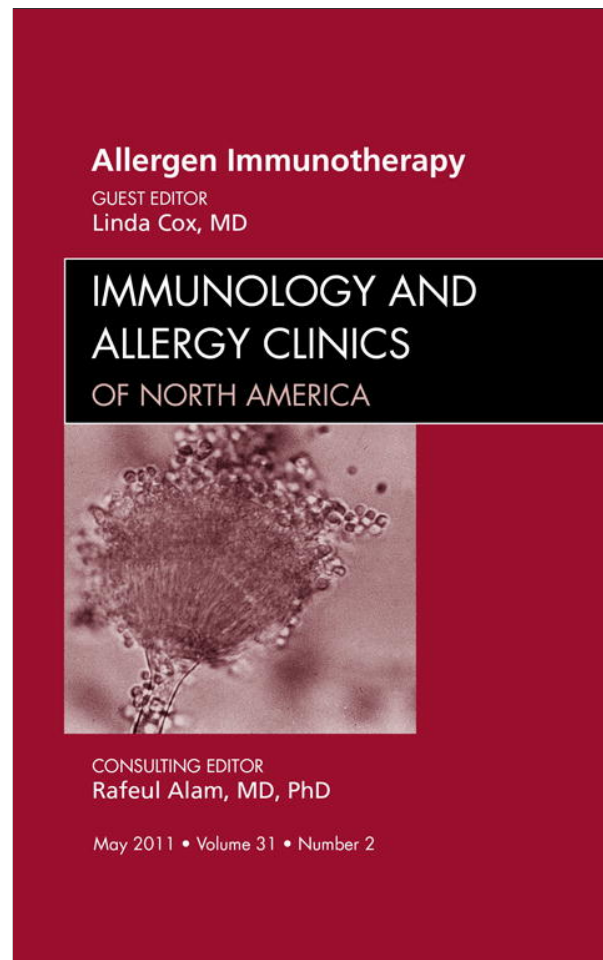


Provided for non-commercial research and education use.  
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

# The Health Economics of Allergen Immunotherapy

Cheryl S. Hankin, PhD<sup>a,\*</sup>, Linda Cox, MD<sup>b</sup>, Amy Bronstone, PhD<sup>a</sup>

## KEYWORDS

- Health economics • Allergen immunotherapy • Allergic rhinitis
- Asthma

More than 50 million people in the United States are affected by allergic diseases, making allergies the sixth leading cause of chronic disease among Americans.<sup>1</sup> Allergic rhinitis (AR), the most common allergic disease, is characterized by congestion, rhinorrhea, sneezing, and itching.<sup>2</sup> AR affects up to 30% of adults and 40% of children,<sup>1</sup> and ranks as the third-leading US chronic disease of individuals younger than 45.<sup>3</sup> AR prevalence is increasing globally, particularly in developed countries.<sup>4</sup>

Although sometimes mistakenly viewed as a trivial disease,<sup>2</sup> AR is associated with substantial clinical burden.<sup>5</sup> Typically a lifelong condition,<sup>6</sup> AR causes year-around symptoms in more than half of sufferers.<sup>7</sup> Symptoms of the illness can significantly reduce quality of life by causing physical discomfort and negative mood; disrupted sleep leading to daytime somnolence and reduced alertness; impaired cognitive functioning and learning; and lost time from work, school, and leisure activities.<sup>8</sup>

Health care expenditures for AR were estimated at \$11.2 billion in 2004 (\$13.5 billion in 2010).<sup>9</sup> Outpatient visits account for approximately one-third (36%) of AR-related direct costs and prescription medications account for nearly the entire remainder (59%).<sup>9</sup> Because costs for over-the-counter (OTC) medications, which were not included in the estimated expenditures shown in the first sentence of this paragraph, are reportedly equivalent to costs for prescription medications, health care expenditures attributable to AR may be substantially underestimated. AR often precedes the development of other chronic related diseases, including chronic sinusitis, otitis media with effusion, recurrent nasal polyps, and asthma.<sup>8</sup> The presence of AR with asthma significantly increases health services use in general,<sup>10,11</sup> and childhood hospitalizations in particular.<sup>11</sup>

In contrast to symptomatic drug treatment (SDT), which only temporarily relieves allergy symptoms,<sup>12</sup> allergen-specific immunotherapy (SIT) has the potential to alter

---

<sup>a</sup> BioMedEcon, LLC, Moss Beach, PO Box, 129 Moss Beach, CA 94038, USA

<sup>b</sup> 5333 North Dixie Highway, Suite 210, Fort Lauderdale, FL 33334, USA

\* Corresponding author.

E-mail address: [CHankin@biomedecon.com](mailto:CHankin@biomedecon.com)

the course of allergic disease, thereby reducing the need for long-term treatment, the progression of allergic rhinitis to asthma<sup>13,14</sup> and the development of new allergies.<sup>10,11</sup> The clinical benefits of SIT have been shown to persist for an additional 3 to 12 years after discontinuation of a 2.5- to 5.0-year treatment.<sup>15</sup> It therefore stands to reason that the clinical benefits of SIT also extend to economic benefits.

## METHODOLOGIC APPROACHES TO ECONOMIC ANALYSES

Given the substantial economic burden associated with allergic disease, it is important to understand how different treatment strategies may mitigate allergy-related outcomes and costs of care (**Table 1**).<sup>16</sup> Cost-effectiveness analysis (CEA) is a method used to evaluate the tradeoffs involved in choosing among interventions.<sup>16</sup> Data regarding resource use may be captured from a variety of sources, including prospective clinical trials, patient or physician reports, or retrospective administrative claims data. Costs may be derived from standardized costs (eg, Medicare reimbursement rates for procedures or wholesale acquisition costs for drugs) or actual charges. Analytic approaches may include decision-tree modeling, Markov modeling, or between-group comparisons of actual mean or median costs. Results may be expressed through the use of a “cost-effectiveness ratio,” in which all health effects of an intervention relative to a stated alternative are captured in the denominator, and changes in resource use relative to the alternative are captured in the numerator and valued in monetary terms.<sup>16</sup> Or, results may be expressed in terms of the health care cost differences between groups (eg, those who receive a specified treatment vs those who do not).

