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EMPIRICAL AND NORMATIVE ASPECTS OF MEDICAL TECHNOLOGY ASSESSMENT. THE CASE OF REDUCED-SIZE LIVER TRANSPLANTATIONS WITH LIVING DONORS

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ABSTRACT. Medical technology assessment deals with the evaluation of novel or existing health care procedures. This paper addresses the interdependence between factual and normative issues, using the controversies about acceptability and desirability of reduced-size liver transplantations with living donors as example.

Key words: medical technology assessment, ethical controversies, scientific controversies, liver transplantation, living donors

1. INTRODUCTION

Medical technology assessment (MTA) deals with the evaluation of novel or existing health care procedures. This definition indicates that MTA is a value-laden enterprise. However, it is often far from clear in precisely what way MTA is value-laden. To label an assessment as value-laden is often held as a suggestion of bad science. This is an unfortunate mistake. Longino has explained how science in general can be value-laden without being bad science. Indeed, Putnam has set out to explain why any fact cannot be but value-laden, and, vice-versa, why any value cannot be but laden with facts. If he is right, this is likely to hold for facts produced by MTA as well.

To illustrate the confusion about fact-value interactions in MTA, consider the evaluation of liver transplantation (LTx).

We know, by and large, what the prognosis was of patients with different types of terminal liver failure before the introduction of LTx. We also know, by and large, the prognosis of patients with the same types of terminal liver failure, who receive a liver transplant (actual, or actuarial). Hence, we can assess the difference, and ascribe this difference to the introduction of LTx. No values involved so far, at least, so it seems. Of course, there are several sources of uncertainty. The number of observations may be low, which renders the data unreliable. Also, for some unknown reason, the prognosis

about the feasibility of RLTx with living donors that is currently available.

3. DIRECT AND INDIRECT EVIDENCE OF FEASIBILITY OF RLTx WITH LIVING DONORS

A literature search in Medline (search strategy: "liver transplantation", combined with either "living donors", "live donors", "live related donors" or "living related donors" (title, MJ, MN, MW and AB) over the years 1990-February 1993, yielded reports on RLTx with living donors from 7 different hospitals. The data are summarized in Table I. The data concern 51 patients who received a partial liver transplant from a living donor. In most cases, the recipient was a pediatric patient. The most common indication was biliary atresia. The most common complications consisted of episodes of rejection of the graft, primary non-function, infections, and vascular-, biliary- and renal complications. The overall picture seems to be that RLTx ld can be performed with little intra- and post-operative risk to the donor. The reports differ, however, with respect to the details that are presented in this respect. In one paper it is simply stated that no serious complications were observed, without further specification. In the absence of generally agreed standards of what constitute "serious complications", such information is inadequate. The papers also provide data on the effects of the procedure to the donors (partial resection of the liver). In this respect, the results are more variable. As can be expected, early experiences were generally poorer than later experiences. Moreover, the Turkish results compare poorly to the other results. In all cases, however, the follow-up period was short.

3.1. Indirect Evidence

The reason to believe that RLTx ld can be expected to be sufficiently effective and safe also rests on indirect evidence: Results of RLTx with cadaver livers (i), results of partial hepatectomy for medical indications (ii), and animal experimentation studies (iii).

3.1.1. Efficacy and safety of RLTx using post-mortal donor livers. Data on efficacy and safety of RLTx are reported by several groups. Emond et al. have shown that RLTx can be carried out in a way that is equally efficacious and safe to the recipient as OLTx, in pediatric patients with extrahepatic biliary atresia (EHBA), familial cholestasis and certain meta-
<table>
<thead>
<tr>
<th>Location</th>
<th>Sao Paulo Brazil</th>
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<th>Izumo Japan</th>
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<tr>
<td>Period</td>
<td>8.XII.88/21.VII.89</td>
<td>VII.89</td>
<td>13.XI.89</td>
<td>XI.89–II.91</td>
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<tr>
<td>Number of RLTx Id</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>12</td>
<td>5</td>
<td>20</td>
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<tr>
<td>Characteristics of the recipients (age, primary, diagnosis):</td>
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<td></td>
<td>4 1/2 yrs (CBA) 19 months (fibrosis and Caroli's disease)</td>
<td>17 months (CBA)</td>
<td>15 1/2 ± 11 1/2 months (M ± SD) CBA (16), alpha-1-antitrypsin deficiency (2), cytomegalovirus hepatitis (1) and giant cell hepatitis (1)</td>
<td>10 months–53 yrs CBA (1), Byler's disease (2), cirrhosis (7) and hepatitis (2)</td>
<td>9 months–12 yrs CBA (4), cirrhosis and hepatocellular carcinoma (1)</td>
<td>8 months–15 yrs CBA (14), cirrhosis (2), Budd–Chiari (2), progressive intrahepatic cholestatis (1), protoporphyria (1)</td>
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<tr>
<td>Characteristics of the donors:</td>
<td>parent (age 23) parent (age 40)</td>
<td>parent (26 yrs) parent</td>
<td>parents (20), uncle (1), grand mother (1) age 21–41 yrs</td>
<td>parent (7)</td>
<td>spouse (3)</td>
<td>sibling (2)</td>
<td>parents</td>
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<td></td>
<td>alive, 1 rejection period, discharge from hospital on p.o. day 285</td>
<td>death on p.o. day 285</td>
<td>survival: 17 out of 20; complications: retransplantation (4), rejection episodes (8), biliary (7), vascular (9)</td>
<td>survival: 4 out of 12</td>
<td>survival: 4 out of 5, 1 still hospitalized. Infections in all 5 cases</td>
<td>survival: 17 out of 18*, Complications: episodes of ejection (2), infections (2), renal (7), vascular (14), tremor (8), itching (4), insomnia (2), vomiting (1)</td>
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</tr>
<tr>
<td>Follow-up period:</td>
<td>1 month</td>
<td>5 months</td>
<td>9 1/2 months</td>
<td>3–18 months</td>
<td>maximally 3 months</td>
<td>4–17 months</td>
<td>1–13 months</td>
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<td>Reference</td>
<td>a</td>
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Abbreviations: CBA - Congenital Biliary Atresia

* two patients with heart - and renal failure, respectively, were excluded from the study.

