THE ETHICAL IMPLICATIONS OF EMERGING GENETIC PREDICTORS OF POOR ORGAN TRANSPLANT OUTCOMES

by

Michael Aloysius Freeman

Bachelor of Arts, Siena College, 2004

Doctor of Medicine, Albany Medical College, 2008

Submitted to the Graduate Faculty of the

Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Arts

University of Pittsburgh

2016

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Michael A Freeman

It was defended on

July 20th, 2016

and approved by

Lisa S. Parker, Professor, Department of Human Genetics, University of Pittsburgh

Mark R. Wicclair, Professor, Department of Philosophy, West Virginia University

Benjamin E. Hippen, Associate Clinical Professor, Department of Medicine

University of North Carolina at Chapel Hill

Thesis Director: Lisa S. Parker, Professor, Department of Human Genetics

THE ETHICAL IMPLICATIONS OF EMERGING GENETIC PREDICTORS OF POOR ORGAN TRANSPLANT OUTCOMES

Michael A Freeman, MA, MD

University of Pittsburgh, 2016

Abstract:

Emerging research is beginning to identify genetic risk factors which may predict an increased likelihood of rejection following transplantation. The identification of these predictors prompt us to consider how we should incorporate this information into the process of transplant candidate evaluation and organ allocation, as well as the ethical implications of such incorporation.   In order to ground this analysis, this thesis begins with an examination of how we consider other predictors of poor transplant outcomes currently, as interpreted in concordance with the US transplant system's dual goals of efficacious and just organ allocation. It then proceeds with a brief summary of the current research on genetic predictors of poor transplant outcome, followed by a specific examination of the mechanisms by which these genes are investigated. This allows an examination of the challenges of appropriately applying the data gained through common methods of genetic research.   Next, it examines the complex ethical and social conflicts which may arise from a decision to incorporate genetic predictors within the current US transplantation system. It then concludes with a proposal for a mechanism for including genetic risk profiles into the transplant evaluation process on a national level that will seek to mitigate these conflicts and support both a just allocation system and ongoing research into this area of medicine.

TABLE OF CONTENTS

GLOSSARY

Note regarding definitions: The language surrounding issues of risk, predictions of poor outcomes, and cause and effect can be quite obtuse, particularly within the context of genetic markers and the like. For the ease of the reader, I will attempt to standardize the use of several of these terms within the context of this manuscript as detailed in the glossary below.

Allograft: A transplant of an organ between two individuals of the same species, but different genotypes.

Candidate Genes: A gene which is being investigated as a potential contributing factor to the outcome under consideration

Genetic Disorder: A disease associated with a genetic variation or series of genetic variations

Genetic Marker: A genetic polymorphism which is associated with an increased likelihood of a given outcome based on population-based studies. These polymorphisms may not result in disordered biologic processes themselves, but may be in close proximity to disease-influencing genetic material within the genome. In general, these genomic spatial relationships are maintained from generation to generation; thus, there is a statistical, but not necessarily causal association between the genetic marker and the outcome in question.

Genetic Polymorphism: Frequently occurring variation in a nucleotide sequence. Nucleotides are the basic units of DNA—namely, adenine, cytosine, guanine or thymine, and deoxyribose, and phosphate. A polymorphism is said to occur when the most common allele has a frequency of no greater than 99 percent. Some forms of some polymorphisms are associated with increased risk of disease.

Genetic Predictor: For the purpose of this text, this will refer to a genetic polymorphism that is being investigated as a potential predictor of transplant outcomes. Please see "Predictor" below.

Genetic Risk Factor: A genetic polymorphism which results in a disordered biologic process, increasing the likelihood that the affected individual will develop a disease (or genetically associated trait), as compared to the general population. One of the most well-known examples of a genetic risk factor are particular polymorphisms in the BRCA1 gene, a tumor suppressive gene.

Multi-genic disorder: A disease which arises due to the influence of many individual genetic variations, none of which are independently sufficient to cause the disease, as well as, in most cases, other factors.

Predictor: A characteristic, which can be assessed prior to initiating a medical intervention, which is associated with either increased or decreased likelihood of a given outcome than would be expected in the population at large. For the purpose of this paper, we will largely be concerned with characteristics which predict an increased risk of a poor outcome following transplantation.

Proximate Cause: An event or condition which, if it occurs, has a high likelihood to directly and unavoidably result in another event or condition of interest. As an example, having low serum immunosuppressant levels may be considered a proximate cause of organ rejection.

Remote Cause: An event or condition which, if it occurs, can contribute to an outcome through mediation by other more proximate causes. As an example, poor medication adherence can result in low serum immunosuppressant levels, which in turn may be considered a proximate cause of organ rejection

Risk: An increased likelihood of a poor or undesired outcome.

Single-Gene Disorder: A single genetic variation which, if it occurs, is sufficient to cause a genetic disorder. This can occur in autosomal dominant, autosomal recessive, or sex-linked forms. In general, to be classified as a "single-gene disorder," the presence of the genetic variation in the requisite number of chromosomes (i.e. on one chromosome for autosomal dominant disorders, on both maternally and paternally contributed chromosomes for autosomal recessive disorders, etc.) should result in the genetic disorder in nearly all occurrences. More recent research has identified that many single gene disorders have variable penetrance (i.e. differing levels of effect on individuals who possess the genetic variation), thus making this definition more tenuous.

1.0   INTRODUCTION

Since the time that organ transplantation entered the scope of non-experimental medical practice

in the 1960s, there has been ongoing discussion among medical practitioners, bioethicists, and

society at large regarding the most appropriate way to allocate the limited supply of organs

available for transplant. Although it would be a gross exaggeration to claim that a consensus has

been reached regarding the optimal construction of an organ allocation system, [1] it is fair to say

that the majority of proposed organ allocation systems have been concerned with two main

goals: 1) ensuring a "just" system of allocation in which a large subsection of the society is

eligible for potential therapy; and 2) maximizing the quantitative benefit of medical outcomes,

thereby making the "best" use of an inherently scarce resource.[2] While each proposed allocation

---

[1] Within this manuscript the term organ allocation will be used to encompass both the process of determining who is eligible for organ transplantation as well decisions regarding the distribution of organs among eligible candidates. This is slightly divergent from common usage, where the term organ allocation is often used to address questions of organ distribution alone. However, many of the issues raised and arguments contained within this manuscript can apply to either the candidate evaluation portion or the organ distribution portion of the transplant system, and use of a single term limits redundancy. Additionally, certain criteria of organ transplant eligibility are incorporated into the rules of the organ allocation system, such as maximal glomerular filtration rate at which a patient can be considered eligible for a deceased donor kidney transplant. As such, a complete distinction between the allocation process and candidate evaluation process is not possible. I have used the more specific terms of transplant candidate evaluation process or organ distribution process where specifically appropriate.

[2] The terms "just" and "best" have been designated with quotation marks to acknowledge the fact that these are value-laden terms which may mean different things to different readers. For the remainder of the text, I will dispense with such punctuation. While questions such as "What is Justice?" are philosophically rich and have been the subject of far more comprehensive treatises than this, deep consideration of these questions is far beyond the scope of this manuscript. Although this ambiguity will be examined in greater depth in section 2 of this manuscript, the reader may benefit from greater clarity regarding these terms from the outset. When used casually in the text, the terms will be used in such a manner as to indicate that the term "best use" is synonymous with efficacious use (i.e., resulting in the longest functional life span for the transplanted allograft or the maximizing the number of years

system has placed a differing degree of emphasis on each of these aims, the majority of these systems seek to implement a nuanced approach, in which both of these aims are sought in varying degrees. Our current organ allocation systems represent such compromises. Certain characteristics associated with poor outcome (i.e., predictors), such as a history of non-adherence to medical care, are considered during the candidate listing and organ allocation process, while others, such as lower socioeconomic status, are not considered due to the judgment that inclusion of such predictors will undermine the aim of a just distribution of organs.

Identifying predictors of poor transplant outcomes has been an arduous project. As organ transplantation progressed from being an experimental therapy offered at only a few institutions to becoming a routine consideration in conditions of end-organ failure, our understanding of the transplant process and its outcomes have similarly progressed. Initial efforts of simply cataloguing the outcomes of transplants performed gave way to broader studies which sought correlation between particular patient characteristics and the transplant outcomes.[3] With these studies came a realization that although identifying the characteristics of patients that were associated with a poor outcome was a technically challenging but otherwise straightforward scientific endeavor, determining how to incorporate these findings into organ allocation policy involved decisions fraught with ethical import.

Some predictors of poor transplant outcome, such as blood group or other immunologic incompatibility are purely biologic in origin. Other predictors of poor outcome however, such as gender, ethnicity, demographic and cultural factors emerge from a complex interplay of biologic,

of life gained among the recipient population). The term "just," in turn, will be used to describe an allocation scheme which seeks to minimize the potential of having a disproportionate number of allografts being dispensed to a given segment of the population.
[3] See Santiago-Delpin et al. (1983) or Coulson et al. (1976).

psychological and societal forces.[4] While consideration of these predictors during the organ

allocation process may allow a more efficacious outcome, it can also lead to a system of

allocation which does not meet the criteria of just distribution discussed previously.[5] With the

non-biologic predictors of poor outcome, the reason for this injustice is clear. Allowing

predictors within this second category to influence organ allocation runs the risk of perpetuating

disparities for which society may already be culpable to a greater or lesser degree. However,

even consideration of biologic predictors of poor outcome can result in allocation decisions

which are not considered just, despite being rooted in largely unbiased scientific fact and

therefore somewhat insulated from the assignation of ethical value. As an example, prior to

2003, the policy of the United Network for Organ Sharing (UNOS) was to given priority to

patients who had 0 mismatches at three human leukocyte antigen (HLA) loci: HLA-A; HLA-B;

and HLA-DR. However it was observed that that African American recipients generally

exhibited different HLA-B markers than the donor population as a whole. As a result, if

allografts were strictly matched by HLA criteria, the effect would be a systematic diversion of

allografts to the White recipient population.[6] In 2003, UNOS made the decision to disregard

HLA-B matching in allocation decisions.[7]   While subsequent research has not demonstrated the

expected worsening of individual recipient outcomes,[8] the fact remains that UNOS, as the body

entrusted with establishing an allocation policy consistent with societal values, has at times

elected to disregard even biologic predictors of poor outcome in circumstances where a just

allocation system would not result from their consideration.

---

[4] See Bunzel and Wollenek (1994) and Bunzel and Laederach-Hofmann (2000).
[5] See Orentlicher (1996) for an interesting evaluation of the ethical and legal interactions between these psychosocial predictors and the Americans with Disabilities Act.
[6] See Roberts et al. (2004).
[7] *Ibid.*
[8] See Ashby et al. (2011).

As the medical field increases its understanding of the remote and proximate causes of poor outcomes following transplantation, it has begun to identify new predictors of these outcomes. In turn, these predictors must be evaluated for technical and ethical validity before they are included in decision making regarding allocation.

Emerging research is beginning to identify genetic risk factors which may predict an increased likelihood of rejection following transplantation, and therefore predict a poor medical outcome if transplantation is performed in the affected populations. This field of research is in its nascency, and while the current investigations of specific genes may or may not result in the identification of verifiable predictors of poor transplant outcome, advances in the fields of pharmacogenomics and genomic medicine suggest that specific genetic risk factors do exist and will eventually be identified. This path of inquiry evokes several important questions. How should we as a society consider data regarding patient populations who are genetically at risk for a poor renal transplant outcome? How should we incorporate this information into the process of organ allocation on both a national and institutional level? What ethical pitfalls may be uncovered if these predictors are incorporated with insufficient consideration of the ethical implications? It is these questions that I will examine more closely throughout this manuscript. I would note that throughout this manuscript I have responded to these questions with respect to the context of the US transplantation system, although many of the arguments may be generalized to other nations and cultures.