## ECONOMIC ANALYSES OF ALLERGIC RHINITIS TREATMENTS

Treatment of AR may include allergen avoidance, pharmacologic treatments, and SIT.<sup>17</sup> Unfortunately, there have been no economic analyses of allergen avoidance measures and only 5 economic studies of pharmacologic treatments for AR to date.<sup>18,19</sup> The few existing economic analyses of pharmacotherapies for AR have been plagued by methodological flaws, such as small sample sizes, extrapolation of costs from short-term outcomes, limited information on the clinical benefits of comparators, and lack of standardized effectiveness measures, which significantly detract from the value of their findings.<sup>18,19</sup>

In contrast, a growing number of studies have evaluated the economic benefits of SIT in patients with AR and/or asthma.<sup>20–34</sup> We critically examine each of these studies from their first published appearance in 1995, to present. Costs reported in foreign currencies were translated to US dollars using specified exchange rates<sup>35</sup> and were updated to 2010 values using the Consumer Price Index for Health Care.<sup>36</sup>

### 1995

#### *Donahue*

The earliest study was a retrospective analysis of administrative claims for 294,000 US health plan enrollees who filed a claim during the period 1988 to 1992.<sup>33</sup> Investigators identified 603 adults and children with AR and/or asthma who had received at least 1 SIT injection and who had continuous membership during the year before and 2 years after their initial SIT administration. Costs related to SIT included all encounters with an SIT code, an allergen skin test, or a code for allergic reaction to SIT. Costs of care for asthma and rhinitis not related to SIT were defined as all encounters or claims with codes for asthma, rhinitis, sinusitis, nasal polyps, and a variety of tests, procedures,

and dispensing for certain prescription drugs. No other costs were considered in this analysis.

The mean annual cost per patient following SIT initiation was \$438 for all patients, \$212 for those with asthma only, \$416 for those with AR only, and \$496 for those with both AR and asthma. The cost of SIT was significantly lower for patients age 10 to 20 years ( $P < .03$ ). Only 33% of patients who initiated SIT completed the desired 3.5 years of treatment. The average annual costs for SIT per patient who completed 3.5 years of treatment were \$698 compared with \$247 for patients who prematurely terminated SIT. Patients who completed SIT also had 20% greater nonimmunotherapy costs than patients who received SIT of shorter duration (mean of \$508 vs \$421 per person-year), primarily attributable to higher prescription costs in the former group.

Several possible explanations have been proposed for the finding of higher costs in patients who completed SIT of longer duration. First, SIT completers may have had a greater disease burden than noncompleters, because the costs for asthma and AR treatment for this group were 30% higher during the year before starting SIT. Second, the follow-up period after completion of SIT (mean of 7 months) may have been too brief to begin to see a cost reduction among SIT completers. Third, the different SIT completion rates in the 2 groups may reflect an underlying tendency toward better adherence among SIT completers, who may have had higher medication costs because they were more likely to follow medical advice.

### ***Buchner***

---

In the same year, a German article described a theoretical cost-benefit analysis of SIT for the treatment of AR and allergic asthma based upon published literature.<sup>27</sup> Two models were created: one for patients with AR, and another for patients with allergic asthma. Among those with AR who received SDT alone, 57% were assumed to continue to experience AR symptoms over 10 years, and 43% were assumed to progress to allergic asthma. For those with AR who initiated SIT, a 90% therapeutic success rate was assumed over a 3-year treatment course (ie, use of SDT would decrease to 30% in the first year, 20% in the second year, and to 10% in the third year of treatment); for the 10% with AR who did not achieve treatment success with SIT, 57% would continue to experience AR symptoms (requiring SDT), and 43% would progress to allergic asthma after 8 years. In the second model, among patients with extant allergic asthma who initiated SIT, a 90% success rate again was assumed, in which the need for SDT would diminish in a parallel manner. Cost components included direct costs of treatment (drugs, physician and hospital services and SIT if appropriate) and indirect costs (days lost from work, disability, and premature death). According to these models, the cost advantage shifted in favor of SIT during the sixth year of treatment for AR. The 10-year total cost per AR patient treated with SDT was 11,054 in 1990 DM (\$16,311 in 2010 USD) compared with 6083 in 1990 DM (\$8976 in 2010 USD) for treatment with SIT. The cost advantage shifted to SIT during the fourth year of treatment for allergic asthma. The 10-year total cost per asthma patient treated with SDT was 16,430 in 1990 DM (\$24,243 in 2010 USD) compared with 6849 in 1990 DM (\$10,106 in 2010 USD) for SIT.

This relatively simplistic model, based on the assumption that 10% of patients receiving SIT would not achieve therapeutic success, had several limitations. First, the investigators provide no justification for their determinations of specific indirect and direct costs. Second, no sensitivity analyses were conducted to test the robustness of the model. Finally, the model examined patients with AR and asthma separately and did not account for that fact that many patients would be diagnosed with both disorders at the onset of treatment.

Table 1 Summary of SIT economic analyses						
Pub Date	Author	Country	Source of Cost Data	Subject Characteristics	Comparisons	Results
1995	Donahue <sup>33</sup>	USA	RACD	603 adults & children with AR $\pm$ asthma	Patients completing 3.5 y SIT vs patients not completing 3.5 y SIT	Mean direct costs per patient-year: 3.5 y SIT: \$698 (1988–2992) <3.5 y SIT: \$247 (1988–1992)
1995	Buchner <sup>27</sup>	Germany	Cost-of-illness study	400,000 adults & children with AR; 400,000 adults & children with asthma	10 y SIT vs SDT	Mean direct costs per AR patient over 10 y: SIT: \$8976 (2010) SDT: \$16,311 (2010) Mean direct costs per asthma patient over 10 y: SIT: \$10,106 (2010) SDT: \$24,243 (2010)
1997	Le Pen <sup>32</sup>	France	Physician survey	851 adults & children with AR $\pm$ asthma (6% other dx)	Various duration of SIT	Mean cost allergy medications per patient-year: <1 y SIT: \$37 (2010) $\geq$ 1 y SIT: \$23 (2010)
1999	Bernstein <sup>34</sup>	USA	Published literature	Patients with AR at 3 medical facilities	5 y SIT + SDT vs SDT	Mean direct costs per patient over 5 y: SIT: \$5000 SDT: \$10,200
2000	Schadlich <sup>24</sup>	Germany	Published literature, cost-of-illness studies	Hypothetical cohort of 2000 patients with AR $\pm$ asthma	10 y SIT vs SDT	Difference (SIT-SDT) in direct costs per patient with AR (pollen) over 10 y: –\$960 (2010) Difference (SIT-SDT) in direct costs per patient with AR (mite) over 10 y: –\$1190 (2010)
2005	Berto <sup>21</sup>	Italy	Medical records	135 children with AR $\pm$ asthma	1 y before SLIT vs 3 y during SLIT	Mean direct costs per patient-year: Before SLIT: \$651 (2010) During SLIT: \$288 (2010)