In none of the reports serious intra- or post-operative complications to the donor were observed. Discharge from the hospital occurred usually within 2 or 3 weeks. In most of the cases they were reported to be able to resume their normal activities after a few weeks. References: a: Raia et al. (1989); b: Strong et al. (1990); c: Nagasue et al. (1992); d: Broelsch et al. (1991), Broelsch, Stevens, Whittington (1991); f: Haberal et al. (1992); g: Kawarasaki et al (1992); h, i, j, k: Yamaoka et al. (1991), Morimoto et al. (1992), Uemoto et al. (1991), Ozawa et al. (1992).
bolic liver disease. The authors conclude that RLTx may considerably contribute to reduction of pre-transplant mortality in children awaiting LTx. An earlier report by the same group shows that long-term survival (up to 48 months) following RLTx is possible in pediatric patients with biliary atresia and fulminant hepatitis. Otte et al. report of their experience with LTx in 117 children, 83 of which underwent OLTx and 54 of which underwent RLTx. The majority (73) of the children was between 0 and 3 years of age and were treated for cholestatic diseases (primarily EHBA). One year actuarial survival rate after OLTx or RLTx was not significantly different. Pre-transplant mortality during these years was relatively low (approximately 14%). The authors conclude that RLTx is equally safe and effective as OLTx. The paper, reporting for the first time long-term survival (25 months) following RLTx, dates from 1984.

3.1.2. Safety of partial hepatectomy. Partial hepatectomy has been carried out as treatment of various benign and malignant liver diseases. As a consequence, mortality and morbidity associated with this procedure are relatively well documented. A paper by Nagao et al. for instance reports on partial hepatectomy in patients with hepatolithiasis (n = 13), with on operative – or hospital mortality. Including unpublished observations of their own institute, Singer et al. conclude that the operative mortality rate following partial hepatectomy is less than 1%.

3.1.3. Data from animal experimentation studies. Finally, the feasibility of partial hepatic resection and transplantation of reduced-size livers has been established in dogs.

4. RLTx WITH LIVING DONORS: JUSTIFICATION OF ITS FURTHER DEVELOPMENT

Singer and his colleagues have argued that it is ethically justified to continue the development of this innovative therapy. Their arguments can be summarized as follows:

- RLTx with living donors has been demonstrated to be technically feasible, and can be expected to be sufficiently effective and safe. For the recipient: with post-mortal livers, RLTx has been demonstrated to be equally effective as orthotopic liver transplantation (OLTx) and to impose no additional risk. For the donor: Partial hepatectomy can be performed with low peri-operative and long-term morbidity and mortality.
• Organ and tissue donation by living persons is accepted in similar contexts (e.g. renal, pancreatic and bone-marrow transplantation).
• RLTx using living donors is in the interest of all those that are directly involved: the physician, motivated by a desire to save lives; the recipient, motivated by a desire to live; the donor, motivated by a desire to contribute to the saving of a life of – in most cases – a close relative.
• In a progressive society, there is an ethical imperative to pursue new knowledge that may benefit the people.

A major conclusion of Singer et al. reads as follows: “Given the scarcity of donor livers, the capability to perform OLTx using living donors, the potential benefits of this procedure, the motivations of the participants, and the acceptance of living donation in other contexts, we believe that it is ethically appropriate to introduce this innovative procedure.”

5. CHALLENGING THE APPROPRIATENESS OF RLTx LD

In the following, I will summarize some counter-arguments, challenging the plausibility of (i) statements about the safety of hemihepatectomy and the acceptability of living donation in similar contexts, (ii) statements about the superiority of living donation over the use of post-mortal donor livers, (iii) statements about the scarcity of post-mortal donor livers and the rate of pre-transplant mortality, (iv) assumptions about the effectiveness of alternative modes of organ procurement, (v) assumptions about the feasibility of alternative modes of treatment and prevent of ESLD, and (vi) statements about the possibility of obtaining a truly informed consent from a parent-donor.

5.1. Safety of Hemihepatectomy

Busutill estimates that in the case of liver donation, the risk of mortality to the donor is at least 1–2%.\textsuperscript{16} This estimate is partly based on data on the risk of kidney-donation. According to Busutill, the available evidence already indicates that partial hepatectomy is likely to cause complications in the donor. Moreover, it is misleading to suggest that living donation in the context of other transplant programmes is uncontroversial. In the context of renal transplantation, for instance, the appropriateness of living donation is challenged.\textsuperscript{17} Busutill cites a review of 8200 kidney donors; 1 out of 1600 donors died, and 2% suffered major complications (sepsis, renal failure, hepatitis, pneumonia).\textsuperscript{18} He concludes that “An absolutely essential pre-
requisite for consideration of living-related transplantation is that the donor hemihepatectomy can be performed with a zero mortality rate, and essentially no morbidity.” According to Busutill, the available evidence about RLTx ld indicates that these conditions are not met.

5.2. Is RLTx With Living Donors Likely to be More Beneficial Than RLTx With Post-mortal Livers?

RLTx with living donors may have a higher probability of success than RLTx with post-mortal livers, because there is more opportunity for carefully planning the transplantation and the quality of the liver segments is better (less damage due to ischaemia). On the basis of these data, one can expect that living donation has a favourable effect on transplant outcome.

