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INDUCTIVE RISK AND JUSTICE IN KIDNEY ALLOCATION

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ABSTRACT
How should UNOS deal with the presence of scientific controversies on the risk factors for organ rejection when designing its allocation policies? The answer I defend in this paper is that the more undesirable the consequences of making a mistake in accepting a scientific hypothesis, the higher the degree of confirmation required for its acceptance. I argue that the application of this principle should lead to the rejection of the hypothesis that 'less than perfect' Human Leucocyte Antigen (HLA) matches are an important determinant of kidney graft survival. The scientific community has been divided all along on the significance of partial antigen matches. Yet reliance on partial matches has emerged as one of the primary factors leading blacks to spend a much longer time than whites on the waiting list for kidneys, thereby potentially impacting the justice of the kidney allocation policy. My case study illustrates one of the legitimate roles non-epistemic values can play in science and calls into question the ideal of a value-free science.

INTRODUCTION

Approximately 99,000 patients await transplants in the United States; but only about 28,000 transplants can be performed each year because organ donations are insufficient to cover the total demand.[1] The effect of this discrepancy is that about 15 patients die every day while waiting, and thousands remain on the waiting list for long periods of time before being given a chance to improve their condition. The gap between supply and demand makes it necessary to choose which patients, among many, will be offered organs.

Given the momentous consequences attached to patients' selection, organ allocation has become a controversial field of health care policy. Since 1986, organ allocation policies have been formulated by the United Network for Organ Sharing (UNOS), a private non-profit organization which holds a contract with the Department of Health and Human Services to oversee and coordinate the allocation procedures in the US.[2]

UNOS is contractually bound to trying to reconcile two main policy values in the allocation of organs: medical utility and justice. The value of medical utility is promoted by the maximization of efficiency in the use of organs; and the value of justice is promoted by ensuring that all candidates have a reasonable chance of being transplanted.

The question I address in this paper is: How should UNOS deal with the presence of scientific controversies on the risk factors for organ rejection when designing its allocation policies? The answer I defend is that when a scientific hypothesis is to be used as the basis of an organ allocation policy, the degree of confirmation required for

[1] The data on the number of registrations and transplants, with frequent updates, are available at: http://www.optn.org/data/ [Accessed 22 Jun 2008].

[2] The Board of Directors of the UNOS includes physicians from different sectors of the organ procurement and transplantation arena.

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accepting it should depend on how the implementation of the policy affects the values of medical utility and justice. This position can be supported by what we may call the *Degree of Confirmation Tracks Error Costs* Principle: the more undesirable the consequences of making a mistake in accepting a scientific hypothesis, the higher the degree of confirmation required for its acceptance.

I support this principle in two ways. Firstly, I provide a general defence of it from the point of view of the philosophy of science. Secondly, I try to show its intuitive appeal, specifically with respect to kidney allocation policies. For decades, UNOS has designed its kidney allocation policies under the assumption that partial Human Leucocyte Antigen (HLA) matches are an important determinant of graft survival. Yet, I argue, the scientific community has been divided all along on the significance of partial matches.

Crucially, reliance on full and partial HLA matches has emerged as one of the primary factors leading blacks to spend a much longer time than whites on the waiting list for kidneys, thereby potentially impacting the justice of the kidney allocation policy.

UNOS eventually lowered the impact of partial HLA matching in the allocation of kidneys in 2003 and is currently in the process of revamping its kidney allocation policy entirely, partially in response to the emerging racial disparities. This being said, its acceptance of a fairly controversial scientific hypothesis has contributed to the production of a severe racial imbalance in the access to kidneys for more than two decades.

I want to emphasize that this case study is not meant as a call to arms against UNOS, a remarkably transparent and efficient organization clearly striving towards an equitable allocation system in very difficult circumstances. Rather, it is a compelling example of what makes the *Degree of Confirmation Tracks Error Costs* Principle appealing when science grounds public policy. It is also a recommendation to UNOS decision makers to apply this principle in the design of their future organ allocation policies. Finally, it is an illustration of one of the legitimate roles non-epistemic values can play in science.

I begin with a general discussion of the roles of values in science, as a prelude to my discussion of the role of policy values in the science of kidney transplantation.

THE ROLE OF VALUES IN SCIENCE

Three views on science and values

There are three main views in the debate over the role values should play in science. I label them the 'naïve positivist view', the 'separatist view' and the 'non-separatist view'. According to the 'naïve positivist view', values should not play any role in the formulation and testing of hypotheses and scientific theories.[3] If they influence the activity of scientists, they do so illegitimately. Values, everyone acknowledges, do influence some decisions made by scientists, for example the selection of the scientific problem to investigate or the choice of what uses to make of scientific knowledge once acquired. But these activities are not considered to be within the domain of science proper. They are regarded as either prior or posterior to the pursuit of scientific knowledge, and therefore not liable to affect its value-freeness. The conclusion is that, whenever scientists make value judgments, they do not make them *qua* scientists.

According to the 'separatist view', there is a distinction to be made between 'epistemic' and 'non-epistemic' values: whereas the former can play a role in the activities of scientists *qua* scientists, the latter should be kept outside the domain of science.[4] Epistemic values are those values taken as instrumental to the pursuit of science. The list of epistemic values is not universally agreed upon, but the following list provided by Thomas Kuhn can be taken as representative: accuracy, consistency, scope, simplicity, and fruitfulness.[5] Non-epistemic values are instead values whose pursuit is not instrumental to the achievement of scientific knowledge. The list contains all those values which do not belong to the list of epistemic values, therefore including all sorts of personal and socio-cultural values. The 'separatist view' represents a move from an ideal of science as *free from values* to an ideal of science as *free from non-epistemic values*.

