



Policy Challenges for Organ Allocation in an Era of “Precision Medicine”

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Abstract

There is increasing interest in the use of precision medicine tools and evidence-based outcome measures for donor-recipient matching to optimize transplant outcomes. Although the shift toward greater precision can provide health and resource benefits, it may be perceived as conflicting with both established equity-focused organ allocation norms and the legal and ethical obligations of health care providers and related institutions. With increasing evidence that various forms of human leukocyte antigen (HLA) mismatch and/or prognostic biomarkers can affect outcomes, the tension between maximizing utility and ensuring equity seems likely to intensify. In Canada, health care providers are generally required by law to put the interests of their patient, such as access to an organ, above the needs of the health care system and other patients. In addition, transplantation right of access lawsuits, which have been successful in the past, could affect the implementation of precision approaches. These legal tensions could be further heightened by media representations, which have historically favored strong rights of access. When implementing new precision technologies in organ allocation, there will be a recurrent need for policymakers to revisit the balance of equity and utility and to assess how to craft rules that reflect our society's conception of a fair allocation system.

Abrégé

Les outils de la médecine de précision et les mesures de résultats fondées sur des données probantes suscitent de plus en plus d'intérêt pour le couplage donneur-receveur afin d'optimiser le résultat d'une transplantation. Bien qu'une plus grande précision offre des avantages sur la santé et pour les ressources, elle peut être perçue comme entrant en conflit avec les normes d'attribution des organes axées sur l'équité, et avec les obligations éthiques et juridiques des fournisseurs de soins et des établissements auxquels ils sont rattachés. Avec le nombre croissant de preuves indiquant que diverses formes d'incompatibilité HLA ou de biomarqueurs pronostiques peuvent affecter les résultats, le différend opposant l'augmentation de leur utilisation au respect de l'équité risque de s'accroître. Au Canada, les fournisseurs de soins sont légalement tenus de placer l'intérêt du patient, tel que l'accès à un organe, devant les besoins du système de santé et des autres patients. De plus, la mise en œuvre d'approches de précision est susceptible d'être influencée par les poursuites liées aux droits d'accès à une transplantation qui ont abouti dans le passé. Ces tensions juridiques pourraient être exacerbées par les représentations qu'en donnent les médias, ces derniers ayant historiquement favorisé le droit à l'accès. Ainsi, au moment de mettre en œuvre de nouvelles technologies de précision pour l'attribution des organes, les décideurs devront constamment revoir l'équilibre entre équité et pertinence, de même que la façon d'élaborer des règles reflétant notre conception sociétale d'un système équitable d'attribution des organes.

Keywords

precision medicine, organ allocation, allocation policy, professional obligations, right of access, public representations

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Introduction

Historically, the ethical principles of equity and utility have been foundations of organ allocation policies in most jurisdictions.¹⁻⁴ Early transplant allocation policy was often dominated by considerations of place and time on an organ recipient wait

list.^{5,6} Policies frequently favored equity—that is, ensuring fair access to organs - over utility.⁷ However, there is increasing momentum to embrace evidence-based outcome measures and the use of precision medicine tools for donor-recipient matching and maximizing transplant survival.⁸⁻¹⁰ These developments could enable patients to live longer and healthier lives post



transplant and improve the ability to maximize the utility of a given organ¹¹—a goal that is increasingly emphasized in allocation policy such as that of the United States.¹² For example, the US Department of Health & Human Services' (DHHS) Organ Procurement and Transplantation Network stated in 2015 that “[t]he probability of a good outcome must be highly emphasized to achieve the maximum benefit for all transplants.”¹²

Although the shift toward greater precision can provide health and resource benefits, the concomitant emphasis on utility could also create a range of policy concerns. It may be perceived, rightly or not, as conflicting with both established equity-focused organ allocation norms and the legal and ethical obligations of health care providers and related institutions. Here, we review some past scientific developments relating to organ allocation, highlighting discoveries and policy changes that have altered the balance of equity and utility. We then consider potential policy challenges associated with an increasingly precise approach to organ allocation.

