

ORIGINAL ARTICLE

Is prevention of atopic eczema with hydrolyzed formulas cost-effective? A health economic evaluation from Germany

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Abstract

Objective: The German Infant Nutritional Intervention (GINI) trial, a prospective, randomized, double-blind intervention, enrolled children with a hereditary risk for atopic eczema (AE). When fed with certain hydrolyzed formulas for the first 4 months of life, the risk was reduced by 26–45% in PP and 8–29% in intention-to-treat (ITT) analyses compared with children fed with regular cow's milk at age 6. The objective was to assess the cost-effectiveness of feeding hydrolyzed formulas.

Patients and Methods: Cost-effectiveness was assessed with a decision tree model programmed in TreeAge. Costs and effects over a 6-yr period were analyzed from the perspective of the German statutory health insurance (SHI) and a societal perspective at a 3% effective discount rate followed by sensitivity analyses.

Results: The extensively hydrolyzed casein formula would be the most cost-saving strategy with savings of 478 € per child treated in the ITT analysis (CI95%: 12 €; 852 €) and 979 € in the PP analysis (95%CI: 355 €; 1455 €) from a societal perspective. If prevented cases are considered, the partially whey hydrolyzed formula is cost-saving (ITT -5404 €, PP -6358 €). From an SHI perspective, the partially whey hydrolyzed formula is cost-effective, but may also be cost-saving depending on the scenario. An extensively hydrolyzed whey formula also included into the analysis was dominated in all analyses.

Conclusions: For the prevention of AE, two formulas can be cost-effective or even cost-saving. We recommend that SHI should reimburse formula feeding or at least the difference between costs for cow's milk formula and the most cost-effective formula.

Atopic eczema (AE; ICD 10 L20) is an inflammatory, chronically relapsing, non-contagious pruritic skin disease (1). It represents the most frequent chronic skin disease in school-aged children (2). Germany is among the high-prevalence countries (13.2% in children) (3).

Atopic eczema relies on an interplay of several factors (4). Allergens contribute to the development of AE. Yet, genetics

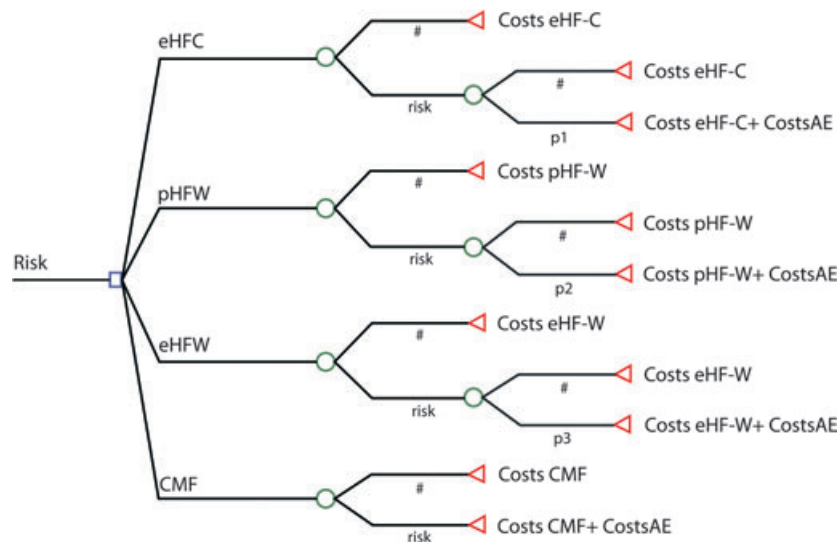
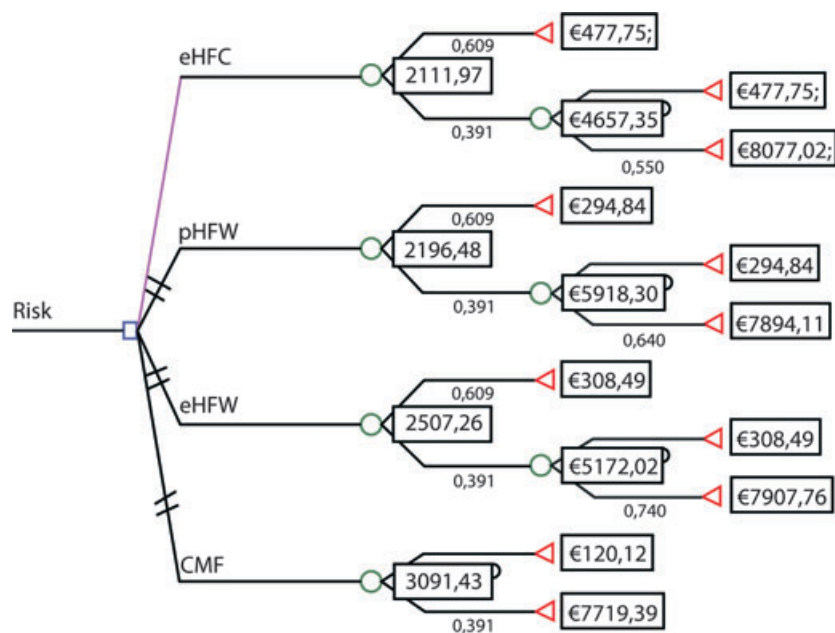
also explains some cases (1). The risk of AE is correlated with maternal or paternal atopy (OR: 3.83; CI95%: 1.20–12.23). If both parents have atopic diseases, the OR increases to 6.12 (CI95%: 2.02–18.50) (5, 6).