The 'non-separatist view', finally, holds that both epistemic and non-epistemic values have a legitimate role

[3] I call this the 'naïve positivist view' because it was echoed in some of the positions expressed by logical positivists between 1930 and 1960. It is dubious than any actual positivist ever held the view in this radical form. For a careful analysis of how best to interpret the ideal of value-free science in logical positivism, see for instance J. Roberts. 2007. Is Logical Positivism Committed to the Ideal of Value-Free Science?. In *Value-Free Science? Ideas and Illusions*. H. Kincaid, J. Dupré & A. Wylie, eds. Oxford: Oxford University Press: 143–163.

[4] See M. Scriven. 1980. The Exact Role of Value Judgments in Science. In *Introductory Readings in the Philosophy of Science*. E. Klemke, R. Hollinger & A. Kline, eds. Buffalo, NY: Prometheus Books: 269–291; E. McMullin. 1983. Values in Science. In *Proceedings of the 1992 Biennial Meeting of the Philosophy of Science Association*. P.D. Asquith & T. Nickles, eds. Philosophy of Science Association: East Lansing: 3–28.

[5] T. Kuhn. 1977. Objectivity, Values and Theory Choice. In *The Essential Tension*. Chicago: University of Chicago Press: 320–339.

to play in science.[6] Some philosophers add that the very distinction between epistemic and non-epistemic values is problematic and cannot be drawn in any principled way.[7] The 'non-separatist view', a fairly recent development in the philosophy of science, has been supported mainly by studies focusing on fields of science directly related to policy, where the influence of non-epistemic 'policy values' is powerful and easy to detect.

For example, several investigations have been devoted to the role of non-epistemic values in risk management policy. Multiple papers have shown that the distinction between *risk assessment*, the supposedly detached collection of scientific facts about risks, and *risk management*, the socio-political decision process through which risks are managed according to policy values, is not as sharp as the 'separatist' would like it to be.[8]

Now, should we be naïve positivists, separatists or non-separatists when it comes to the role of values in science? In this paper, I single out a specific area of legitimate influence for non-epistemic values, and focus on a case study pertaining to it in the science of kidney transplantation. I remain neutral on whether there are other areas of legitimate influence for non-epistemic values in science.[9]

Inductive risk introduced

It is common knowledge that scientific hypotheses are rarely if ever conclusively confirmed by the empirical evidence. What the empirical evidence does is to provide scientific hypotheses with varying degrees of inductive support. This being the case, the acceptance of a scientific hypothesis H carries the *inductive risk* of accepting a false hypothesis. By the same token, the rejection of H carries the *inductive risk* of rejecting a true hypothesis. A number of philosophers have argued that non-epistemic values have an essential role to play in the management of inductive risk.[10]

I will focus on the analysis of this role provided by philosopher of science Carl Hempel.[11] Hempel argued that scientists faced with inductive risk must formulate two types of rules: *rules of confirmation* and *rules of acceptance*. Rules of confirmation 'specify what kind of evidence is confirmatory, what kind discomfirmatory for a given hypothesis' and in some cases 'determine a numerical *degree* of evidential support . . . which a given body of evidence could be said to confer upon a proposed hypothesis'.[12] Rules of acceptance, on the other hand, 'specify how strong the evidential support for a hypothesis has to be if the hypothesis is to be accepted into the system of scientific knowledge'.[13]

Rules of acceptance are 'special instances of decision rules,' where 'the decisions in questions are either to accept or to reject a proposed hypothesis on the basis of given evidence'.[14] The possible outcomes of the decision are the following: '(1) the hypothesis is accepted (as presumably true) in accordance with the rule and is in fact true; (2) the hypothesis is rejected (as presumably false) in accordance with the rule and it is in fact false; (3) the hypothesis is accepted in accordance with the rule, but is in fact false; (4) the hypothesis is rejected in accordance with the rule, but is in fact true'.[15]

The former two cases are 'what science aims to achieve,' whereas the 'possibility of the latter two represents the inductive risk that any acceptance rule must involve'.[16] Hempel concluded that 'the problem of formulating adequate rules of acceptance or rejection has no clear meaning unless standards of adequacy have been provided by assigning definite values or disvalues to those different possible 'outcomes' of acceptance or rejection'.[17]

The evaluation of the consequences of accepting a false hypothesis, as well as rejecting a true one, is where non-epistemic values come into play. 'In the cases where the hypothesis under test, if accepted, is to be made the basis

[6] See H.E. Longino. 1990. *Science as Social Knowledge*. Princeton: Princeton University Press; H. Douglas. 2007. Rejecting the Ideal of Value-Free Science. In Kincaid, Dupré & Wylie, *op. cit.* note 3, pp. 120–139.

[7] See P. Rooney. 1992. On Values in Science: Is the Epistemic/Non-Epistemic Distinction Useful. In *Proceedings of the 1982 Biennial Meeting of the Philosophy of Science Association.* D. Hull, M. Forbes & K. Okruhlik, eds. Philosophy of Science Association: East Lansing: 13–22; P. Machamer & H. Douglas. 1999. Cognitive and Social Values. *Science and Education* 8: 45–54.

[8] See K.S. Shrader-Freschette. 1985. *Science Policy, Ethics, and Economic Methodology*. D. Reidel Publishing Company; F.M. Lynn. 1986. The Interplay of Science and Values in Assessing and Regulating Environmental Risks. *Science, Technology and Human Values* 11: 40–50; H. Douglas. Inductive Risk and Values in Science. *Philos Sci* 2000; 67: 559–579.