Increasing Precision in Organ Matching

Over the past few decades, histocompatibility testing for organ allocation has changed immensely.¹³ The first human leukocyte antigen (HLA) was discovered in 1958. Three more were revealed by 1963.¹³⁻¹⁶ Alleles encoding HLA were gradually discovered, and thousands of HLA genes have now been identified.¹⁷ Antibodies to these HLA are strongly correlated to rejection,¹³ and introduction of the cross-match test in 1969 was critical in detecting and avoiding this risk.¹⁸⁻²¹ HLA typing and antibody testing were initially performed using serological techniques, but DNA-based molecular assays and solid-phase immunoassays have greatly advanced this process.¹³ Other potential biomarkers for assessing transplant risk are now also being incorporated into this process.²²

Institutions responsible for developing organ allocation norms and policies, such as Canadian Blood Services, the United Network for Organ Sharing, and organ procurement organizations, create algorithms to guide this process and then periodically review and sometimes alter them as more evidence becomes available.²³ With the advance of science, these allocation policies and algorithms have become more and more complex, folding in consideration of relevant clinical characteristics, biomarkers, and health outcome data. Among other goals, precision technologies seek to provide a

better indication of transplant survival to maximize benefit and prevent organ waste.

The impact increasing specificity of compatibility matching could have on allocation utility and issues of fairness has been recognized by the transplant community in the past. For example, a working group at a 2003 American national kidney transplant conference raised concerns that the application of “lesser” forms of HLA matching—that is to say, matches of lesser or even no importance to survival—in recipient selection could divert kidneys “from those candidates who have waited lengthy periods of time to others listed much later but less difficult to match, an impact disproportionately borne by minority patients.”²⁴ This led to a recommendation to alter the United States' United Network for Organ Sharing allocation algorithm to eliminate priority for HLA-B similarity.²⁴ The recommendation was adopted in 2003 and a subsequent study showed that, in fact, the change had no adverse effect on survival but reduced the disparity in transplantation rates between ethnic minorities and Caucasians.²⁵

These kinds of policies are focused on preventing marginally valuable data relevant to utility from eroding a commitment to the fair distribution of organs. Such concerns are compounded by the reality that the complexity of histocompatibility testing has increased to the point where there is vigorous debate as to whether matching at specific gene loci should be implemented in an attempt to improve outcomes and whether, or to what extent, this would disadvantage some patients.²⁶ In addition, there are strategies other than HLA incompatibility to address some treatment parameters, including closer monitoring of patients and the optimization of adherence to immunosuppression regimes.^{27,28}

But with increasing evidence that various forms of HLA mismatch²⁹ and/or biomarkers for transplant pathologies²² can affect outcomes, the tension between maximizing utility and ensuring equity seems likely to intensify. For example, HLA epitopes, short structural segments shared by different HLA antigens and critical for antibody binding, make certain antigen mismatches “permissible,” and epitope matching may serve as an important method to improve transplantation outcomes.³⁰⁻³⁵ Innovative typing methods such as next-generation sequencing (NGS) can allow inference of eplet mismatches, whereas new solid-phase platforms enable the detection of pre-transplant HLA antibodies to avoid rejection.¹³

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Policy Challenges

Liability and Professional Obligations

The increasing precision of molecular diagnostics in organ matching creates legal pressures for health care providers and challenges for the development of allocation guidelines. Physicians have a legal obligation to focus on the best interest of patients, even in the face of explicit allocation policies.³⁶ In Canada, for example, health care providers are generally required by law to put the interests of their patient above the needs of the health care system or, indeed, other patients.³⁷⁻⁴⁰ These obligations flow from both the legal norms, such as standard of care and fiduciary obligations,³⁶⁻⁴¹ and professional ethics guidelines and standards of practice.^{38,42} There is some evidence that these professional norms have been internalized by the physician community and also drive physician behavior. One study, for instance, found that 70% of physicians agree that “[t]he physician’s main responsibility is to each individual patient rather than to society.”⁴³ Other research has found that physicians often err on the side of providing treatment regardless of cost, even in the face of resource considerations—a tendency that has been called “the rule of rescue.”⁴⁴⁻⁴⁶ A study about the allocation of ICU beds found that the rule of rescue was often used because “clinicians perceived strong obligations to identifiable living patients.”⁴⁶ Rightly or not, the existence of the legal and ethical norms is a key factor driving this tendency.