Thus, the primary prevention of atopic diseases includes minimizing exposure to known allergens. Exclusive breastfeeding during the first 3 months of life is associated with

Table 1 Cumulative Incidence of Atopic eczema at Age 6 (von Berg 2008)

Intention-to-treat	CMF (n = 556)	pHF-W (n = 557)	eHF-W (n = 559)	eHF-C (n = 580)
Cases (%)	169 (37.9)	135 (31.1)	151 (33.1)	120 (27.1)
RR	1	0.79 (0.64–0.97)	0.92 (0.76–1.11)	0.71 (0.58–0.88)
Per protocol	CMF (n = 270)	pHF-W (n = 256)	eHF-W (n = 242)	eHF-C (n = 220)
Cumulative Incidence, birth to 6y	90 (39.1)	58 (27.4)	64 (29.9)	41 (22.5)
RR (%)	1	0.64 (0.48–0.86)	0.74 (0.56–0.98)	0.55 (0.39–0.76)

CMF, Cow's milk formula.

**Figure 1** Decision Tree as Programmed for the Cost-Effectiveness Analysis.**Figure 2** Decision Tree presenting the Results from the Societal Perspective at Age 6, per protocol analysis.

a protective effect in children with a family history of atopy (OR: 0.58; CI95%: 0.41–0.92) (7) although—and the authors are aware of this fact—no strong association between breast-feeding and AE in general could be proven (8).

Until 2003, there was limited evidence that feeding with a hydrolyzed formula compared with a cow's milk formula reduces childhood allergy in high-risk infants who are not or not exclusively breast-fed (9, 10). The German Infant Nutritional Intervention (GINI) trial proved a significant drop in the incidence of AE up to 6 yrs, when infants had been fed with certain hydrolyzed formulas in the first 4 months. The objective of this paper is to evaluate whether the prevention of AE with hydrolyzed formulas is cost-effective over cow's milk formula.