[9] For further discussion, see Kincaid, Dupré & Wylie, *op. cit.* note 3.

[10] See C.W. Churchman. Science and Decision Making. *Philos Sci* 1956; 33: 247–249; R. Rudner. The Scientist qua Scientists Makes Value Judgments. *Philos Sci* 1953; 20: 1–6.

[11] C. Hempel. 1965. Science and Human Values. In *Aspects of Scientific Explanation and Other Essays in the Philosophy of Science*. New York: The Free Press: 81–96.

[12] Ibid: 92.

[13] Ibid: 92.

[14] Ibid: 92.

[15] Ibid: 92.

[16] Ibid: 92.

[17] Ibid: 92.

of a specific course of action,' Hempel argued, both false negatives and false positives will bear practical consequences.[18]

The degree of confirmation required for a hypothesis to be accepted will depend on how the scientist evaluates these practical consequences. Evaluating them, in turn, requires *categorical value judgments*, namely judgments 'to the effect that a certain state of affairs . . . is good, or that it is better than some specified alternative'.[19]

When 'no practical applications are contemplated,' Hempel added, the evaluation of inductive risk will be 'more problematic.' The hypothesis will have to be evaluated only in the light of epistemic values, namely those values which serve the objective of 'the attainment of an increasingly reliable, extensive, and theoretically systematized body of information about the world'.[20]

Various criticisms have been addressed to the view that non-epistemic values play a legitimate role in science through their influence on rules of acceptance.[21] The most common objection, variously elaborated by different authors, has been that accepting a hypothesis is not equivalent to choosing to act on the basis of it.[22] If one does not act, the argument goes, there are no practical consequences to be judged in light of non-epistemic values. And even if one does act, different actions may lead to different practical consequences, so what is evaluated is *at best* a combination of a scientific hypothesis and a specific course of action based upon it.

These criticisms can successfully be addressed to some earlier formulations of Hempel's thesis, such as Rudner's and Churchman's.[23] In these early accounts, little consideration is given to the open-ended nature of hypothesis acceptance in science. But Hempel did not claim that non-epistemic values are involved in *every* case of hypothesis acceptance. He argued that this is the case only when a scientific hypothesis is accepted in the context of a specific practical application to be based upon it. Following Hempel, I claim that whenever the acceptance or rejection of a scientific hypothesis H bears practical consequences C, the evaluation of C is a place of legitimate influence for non-epistemic values.

In such cases, rules of acceptance should satisfy the following meta-principle: the more undesirable the consequences C of making a mistake in accepting some hypothesis H, the higher the degree of confirmation required for the acceptance of H.[24] I call this the *Degree of Confirmation Tracks Error Costs* Principle. My aim is to defend the appeal of the Principle when the acceptance of a scientific hypothesis is clearly connected to a specific course of action that bears practical consequences in public policy.

I will now argue that this is precisely the case with respect to the hypothesis that the number of antigen matches affects tissue incompatibility between donor and recipient in the context of kidney allocation policies.

ANTIGENS AND KIDNEY ALLOCATION

Human Leucocyte Antigens

To introduce my main point, I need to provide some background on Human Leucocyte Antigens (HLA). HLAs are proteins located on the surface of cells whose function is to stimulate an immune response. Antigens in effect enable white blood cells – the primary immunological active cells of the body – to distinguish tissue as self (to be preserved) and as foreign (to be eliminated).[25]

The HLA antigens belong to two main classes: class I molecules, expressed by plasma membranes of most cells and tissues, and class II molecules, expressed on a small number of cell types (B cells, dendritic cells, macrophages). Class I molecules are encoded by three genetic loci

[18] Ibid: 92–93.

[19] Ibid. 85. Categorical value judgments are to be contrasted with instrumental value judgments, namely judgments to the effect that 'a certain kind of action . . . is good . . . if a specified goal G is to be attained' (Ibid: 84).

[20] Ibid: 93.

[21] See R.C. Jeffrey. Valuation and Acceptance of Scientific Hypotheses. *Philos Sci* 1956; 33: 237–246; I. Levi. Must the Scientist Qua Scientist Make Value Judgements?. *J Philos* 1960; 57: 345–357; McMullin, *op. cit.* note 4.

[22] Jeffrey, *op. cit.* note 21, also claimed that scientists do not accept hypotheses but simply establish their degree of confirmation. Anticipating the criticism, Rudner, *op. cit.* note 10, had argued that this view is untenable, not only because it contrasts with what scientists think of themselves as doing but also because it is self-contradictory. The very activity of establishing a degree of confirmation entails the acceptance of the hypothesis that the degree of confirmation is some value p. Jeffrey's response was that one does not accept such an hypothesis either, but only establishes its degree of confirmation. This leads to a different sort of problematic regress, the discussion of which lies outside the scope of this paper.

[23] Churchman, *op. cit.* note 10; Rudner, *op. cit.* note 10.

[24] Rudner, *op. cit.* note 10; Douglas, *op. cit.* note 8, applies this principle to examine the impact of non-epistemic values on the way pathologists study the cancerous effects of dioxin exposure in rodents.

