Cost-effectiveness of lung transplantation in The Netherlands: a scenario analysis

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Cost-effectiveness of Lung Transplantation in the Netherlands*

A Scenario Analysis

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Study objectives: **To calculate cost-effectiveness of scenarios concerning lung transplantation in the Netherlands.**
Design: **Microsimulation model predicting survival, quality of life, and costs with and without transplantation program, based on data of the Dutch lung transplantation program of 1990 to 1995.**
Setting: **Netherlands, University Hospital Groningen.**
Patients: **Included were 425 patients referred for lung transplantation, of whom 57 underwent transplantation.**
Intervention: **Lung transplantation.**
Results: **For the baseline scenario, the costs per life-year gained are G 194,000 (G=Netherlands guilders) and the costs per quality-adjusted life-year (QALY) gained are G 167,000. Restricting patient inflow ("policy scenario") lowers the costs per life-year gained: G 172,000 (costs per QALY gained: G 144,000). The supply of more donor lungs could reduce the costs per life-year gained to G 159,000 (G 135,000 per QALY gained; G1=US$0.6, based on exchange rate at the time of the study).**
Conclusions: **Lung transplantation is an expensive but effective intervention: survival and quality of life improve substantially after transplantation. The costs per life-year gained are relatively high, compared with other interventions and other types of transplantation. Restricting the patient inflow and/or raising donor supply improves cost-effectiveness to some degree. Limiting the extent of inpatient screening or lower future costs of immunosuppressives may slightly improve the cost-effectiveness of the program.** ***(CHEST 1998; 113:124-30)***

Key words: cost-effectiveness; cost utility; lung transplantation; microsimulation; scenario-analysis

Abbreviations: QALY=quality-adjusted life-year

Lung transplantation is a fast-growing and expensive medical intervention. Worldwide, about 6,000 lung transplants have been performed in more than 100 centers.[1] However, reliable information on cost-effectiveness of lung transplantation programs is lacking. To our knowledge, only one retrospective pilot study on this topic was published thus far.[2] Its small sample size and limited cost-analysis prohibited firm conclusions. In this article, we will estimate the cost-effectiveness of various scenarios of future lung transplantation, based on detailed data from a large technology assessment of the Dutch lung transplantation program, as performed during 1990 to 1995.[3] This study was initiated by the Dutch National Health Insurance Board, to support public reimbursement decisions.

The scenario analysis describes future transplantation programs, operational for 15 years. This simulation period is necessary to reach a stable number of patients on the waiting list, which has not yet been established during the observation period. Societal costs, survival, and quality of life are followed up to 40 years, comparing the situation with and without a lung transplantation program.

Several scenarios will be presented: a baseline

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scenario, a prolongation of the current program; a policy-scenario, restricting the inflow of patients on the waiting list; and a donor scenario, assuming a larger supply of donor lungs.

Materials and Methods

From November 1990 until April 1995, data were gathered on all patients who entered the Dutch lung transplantation program. Patients are eligible for the program if they have irreversible, progressively disabling, end-stage pulmonary or cardiopulmonary disease with a predicted life expectancy of <12 to 18 months.[4] The first phase of the program is the application phase in which potential candidates are identified on the basis of written information of the referring physician. The other phases of the program are outpatient screening, inpatient screening, pretransplantation, waiting list, transplantation (perioperative and intensive care), inpatient follow-up, and outpatient follow-up. A total of 425 patients was referred to the program. Of these patients, 303 entered the outpatient screening phase and 179 were accepted for the inpatient screening. One hundred twenty patients were placed on the waiting list. Finally, 57 patients received a transplantation. Two patients died during the transplantation phase and nine patients died during the follow-up.

During the screening phase, patients may be rejected, screening may be deferred, or patients do not contact the lung transplantation team for >12 months. With exception of the application phase, for all phases and for all patients, length of stay was registered, with the reason for leaving the phase. Furthermore, all costs (direct medical, direct nonmedical, and indirect nonmedical) and data on quality of life were collected. In addition, several other patient characteristics were registered, of which we used diagnosis, age, body length, and blood type. Diagnosis and age were used as explanatory variables for length of stay in various phases and for survival. Length and blood type were used for matching donor and recipient.

For the same period, we also collected data on donor lungs: acquisition date of the lung and length and blood type of the donor.