Dealing with conflicting obligations is a common challenge for physicians.^{47,48} It is no surprise, then, that there are statements from leading physician organizations, like the Royal College of Physicians and Surgeons of Canada and the American Medical Association,^{49,50} that seek to provide guidance on how to balance responsibilities. But these statements are not binding (ie, they do not change legal obligations) and in some respects only restate and, perhaps, intensify the problem by asking physicians to prioritize both patients and society. For example, the Royal College’s framework for “effectively meeting the needs of the people they serve” simply states that physicians should seek to “engage in the stewardship of health care resources” by “allocat[ing] health care resources for optimal patient care.”⁵¹ This is sensible advice. But it does not provide guidance on how this is to be done in the face of the more formal and actionable legal obligations to individual patients.

Given this legal and ethical reality, it should be no surprise that studies have found that some physicians will (consciously or unconsciously) game the allocation system—such as by exaggerating the severity of the condition of their patient—to increase the likelihood of receiving an organ.⁵²⁻⁵⁴ Indeed, some commentators have gone so far as to ask whether gaming the system could, due to the clear obligations physicians have toward their patients, be an ethical course of action.^{55,56} The increased use of biomarkers and outcomes criteria may inject more opportunities for interpretation and the weighing of benefit/risk for each patient. As

noted by David Hunter, “the new tools for tailoring treatment will demand a greater tolerance of uncertainty and greater facility for calculating and interpreting probabilities than we have been used to as physicians and patients.”⁵⁷ This may mean that the potential for gaming may be heightened, undermining the goals of increased precision.⁵⁴ The application of a precision medicine-informed algorithm—aimed at maximizing utility, including health outcomes and the efficient use of organs—may move a patient down a wait list just far enough to significantly alter the chance of that patient receiving the next available organ, even though that patient would still clearly benefit from the transplant but just marginally less so than another patient. In such a situation, physicians might feel pressure to advocate for their patients, which could have an impact on the implementation of precision medicine approaches.

At a minimum, some physicians may feel that case-by-case clinical judgment, and not data-driven decision-making, should remain central. Indeed, a survey of nephrologists found that although they felt more data from precision medicine would be helpful, “a place must be retained for the clinical judgment that allows a physician to make decisions based on medical data, professional expertise and knowledge of the patient.”⁵⁸ The authors of the study conclude “to act in the best interests of the patient is key to whether the calculation of the global immunological risk is employed.”⁵⁹

Clearly, there is a tension between some goals of precision medicine in organ allocation and the legal obligations of health care providers and the health care system.⁶⁰ As noted, precision technologies seek to provide a better indication of transplant survival to maximize utilitarian benefit and prevent organ waste. Providing more data to consider when allocating organs has the potential to narrow the pool of optimal organ recipients, raising a question regarding the degree to which a physician has an obligation to advocate for patients who fall outside or on the margins of increasingly precise allocation criteria.^{55,60} Given this uncertainty, it is possible that existing patient-centered legal norms will significantly affect the adoption and use of some precision medicine allocation tools.

Right of Access

At least 8 US states have laws prohibiting discrimination against individuals on organ transplant lists on the basis of physical or intellectual disability.^{61,62} Although there are clear cases of disability, such as Down syndrome, that have received media attention in relation to transplant discrimination,⁶³ the definition of disability can be interpreted broadly. For example, according to the Supreme Court of Canada, disability includes

a multiplicity of impairments, both physical and mental, overlaid on a range of functional limitations, real or perceived, interwoven with recognition that in many important aspects of life the

so-called “disabled” individual may not be impaired or limited in any way at all.⁶⁴

With a broad and potentially expanding legal definition of disability, it is possible that some disadvantageous differences in histocompatibility that otherwise have no effect on day-to-day life could qualify. As such, if matching criteria become so specific that they discriminate on the basis of differences in histocompatibility that have only a minor effect on transplant outcomes, or that lack associated research demonstrating significant differences in transplant outcomes, there is the possibility of successful legal action from excluded patients on the basis of discrimination under human rights law. If there is any question as to clinical relevance of a matching test, it becomes a potential source of legal challenge.