Before addressing these questions, it is important to establish the framework that will ground this analysis. To that end, I will begin in the next (second) section with a discussion of how we consider predictors of poor outcomes currently, as interpreted in concordance with our dual goals of an efficacious and just outcome. An understanding of current evaluation of these

predictors is essential to understand how genetic polymorphisms that are being investigated as potential predictors of transplant outcomes (these will be referred to as genetic predictors in the remaining body of the text) should interlace with our current models. After the foundational blocks of the analysis are established, I will then proceed to a consideration of the emerging genetic predictors themselves.

I will begin the third section with a brief summary of the current research on genetic predictors of poor transplant outcome. While the specific genes that are being investigated are of limited importance for my argument (particularly given the preliminary nature of this area of research), an examination of the mechanisms by which these genes are investigated can offer insight into any parallels that may exist between genotype as a predictor and the broad categories of predictors examined in section two. Additionally, I will consider implications of questions regarding the quality of the data gained through common methods of genetic research. I will also discuss the means by which common genetic research methods can instill an unwarranted faith in the applicability of genetic findings which may have significant influence on the decision making processes of individual transplant programs.

In the fourth section of the manuscript, I will examine the implications of genetic predictors of poor transplant outcome in relation to the notion of justice as an issue of distributive justice among social groups. I will examine the how the effects of including these genetic predictors of poor transplant outcome in the organ allocation process would be altered depending on the strength of the predictors identified and the prevalence of a given predictor within society as a whole. As the final topic within this section I will also examine both the ethical and social implications of incorporating genetic predictors within two broad organ

categories: those organs which are necessary to sustain life (such as the heart, lungs and liver) and those organs for which a sub-optimal but functional replacement exists (i.e., kidneys).

In the fifth and final section of this manuscript, I will consider how the use of genetic risk profiles may be incorporated into national and institutional policies for organ allocation. I will also examine the implications of incorporating genetic risk factors within our current system of transplant program evaluation, which assesses the outcomes obtained by individual programs with only limited adjustment for the overall risk profile of individual transplant candidates. As part of this discussion, I will consider the ethically perverse incentives for programs to "cherry-pick" genetically identified low-risk candidates and how this tendency to select low risk candidates may be further potentiated by the move towards "pay-for-performance" models within the broader healthcare system. Finally I will propose a mechanism for incorporating genetic risk profiles into the transplant evaluation process on a national level. This mechanism will seek to support both a just allocation system and ongoing research into this area of medicine.

Ultimately, the aim of this manuscript is a pragmatic one, as I will attempt to detail the manner in which we can both practically and appropriately incorporate within our current system our burgeoning understanding of the role that genetic factors play in organ transplant outcomes. As such, my discussion regarding current transplant processes will be largely descriptive, focused on my interpretation of the ethical underpinnings and principles that influence the system as it currently exists, rather than providing an ethical critique of the existing system. However, as I begin to discuss our understanding of genetic predictors and analyze their similarities and dissimilarities to the predictors of poor transplant outcome currently used within the existent transplant system, I will begin to take both a more critical, normative approach. Although we are bound by some of the limitations of the current transplant system, each addition

or revision offers the opportunity to make the system more ethically sound, and I am hopeful that

our thoughtful discussion of the optimal way to incorporate emerging genetic predictors of poor

organ transplant outcomes will support that goal. Indeed, critical reflection on the incorporation

of such genetic predictors of outcome may ultimately lead to criticism of currently used outcome

predictors and even other aspects of the existing transplantation system. Such wholescale critique

is, however, beyond the scope of the current project.

2.0 THE CRYSTAL BALL: HOW WE CONSIDER PREDICTORS OF OUTCOME IN ORGAN ALLOCATION DECISIONS

Not all predictors of poor outcome are considered equal within our current organ allocation systems. If they were, the allocation process would be relatively simple. We would simply use the best available research to assess the impact of each predictor, quantify the effect of all potential predictors of poor outcome which could influence a potential organ recipient and incorporate the resulting value within our allocation formula. We have instead adopted a system that places ethical weight on both the reason that the predictors affect a given individual and the influence that the inclusion of such predictors in the organ allocation process will have on the outcomes of the allocation process as a whole.

While issues of organ allocation policy have provided fertile soil for the growing corpus of the bioethics literature, the field as a whole has focused on the questions that arise from the consideration of individual predictors rather than a systematic analysis of how we consider these predictors in general. As a result, while bioethicists have examined questions such as individual recipients' culpability for their diseases[9] or the implications of socially induced predictors of

---

[9] See Moss and Siegler (1991) or Ho (2008) as examples.

poor transplant outcomes,[10] development and examination of systems for classification of predictors have been neglected. This is unfortunate, as such classification systems can be a useful aid in in evaluating the ethical implications of novel predictors of poor transplant outcomes by highlighting the similarities between these novel predictors and those which been more thoroughly analyzed. Absent such a prevailing system of classification, I will proffer my own interpretation of how predictors of poor outcome are considered within the ethics of organ allocation.

The consideration of various predictors of poor transplant outcome is, at its heart, a re-capitulation of the broad concern regarding the dual goals of an efficacious and just transplant process. In regard to efficacy, we first consider the magnitude of the risk for poor outcome associated with a given predictor. For example, any behavior associated with a decreased life expectancy, such as riding a motorcycle or engaging in other risky recreational activities, will necessarily be associated with decreased allograft longevity to the extent that the behavior is associated with increased morbidity and mortality, because a transplant patient who dies as a result of risky behavior will die with a functioning allograft in place. Within current transplant policies, such deaths are indicative of a less than maximally efficacious transplant outcome. However, for many such activities, the increased risk resulting from participation is very small and therefore is not considered while making transplant allocation decisions. In contrast, other predictors, such as poor medical adherence or other the presence of other concurrent serious illnesses, are associated with a more substantial risk of poor transplant outcome.

We then consider the question of whether or not the inclusion of said predictor in the transplant process would unduly disadvantage a subset of potential participants within the

---

[10] See Lowe et al. (1995).

transplant process, i.e., we ask whether the outcome of employing the predictor as an allocation criterion is just. When we discuss the broad concept of justice as applied to questions of transplant organ allocation, we are primarily concerned with the notion of justice in two ways: as a notion of fairness and equitable opportunity for transplant as it applies to the individual and as the notion of distributive justice as it applies to populations. Both types of justice affect the way in which we judge individual predictors of poor transplant outcome, as we will discuss further below.

The intersection of these two factors (efficacy and justice) yield four potential categorizations: 1) those predictors which are associated with an excessively high magnitude of risk of poor outcome for which consideration of in the allocation system is just; 2) those predictors which convey an excessively high magnitude of risk of poor outcome for which consideration in the allocation system is unjust; 3) those predictors which convey an measurable but not excessive risk of poor outcome for which inclusion in the allocation system is just; and finally, 4) those predictors which convey a measurable but not excessive risk of poor outcome for which inclusion in the allocation system is unjust.

The stark simplicity of this categorization, however, obfuscates a crucial underlying uncertainty: we have no definite criteria for determining what denotes an *excessive* risk of poor outcome or what results in an *undue* exclusion or disadvantage within the allocation system. Each of these categories is somewhat ill-defined, influenced by a variety of technical, social and cultural considerations.

2.1 AN EXAMINATION OF CATEGORIES OF EXCESSIVE RISK

In general, what is universally considered a predictor of excessive risk has been limited to very few circumstances. These include severe co-morbid conditions that are expected to severely limit lifespan after transplantation or result in intra-operative mortality (such as active infection, poor overall health or extreme age), conditions with a high level of recurrence following transplant (such as atypical hemolytic uremic syndrome or certain autoimmune conditions) or a positive cross-match indicating an immunologic sensitivity to the potential allograft. In light of the inherent pragmatism of the organ allocation system, the severity of the risk of poor outcome conveyed by these predictors is generally considered to be sufficient justification for their inclusion among the criteria assessed in the allocation process.

The second category, composed of predictors of excessive risk which should not be included in the allocation system due to resulting injustices in organ allocation, is more difficult to understand. As such, conducting a thought experiment to better characterize this category may be helpful. For the purpose of this exercise, accept for a moment that we have been able to firmly establish what magnitude of risk of a poor outcome should be considered excessive. Within this system, any predictor which is associated with a 10x or greater risk of poor outcome as compared to the general population is considered sufficient justification to not consider transplantation in any individual who has that predictor. This policy is then incorporated into the allocation system. In a certain sense this policy is completely just in that it focuses exclusively on the expected outcome for the patient and is applied to all potential organ recipients.

However, imagine for a moment the predictor in question is an individual's ethnicity or gender. Does this change whether or not patients with this predictor should be excluded from the transplant process (e.g., all women per our example)? If we say that these individuals should be

excluded due to the risk of poor outcome, we are, in a way, saying this criterion is acceptably just. If instead we decide that we will tolerate worse transplant outcomes overall to allow individuals who possess these predictors to participate, aren't we also saying that the risk is, in fact, acceptable? Given the inherent malleability of our thresholds of excessive risk and acceptable injustice, it becomes clear that populating this category with examples from the real world is incredibly difficult.

In order to shed the complexities of the question of what counts as excessive risk, one could consider a circumstance in which the predictor was associated with a poor outcome in 100% of all cases. Such a predictor would be contained in this category if it was guaranteed to result in a poor outcome, but was disregarded while making allocation decisions because taking it into account resulted in unjust allocation outcomes. In a practical sense, however, such guaranteed poor outcomes could not be ignored based on considerations of justice, because it would be inappropriate to "inflict" poor medical outcomes on individual patients and unjust to inflict them on identifiable groups of patients for the sake of treating that group like members of other groups. With a guarantee of a poor outcome, that group is relevantly different from others. In its most minimal, formal conception, justice requires treating relevantly similar people similarly and relevantly dissimilar people dissimilarly. Although process-oriented ethical systems such as deontological or virtue-based ethics do attribute an ethical value to the intrinsic nature of an act independent of the outcomes reached, they would be rendered nonsensical if they urged that all considerations of resulting outcomes be disregarded. As such, while this second category of predictors exists as a philosophical consideration, it plays relatively little role in the day to day considerations of allocation policy.

2.2 AN EXAMINATION OF CATEGORIES OF ACCEPTABLE RISK

The primary focus for the remainder of this section is the third and fourth categories of predictors: those predictors associated with a measurable but not overwhelming risk of poor outcome for which their inclusion in allocation decisions is considered just or unjust respectively. In order to distinguish these categories from one another, it is clear that a more explicit description of what is meant by the terms *just* and *justice* within the context of organ allocation is required.

Unfortunately, such a description is very difficult to undertake. Within the context of Principlism,[11] the dominant ethical approach in contemporary bioethics literature, the principle of justice clearly encompasses a larger scope than the other principles considered (beneficence, non-maleficence and autonomy respectively). The concept of justice arises from moral and ethical questions within the context of human interactions and, as such, can be expressed in an almost innumerable array of general and specialized theories. Moreover, the ideas and themes used to discuss questions of justice have shifted over time, making any attempt to provide a broad overview of the scope of the question even more difficult.[12] As one moves away from philosophical theories expressly designed to instill a degree of universality into the question of justice towards the more concrete and pragmatic expressions of justice within cultural and social contexts, the issue becomes even more muddied. Within the realm of political and social policy, justice is rarely considered as an abstract concept per se. Instead, considerations of justice are

---

[11] Beauchamp and Childress (2013)
[12] Despite this difficulty, David Wiggins (2004) provides an interesting discussion of the contrast between the Aristotelian and Neo-Aristotelian and the more modern liberal concepts of justice in his aptly named "Neo-Aristotelian Reflections on Justice." Michael Sandel's (2007) "Justice: A reader" offers reasonable excerpts from a variety of prominent philosophers on the subject.

often expressed as certain aspirational goals which help to define the purposes and aims of the society in question.

How then, do we consider issues of justice within the context of organ allocation for transplant? I would argue that as a pragmatic matter the organ allocation process is primarily concerned with justice at two levels. The first is the notion of justice as fairness as experienced by the individual patient. Within this context, each individual patient is concerned with the notion of equitable access to organ transplantation on a personal level.[13] This amounts to asking whether one has as much opportunity as the next individual to be considered for a potential transplant. Such concerns provided the impetus for many of the characteristics of the deceased donor organ allocation programs as they are currently constructed.