Quality of Life

The health-related quality of life of the patients was measured through a self-administered questionnaire. It contained several domain-specific instruments (Karnofsky Performance Index, Index of Well-Being, Self-rating Depression Scale, State-Trait Anxiety Inventory, activities of daily living) and two generic instruments: the Nottingham Health Profile and the EuroQol. Patients were asked to fill out the questionnaire at the entry of the outpatient screening phase, and from then on every 3 months. Following transplantation, quality of life was measured after 1, 4, and 7 months and from then on every 6 months.

In this analysis, effectiveness is measured both as life-years gained and quality-adjusted life-years (QALY) gained. For the latter, it is necessary to express quality of life as a number between 0 and 1 (utility), where 0 represents the worst possible health state, and 1 the best. The EuroQol group has developed an algorithm that allows the calculation of the utility that represents the health state reported by the patient.[5] Note that this utility reflects the value the general population assigns to health states.

Table 1 presents the average quality of life (as measured by the EuroQol score) of patients who did not die while on the waiting list. It shows that the health-related quality of life, already poor during the screening, deteriorates further if patients remain on the waiting list for a year or longer. For patients who died within 1 year after being placed on the waiting list, the utility was lower: on average, 0.4 (n=10). For those patients, the utility in the 3 months before death was 0.31.

Immediately after transplantation, while the patient is still in the hospital, for survivors the average utility has increased to 0.69 (n=24) and improves further, reaching normal values. Table 2 presents the utilities associated with patients' quality of life during the outpatient follow-up phase. The other quality of life instruments also showed a substantial improvement of quality of life after transplantation.[6]

In all phases, except for the waiting list, fewer than five observations were available of quality of life during the last 3 months before death. Therefore, we assume that in every phase, patients' quality of life is 0.30 during the last 3 months before death. Furthermore, for the phases until outpatient follow-up, we have used the utilities as presented before. For the first 2 years of outpatient follow-up, we have assumed that quality of life has a value of 0.85; after 2 years, this increases to 0.90.

Costs

Data on all direct medical, direct nonmedical, and indirect nonmedical costs, *ie*, value of production losses (paid or unpaid work), related to the lung disease, were gathered for all patients, from the moment they entered the outpatient screening phase until they left the program. Where possible, full resource costs were estimated (base year 1992).[7] Table 3 presents for each phase the average costs per patient per cost category. (Please note that values and rate of exchange [G1=US$0.6] are those in effect at the time of the study, where G=Netherlands guilders). The highest costs occur during inpatient screening, on the waiting list, in the transplantation phase, and during follow-up. In general, average costs per patient are higher than median costs and SDs are substantial, reflecting skewed distributions of costs (Table 3). This skew is due to a minority of patients causing very high costs (*eg*, due to complications). This pattern is very normal in numerous studies of medical consumption.[8]

We used the sum-limit method as described by van Hout et al[9] to calculate cumulative costs by length of stay per phase, per patient, and per reason for leaving the phase. These cumulative costs were then used to extrapolate the cost data beyond the

Table 1—*Quality of Life on Waiting List

		Waiting List				
Phase	Screening	0-6 mo	6-9 mo	9-12 mo	12-15 mo	>15 mo
Utility	0.52	0.55	0.50	0.45	0.40	0.40
(SD)	(0.2)	(0.16)	(0.18)	(0.2)	(0.15)	(0.12)
N	169	30	30	27	18	11

*Patients who did not die while on waiting list. Average EuroQol score and SDs (in parentheses).

Table 2—*Quality of Life After Transplantation

Phase	Follow-up					
	1-3 mo	4-6 mo	7-12 mo	13-19 mo	20-25 mo	>25 mo
Utility	0.83	0.85	0.84	0.86	0.91	0.90
(SD)	(0.16)	(0.14)	(0.15)	(0.12)	(0.1)	(0.12)
N	30	24	17	15	12	11

*Average EuroQol score and SDs (in parentheses).