Another reason why RLTx with living donors is thought to be more effective than RLTx with post-mortal livers is related to the fact that in the majority of cases a familial relationship will exist between donor and recipient. As a result of such relationship, there is an increased probability of immunological matching between donor and recipient. Such histocompatibility is likely to improve transplant outcome by reducing the probability of rejection. This argument is, however, controversial. An inverse relationship has actually been established between antigen matching and transplant outcome. A possible explanation for this unexpected finding may be that in a relatively large number of cases of LTx, the cause of the recipient’s liver dysfunction is immunological. In these cases, antigen compatibility has a dualistic effect: it reduces transplant rejection, but it also renders the transplant more susceptible to the immunological mechanisms which are responsible for the dysfunction of the recipient’s liver.

Among liver diseases with a possibly immunological origin are primary biliary cirrhosis, sclerosing cholangitis, autoimmune chronic active hepatitis and viral hepatitis. In these cases, recurrence of liver failure may result from the persistence of disease-associated immunological mechanisms after transplantation. This would imply that from this point of view, donors that do not have a familial relationship with the recipient are preferred over donors that do have a familial relationship, at least in certain cases of RLTx using living donors.

5.3. Are Post-mortal Donor Livers Scarce?

How many deaths among infants with ESLD can be prevented by the utilization of living donors? According to proponents of living donation,
approximately 50% of infants with ESLD dies while waiting for a transplant. This figure is disputed by Busutill.\textsuperscript{23} His estimate of the need for transplants among infants in the U.S., based on data on the incidence of ESLD, is 249 per year. His estimate of the supply of cadaver livers for this group of patients, based on Donor Demographic Data of the United Network for Organ Sharing, is 257 per year. Included in this figure is one quarter of reduced-size livers from adolescents. Hence, no scarcity and considerably lower pre-transplant mortality among infants with ESLD. The latter is estimated between 15 and 25%. In addition, Busutill maintains that improved techniques for preserving cadaver livers allows utilization at a higher rate of these livers.

Similarly, Emond \textit{et al.} maintain that using larger donors for small recipients does not place larger recipients at a greater risk of not receiving a transplant: Review of patterns of donor utilization suggests that there is a relative abundance of full-size grafts.\textsuperscript{24} In 1987, there were approximately 3,500 cadaver donors whereas 1,199 liver transplants were performed in the U.S. in that year. According to these authors, the major problem is not scarcity of post-mortem donor livers \textit{per se}. Rather, it is the disparity between the epidemiology of liver disease in children and the occurrence of brain death and organ donation in this age group. This problem can be largely overcome by using RLTx, and there is no need to include living donors. Otte \textit{et al.} also note that the supply of donor livers exceeds the demand, stressing that the major problem is size disparity.\textsuperscript{25} This is consistent with data from Eurotransplant.\textsuperscript{26} In a report by the Dutch Health Council, the conclusion was reached that at present there is no scarcity of post-mortem donor livers in the Netherlands either.\textsuperscript{27}

The question of scarcity of cadaver livers is closely related to the question of the feasibility to increase the supply of these cadaver livers or decrease the demand for them. To the former, assumptions about effectiveness of organ procurement arrangements are relevant. To the latter, assumptions about alternative modes of treatment or prevention of ESLD are of importance. Both issues will be taken up below.

5.4. \textit{Effectiveness of Alternative Organ-procurement Arrangements}

Can a future increase in demand be matched by changes in legislation on organ procurement, or by increasing public awareness? The groups of Michielsen and of Gnant have argued that the availability of donor organs in Belgium is relatively high, as a result of the "presumed consent" system that has been implemented.\textsuperscript{28} This conclusion was challenged by Jakobson and by Land and Cohen.\textsuperscript{29} The controversy is unresolved at
present; some authors conclude that the picture is complicated since multiple factors determine donor organ availability, or because there are direct as well as more subtle, indirect effects of organ procurement methods.

5.5. Feasibility of Alternative Modes of Treatment and of Prevention of ESLD

Can the need for LTx be decreased by alternative modes of treatment or primary prevention of liver failures, ultimately leading to ESLD? Is it reasonable to expect break-throughs that will lead to a significant reduction in the demand for transplants? Currently, a number of developments take place that suggest that this may indeed be the case. The following developments warrant mentioning:

Treatment of primary biliary cirrhosis with ursodiol. A two-year, multicenter, double blind trial to compare the efficacy of ursodiol with that of placebo showed that ursodiol is a safe and effective treatment of primary biliary cirrhosis, which is a major indication among adults for LTx. Therapeutic interventions in the case of liver failure, other than solid-organ transplantation, include liver cell transplantation, enzyme substitution therapies, Kasai’s procedure, and dietary prescriptions. Among preventive measures are the prevention of viral infections (hepatitis), and the prevention of alcohol abuse.

5.6. Can a Truly Free and Informed Consent be Obtained From the Donor?

Doubt persists with respect to the feasibility of obtaining a true informed consent from the donor, if the donor is the parent and hemihepatectomy is the only way to save the life of their child. This in spite of the special procedures that were proposed by Singer et al. The point is raised by Busutill: “... how can a parent be expected to make an informed, uncoerced, free choice when asked to consider donating an organ to his or her dying child?”

Bio-ethicist Caplan also argued that it can never be a matter of free choice to the parents, whether or not to provide liver segments for their own.

The doubt, whether in this context people can really freely decide whether to donate or not, is discussed by Fox and Swazey. They extend it to the obligation felt by the recipient to accept a donor organ. They discuss why, in spite of these felt obligations, reservations with respect
to the transplantation may persist on both parts. They also discuss the social strains that are produced if people fail to live up to these obligations.

