Defective lymphotoxin-beta receptor-induced NF-kappaB transcriptional activity in *NIK*-deficient mice. *Science* 2001;291:2162-5.
5. Petersheim D, Massaad MJ, Lee S, Scarselli A, Cancrini C, Moriya K, et al. Mechanisms of genotype-phenotype correlation in autosomal dominant anhidrotic ectodermal dysplasia with immune deficiency. *J Allergy Clin Immunol* 2018;141:1060-73.e3.
6. Willmann KL, Klaver S, Dogu F, Santos-Valente E, Garncarz W, Bilic I, et al. Biallelic loss-of-function mutation in *NIK* causes a primary immunodeficiency with multifaceted aberrant lymphoid immunity. *Nat Commun* 2014;5:5360.
7. Schlechter N, Glanzmann B, Hoal EG, Schoeman M, Petersen BS, Franke A, et al. Exome sequencing identifies a novel MAP3K14 mutation in recessive atypical combined immunodeficiency. *Front Immunol* 2017;8:1624.
8. Alimzhanov MB, Kuprash DV, Kosco-Vilbois MH, Luz A, Turetskaya RL, Tarakhovskaya A, et al. Abnormal development of secondary lymphoid tissues in lymphotoxin beta-deficient mice. *Proc Natl Acad Sci U S A* 1997;94:9302-7.
9. Furtado GC, Pacer ME, Bongers G, Benezech C, He Z, Chen L, et al. TNF α -dependent development of lymphoid tissue in the absence of ROR γ (+) lymphoid tissue inducer cells. *Mucosal Immunol* 2014;7:602-14.

Available online November 14, 2018.
<https://doi.org/10.1016/j.jaci.2018.11.003>

Cost-effectiveness of diagnostic algorithms for peanut allergy in children



To the Editor:

Peanut allergy, one of the most common food allergies globally, leads to health consequences ranging from mild to severe reactions including life-threatening anaphylaxis.^{1,2} An accurate diagnosis is paramount to prevent erroneously diagnosed peanut allergy and, consequentially, reduced quality of life among individuals who actually tolerate peanuts.³

Diagnosing peanut allergy involves diagnostic procedures including careful review of clinical reactions, peanut-specific IgE, skin prick test (SPT), and an oral peanut food challenge (FC), optimally performed using a double-blind placebo-controlled FC approach. In addition, component-resolved allergen diagnosis⁴⁻⁶ (CRD) and possibly also peanut conjunctival allergen provocation test⁷ (CAPT) may improve peanut allergy diagnosis. Testing CRD in diagnosis of peanut allergy has been found useful in assessing the likelihood of clinical allergy or cross-reactive allergic manifestations.^{4-6,8,9} The CAPT was recently shown to be feasible and of diagnostic value in peanut allergy⁷ and could potentially be

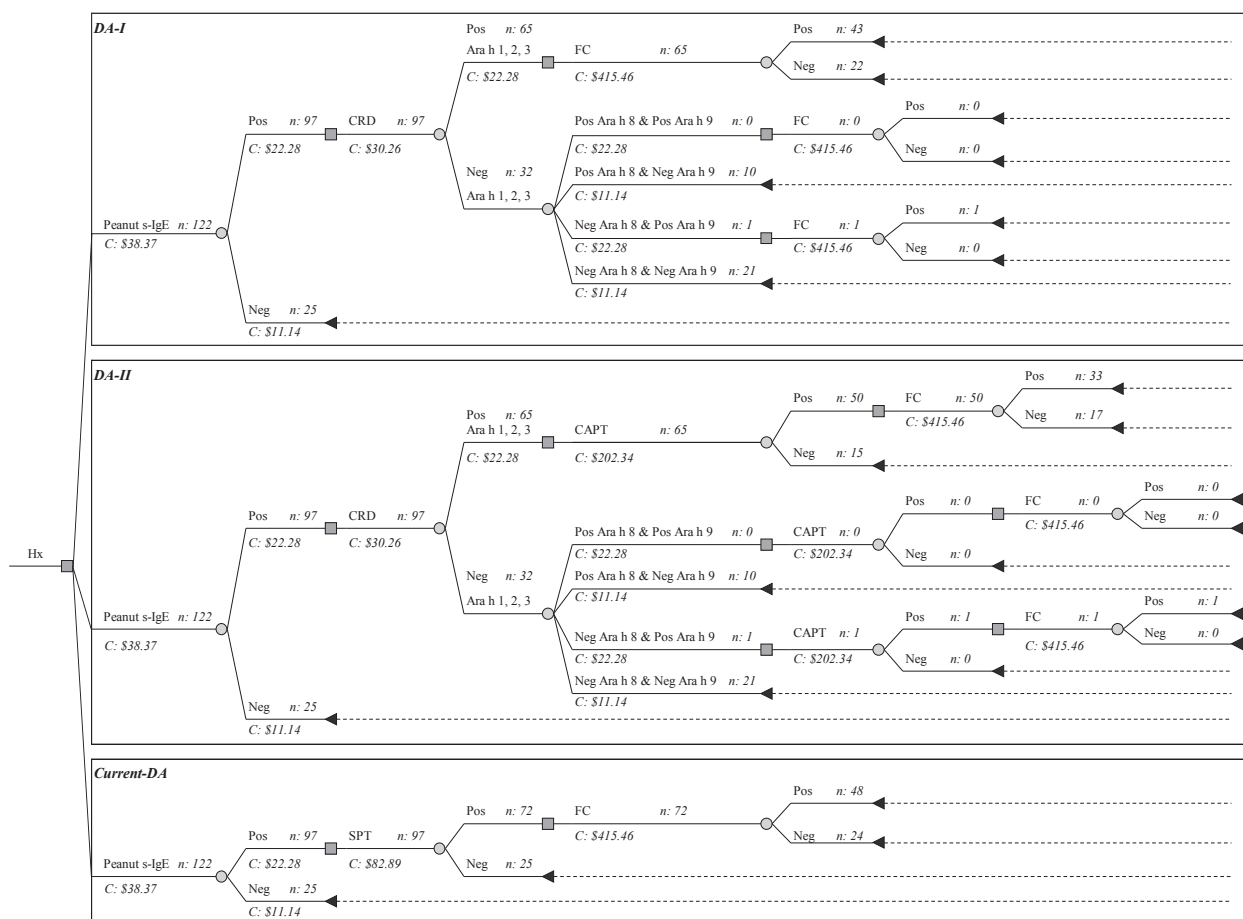


FIG 1. Decision tree. The base-case analysis excluded SPT from DA-I and DA-II (for scenario analyses including SPT incorporated in the algorithms after testing CRD, see this article's Online Repository at www.jacionline.org). The peanut CRD (Ara h 1-3, 8-9) were measured additionally to peanut s-IgE. Ara h 8 and Ara h 9 were presented separately to illustrate the proposed decision making. Some of the costs depended on the test result (different costs were assigned for a negative test result and a positive test result). Branches with Neg Ara h 1, 2, 3 were not assigned any costs because the additional costs depended on the Ara h 8 and Ara h 9 results. C, Costs of diagnostic procedures based on detailed cost breakdown; Hx, clinical reaction history; n, patient distribution moving through the diagnostic algorithms based on transition probabilities derived from the Oslo Peanut Allergy Study; Neg, negative result; Pos, positive result; s-IgE, peanut-specific IgE. Nodes: square, decision node; circle, event node; triangle, terminal node.

TABLE I. Probabilistic cost-effectiveness results

Probabilistic results	Costs (95% PPcrl)	QALYs (95% PPcrl)	ICER*
DA-I	\$1376.94 (\$1082.72-\$1621.11)	7.29 (5.41-8.07)	—
DA-II	\$1384.95 (\$1073.73-\$1635.11)	7.31 (5.37-8.08)	\$353.75
Current-DA	\$1572.14 (\$1283.76-\$1821.81)	7.22 (5.42-8.04)	Strongly dominated

PPcrl, Posterior-predicted credible interval.

*ICER presents the incremental costs per incremental QALYs associated with the particular strategy in comparison with the next more costly alternative. Strategies are categorized as weakly dominated if they result in a less favorable ICER compared with the next more effective strategy, and as strongly dominated if they lead to lower QALYs at higher costs.

a safe *in vivo* alternative to FC (for details, see this article's Online Repository at www.jacionline.org), but further clinical evaluation is still needed. Although not sufficient to replace other diagnostic methods, both CRD and CAPT may improve diagnostic accuracy.⁴⁻⁷

Several diagnostic algorithms, often including CRD, have recently been published⁶; however, there is a remarkable paucity of economic evaluation of peanut allergy diagnostic tests and

algorithms. We therefore aimed to determine the cost-effectiveness of available diagnostic algorithms and identify the strategy that provides the highest diagnostic accuracy and effectiveness at acceptable costs.