Table 3—*Average Costs per Patient per Phase During Study Period

Phase	Direct Medical Costs Within UHG (G)	Direct Medical Costs Outside UHG (G)	Direct Nonmedical Costs† (G)	Indirect Nonmedical Costs‡ (G)
Outpatient screening	964 (260/1,941)	8,107 (2,583/16,289)	1,244 (590/1,859)	2,678 (1,010/4,326)
Inpatient screening	24,334 (22,587/14,003)	10,290 (8,092/8,441)	2,749 (2,302/2,095)	4,966 (3,752/5,711)
Pretransplantation	603 (37/1,459)	3,471 (1,453/6,155)	691 (465/1,344)	838 (570/1,078)
Waiting list	16,448 (9,299/23,043)	30,174 (20,736/28,380)	5,099 (4,255/4,403)	9,372 (7,178/8,917)
Transplantation	82,557 (67,956/44,228)	121 (0/329)	602 (451/608)	121 (15/234)
Inpatient follow-up	55,766 (53,796/21,005)	517 (0/948)	1,401 (1,076/1,248)	522 (0/950)
Outpatient follow-up (on average 510 days)	71,521(70,129/47,422)	39,186 (28,473/30,964)	5,589 (5,130/3,989)	6,966 (3,429/9,368)

*1G=US$0.6. Median costs and SDs in parentheses (median/SD). UHG=University Hospital Groningen; G=Netherlands guilders.
†Such as travel costs, diet costs, costs of medical supplies.
‡Costs of absence from work (paid work and unpaid work, *eg*, household work).

observation period (or beyond the date for which fewer than five observations were available). Almost all cumulative costs could be estimated by a linear function or by a combination of two linear functions (R^2>95%). For instance, for patients who died during the inpatient screening phase, direct nonmedical costs were G 104 per week whereas indirect nonmedical costs were G 174 per week in the first 15 weeks, and from then on G 110 per week.

Costs for the situation without transplantation were derived from the cost data as gathered for the situation with the transplantation program. It was assumed that until transplantation, the conventional treatment of patients was not influenced by the existence of the transplantation program. The following cost categories are only relevant in case of a transplantation program: all direct medical costs within the University Hospital Groningen (except for a few patients who receive their conventional treatment in Groningen), all costs in the transplantation phase and follow-up, indirect nonmedical costs during the inpatient screening phase, conditioning costs on waiting list (medication, special diets, and physiotherapy), and traveling costs to Groningen.

Survival

To estimate survival without transplantation, survival on the waiting list was used, by defining transplantation as censoring. A parametric model (Weibull) was used to estimate survival, thus allowing extrapolation beyond the observation period. Figure 1 shows both the product limit and the parametric estimates for survival on the waiting list.

After transplantation, the 1- and 2-year survival rates were 86% and 75%, respectively. Not enough data were available to extrapolate survival beyond 3 years. We therefore combined our data with international data on survival after heart and lung transplantation.[1,10] The data available from the St. Louis International Lung Transplant Registry clearly show that cumulative survival after lung transplantation decreases with 5%/yr from year 3 till year 6. Furthermore, data on heart transplantation show that after 1 year, the cumulative survival decreases with 4%/yr until year 11. Combining this information, we have estimated survival after transplantation for the first 3 years with a Weibull model and after 3 years, cumulative survival decreases with 5%/yr (Fig 2).

Method

A microsimulation model was used to calculate the cost-effectiveness of the Dutch lung transplantation program in the next 15 years. A period of 15 years was chosen to make sure that a steady state was reached, *ie*, a situation in which the number of

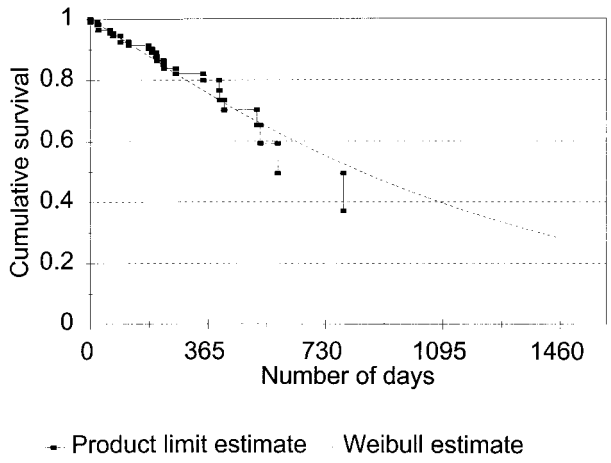

FIGURE 1. Product-limit and parametric estimates for survival on the waiting list for lung transplantation.