Methods

German Infant Nutritional Intervention (GINI) trial

The GINI trial is a prospective, randomized, double-blind controlled intervention study in Germany (recruited 1995–1998) that follows a cohort of 2252 infants with single (one parent or sibling) or biparental heredity for atopy (10–12). In case of insufficient breast-feeding, the intervention consisted of four formulas: partially hydrolyzed whey (pHF-W), extensively hydrolyzed whey (eHF-W), extensively hydrolyzed casein (eHF-C), and standard cow's milk formula (CMF).¹

Compared with CMF, the risk of AE decreased to 0.79 (CI95%: 0.64–0.97) for pHF-W, to 0.71 (CI95%: 0.58–0.88) for eHF-C, and to 0.92 (CI95%: 0.76–1.11) for eHF-W in the intention-to-treat (ITT) analysis. In the per-protocol (PP) analysis, where fully breast-fed children and non-adherent families were excluded, the relative risks diminished to 0.64 (95%CI: 0.48–0.86) for pHF-W, to 0.55 (95%CI: 0.39–0.76) for eHF-C, and to 0.74 (95%CI: 0.56–0.98) for eHF-W (11) (Table 1).

Further epidemiologic data

Data on the level of severity of AE were not gathered in the GINI trial. Therefore, we assumed that the distribution of cases prevented is similar to the distribution among all children affected with AE as detected in a recent nationwide epidemiologic study in Germany, the German health interview and examination survey for children and adolescents [=Kinder- und Jugendgesundheits- (KiGG-) Survey] (3). The data on prevalence of severity of AE were applied to estimate the average annual costs of a single child with AE in the age group up to age six.

¹1. CMF: Nutrilon premium, Nutricia/Numico, Zoetermeer Netherlands 2. pHF-W: Beba HA, Nestlé, Vevey, Switzerland, 3. eHF-W: Hipp HA, Hipp, Pfaffenhofen, Germany, until 1999 on the German market and identical to Nutrilon Pepti, Nutricia/Numico, Zoetermeer Netherlands, and 4. eHF-C, Nutramigen, Mead Johnson, Dietzenbach, Germany.

Overall cost calculation

The analyses of cost-effectiveness were performed from a societal perspective and from the perspective of the German statutory health insurance (SHI). Depending on the perspective, ambulatory care, in-hospital care, training programs, and drug costs were included besides sickness benefits for parents absent from work, expenses for various kinds of complementary services including homeopathy, out-of-pocket expenses for additional items such as bed encasings, and time costs. In addition, we calculated indirect costs based on parental sick leave.

Because we could not obtain real-world data from a SHI fund, we applied a top-down approach for in-hospital treatment, for instance, and followed guidelines and experts' opinions (pediatricians from Cologne and Munich) for drug use for the three levels of severity of AE. In-hospital costs and number of annual rehabilitations for the pediatric population with AE were taken from the official statistics with the major diagnosis 'Severe disease of the skin' (ICD-10 L.20) (13) in children below 18 yr (14). Prices were taken from the current tariffs and catalogs for ambulatory care, in-hospital care, drug reimbursement, and complementary services, as applicable. Further resources and their costing were based on data from the German Federal Statistical Bureau and the most recent scientific literature, for example, on time spent treating a child with AE. Age-specific differences were not included as we only looked at the population up to age six.

Resources and costs in detail

Current market prices of the formulas were calculated per 100 g. The prices were multiplied with the average amount of nutrition necessary for children for the first 4 months of life (see Table 2).

The average number of physician consultations is 5.4 per year (15). 58.3% visited a pediatrician, while 24% consulted a dermatologist. The remaining 17.7% are consultations with allergologists or general practitioners. The average physician consultations are multiplied by the specific contact values for the societal and the SHI perspectives (16).

Treatment with topical corticosteroids and topical immunomodulators (tacrolimus, pimecrolimus) is indicated for

Table 2 Costs of full formula feeding. This is the maximum amount if children are fully fed with formula during first 4 months of life which is rather unlikely in most cases according to German Infant Nutritional Intervention trial data.

Nutrition	Month 1 (€)	Month 2 (€)	Month 3 (€)	Month 4 (€)	Sum (€)
eHF-C	88.20	110.25	132.30	147.00	477.75
eHF-W	56.95	71.19	85.43	94.92	308.49
pHF-W	54.43	68.04	81.65	90.72	294.84
CMF	22.18	27.72	33.26	36.96	120.12

CMF, Cow's milk formula.