Although the organ transplantation system itself cannot address (or at least to date has not attempted to) sources of inequity such as differences in wealth or personality that may influence how early in the disease process a patient enters the transplantation system as a potential candidate, within kidney transplantation, the goal of equitable access is expressed by the fact that the time a potential transplant candidate spends on the transplant waiting list is the primary determinant of organ allocation. It should be noted that this is not an absolute goal, as the organ allocation system as constructed is designed to avoid rampant injustices in access and allocation, rather than being designed to target one single conception of justice. As such, some modification and exceptions are permitted to match organs with recipients who are particularly well-suited to that organ, as in the case of perfectly matched HLA markers. Although an individual recipient may be harmed (or, at least, fail to be benefitted) by such a diversion of the organ from a more strict first come, first served system, the deviation is deemed acceptable because everyone on the

---

[13] This notion of equitable access is derived from Norman Daniel's (1985) book "Just Healthcare."

14

list has an opportunity to benefit from such a diversion. In other circumstances, donor kidneys

are diverted to patients who otherwise have difficulty being matched due to a high rate of

immunologic incompatibility with the donor population as a whole, generally described as

having a high panel reactive antibody (PRA) percentage. While this practice may not benefit the

majority of patients, the benefit is *potentially* available to any individual. Prior to the evaluation

process a potential recipient does not know if he or she will have a high PRA or if he or she will

develop a high PRA during the course of his or her treatment. As is the case with diversion of

organs to individuals with a perfect HLA match, this deviation from the just structure of

allocation based purely on the criterion of time spent on the waiting list is deemed acceptable

because any patient, prior to beginning the transplant evaluation process, has a similar potential

to benefit from this deviation. Thus, the goal of equitable access is supported. In general, these

deviations from the so-called "standard" practice of the allocation of deceased donor kidneys

based on waiting time are generally well tolerated by theorists and the public.

The second level at which justice is considered is at the level of social policy. Such

social policy is concerned with the equitable distribution of resources (organs available for

transplant) among broadly recognizable social groups, such as specific racial minorities or age

categories.[14]   I will acknowledge that the distinction between the broader discussion of

individual and categorical (or class) equity can be difficult, since all members of a class are also

individuals; inequities due to distribution policies between categories of people can be

experienced as individual inequities within populations, and importantly for this paper's

argument, characteristics of individuals can form the basis for identifying a social group.

Nevertheless, there is a broad understanding that some distributive policies can disadvantage

---

[14] See Lamont (2014).

certain classes, even if the mechanism resulting in such disparity may be acceptable on the individual level.

The clearest example of this phenomenon can be demonstrated by the efforts of the United Network of Organ Sharing (UNOS) to address racial disparities in deceased donor kidney allocation in the early 2000s that was discussed in the introduction of this manuscript. To review, in 2003, UNOS re-wrote its deceased donor allocation rules so that one component of human leukocyte antigen (HLA) matching, HLA-B matching, was no longer considered in the allocation process.[15] This revision was due to concerns that HLA-B matching greatly restricted the number of organs allocated to African-Americans, while offering only a limited improvement in transplant outcomes. As a group, African-Americans demonstrate clustering of HLA-B genotypes which were less prevalent among the majority White population. The fact that African-Americans are disproportionately likely to develop End-Stage Renal Disease (ESRD) in comparison to their White counterparts,[16] coupled with strict adherence to HLA-B matching criteria, resulted in a large subsection of potential African-American transplant recipients being restricted to receiving transplants from a disproportionately small subsection of the total pool of deceased donor organs.

For the purpose of this discussion, the policy revision represents a fascinating and ethically salient policy shift, as the inclusion of HLA-B matching criteria can be deemed either just or unjust, *depending on whether it is viewed through an individual or societal lens.* From the individual's standpoint, the inclusion of HLA-B matching criteria is easy to justify. The inclusion of HLA-B matching represents an effort to obtain the best possible outcome for the recipient who receives the donor organ. For a given individual, the expectation is that a closer

---

[15] See Ashby et al. (2011) for a description of this policy change and the resulting effects.
[16] See U.S. Renal Data System (2013).

HLA match will improve longevity of the organ after transplant. Thus, the individual may gain some benefit from the more restrictive matching criteria. It is true that any given individual may benefit more from disregarding such restrictive matching criteria—thereby receiving an allograft more quickly—than they would from receiving an allograft that is more closely matched, but one would be hard pressed to say either approach is *inappropriate or unjust* when examined from the viewpoint of an individual patient.

In contrast, from the standpoint of the societal concerns of distributive justice, the argument against the inclusion of HLA-B matching in the allocation process is much more clear. The inclusion of HLA-B matching criteria resulted in the systematic diversion of potential transplant allografts from a minority group (which historically has experienced numerous health disparities) to a majority group. If the improvement in post-transplant allograft longevity resulting from consideration of the HLA-B matching criteria were profound, the resulting racial disparity in transplantation rates might be considered an unfortunate but justifiable trade-off; absent those profound differences in post-transplant allograft longevity, these disparities in distribution were considered unacceptable.

Now that these two levels of justice (individual equity and distributive justice among social groups) have been characterized, we can return to our consideration of the third and fourth categories of predictors: those predictors associated with a serious (but not overwhelming) risk of poor outcome for which consideration in the allocation system is just and those for which consideration in the allocation system is unjust.

How do we determine whether the consideration of a given predictor in the allocation process is just? In practice, I would argue that such decisions have hinged largely on whether or not we believe that the predictor is *modifiable* (or was at one time modifiable) by the potential

transplant recipient. If the predictor is deemed modifiable, there is a societal inclination to argue that those potential recipients are somewhat culpable for their disease. In those circumstances, we (as a society) have deemed it just that these predictors be considered in allocation decisions.

The predictors which are generally considered to be modifiable by the potential transplant recipient are those factors which are primarily the result of health behaviors. These include alcohol or drug abuse, tobacco usage, obesity and a history of medication non-adherence. While medical research has established that many of these health behaviors can be influenced by complex genetic, psychological and environmental factors,[17] there continues to be a broad social perception that these behaviors are, at their core, volitional. This societal perception is not incorrect. There is an important distinction between a pre-disposition to alcohol dependence, which can be avoided through adherence to a decision to abstain, and an increased risk of breast or colon cancer, which may only be avoided through radical surgery. While this difference may seem to be intuitively obvious to many individuals, it bears some further examination.

Why exactly are these cases different? On superficial examination, it may be the burden of the preventative steps that we expect an individual to take. Abstaining from alcohol is seen as a relatively minor sacrifice, one that is undertaken by a large number of individuals for a variety of health, social, philosophical and religious reasons. In contrast undergoing a prophylactic mastectomy because one has a BRCA1 or BRCA2 mutation, or undergoing a colectomy due to the presence of an APC gene mutation, seems to be a much greater burden, and we understand why individuals would elect to proceed with or forgo these procedures. This is not the sole difference between these two categories however. If an individual with a pre-disposition to a

---

[17] See O'Rahilly and Farooqi (2006) and Feng et al. (2010) for an interesting discussion of the genetic and environmental factors influencing obesity. See Melotti et al. (2011) for a large scale cohort study examining the association between socio-economic status and tobacco experimentation.

disease such as cancer were to forgo standard monitoring for cancer prevention, such as mammograms or colonoscopy, we might find that decision foolish, but if those individuals then develop cancer we are unlikely to consider them morally culpable in the same way that we find an alcoholic responsible for his or her liver disease. In many ways, our notion of the potential transplant recipient's responsibility for his or her illness continues to have roots in traditional moral theory and intuitions. Within the field of formal bioethics, there has been extensive discussion regarding whether or not such moral evaluations accurately reflect our contemporary understanding of illnesses such as alcoholism, addiction and substance dependency and whether or not such moral evaluations are appropriate, but no singular consensus has been reached.[18] One potential difference between the circumstances described (the alcoholic who continues drinking and the patient with a known predisposition to serious illness who fails to take available precautionary measures) is that we consider the need to moderate one's alcohol consumption within the bounds of safety and the social propriety of the circumstance to be ethically obligatory, an obligation which met by many people in many circumstances. Therefore, we are not particularly forgiving of lapses in this regard and deem the individual responsible for the outcome, whether it be an automobile accident which occurs when one is drunk or cirrhosis which develops after years of heavy drinking. In contrast, the need to undergo unusual or invasive medical testing and therapies may be viewed as supererogatory to the common human experience and as such we are more forgiving of failures to pursue these measures. What is deemed to be obligatory and what is deemed to be supererogatory are themselves an extension of our common moral intuitions and a reflection of social attitudes. As such, this distinction

---

[18] See Moss and Siegler (1991) and Glannon (1998) for examples of con and pro arguments, respectively.

remains one of description of our practices, rather than the product of pure ethical reasoning.

Hence the lack of philosophical or social consensus on this issue as noted above.[19]

However, it is important to recall that while organ allocation policy is informed by careful philosophical consideration, it is not strictly the product of such consideration. Instead it represents a pragmatic approach attempting to reflect many societal stakeholders and viewpoints. Moreover, as a social system that relies on public support, the organ transplantation system has traditionally taken into account some prevailing social attitudes and values, for example, in accepting the notion that organ donors would prefer to donate their organs to recipients locally, rather than to those geographically distant. Thus, the uncertainty of "professional" ethicists regarding the meaning and degree of culpability that many patients have for their illnesses is only one of many considerations taken into account when establishing organ allocation policies and practices; the opinion of the general populace is important as well. Although contemporary data on public opinions about organ transplantation in the case of diseases for which the potential recipient is deemed culpable is sparse, previously published reports demonstrate a unanimity which is difficult to come by in empiric research; the public places lower priority on medical treatment for those who are deemed responsible for their illness. In 1990, in response to state bill SB 27, for example, the state of Oregon sought to explicitly prioritize different medical treatments to provide a rational basis for determining the priorities of Medicaid, the state based

---

[19] As an aside, I would note that the difficulty with this construction is that what we deem ethically obligatory and ethically supererogatory may be influenced by our own projected experience. Given that many of us have not experienced an overwhelming psychologic or physiologic compulsion to consume alcohol for example, our experience regarding the ease of abstaining may be very misleading. If the compulsion to consume alcohol is near absolute for example, resistance of such a compulsion might be considered a supererogatory act, just as it might be considered supererogatory to share one's food with a starving individual if you were starving yourself. I personally feel that the distinctions in culpability between the alcoholic who develops cirrhosis from heavy drinking and the individual who suffers a poor health outcome in the setting of blatant disregard of known medical risk factors are far more dependent on how the burdens of "appropriate" behavior are experienced by the individuals in question and therefore cannot be determined categorically. However, a further discussion of this topic is beyond the scope of this manuscript.

insurance program for the indigent. Although the technical procedures used to arrive at this prioritization were complex, they depended substantially on public opinion regarding the importance of treating each condition with a given therapy.   The disparity in prioritization of liver transplant for patients with alcoholic and non-alcoholic cirrhosis was stark; liver transplantation for non-alcoholic cirrhosis was listed with a priority of 361 out of 714 possible topics, while liver transplantation for alcoholic cirrhosis was given a priority ranking of 695.[20] More recent surveys have demonstrated similar preferences.[21]

Nor is alcohol use the only behavior which is stigmatized. Surveys of the public have revealed that they feel that patients with a history of smoking should be given a lower priority for heart transplant.[22] Moreover, certain activities are treated with greater moral opprobrium. In a study released in 1999, Peter Ubel and colleagues surveyed a group of potential jurors in Philadelphia to determine how they would allocate hearts for transplants between three potential recipients: one with a history of eating high fat and cholesterol foods, one who was a smoker, and one who had used intravenous drugs.[23]   The respondents were least likely to allocate the organs to a potential recipient who had used intravenous drugs, *even in circumstances in which the expected outcome would be best for that patient*. Social support for the allocation of health care resources, particularly organs for transplant, based on an assessment of a recipient's culpability for a given illness has been established by a variety of other studies as well.[24]

---

[20] See Dixon and Welch (1991).
[21] See Neuberger et al. (1998), Ratcliffe (2000).
[22] See Ratcliffe (2000, Sears Jr et al. (2000).
[23] See Ubel et al. (1999). Note, the use of potential jurors in this circumstance represented a sample of opportunity, but one that was thought to be somewhat ideal as the juror pool is drawn from a broad swath of the public at large and therefore was deemed to be largely representative.
[24] See the meta-analysis by Tong et al. (2010)   for an assessment the literature on this topic.