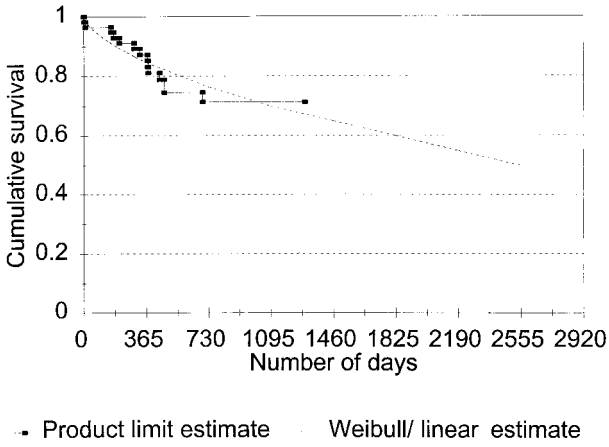

FIGURE 2. Product-limit and parametric estimates for survival after lung transplantation.

patients per pretransplantation phase is stable. After these 15 years, no transplantations are performed, but survival, costs, and quality of life are calculated for a follow-up period of 25 years after the program has stopped; thus, the total evaluation period is 40 years.

The model simulates individual patient histories, containing the exact date a patient enters and leaves a phase. By linking length of stay in each phase with cost and quality of life estimates, the total costs and effects of the program are estimated. To simulate length of stay in, for instance, the outpatient screening phase, four distributions were estimated, based on the Groningen data: one regarding duration until death, one until referral to the next phase, one until rejection, and one until the patient had not contacted the lung transplantation team for >12 months. These distributions were estimated by means of survival analysis, thus allowing for censoring of the data. If the duration distribution until death is estimated, censoring will occur if the patient is rejected, referred, or "has no contact," or if no event has taken place before the end of the study. With the same technique, duration distributions for the other three events are calculated.

Using these distributions, for every patient and for each of the four events, a date for the event is simulated. The event related to the first of these dates is assumed to have taken place. If the event is referral to the next phase, this procedure is repeated until the patient leaves the program or dies.

First, only patient history until waiting list is simulated. For every patient on the waiting list, a date of death is simulated using the cumulative survival curve as presented in Figure 1. This reflects the situation without transplantation program. So, by using this simulation method, a control group was constructed.

Subsequently, a fixed number of donor lungs is simulated to become available, distributed randomly over a year. When a donor lung becomes available, the model checks the waiting list, and of those patients having the appropriate blood type and body length, the longest-waiting patient receives the donor lung. From that moment, the date of death as predicted earlier is canceled and a new date of death according to survival after transplantation is simulated.

After having simulated patient histories, costs and effects were linked to each phase. Then, costs and effects were summed per year, and for years 1 to 15, the fixed program costs were added. To take into account different time profiles for costs and effects, both costs and effects were discounted by 5%/yr, taking year 1 as the base year.

In the baseline scenario, which is basically the situation of 1995, it is assumed that every year the program is effective, 100 patients enter the outpatient screening phase and 17 donor lungs are approved for transplantation.

The cost-effectiveness of two other scenarios will be assessed as well. First, it is anticipated that the baseline scenario will show a rapid increase of the number of patients on the waiting list, due to the small number of available donor lungs. Therefore, a scenario (the policy scenario) will be assessed in which the number of patients entering the program is restricted.

Second, it has been estimated that with extensive effort, the supply of donor lungs in the Netherlands may be increased to 27/yr.[3] In the donor scenario, the impact of such an increase on the cost-effectiveness of the program is calculated.

RESULTS

Baseline Scenario

Patient Flow: Each program year, 100 patients will enter the outpatient screening phase. After 4 years, the number of patients per year who enter a specific phase becomes stable: 65 patients enter the inpatient screening; 50 patients are placed on the waiting list; and 17 undergo transplantation.

The first years of the program, more patients enter the waiting list than leave (either because of transplantation or death). After 10 program years, the number of patients on the waiting list at the end of the year stabilizes (n=105). In this situation, 50 patients enter the waiting list, 17 undergo transplantation, and 33 die. During the 15 program years, the number of patients in the follow-up phase at the end of each year increases. This reflects the fact that each year, more patients undergo transplantation than die. The number of deaths per year during the follow-up phase is 12 in year 10, and 15 in year 15.

Because survival, both on the waiting list and after transplantation, differs for each diagnosis group, we also studied the distribution across diagnosis groups before and after transplantation. In the outpatient phase, 42% of patients have emphysema/COPD vs 58% of the patients with transplants. The percentage of patients with pulmonary hypertension drops from 17% in the outpatient screening phase to 11% after transplantation; for lung fibrosis patients, the percentage decreases from 19 to 10%. The share of patients having cystic fibrosis or other diagnoses remains the same before and after transplantation.