Based on the Oslo Peanut Allergy Study (OPAS) that investigated 122 children aged 4 to 18 years of whom 94 children were recruited with possible peanut allergy and 28 children were known to tolerate peanuts,⁷ we performed an economic evaluation

of diagnostic algorithms for peanut allergy (for details, see this article's Online Repository at www.jacionline.org). Our decision-analytic model compared 3 strategies for diagnosing peanut allergy using a decision tree, as outlined in Fig 1, as well as a Markov model. The decision tree helped in simulating patients' transitions through the sequences of diagnostic tests included in the proposed diagnostic algorithms and provided the proportion of patients being true positive, false positive, true negative, and false negative together with the associated costs. These cohorts of patients, distributed by the decision tree, proceeded to one of the Markov model's health states (see Fig E1 in this article's Online Repository at www.jacionline.org). The Markov model was developed to analyze the long-term outcomes of the proposed diagnostic algorithms, simulating the transitions of patients between mutually exclusive health states over 10 years. The first diagnostic algorithm (Current-DA) reflected current Norwegian clinical practice and was composed of a careful history of clinical reactions, peanut-specific IgE, SPT, and an FC. The 2 subsequent diagnostic algorithms additionally implemented CRD (DA-I) and CRD as well as CAPT (DA-II) to the sequence of diagnostic tests used in Current-DA. The SPT was excluded from DA-I and DA-II because of its minor diagnostic value in the 2 proposed algorithms (for scenario analyses showing the cost-effectiveness results when including SPT, see Table E3 in this article's Online Repository at www.jacionline.org).

The decision-analytic model measured outcomes expressed in quality-adjusted life-years (QALYs) and accounted for specific costs of each diagnostic test and health state from an extended health care perspective (for details, see Methods and Table E1 in this article's Online Repository at www.jacionline.org; for detailed cost breakdown, see Reference E14 in this article's Online Repository at www.jacionline.org). The principal result was an incremental cost-effectiveness ratio (ICER). We considered a diagnostic algorithm to be cost-effective if (1) it resulted in higher effects at the same or lower costs or (2) its ICER was beneficial compared with that of the next more effective diagnostic alternative. Diagnostic strategies were categorized as weakly dominated if their ICER was less favorable compared with the ICERs of alternatives that were more effective, and as strongly dominated if they provided lower effects at higher costs.

The Oslo Peanut Allergy Study results have been reported previously.⁷ Briefly, all 81 children with a positive FC had a positive CAPT result, and in addition 12 children had a positive CAPT result with a negative FC. Fig 1 presents the patient flow and costs of the diagnostic procedures nested within each diagnostic algorithm. Our decision-analytic model predicted DA-II to be the most cost-effective algorithm for diagnosing peanut allergy in children (ICER of \$353.75/QALY; Table I). More specifically, DA-II was superior to DA-I, whereas Current-DA led to lower QALYs at higher resource use indicating its lack of cost-effectiveness.

We performed a number of analyses to handle the uncertainty in the model. The probabilistic sensitivity analyses, performed using 5000 Monte Carlo simulations, identified DA-II to be the most cost-effective diagnostic strategy. DA-II had higher cost-effectiveness probability and net monetary benefit compared with DA-I at all willingness-to-pay thresholds above \$1000/QALY. After accounting for uncertainty, the results also concurred that Current-DA was constantly associated with lower effects and higher costs (ie, a strongly dominated strategy). We present the uncertainty in the obtained cost-effectiveness results in the form

of cost-effectiveness acceptability curves and a cost-effectiveness acceptability frontier in Fig E2 in this article's Online Repository at www.jacionline.org. We additionally conducted a number of scenario and one-way sensitivity analyses that led to similar results and presented no substantial divergence from the model's base-case results (see this article's Online Repository at www.jacionline.org).

Because an appropriate selection of patients is crucial for determining the optimal diagnostic strategy, we further analyzed the cost-effectiveness of the strategies at different prevalence levels. The results suggested that DA-II was the most cost-effective strategy in a population with a peanut allergy prevalence of at least 5% (see Fig E4 in this article's Online Repository at www.jacionline.org). The analyses projected that a more heterogeneous patient population, resulting in less than 5% of patients being diagnosed with peanut allergy, would lead to borderline cost-effective results based on the lowest willingness-to-pay threshold proposed in Norway (see Methods in this article's Online Repository at www.jacionline.org). Hence, careful selection of the patient population with suspected peanut allergy would ensure a high degree of cost-effectiveness of the diagnostic strategy.

Concluding, the decision-analytic model indicates the cost-ineffectiveness of the currently used diagnostic algorithm. Compared with DA-I and Current-DA, the diagnostic algorithm DA-II, which incorporates CRD and CAPT, appears to represent the most cost-effective strategy to diagnose peanut allergy in children. Yet, although our results indicate that CAPT⁷ may improve the cost-effectiveness of diagnosing peanut allergy, this procedure is still rarely used in clinical practice and further assessment of its clinical benefits and its possible value as a safer substitute for FC is needed.

We thank Thermo Fisher Scientific/Phadia AB for financial support to conduct the present study. We also thank Fernando Alarid-Escudero for valuable methodological discussions and input.

Natalia R. Kunst, MSc^{a,b,c,d}

Helene Lindvik, MD^e

Kai-Håkon Carlsen, MD, PhD^{e,f}

Geir Håland, MD, PhD^e

Eivind Jørgensen, MPhil^d

Karin C. Lødrup Carlsen, MD, PhD^{e,f}

From ^athe Department of Health Management and Health Economics, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway; ^bthe Department of Health Policy and Management, Yale School of Public Health, New Haven, Conn; ^cthe Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; and ^dLINK Medical Research, ^ethe Department of Paediatrics, Oslo University Hospital, and ^fthe Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. E-mail: n.r.kunst@medisin.uio.no. Or: natalia.kunst@yale.edu.

Disclosure of potential conflict of interest: The Oslo Peanut Allergy Study was funded by the South-Eastern Norway Regional Health Authority, the Kloster Foundation, and the Norwegian Asthma and Allergy Foundation. Immunologic analyses were performed at Fürst Medical Laboratory, who received relevant kits free of charge from Thermo Fisher Scientific/Phadia AB. N. R. Kunst and E. Jørgensen received financial support from Thermo Fisher Scientific/Phadia AB through LINK Medical Research. N. R. Kunst's PhD position was funded by the Research Council of Norway (276146) and LINK Medical Research. Two employees of Thermo Fisher Scientific/Phadia AB attended 2 discussion meetings with the authors and provided brief feedback on the content of the article. N. R. Kunst had full access to the data set and was responsible for developing and analyzing the decision-analytic model. H. Lindvik was responsible for all clinical data collection. H. Lindvik, K.-H. Carlsen, G. Håland, and K. C. L. Carlsen had full access to all clinical data analyses and declare no conflict of interest for the analyses beyond the contribution by Thermo Fisher Scientific/Phadia AB for immunologic analyses, as stated above.

REFERENCES

1. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-9.
2. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
3. Roy KM, Roberts MC. Peanut allergy in children: relationships to health-related quality of life, anxiety, and parental stress. *Clin Pediatr (Phila)* 2011;50:1045-51.
4. Kattan JD, Wang J. Allergen component testing for food allergy: ready for prime time? *Curr Allergy Asthma Rep* 2013;13:58-63.
5. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016;27:1-250.
6. Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. *Clin Exp Allergy* 2017;47:719-39.
7. Lindvik H, Lodrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy* 2017;47:785-94.
8. Moverare R, Ahlstedt S, Bengtsson U, Borres MP, van Hage M, Poorafshar M, et al. Evaluation of IgE antibodies to recombinant peanut allergens in patients with reported reactions to peanut. *Int Arch Allergy Immunol* 2011;156:282-90.
9. Asarnoj A, Nilsson C, Lidholm J, Glaumann S, Ostblom E, Hedlin G, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol* 2012;130:468-72.

Available online November 14, 2018.
<https://doi.org/10.1016/j.jaci.2018.10.050>

Ordinary vibratory angioedema is not generally associated with ADGRE2 mutation



To the Editor:

We report on the prevalence and pathogenesis of vibratory angioedema, an under-investigated subtype of inducible urticaria, first described as an occupational disease in which patients working with a pneumatic hammer had severe swelling of the whole arm, but later also as sporadic cases in occupations in which only mild vibrations occur, for example, in a saxophonist and trumpet player,^{1,2} or following everyday vibratory stimuli such as riding a bicycle over cobblestone pavement. Regarding the prevalence and pathogenesis, little is known but recently a mutation with missense substitution in *ADGRE2* was described in an affected family.³ To better understand the condition, we studied a representative group of 91 medical students in China and 81 in Germany (all undergoing a lecture on dermatology in a compulsory course at the university). They received a 3-minute introduction about the disease and a questionnaire (see Fig E3 in this article's Online Repository at www.jacionline.org) asking whether pruritus or swelling occurred during everyday vibrations (such as riding by bicycle or motorcycle on cobblestone pavement). All study subjects responding positively in the questionnaire (7 in China, 18 in Germany) were asked to participate in a provocation test using a vortex. In China 5 and in Germany 9 of those asked agreed. In addition, 6 healthy controls in Germany and 7 healthy controls in China were included.

For provocation, 1 palm was put on the vortex for 5 minutes as described in Zuberbier et al.^{4,5}

The differential diagnosis symptomatic dermatographism was excluded by using sheering forces according to the guideline.⁵

A blood sample was taken for the measurement of serum-histamine content from the draining vein before (0) and at 5, 15, and 30 minutes after the vortex provocation. Palm thickness was measured with vernier caliper at the thickest part of the palm before and after provocation. Three of the 5 Chinese patients who showed positive symptoms on the provocation test in addition were checked for a mutation in *ADGRE2* (see this article's [Methods](#) section in the Online Repository at www.jacionline.org).

Eighty-one participants in Germany with the mean age of 24 years (range, 22-37 years) were evaluated; 22.2% of the participants of the questionnaire stated to have symptoms in the palms after vibratory stimuli. The main symptoms were pruritus (100%), wheals (16.7%), and angioedema (5.6%). Women were more frequently (2:1) having a positive anamnesis of vibratory angioedema/pruritus than did men.