Table 3 Utilization of services

Service	Mild (84%)	Moderate (14%)	Severe (2%)
Ambulatory visits to physician	5.4 visits on average calculated over all levels of severity		
Assumptions for topical ointment	50% basic treatment year round 10% corticoid treatment in acute phases 5% non-corticoid treatment in acute phases	70% basic treatment year round 20% corticoid treatment in acute phases 10% non-corticoid treatment in acute phases	80% basic treatment year round 40% corticoid treatment in acute phases 20% non-corticoid treatment in acute phases
Topical ointment (basic)	Year round lipophil crèmes and lotions 5 g twice a day		
Topical ointment (corticoid)	Six acute phases lasting 11 days per annum on average 5 g once a day for acute phases		
Topical ointment (non-corticoid)	Six acute phases lasting 11 days per annum on average Non-steroidal treatment (e.g., tacrolimus, pimecrolimus) 5 g twice a day for acute phases		

acute phases while the basic treatment should be applied year round. Severity dependent assumptions for utilization were made (see Table 3).

We assume that only 10% of the patients with AE participate in a structured educational program once over a 6-yr period (400 €).

The average length of duration for rehabilitation also for AE is 28 days and entails costs of 120 € per day (17). The average costs of a rehabilitation stay for a child under 6 yr with AE are calculated with a parent accompanying the child (surcharge of 50 € per day).

For consultations with complementary care services data from the German Life style Immune System Allergy KiG-G(LISA)-birth cohort (18). Accordingly, we presume that 15% of the patients have yearly consultations—half of them follow-up visits—with homeopaths. 4% have annual consultations with other kinds of complementary medical practitioners. Charges are taken from the current tariffs (19, 20).

Household items such as bed encasings, special diet, etc., and expenses for seeing complementary services are considered (19). We assume that expenditures for household items accrue to 100 € per patient per year.

Costs for parental absenteeism need to be calculated differently from SHI and societal perspectives. As the German SHI compensates the loss of earnings through sickness benefits for a maximum of 10 days per year, the following assumptions were made: In general, 80% of the necessary childcare is managed by mothers and 20% by fathers (21). On the basis of the assumptions on exacerbations, 17% of the working parents of children with AE take these benefits (15). A parent who is absent from work because of sick children aged below 12 receives an average amount of 43.10 € per day (1/365 of 70% of the average German gross earnings) (5). For the German SHI, the expenditures for sickness benefits add up to 59 € per day because of additional social security contributions.

From a societal perspective, parental absenteeism is to be estimated on the basis of gross earnings per hour which are at 21.10 € for men and 16.06 € for women according to current federal statistics (22). These estimates are based on full-time and part-time employment. The loss of earnings is projected by 80% of a woman's salary and 20% of a man's

Table 4 Annual net costs per child with atopic eczema

Cost/Perspective	Societal	Statutory health insurance
In-hospital care	8.08	8.08
Rehabilitation	42.13	42.13
Medication	273.75	273.75
Physicians' fees	106.22	95.53
Sickness benefits	38.53	38.53
Training programs	6.67	6.67
Complementary medicine	23.84	N/a
Additional household items	100	N/a
Lost productivity	141.10	N/a
Time costs	624.69	N/a
Total	1364.91	464.69

Table 5 Input data for the sensitivity analyses

Definition	Effect or costs mean	Low	High
Relative Risk eHF-C (PP)	0.55	0.39	0.76
Relative Risk pHF-W (PP)	0.64	0.48	0.86
Relative Risk eHF-W (PP)	0.74	0.56	0.98
Relative Risk eHF-C (ITT)	0.71	0.58	0.88
Relative Risk pHF-W (ITT)	0.79	0.64	0.97
Relative Risk eHF-W (ITT)	0.92	0.76	1.11
In-hospital care	8.08	2	20
Rehabilitation	42.13	10	80
Medication	273.75	150	400
Physicians' fees (societal)	106.22	50	250
Physicians' fees (SHI)	95.53	50	250
Sickness benefits	38.53	10	100
Structured educational program	6.67	3	25
Additional household items	100	50	150
Complementary medical services	23.84	10	90
Time costs	624.69	200	800
Work loss	141.10	50	300

ITT, Intention-to-treat; SHI, Statutory health insurance; PP, Per protocol.