Costs: The total discounted costs with the program amount to G 246 million and without the program to G 130 million. Table 4 presents the total costs in four categories for the evaluation period of 40 years.

For the situation with the program, the costs outside the transplant center are the highest, whereas during the study period 1991 to 1995, the costs inside the transplant center dominated. This is explained by the rapid increase of the number of patients on the waiting list, predicted with the

Table 4—*Baseline Scenario

	Direct Medical Costs Inside UHG	Direct Medical Costs Outside UHG	Direct Nonmedical Costs	Indirect Nonmedical Costs	Total
Costs with program	88	112	16	30	246
Costs without program	0	88	13	29	130
Incremental costs	88	24	3	1	116

*Total costs for the full evaluation period, per type of costs, discounted by 5%, in million guilders. Costs are for 1992. See Table 3 footnotes for explanation of abbreviations.

simulation model. Patients on the waiting list induce much higher costs outside the center.

Health Effects: Without discounting, the total number of life-years during the evaluation period (40 years), in the situation with the program, amounts to 5,494. The number of life-years gained, compared to the situation without program, are 1,232. The total number of transplantations during the evaluation period are 242, yielding 5.1 life-years gained per patient with transplant. The number of QALYs gained is somewhat higher: 1,358, due to the large difference between quality of life on the waiting list and after transplantation. Table 5 presents both life-years and QALYs after discounting by 5%/yr. The total costs per life-year gained (after discounting) amount to G 194,000 (Table 6), the costs per QALY gained are lower: G 167,000. If only direct medical costs are taken into account, the cost-effectiveness ratios are slightly lower. From Table 6 it is clear that the cost-effectiveness ratios are notably influenced by discounting: the cost per life-year/QALY gained increased by 15 to 20% after discounting.

Policy Scenario

In the baseline scenario, two thirds of patients on the waiting list die, which is a highly undesirable situation, both for the patients and for the physicians involved in the program. Therefore, we calculated cost-effectiveness if the program inflow is restricted in such a way that the number of patients admitted to the outpatient screening is such that no more than 50% of the patients eventually die on the waiting list (assuming that the probability of entering the waiting list remains unchanged). This would mean that no more than 68 patients per year should enter the outpatient screening phase. Of these 68 patients, 35 would be placed on the waiting list, and 17 patients would then undergo transplantation per year. If the number of patients entering the program would decrease to <65, not enough patients would be on the waiting list to find a match for all 17 donor lungs. After 10 years, a steady state would be reached, where at the end of the year, 55 patients would be waiting for transplantation.

In this scenario, the additional costs with the program, after discounting, amount to G 95 million, G 22 million less than in the baseline scenario. The number of life years gained and QALYs gained are 550 and 656, respectively (after discounting). Thus, the costs per life-year gained are more favorable, G 172,000, and the costs per QALY gained are G 144,000. If only direct medical costs are taken into account, these ratios are G 168,000 and G 141,000, respectively.

Table 5—*Baseline Scenario

	Life-yr	QALYs
Effects with program	3,264	1,996
Effects without program	2,664	1,297
Life-years or QALYs gained	600	699

*Life-years and QALYs for the full evaluation period, discounted by 5%.

Donor Scenario

In this scenario, the number of patients entering the screening phases and waiting list are the same as in the baseline scenario. From year 4 on, 27 patients undergo transplantation per year, whereas 23 patients die on the waiting list. In the steady state, which is reached after 10 years, the number of patients waiting for a transplant is 75, compared to 100 in the baseline scenario.

With 100 patients entering the outpatient screening each year, all 27 available donor lungs match with at least one patient on the waiting list. If the number of patients entering the program falls below 95, this may not always be the case.

The total costs in this scenario are 26% higher than in the baseline scenario, G 147 million. The number of life years gained and QALYs gained are about 55% higher, 923 and 1,089, respectively. The cost-effectiveness ratios are G 159,000 per life-year gained and G 135,000 per QALY gained (after discounting costs and effects).