Of the 91 participants in China (mean age, 27.2 years), 7 study participants (7.7%) reported symptoms of vibratory angioedema, including erythema and pruritus (100%). Further clinical reactions were angioedema of the hand (33.3%) and wheals (22.2%). In China, the male/female ratio was 1:6. In all subjects (Germany: 6 males, 12 females; China: 1 male, 6 females) with a positive anamnesis, symptoms could be reproduced in objective testing with a vortex.

Dermographism was only red but not urticarial after applying a sheering force in all. Fig E1 in this article's Online Repository at www.jacionline.org shows the swelling of hands after the provocation test and the administration of visual analogue scale in the Chinese group.

Study participants ($n = 3$) with vibratory angioedema showed a significant ($P = .001$) increase in serum-histamine content after provocation in contrast to the control group without anamnestic vibratory angioedema both in China and in Germany (see Fig E2 in this article's Online Repository at www.jacionline.org) with a rapid time course (Fig 1, B) indicating clearly a mast cell involvement.

Fig 1 shows the time course of increased levels of histamine after provocation. The testing with the vortex showed a positive result in all participants who had mentioned a history of vibratory angioedema/pruritus. Those exhibiting worst symptoms (total 5 persons) were checked for the mutation in *ADGRE2*; however, the mutation in *ADGRE2* described recently could not be detected.

The study was conducted to also better understand the frequency of mild forms, which may not necessarily lead to a visit to the dermatologist's office because the eliciting stimulus can be easily avoided and to understand whether the recently detected *ADGRE2* mutation causing familial vibratory angioedema was also relevant for nonfamilial forms.

With an overall prevalence of more than 14.4% in the group of young adults tested in this study, it is clear that vibratory angioedema/pruritus is an underdiagnosed entity.

Like in other subtypes of inducible urticaria, for example, cholinergic urticaria, different forms of severity appear to occur.^{6,7}

Although in some patients only pruritus and mild erythema occurred, in others wheals and/or angioedema are signs of a more pronounced mast cell degranulation, and vibratory urticaria can have a high impact on quality of life in general and be an impairment in work.

For diagnosis, patient history is of highest importance. In all subjects claiming to have symptoms in the questionnaire,

II. Methods

A. Clinical study design

Written informed consent was obtained from all parents as well as from all children 12 years and older. The OPAS study was approved by the Regional Ethical Committee for South-East Norway (2010/2362), and registered by the Norwegian Biobank register (reference number 2010/2362a).

Details of the investigations have been previously reported^{E1} but briefly outlined in here. Study investigations included parental structured interviews, clinical examination, SPT, blood sampling for s-IgE to peanut and other common inhalant and food allergens, CAPT, and lung function tests during the first visit. Children with possible peanut allergy had subsequently a two-day randomized peanut double-blind placebo-controlled food challenge (DBPCFC). Controls, on the other hand, underwent an open peanut FC included in their one-day evaluation. The FCs were performed double-blinded using the recipe developed by van Odijk et al.,^{E2} starting with 3 mg peanut and increasing the dose to 10 mg, 30 mg, 100 mg, 300 mg, 1 g, and 5 g of peanuts in chocolate balls. The placebo doses were the same amount of chocolate balls without peanut. The open peanut FC consisted of one dose of 8 peanuts.

Sera drawn on the first investigative day were analyzed for total IgE, s-IgE to peanut and birch, and s-IgE to peanut and birch allergen components using the UniCAP fluoroenzyme immunoassay (FEIA) according to the manufacturer's instructions (Thermo Fisher, Uppsala, Sweden) and reported quantitatively in kU/l. The lower detection level was 0.10 kU/l, and a positive result was defined as ≥ 0.35 kU/l.

The SPTs were performed according to European standards^{E3} with Soluprick[®] allergens (ALK Abello, Denmark) for all tested allergens. A positive SPT result was defined as a wheal with a diameter (i.e., mean of longest and the midpoint orthogonal diameter) ≥ 3 mm larger than the negative control. Histamine dihydrochloride in dose of 10 mg/mL (ALK Abello, Denmark) served as positive control and NaCl 0.9% as negative control.

The peanut conjunctival allergen provocation test has been described in detail elsewhere^{E1} but is briefly summarized here for completeness. The provocation test was performed double-blinded with commercially available peanut extract from GREER[®] (Greer Laboratories, Lenoir, DC) in NaCl 0.9% without preservatives. Prior to each test, the solution was prepared into vials containing NaCl 0.9 % (placebo) and peanut concentrations of 1:80, 1:40, 1:20, 1:10, and 1:1. One test drop was randomly assigned to either right or left lower conjunctival pouch at every test step, with 30 minutes between each step. The test was considered positive in case of two or more signs of redness, itching, chemosis, and tearing observed within 30 minutes.

A positive peanut FC was defined as occurrence of any of the following objective symptoms: rhinitis, conjunctivitis, upper or lower airway obstruction, cough, dyspnea, urticaria, angioedema, stomach cramping, vomiting, diarrhea, or hypotension. Clinical peanut allergy was defined as having a positive peanut FC. Anaphylaxis was defined according to the position paper^{E3} from the European Academy of Allergy and Clinical Immunology (EAACI).

B. Model overview

The model framework was designed relying on the common clinical practice, aiming at primary healthcare and subsequently at specialist care in line with Norwegian national reimbursement

policies, and on a literature search. While most health economic evaluations assess a single health technology, we aimed to simultaneously evaluate and compare three different sequences of diagnostic tests, incorporating the two introduced health technologies, i.e., CRD and CAPT, into the currently established diagnostic algorithm in Norway.

The mathematical model, developed in Microsoft Excel 2013, comprised a decision tree and a Markov model. The model's design and its assumptions were decided upon based on the national and international guidelines for performing model-based economic evaluations.^{E4-7}

The decision tree was built using data from the OPAS study. Patients distributed by the decision tree proceeded to one of the Markov model's health states (see Fig E1). The Markov model helped analyzing the long-term outcomes of the diagnostic algorithms and included four main health states, i.e., Allergy True Positives, Allergy False Positives, No Allergy True Negatives, and No Allergy False Negatives. The analyzed cohort either remained in one of the main health states or transitioned to one of the temporary health states included in the model. Three health states, i.e., Allergy False Positives, No Allergy True Negatives, and Death, were “absorbing,” meaning that once an individual moved into one of these states, there was no possibility of transiting to another state. The rest of the health states were so-called temporary states allowing patients to remain there only for one cycle. The model's temporary states included experiencing minor or major allergic reactions and undergoing diagnostics again. The model also distinguished newly diagnosed Allergy True Positives and Allergy False Positives by using temporary states in order to capture the costs occurring directly after making the diagnosis. Table E1 outlines the selected assumptions of the model.

Our literature search retrieved few sources of occurrence estimates of minor and major allergic reactions, needed for the calculation of the transition probabilities. Gupta et al.^{E8} estimated a 0.012% probability of major allergic reactions based on children's hospital admissions caused by allergic reactions. Fajt and Green^{E9} provided a 14.00% proportion estimate of individuals diagnosed with allergy who experience allergic reactions due to being insufficiently cautious when exposed to the allergen. The provided estimate concerned diagnosed individuals, and we expected persons without the diagnosis to be less cautious. Yet, we employed this probability for all allergic individuals regardless of whether they were diagnosed or not. This conservative assumption was made because of the lack of published sources supporting our anticipation. We performed several scenario analyses applying increased and decreased values of this parameter to account for the uncertainty. The model also incorporated a 0.00012% probability of fatal reactions taken from Hourihane^{E10} and mortality in the general Norwegian population from Statistics Norway.^{E11} Importantly, most of these sources were previously utilized in the health economic analysis of peanut allergy diagnostics conducted in the National Institute for Health and Care Excellence (GB) and Centre for Clinical Practice^{E12} clinical guideline.

Our model assumed that each misdiagnosed patient in the health state No Allergy False Negatives who experienced a severe allergic reaction underwent diagnostic algorithm again. However, this assumption was considered as not applicable for persons experiencing a minor reaction. We expected only some of the false-negative individuals experiencing a minor reaction to be referred to diagnostics. To our knowledge, there is no published data on the proportion of these individuals being examined again. The expert board concluded that a conservative assumption of 20% should be taken in the base-case analysis. To address the uncertainty in this estimate, we performed scenario analyses assuming the value of 0%, 50%, and 100%.

The expert board estimated that DBPCFC and open peanut FC were performed in approx. 10% and 90% of patients referred to FC, respectively. Occurrences of anaphylaxis and severe reactions among patients referred to a FC were approximated to 1% and 5%, respectively. These estimates were used further to approximate the proportion of anaphylaxis cases among the misdiagnosed individuals in the health state No Allergy False Negatives experiencing severe reactions.