Table 6 Incremental cost-effectiveness ratios of hydrolysed formulas

Perspective	Denominator	ITT			PP		
		eHF-C	eHF-W	pHF-W	eHF-C	eHF-W	pHF-W
Societal	Child treated	-477.61 [-852.02, 12.01]	-42.04 [-502.86, 505.18]	-430.11 [-862.12, 88.32]	-979.46 [-1454.87, -355.49]	-584.17 [-1119.01, 128.94]	-894.95 [-1370.36, -241.26]
	Case prevented	-4345.43 [-5352.57, 264.18]	-1386.54 [-5528.36, 12,117.62]	-5404.02 [-6318.70, 7767.48]	-5566.71 [-3788.21]	-5746.33 [-6504.35, 16,488.96]	-6358.01 [-6739.93, -4407.46]
SHI	Child treated	73.27 [-54.20, 239.96]	109.93 [-46.96, 296.23]	-31.20 [-178.28, 145.30]	-97.59 [-259.44, 114.85]	-74.65 [-256.73, 168.14]	-189.46 [-351.31, 33.10]
	Case prevented	666.64 [-340.51, 5276.25]	3625.52 [-516.30, 7105.56]	-391.96 [-1306.65, 12,779.55]	-554.64 [-1087.77, 1223.85]	-734.27 [-1492.29, 21,501.03]	-1345.94 [-1727.87, 604.61]

ITT, Intention-to-treat; PP, Per protocol; SHI, Statutory health insurance.

All costs in €. 95%CI in parentheses. minus indicating cost-saving. The most cost-effective strategy in each perspective is highlighted in bold. The results are based on treating 1000 children with a genetic risk (see defined in the introduction) to suffer from AE and are calculated as an incremental cost-effectiveness ratio (ICER) in comparison with treatment with CMF.

salary to an average loss of earnings of 141.10 € per child with AE per year. On top of that, we calculated an average of 50.37 h per annum for the continuous daily care for a child with AE resulting in 624.69 €. (Table 4).

Cost-Effectiveness Analysis

The evaluation was undertaken as cost-effectiveness analysis for cohorts of 1000 children at hereditary risk for AE. The time horizon based on the data of the GINI-study was 6 yr. Results are presented as incremental cost-effectiveness ratios of formulas vs. the base case CMF based on a decision tree model (Fig. 1). The denominator is presented as per child treated and as per case of AE prevented. The analyses are based on discount rates of 5% (23) and inflation rates of 2% (22).

Sensitivity analysis

One-way deterministic sensitivity analyses were undertaken on a range of parameters (for input values, see Table 5). Moreover, low- and high-value scenarios were explored.

Software

The model of the decision tree was programmed using the software TreeAge (TreeAge Software Inc., Williamstown, MA, USA).

Results

Following a cohort of 1000 newborns with a hereditary risk of AE until age six, all three hydrolyzed formulas prove to be cost-saving from a societal perspective (see Table 6). Both in the ITT and the PP analysis eHF-C are the most cost-saving per child treated with 477.61 and 979.46 € (Fig. 2). If one takes the sum saved per case prevented pHF-W is more cost-saving with 5404.02 € (ITT) resp. 6358.01 € (PP). From SHI perspective, pHF-W remains cost-saving, yet the margin is with 31.20 € (ITT) and 189.46 € (PP) per child treated lower than from the societal perspective. EHF-W is dominated in all scenarios. Overall, ITT and PP analyses by case prevented point in the same direction, ITT being less cost-saving by about 1000 €. For the denominator, 1000 cases treated the ITT effects for eHF-C and pHF-W are about half the size of the respective PP analyses, but still cost-saving.