Moreover, individual transplantation programs are given wide latitude in determining

which potential recipients are acceptable candidates for organ transplantation.[25]   While the

refusal to proceed with transplantation due to perceptions of such culpability alone has been

condemned by the American Medical Association,[26] among others, the fact that individual

programs are the ultimate arbiters of whether or not a given individual should be listed for

transplantation allows for the influence of factors such as the perceptions of the culpability of the

patient for his or her medical condition to influence candidate evaluation and listing decisions.

Further, prohibition of denying access to transplantation services based on the cause of organ

failure is complicated by the fact that behaviors associated with organ failure may very well

contribute to poor health or allograft failure after transplantation. Consideration of these

behaviors, particularly if ongoing (such as smoking) or unresolved (such as obesity) may have a

justifiable role in determining a patient's candidacy for transplantation. Unfortunately, there is

evidence to suggest that assessments of culpability, whether conscious or unconscious, play a

role in candidate evaluation by individual programs above and beyond the quantitative risks of

poor outcomes for the patient or allograft following transplantation. An archetypical example of

this issue is the allocation of livers for transplantation within the United States.

While an in-depth examination of the allocation protocols is beyond the scope of this

manuscript, the basic premise behind liver allocation is relatively straightforward. Patients are

given a score (MELD or PELD for potential adult and pediatric recipients respectively) based on

how ill they are, which is used to determine the urgency of transplantation; those who require

---

[25] This approach has its own inherent strengths and weaknesses. From a justice standpoint, this variation in practice can be highly problematic. A given patient in transplant center A may be deemed an appropriate candidate for transplant, while a near identical candidate at transplant center B is not, a clear failure to achieve the goal of equitable access.

[26] See Clarke et al. (1995).

transplantation most urgently are given top priority.[27] While it is possible that an individual will

be deemed too sick to be a transplant candidate, that threshold is high. Within the allocation

system priority is given to those individuals expected to die within 7 days without a transplant,

which illustrates that extreme illness is not a clear contraindication. Moreover, many systemic

illnesses, such as cystic fibrosis, which would be expected to limit the recipient's overall life

span significantly, are incorporated into the allocation system with patients who have such

illnesses being *granted priority* within the allocation system. As such, it is clear that obtaining

the maximal utility from each graft is not the primary goal of the liver allocation process.

Instead, the primary goal is to "rescue" patients from what would be an otherwise fatal illness.

As such, one might presume that the etiology of the patient's liver illness would play a limited

role in allocation decisions, apart from the determination of the patient's MELD or PELD score

as detailed above. The reality for patients who have alcoholic liver disease is much different

from this presumption however.

The formal UNOS allocation system does not discuss the issue of alcoholic liver disease

in any form. However, individual programs often require potential transplant recipients with

alcoholic liver disease to meet strict criteria before they are registered with UNOS as a transplant

candidate. A study performed in in 1996 by Everhart and Beresford demonstrated that over 80%

of US liver transplantation programs would consider active alcohol use to be an absolute

contraindication to liver transplantation.   While more contemporary data from the United States

has not been published, policies of requiring patients with alcoholic liver disease to be abstinent

from alcohol use for at least six months prior to transplant continue to be common place.[28]

---

[27] See the UNOS website [http://optn.transplant.hrsa.gov/governance/policies/] for current policies and procedures
United Network of Organ Sharing (2015)
[28] See Lucey (2011).

23

Policies regarding liver transplant for alcoholic liver disease are interesting from an

ethical standpoint, however, because there is little evidence that patients with alcohol related

liver disease do worse after transplant.[29] Although alcohol recidivism is associated with a worse

outcome 10 years after transplant,[30] there is little to no evidence that being abstinent for 6

months or more prior to transplant results in lower rates of alcohol use recidivism.[31] Therefore,

there is no clear medical evidence that suggests that patients who are using alcohol until shortly

before transplant are at an increased risk of poor outcome. Why, then, do we treat active alcohol

use as a contraindication to liver transplant? Since there is no difference in the risk of a poor

outcome between the population using alcohol prior to liver transplant and the population not

using alcohol prior liver transplant, the decision of transplant programs to use active alcohol use

as a criterion for determining whether or not they should proceed with transplantation is not

based on a determination of acceptable versus excessive risk. Instead, it is a reflection that the

transplant programs feel that it is *just* to consider alcohol use as sufficient criteria to not proceed

with transplant, thereby precluding consideration of patient's actively using alcohol within the

formal deceased donor allocation system.

In light of the studies and practices described previously, it appears clear that as a society

we believe that when we are considering priorities in organ allocation for transplantation there is

an ethically relevant difference between individuals whose illnesses are proximately related to

modifiable behaviors and those individuals whose illnesses appear to arise from random chance

alone. This social belief may, however, rely on an unsophisticated understanding of both the

---

[29] See Lim and Keeffe (2004).

[30] See Faure et al. (2012).

[31] See Rodrigue et al. (2013). A recent study performed by Mathurin et al. (2011) examining the use of emergent transplantation for acute decompensation in acute alcoholic liver disease in which there was no abstinence prior to being emergently hospitalized shows rates of recidivism equivalent to the population of patients with alcoholic liver disease at large.

culpability of the "bad" actors and the lack of culpability of other parties. Nevertheless, given the known influence that a variety of health behaviors can have on the course of many diseases, I do agree that the categories of culpable and non-culpable appropriately carry a degree of ethical weight, but also believe that while this determination of culpability has ethical value, it is an insufficient reason to deny someone access to transplantation. For the purpose of this project's argument, what is critical is the fact that society does currently embrace, and employ in transplantation policy, a distinction between causes of organ failure for which a person is deemed culpable and those for which a person is not. What is at issue here is how perceptions of culpability interact with beliefs about emerging genetic predictors of transplant outcomes and perceptions of the immediacy of the impact of those genetic factors.

2.3 IMPLICATIONS FOR GENETIC PREDICTORS OF POOR TRANSPLANT OUTCOMES

The preceding examination of how the public, practitioners and transplant allocation systems employ predictors of poor transplant outcomes was intended to provide a framework within which we can examine the emerging genetic predictors of poor transplant outcome. The next (third) section will briefly examine current research on those genetic predictors with an emphasis on the how the nature of the information obtained correlates with degrees of risk of a poor outcome. This will allow us to consider how different types of genetic predictors should be considered along the axis of risk assessment. Then, in the fourth section we will consider the use of these genetic predictors from the standpoint of justice.

3.0 RESEARCH METHODOLOGIES AND EPISTEMOLOGICAL QUESTIONS: CURRENT RESEARCH INTO GENETIC PREDICTORS OF POOR TRANSPLANT OUTCOME

3.1 THE ACADEMIC GOLD RUSH

One needs to only open any medical journal or newspaper to encounter the ways in which genetic research will begin to shape the future of modern medicine. The field of organ transplantation is no exception. A review article by Almoguera, Shaked and Keating within the *American Journal of Transplantation*[32] examines the current status of genetic research within the field of solid organ transplantation. During the course of their review they evaluated over 1000 published studies. Although the number of the studies reviewed is not profound, the short time span over which these studies were produced is staggering. In a 2000 editorial review in *Current Opinions in Nephrology and Hypertension,*[33] the use of genetic polymorphisms to predict and shape transplant outcomes is cited as an area of *emerging* research that will shape the field of organ transplantation in the coming century and by 2014 there were 1000 studies to review.

A comprehensive overview of the scientific findings of the research thus far is not necessary for the present project. However, it is important for the purposes of this manuscript to turn a philosophical eye toward these data and to understand the type of information being

---

[32] See Almoguera et al. (2014).
[33] See Suthanthiran (2000).

produced. Studies have begun to identify genetic markers which predict an increased risk of

poor outcome following solid organ transplantation through a variety of mechanisms. Some

have studied post-transplant outcomes directly. For example, Mytilieneos et al. investigated a

variety of gene polymorphisms associated with cytokines which are thought to play a role in

modulating the body's immune response to the transplanted organ.[34] They studied a cohort of

2298 primary and 1901 repeat recipients of deceased donor kidney transplant. Although the

majority of the genetic polymorphisms they investigated showed no clear association with post-

transplant outcomes, one gene polymorphism identified at the 308 position of the Tumor

Necrosis Factor Alpha (TNFα) gene (a potent pro-inflammatory protein), which resulted in a

high rate of production of TNFα, was found to be associated with a significantly greater risk of

graft failure in the setting of a repeat kidney transplant. Patients with this genetic polymorphism

had a relative risk of graft failure within the first 3 years post-transplant of 1.96, as compared to

genotypes associated with less TNFα production. A study by Golshayan et al. examining

outcomes of over 700 kidney transplant recipients enrolled in the Swiss Transplant Cohort Study

demonstrated that gene polymorphisms of the manose-binding lectin(MBL) 2 gene associated

with low MBL levels were associated with an a 1.75 times greater risk of acute cellular rejection

within the first post-transplant year.[35]

Other studies have identified polymorphisms associated with an increased risk of serious

infection after transplantation. A study from the OPERA study group, a prospective

observational cohort of 315 recruited through 25 Spanish transplant centers investigated the

influence a number of single nucleotide polymorphisms (SNPs) associated with a variety of

immuno-regulatory molecules had on the likelihood of developing active infections with the

---

[34] See Mytilineos et al. (2004).
[35] See Golshayan et al. (2016).

cytomegalovirus after kidney transplantation. This study examined the effects of both individual polymorphisms, as well as "profiles" based on the number of unfavorable polymorphisms (identified as being associated with an increased risk of CMV infection by the preliminary phases of the study) possessed by the patients. This study demonstrated that patients with 2 unfavorable polymorphisms were 2.29 times as likely to develop a CMV infection, and patients with 3 unfavorable polymorphisms were 2.36 times as likely to develop a CMV infection, in the 12 month period after transplantation, as compared to the patients with only 0 or 1 unfavorable markers.[36]

Others have focused on the effects that an individual's genes have on his or her response to the medications used in the post-transplant setting, contributing to the field of pharmacogenomics. A 2015 meta-analysis performed by Rojas et al. evaluated the effects that CYP3A5 6986A>G polymorphism had on tacrolimus levels and transplant outcomes. [37] This polymorphism has been associated with increased expression of CYP3A5 and increased metabolism of tacrolimus (a commonly used immunosuppressant medication) from its active to inactive form. They demonstrated that kidney transplant recipients who carry this allele have an increased risk of acute rejection (odds ratio (OR) of 1.32) and chronic nephrotoxicity (OR of 2.42) as compared to the transplant recipients who did not carry the CYP3A5 6986A>G polymorphism.

If the iterative nature of scientific research has taught us anything, it is that our understanding of individual scientific facts is often obsolete almost as soon as it is reached. It is important to note that this research is investigational and will require further verification before implementation in the clinical setting should be considered. Certification of tests for clinical use

---

[36] See Fernández-Ruiz et al. (2015) for further details.
[37] See Rojas et al. (2015).

involves a lengthy regulatory process and is generally reliant on results of multiple studies. However, some of these barriers are becoming less absolute then they may have been previously. Outside of the clinical setting, consumers are gaining access to their own genetic data, which may one day be useful for informing medical decisions. Genetic testing in the medical setting is becoming more common and may identify findings whose significance becomes more evident over time. Finally, the developing availability of next generation sequencing techniques which allow for approaches such as whole exome sequencing have the potential to identify numerous abnormalities, some of which could inform assessments within the organ transplantation process. The question of what to do with these incidental genetic findings remains a controversial one.[38] Although current guidelines from organizations such as the American College of Medical Genetics recommend reporting only particular findings of clear medical significance, both what is considered significant and the overall approach of only reporting findings pertinent to the reason for testing (or, alternatively, only clearly medically actionable findings) have the potential to change in the future. Therefore, it is important that we begin to consider how we will choose to incorporate information regarding genetic predictors of risk of poor transplant outcomes when it becomes better established.