C. Costs

The expert board discussed and specified the components of the diagnostic tests considered in the model and associated resource use. Where possible, the unit costs of components were assembled from the OPAS study. Similarly, we identified the breakdown of costs related to the health states based on the opinion of the expert board and the literature search. The breakdown of costs, which primarily comprised the cost of drugs, medical consumer goods, and required personnel, was estimated using unit costs taken from the Norwegian cost sources in 2017. All costs were collected in Norwegian Krone (NOK) 2017 and converted to US Dollars (\$) using the rate \$1=NOK8.2630.^{E13} Unit costs retrieved from earlier years were inflated to 2017 by using Norwegian Consumer Price Index. The detailed breakdown of costs is provided in the online supplementary materials at

https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.^{E14}

Although the decision-analytic model took into account both direct and indirect costs, we, in line with Norwegian recommendations,^{E15-17} chose the extended health care perspective including travel costs.^{E17} The main costs utilized in the analysis are summarized in Table E1.^{E14}

D. Outcomes

The estimates provided by Protudjer et al.^{E18} for presence and absence of food allergy, and by Peterson et al.^{E19} for utility decrements due to allergic reactions, were assessed as the most appropriate sources for the present analysis. The estimates provided by Voordouw et al.,^{E20} Mittmann et al.,^{E21} Armstrong et al.,^{E22} and National Institute for Health and Care Excellence (GB) and Centre for Clinical Practice^{E12} were also incorporated in the model and used in scenario analyses. Details on the model assumptions regarding the utility weights are available in the online supplementary materials at https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.^{E14}

E. Other model parameters

The prevalence of peanut allergy in the population undergoing diagnostic procedures can have a significant impact on the results of the decision-analytic model. The patient population considered in the analysis included individuals with suspected peanut allergy, and the base-case prevalence of 65% was taken from the OPAS study.

The decision-analytic model employed a cycle length of three months and a time horizon of 10 years to capture all the costs and benefits resulting from the investigated diagnostic algorithms. In line with Norwegian recommendations,^{E15} the base-case analysis applied an annual discount rate of 4% for the costs and outcomes. We performed several scenario analyses on these assumptions (see Table E3).

F. Analyses

The principal result of our model-based economic evaluation was an ICER, estimating the incremental costs needed to obtain an additional QALY when compared with the next more costly alternative. The decision-analytic model examined results for costs and QALYs associated with each particular diagnostic strategy, used in calculation of ICERs.

The analysis helped in estimating deterministic and probabilistic results for incremental costs, incremental QALYs and ICERs. We performed probabilistic sensitivity analyses, one-way sensitivity analyses and a number of scenario analyses to address and examine uncertainty in the decision-analytic model, in line with the literature.^{E5,E23,E24} To handle the uncertainty in the analysis, probabilistic sensitivity analyses were conducted using 5,000 iterations, by assigning probability distributions to all of the relevant parameters of the analysis. We chose the appropriate distributions based on the recommendations in the literature.^{E5} The main parameters and their distributions are outlined in Table E1 (more detailed information can be found in the online supplementary materials at https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c^{E14}). The main probabilistic results are presented graphically as cost-effectiveness acceptability curves and a cost-effectiveness acceptability frontier^{E23,E25} evaluating the three diagnostic algorithms at once. At a range of willingness-to-pay thresholds, the cost-effectiveness acceptability curves presented the probability of each diagnostic strategy to have the greatest net monetary benefit and the cost-effectiveness acceptability frontier indicated the probability that the strategy providing the greatest net monetary benefit was cost-effective, determining the optimal strategy.

We investigated the extent to which the uncertainty in individual parameters affected the deterministic ICERs by conducting a one-way sensitivity analysis. The one-way sensitivity analysis varied substantially ($\pm 30\%$) the base-case value of the parameters to examine their impact on the ICER. We also performed a number of scenario analyses by changing several distinct values. Finally, we conducted deterministic and probabilistic analyses investigating ICER results for different prevalence levels in the tested population.

III. Results

The results of the OPAS study have been reported previously.^{E1} Briefly, the 94 children (58.5% boys) with suspected peanut allergy were slightly younger than the controls (32.1% boys; mean age [min, max] of 9.9 [4.9 – 18.6] versus 10.5 [5.6 – 14.9] years, respectively). The FC was positive in 86% of the children with suspected peanut allergy and in none of the controls. The CAPT was positive in 98% of the suspected peanut allergic children as well as in 1 (4%) control child, who was allergic to birch pollen. None of the children with a negative CAPT had a positive FC. A positive SPT for peanut was observed in 94.1% of the patients and in 1 control child.

Of the three algorithms, the results of the decision-analytic model identified the diagnostic algorithm DA-II, incorporating CRD and CAPT, as the most cost-effective diagnostic strategy in Norway. The analysis provided a deterministic ICER for DA-II of \$316.04, which is considerably lower than the lowest willingness-to-pay threshold per QALY proposed in Norway (\$33,800^{E26}). The model indicated that Current-DA was strongly dominated giving its higher costs and lower effects. Because choosing DA-II rather than DA-I led to higher benefits at slightly higher resource use, the results projected DA-II to be the most cost-effective diagnostic algorithm.

The probabilistic results, in line with the deterministic results, predicted DA-II to represent the most cost-effective diagnostic strategy with a low ICER of \$353.75 (see Table I). Table E2 presents the detailed probabilistic results for costs and QALYs.

The cost-effectiveness acceptability curves and frontier predicted that at a willingness-to-pay threshold below \$1,000, DA-I would be deemed as the optimal strategy (see Fig E2). When the

willingness to pay exceeded \$1,000, irrespective of its level, DA-II would represent the most cost-effective diagnostic strategy because of its continuously highest net monetary benefit as well as highest probability of cost-effectiveness. After accounting for the uncertainty, the results concurred that Current-DA was not a cost-effective strategy. Despite the minor differences between DA-I and DA-II, the probabilistic sensitivity analyses, conducted with 5,000 iterations, predicted DA-II to be the most cost-effective diagnostic strategy, taking as the basis the lowest indicated willingness-to-pay threshold in Norway.

The degree of cost-effectiveness of the interventions improved with increasing peanut allergy prevalence in the tested population. Provided a minimum peanut allergy prevalence of 5%, the prevalence analysis for DA-II compared with DA-I predicted the former to represent a favorable cost-effective strategy regardless of the prevalence level (see Fig E4). However, low prevalence in the tested population resulted in a higher ICER that was closer to the lowest willingness-to-pay threshold proposed in Norway. None of the scenario analyses resulted in an ICER above this willingness-to-pay threshold. Results of the prevalence analyses, scenario analyses, and one-way sensitivity analysis are presented in Fig E4, Table E3 and Fig E5, respectively. The detailed results are available in the online supplementary materials at

https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.^{E14}

As the clinical benefit of CAPT in diagnosis of peanut allergy requires further assessment, we conducted a secondary analysis comparing DA-I with Current-DA. The results, both probabilistic and deterministic, indicated that DA-I was associated with higher QALYs at lower resource use, dominating Current-DA. The cost-effectiveness acceptability curve for this comparison presented an approximately 90% probability of DA-I representing the cost-effective diagnostic strategy

compared with Current-DA (see Fig E6). The probabilistic prevalence analyses for DA-I vs. Current-DA are presented in Fig E7.

Our analysis has several limitations. The development of a decision-analytic model involved a great number of parameters and assumptions, generating some degree of uncertainty. The literature regarding some of the parameters needed for our model was scarce. We estimated the values of these parameters based on clinicians' opinions that were expressed during the expert board meetings. Although this source provided the best available knowledge and reflected Norwegian practice, it could generate uncertainty in the analysis. To address the uncertainty in the estimates, we conducted several scenario analyses, in addition to varying the parameters' values in the probabilistic sensitivity analyses. No significant divergence from the base-case results was observed, indicating that the results provided by the decision-analytic model were insensitive to the assumptions. Another potential limitation of the present study was linked to the utility values incorporated in the analysis. We were unable to identify studies reporting health-related quality of life associated with peanut allergy that could be utilized in an economic evaluation (i.e., transformable to QALY). A few studies that were conducted within this area concern health-related quality of life for food allergy in general. For the purpose of our analysis, we used a recent study investigating the utility values in the Swedish child population provided by Protudjer et al.^{E18} focusing on allergies to milk, egg, and/or wheat. Importantly, 42.4% of the children were also allergic to peanuts, supporting the applicability to the present study. Data on utility decrements due to allergic reactions were also scarce. As the base case, we chose the estimates provided by Peterson et al.^{E19} on utility decrements due to allergic reactions induced by drugs, varying in severity. We dealt with the potential uncertainty generated by these assumptions by performing probabilistic sensitivity analyses. We further addressed this weakness by

conducting scenario analyses using other sources for these parameters. The obtained results were consistent with the base-case results. Lastly, we built the decision-analytic model upon a clinical study that included children highly suspected with peanut allergy. While this patient population was assessed as the most relevant, we conducted additional analyses varying the prevalence in the tested population. Still, the type of clinical data utilized in the analysis should be considered when interpreting the results.

IV. References

- E1. Lindvik H, Lodrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy* 2017;47:785-94.
- E2. van Odijk J, Ahlstedt S, Bengtsson U, Borres MP, Hulthen L. Double-blind placebo-controlled challenges for peanut allergy the efficiency of blinding procedures and the allergenic activity of peanut availability in the recipes. *Allergy* 2005;60:602-5.
- E3. Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48:48-82.
- E4. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, G.L. S. Methods for the economic evaluation of health care programmes. Third ed. Oxford: Oxford University Press; 2005.
- E5. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
- E6. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices-overview: A report of the ISPOR-SMDM modeling good research practices task force-1. *Med Decis Making* 2012;32:667-77.
- E7. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force-2. *Med Decis Making* 2012;32:678-89.
- E8. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: Secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-6.
- E9. Fajt M, Green T. Update on peanut allergy in children. *Ped Health* 2008;2:367-76.
- E10. Hourihane J. Are the dangers of childhood food allergy exaggerated? *Br Med J (Clin Res Ed)* 2006;333:496-8.
- E11. Life tables. Statistics Norway, 2016. Nov. 15, 2017.
(<http://statbank.ssb.no/en/befolkning/statistikker/dode/aar/2017-03-09?fane=tabell#content>.)
- E12. National Institute for Health and Care Excellence (GB), Centre for Clinical Practice. Food allergy in children and young people: Diagnosis and assessment of food allergy in children and young people in primary care and community settings. NICE Clinical Guidelines. Feb. 2011. Report No.: 116.