[25] HLA antigens are encoded by genes located on the short arm of chromosome 6 in a region known as the Major Histocompatibility Complex (MHC). The concentration of these genes in one defined area of the chromosome allows them to be inherited as a packet (haplotype). Each individual inherits a 'half-set' of MHC genes from each parent. The key role of HLA antigens is to capture fragments of antigen for presentation on cell surfaces to T cells. In presenting foreign antigen to T cells, HLA molecules orchestrate an immune response by evoking cytotoxic T-lymphocyte and helper T-cell responses.

known as HLA-A, B and C. Class II molecules are encoded by three genetic loci known as HLA-DR, DP and DQ. Within human populations, HLA-A, B, C, DR, DP and DQ loci are highly polymorphic, with dozens and sometimes more than one hundred alleles for each locus. The three loci whose influence on kidney survival has emerged as most significant are HLA-A, B and DR.

Antigen mismatches play a determinant role in the allocation of kidneys. If a recipient is found on the UNOS Waiting List who shares six antigens with the donor – two at the A locus, two at the B locus and two at the DR locus – the kidney is automatically matched to that patient. On the other hand, if a zero antigen mismatch is not found, the kidney is allocated according to a point system in which the number of partial antigen mismatches between donor and recipient plays a critical role.

Up until May 2003, the number of antigen mismatches at the B and DR loci was the single most important factor in the point system: 7 points were allocated for having no mismatches at the B and DR loci, 5 points for one mismatch at either of the two loci, 2 points for two mismatches – one for each locus. Just to give an example of how important HLA matching was compared to other factors, consider that patients got *1 point for each year waiting* plus 1 point to the patient waiting for the longest period with fractions of points being assigned proportionately to all other patients, according to their relative time of waiting.[26]

After May 2003, UNOS started giving less weight to partial antigen mismatches, but still holds for them an important role: at the time of writing, 2 points are allocated for having no mismatches at the DR locus, and 1 point is allocated if there is 1 DR mismatch.

The evidence for the HLA Hypothesis

The reliance of the allocation policy on antigen matching is based on the acceptance on the part of UNOS scientists of the following hypothesis:

> HLA Hypothesis (HLAH): 'The greater the number of antigen mismatches, the greater the degree of tissue incompatibility between a donor and a recipient and the more likely a graft will be rejected.'[27]

How strong is the evidence for this hypothesis? A survey of the available medical literature reveals that in the past three decades a scientific controversy has surrounded the topic of antigen matching. Medical experts equally acquainted with the relevant facts disagree on whether they support the hypothesis. I will now provide a few highlights from this controversy, aiming to document the extent to which HLAH is supported by evidence.

An important distinction must be drawn between the effect of perfect antigen matching (6 antigens in common between donor and recipient) and the effect of imperfect antigen matching (less than 6 antigens in common). Whereas there has been wide consensus since the mid-1980s that 'perfect matches' are a predictive factor for kidney survival,[28] the impact of 'less than perfect matches' is still debated. The positions of the medical experts on the topic have historically ranged from flat denial of any positive effect, to affirmation of a positive effect for any additional antigen match.

As early as 1990, Matas et al. found this phenomenon puzzling: 'given the number of kidney transplants that have been performed worldwide, it seems amazing that little consensus has been reached on the value of matching for HLA antigens'.[29] As we shall see, almost 20 more years have gone by, but the controversy has not abated. The main reason underlying the lack of agreement is that the causes of chronic rejection, the slow process of deterioration of the kidney responsible for most of the cases of graft loss in recent years, are still not fully understood.

Matas et al. concluded their study – based on 1329 kidney transplants performed at the University of Minnesota between 1970 and 1989 – by saying that 'except for perfectly matched . . . recipients, matching showed no effect on the outcome of cadaver transplantation'.[30]

[26] According to this rule, if there are n patients on the waiting list, the patient who has waited the longest will get 1 point. The next person in order will get (n – 1)/n points, the next person in order (n – 2)/n points and so on. The person who is i-th in order of waiting will get (n – i + 1)/n points. The calculation of waiting points is conducted separately (locally, regionally and nationally) on each geographic level of kidney allocation.

[27] This formulation of the hypothesis could be read as part of the definition of Human Leucocyte Antigens in the UNOS Glossary, originally available at: http://www.unos.org/Data/survival_userguid_gloss.htm [Accessed 2 July 1999]. This specific formulation is no longer available on the website. The current and more succinct formulation states that '[g]enerally speaking, the smaller the number of HLA mismatches the better the compatibility between donor and recipients'. It is available at: http://www.unos.org/resources/glossary.asp#H [Accessed 12 May 2008].

[28] F. Sanfilippo et al. Benefits of HLA-A and HLA-B Matching on Graft and Patient Outcome after Cadaveric-donor Renal Transplantation. *N Engl J Med* 1986; 311: 358–361.

[29] A.J. Matas et al. The Impact of HLA Matching on Graft Survival and on Sensitization after a Failed Transplant-evidence that Failure of Poorly Matched Renal Transplants Does Not Result in Increased Sensitization. *Transplantation* 1990; 50(4): 599–607: 601.

[30] Matas, *op. cit.* note 29, p. 606.