In many ways, genetic information has captured the public attention in a more dramatic way than other areas of scientific research. It has become linked to the historic understanding of one's "nature," the essence of one's self which cannot be shifted or changed. This in turn has influenced how we think about genetic predictors, as absolute indicators of one's genetic destiny. The reality however, is much less definite. Although one's genome is relatively immutable, the effects of the code on an organism level are much less fixed. In order to best consider how we

---

[38] See Green et al. (2013) and Burke et al. (2013) as two representative arguments regarding the merits of either disclosing or withholding incidental findings of next-generation genetic testing.

should incorporate these newly identified genetic predictors of transplant outcome, it would be useful to consider the epistemological implications of the major types of genetic research, to allow us to draw parallels to how we consider already established predictors of transplant outcome.

3.2 THE IMPORTANCE OF GOOD BREEDING: THE PEDIGREE APPROACH

Our original insights into the field of genetics were gleaned through the examination of carefully recorded pedigrees, examining the familial nature of certain traits. Although we have moved beyond the scrivenings of Gregor Mendel and his seemingly innumerable pea plants, this approach has still played a crucial role in modern medical genetics. These techniques, refined over the past century, served as the basis for identifying that abnormalities in the CFTR gene can cause cystic fibrosis[39] and that polymorphisms of the BRCA tumor suppression gene are associated with a much greater risk of developing breast cancer or ovarian cancer than the general population.[40] Using the pedigree approach, families were identified in which the genetic disorder of interest was more common than in the general population at large. This allowed for genetic analysis to identify changes in the genome that were evident in patients who had the condition of interest, but were not present in individuals who did not have that condition. By repeating these studies in multiple families we were slowly able to identify first the general chromosome locations of concerning genes, and then the genes themselves. Such approaches only provide part of the necessary information however. Once these genes of concern are

---

[39] See Cutting (2015).
[40] See Xu and Solomon (1996).

identified, the next stage is often an attempt to generalize this information outside of a given pedigree. To determine this, researchers frequently utilize a technique known as the candidate gene approach.

3.3 CLASSICAL EXPERIMENTS BY ANOTHER NAME: THE CANDIDATE GENE APPROACH

The second major category of research utilizes what is known as the candidate-gene approach. In many ways, it is these studies that most closely parallel the techniques used in other, non-genetic, sub-disciplines of biology and the other sciences. In the candidate-gene approach, the researcher first hypothesizes that a given gene may have an effect on the process of interest, based on a pre-existing understanding of molecular biology, cellular biology or physiology. The researcher then seeks to identify variants in or near those genes which may affect the process being studied. Finally, the researcher studies variations in these genes within a population and seeks to determine if variations in these genes are associated with a given outcome (e.g., the disease being studied.)[41]

Ultimately, these studies seek to identify abnormalities that cause, at least in some small measure, the diseases being studied. As such, this represents a disease focused, rather than population focused approach. By basing the selection of the genes being studied on a pre-existing belief that an observed association between a genetic marker and a given disease is plausible, it lends credence to the belief that the genetic marker and the outcome in question are

---

[41] See Tabor et al. (2002) for a more detailed description of the candidate-gene approach as well as a discussion of some of the strengths and weaknesses of these studies.

causally linked. These studies are not without their critics however. One commonly raised

criticism is that our current body of knowledge is insufficient to provide enough plausible genes

to study.[42] Although other research, such as the aforementioned pedigree studies, can help

supply new testable hypothesis, these processes are insufficient. Furthermore, despite designs

that are intended to identify genetic markers of broad significance, in many cases attempts to

replicate the findings of candidate gene studies fail.[43] This failure may be due to a variety of

factors. First, genetic studies are quite sensitive to sampling biases, as the result of the genetic

heterogeneity both within and between given populations. Thus, what is found to be significant

in one population which shares certain genetic tendencies may not be significant when applied to

other populations. Second, given the vast array of testable genetic hypothesis, elementary

statistics suggest that some findings thought to be clinically significant will be false associations.

Given the well characterized phenomenon of publication bias, in which studies that identify

significant findings are more appealing to journals, whereas similar studies which show no

significant effects are rarely offered or accepted for publication, these findings may be published

in rates that are disproportionate to their occurrence in research as a whole and studies which

would contradict these findings may not be as frequently published.[44] It is partly due to these

limitations, that the third broad approach that we will consider has been developed: the genome

wide association study.

---

[42] See Zhu and Zhao (2007).
[43] See Ioannidis et al. (2001).
[44] See Ioannidis et al. (2014) for a good discussion of publication bias in general. See Clarke et al. (2012) for a confirmed example of profound publication bias through comparison to unpublished data.

3.4 THE ALLURE OF *BIG* DATA: THE PROMISES AND PITFALLS OF GENOME WIDE ASSOCIATION STUDIES

As I have just mentioned, one of the common critiques of the candidate gene approach is that we don't know enough about the genetic underpinnings of diseases to generate informed hypothesis regarding candidate genes. What if it was possible to look for genetic markers associated with a particular disease without any fore-knowledge of plausible connections between those genetic markers and the disease in question? Such an approach would bypass the limitations that result from our incomplete understanding of disease processes. Moreover, these approaches would avoid investigator bias toward studying specific sections of the genome, which could slow the progress of our understanding if those sections of the genome were eventually found to yield little useful information.

Genome wide association studies (GWAS) are designed expressly to address those aforementioned limitations of the candidate gene approach. GWAS are designed to examine either large portions of or the entirety of an organism's genome through comprehensive genetic sequencing and to repeat this analysis on many individuals. This then allows researchers to identify numerous small variations in the genome, known as single nucleotide polymorphisms (or SNPs). Many of these SNPs occur in portions of the genome that have no known significance and do not appear to influence how an organism functions; if these SNPs were randomly distributed among the population they would not be useful for identifying any influence of genes on a given disease. The reason identifying SNPs can be helpful is that these changes are not randomly distributed among the population or across the genome. Instead, when an individual inherits a given variation at one of the SNP sites from his or her parents, they also

likely to inherit the portions of the genetic code which are adjacent to that SNP. By examining

large groups of individuals, GWAS seek to identify portions of the genome that seem to be

associated with manifestation of a disease. These findings can then be used to direct future

investigatory efforts (by identifying genes that can then be examined through the previously

discussed candidate gene approach) or can be used as a direct means of assessing genetic risk.[45]

The primary appeal of this approach is that it is not dependent on an *a priori* presumption

of the influence that a given section of the genome will have on a particular disease. As a result,

it allows for the discovery of new avenues of inquiry, much in the way that pedigree studies do,

rather than simply existing as a means to test existing hypothesis. This approach has many

limitations however. The first is the technical challenge of obtaining the data. This approach is

computationally difficult and requires a vast amount of information to obtain significant results.

This need for large data sets can make verification of the findings of any single study difficult.[46]

In contrast to those used in more traditional study designs, the statistical tools and approaches

necessary to perform a robust analysis of the data provided by GWAS are still being

developed.[47] There continues to be controversy regarding the optimal statistical design, and

different statistical approaches vary widely in how conservative they are in identifying as

significant particular associations within a given data set.[48] This is especially problematic

because many clinicians, as well as the public, lack the statistical savvy to understand these

limitations. The final statistical output, the p-value, is commonly used in scientific literature and

---

[45] See Wray et al. (2013) for a discussion of the limitations of the use of GWAS for this purpose. I will expand on this analysis in a later section.
[46] *Ibid.*
[47] See Sham and Purcell (2014) for a discussion of some of these techniques.
[48] *Ibid.*

as such there may be an inclination to interpret and use the outcomes of these more complex genetic studies in a manner similar to interpreting more straightforward statistical constructs.

Moreover, there are certain complexities that arise from the fact that these studies reveal findings that are meaningful within a particular genetic cohort. For example, a certain SNP may be associated with overall height within study subjects of a Norwegian background, but not among those of a Southeast Asian background. If these populations are studied independently, this conclusion is simple; the association is found in one study but not the other. If these populations are studied concurrently however, such as studying associations within a broad US cohort for example, a statistically significant association may be found which only applies with validity within a subgroup of that cohort, even though clinically, or even in additional scientific research, the association is applied to the population as whole. Moreover, although nationality can be a useful proxy by which to identify a biologic cohort in some homogeneous populations, even in this circumstance it has its limitations. The limitations of nationality and other social identifiers were examined in depth by Foster and Sharp.[49] As they note, our social identity is multifactorial, including geographic, familial, ethnic and national identities. A given genetic polymorphism may be associated with any one of those sources of identity, making attribution difficult. Although our own understanding of our social identity can be a powerful tool in identifying these associations, our social identity may not include all pertinent biological facts. Studies examining the utility of self-identification of race and ethnicity for medical research have produced mixed results.[50] This has led to efforts to identify pertinent population groups solely on the basis of comprehensive genotyping alone, but this approach remains technically

---

[49] See Foster and Sharp (2002).
[50] See Tang et al. (2005) and Campbell et al. (2005) for examples where self-identification of race and ethnicity were respectively predictive and non-predictive of population stratification.

challenging and remains incapable of answering important questions.[51] How do you define these

population subgroups? How do you determine the implications for subjects who clearly fall

within multiple subgroups?[52]

Essentially, GWAS studies suffer difficulties in population identification to an extent

that, I would argue, many forms of medical research do not.   In most medical research,

increasing the study sample size is one of the (theoretically) easiest ways to improve the quality

of the data generated; in GWAS studies non-targeted expansion can limit the data applicability

by obscuring the population to which the information is most applicable.

---

[51] See Tian et al. (2008) for a broad discussion of some of the issues involved. For a more technical overview of
potential methods of statistical correction see Nsengimana and Bishop (2012) or Qin and Zhu (2012).
[52] For a more thorough discussion on the complex history of and academic debate regarding genetic markers of
racial and ethnic identity I would recommend reading the excellent paper by Morris Foster (2009), "Looking for
race in all the wrong places: analyzing the lack of productivity in the ongoing debate about race and genetics."
Unfortunately, further discussion of this fascinating topic is beyond the scope of this paper.

3.5 BEYOND THE METHODS TO THE MEANING: HOW WE APPLY GENETIC

RESEARCH TO INDIVIDUALS

I have now detailed three major methods of genetic research, each with their own strengths and

weaknesses. With this information in hand, I will shift my focus to the nature of the information

provided by these studies and how it may be applied to aid decision making with regard to the

individual patient. As an exercise, it may be useful to consider how the evolution of the

methodologies themselves, from pedigree studies to candidate gene studies and onward to

GWAS have paralleled the shifting meaning of the information gained from genetic research.

When genetic research was in its nascency, the initial pedigree studies sought to identify

families who have demonstrated a greater frequency of developing the genetic disorder in

question. In a sense, the research identified a class of individuals (in this case the family

grouping), each of whom is presumed to be at greater risk of developing the genetic disorder

than the "average person." This risk is not based on the assessment of any individual's inherent

risk *per se*, but simply due to that individual's membership within a given class.   In turn, the

candidate gene studies sought to move from this broad description of presumptive risk toward an

assessment of the risk experienced by a given individual, rather than a *type* of individual. This is

done by identifying the genetic polymorphisms that are associated with the genetic disorder

being researched. Theoretically, if these are identified and confirmed, it allows us to assess an

individual's risk for an outcome based on the presence of the polymorphism in that individual,

rather than based on the individual's membership in a group at greater risk.