Sensitivity analyses

The sensitivity analysis (Table 5) of total costs of AE until age 6 (varying the total cost of about 20%) shows eHF-C to be the cost-effective choice between 6079.77 and 9119.66 € from a societal perspective. In a kind of extreme sensitivity analysis with total costs being varied from 1091.99 to 9119.66 € for the 6-yr period, one may detect an optimal choice changing from CMF to pHF-W at the threshold value of 1341.67 € (which would be equal to a

total disease duration of 0.9 yr) and from pHF-W to eHF-C at 4822.22 € (which would be equal to a total disease duration of about 3.6 yr). If one assumed a disease onset in year two instead of year one for 80% of the children (resulting in about 6507.73 € costs after 6 yr), the choice of the first year would be CMF, but still eHF-C in year six. If one assumed more children to have a disease onset later than the first or second year of life, the optimal choice of nutrition would be pHF-W.

From the SHI perspective, the optimal choice (varying the overall costs from 2069.78 to 3104.66 €) is pHF-W in year six. Varying the total costs of AE from 292.10 to 2439.42 €, the threshold value is 1241.26 € corresponding to 3.5 yr of disease given the annual costs as is in our study.

Discussion

The analysis demonstrates the prevention of AE in children to be cost-effective and even cost-saving per child treated and per case prevented in all scenarios investigated. In the societal perspective, eHF-C was the most cost-saving per child treated, in all other cases pHF-W dominated. The third formula, eHF-W, was dominated in all scenarios. The question whether formula feeding to prevent AE in children prone by hereditary risk is a cost-effective intervention can be answered positively. Results were sensitive to total costs as well as time costs and costs of medication insofar as cost-effectiveness would switch between formulas, but never to CMF. Also, the costs of the formula would have an effect on our results, but within realistic ranges would not alter our overall results.

Strengths of this study are the data basis—a large double-blind randomized controlled trial RCT with three hydrolyzed formulas with blinding up to 3 yr and a follow-up of 6 yr—and its independence from industry. As pointed out in recent meta-analyses more or less confirming the effects applied in this analysis, the GINI trial was the only methodological sound (24).

Our results represent a conservative estimate. (i) Data from the ITT analysis were taken. (ii) In the GINI trial, the infants had varying amounts of formula nutrition. Only 48.6% of the infants received the formula nutrition as supplement to breast milk from the first month onwards. 13.3% started with the formula nutrition after the first month of life, 10.9% after the second, and 27.2% after the third month, respectively. In the GINI trial, only 7% of all children were exclusively given the formula nutrition for the entire 4 months (see Table 2). Subsequently, the overall costs for formula nutrition could be estimated much lower as was done in our calculations. (iii) Because we did not model beyond the time horizon of the study, uncertainty could be minimized.

As a weakness, it was repeatedly pointed out that the results of the GINI trial only reflect parental recall. However, in a previous publication, the concordance between parent reported and physician diagnosis was to be found high at 3 yr in the GINI cohort (11): 'The concordance between these two outcome definitions was checked at 3 yr and

showed rather good agreement, although the preventive effects for atopic dermatitis/atopic eczema (AD) and atopic manifestation (total of AD, asthma and allergic rhinitis) (AM) are slightly stronger throughout the study groups if the diagnosis is based on parental reported physician's diagnoses.' In this context, we are also fully aware that unblinding after the 3 yr follow-up is a limitation of the study. It may also be considered one explanation for the 'late-onset' effect of the eHF-W.

Another limitation is that no data were gathered on the distribution of the severity levels among the cases detected, but not prevented in the GINI trial. Thus, we had to make the following assumptions: (i) The distribution of severity categories among the cases prevented was the same as in the KiGG-Survey though these could be different in the group of hereditary AE looked at in general and in the group of cases prevented in particular. (ii) The effect on the severity categories was the same for all formulas. Because no data were available, we declined to perform sensitivity analyses on all of these scenarios as they would be merely speculative. However, if one reduced the medication costs representing a much higher share of cases prevented in the light category of AE, all three formulas would still be cost-effective over CMF.