Fox and Swazey apply the “gift-exchange paradigm,” described by Mauss to the exchange of organs for transplantation. This paradigm entails that “to offer and give, to receive and accept, and to seek and find an appropriate way to repay” are the entwined obligations constitutive of any gift-relationship.

According to Fox and Swazey, the application of this gift-exchange paradigm to organ transplantation “illuminates many of the distinctive psychological and social phenomena that donors, recipients, their families, and the transplant team mutually encounter.” Fox and Swazey express the obligations on the part of the donor as follows: “... even though the American organ donation system has been organized around the cardinal societal principles of voluntarism and freedom of choice, in the type of situations where transplants are performed, prospective donors and their families are subject to strong inner and outer pressures to make such a gift.”

As we saw above, similar doubts were expressed by Busutill and Caplan. Fox and Swazey put these in wider framework, involving recipients as well. The obligation to accept an organ and to seek and find an appropriate way to repay are expressed as follows: “Whatever the potential recipient’s reservations may be about a transplant, great reluctance or outright refusal to accept the life-saving gift that is offered symbolically implies a rejection of the donor and of the donor’s relationship to the recipient.”

With respect to the role of the surgeons, Fox and Swazey state that there is uneasiness among them “about the fact that transplanting an organ from a living donor requires them to aggressively violate the basic moral tenet of their profession to do no harm by seriously wounding an individual who is neither sick or a conventional patient – albeit on behalf of someone who is mortally ill and has sought their help.”

By the way of conclusion Fox and Swazey state that “The giving and receiving of a gift of enormous value is ... the most significant meaning of human organ transplantation.”

6. ANALYSIS OF THE CONTROVERSIES:
FACTUAL INFORMATION AND NORMATIVE JUDGMENT

What are we to make of the aforementioned controversies? It is surprising that a number of seemingly empirical questions are resistant to closure. This holds for pre-transplantation mortality and organ scarcity, impact of
organ procurement legislation on organ availability, as well as for the risks and benefits of RLTx with living donors to the donor and the recipient. Part of the explanation is that a number of normative standards are involved; difference of opinion may exist with respect to the adequacy and relative weight of such standards.

On the basis of the account given so far, two extreme positions with respect to the different issues related to RLTx can be distinguished. The first position (A) can be characterized as follows: It is held that there is considerable discrepancy between demand and supply of livers for transplantation. Such a discrepancy results in a high pre-transplant mortality rate: a considerable number of patients with ESLD who are waiting for a transplant die before a suitable transplant is found. Moreover, such scarcity of transplants necessitates strict selection between candidates: who should get the transplant if not all can have one? All measures that could mitigate this situation are considered to be largely exhausted. Hence, mortality among ESLD patients waiting for a transplant can be avoided if, and only if, alternative sources of transplants are used, in this case living donors. It is deemed that morally there is an imperative to prevent or reduce mortality and suffering as the result of ESLD. Any of this mortality or morbidity that is unnecessary, in the sense that it could have been prevented, is considered morally unacceptable. Selection among transplant candidates, necessary because of scarcity of transplants, is also deemed arbitrary and unjust: there do not seem to be any generally acceptable criteria to select among patients. These considerations act to justify the search for and enactment of alternative modes to increase supply of organs, in this case through the use of living donors. Of course, the risks to the donor should not be too high, but the available evidence suggests that the risks are within acceptable limits. Similarly, it is deemed morally unacceptable if individuals would be coerced to donate; informed consent procedures are considered to be capable to prevent this from happening. Any doubts with respect to adverse effects of living donation on human relationships or on our view of human life, are ignored, or brushed aside as subordinate to the saving of human lives and the reduction of suffering associated with ESLD.

The other position (B) is as follows:

It is held that there is hardly any discrepancy between demand and supply for organs. As a result, the estimate of pre-transplant mortality is much lower than in (A). The difference is partly due to the fact that the estimate of the actual need for transplants is lower than in (A). This need for transplants is not given. Of course, it is to a large extent determined
by the incidence and prevalence of ESLD. But it also depends on criteria of eligibility: who, among the patients with terminal liver failure, is likely to benefit sufficiently from a transplant?

Such criteria shift in time, and differ geographically. Patients with certain characteristics may have been excluded from transplantation which, after some time, hardly seems to be justified. A striking example of this is given by patients with liver cirrhosis as the result of alcohol abuse. Conversely, certain indications may have been included which, after some time, turns out to be unjustified. Examples may be hepatitis with active viral replication, or primary liver tumors. Criteria of eligibility are related (1) to standards of minimally required outcome of a transplantation program, (2) to trade-offs between benefits and burdens to the individual patient and (3) to the society at large (employment of resources and their opportunity costs). A lower estimate of the need for transplants may also result from higher expectations with respect to effective prevention or alternative mode of treatment of ESLD. The low estimate of transplant scarcity is partly due to higher estimates of the actual supply and utilization rate of transplants. This supply of organs is not given either, and depends on criteria of post-mortem donor eligibility. Is it, for instance, justified to include "marginal donors" (post-mortem organ donors fifty years of age or more)? Age and health status of the donor may adversely affect transplant outcome, but the issue seems to be unresolved at present. There is also the question whether organ procurement arrangements affect the availability of post-mortem organs. Estimates of the rate of utilization of transplants depend on assumptions concerning the impact of organ preservation techniques, immunosuppression, organizational aspects, etc.

According to this position, the estimate of pre-transplant mortality is low, and the selection of patients for transplantation appears to be settled. Hence, there is no justification of using living donors as organ suppliers. The actual risk to the donor may be estimated higher than in (A), and is at any rate not acceptable: the use of living donors does not result in a significant decrease of pre-transplant mortality. These judgments may at least partly be prompted by considerations related to the "gift-exchange paradigm": the obligations and the reservations with respect to offering and accepting an organ, and the social strains that ensue from these. Often, however, such considerations are left implicit.