Of course, this theoretical goal is not always achieved. Some conditions are single gene

disorders, where the genetic disorder is associated with changes within a single gene. In most

cases, this change is both necessary and sufficient to cause the genetic disorder in question. If

the presence of this genetic abnormality is sufficient to result in the genetic disorder, interpreting

an individual's genetic testing is relatively straightforward. If an individual has the genetic

polymorphism which causes the disease (or two copies of the genetic polymorphism in the case

of recessive conditions), than that individual likely either has the genetic disease or will develop

it in the future. If those genetic polymorphisms are not present, the individual does not have the

disease or risk thereof. Although the information that serves as the basis of the genetic testing

was derived from studies assessing risk as member of a group, it can know be interpreted in

relation to the individual patient, independent of group status.

In other circumstances, such as is exemplified by our experience with the BRCA1

mutation, the gap between our analysis of group risk and individual risk is more difficult to

bridge. Although the presence of a BRCA1 mutation is known to contribute to the likelihood of

an individual developing breast cancer, the fact that not all individuals who have this

polymorphism go on to develop breast cancer shows that the mutation alone is not sufficient to

cause cancer; those breast cancers that are associated with BRCA1 mutations are considered

complex conditions, as it is the mutations in association with environmental factors that result in

disease. The initial research on BRCA1 examined the risk of developing breast cancer for

individuals who also had a family history of the disease.[53] The risk faced by individuals with the

BRCA1 mutation who do not have a family history of breast cancer is much less clear.[54] This

led the United States Preventive Services Task Force to recommend against population based

---

[53] See Moyer (2014).
[54] See McClain, Palomaki, et al. (2005) for a discussion as to why extrapolation of BRCA1/2 gene penetrance within a family based study population is likely not applicable to the general population.

screening for the BRCA1 and BRCA2 mutations when they reviewed the available data in

2014.[55]

In regard to our broader analysis, it is clear that in the general population without any

family history of breast cancer, the risk associated with having BRCA1 mutation remains

unknown. This creates the interesting circumstance in which in some populations (i.e., those

with a family history of breast cancer) a finding of a BRCA1 mutation can be considered a risk

factor for developing breast cancer while in other populations (i.e. those without a family

history) it cannot (or at least cannot be considered a risk factor to the same degree). Though this

line of analysis remains in principle correct with regard to the BRCA1 and BRACA2 mutations,

there is growing interest in population screening (i.e., screening among individuals without

family history).[56] The example of the utility of BRCA1/2 testing to assess a person's risk within

the context of group membership remains relevant for the purpose of comparison within this

paper.[57]

We have now established three broad categories detailing the relationship between an

individual and a given genetic marker: 1) Those for whom genetic testing has revealed an

individualized risk; 2) Those for whom genetic testing can reveal a person's risk within the

context of group membership; and, 3) Those for whom genetic testing has not provided

information about risk, even if those same findings might be informative in another context.

These categories will be important as we examine the implications of incorporating these

findings into organ allocation decisions.

---

[55]*Ibid.*
[56] See King et al. (2014)for one such argument.
[57] See Nelson et al. (2014) for a summary of published research supporting the use of BRCA1/2 testing in high risk populations.

As we consider pedigree studies, they most clearly fall within the second category, whereas an individual's degree of risk may be ascertained with some accuracy due that individual's membership within a certain group (i.e., the family cohort). Candidate gene studies, if they successfully identify genetic abnormalities which appear to have a causative (though not deterministic) role in producing the outcomes studied, seek to identify the subject's individualized risk. Therefore, they would fall within the first category. The information obtained from GWA studies is interesting because insofar as one falls squarely within the parameters of a study population, if the finding of risk was robust, it may reflect an individualized risk (i.e., the first category). As one moves to the margins of the population definition, however, or as the findings become less robust, the information provided by GWA studies, as applied to the individual, may begin to fall in the second or third categories.

This notion of variable meaning is not unique to GWAS. All empirically derived data are epistemologically uncertain in similar degrees. Just as a medication may be found to be broadly effective in treating a certain condition but may not be efficacious for every individual who takes that medication, the findings of genetic studies may be more or less applicable to a certain population or be of greater or lesser significance given the nature of the genetic variation. If this information is used to decide which is the best course among a variety of reasonable medical therapies, we take this uncertainty in stride, as such an uncertainty is a necessary result of our incomplete knowledge. If we are using this empirically derived data to determine whether or not one should be given access to superior or life-sustaining therapy, however, the question of how applicable the data is to the person for whom the decision is being made is of vital ethical importance. Given that the findings of GWA studies are often very sensitive to what might be

thought to be small variations in population characteristics,[58] as opposed to more "traditional"

studies which depend on more crude designations of population characteristics (e.g., age, gender,

disease type,) the likelihood that research results derived from GWAS will be used to inform

decision making in an inappropriate population may be much greater. It is this difference which

raises some, albeit not all, of the ethical questions that arise when considering incorporation of

genetic information into the organ allocation decision making process.

3.6 A PLACE FOR EVERYTHING AND EVERYTHING IN ITS PLACE

Drawing a precise line between what is considered an acceptable and unacceptable risk of poor

outcome is beyond the scope of this analysis. Moreover, it is impossible to do so without

recourse to normative analysis that is also beyond the paper's scope, as the precise delineation

between an acceptable or unacceptable risk is better addressed by means of a societal consensus

determining acceptable rules and guidelines, rather than by a declarative statement of the

fundamentally "correct" answer. Nevertheless, for the purpose of this project's consideration of

the appropriateness—and especially the justice—of using genetic predictors of transplant

outcome in allocation decision, it is helpful to stipulate some level of unacceptable risk. This

enables us to consider on a how different types of genetic predictors—i.e., genetic predictors

resulting from different types of research—should be considered within the conceptual model of

acceptable and unacceptable risk that I have presented. Therefore, for the purpose of this

discussion, I will posit that any genetic polymorphism associated with an 80% or greater

---

[58] See Qin et al. (2010) for a description of the problem of population variation in GWAS and how it can affect our understanding of previous study results.

likelihood of allograft loss or death within 5 years confers an unacceptable level of risk, while

one associated with a 79% or less likelihood allograft loss or death within 5 years does not

confer an unacceptable level of risk.   How would we categorize each type of genetic finding?

The findings of a pedigree study are reasonably parsable under this framework.   Let's

begin by considering a theoretical neurodegenerative disease that has been described in a single

family spanning many generations. The disease has been found to have either a more severe or

less severe course based on the presence of particular modifying genes. If a member of the

family has this disorder along with genetic polymorphism A, it has been associated with a very

rapid progression of the disease, with a 90% chance of that family member proceeding to

complete respiratory failure and subsequent death within 5 years of developing the first clinical

signs of the disease. In contrast, members of the family has this neurologic disorder along with

genetic polymorphism B are much more likely to have a more indolent course with a 30%

chance of proceeding to complete respiratory failure within 5 years of developing their first

symptoms. Based on the stipulated criteria demarcating an unacceptable level of risk,

individuals from this family who have developed clinical symptoms of this neurologic condition

and have genetic polymorphism A would not be considered acceptable candidates for kidney

transplant in the setting of kidney failure, as that individual's likelihood of suffering death from

respiratory failure in the next 5 years would be 90%, i.e., greater than the 80% likelihood of

death or allograft failure that we have established denotes an unacceptable risk of poor outcome.

In contrast, individuals from this family who have developed clinical symptoms of this

neurologic condition and have genetic polymorphism B would be considered acceptable

candidates for kidney transplantation as their likelihood of suffering death from respiratory

failure in the next 5 years would be 30%, which falls within the range of what we have

established denotes an acceptable degree of risk. If the findings of this pedigree study have not been replicated in populations beyond this family (i.e., a candidate gene study had never been performed to determine if genetic polymorphism A and genetic polymorphism B had predictive value for this neurodegenerative disease more universally), the presence of these genetic polymorphism should be treated as meaningless for an individual outside that family. It could not be presumed to constitute any meaningful information and as such could not be considered a risk factor for that individual at all. As such, for individuals with this neurodegenerative disease who were not a members of the initial pedigree family, a determination of whether that individual had possessed either genetic polymorphism A or B would have not provided any meaningful information on their respiratory prognosis. Therefore, the presence or absence of these polymorphisms could not serve as the basis for determining if that individual's neurodegenerative disease should be considered an acceptable or unacceptable degree of risk of poor outcome within the context of potential kidney transplantation. In contrast, if the predictive value of genetic polymorphisms A and B in the setting of our theoretical neurodegenerative disease were established across a broad population through a candidate gene study with robust findings (and ideally several confirmatory candidate gene studies), the presence or absence of these polymorphisms among potential transplant candidates could be validly used to inform the decision as to whether or not their neurodegenerative disease represented an acceptable or unacceptable risk of poor outcome when being considered for a potential kidney transplantation.

The distinction between the scenario in which our understanding of the prognosis of a given disease state is informed by pedigree-based research and one in which it is informed by a candidate gene study is a profound one. Both may illustrate an identical biological fact, that in the setting of this neurologic disease having genetic polymorphism A is associated with an

43

increased likelihood of a rapid progression of your illness, but what physicians can claim to "know" about a given patient's prognosis is radically different based on how this biological fact was identified.

How then would we interpret the results of a GWA study? The study might identify dozens or even hundreds of markers, each associated with an increased risk of a poor outcome. Using modern computational analytics it will likely be possible to construct an individualized "risk profile" which could result in a numerical assessment of the overall risk of a poor outcome following organ transplantation. The ability of these risk profiles to accurately assess risk within a given population will likely improve as multiple GWA studies are used to generate them. However, the fundamental difficulty of determining whether or not these risk profiles are appropriate for use for an individual may be persistent, limited by our ability to generalize the findings of GWA from one population to another or to appropriately interpret the influence that sub-populations have on data interpretation.   It remains to be seen if new statistical methodologies will address this problem sufficiently.[59]

Broad based genetic sequencing techniques are already being used in the clinical setting. While many laboratories performing genetic sequencing attempt to limit their reports to information relevant to the specific clinical question being investigated (and/or other specified important incidental findings) reporting practices are not uniform in this regard.[60] By examining the polymorphisms detected by these clinically approved tests, in conjunction with published

---

[59] See Lacour et al. (2015, Chen et al. (2016, Jelizarow et al. (2016, Stephan et al. (2015) for discussion of new approaches to address population stratification.

[60] As an example, Baylor Miracia Genetics Laboratories currently offers the option of an expanded whole exome sequencing report which will provide information on genes that do not appear to be relevant to the question being addressed, including "pathogenic variants and unclassified variants (VUS) in genes unrelated to the disease phenotype" as well as "deleterious mutations in genes with no currently known association with disease in humans." They also offer an "Adult Screening Exome Sequencing" test which is used when "…a patient's medical history and physical exam findings are normal, but the patient desires information about potential future risk of developing a genetic disorder." See http://bmgl.com/resources/educational-materials for additional information.

research findings identifying genetic polymorphisms associated with poor transplant outcomes, a transplant center may use this information in making the clinical decision regarding whether a potential transplant candidate has an acceptable or unacceptable degree of risk of a poor transplant outcome. Furthermore, while genetic-based risk profiles are rare within clinical medicine at this time, there have been multiple publications within the medical literature which have called for their development.[61] These genetic-based risk profiles will likely be derived in large part from GWAS, thereby incorporating a measure of such studies limitations.

Although the use of information obtained from GWAS underscores the difficulties in translating exploratory research into a suitable and substantial basis for policy or clinical decision making, a reasonable counterargument would be that this difficulty may simply be one of degree, rather than one of kind. Questions about the quality and applicability of any research finding to a given clinical question are not new. Moreover, it may be argued that eventually there should be sufficient research data existent to enable the findings of studies investigating a genetic predisposition to an increased risk of poor transplant outcomes to inform decisions regarding whether or not organ transplantation is appropriate for a given patient. I contend, however, that an important limitation will remain: the risk profiles derived from GWA studies will always be generated from an observed statistical association between certain genetic polymorphisms and the outcome being studied within a *specified population,* and therefore it will always be difficult to quantify the degree of uncertainty when applying this profile to an individual patient who may or may not fall within that population. Appropriately, there is a strong presumption that this limitation is less pronounced when using information derived from candidate gene studies, where the information derived can be interpreted in light of our

---

[61] See Carbone et al. (2014), Abraham and Inouye (2015), and Muller et al. (2016).

understanding of biochemical, cellular and physiologic processes that are thought to be near-universal among people.