- E13. Average exchange rates 2017. Central Bank of Norway, 2017. Oct. 1, 2017
(http://www.norges-bank.no/en/Statistics/exchange_rates/currency/USD.)
- E14. Supplementary material accompanying the manuscript: Cost-effectiveness of diagnostic algorithms for peanut allergy in children. 2018. July 23, 2018.
(https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.)
- E15. Norwegian Ministry of Health and Care Services. Principles for priority setting in health care: Summary of a white paper on priority setting in the Norwegian health care sector. 2016:19-20.
- E16. Norwegian Medicines Agency. Guidelines on how to conduct pharmacoeconomic analyses. 2012. July 23, 2018.
(<https://legemiddelverket.no/Documents/English/Price%20and%20reimbursement/Application%20for%20reimbursement/Pharmacoeconomic%20guidelines%20-%20Norway.pdf>.)
- E17. Norwegian Medicines Agency. Guidelines for Health Technology Assessment of pharmaceuticals. [Retningslinjer for dokumentasjonsgrunnlag for hurtig metodevurdering av legemidler]. 2018. Dec. 4, 2018.
(<https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Dokumentasjon%20til%20metodevurdering/Retningslinjer%20151018.pdf>.)
- E18. Protudjer JLP, Jansson SA, Ostblom E, Arnlinde MH, Bengtsson U, Dahlen SE, et al. Health-related quality of life in children with objectively diagnosed staple food allergy assessed with a disease-specific questionnaire. *Acta Paediatr* 2015;104:1047-54.
- E19. Peterson G, Tenni P, Jackson S, Bereznicki L, Hughes J, Kong D, et al. Documenting clinical interventions in community pharmacy: PROMISE III. Canberra: Australian Government, Department of Health and Aging. 2009.
- E20. Voordouw J, Fox M, Cornelisse-Vermaat J, Antonides G, Mugford M, Frewer L. Household costs associated with food allergy: An exploratory study. *Br Food J* 2010;112:1205-15.
- E21. Mittmann N, Trakas K, Risebrough N, Liu BA. Utility scores for chronic conditions in a community-dwelling population. *Pharmacoeconomics* 1999;15:369-76.
- E22. Armstrong N, Wolff R, van Mastrigt G, Martinez N, Hernandez AV, Misso K, et al. A systematic review and cost-effectiveness analysis of specialist services and adrenaline auto-injectors in anaphylaxis. *Health Technol Assess* 2013;17:1-117.

- E23. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making* 2012;32:722-32.
- E24. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17:479-500.
- E25. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health* 2008;11:886-97.
- E26. Severity of illness and priority setting in Norway. Summary of a report from a working group appointed by Ministry of Health and Care Services. Norwegian Ministry of Health and Care Services, 2015. Feb. 1, 2018. (<https://www.regjeringen.no/en/dokumenter/severity-of-illness-and-priority-setting-in-norway/id2460080/>.)
- E27. van der Valk JPM, Gerth van Wijk R, Dubois AEJ, de Groot H, Reitsma M, Vlieg-Boerstra B, et al. Multicentre double-blind placebo-controlled food challenge study in children sensitised to cashew nut. *PLoS One* 2016;11:e0151055.

Table E1. Selected model inputs used in the base-case analysis

General	Base Case	95% PI	Distribution	Source
Discount rate*	0.04	0.03 - 0.05	Beta	E15
Probability of minor reaction†	0.037	0.030 - 0.044	Beta	E9
Probability of severe reaction†	0.0000295	2.37E-05 - 3.53E-05	Beta	E8
Probability of fatal reaction†	0.0000003	2.41E-07 - 3.59E-07	Beta	E10
Utilities	Base Case	95% PI	Distribution	Source
Allergy	0.84	0.68 - 1.00	Beta	E18
No Allergy	0.94	0.76 - 1.00	Beta	E18
Utility decrement: Minor reaction†‡	0.0027	0.0021 - 0.0032	Gamma	E19
Utility decrement: Severe reaction†	0.0144	0.0116 - 0.0171	Gamma	E19
Utility decrement: Anaphylaxis†	0.1122	0.0903 - 0.1342	Gamma	E19
Duration: Minor reaction§	1.5	1.2 - 1.8	Gamma	E19
Duration: Severe reaction§	3.8	3.1 - 4.6	Gamma	E19
Duration: Anaphylaxis§	10.2	8.2 - 12.3	Gamma	E19
Accumulated costs of health states	Base Case	95% PI	Distribution	Source
Allergy TP and FP†	\$59.37	\$47.73 - \$71.01	Gamma	CBD
Newly Diagnosed ATP and AFP†	\$157.50	\$126.63 - \$188.37	Gamma	CBD
Minor Reaction: ATP¶	\$110.39	\$88.75 - \$132.03	Gamma	CBD
Minor Reaction: NAFN	\$51.02	\$41.02 - \$61.02	Gamma	CBD
Major Reaction: Severe reaction ATP¶#	\$1,116.13	\$897.37 - \$1,334.89	Gamma	CBD
Major Reaction: Severe reaction NAFN#	\$1,056.77	\$849.64 - \$1,263.90	Gamma	CBD
Major Reaction: Anaphylaxis ATP¶**	\$2,181.33	\$1,753.80 - \$2,608.87	Gamma	CBD
Major Reaction: Anaphylaxis NAFN**	\$2,105.83	\$1,693.09 - \$2,518.57	Gamma	CBD

Accumulated costs of diagnostic algorithms 	Base Case	95% PI	Distribution	Source
DA-I: Positives	\$190.78	\$153.39 - \$228.17	Dirichlet††	DT/CBD
DA-I: Negatives	\$133.44	\$107.29 - \$159.59	Dirichlet††	DT/CBD
DA-I: Total	\$324.22	\$260.67 - \$387.77	Dirichlet††	DT/CBD
DA-II: Positives	\$201.10	\$161.68 - \$240.52	Dirichlet††	DT/CBD
DA-II: Negatives	\$179.43	\$144.26 - \$214.60	Dirichlet††	DT/CBD
DA-II: Total	\$380.53	\$305.95 - \$455.11	Dirichlet††	DT/CBD
Current-DA: Positives	\$220.38	\$177.19 - \$263.57	Dirichlet††	DT/CBD
Current-DA: Negatives	\$150.89	\$121.32 - \$180.46	Dirichlet††	DT/CBD
Current-DA: Total	\$371.27	\$298.50 - \$444.04	Dirichlet††	DT/CBD
Costs of diagnostic procedures	Base Case	95% PI	Distribution	Source
Specific IgE to peanuts				
Peanut specific IgE test	\$38.37	\$30.84 - \$45.90	Gamma	CBD
Additional cost if NR	\$11.14	\$8.96 - \$13.32	Gamma	CBD
Additional cost if PR	\$22.28	\$17.91 - \$26.65	Gamma	CBD
Specific IgE to allergen components				
Specific IgE to one allergen component	\$6.05	\$4.85 - \$7.25	Gamma	CBD
Additional cost if NR	\$11.14	\$8.96 - \$13.32	Gamma	CBD
Additional cost if PR	\$22.28	\$17.91 - \$26.65	Gamma	CBD
Skin prick test				
SPT	\$82.89	\$66.64 - \$99.14	Gamma	CBD
Additional cost if NR	\$11.14	\$8.96 - \$13.32	Gamma	CBD
Additional cost if PR	\$22.28	\$17.91 - \$26.65	Gamma	CBD
Conjunctival provocation test				

Total cost of CAPT	\$202.34	\$162.69 - \$241.99	Gamma	CBD
Oral food challenge				
DBFC - cost of test performance	\$658.31	\$529.28 - \$787.34	Gamma	CBD
OFC - cost of test performance	\$358.81	\$288.49 - \$429.13	Gamma	CBD
Additional cost to FC if no severe reactions	\$24.98	\$20.08 - \$29.88	Gamma	CBD
Additional cost to FC if severe reaction†	\$383.17	\$308.06 - \$458.28	Gamma	CBD

AFP, Allergy False Positives; *ATP*, Allergy True Positives; *DBFC*, double-blind food challenge; *CAPT*, peanut conjunctival allergen provocation test; *CBD*, cost breakdown; *CRD*, component-resolved allergen diagnosis, *Current-DA*, current diagnostic algorithm; *DA-I*, diagnostic strategy incorporating CRD into the current algorithm; *DA-II*, diagnostic strategy incorporating CRD and CAPT into the current algorithm; *DT*, decision tree; *FC*, oral food challenge; *FP*, false positives; *NAFN*, No Allergy False Negatives; *Negatives*, true and false negatives; *NR*, negative test result; *OFC*, open food challenge; *PI*, prediction interval; *Positives*, true and false positives; *PR*, positive test result; *SPT*, skin prick test; *TP*, true positives.

*The discount rates for costs and utilities were varied separately.

†Unit per three months.

‡Utility decrement due to a minor reaction was utilized only for false negatives. For diagnosed patients (i.e., true positives), this decrement was assumed to be captured in the allergy utilities.

§Unit in days.

||Detailed breakdown of costs is provided in the online supplementary materials at

https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.