There have been instances when right of access lawsuits have successfully overridden or changed organ allocation policy. The US lung allocation policy was altered in 2017 when a woman needing a transplant sued for right of access on the basis that geographic boundaries for organ allocation were discriminatory.^{65,66} The lawsuit was initially dismissed but the court ordered the DHHS to review its lung allocation policy, which resulted in a change in boundaries.⁶⁶ This, among other factors, has precipitated similar changes to the US system of allocation for other transplant organs like liver.⁶⁷ In 2013, a young patient who rated low on the existing United Network for Organ Sharing lung allocation score largely due to her age received a temporary restraining order against the DHHS and its allocation policy, allowing her to be placed on the transplant list and subsequently receive a transplant.⁶⁸ In Canada, a constitutional challenge of the “six months sober” rule for alcoholic liver transplant candidates resulted in a provincial organ procurement organization piloting a new system without this rule.^{69,70} Such examples illustrate how right of access lawsuits, and related public and/or political pressure, could affect the implementation of precision approaches in organ allocation.

Public Perceptions and Popular Representations

Public representations and attitudes may also affect adoption of new precision technologies. There may be, for example, variation in allocation-related ethical preferences among patients, health care providers, and the general public.⁷¹ A systematic review of research on public preferences identified social valuation (eg, preferences for patients with dependents), moral deservingness, priority for first transplant, and younger patients to be key preferred determinants in organ allocation.⁷⁰ In some ways, this can contrast with health care provider perspectives that, while still including equity considerations, can tend toward maximizing clinical benefit.⁷² In addition, different jurisdictions may have different patient preferences than in the United States and Canada.⁷³ These discrepancies highlight the complexities and contextual nature of allocation decisions and the potential for conflicts with more objective and evidence-informed policies. Some

have suggested, for example, that organ allocation policy should reflect and be informed by public opinion to build and maintain confidence in the allocation system.⁷⁴ But what if public opinion differs, as it seems likely to do at least occasionally, from the goals of precision medicine and evidence-informed, outcome-based policies?

Public representations, which may or may not align with evidence-based perspectives, can also have an impact on public preferences and allocation practices. Media representations can affect support for public health endeavors, can shape public debate, and can ultimately contribute to allocation and utilization patterns.^{75,76} Indeed, one media study found that “hoaxes about brain death and organ transplantation adversely affect organ donation rates in both Western and Eastern societies.”⁷⁷ Research has shown that news media favors a patient access ethos,⁷⁵ reflecting the general perspective of the rule of rescue.⁷⁴ This suggests that public representations highlighting a deviation from an allocation policy that does not align with what is viewed as fair access—such as one emphasizing utility—may engender public resistance. This may, in turn, lead to legal action.⁷⁸ Of course, in this age where social media has become a key source of health information among the public,^{79,80} it seems likely that these platforms will play a significant role in the relevant public debates.⁸¹ Unfortunately, the quality and reliability of health information on social media can often be low.⁸² Inaccurate or intentionally misleading news can often spread quickly on social platforms,⁸³ and echo chambers of confirmation bias can polarize and mobilize certain groups.⁸⁴

In total, it seems likely that public discourse about allocation policy could affect how precision medicine strategies are implemented and even the degree to which they are integrated into allocation policies. It is even possible that a single personal narrative with viral qualities or a publicized right of access lawsuit could change public perspective in a way that significantly alters allocation policy and/or the trajectory of precision technologies related to allocation.⁸⁵

Conclusions

New scientific advances, including the use of better tissue matching technologies and algorithms,⁸⁶ have the potential to generate more precision that meaningfully changes the way in which we allocate organs. It seems inevitable that these promising developments will create challenges for the policies associated with the allocation of organs. Although the hope is that precision medicine technologies will create more certainty, this may not always be the case. The introduction of precision medicine tools will generate more data, which will invite more decision points and overall complexity.⁵⁷

Still, some developments seem likely to create tensions between the goals of equity and utility. We need to be aware that existing legal and ethical norms—and public perceptions and media representations—may heighten the practical impact of these tensions. As precision medicine technologies make their way to the clinic, it will become increasingly

necessary to recognize the potential influence of these forces and to consider the type of policy action required to ensure that the benefits of precision medicine are maximized. At a minimum, it seems certain that there will be a recurrent need for policymakers to revisit the balance of equity and utility, assessing how to craft rules that reflect our society's conception of a fair allocation system.

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Not applicable for this work.

Consent for Publication

We have the authors' consent for publication.

Availability of Data and Materials

Not applicable for this work.

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