Several other reports from large transplant programs have not observed any benefit for 'less than perfect matches'.[31] A lack of statistical correlation between graft survival and less than perfect matches has also been reported in studies on kidney transplantation in Europe.[32]

On the contrary, other researchers have claimed that less than perfect matches have a statistically significant positive effect; but that this effect is not linear with the number of matches and tends to become unnoticeable when the number of mismatches becomes more than 3 or 4.[33] An alternative view is that matches have an effect, but only if they take place in one or two of the three loci A, B and DR (e.g. matches only in locus A).[34] Some researchers finally believe that the impact of any single antigen mismatch is significant, regardless the total mismatches.[35]

Several large-scale analyses of registry data have been performed; but they have failed to settle the issue of less than perfect HLA matches. In 1997, UNOS issued a *Report of Center Specific Patient and Graft Survival Rates*. The *Report* marshals very strong evidence in favour of the hypothesis that there is a significant statistical difference between the likelihood of survival of patients with perfect matches and the likelihood of survival of patients with less than perfect matches. According to UNOS 1997 Report, the conditional 3-year survival[36] of a patient with a perfect antigen match is 52% more probable than that of a patient with 1 mismatch, 61% more probable than that of a patient with 2 mismatches, 64% more probable than that of a patient with 3 mismatches, 74% more probable than that of a patient with 4 mismatches, 59% more probable than that of a patient with 5 mismatches (notice here an inversion of the trend), 82% more probable than that of a patient with 6 mismatches.[37]

These calculations, however, do not help dissolve the medical controversy concerning the impact of less than perfect matches. The data bring further support to what is already widely accepted, namely than patients with perfect matches have a higher likelihood of survival that patients with less-than-perfect matches. They do not show that there is a statistically significant difference between the likelihood of survival of patients with different numbers of mismatches. No data in the 1997 *Report* showed that, for example, a patient with 3 mismatches is less likely to reject the kidney than a patient with 4 mismatches, because the analysis of statistical significance was limited to comparisons between perfect matches and imperfect matches. It did not include comparisons between imperfect matches themselves.

The medical controversy continues to this day. Su et al. recently analysed data on graft survival from a sample of 33,443 patients who received a kidney transplant between December 1994 and December 1998.[38] Their conclusion was that 'time trends suggest that HLA matching is of diminishing significance, while non-immunological factors remain equivalently important'.[39] Whereas in 1995 'three- to six-antigen mismatches were significantly associated with a higher risk of graft failure', they argued, in '1998 the risk of graft failure was significantly increased only with mismatches at all six loci'.[40] The biological explanation for this trend, they concluded, is unclear, but increasingly powerful immunosuppressant drugs may be part of the explanation.

[31] J.W. Alexander, W.K. Vaughn, & W.W. Pfaff. Local Use of Kidneys with Poor HLA Matches is as Good as Shared Use with Good Matches in the Cyclosporine Era: an Analysis at One and Two Years. *Transplant Proc* 1987; 19: 672–678; J.S. Najarian et al. Effects of HLA Matching in Cadaver Renal Transplants. *Transplant Proc* 1988; 20: 249–254; R.M. Ferguson. Treatment Protocols: is There a Role for Tissue Typing in Renal Transplantation. *Transplant Proc* 1988; 20: 42–50; R.J. Tesi et al. Predictors of Long-term Primary Cadaveric Renal Transplant Survival. *Clin Transplant* 1993; 7: 345–354.

[32] J. Thorogood et al. The Effect of HLA Matching on Kidney Graft Survival in Separate Post-transplantation Intervals. *Transplantation* 1990; 50: 146–150.

[33] G.C. Persijn et al. Modulation of the HLA-A, B and DR Matching Effect by Cyclosporine Therapy. *Transplant Proc* 1989; 21: 656–663; C.B. Carpenter, J.E. Goguen & J.W. Bradley; HLA-B, DR Matching and Cadaver Renal Allograft Survival in New England. *Transplant Proc* 1989; 21: 663–670.

[34] W.R. Gilks et al. Substantial Benefits of Tissue Matching in Renal Transplantation. *Transplantation* 1987; 43(5): 669–674.

[35] S. Takemoto et al. Survival of Nationally Shared, HLA-matched Kidney Transplants from Cadaveric Donors. *N Engl J Med* 1992; 327(12): 834–839; F. Sanfilippo et al. HLA Matching in Renal Transplantation. *N Engl J Med* 1984; 331(12): 803–805; H. Fenstenstein, P. Doyle & J. Holmes. Long-term Follow-up in London Transplant Group Recipients of Cadaver Renal Allografts. *N Engl J Med* 1986; 314: 7–15; D. Middleton et al. The Influence of HLA-A, B, and DR Matching on Graft Survival in Primary Cadaveric Renal Transplantation in Belfast. *Transplantation* 1985; 39(6): 608–610; G. Opelz & B. Dohler. Effect of Human Leukocyte Antigen Compatibility on Kidney Graft Survival: Comparative Analysis of Two Decades. *Transplantation* 2007; 84(2): 137–143.

[36] The conditional 3-year survival is the survival at 3 years post transplant for those who survived at least one year. The choice of 'conditional' rather than 'unconditional' survival is explained by UNOS with the fact that 'the conditional 3-year analysis provides an assessment of characteristics independent of those limited to the first year (e.g. surgical complications and early acute rejection events).'

[37] The data on survival I cite can be found in the 'Kidney Summary' section of the *Report*, which can be requested at the following address: http://www.unos.org/data/request_main.asp [Accessed 12 May 2008].

[38] K. Su et al. Diminishing Significance of HLA Matching in Kidney Transplantation. *Am J Transplant* 2004; 4: 1501–1508.

[39] Su, *op. cit.* note 38, p. 1507.

[40] Su, *op. cit.* note 38, p. 1502.

Opelz et al. have responded to these findings, examining data from the Collaborative Study Database (CSD) in the period 1985–2004, which includes a total of 135,970 transplants.[41] Their conclusion, contra Su et al., is that '[w]e find that the effect of HLA matching on the survival rate of kidney transplants . . . continues to be influential, in spite of improvements in immunosuppression'.[42]

I could go on listing divergent opinions on the effects of HLA matching, but I take it that my point is clear: the medical community has been, and to some extent still is, divided on the impact of less than perfect HLA matches on graft survival, and on the differential impact of specific numbers of mismatches (e.g. on the impact of two versus three antigen mismatches). This being the case, both the acceptance and the rejection of HLAH qualify as scientifically plausible given the available evidence.[43] So far, the HLA Hypothesis has been accepted, as revealed by the strong emphasis placed on less than perfect antigen matching in kidney allocation policies.