¶Including the 3-month costs of having food allergy.

#Severe reaction not requiring inpatient hospitalization.

**Severe reaction requiring inpatient hospitalization.

††The total costs of diagnostic tests were obtained from DT and therefore varied using the Dirichlet distribution. All unit costs were assigned the Gamma distribution.

Table E2. Detailed probabilistic cost-effectiveness results

Probabilistic results	Diagnosed with Allergy*		No Allergy†	
	Costs	QALYs	Costs	QALYs
	(95% PPCrI)	(95% PPCrI)	(95% PPCrI)	(95% PPCrI)
DA-I	\$1,219.33	3.76	\$157.61	3.53
	(\$908.43 – \$1,470.58)	(2.48 – 4.53)	(\$123.02 – \$187.15)	(1.92 – 4.22)
DA-II	\$1,187.90	3.58	\$197.05	3.73
	(\$855.94 – \$1,446.90)	(2.27 – 4.36)	(\$152.03 – \$236.42)	(2.05 – 4.49)
Current-DA	\$1,434.10	4.34	\$138.04	2.88
	(\$1,144.32 – \$1,681.80)	(2.88 – 5.04)	(\$109.54 – \$164.41)	(1.58 – 3.32)

Current-DA, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *PPCrI*, posterior-predicted credible interval; *QALY*, quality-adjusted life-year .

**Diagnosed with Allergy* includes true positives and false positives.

†*No Allergy* includes true negatives and false negatives.

Table E3. Scenario analyses for DA-II vs. DA-I in the time horizon of 10 years

Scenario analysis		ICER
1	Deterministic base-case result	\$316.04
2	SPT included in DA-I and DA-II	-\$661.18*
3	Societal perspective†	\$4,831.94
4	SPT included in DA-I and DA-II and societal perspective†	\$1,559.02
5	Percentage having anaphylaxis under FC based on van der Valk et al. ^{E27}	-\$3,265.69*
6	Proportion having different types of FC: 50% DBFC 50% OFC	-\$371.77*
7	Proportion having different types of FC: 90% DBFC 10% OFC	-\$1,059.58*
8	Proportion of FN with minor reaction undergoing diagnostics again: 50%	\$442.70
9	Proportion of FN with minor reaction undergoing diagnostics again: 0%	\$199.99
10	Proportion of FN with minor reaction undergoing diagnostics again: 100%	\$568.71
11	Probability of minor reactions (ALL‡) per year: Doubled (28%)	\$395.17
12	Probability of minor reactions (ALL‡) per year: None (0%)	\$199.31
13	Probability of minor reactions: Difference between HS Allergy and No Allergy 50%	\$390.36
14	Probability of minor reactions: Difference between HS Allergy and No Allergy 100%	\$454.48
15	Probability of severe reactions per year: Doubled (0.024%)	\$316.32
16	Probability of severe reactions per year: None (0%)	\$315.77
17	Probability of severe reactions per year: Alike minor reactions (14%)	-\$55.99*
18	Utility weights based on Voordouw et al. ^{E20}	\$376.48
19	Utility weights based on Mittmann et al. ^{E21}	\$794.00
20	Utility decrement based on Armstrong et al. ^{E22}	\$315.01

21	Utility decrement based on National Institute for Health and Care Excellence (GB) and Centre for Clinical Practice ^{E12}	\$315.01
----	--	----------

DBFC, double-blind food challenge; *FC*, oral food challenge; *FN*, false negatives; *HS*, health states; *ICER*, incremental cost-effectiveness ratio; *OFC*, open food challenge; *SPT*, skin prick test.

*Details on societal perspective are provided in the online supplementary materials at https://osf.io/grp3d/?view_only=9eb9ff5f31aa41438b8d96b2c2a2610c.

†Changing the estimate provided by Gupta et al.,^{E8} which considered all individuals with peanut allergy without distinguishing between diagnosed and misdiagnosed patients.

‡DA-II led to higher QALYs and lower costs and thus dominated DA-I.

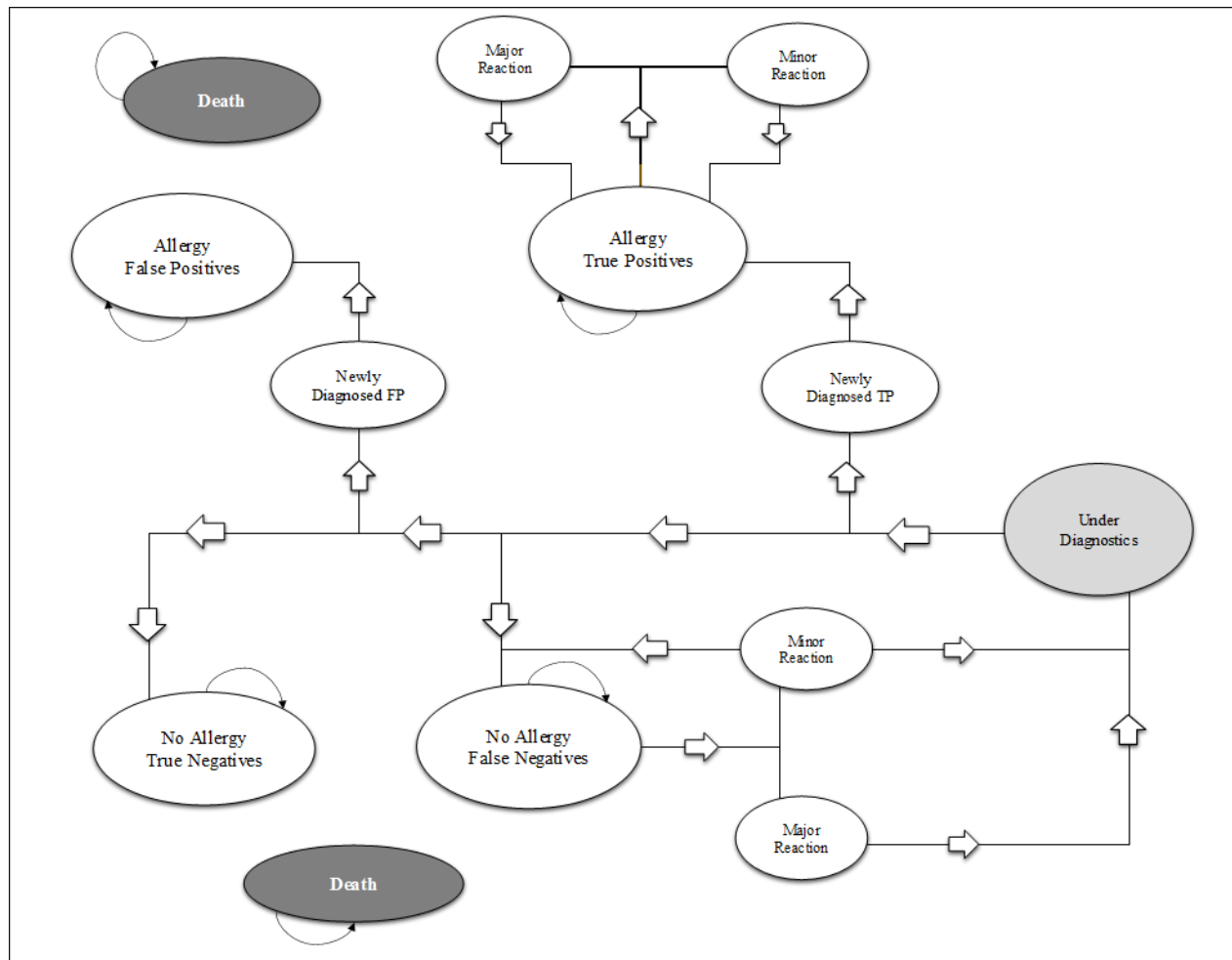


Fig E1. Markov transition-state model. Diagram of the health states and transitions in the Markov model used to analyze the long-term health and cost consequences of the three diagnostic strategies, that is, Current-DA, DA-I, and DA-II. *Current-DA*, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *FP*, false positives; *TP*, true positives.