The foregoing illustrates how moral judgment about acceptability and desirability of RLTx Id depends on factual information and how this factual information in turn involves several normative judgments. To name a few of such normative judgments:
• How safe and effective should RLTx Id be, and how safe and effective is it? There is disagreement about both of these issues. The two questions are indeterminate as long it is unspecified what is understood by “effective” and by “safe” and what is considered acceptable evidence to establish this (for instance statistical power and prospective nature of studies).

• What is the appropriate outcome measure: should safety be expressed by the mortality rate, by morbidity and complications, or by quality of life? Should the social strains associated to the “gift-exchange relationship be taken into account, and if so, what is their relative weight? Such questions can only be answered if the context in which they arise is taken into account. An operative mortality rate of 1% may be quite acceptable in one context, but not in another.

• What is the appropriate time horizon: Should we follow donors after hemihepatectomy for 6 months, 1 year, 5 years? Here, judgment is likely to be related to an estimate of the probability of adverse effects of hemihepatectomy in the long run: Is there any reason to believe that such long-term effects could occur, and what sort of effects should we look for? The same holds for the follow-up of the recipients: Is there any reason to expect complications from RLTx Id in the longer run (say 5 or 10 years)? And if so, does that affect our judgment about acceptability and desirability of RLTx Id? There is uncertainty about the question how reduced-size livers implanted in very young children grow and develop along with the developing child, uncertainty about adverse effects of the use of immunosuppressiva on the development of very young children, and uncertainty about full recovery of the liver function of the donor. But is it not decisive that, at this moment, the lives of young children can be rescued?

• The supply of grafts nor the demand for them is given; they depend on criteria of eligibility of donors and recipients. These, in turn, depend on requirements concerning the minimally required outcome of the procedure, in view of burdens to patients and their relatives, burdens to rejected patients, its opportunity costs, etc. An estimate of scarcity of grafts also depends on judgment about alternative modes to increase supply of grafts or decrease the demand for them. Here, methodological criteria are involved, determining the acceptability of evidence.

• In each of these cases, the question turns up: What level of certainty is necessary, in order to make accountable decisions?
The nature of the normative standards that are implicated in the empirical evidence concerning RLTx Id is partly cognitive and partly moral. In the two following sections I will further elaborate the involvement of cognitive and moral values, respectively.

7. CREDIBILITY: THE CRITERION OF COHERENCE

In order to be taken into account, facts about RLTx Id have of course "to make sense." The findings of Markus et al. are puzzling in view of our knowledge about histocompatibility and probability of immunological rejection of the transplant. The authors try to provide a satisfactory explanation for the observed phenomena. As long as they do not succeed in this, their data are likely to be considered as anomalies: findings that cannot be explained within the framework of accepted medical knowledge. As such, they are likely to be dismissed as irrelevant. What, then, is a satisfactory explanation of these results? Here, the methodological criterion of coherence is of decisive importance. By pointing to the immunological origin of certain terminal liver failures, Markus et al. succeed in providing a satisfactory explanation for the dual effect of histocompatibility on transplant outcome. This would explain the increased probability of recurrence of the disease after transplantation in the case of HLA-antigen matching between donor and recipient. If it can be convincingly established that immunological origins of terminal renal or heart failure are much rarer, the findings of Markus et al. gain credibility. This example shows how the relative weight that is attributed to empirical evidence depends on a methodological criterion. This is particularly important in view of the conflicting evidence: what weight should be given to studies with conflicting outcomes? This issue is complicated by the fact that there are several methodological criteria with often conflicting requirements. Relatively little has been done to assess the relative weight of different methodological criteria in a particular context, and to resolve conflicting requirements.

7.1. Cognitive Values: Standards of Rational or Justified Belief

The claim that, generally, cognitive values are implied in statements about effectiveness and safety of RLTx Id, can be further substantiated as follows: The statement "partial hepatectomy is sufficiently safe to the donor"
is short-hand for the statement

"On the basis of the available evidence it is rational to believe that partial hepatectomy is sufficiently safe to the donor."

If it is accepted that such rephrasing does not alter the content of the statement, and that rationality is a cognitively normative concept, it follows that the first statement about safety implies cognitive standards, bearing on the acceptability of evidence.

Another way of arguing that statements like the one above involve cognitive values is by asking: What sort of procedure would be required in order to settle a controversy? Any answer that is given to this question involves methodological standards. In the case of this type of controversy, it is important to make such standards explicit.

The question, which procedure should be followed in order to settle the issue, seems to be particularly pressing with respect to the possibility to obtain informed consent. How can it be proved that someone has made an uncoerced decision on the basis of an adequate understanding of what is at stake? Can such proof be hard at all? There are instances where it can be fairly confidently concluded that the decision to donate was not made freely. For instance, someone who is imprisoned and acts as a donor and who expects, perhaps erroneously, to be released. Or, in the case of financial rewards, someone who acts as a donor because he desperately needs money. It seems to be much more difficult to reach a similar level of certainty to establish that someone did consent freely, well-informed and on the basis of an adequate understanding. However, if, in case of doubt about the consent procedure, parents are not allowed to donate, this certainly seems to infringe on their freedom to act. Who, but the parents themselves, should decide whether they consent freely or not, or, for that matter, accept that it can never be a matter of free consent? The questions raised here are questions of explication of a moral concept. I will take up this subject in the following section.

8. MORAL CONCEPTS DETERMINE THE RELEVANCE OF FACTS

In the foregoing, I stated that judgment about the desirability and acceptability of RLTx Id depends on factual information. I also stated that this factual information itself is not value-free. In this section, I will explore this interdependence between normative and empirical issues further.