Very recently, the legislation in the Netherlands concerning organ donation has changed.[11] The previous system assumed no permission for donation,

Table 6—*Baseline Scenario

	Costs per Life-Year Gained (G)		Costs per QALY Gained (G)	
	0% Discount	5% Discount	0% Discount	5% Discount
Direct medical costs	155,000	188,000	140,000	161,000
Total costs	162,000	194,000	147,000	167,000

*Costs per life year/QALY gained of lung transplantation. Costs are for 1992 and are given in Netherland guilders (G).

unless explicit permission was given by the donor (*eg*, by means of a "donor codicil") or his/her relatives. In the new system, any Dutch citizen will be invited to fill in a response card giving (or not) permission to donate specific organs. A national registry will keep an up-to-date database of these responses, which can be consulted if necessary. It is expected that if this system is fully operational, the number of donor organs will increase.

Sensitivity Analysis

The lifelong use of immunosuppressive medication during follow-up after transplantation is a major element in the costs of lung transplantation. For one of the most often used immunosuppressive drugs, cyclosporine, the future costs may fall as a result of completing the patent period. It is difficult to predict the extent of a possible price decrease. However, if we would assume a 50% cost reduction in follow-up medication, total incremental costs for the baseline scenario would fall by G 11.8 million (5% discounting). The costs per life-year gained (and per QALY gained) would be 10% lower.

However, new, more expensive, immunosuppressive medication is already being used. Widespread application of these drugs will lead to cost increases, but this might be offset by a better survival and/or less drug toxicity, which may improve quality of life.

During the inpatient screening phase, patients are hospitalized for several weeks in the University Hospital Groningen to undergo an extensive number of tests. As lung transplantation is still relatively new, it may be expected that evaluation of the screening process will result in a more limited, but equally effective, screening in the future. If the costs of inpatient screening in the transplant center could be halved, incremental costs and cost per life-year (and QALY) gained would decrease by 6% in the baseline scenario.

The long-term survival after lung transplantation is still very uncertain. If future long-term survival would deviate significantly from the survival as assumed above, it could clearly result in a substantial change in effectiveness. The influence on cost-effectiveness could be considerable, but depends also on the specific costs during the additional life-years gained.

Discussion

Lung transplantation is an expensive, but effective intervention; survival and quality of life improve substantially after transplantation. This analysis suggests that regardless which scenario would effectuate in the near future, lung transplantation remains expensive in terms of costs per life-year (or QALY) gained.

Crucial elements determining cost-effectiveness are the number of patients screened and placed on the waiting list as compared to the number of available donor organs as well as the substantial costs of follow-up after transplantation. As more patients are screened and more patients are waiting (longer) for transplantation, then more costs are incurred without any gains in health effects. Restricting the inflow in the screening phase (*eg*, being even more restrictive concerning contraindications) can improve the balance between the costs of screening and the health effects of transplantation.

We did not try to establish a true "optimal scenario" in terms of cost-effectiveness, but combining the policy and donor scenario (restricted inflow and more donors) would result in G 151,000 per life-year gained (G 124,000 per QALY), which is slightly more favorable than the results of the donor scenario. This scenario has the disadvantage that not all donor organs will be used for transplantation.

The quality of life and utility scores for patients with transplants improved substantially. This is in accordance with the findings of Ramsey et al[12] for lung transplantation patients. About the same improvements in utility scores were found in the Dutch heart transplantation study.[9]

Sensitivity analysis showed that a more limited inpatient screening process could result in some cost reduction. However, the feasibility of such a rationalization should first be investigated.

Comparison with Dutch programs for heart and liver transplantation shows that cost-effectiveness for lung transplantation is relatively unfavorable. Costs per life-year gained (5% discounting) for heart and liver transplantation were G 66,000[9] and G 54,000[13] (costs adjusted to 1992).

This difference cannot be explained fully by different methods of analysis or inclusion of different

cost categories. For heart and liver transplantation, the average number of life-years gained per patient with transplant is higher: 10.5 and 7.6 years, respectively.

Furthermore, the costs during a year on the waiting list or a year of follow-up after transplantation are substantially higher for lung transplantation as compared to heart and liver transplantation.

In the meantime, the Dutch National Health Insurance Board advised the minister of Health Affairs for the moment not to include lung transplantation in the benefit package. The transplantation program will proceed (subsidized by a development grant) but further research should indicate if costs can be reduced, especially during the screening phase (by reducing the number of patients screened and/or lowering the costs per patient screened) and the follow-up phase.

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