The question is: Is the acceptance of the HLA Hypothesis in circumstances of high inductive risk compatible with the non-epistemic values at the foundation of the kidney allocation policy?

MANAGING INDUCTIVE RISK

What are the policy values held by UNOS?

As recently emphasized by Tim Pruett, MD, OPTN/UNOS President, UNOS should strive to 'develop a kidney allocation system that balances utility . . . with justice'.[44] *Medical utility* and *justice* are singled out as the two fundamental values to be jointly promoted by organ allocation policies in the most specific document written on this topic by UNOS, namely the 1991 White Paper 'General Principles for Allocating Organs and Tissues'.[45]

The policy value of 'medical utility,' under UNOS interpretation, 'suggests that when the demand for transplantable organs exceeds supply, the organs should be allocated to patients who have the best chance of benefitting from a transplant,'[46] i.e. to patients with the best chance of graft survival.

The policy value of 'justice' makes it desirable to 'provide transplant candidates reasonable opportunities to be considered for organ offers *within comparable time periods*, taking into consideration similarities and dissimilarities in medical circumstances'[47] (emphasis added). The 'value of justice' requires UNOS to formulate an allocation system that attempts to equalize waiting times for patients 'similar' in those characteristics which are 'relevant to considerations of justice,' and establishes priorities between 'dissimilar' patients in proportion to their differences.

Clearly, there is a potential tension between the pursuits of medical utility and justice. The characteristics of some patients make them unsuitable candidates for most transplants, and it is unreasonable to expect that their waiting time will be equal to the waiting time of patients with an advantage in terms of compatibility. What the value of justice requires is that efforts are made to 'maximize opportunity for patients with biological or medical disadvantages to receive a transplant,'[48] finding ways to compensate for disadvantaged patients by giving them preferential treatment in the rare occasions in which a compatible organ becomes available.[49]

In other words, the ideal towards which UNOS has to strive is the *equal balance* between the value of medical utility and the value of justice. How should UNOS deal with the high inductive risk associated with the HLA Hypothesis in light of the need to preserve this equal balance?

False negative vs. false positive: Which is preferable?

I have argued that whenever the acceptance or rejection of a scientific hypothesis bears practical consequences,

[41] Opelz & Dohler, *op. cit.* note 35.

[42] Opelz & Dohler, *op. cit.* note 35, p. 142.

[43] On the other hand, the degree of confirmation of the hypothesis that perfect antigen matches impact the likelihood of graft survival is at this stage very high. Whether or not UNOS scientists should accept HLAH, it is clear that they should accept the weaker hypothesis that zero antigen mismatches make it more likely that a graft will be rejected (HLA*). The HLA Hypothesis, unlike HLA*, includes both perfect and partial antigen matches.

[44] Report of the OPTN/UNOS Kidney Transplantation Committee, 2007. p. 3. The document is available at: http://www.unos.org/CommitteeReports/board_main_KidneyTransplantationCommittee_9_20_2007_16_41.pdf [Accessed 22 Jun 2008].

[45] The White paper is available at: http://www.unos.org/Resources/bioethics.asp?index=10 [Accessed 22 Jun 2008].

[46] Excerpt from a testimony on 18 June 18, 1998 of Dr. L. Hunsicker, then President of UNOS, during a joint hearing of the House Commerce Committee and the Senate Labor and Human Resources Committee.

[47] This passage can be found in section E.4 of the document 'Background regarding the OPTN and Liver Allocation Policy', which can be requested at: http://www.unos.org/data/request_main.asp [Accessed 1 Jun 2008].

[48] The passage can be found in section 5 of the White Paper 'General Principles for Allocation Organs and Tissues', available at: http://www.unos.org/Resources/bioethics.asp?index=10 [Accessed 22 Jun 2008].

[49] This is the rationale for the rule reserving kidneys from blood type O patients (compatible with recipients of all blood types) for blood type O recipients (compatible only with blood O donors).

the evaluation of these consequences in terms of inductive risk is a place of legitimate influence for non-epistemic values. More specifically, I have argued that rules of acceptance should satisfy the *Degree of Confirmation Tracks Error Costs* Principle: a high (low) cost of error associated with acceptance requires a high (low) degree of confirmation to accept. I now want to show the intuitive appeal of the Principle with respect to the HLA Hypothesis.

This is an especially interesting test case for a number of reasons. The first is that the acceptance of the hypothesis is clearly related to a specific practical application to be based upon it, namely the allocation of cadaveric kidneys. This is to say that a standard worry of holders of the 'separatist view' on science and values, namely that no specific action may depend upon the acceptance of a scientific hypothesis, does not apply.

The second reason is that, as I have documented, the hypothesis under consideration has been quite controversial in the scientific community for a long time. If non-epistemic values have a legitimate influence to play in hypothesis acceptance, this will be most apparent in cases where the evidential support for a hypothesis is far from conclusive to begin with.

The third reason why this is an especially interesting case is that picking among candidates for a kidney transplant qualifies as a paradigmatic 'tragic choice'.[50] In such circumstances, the temptation to hide potentially controversial value judgments under the cloak of scientific objectivity is especially strong. The temptation is in effect to substitute the hard job of defending value judgments in the forum of public opinion with a knee-jerk endorsement of an alleged great divide between the 'science of transplantation' – the realm of objective facts – and the 'policies of allocation' – the realm of value judgments. If the policies can be shown to derive their legitimacy from the objectivity of the science on which they are based, the thought goes, the tragic nature of the organ allocation can be partially neutralized.