The following issues need further clarification:
1. The foregoing sections suggest that the debate about RLTx ld revolves around a limited set of moral concepts, like beneficence, non-maleficence, and autonomy. Many disagreements take the form of “If hemihepatectomy would be safe (consistent with the requirements of non-maleficence), then RLTx ld would be morally acceptable.” However, there is disagreement about the question whether it is safe. Similarly: “If the decision to offer a portion of the liver could be made in a non-coercive way (consistent with the requirements of autonomy), then RLTx ld would be morally acceptable.” Again, however, there is disagreement about the question whether such a non-coercive decision can be made in this context. What is the exact nature of these disagreements? Are they about factual issues? Partly, yes, but these facts are themselves laden with values. Are these rival interpretations of moral concepts, and if so, can it be established which one is correct? Do the disagreements result from a different weighing of moral values?

2. How are certain aspects of RLTx ld recognized as relevant to our judgment about its moral propriety? In the following, I will discuss how moral concepts are brought to bear on empirical facts about RLTx ld, and how this, in turn, affects the content of the relevant moral concept. To this end, I will present a model of moral discourse elaborated by Brennan, which, in my view, is compatible with Putnam’s theory of facts and values.

8.1. The Structure of Moral Argument

In Brennan’s model, moral concepts play a diagnostic role: Through them, neutral facts are transformed and charged with moral significance. Examples of moral concepts are beneficence and autonomy. If we are committed to the concept of beneficence, and have a particular understanding of what the concept entails, we are capable of identifying certain actions or situations as beneficent or as non-beneficent. More often than not, there is difference of opinion about the question whether certain actions are beneficent or not. In such cases, we may start by asking whether there is agreement on the formal content of the concept. An example of the formal content of the concept of beneficence is: the obligation to help others further their important and legitimate interests. And, in the case of autonomy: Autonomy is the capacity of individuals to reflect critically upon preferences, desires, wishes etc., and the capacity to accept or attempt to change these in light of considered value commitments. By exercising such a capacity, individuals define their nature, give meaning and coher-
ence to their lives, and take responsibility for the kind of person they are.44

These definitions of the formal content reveal their complexity, and their relation to other concepts. If agreement can be reached on the formal content of these concepts, we proceed by asking what follows from these concepts in the particular context. In Brennan's terms, this is the *explication* of the concept. Part of the argument of Singer et al.45 amounts to the statement that RLTx with living donors is an instance of beneficence in the context of health care. This statement is clearly not shared by Busuttil, or by Fox and Swazey. The question is, then, of course: which of the competing explications is correct? In Brennan's model, to address this question we need to identify and agree upon paradigm cases of autonomous (and beneficent) and non-autonomous (and non-beneficent) actions and situations. Only then we can begin to grasp the meaning of the concept. Subsequently, we have to determine similarities and dissimilarities between the present case and these paradigmatic cases, in order to arrive at a moral judgment about the case at hand. If agreement on the correct explication of a moral concept fails to materialize, we have to take recourse to its *rationale*.46 The rationale should provide an answer to the question why it is, that we are committed to the concepts of beneficence and autonomy. Why should we further other people's important and legitimate interests? Why should we enable them to exercise their autonomy? The rationale of a moral concept acts as a controlling norm on its explication. For an explication of a moral concept to be correct, it should be plausible in view of its rationale. Again, different reasons may be provided and such different rationales may yield different and conflicting explications of the concept. As such, there is not the prospect that a conflict can be resolved with certainty.

Of course, complications may arise because of possibly conflicting requirements between different moral concepts, but I will leave this important point aside. Brennan's model is a formal model: It is silent with respect to the question whether RLTx Id is morally right or wrong. Its value stems from the fact that by distinguishing between different components of moral concepts, and by making explicit the interdependence between moral concepts and empirical facts, it helps to locate sources of disagreement. The practical significance consists in the determination of the appropriate way to proceed in trying to resolve the conflict. In addition, the model indicates certain logical constraints on moral inquiry. Notably, it states that as the result of the open-texture of moral concepts, conflicts involving moral judgments can never be conclusively settled through deductive argument.
8.2. **Paradigm Cases and Open-texture: Morality's Continuity and Change**

Brennan summarizes the properties of moral concepts by qualifying them as *open-textured concepts*. By this he means that it is not possible to state criteria that are necessary and sufficient for their correct application. Rather, criteria for application are implied by provisionally established instances of the moral concept. Hence, the importance of knowledge about these "paradigm" cases. It is the key to improve our understanding of any moral concept. However, since moral concepts are open-textured, there is always the possibility of cases arising where their applicability is in doubt.

Thus, in moral inquiry, we can distinguish between a *moral hypothesis* and a *moral judgment*. The moral hypothesis is a statement saying that a particular act or situation belongs to a certain type, classified by a moral concept and can therefore be judged morally right or wrong. The moral judgment is a statement about the truth or falsity of this hypothesis. Such a moral judgment implies our commitment to the concept; if we are not committed to the relevant moral concept, we are not likely to be interested in the question whether acts or situations are morally right or wrong. It also implies a certain understanding of the concept: Only if we have a certain understanding of the concept of beneficence are we likely to be able to recognize acts as beneficent or non-beneficent. Moral judgment also implies adequate knowledge about the facts that may be relevant to our judgment.