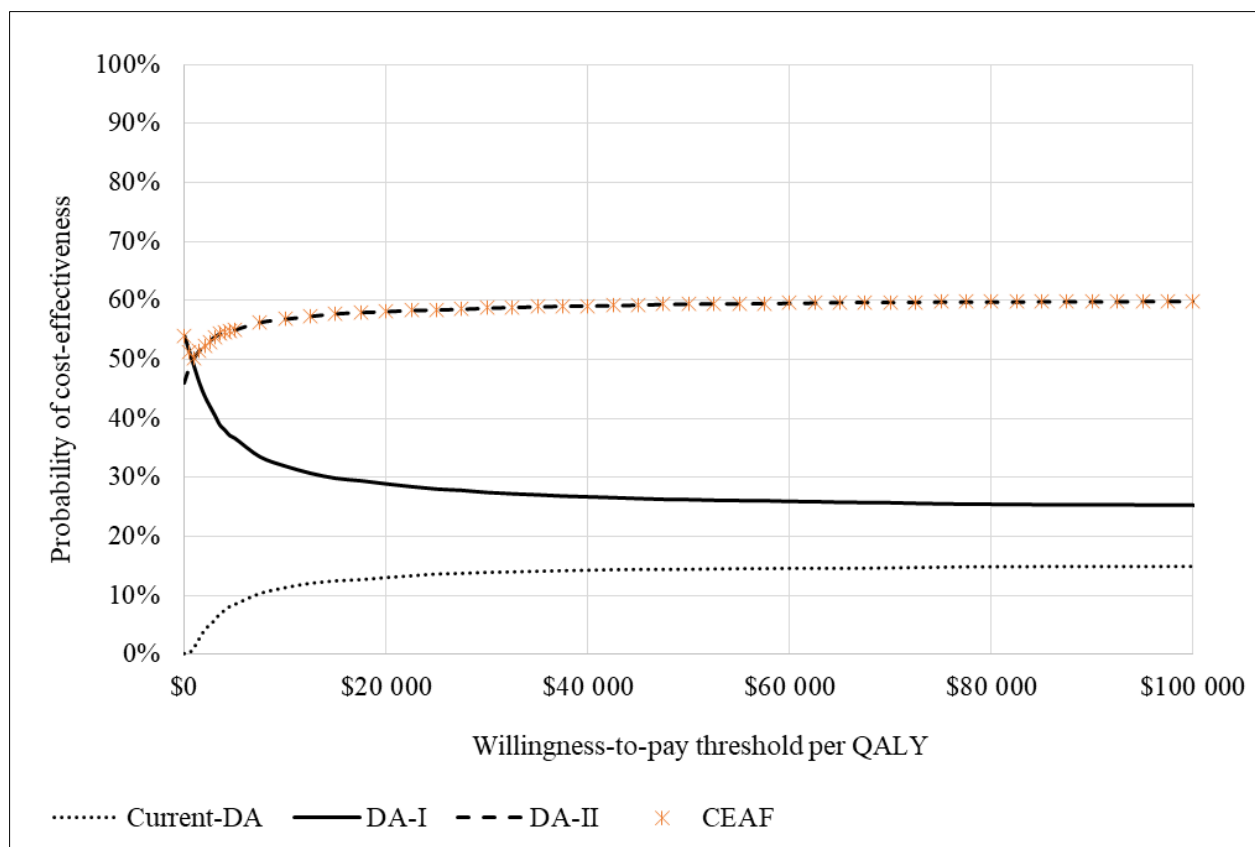


Fig E2. Cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier. The cost-effectiveness acceptability curves report the probability of each of the three diagnostic strategies (i.e., Current-DA, DA-I, and DA-II) to provide the greatest net monetary benefit at different willingness-to-pay thresholds. The cost-effectiveness acceptability frontier (CEAF) presents the probability that the strategy providing the highest net monetary benefit is cost-effective at each willingness-to-pay threshold. *CEAF*, cost-effectiveness acceptability frontier; *Current-DA*, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *QALY*, quality-adjusted life-year.

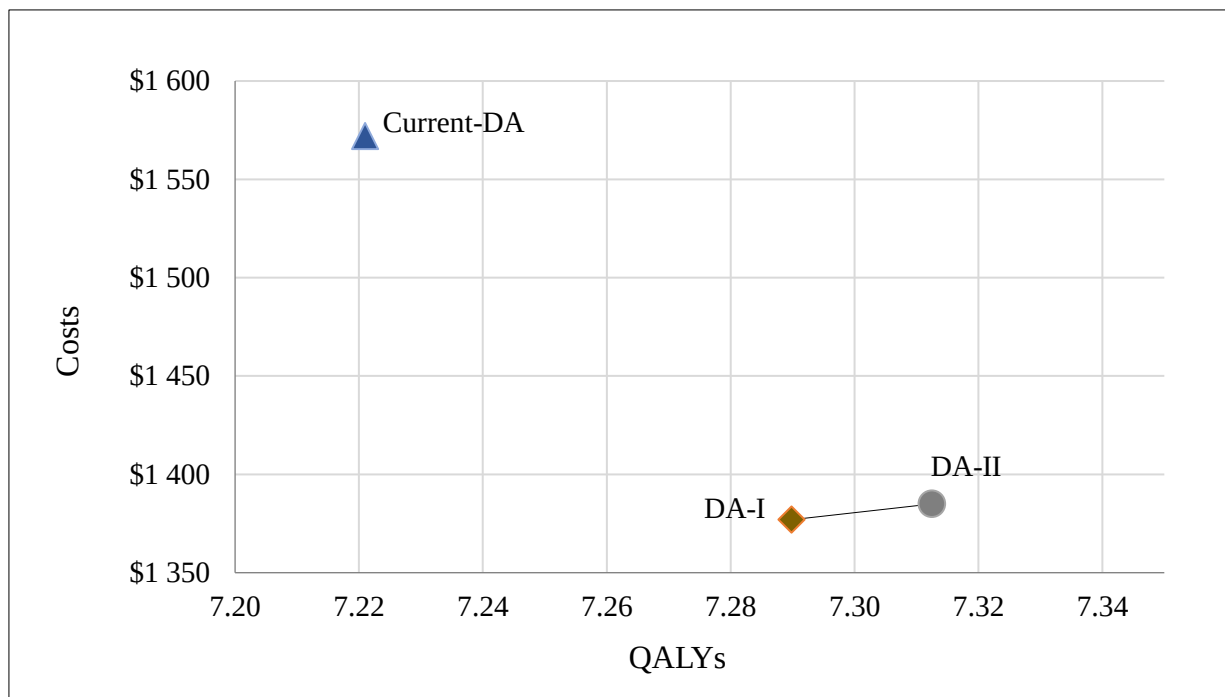


Fig E3. Probabilistic cost-effectiveness plane identifying cost-effective diagnostic strategies. The plane presents the average of the probabilistic sensitivity analysis results for each diagnostic strategy. Total costs and total QALYs of Current-DA, DA-I, and DA-II diagnostic strategies. The line segment represents the cost-effectiveness frontier indicating the diagnostic strategies associated with the lowest costs per QALY. The diagnostic strategies DA-I and DA-II are located on the frontier. The diagnostic strategy Current-DA, represented by the triangle, is located outside the frontier and indicates that this strategy leads to lower health effects at higher costs. *Current-DA*, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *QALY*, quality-adjusted life-year.

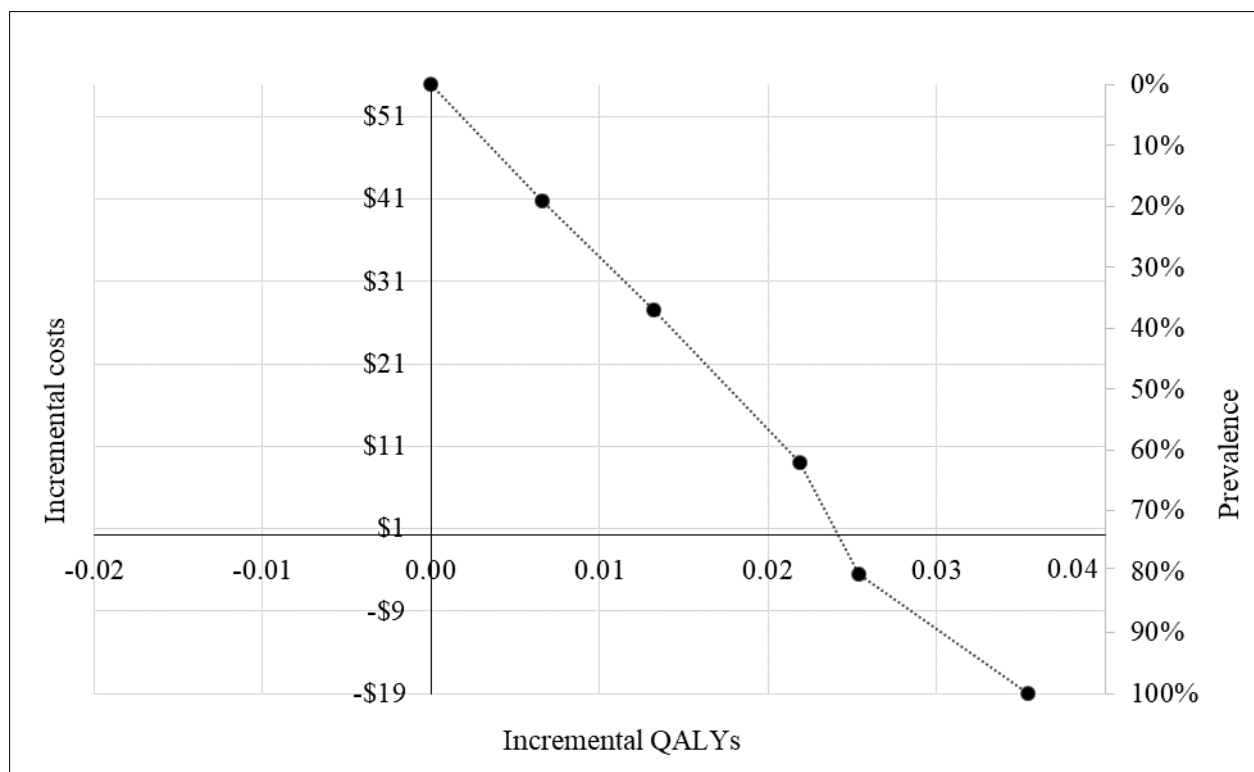


Fig E4. Probabilistic prevalence analyses for DA-II vs. DA-I. Incremental costs and incremental QALYs associated with DA-II compared with DA-I at different prevalence levels of peanut allergy in the tested population. The ICER results present the incremental costs needed to obtain an additional QALY. *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year.