2005	Petersen <sup>23</sup>	Denmark	Medical records & patient survey	253 patients aged 16–60 with AR ± asthma	4 y SIT vs SDT	Mean direct costs per patient over 4 y: SIT: \$2802 (2010) SDT: \$1335 (2010)
2006	Ariano <sup>20</sup>	Italy	Randomized controlled trial	30 adults with AR ± asthma	3 y SIT vs SDT; 3 y FU	Difference (SIT-SDT) in direct costs per patient in the 6 <sup>th</sup> year: –\$932
2006	Berto <sup>22</sup>	Italy	Physician survey	Hypothetical cohort of 1000 patients aged 16–45 with AR ± asthma	3 y SLIT + SDT vs SDT; 3 y FU	Difference (SIT-SDT) in direct costs per patient over 6 y: –\$759
2007	Bachert <sup>25</sup>	Northern Europe	Randomized controlled trial	634 adults with AR ± asthma	3 y SLIT + SDT vs SDT; 6 y FU	\$19,345 to \$27,324 (2010) cost per QALY gained (payer perspective)
2007	Keiding <sup>26</sup>	UK	Randomized controlled trial	306 adults with AR	3 y SLIT + SDT vs SDT; 6 y FU	\$14,536 to \$38,695 (2010) cost per QALY gained (payer perspective)
2007	Omnes <sup>28</sup>	France	Delphi panel	Hypothetical cohort of 1000 adults & children with AR ± asthma	3–4 y SIT; 3 y FU	ICER per additional improved patient: SCIT vs SDT: \$517 to \$1069 (2010) SLIT vs SDT: \$933 to \$3509 (2010) ICER per additional asthma case avoided:
2008	Hankin <sup>29</sup>	USA	RACD	354 children with AR ± asthma	6 months before SIT vs 6 months after SIT	SCIT vs SDT: \$582 to \$1964 (2010) SLIT vs SDT: \$1120 to \$5829 (2010) Difference (postSIT-preSIT) in direct costs (excluding cost of SIT) per patient over 6 months: \$401
2010	Hankin <sup>30</sup>	USA	RACD	13,781 children with AR ± asthma	18 months SIT vs SDT	Difference (SIT-SDT) in direct costs per patient over 18 months: –\$1625 over 18 months
2011	Hankin <sup>31</sup>	USA	RACD	6443 adults with AR ± asthma	18 months SIT vs SDT	Difference (SIT-SDT) in direct costs per patient over 18 months: –\$7286 over 18 months

Abbreviations: AR, allergic rhinitis; dx, diagnosis; FU, follow-up; QALY, quality-adjusted life year; RACD, retrospective administrative claims database; SDT, symptomatic drug treatment; SIT, allergen-specific immunotherapy; SLIT, sublingual allergen immunotherapy; ±, with or without.  
 Note: For cost differences, negative numbers indicate a cost savings conferred by SIT.

**1997*****Le Pen***

---

In a French study, investigators used physician survey data of patients receiving SIT to test the hypothesis that greater duration of SIT is directly related to the magnitude of decrease in the use of SDT.<sup>32</sup> Among 1000 patients who had received SIT for a variety of allergies, 851 (85%) had completed surveys regarding aspects of their SIT treatment (duration and reasons for desensitization), and past 15-day allergy symptoms, other allergy treatments received, physician visits, allergy-related hospitalizations, and work missed. Among respondents, 333 (29%) had received SIT for less than 1 year. For all respondents regardless of SIT duration, past 15-day self-reported physician visits accounted for 150 F (1996 value, \$49.98 in 2010 USD), SDT 55 F (1996 value, \$18.30 in 2010 USD), SIT 14.5 F (1996 value, \$4.82 in 2010 USD), hospitalizations 1.6 F (1996 value, \$0.53 in 2010 USD), and missed work 28.9 F (1996 value, \$9.62 in 2010 USD). Costs for SDT were significantly lower (*P*-value not provided) for patients who received 1 to 2 years of SIT versus those who received less than 1 year. This benefit plateaued after 1 to 2 years; in other words, there were no significant additional cost benefits for SIT duration of more than 2 years.

This short-term retrospective study was limited by some key weaknesses. First, data were derived from a physician survey rather than from an administrative database. Thus, self-selection (149 refused participation) and/or biases associated with self-reported data may have affected the results. Second, SDT costs were estimated over a very short period of time (15 days). Third, as the investigators acknowledge, only a small proportion (undisclosed) of patients completed more than 2 years of SIT. Fourth, the absolute between-group differences in SDT costs and *P*-values were not provided. Finally, the authors did not compare total medical costs among patients with different durations of SIT. Although the cost of SDT appeared to be reduced among patients with longer duration of SIT, the meaning of this finding is questionable unless SIT also reduced the total costs of care.

**1999*****Bernstein***

---

A 1999 US study used data from a 1996 American College of Allergy, Asthma and Immunology report to compare the estimated the 5-year average cost of SIT plus SDT versus SDT alone among patients with AR.<sup>34</sup> Data from 3 allergy treatment centers in different geographic regions in the United States provided the basis for estimating costs. Costs for SIT were based on the assumption that patients with AR would require daily use of an antihistamine/decongestant and intranasal corticosteroid spray. The authors estimated 5-year SIT costs to be \$5000 (\$8511 in 2010 USD) versus SDT \$10,200 (\$17,362 in 2010 USD) for SDT, and concluded that SIT was more "cost-effective" than SDT. This casual analysis is limited by rough estimates of costs that were not further substantiated or validated, assumptions that patients who received SIT do not concomitantly use symptomatic drug treatment, and the exclusion of other costs of care associated with SIT, or undertreated AR.

**2000*****Schadlich***

---

In 2000, a study used retrospective data from clinical trials, observational studies, and epidemiologic sources to model health outcomes associated with 3 years of SIT versus SDT in patients with AR over 10 years of follow-up.<sup>24</sup> Direct costs included outpatient medical services, outpatient drug treatment, inpatient medical services, allergy-related

diagnostic tests, treatment for adverse events, SIT allergen extract, and allergy medications. Resource use (physician visits, diagnostic tests) for patients receiving SIT was estimated based on results of a provider survey and the quantity of allergen extract used each year was estimated based on expert interviews. The frequency of systemic adverse events was based on clinical trial and observational study results.

A decision-tree model was constructed using change in the proportion of patients with asthma as the measure of effectiveness. Clinical trials data suggested that the proportion of patients with asthma would decrease from 30% at the start of treatment to 19% after 10 years in the SIT-treated group and would increase from 30% to 35% in patients treated with SDT. The costs incurred by patients treated with SIT were modeled and compared with the annual costs for patients with AR and/or asthma based on cost-of-illness studies.