Finally, if we are successful in convincing others that certain types of actions are beneficent, we thereby add to the meaning of the concept. That is: If our hypothesis is considered right, and our judgment sound, we have thereby established a fact which, in turn, may be used to judge other cases. This may, but need not, entail that the meaning of the concept is slightly altered. What is at stake in moral inquiry, then, is to try to achieve agreement on the correct explication of moral concepts, and to get certain cases "established." This process involves a fundamental, and inevitable paradox: To know what follows from a moral concept, we have to understand its meaning. To understand its meaning, however, entails knowing what follows from it. Moral meaning emerges, so to speak, from bringing facts and moral concepts to bear on each other. Differentiating between more and less established cases is an attempt to resolve the paradox. Sufficient agreement in a society is postulated on the questions, which types of actions or situations can be classified as paradigm cases, in order to convey the
meaning of particular moral concepts. The open-texture of these concepts admits for rival interpretations and moral innovation.

8.3. The Value-ladenness of Facts

In the introduction I mentioned the confusion about the value-ladenness of medical technology assessment (MTA). In what way, exactly, are facts produced by MTA laden with moral values? In the foregoing I have tried to demonstrate that the key-answer to the question is: through relevance. There is an infinite number of facts about RLTx 1d, none of which is relevant to our judgment about its moral acceptability and desirability, unless we are committed to and understand the meaning of certain moral concepts. The saving of a human life, and the reduction of psychical and physical suffering are so broadly supported objectives that their normative nature frequently goes unnoticed. It is a particular explication of moral concepts like beneficence and non-maleficence in the context of health care. The same holds for the informed consent procedure: It is a particular explication of the moral concept of autonomy in a medical context. The entire issue of social justice (the costs and opportunity costs of the program) is largely ignored. From within transplantation medicine, this main-stream methodology has been recently criticized by Guttman.\textsuperscript{48} He considers the figures that are used to express the characteristics of transplants inadequate to reflect aspects of these medical procedures that are relevant to a judgment about their moral acceptability. Others have argued that these figures frequently testify of an overly optimistic view on the benefits of transplantation technology.\textsuperscript{49} They state that “the real long-term results are not satisfactory even in patients with initial good graft function” (a statement that involves several normative judgments). Moreover, they state that the rejected patients and the patients with only partial rehabilitation must not be forgotten. In children, reduced function level of a grafted kidney often results in retardation in development. Also, reversibility of pre-transplant retardation and deficiencies often appears to be limited. Fox and Swazey set some of these drawbacks in a wider theoretical framework, trying to explain why living donation causes moral perplexity. \textit{Spare Parts} can be considered as a final attempt of the two authors to remind us that emphasis on graft and patient survival curves testifies of a gross underrating of the complexity of the moral dimensions involved in RLTx 1d, indeed, of the complexity of our morality itself. They emphasize the impact of organ transplantation and the donation and receiving of organs on human relationships (“the gift relationship”).

Implicitly, Fox and Swazey hold that the “gift-relationship” as described
by Mauss is a valuable aspect of our social life. It is something that deserves to be actively preserved and the required efforts are worth making. On the other hand, proponents of RLTx ld maintain that donors are plentifully rewarded if, through their act of donation, the recipient recovers and stays alive. If social strains result from living donation, we should not give in to them. Rather than accepting these strains as given, we ought to consider such feelings as inappropriate, opening up the way for further technological innovations. In other words, a good case can be made for moral innovation. In Brennan's terms, these are rival explications of moral concepts. In such cases we may have to raise the question of the rationale of moral concepts. Why is it that we should further other people's important and legitimate interests? Why is it that we should allow people to exercise their autonomy? I feel that without facing more squarely such questions of the rationale of moral concepts, there seems little hope of resolution of these controversies.

9. CONCLUSIONS AND DISCUSSION

In this paper I have tried to address the issue how facts and values are entwined in assessing medical technologies. I have taken the case of RLTx ld to illustrate the following points:

- The acceptability and desirability of this particular medical technological development is controversial. Analysis of the controversies shows that methodological standards are implied, determining the acceptability of evidence. I tried to substantiate this point by arguing that statements about effectiveness, safety and feasibility of alternative options can be rephrased, without altering their content, in the following way: "On the available evidence, and in view of accepted knowledge, it is rational to believe that etc etc." Different arguments can be used to settle the question of rationality, making use of various methodological procedures. This is one source of indeterminacy.

- The factual evidence about RLTx ld partly determines our judgment about its moral propriety. Examples of such factual issues are: What is the rate of pre-transplant mortality that can be avoided by including living donors? What is the risk of partial hepatectomy to the donor? What is the feasibility of options to raise the supply of organs? The fact that such data are broadly considered relevant to our judgment indicates adherence to the same moral values. These controversies are of the following form:
if post-mortem livers were scarce, and, consequently, pre-transplant mortality rates high, then RLTx Id would be morally acceptable. However, it is not clear whether there actually is such scarcity;

if partial hepatectomy were safe, then it would be morally acceptable. However, it is unclear whether the procedure actually is safe;

if a meaningful, truly informed consent could be obtained, then RLTx Id would be morally acceptable. However, it is unclear whether this is so or not.

This was one aspect of Putnam’s statement, viz. that moral values are laden with facts.

- Our commitment to and understanding of moral concepts determines which facts are relevant to consider, when judging about the propriety of a medical procedure like RLTx Id. This was the other part of Putnam’s statement, viz. the value-ladenness of facts. I relied on Brennan’s model to clarify the interdependency between facts and moral concepts. There are no criteria that are necessary and sufficient for the correct explication of moral concepts. This is another source of indeterminacy.

- A judgment about the acceptability of risks, associated with RLTx with living donors, includes a judgment about the feasibility of alternative options. In the case of RLTx Id this includes, for instance, a judgment about the question whether strategies to increase post-mortem organ availability are effective.