But I have argued that this picture of the science of transplantation fails to reflect that there is a scientific controversy with respect to one of the central medical criteria at the foundation of the kidney allocation policy. The very acceptance of the HLA hypothesis, I have suggested, is to be partially explained by an implicit assessment of the consequences of making a mistake.

We are now clear about which policy values UNOS scientists should use in the management of inductive risk. Since UNOS is committed to balancing utility and justice, the different possible outcomes of acceptance and rejection of the HLA Hypothesis must be evaluated in the light of the joint promotion of utility and justice.

The non-epistemic value of medical utility would clearly favour acceptance. If we reject a true HLAH, the possibility of promoting the value of medical utility will be lost, because we will not allocate kidneys to those who could most benefit from them. This has been all along the rationale for basing the kidney allocation policy largely on HLA matching. However, a rule of acceptance should not be designed just in light of the consequences of false negatives. The consequences of false positives are equally important.

If we accept a false HLAH, there will be no setback to the value of medical utility, because antigen matching does not diminish the likelihood of survival. However, when the non-epistemic value of justice – understood as equality of opportunity for transplantation – enters the picture, a strong reason to prefer rejection rather than acceptance emerges. A key consequence of a false positive would be the creation of a remarkable disparity in access to kidney transplantation for minorities without any medical benefits to make up for it (other than those emerging from 'perfect' antigen matches).

As reported in the *1997 Report of the OPTN: Waiting List Activity and Donor Procurement*, the median waiting time for kidneys was 553 days for whites and 1083 days for blacks. The reason behind the differential impact of antigen matching is that donors are mostly white and antigens are not uniformly distributed among races. This makes it more difficult to find a well matched kidney for blacks, who represent approximately 35% of the recipient pool but only 12% of the donor pool, than it is for whites, who represent approximately 50% of the recipient pool and 75% of the donor pool.[51]

The adverse impact of HLA matching on equitable access to kidney transplants has been known for twenty years.[52] In a wide-ranging study of racial disparities in

[50] G. Calabresi & P. Bobbitt. 1978. *Tragic choices.* New York: Norton.

[51] The problem is bound to worsen once the allocation policy is perceived as not providing equal opportunity of access to minorities. This will affect the rate of donation of minority donors, making it even harder for minority recipients to find a match, and further decreasing opportunity of access.

[52] See S.M. Greenstein et al. Does Kidney Distribution Based upon HLA Matching Discriminate against Blacks? *Transplant Proc* 1989; 21(6): 3874–3875; I. Ayres, L. Dooley & R.S. Gaston. Unequal Racial Access to Kidney Transplantation. *ABF Working Paper* # 9111 1991; R.S. Gaston et al. Racial Equity in Renal Transplantation: the Disparate Impact of HLA-based Allocation. *JAMA* 1993; 270: 1352–1354; A.M. Epstein et al. Racial Disparities in Access to Renal Transplantation – Clinically Appropriate or Due to Underuse or Overuse? *N Engl J Med* 2000; 343: 1537–1544; J.P. Roberts et al. Effect of Changing the Priority for HLA Matching on the Rates and Outcomes of Kidney Transplantation in Minority Groups *N Engl J Med* 2004; 350: 545–551.

renal transplantation, Epstein et al. reiterated that 'racial differences in rates of transplantation may be related in part to immunological matching criteria that result in more frequent donor matches for whites than for blacks'.[53] Roberts et al. argued that 'eliminating the HLA-B matching as a priority while maintaining HLA-DR matching as a priority . . . would increase the number [of kidney transplantations] among nonwhites by 6.3%'.[54]

In light of these considerations, the degree of confirmation required for accepting the HLA Hypothesis should be very high, as recommended by the *Degree of Confirmation Tracks Error Costs* Principle. The consequences of being wrong in accepting it contrast so blatantly with the commitment to giving each patient 'reasonable opportunities to be considered for organ offers *within comparable time periods*', that the acceptance of the hypothesis as ground for allocation demands a great deal of evidence for HLAH.

My point is that the presence of a scientific controversy on the impact of less than perfect antigen matches spanning decades is hard to reconcile with the claim that the HLA Hypothesis has always (or ever) enjoyed a high degree of confirmation.

Two important points need to be emphasized. Firstly, if antigen matching had no adverse impact on the opportunities for transplantation for minorities, the *Degree of Confirmation Tracks Error Costs* Principle would recommend *accepting* the HLA Hypothesis even if a medical controversy surrounds it. The consequences of making a mistake would in such case clearly *not* be in contrast with the need to balance utility and justice. The only effect of being wrong would be failure to promote the value of medical utility.

Secondly, I am not proposing that justice should trump medical utility in all cases. If the HLA Hypothesis were supported by compelling evidence, policy makers would still have to decide the weight to be given to antigen matching in light of its adverse impact on the opportunities for transplantation for minorities. They may decide that the medical advantages are worth the inequity costs. Or they may decide that the medical advantages fail to compensate for the loss of equal access to kidney transplantation. A separate argument would be needed to discuss how best to balance utility and justice in such case.