The total direct costs associated with SIT were higher for the first 6 years, after which SIT became cost saving relative to SDT. The average, 10-year, per-patient net savings with SIT, as evaluated from the payer perspective, ranged from 580 DM (1997 value, \$960 in 2010 USD) for mite allergy to 670 DM (1997 value, \$1109 in 2010 USD) for pollen allergy. Although this study used a sophisticated model, estimation of cost savings was based strictly on the potential of SIT to reduce the development of asthma, and therefore likely underestimated the true savings that are possible with SIT. In addition, the model assumed that patients were 100% adherent to SIT, which is unrealistic and contradictory to SIT adherence data reported in various studies.<sup>33,37–40</sup>

## 2005

### *Berto*

---

In another study, investigators analyzed the medical records of children receiving care for allergic disease at a single allergy center in Italy.<sup>21</sup> Subjects who had 1 year of data before receiving sublingual immunotherapy (SLIT) and at least 3 years of data while on SLIT were selected. Of the 135 identified children, 34% had seasonal allergies and 66% had perennial allergy (house dust mites). About 61% had AR and asthma, 38% had asthma, and fewer than 1% had AR only. Outcome measures used to calculate direct costs included the number of physician and specialist office visits, pharmacologic treatment, and use of SLIT. Data on hospitalizations were not available from the patient medical records. The number of school absences served as a proxy for the number of lost work days by parents, which was used to estimate indirect costs.

Clinical effectiveness, indicated by the number of asthma and rhinitis exacerbations, improved after SLIT: the mean number of exacerbations was 5 times lower during the 3 years on SLIT compared with the year before SLIT. The number of medical visits decreased threefold during an average year under SLIT compared with the year before SLIT. The mean cost per patient was €506 (\$651 in 2010 USD) during the year before SLIT and €224 (\$288 in 2010 USD) per year during the 3 years of SLIT. When indirect costs were included, the total cost per patient decreased from €2672 (\$3436 in 2010 USD) in the year before SLIT to €629 (\$809 in 2010 USD) per year during SLIT.

Investigators also conducted a case-control analysis involving a subgroup of SLIT-treated patients with allergic asthma who were matched with a group of similar patients who had not received SLIT and were not from the same data source as those who received SLIT. This analysis revealed comparable direct costs between SLIT-treated patients (€1182 in 2002; \$1520 in 2010 USD) and controls (€1100 in 2002; \$1414 in 2010 USD) over 4 years of follow-up.

Although the results of this study suggest that SLIT reduces the use of health care resources and can alleviate the economic burden of allergic illness, several limitations

should be noted. First, the investigators apparently did not conduct significance testing, and so it is impossible to conclude that SLIT significantly reduced direct or total costs. Second, because the economic analyses did not include hospitalizations, the true effect of SLIT on costs may have been underestimated. Third, the involvement of allergic children from a single allergy center limits the generalizability of study findings. In addition, the case-control analysis was limited by the selection of matched controls from a different database than the one used to select SLIT-treated patients, and by the lack of matching based on demographic or illness characteristics.

### **Petersen**

---

A 6-year retrospective analysis involving 253 adults who received SIT for grass pollen and/or dust mite allergy at a hospital or allergy specialist office in Denmark from 1996 to 2002 was one of the few studies that failed to find a reduction in direct costs related to SIT.<sup>23</sup> Patients were surveyed regarding the number of emergency visits and hospital admissions they had during the year before starting SIT, 4 years of SIT, and the year following SIT. Information on outpatient visits was obtained from local county records for the period 1997 to 2002. Outpatient visit data were not available for 26 patients who initiated SIT in 1996. Because medical records contained only medication use data for the latest 16 months, information on pre-SIT medication use was obtained from a different cohort of 53 patients who started SIT in 2002. Post-SIT medication use was based on data from a minority of patients who had completed SIT; because only 7 months of medication use data were available for these patients, data were extrapolated to estimate 1-year post-SIT medication use. Indirect costs were estimated using the number of lost work and leisure days.

Costs for medications (2002 values) averaged Danish krone (DKK) 1309 (\$226 in 2010 USD) per patient in the year before SIT, increased to DKK 2776 (\$479 in 2010 USD) during the first year of SIT, and fell to DKK 1629 (\$281 in 2010 USD) during years 2 to 4 of SIT and to DKK 338 (\$58 in 2010 USD) in the year following SIT completion. Use of medical doctors increased after the initiation of SIT and continued to be higher after SIT was completed. Outpatient costs increased from DKK 609 (\$105 in 2010 USD) before SIT to between DKK 1041 (\$180 in 2010 USD) and DKK 3247 (\$560 in 2010 USD) during SIT and DKK 825 (\$142) in the year after SIT. Finally, costs for hospitalizations and emergency visits fell from DKK 46 (\$8 in 2010 USD) before SIT to DKK 13 (\$2 in 2010 USD) after SIT after increasing to DKK 127 (\$22 in 2010 USD) per year during SIT.

Although the total mean direct cost per patient decreased from DKK 1964 (\$445 in 2010 USD) in the year before SIT to DKK 1176 (\$203 in 2010 USD) in the year after SIT, the average cost for 4 years of SIT (DKK 16,248 or \$2802 in 2010 USD) exceeded that for 4 years of SDT (DKK 7856 or \$1355 in 2010 USD). Based on these calculations, breakeven with SIT would not occur until the 10<sup>th</sup> year following a 4-year course of SIT (Year 15).

This study had several methodological flaws that should be noted. First, hospital and emergency department use over 6 years were obtained by self-report, and it is likely that patient recall was imprecise over this period of time. Second, indirect costs were also obtained by patient self-report, which was subject to bias. Specifically, patients were asked whether SIT had improved the quality of their well-being over the previous 1 to 7 years, and they were asked to provide the number of work and leisure days lost due to allergy and asthma prior, during and following SIT. Third, investigators collected data on pre-SIT medication use from a different sample, and extrapolated 7 months of post-SIT medication use to 12 months to calculate pre-versus post-SIT changes in medication costs. Furthermore, because the 7-month period post-SIT medication use information included the grass pollen season, when

allergy medication use peaks, medication use during the 12-month post-SIT period may have been overestimated. Finally, patients were followed for only 1 year after SIT was completed, and potential long-term reductions in costs could not be detected.

**2006**

**Ariano**

---

An economic analysis of SIT was performed using data from a prospective, single-site study in which 30 Italian adults with *Parietaria* pollen-induced rhinitis and asthma were randomly assigned to 3 years of SIT plus SDT ( $n = 20$ ) or SDT alone ( $n = 10$ ) and then followed for 3 years after completion of SIT.<sup>20</sup> During the 4-month pollen season, patients recorded symptom scores, allergy drug use, and adverse drug reactions on a daily diary card; each month during the study, they recorded the number of general practitioner or specialist office visits attended, SIT injections received, and boxes of allergy medications used. At 6-month intervals, patients completed study visits and turned in their daily diary and health care use cards.