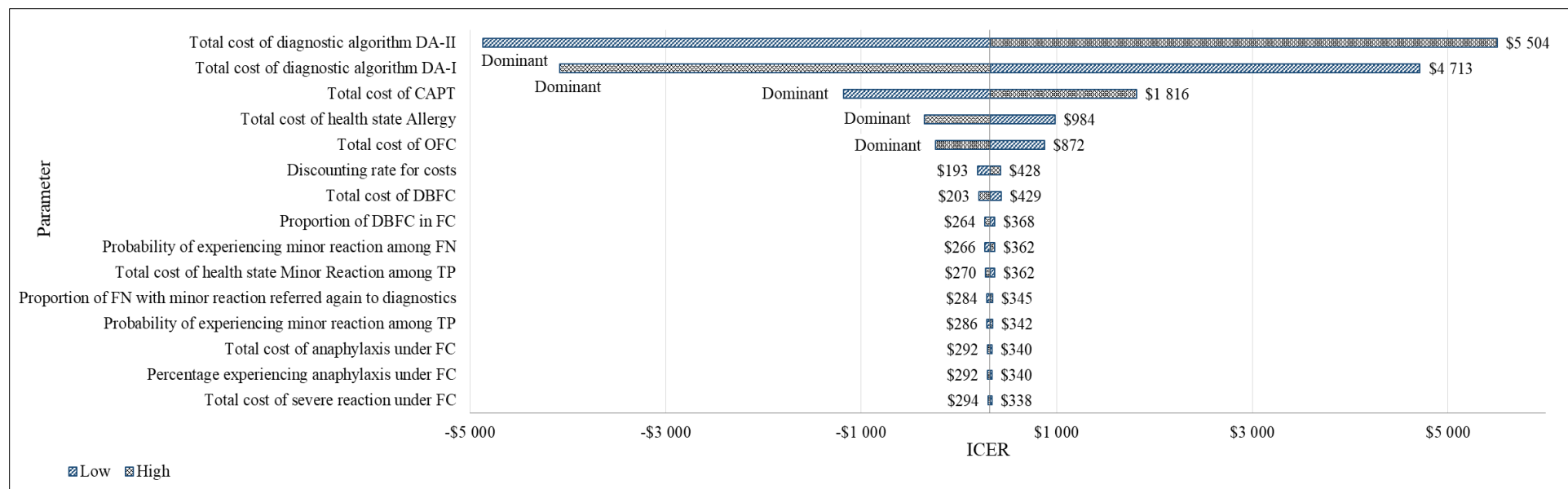


Fig E5. Tornado diagram presenting the results of one-way sensitivity analysis (change +/- 30%). Diagram presents the change in the base-case ICER of DA-II compared with DA-I when varying (+/- 30%) the base-case value of each model parameter, changing one parameter at a time. *CAPT*, peanut conjunctival allergen provocation test; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *DA-II*, diagnostic strategy incorporating specific IgE to allergen components and peanut conjunctival allergen provocation test into the currently used algorithm; *DBFC*, double-blind food challenge; *Dominant*, DA-II leads to higher QALYs and lower costs dominating the diagnostic strategy DA-I; *FC*, oral food challenge; *FN*, false negatives; *ICER*, incremental cost-effectiveness ratio; *OFC*, open food challenge; *TP*, true positives.

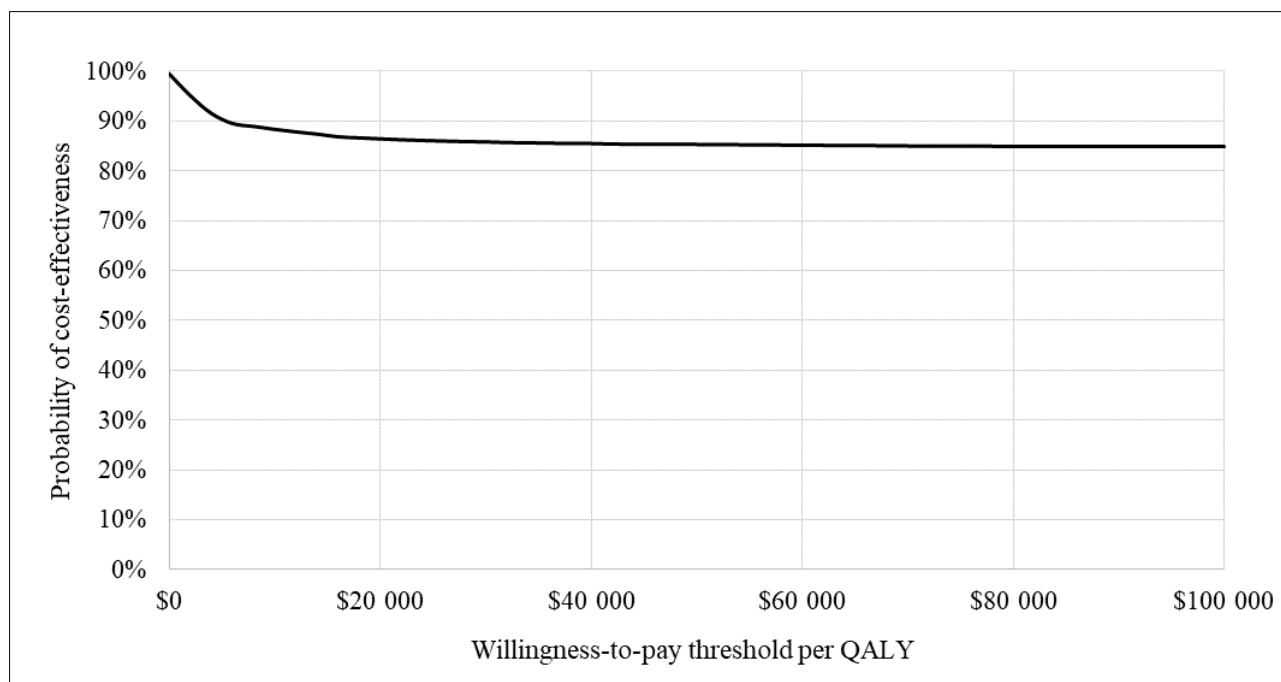


Fig E6. Secondary analysis: Cost-effectiveness acceptability curve for DA-I vs. Current-DA. The cost-effectiveness acceptability curve presents the probability of DA-I, when compared with Current-DA, to provide the greatest net monetary benefit at a range of willingness-to-pay thresholds. *Current-DA*, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *QALY*, quality-adjusted life-year.

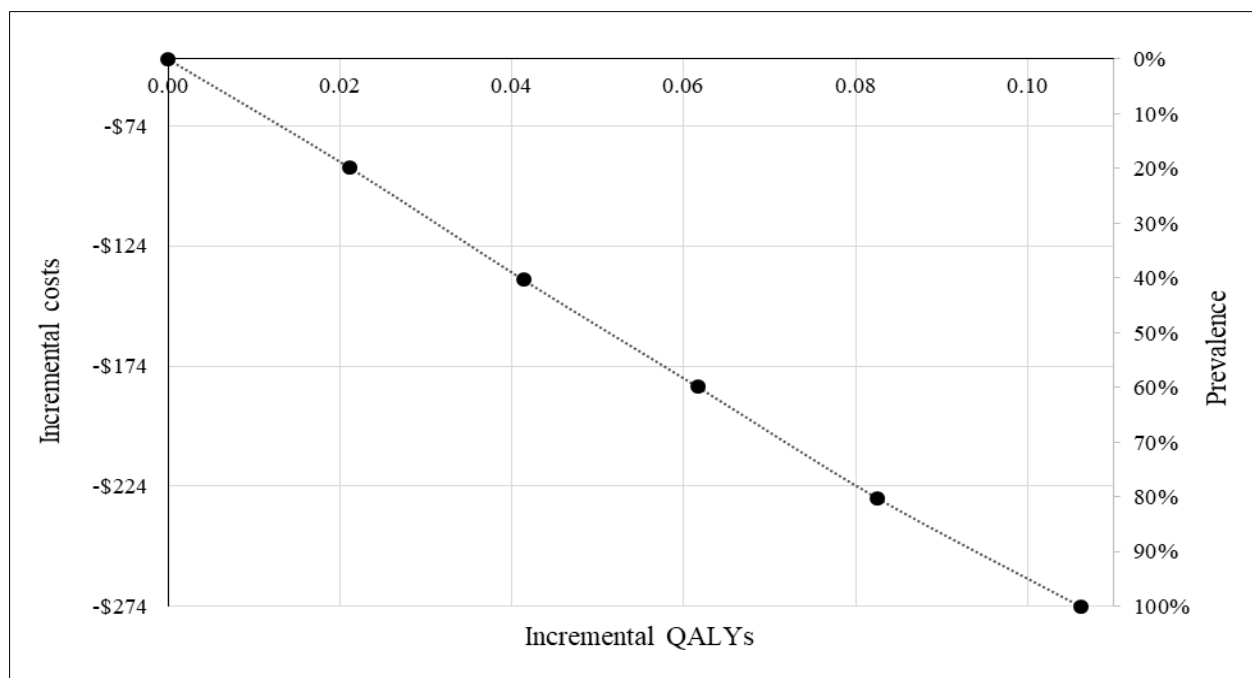


Fig E7. Secondary analysis: Probabilistic prevalence analyses for DA-I vs. Current-DA. Incremental costs and incremental QALYs associated with DA-I compared with Current-DA at different prevalence levels of peanut allergy in the tested population. The ICER results present the incremental costs needed to obtain an additional QALY. *Current-DA*, diagnostic algorithm currently used in clinical practice; *DA-I*, diagnostic strategy incorporating specific IgE to allergen components into the currently used algorithm; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year.