Likewise, one might argue that the resource use and the subsequent costs were solely based on expert opinions. As experts may over- or underuse as well as over- or underestimate the resource use, this might have an effect toward a more or a less favorable outcome of the current analysis. Same could happen if more parents utilized an education program that could result in higher rates of prescriptions meaning better adherence on behalf of the parents or lower rates as acute flares might be prevented that cause overall much higher costs. We can only speculate, but assume that the wide intervals for all inputs of the sensitivity analyses are a reflection of these constraints.

In relation to (8), the argument arose that further prospective studies are needed to confirm the exact proportion of AE that can be prevented by hydrolyzed formula vs. breastfeeding. We agree that breastfeeding mothers might significantly differ from non-breastfeeding mothers. In addition, it would seem rather unfeasible to randomize mothers to breastfeeding vs. formula. Yet, we think that our estimate is based on the 'worst case' meaning full formula feeding from birth. Should formula feeding right from birth prevent even more cases of AE our results would be more favorable.

In our study, we calculated total costs of 1364.20 € per patient per year to be relevant for society and 464.69 € to be relevant for SHI. In 2005, Ehlken et al. (15) estimated total annual costs per child from 1 to 6 yr in Germany for society of 1467 € and direct costs for SHI of 766 € based on bottom-up strategies. In another study on the costs of AE using a sample of 204 German children suffering from moderate or severe AE, the direct costs were as high as 2577 € per child per year. On top of that, indirect costs of 1843 € per child per year were accrued (21). In other studies based on moderate to severe symptoms, direct medical costs for the SHI of 1448 € (21) per patient per year could be obtained. In 2003, the direct costs by Weinmann et al. (25)

were estimated according to level of severity. The study estimated direct costs of 164 € (mild symptoms), 417 € (moderate symptoms), and 1023 € (severe symptoms) per patient per year. This is closer to the average direct costs in our study.

The estimation of work loss (indirect costs) of 141.10 € per patient per year (societal perspective) is a low estimate compared with 339 € per patient per year (26) or even 1506 € per patient per year in children with severe symptoms (19).

A limitation of this model arising from the original GINI trial is the effect of non-adherence to the feeding recommendations. If the relative risks of the ITT analysis are applied, however, the choice will remain eHF-C in the sixth year (societal perspective). The same holds for the sixth year in the SHI perspective. The only difference is that there are either no savings or they are much lower, if ITT and PP are compared (see Table 5).

As the GINI trial cohorts are still under follow-up, we are aware that unexpected side effects or a sudden change in prevalence with the various formulas could appear at any time. This argument can be raised against any preventive intervention that is supposed to have an effect on a life-time course (e.g., HPV vaccination). For other countries, there are only studies covering much shorter time horizons, yet pointing into the same direction (27).

This economic evaluation particularly concentrates on the monetary aspects of AE and the costs of the formula nutrition. Eventual improvements of severity or quality of life were not investigated (no data in GINI trial).

Causes of family stress related to caring for children with moderate or severe AE (e.g., sleep deprivation and time-consuming treatment) may equal to those related to caring

for children with diabetes mellitus type 1 (28). Between two and three hours each day are generally spent treating AE, and a nightly average of one to two hours of sleep is lost (29). Thus, not only costs for absenteeism, but also because of presenteeism (30) should be included, a condition that would heighten the costs from a societal perspective.

Indirect costs of 1843 € per child per year were accrued as reported elsewhere (21). This reveals the enormous economic burden also for the parents themselves. More than 60% of the total costs were borne by the parents. Considering this aspect of a future burden as well, parents of children with a hereditary risk of AE should be interested in feeding their children with formula.

In conclusion, the results of our economic analysis highly suggest SHI to reimburse hydrolyzed formula. At minimum, we recommend the coverage of the cost difference between CMF and the most cost-effective alternative.

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Conflict of Interest

Berg A, Koletzko S, and Bauer C-P have declared conflicts of interest. All other authors do not have any conflicts of interests.

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