Patients in the SIT plus SDT group began to show a significant reduction in allergy symptoms and medication use compared with the SDT-alone group beginning in the first year of treatment. The superior effectiveness in the SIT plus SDT group continued throughout the 6-year study, even during the 3 years after discontinuation of SIT.

The mean annual cost for patients in the SIT plus SDT group was similar to that of patients in the SDT-only group for the first 2 years of treatment. In the third year, the SIT plus SDT group showed a 48% reduction in costs ( $P < .0001$ ) compared with the SDT-only group. This cost reduction progressively increased over time, such that, in year 6 of the study, annual costs were 80% lower (€623 in 2005, \$932 in 2010 USD) in the SIT plus SDT group.

The main strength of this study was its use of data from a prospective, randomized, long-term study. Investigators were able to show that, even though significant clinical benefits were evident during the first year of treatment with SIT, cost benefits were not seen until the third year. Further, maximum cost benefits did not occur until 3 years after discontinuation of SIT, indicating that a long-term perspective is critical when evaluating the economic impact of SIT.

A disadvantage of this study was its reliance on patient self-report to assess health care use. Although patients were to record doctor visits, SIT injections, and allergy medication use every month, the only monitoring of this activity occurred at the 6-month study visits. In addition, because this economic analysis did not take into account hospital admissions or emergency room visits (except for drug reactions), the results may have underestimated the true cost savings associated with SIT. Finally, the ability to generalize from these study findings is limited by the nature of the sample (adults with seasonal AR and asthma), the small number of patients involved, recruitment of patients from a single allergy center.

**Berto**

---

The Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study compared costs, clinical outcomes, and cost-effectiveness ratios for 2 AR and asthma management strategies: SLIT with SDT and SDT alone.<sup>22</sup> A decision-tree model was populated using retrospective data from the clinical records of 100 young adults (age 16–45) with pollen-induced AR with or without asthma who were treated by a panel of 27 physicians from 25 allergy centers in Italy. Retrospective data included allergy treatments received, use of health care resources (office visits, diagnostic procedures, and hospital admissions), physician ratings of improvement, and patient diagnoses;

however, it was unclear as to whether the source(s) of health care resource data were patient self-report, medical records, or administrative claims. Direct costs included physician office visits, diagnostic procedures, hospitalizations, SLIT, and antiallergy drugs; indirect costs included lost workdays. The cost of SLIT and antiallergy medications was based on recommended dosing schedules as opposed to actual use. The number of follow-up visits per year by disease severity and number of hospital admissions was obtained from analysis of data provided by the physician panel; the same rate of hospitalizations was applied to both treatment groups.

A cost analysis was performed to determine, from the payer perspective, the mean direct cost per patient during a 6-year period for patients receiving 3 years of SLIT plus SDT (€1901 or \$2844 in 2010 USD) or SDT alone (€2408 or \$3603 in 2010 USD; net savings = \$759 in 2010 USD). The break-even point occurred 4 years after the initiation of SLIT, even though reduction in costs began in the first year of treatment. From the societal perspective, which included direct costs paid by the patient and indirect costs, the break-even point was reached in year 2, and the net savings in 6-year total costs was €2113 (\$3161 in 2010 USD) for patients receiving SLIT.

A decision-tree model was constructed to determine the cost per improved patient and per asthma case avoided for SLIT versus no SLIT. For a hypothetical cohort of 1000 patients, physicians estimated that SLIT would have improved symptoms of 631 patients versus 232 patients in the no SLIT arm and that SLIT would have prevented asthma in 518 patients versus 289 in the no SLIT arm. From the payer perspective, the cost per additional improved patient was €4313 (\$6453 in 2010 USD) for SLIT plus SDT and €6426 (\$9614 in 2010 USD) for SDT alone and the cost per additional asthma case avoided was €1901 (\$2844 in 2010 USD) for SLIT plus SDT and €2408 (\$3603 in 2010 USD) for SDT alone. SLIT was less costly for both endpoints from the societal perspective as well.

It is unfortunate that the cost analysis was based on health care use data of questionable validity. Although these data were supposedly derived from patient "clinical records," investigators failed to specify the precise methods used to estimate these outcomes. For example, it is unclear why investigators assumed that hospital admission rates were equal in the 2 treatment groups if objective data were available to determine these rates. Patient use of allergy medications and SLIT were estimated based on the prescribed regimens rather than on actual patient use. It is possible, for example, that patients who were experiencing symptom relief may have used less medication than was prescribed. Finally, outcomes were determined by unblinded physician ratings, which may have been influenced by physicians' knowledge of the treatments patients had received.

## 2007

### *Bachert*

---

A cost-utility analysis was conducted using data from a large, international (8 countries), randomized, double-blind, placebo-controlled trial in which 316 patients were randomized to a grass allergen tablet arm and 318 to a placebo (SDT) arm.<sup>25</sup> During the clinical trial, patients received preseasonal SLIT for 16 to 35 weeks. To estimate the long-term effectiveness of SLIT, it was assumed that 3 years of treatment with the grass allergen tablet would result in sustained clinical benefits for another 6 years.

All study patients were permitted the use of allergy medications according to need. Patient use of health care resources (physician visits, use of allergy medication, hospitalizations, and time missed from work because of AR) and quality of life data were collected prospectively. Medication use was assessed by daily patient diaries and

physician visits and missed work assessed by weekly patient diaries. In addition to the physician visit data collected during the weekly diaries during the pollen season, the annual number of physician visits for patients receiving SLIT was estimated using data from a European survey.

Patients who received SLIT experienced a 30% reduction in allergy symptoms and a 38% reduction in medication score ( $P < .0001$ ) compared with placebo during the allergy season of the first treatment year. SLIT-treated patients gained 0.0287 additional quality-adjusted life years (QALYs) per season (0.222 QALYs gained over 9 years) compared with patients receiving only SDT ( $P < .001$ ). No patients were hospitalized and there were no significant differences between groups in the number of physician visits during the pollen season. The mean use of symptomatic medication and hours of lost work because of AR were significantly higher in the placebo group. From a payer perspective, assuming an annual cost of SLIT of €1500 (\$2244 in 2010 USD), the cost per QALY gained ranged from €12,930 (\$19,345 in 2010 USD) in the Netherlands to €18,263 (\$27,324 in 2010 USD) in Germany.