- In Brennan’s terms, the controversy indicates that the use of living donors in transplantation is one of the developments in modern medicine that causes moral perplexity: we are not sure whether to proceed with this medical development if morally right or wrong. Brennan tries to provide an explanation for this phenomenon of moral perplexity. His explanation can be summarized as follows:

  1. We are committed to certain moral concepts. This means that we are prepared to live in a way which is consistent with the requirements that in our view ensue from these moral concepts.

  2. We have a certain understanding of these moral concepts. This means that we are capable of recognizing moral dimensions of empirically ascertainable acts and situations.

  3. This is, of course, a highly idealized account of our commitment to and understanding of moral concepts: Our knowledge and understanding are (also in this respect) incomplete and subject to revision or refutation. This moral uncertainty is partly the cause of moral perplexity. Moral perplexity comes in yet another form: the second occurs in case of conflicting requirements between two or more
moral concepts. In such cases, trade-offs need to be made between conflicting requirements, ensuing from different moral concepts. How these trade-offs are made is context-dependent. These features of moral inquiry explain why persistent and pervasive moral disagreement is possible, in spite of adherence to the same moral concepts. Moral inquiry, in this view, is a social process aimed at consensus about the correct explication of moral concepts.

Thus, the conclusions that were reached by Singer et al.,⁴⁵ that RLTx ld can and should be done, may be premature. They argue that, in spite of the fact that the case of RLTx using living donors is as yet relatively poorly documented, there is sufficient ground to proceed. Of course, it is conceivable that decisions, aimed at constraining the diffusion of the technology in order to obtain more data on efficacy and safety in a carefully controlled way, result in death of patients that might have been rescued by the technology. It is precisely this assertion that frequently acts to justify pursuance of development of a particular medical technology. If the result of not implementing a technology is that patients will surely die, then relatively low probabilities of benefit and/or relatively high probabilities of adverse outcome may be considered acceptable. In this way, the necessity to carefully establish efficacy and safety is more or less “bypassed.” It is also frequently suggested that in time, with further development of the technology, the benefit/risk ratio will improve (cf. the development of LTx itself).⁵⁰ It is probably because of the fact that potential benefits can never be ruled out, that it is extremely difficult to justify not to pursue developments in medical technology. This might be one of the reasons that development of medical technology appears to have a momentum of its own, and that there is very little possibility to exert control. However, there is a serious drawback: Some of the risks will inevitably appear to have been unwarranted, but only in hindsight.⁵¹

I think it is safe to say that by no matter which standards, RLTx ld should be qualified as an experimental procedure. Such a statement is not likely to stir the emotions. The statement is, however, gratuitous, unless it is specified what the exact implications are of such a qualification. (a) What implications does it have for its further documentation, eligibility, consent-procedure, financing, etc.?; (b) more importantly, it should be specified on the basis of which evidence it will be decided to continue to qualify RLTx ld as experimental, to qualify RLTx ld as common practice, or to abandon the procedure. These questions are the more pressing, in view of conflicting evidence and indeterminacy of methodological standards.

The current state of art seems to be that the questions are raised, but that no satisfactory answers are as yet provided. They can probably best
be conceived as setting a research agenda for the next years. There are no generally accepted methodological criteria that are necessary and sufficient to validate our knowledge. Trade-offs between different criteria have to be made. This makes it difficult, if not outright impossible, to conclusively settle the sort of controversies surrounding the issue of RLTx Id. It also means that there will always be a degree of uncertainty, of indeterminacy. This indeterminacy raises a number of important questions:

Who bears the burden of proof? Do we give medical technology the benefit of the doubt and does the burden of proof rest with the one who wishes to establish that it is not advisable to proceed with a particular development in this context? Or do we stick more rigorously to “primum non nocere,” and does the burden of proof rest with the one who wishes to establish that it is, after all, desirable and acceptable to proceed with it?

Cognitive and moral uncertainties are closely related in these questions. Will the introduction and further development of this medical technology adversely affect certain aspects of human relationships that are deemed valuable? Will the content of certain moral concepts change if living donation becomes gradually more and more accepted? I hope to have shown that moral philosophy can, in various ways, be of use when addressing these questions; however, the processes that ultimately seem to settle these questions have a much broader social scope.

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REFERENCES


13. Singer et al. ibid.


15. Singer et al. ibid.


20. Ibid. 1093.


22. Ibid: 375.


24. Emond et al. ibid: 870.


34. Busutill: ibid 44.
38. Living donors are not the sole alternative source for transplants. Other sources are fetuses, anencephalic newborns and genetically engineered animals. Here, the same question arises: are such uses morally justified? I will not discuss these questions here. It is important to note, however, that these issues may affect the overall judgment of transplantation technology. Another question that I leave untouched is the question of incentives for donation: is it morally justified to financially reward donation of organs in order to increase supply of these organs? This possibility of commercialization is certain to have an impact on the public judgment of organ transplantation.
40. In this particular case, a theory is involved which aims to explain the recurrence of disease after transplantation, and to predict the probability of recurrence in view of the nature of the liver failure. The adequacy of such a theory can be assessed by reference to its generality, testability and degree of confirmation, explanatory and predictive power, coherence, etc. See for instance Steen, WJ van der. *A Practical Philosophy for the Life Sciences.* Albany NY: State University of New York Press, 1993.
42. Putnam ibid: Chapters 6 and 9.
46. For a discussion of the rationale of autonomy see Dworkin ibid: 21–33.
47. An example of a closed concept is triangle; of any geometric figure we can establish whether or not it is a triangle. There are criteria that are both necessary and sufficient for a geometric figure to qualify as a triangle.
50. The predicament is known as the control-dilemma: in order to proceed in a responsible way, we need more data; in order to obtain more data, we need to proceed anyhow (D. Collingridge. *The Social Control of Technology.* London: Francis Pinter, 1980).