Despite these limitations, specific features of the transplantation landscape may make utilization of genetic factors that ostensibly predict clinical outcomes and graft survival very attractive. The next section discusses these features and ethical concerns associated with such utilization of genetic information.

4.0 GENETICS AND JUSTICE: AN EXAMINATION OF THE ETHICAL AND SOCIAL IMPLICATIONS OF THE USE OF GENETIC PREDICTORS IN ORGAN ALLOCATION DECISIONS

4.1 PERVERSE OR APPROPRIATE: PROGRAM INCENTIVES AND ORGAN ALLOCATION

One important way in which organ transplantation and organ allocation process differs from many areas in medicine is in the rigorous way in which the outcomes of organ transplantation are tracked. Since 2007, the Center for Medicaid Services (CMS) has formally tracked individual transplant program outcomes as a criterion for determining whether or not they will contract with those programs to provide transplantation services for their patients.[62] Although CMS managed programs (i.e., Medicaid and Medicare) serve as the guarantor for only a portion of all transplantations performed, their regulations and payment agreements often serve as an important model for other private insurers.[63] Although the methods of calculating the expected rates of poor transplant outcomes have shifted over time,[64] the implications—for transplantation programs and their overarching institutions—of falling outside those expected rates have

---

[62] See Centers for Medicare and Medicaid Services (2007).
[63] See Gupta et al. (2015).
[64] *Ibid.*

remained serious: potential suspension or revocation of the agreement to allow those programs to participate in transplantations occurring under CMS oversight.   The implementation of these program-specific reports and the associated potential for penalties incurred for poor outcomes have shifted programs' clinical approach. In a survey performed in 2009, Schold and colleagues found that 58% of responding programs had increased the strictness of their selection criteria in order to exclude potential transplant recipients deemed to be at a relatively higher risk of a poor outcome post-transplant in an effort to improve outcomes and avoid CMS censure.[65]

Whether or not this move toward transplant programs being more selective when considering patient eligibility for organ transplantation represents an overall improvement of the transplant process depends on one's viewpoint. There is a relatively broad consensus that transplant should be avoided in circumstances where a poor outcome is very likely (as per my designation of unacceptable risk). However, whether or not a marginal improvement in survival rates in exchange for more restricted access to transplantation for potential transplant recipients is appropriate/acceptable depends on the relative value that one places on the various goals of transplantation (e.g., efficacy, justice, fairness).

Irrespective of whether or not one sees this increased selectivity exhibited by transplant programs as desirable, we should not be surprised that this increased selectivity has occurred in the wake of CMS oversight. If a transplant center's authorization to perform organ transplants for CMS patients is revoked due to poor outcomes, that center will suffer a significant economic and reputational blow, particularly since many private insurers will also refuse to pay for organ transplants at non-CMS approved centers as well. Economic theory has identified that when faced with decisions involving risks, economic agents place a greater emphasis on protecting

---

[65] See Schold et al. (2010).

48

those goods they already possess, rather than objectively assessing the relative value of actions to expand those goods. This concept, known as prospect theory, was first proposed in in 1979 by Khaneman and Taversky.[66] Subsequent economic research has re-affirmed the role that psychological perceptions or risk play in the decision making process.[67] Given these findings, the tendency of individual transplant programs to place increased restrictions on eligibility for transplantation in light of the risk of receiving a poor program specific report is very much in line with our current understanding of human behavior.

In light of this tendency that many transplant programs may have toward risk avoidance and loss aversion, it would seem possible to predict what effect the identification of emerging genetic polymorphisms which predict poor transplant outcomes may have on the behavior of transplant programs. While such predictions are inherently speculative, I think the emergence of a multitude of new "risk factors" may only serve to reinforce the tendency of many individual programs to avoid listing these presumably "high–risk" patients as candidates for transplantation.

There is a great deal of complexity involved in appropriately assessing and applying the findings of genetic research studies as a tool to either develop tests for clinical application or inform the interpretation of existing clinical data. Although errors resulting from this complexity can be mitigated by rigorous science and careful consideration of the available literature, it is important to note that the incentives inherent in the CMS overview program do not support a position of studied neutrality as a broad scientific consensus emerges. These incentives instead support an approach much akin to the "precautionary principle" of risk management, wherein if a potential risk is identified, it should be treated as a presumed risk unless there is clear indication otherwise. There is very little downside on a programmatic level to doing so. In contrast, the

---

[66] See Kahneman and Tversky (1979). This line of inquiry was suggested by Gupta et al. (2015).
[67] See Barberis (2012).

potential negative implications of losing CMS certification due to poor transplant outcomes for the program are immense.

As genetic testing becomes more affordable and efficient, the likelihood that individual patients will have pre-existing genetic data available will become greater. Moreover, increasing research into genetic markers of poor transplant outcome are very likely to eventually yield clinical tests to assess for a pre-disposition to a poor transplant outcome. These tests are likely to yield a vast amount of information, some of which may be easy to apply, but much of which will be of uncertain value. Aside from concerns about the pernicious effect that the "identification" of these genetic risk factors may have on the candidate evaluation decisions made by individual risk averse programs, we should also consider the ethical and sociological implications of incorporating these predictors into allocation decisions more broadly. How do these risk predictors compare to the other predictors which we have formally or uniformly incorporated?

4.2 THE ETHICAL IMPLICATIONS OF THE USE OF GENETIC PREDICTORS OF POOR TRANSPLANT OUTCOMES

4.2.1 Genes whose effect on outcome is not mediated by behavior

In the previous sections we discussed how to consider genetic predictors along the axis of acceptable and unacceptable degrees of risk. I explicitly avoided attempting to determine what should be considered an unacceptable degree of risk of poor outcome. But, if either an individual transplant program or the organ allocation system as a whole has defined (even

loosely) what constitutes an unacceptable degree of risk of a poor outcome, then consideration of

a newly identified genetic predictor is comparatively straightforward. One simply has to

compare the likelihood of a poor transplant outcome predicted by the presence of the genetic

polymorphism in question to the likelihood of a poor transplant outcome predicted by a currently

considered clinical or historical factor. If both predictors (genetic and non-genetic) predict a

similar likelihood of risk of a poor outcome, both should either be considered acceptable or

unacceptable degrees of risk. It is also possible that a given predictor (genetic or non-genetic) as

an isolated factor predicts an acceptable degree of risk, but when that predictor is combined with

a patient's other health information, the overall risk of a poor outcome following transplantation

is deemed too great Again, provided that all predictors which suggest a similar likelihood of risk

of a poor outcome are treated similarly when considering whether or not a patient is eligible for

transplantation, there is little ethical concern. In practice this will be much more complicated

due to the difficulty of appropriately applying the findings of genetic research to the assessment

of individual patients, as well as the fact that many candidate eligibility decisions are based on

qualitative clinical judgement rather than a precise quantitative determination of risk. However,

the conceptual model for determining if a genetic predictor of poor transplant outcome indicates

either an acceptable or unacceptable degree of risk is relatively straightforward.

4.2.2 Genes whose effect on outcome is mediated by behavior

A more ethically rich analysis is called for when the increased risk predicted by a genetic marker is mediated by behaviors. Should consideration of these genetic risk factors within the allocation system be considered just or unjust?

 Again, comparison to other risk factors and their treatment within the candidate evaluation process should be made. Justice demands that similar risks be treated similarly. An initial question is whether genetic risk factors mediated by behavior can be regarded like those health behaviors which, as a matter of social consensus, have led to patients being assigned lower priority in access to organs (e.g., alcoholism). Patients have no control over their genome; it is inherited from their parents. Thus patients cannot be considered to have moral agency in regard to the genetic risk itself. [68] This suggests that genetic risk factors themselves should not be subject to the special consideration given to behavior driven risk factors (e.g., tobacco or alcohol use) discussed previously in section 2.

 Next we must ask whether, even if the potential recipient is not culpable for his or her genetic predisposition, those individuals may be regarded as culpable either for not pursuing what are deemed to be reasonable steps to mitigate the genetic risk or for engaging in behaviors which potentiate this genetic risk, and if so, whether this can ground their being given lower priority for, or being excluded from, access to organs. In the case of patients for whom the combination of genetic risk factors and behaviors results in a degree of risk of an unacceptable risk of poor transplant outcome, it is appropriate to determine that such patients are not transplant candidates. However, it is important to note that in this circumstance it this is due to

---

[68] See Tognazzini (2014) for a discussion of some of the morally relevant concepts.

the *quantity* of increased risk, not because this increased risk was mediated by behavior. As an

example, consider the circumstance in which an individual is deemed not to be a transplant

candidate due to morbid obesity. Many transplant centers will not transplant patients with body

mass indexes (BMI) greater than 35 or 40 kg/m^2, due to concerns of increased surgical morbidity

and mortality in this population.[69] This determination is not dependent on whether the patient

has a medical condition (genetic or otherwise) that predisposes him or her to becoming obese or

whether the patient's obesity was the result of behavior alone; it is simply the result of patient's

perceived increase in risk. In this circumstance, the patient's genotype is irrelevant; only the

outcome matters.

One might ask whether we should consider a genetic predisposition to poor health

behaviors (and the resulting illnesses) as an excusing factor that should cause us to discount or

disregard the associated increased risk of poor transplant outcomes. This in turn might cause us

to deem a patient an acceptable transplant candidate when a simple quantitative assessment of

risk would indicate otherwise. Taking genetic predisposition into account in such a manner

would be inappropriate given our prevailing transplant eligibility criteria. There has been no

broad effort to do so for conditions, such as alcoholism, which are already known to have a

significant genetic component, as discussed previously. To consider genetic predisposition for

only some health behaviors resulting in deleterious conditions would violate the tenet that similar

risks should be treated similarly.

Finally, we can consider the circumstance in which patients are known to have a genetic

trait that would predispose them to an especially poor transplant outcome if they were to engage

in particular behaviors, but they have yet to exhibit such behaviors. As an example, consider a

---

[69] See Bunnapradist and Danovitch (2007).

patient who is known to be a hyper-metabolizer of calcineurin inhibitors, the primary class of immunosuppressant used in the post-transplant setting. One might reasonably presume that if such patients were to miss scheduled doses of their medication in the post-transplant setting they would be at an increased risk of rejection as compared to patients who missed a similar number of doses but were slower metabolizers of the medications, simply because the patients who hyper-metabolize would have insufficient drug levels for a longer period of time.[70] However, if we have no reason to think that it is likely that a given patient will be non-adherent in the post-transplant setting, is this *potentially* increased risk of poor transplant outcome a sufficient reason to deem that patient ineligible for organ transplantation? I would argue that it is not, as such speculation could be applied to almost any health outcome. A previously adherent patient could become floridly non-adherent following the stress of undergoing organ transplantation. A patient who is considered an ideal transplant candidate could experience a motor vehicle accident shortly after transplantation, resulting in a degree of chronic illness which would have precluded transplantation if it was known that this would occur. We do not generally consider patients to be ineligible for transplant due to these speculative concerns. As such, absent evidence of the behavior of concern, a genetic predisposition to a poor transplant outcome that is contingent on such behavior should be insufficient to consider a patient ineligible for transplant as well.

---

[70] This is consistent with the findings of Rojas et al. (2015)

4.2.3 Genetic predictors and individual equity of transplant opportunity

How would the inclusion of genetic predictors of poor transplant outcome in allocation decisions affect the individual equity of opportunity to benefit from the transplant program?   As an experiment, let us presume that over the next few years, researchers identify 10 genetic markers which are closely linked to a five-fold increase in the likelihood of rejection within the first 5 years after transplant. These predictors have been confirmed by several studies, all represent mutations within biochemical pathways known to modulate immune response to foreign tissue, and have similar probabilistic weight through all gender and ethnic groups studied thus far. After much consideration, UNOS has elected to exclude patients with these genetic markers from transplant of any organs. Does such a decision preserve individual equity of access?