Although this study incorporated data from a well-controlled and large clinical trial, the trial was relatively short in duration and long-term outcomes were based on assumptions that may have resulted in the overestimation or underestimation of cost effectiveness. For example, patient-reported health care resource use over the first pollen season after treatment was extrapolated to a 9-year period, yet there is no reason to assume that health care use remained constant throughout this long period. In addition, the assumption that 3 years of SLIT would result in sustained clinical benefits for all patients is doubtful; it is likely that some long-term users of SLIT would have experienced a relapse of symptoms after discontinuation of treatment.

### ***Keiding and Jørgensen***

---

Similar to the study just described, Keiding and Jørgensen conducted a 9-year cost-effectiveness analysis of SIT based on results of a 1-year clinical trial.<sup>26</sup> The UK Immunotherapy Study Group (UKIS) trial was a 1-year, multicenter, randomized, double-blind, parallel-group study comparing SIT (Alutard SQ; ALK-Abelló, Hørsholm, Denmark) and placebo (SDT) in patients with seasonal grass pollen-induced rhinoconjunctivitis whose symptoms were uncontrolled using SDT.<sup>41</sup> Patients received 15 injections over the first 7 to 8 weeks (induction period) followed by maintenance injections every 6 weeks. Acrivastine, fluticasone propionate nasal spray, and sodium cromoglycate eye drops were freely available throughout the study for both groups. Where necessary, rescue medication was given according to written protocols. Clinical outcomes, including symptom and medication scores and quality of life, were assessed before and after a 15-week pollen season.

The direct costs of treatment were estimated by combining the resource use found in the UKIS study (cost of SIT, follow-up visits to specialists/general practitioners, and use of pharmacologic treatments) with national price data from 6 European countries. Although use of pharmacologic medications was documented by patients, and visits to health care professionals for SIT administration were documented by investigators, other use of health care resources during the study does not appear to have been captured. The cost of maintenance SIT was included for an additional 2 years (assuming a 3-year SIT treatment period); differences between groups in the use of emergency medications observed during the clinical trial were assumed to continue through the remaining 8 years. Indirect costs were estimated using the number of workdays lost (0.6 for SIT and 2.7 for SDT) in a previous study of rhinoconjunctivitis. A 3% discount rate was applied. Treatment effects were measured as the percentage

of symptom-free days (31.2% for SIT and 23.6% for SDT) and well days (36.6% for SIT and 28.2% for SDT) during the pollen season in the UKIS.

The incremental cost-effectiveness ratio (ICER), calculated as the cost difference between SIT and SDT divided by the difference in effect, for direct cost per symptom-free day and well day ranged from €26 (\$39 in 2010 USD) in Austria to €68 (\$102 in 2010 USD) in the Netherlands and from €24 (\$36 in 2010 USD) in Austria to €61 (\$91 in 2010 USD) in the Netherlands, respectively. When indirect costs were included, SIT dominated SDT (ie, reduced costs and increased effects) in 4 of the 6 countries for both variables. When only direct costs were considered, the cost-effectiveness ratio ranged from €9716 (\$14,536 in 2010 USD) to €25,863 (\$38,695 in 2010 USD) per QALY, below the \$40,000 to \$60,000 threshold for cost-effective therapies established by the National Institute for Clinical Excellence.<sup>42</sup> When indirect costs were included, SIT was dominant over SDT in all countries except the Netherlands and Sweden. Sensitivity analyses conducted on the number of up-dosing visits, cost of IT visit, cost of general practitioner and/or specialist visit, cost of emergency medicine, and effectiveness of SIT showed that only very considerable changes in the base values turned the cost-effectiveness ratios into unfavorable ones that exceeded the threshold of \$60,000.

As with the Bachert and colleagues study,<sup>25</sup> the main weakness of this analysis is the extrapolation of short-term costs and effects to 9 years. This may have resulted in an underestimation of cost savings associated with SIT, as it failed to account for the potential reduction in the use of health care resources over time (due to lower rates of asthma and other comorbid disorders) among those receiving SIT. Further, documentation of health care resource use during the clinical trial appears to be incomplete in that non-allergy-related outpatient visits, inpatient care, and emergency services use were not assessed.

### ***Omnes***

A cost-effectiveness analysis conducted from a French health insurance perspective compared SCIT, SLIT, and SDT in pollen or dust mite allergic patients with AR or asthma.<sup>28</sup> Unlike the previous 2 economic modeling studies, which used data from a clinical trial to estimate key variables, this study used a Delphi expert panel to populate a decision-tree model with both efficacy (number of improved patients and asthma cases avoided) and resource use variables (clinic visits, diagnosis and follow-up tests, drugs, and SIT); hospitalization costs were not included.

The model time horizon was 6 years for adults and 7 for children. Patients were assumed to receive SIT for 3 (adults) or 4 (children) years. After 1 year of SIT, patients were (1) asymptomatic and assumed to stop use of rescue medications, (2) improved and assumed to reduce rescue medication use, or (3) unchanged or worse, resulting in treatment discontinuation and initiation of SDT. Treatment was discontinued after 3 or 4 years of SIT and patients were assumed to be either stabilized or worse at the end of the 6- to 7-year study. Patients receiving SDT were assumed to continue therapy throughout the study and symptoms were either improved, stabilized, or worsened.

SIT was found to be more effective both in terms of the number of patients with improved symptoms and asthma cases avoided. SDT was the least expensive treatment regardless of group (adult vs child) or indication (pollen vs dust mite allergy). SCIT was more cost effective than SLIT. Comparing SCIT to SDT, the ICER per additional improved patient ranged from €349/\$517 in 2010 USD (children-dust mite allergy) to €722/\$1069 in 2010 USD (adults-pollen allergy) and ICER per additional case of asthma avoided ranged from €393/\$582 in 2010 USD (adults-dust mite allergy) to €1327/\$1964 in 2010 USD (adults-pollen allergy). Comparing SLIT to

SDT, the ICER per additional improved patient ranged from €630/\$933 in 2010 USD (children-pollen allergy) to €2371/\$3509 in 2010 USD (children-dust mite allergy) and ICER per additional case of asthma avoided ranged from €824/\$1220 in 2010 USD (children-pollen allergy) to €3938/\$5829 in 2010 USD (children-dust mite allergy).

The main limitation of this study was its use of an expert panel to estimate both efficacy and health care resource variables. Although decision models commonly use expert opinion to develop and populate models, groups of experts often disagree and the notion of expert “consensus” may be an illusion.<sup>43</sup> The investigators claimed to have “cross-validated” the medical outcomes of the model with those of published clinical trials, but it is not clear whether these clinical trials were selected to develop the model efficacy parameters (and whether other trial data were rejected) or whether these parameters were estimated using other sources. In addition, the expert panel’s assumptions regarding health care resource use were faulty in at least one respect. Although the expert panel had determined that hospitalization was a rare event in patients with AR and asthma, and thus did not include inpatient use in the model, subsequent examination of French retrospective data indicated that hospitalization of asthmatic children and adults occurred each year. The investigators acknowledged that the failure to include hospitalization costs likely underestimated the cost effectiveness of SIT relative to SDT.