What I am saying is, rather, that the amount of evidence required for accepting the hypothesis that less than perfect matches are medically useful to begin with ought to be a function of the cost of being wrong, in terms of equality of opportunity of access. The ethical problem raised by the differential impact of antigen matching on minorities would not go away if there was compelling evidence that the greater the number of antigen mismatches, the greater the degree of tissue incompatibility between a donor and a recipient. But the ethical problem becomes significantly more troubling when there is high inductive risk, as testified by a long and ongoing medical controversy, that less than perfect matches may have no significant impact at all on graft survival.[55]

The science of transplantation plays a crucial role in the achievement of medical utility in organ allocation, in that it must establish which characteristics impact the likelihood of graft survival. But the science of transplantation is a young science, and several areas of uncertainty remain concerning the mechanisms of organ rejection. In some cases, the negative or positive impact of a particular characteristic has been confirmed to a very high degree (e.g. the negative impact of preformed antibodies against the donor). In other cases, the medical evidence is still inconclusive and the medical community remains divided.

I gave the example of the HLA Hypothesis, but this is not a solitary example. Another hypothesis, the acceptance of which carries high inductive risk, is the one according to which the time of transportation of an organ, i.e. the number of hours of 'cold ischemic time,' has an impact on the likelihood of graft survival. The acceptance of this hypothesis has led to the priority given to local transplant candidates. In this case, too, the evidence is far from decisive and careful consideration should be given to whether a false positive is really more desirable than a false negative in light of the non-epistemic policy values of utility and justice as equality of opportunity of access.

If I am right, in its ongoing revision of the kidney allocation policy, UNOS scientists should not treat all the

[53] Epstein et al., *op cit.* note 52, p. 1543.

[54] Roberts et al., *op. cit.* note 52, p. 545. This may in turn increase the rate of donation among blacks.

[55] A defender D of less than perfect antigen matching may buy the general structure of my argument, but retort that the best balance of utility and justice is in fact served by the avoidance of a false negative rather than a false positive as I have argued so far. This move may be at the core of an argument to justify accepting the HLA hypothesis even in the presence of a scientific controversy surrounding it (more radical options would be to deny the existence of a genuine scientific controversy, or to argue that HLHA has a high degree of confirmation despite the controversy). I disagree that favouring false negatives over false positives would best preserve the balance between utility and justice, but absent more details I will not engage with D. What I want to notice is that D's approach is much more transparent than hiding the value judgments underlying hypothesis acceptance under the cloak of scientific objectivity.

hypotheses on which the kidney allocation policy is based equally.[56] In principle, two (non-competing) hypotheses H_1 and H_2 may have the same degree of confirmation, but only H_1 should be accepted as a basis for the kidney allocation policy, because H_2, unlike H_1, has adverse effects on justice.

More to the point of the paper, a given hypothesis H may be accepted *until* it is revealed as having adverse effects on justice, at which point balancing medical utility and justice may lead to a demand for a higher degree of confirmation prior to acceptance. This is arguably the case for the HLA Hypothesis, which started its career as a potentially controversial hypothesis worth accepting because false positives had no foreseeable ethical costs, but has slowly developed (more so after improvements in immunosuppression) into a potentially controversial hypothesis not worth accepting because of its major emerging costs in terms of equitable access to kidney transplantation between black and white patients.

CONCLUSION

In this paper, I have analyzed the allocation policy for kidneys and focused on one of the key medical hypotheses on which it is based, namely that the higher the number of antigen mismatches, the higher the probability of rejection (HLAH). A review of the medical literature concerning HLAH has revealed the presence of a scientific controversy surrounding the impact of antigen matching that spans three decades.

When the acceptance or rejection of an uncertain hypothesis such as HLAH leads to consequences in terms of access to organs, it seems reasonable to evaluate such consequences in light of the policy values of the allocation, namely medical utility and justice. Since antigen matching is one of the primary causes of racial disparities in access to transplantation, I have argued that acceptance of the HLA hypothesis would require a higher degree of confirmation than the hypothesis appears to enjoy. I have also pointed out that the ethical problem of racial disparities in access to kidney transplantation would not go away in the absence of high inductive risk in accepting HLAH, but that it is gravely exacerbated by the presence of such risk.

By way of illustration, the case study I proposed supports a 'non-separatist view' on science and values. The 'non-separatist view' argues, in contrast to the 'naïve positivist' and the 'separatist' positions, that non-epistemic values have a legitimate role to play in science. I have shown what one of the legitimate functions of non-epistemic values could be, namely helping scientists make decisions in conditions of high inductive risk. When both the acceptance and the rejection of a hypothesis carry a high risk of being wrong and bear practical consequences, it seems legitimate for scientists to evaluate the effects of their possible mistakes and act upon those evaluations.

The 'non-separatist view' has the virtue of taking seriously the presence of genuine uncertainty in science. In several areas of scientific research, it is common that the observational evidence is not such as to compel a choice. When a mistake in accepting and rejecting a hypothesis with indecisive evidence has social consequences, the scientist's abstention from their evaluation is both unrealistic and unappealing.

It is unrealistic because the problem of deciding which hypothesis to accept when the 'evidence' does not compel a choice would be left undefined. It is unappealing because, even if it could be assumed that scientists leave the evaluation of the non-epistemic consequences to a third party (e.g. a professional ethicist), their lack of social concern would amount to a moral abdication which does not seem to serve any obvious epistemological purpose. Moreover, scientists are often the only ones in a position to understand fully the consequences of false negatives and false positives, as well as their likelihoods of occurrence.[57]

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[56] UNOS, in line with its tradition of transparency and public involvement, has been holding hearings to collect input on how best to develop a new kidney allocation policy since early 2007.

[57] On this point, see Douglas, *op. cit.* note 6.