## 2008

### *Hankin*

---

A 7-year (1997–2004) retrospective analysis of Florida Medicaid claims data evaluated treatment outcomes and costs of children who were newly diagnosed with allergic rhinitis and naïve to SIT.<sup>29</sup> Patients were selected who were newly diagnosed with AR, had at least 1 year of data preceding and 4 years of data following their first AR diagnosis, had received SIT following their first AR diagnosis, and had at least 6 months of data following termination of SIT. Among these 354 patients, medical costs accrued during the 6 months before SIT initiation were compared with costs accrued during the 6 months following termination of SIT. Although only 16% of patients completed at least 3 years of SIT, and more than half of patients received 1 year or less of SIT, pharmacy, outpatient, and inpatient costs were significantly reduced in the 6 months post-SIT compared with the 6 months before SIT initiation. The mean weighted 6-month cost reduction was \$401 per patient, which offset the mean cost of SIT (\$424 per patient). The main limitations of this study were its short-term follow-up and the specialized nature of the sample.

## 2010

### *Hankin*

---

A 10-year (1997–2007), retrospective claims, matched cohort study compared the median, 18-month, per-patient direct costs (pharmacy, outpatient visits, inpatient admissions) of Florida Medicaid-enrolled children (age <18 years) newly diagnosed with AR who subsequently received versus did not receive SIT.<sup>30</sup> Those with AR who received at least 2 administrations of SIT were matched by age at AR diagnosis, sex, race/ethnicity, comorbid illness burden, and the presence of asthma, conjunctivitis, or dermatitis to children newly diagnosed with AR who did not subsequently receive SIT.

Compared with matched controls who did not receive SIT, children who received SIT had significantly lower 18-month, median, per-patient, total health care costs (\$3247 vs \$4872), outpatient costs exclusive of SIT (\$1107 vs \$2626) or inclusive of SIT (\$1829 vs \$2594), and pharmacy costs (\$1108 vs \$1316;  $P < .001$  for all).

Significant differences in total median health care costs were evident as early as 3 months after SIT initiation and increased throughout the 18-month analysis. At 3, 6, 12, and 18 months, median, per-patient, total health care cost savings in favor of SIT were \$248, \$527, \$1061, and \$1625, respectively, ( $P < .001$  at all time points). As previously noted, limitations include the short-term follow-up and the specialized nature of the sample.

## 2011

### *Hankin*

In an 11-year (1997–2008), matched cohort, retrospective claims analysis of Florida Medicaid adult enrollees newly-diagnosed with AR, investigators reported even more compelling findings than those reported for children.<sup>31</sup> At 18 months, total mean health care costs for inpatient (\$10,352 vs \$14,796,  $P = .003$ ), outpatient excluding (\$2466 vs \$4181,  $P < .0001$ ) or including (\$2668 vs \$4101,  $P < .0001$ ) SIT, pharmacy (\$5636 vs \$6321,  $P < .0001$ ) and total health care services (\$10,626 vs \$17,912,  $P < .0001$ ) were significantly lower for patients who received versus did not receive SIT. Significant total health care savings were realized within 3 months of SIT initiation (\$1932 vs \$3189,  $P < .0001$ ), and exceeded the mean 18-month outlay for SIT (\$337). Per-patient, 18-month total cost savings with SIT were 41%. Again, limitations include the short-term follow-up and the specialized nature of the sample.

## SUMMARY

We identified 15 studies from 1995 to 2011 that have examined the health economics of SIT. All focus on AR with or without asthma. Five studies specifically pertain to treatment of US patients<sup>29–31,33,34</sup> and the remainder examine the economics of SIT among patients in Europe. Routes of SIT administration include subcutaneous injection,<sup>20,23,24,27–34</sup> and sublingual immunotherapy.<sup>21,22,25,26</sup> There is wide variation in primary sources for health services use and costs: retrospective administrative claims data were the basis for 4 studies,<sup>29–31,33</sup> randomized, controlled trials for 3 studies<sup>20,25,26</sup> published literature for 3 studies,<sup>24,27,34</sup> physician surveys for 2 studies,<sup>22,32</sup> and medical records,<sup>21</sup> medical records and patient survey,<sup>23</sup> and Delphi panel expert opinion,<sup>28</sup> for 1 study each. Duration of evaluated outcomes ranges from 6 months pre- versus post-SIT<sup>29</sup> to 6-year follow-up after a 3-year course of SIT.<sup>25,26</sup>

Despite the wide variation in AR comorbidity, geographic location of analysis, route of administration, sources from which economic evaluations are based, and duration of treatment outcomes, the resounding message is that SIT provides cost benefit that ranges from \$96<sup>24</sup> to \$5465<sup>31</sup> per year. Of the 2 studies that reported a cost disadvantage for SIT, one failed to adjust for group differences in baseline illness severity<sup>33</sup> and the other<sup>23</sup> predicated much of its findings upon potentially biased patient self-report and extrapolations from unrelated populations.

There are unique limitations associated with each type of economic analysis included in this review. Whereas analyses based upon prospective, randomized trials offer the greatest control of clinical and economic variables, particularly with regard to the quality and quantity of treatment received, clinical trials may be limited by their lack of generalizability due to potentially contrived study design, recruitment of patients who are unrepresentative of those who actually receive treatment, unrealistically intensive patient attention and monitoring, and short time horizons.<sup>44</sup> In contrast, although retrospective analysis of administrative claims data does not allow for the selection of variables beyond those already provided within the database, this type of analysis offers objective information about medical resource utilization of patients

receiving treatment in the “real world.” Finally, while economic analyses based upon pharmacoeconomic models have consistently found SIT to confer cost advantages relative to SDT over an 8- to 10-year period,<sup>22,24–28</sup> the underlying assumptions upon which these analyses are based often remain opaque to the reader, have not been well validated, and are not routinely tested for sensitivities.

Compared to SDT, which provides temporary symptomatic relief, SIT is the only potentially disease-modifying treatment currently available.<sup>15</sup> Unfortunately, SIT is initiated by only a minority (2–6%) of potentially appropriate patients in the US<sup>29,33,45</sup> and patient adherence to the generally recommended 3-year minimum course of treatment<sup>46</sup> is rare.<sup>29</sup> Underserved populations are generally the least likely to initiate SIT, and are the most likely to prematurely discontinue treatment.<sup>47</sup>

The magnitude of cost savings associated with SIT varies across studies cited in this review. Savings of as much as 80% have been reported among Italian adults with AR and asthma 3 years after completion of a 3-year course of SIT.<sup>20</sup> In the US, total health care cost savings of 33% and 41% have been reported for US children<sup>29</sup> and adults<sup>30</sup> with AR (with or without asthma), respectively, within 18 months of SIT initiation. Given the suboptimal duration of SIT reported for US patients<sup>30,33</sup> estimated US cost savings conferred by SIT are likely to be greater among patients who adhere to the suggested 3-year minimum course of treatment.

Although SIT lacks the glamor and allure of more sophisticated (and more expensive) SDTs, SIT remains the current, albeit underutilized, standard of care for the treatment of allergic disease. As new SDTs proliferate and health care costs continue to spiral, the comparative clinical and cost effectiveness conferred by these new market entries over SIT must be carefully and thoughtfully examined.

## REFERENCES

1. The American Academy of Allergy, Asthma and Immunology (AAAAI). The Allergy Report. Milwaukee (WI): AAAAI; 2000.
2. Wallace D, Dykewicz M, Bernstein D, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122(2): S1–84.
3. Chronic conditions - a challenge for the 21st century. Washington, DC: National Academy on an Aging Society; 1999.
4. Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2000;21(1):1–6.
5. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 2009;124(Suppl 3):S43–70.
6. Schoenwetter WF, Dupclay L Jr, Appajosyula S, et al. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004;20(3):305–17.
7. Allergies in America. A landmark survey of nasal allergy sufferers. Allergies in America: executive summary 2006. [January 9, 2007]; Available at: <http://www.myallergiesinamerica.com/healthcare/overview.aspx>. Accessed August 16, 2010.
8. Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001;108(1):S45–53.
9. Soni A. Allergic rhinitis: trends in use and expenditures, 2000 and 2005; Statistical brief #204. Bethesda (MD): Agency for Healthcare Research and Quality; 2008.
10. Halpern MT, Schmier JK, Richner R, et al. Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004;41(1): 117–26.

11. Thomas M, Kocevar VS, Zhang Q, et al. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics* 2005;115(1):129–34.
12. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985–97.
13. Leger D, Annesi-Maesano I, Carat F, et al. Allergic rhinitis and its consequences on quality of sleep: an unexplored area. *Arch Intern Med* 2006;166(16):1744–8.
14. Stewart MG. Identification and management of undiagnosed and undertreated allergic rhinitis in adults and children. *Clin Exp Allergy* 2008;38(5):751–60.
15. Cox L, Atwater S. Allergen immunotherapy for allergic rhinitis and asthma. *Drug Benefit Trends* 2008;20:1–6.
16. Gold MR, Siegel JE, Russell LB, et al. *Cost-Effectiveness in Health and Medicine*. New York (NY): Oxford University Press; 1996.
17. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(Suppl 1):S1–55.
18. Sullivan SD, Weiss KB. Health economics of asthma and rhinitis. II. Assessing the value of interventions. *J Allergy Clin Immunol* 2001;107(2):203–10.
19. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004;22(6):345–61.
20. Ariano R, Berto P, Tracci D, et al. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006;27(2):159–63.
21. Berto P, Bassi M, Incorvaia C, et al. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. *Eur Ann Allergy Clin Immunol* 2005;37(8):303–8.
22. Berto P, Passalacqua G, Crimi N, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol* 2006;97(5):615–21.
23. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)* 2005;33(6):296–302.
24. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics* 2000;17(1):37–52.
25. Bachert C, Vestenbaek U, Christensen J, et al. Cost-effectiveness of grass allergen tablet (GRAZAX(R)) for the prevention of seasonal grass pollen induced rhinoconjunctivitis—a Northern European perspective. *Clin Exp Allergy* 2007;37(5):772–9.
26. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin* 2007;23(5):1113–20.
27. Buchner K, Siepe M. Nutzen der Hyposensibilierung unter wirtschaftlichen Aspekten. *Allergo J* 1995;4:156–63 [in German].
28. Omnes LF, Bousquet J, Scheinmann P, et al. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. *Eur Ann Allergy Clin Immunol* 2007;39(5):148–56.
29. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 2008;121(1):227–32.

30. Hankin CS, Cox L, Lang D, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol* 2010;104:79–85.
31. Hankin CS, Cox L, Wang Z, et al. Does allergen-specific immunotherapy provide cost benefits for children and adults with allergic rhinitis? Results from large-scale retrospective analyses jointly funded by AAAAI and ACAAI. Oral presentation to be presented at the 2011 Annual Conference of the American Academy of Allergy, Asthma and Immunology. San Francisco (CA), March 18–22, 2011.
32. Le Pen C, Rumeau-Pichen C, Lillin H. L'impact de l'immunothérapie spécifique sur le couts directs de la maladie allergique: une etude pragmatique. *Rev Franc Allergol Immunol Clin* 1997;37:11–4 [in French].
33. Donahue JG, Greineder DK, Connor-Lacke L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 1999; 82(4):339–47.
34. Bernstein JA. Pharmacoeconomic considerations for allergen immunotherapy. In: Lockey RF, Bukantz SC, editors. *Allergens and allergen immunotherapy*. New York: Marcel Dekker, Inc; 1999. p. 445–53.
35. Available at: <http://www.measuringworth.com/index.php>. Accessed February 15, 2011.
36. Bureau of Labor Statistics. Consumer Price Index. Available at: <http://data.bls.gov/cgi-bin/surveymost?cu>. Accessed February 15, 2011.
37. Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. *Ann Allergy* 1993;70(6):480–2.
38. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993;91(3):734–7.
39. Tinkelman D, Smith F, Cole WQ 3rd, et al. Compliance with an allergen immunotherapy regime. *Ann Allergy Asthma Immunol* 1995;74(3):241–6.
40. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol* 2002;88(4):391–4.
41. Frew AJ, Powell RJ, Corrigan CJ, et al. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117(2):319–25.
42. National Institute for Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2004.
43. Sheldon TA. Problems of using modelling in the economic evaluation of health care. *Health Econ* 1996;5:1–11.
44. Sculpher MJ, Claxton K, Drummond M, et al. Whither trial-based economic evaluation for health care decision making? *Health Econ* 2006;15(7):677–87.
45. Law AW, Reed SD, Sundry JS, et al. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2003;111(2):296–300.
46. Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? *Ann Allergy Asthma Immunol* 2007;98:416–26.
47. Hankin CS, Lockey RF. Patient characteristics associated with allergen immunotherapy initiation and adherence. *J Allergy Clin Immunol* 2011;127:46–8.