From a purely objective viewpoint it appears that at least in one sense, the answer is yes. If the likelihood of a poor transplant outcome indicated by these genetic predictors was great enough, they could be considered in a similar manner to any other predictor of an unacceptable degree of risk, such as extremely poor health. However it should be noted that, as discussed in section 2, there are currently few system-wide exclusionary criteria. Most comparisons for questions of individual equity involve questions of prioritization, rather than inclusion or exclusion. This distinction between lower prioritization and complete exclusion is of relatively little importance from an ethical standpoint, as any factor which could grant priority for transplantation for one individual over another may have the practical effect of denying organ transplantation for the party given lower priority who will either die while awaiting an organ transplantation or experience health deterioration rendering him or her no longer eligible for transplantation.   However, I suspect that socially and psychologically outright exclusion based

on genotype would be seen as a distinct phenomenon, an argument that I will explore more fully in the next section.

However, even if one were to deem the inclusion of genetic predictors in the candidate selection process just because it represents a rule that is universally applied, one could still criticize their use for being arbitrary. There are likely numerous other predictors which, if thoroughly studied, would yield a similar degree of risk as theorized genetic markers. For example, it is possible to construct profiles of associated co-morbidities which are associated with poor transplant outcomes. At the moment, profiles such as the Charlson Comorbidity Index[71] are primarily used as research tools, but they could be converted to formal decision tools within the UNOS guidelines. No ethically relevant difference exists between a genetic predictor and these other forms of outcome prediction. Thus, the inclusion of particular predictors (which have otherwise been deemed to not implicate an unacceptable degree of risk and for which the potential transplant recipient cannot be deemed to be morally culpable) within a formal allocation scheme while disregarding other similar predictors is arbitrary and therefore difficult to justify from an ethical standpoint.

Thus far this section has addressed ethical difficulties which may arise from the inclusion of genetic predictors within the formal allocation criteria of UNOS or other overarching allocation programs. However, it is important to examine the ethical implications of individual transplant programs electing to include genetic predictors among candidate evaluation criteria. In this case, the ethical concerns do not arise from the nature of predictors used (i.e., that they are derived from genetic data) but instead the furthering of variance between the practices of various programs.

---

[71] See Grosso et al. (2012) for an example of the used of the CCI for research purposes.

The ethical concerns raised by program to program differences in candidate evaluation criteria in general have been discussed elsewhere.[72] There are substantial differences in expected wait time between various geographic regions within the United States and significant variation in expected wait times for organ allografts within a given region.[73] There are also differences in the quality of the organs accepted for transplantation,[74] differences which result in significant variation in overall transplant outcome. Although in theory any given transplant center is open to any patient, there are significant logistical, economic and insurance barriers which serve as practical limitations on this option. The transplant candidate evaluation process is a lengthy one, requiring many days or weeks of testing. As such, it can be quite difficult for individuals outside the immediate vicinity of a given transplant center to participate. Moreover, the time commitment necessary to complete mandatory testing and interviews may be prohibitive for some individuals who lack the requisite flexibility in personal obligations. Insurance policies may have agreements in place which limit the policy holders to transplantation only at certain institutions. While it is possible for a potential recipient with sufficient economic resources to overcome some of these barriers, the differentiation of potential recipients based on economic resources is contrary to the ethical foundation of our organ allocation policy as currently constructed.[75]

The current system accepts substantial program-to-program variation for a variety of pragmatic reasons. The aforementioned geographic variation in organ allocation, for example, reflects the regionalized origins of our allocation system, as well as the fact that any changes in

---

[72] See Barshes et al. (2006).
[73] See the staff working and discussion paper titled, "The Ethics of Organ Allocation" by Davis and Wolitz (2006) prepared for the September 2006 meeting of the President's Council on Bioethics for a succinct and well-written characterization of this issue.
[74] See Axelrod et al. (2010) and Volk et al. (2011) as examples of this phenomena.
[75] See the UNOS website at (https://optn.transplant.hrsa.gov/governance/strategic-plan/) for a statement of the strategic and policy goals of UNOS/OPTN.

our current system will result in harms as well as benefits to individual parties, whether or not such a development would be objectively more "just." Indeed, given the improved modes of transportation and organ preservation, the regional allocation system is being increasingly questioned.[76] Additionally, the current system as constructed reinforces the responsibility that individualized transplant centers have for the outcomes of their patients and such responsibility is hard to instill if those programs are not granted any agency in the decision making process.

However, while there is a "natural" or "historical" explanation for much of the existing variation between individual center practices, introducing additional variation between centers should not be undertaken lightly, particularly if doing so exacerbates the situational inequities noted above. Individual centers incorporation of genetic predictors as part of their candidate evaluation criteria would create a substantial variation in practice that would reduce the equity of access to organ allocation as determined by our current framework and goals.

---

[76] See Vladeck et al. (2012) for one such argument.

4.3 THE SOCIAL IMPLICATIONS OF THE USE OF GENETIC PREDICTORS OF POOR

TRANSPLANT OUTCOMES

There are some broader concerns regarding the use of genetic predictors relevant to the integrity

of and trust in the transplantation system as a whole. The transplantation system within the

United States is dependent upon the voluntary donation of deceased donor organs. As such,

societal concerns about justice in the organ allocation system have the potential to greatly affect

the number of organs made available for transplantation.[77] The use of genetic predictors of poor

transplant outcomes may have substantial implications for public perception of the justice of the

system, its trust in it, and its willingness to support it.

The exclusion of some groups of patients—for example, those who are very ill and

unlikely to survive transplantation—is generally accepted by the public presumably for three

reasons: the criterion is uniformly applied, all people have a similar chance of being excluded

due to the criterion, and most importantly, the criterion is tied to the efficacious use of available

organs. In contrast, the notion of excluding individuals based on their genotype, with no outward

manifestations of their "unsuitability" for transplant may not be as widely accepted. Even if the

genetic criteria are applied to all who are evaluated, the use of genetic information seems to sort

people according to their natures, not according to some transplantation-relevant contingent

feature of them. Further, the connection between genotype and transplant outcome will be far

less obvious than a connection between current health status and transplant outcome ("he is too

---

[77] There was a significant decrease in organ donation rates in Germany after it was revealed in 2013 that four
German hospitals were manipulating the organ transplant allocation system to secure organs more quickly for their
patients. See Shaw et al. (2013) for further details.

sick to benefit"). While both genotype and health status are predictors of transplant outcome, health status is more obviously and likely is more proximately related to that outcome.

If genetic predictors are found to be more prevalent among ethnic groups which have historically been disadvantaged in medicine in general and transplant in particular, questions of justice and concerns about maintaining public confidence would likely arise. [78] Although no such markers have been identified thus far, the potential for this to occur exists. Moreover, there are clearly documented differences in outcomes after transplantation, for particular minority groups.[79,80] While these differences have largely been attributed to social, systemic factors (e.g., economic, demographic, and sociologic factors, as well as disparities in the care experience) the question of race/ethnicity-associated biological differences affecting transplant outcomes have been raised.[81] This question is further complicated by the fact that for several decades minority populations have been under-represented in medical research,[82] which may result in an inaccurate or incomplete scientific understanding of how different therapeutic regimens affect different populations. As an example, research has identified important ethnic differences in response to tacrolimus, a medication which has been the mainstay of kidney (and other solid-organ transplantation) for the past two decades.[83]

It would be difficult to overstate the enormity of the controversy which could arise if genetic predictors of a poor transplant outcome were found to be substantially more prevalent

---

[78] Research into ethnic differences in biology and health is fraught for a variety of scientific and historical reasons. See Lee et al. (2001) for a discussion into some of these issues.

[79] Note: For the purpose of this discussion I will use the term minority group as a descriptor for groups that are generally thought to be disadvantaged as compared to the majority culture (i.e., white Americans). The language used in this area of research has shifted over time, so there is not a single unifying terminology. I make this distinction to note that these disparities exist even in circumstances where the majority of patients represent "minority" groups.

[80] See Fan et al. (2010), Kemmer and Neff (2010), or Kilic et al. (2015) as examples.

[81] *Ibid.*

[82] See George et al. (2013) for a broad overview of this issue.

[83] See Taber et al. (2015).

within a historically disadvantaged minority group.[84] Such a finding would draw attention to the

inherent complexities of the ethics of justice I discussed in section 2, particularly the tension

between the goal of treating potential transplant recipients equitably as individuals, respecting

their rights to "fair" rules and consistent standards for acceptable efficacy which are applied to

all individuals equally, and the concurrent goal of achieving distributive justice among various

societal groups.

If such a genetic predictor of poor transplant outcome is identified and if it is more

prevalent among a particular minority group or groups, it may nevertheless be considered as

equivalent to—and employed in a manner similar to—any other predictor that identifies a risk of

poor outcome of similar magnitude. Employing such predictors that are disproportionately

prevalent among minority groups would be contrary to the widely held goal of reducing ethnic

disparities in organ transplantation, as well as the specific goals listed in the Organ Procurement

and Transplantation Network strategic goals.[85] The community response to consideration of a

predictor that disproportionately disadvantages a minority group in terms of access to

transplantation may be profound. Members of that minority group (and perhaps other groups)

may reduce their organ donation rates. Moreover, to the extent that the public as a whole

perceives disparities, and thus injustice, in the transplantation system, there may be an overall

reduction in organ donation.[86]

---

[84] I would note that these concerns are predicated on the presumption that any identified genetic predictor would:
A) Reflect an increased risk of sufficient magnitude that inclusion of this predictor in organ allocation decisions on either an institutional or system-wide level would be considered; and, B) The number of people affected would be sufficient that it would be noted by society at large. The exact thresholds for either of these conditions are beyond the scope of this manuscript.

[85] See Organ Procurement and Transplantation Network (2016).

[86] Again see Shaw et al. (2013) for further details regarding reductions in organ donation following a 2013 scandal in Germany.

The identification of a genetic predictor of poor transplant outcome which is more prevalent in a given racial ethnic group (or any other socially disadvantaged group) would be reminiscent of the debate over the decision to disregard HLA-B matching as discussed in section 2. There would, however, be several important differences. In regard to the HLA-B issue, the question at hand was whether to move from a more restrictive allocation policy to a more open one. In the situation described above, in contrast, the decision would be whether or not to move from a more open to a more restrictive allocation policy. From an ethical standpoint the two should be considered equivalent. Both offer a choice between two potential algorithms, one which values efficacy over questions of distributive justice and one that values questions of distributive justice over efficacy. (The uniformity and objective nature of the rules established limit objections with regards to equity of individual access, provided other similar predictors were treated similarly.)

From an experiential standpoint however, the decision of whether one should expand the availability of transplant by offering a given organ to a broader array of individuals or if one should be more restrictive and allow fewer individuals to be potential recipients of a given organ is markedly different.[87] By defining the initial state as either more or less restricted, our sense of responsibility for deviation from that initial state differs. In many ways, this is similar to the discussion surrounding withholding and withdrawing care. Although they are viewed to be equivalent from a dispassionate ethical viewpoint, they are experienced by many as radically different acts.[88] Because of the importance of maintaining public support for organ

---

[87] See Bostrom and Ord (2006) for an interesting discussion of this phenomenon and a review of some of the pertinent psychological literature.
[88]See Anonymous (1992)

transplantation, the manner in which a decision to expand or restrict access is experienced

matters.

Finally, we must consider the fact that inclusion of genetic test results among the criteria

for determining transplantation eligibility has the potential to create new "at-risk" populations,

similar to the gender, ethnic and socio-economic groups already considered at-risk for poor

health outcomes and health care in this country. Given that genetic testing remains relatively rare

throughout society as a whole, it is difficult to predict the extent to which identification of a

genetic marker predicting a poor transplant outcome would contribute to the formation of a

meaningful social group or give rise to significant social stigma. However, we may gain some

insight into this phenomenon by examining groups in which genetic testing is more prevalent.

One such group is the Hassidic Jewish community.[89] This community is predominantly of

Ashkenazi heritage, and members have a disproportionally greater likelihood of being a carrier

of several serious genetic conditions, such as Tay-Sachs disease or the BRCA1 mutation, as

compared to the population as a whole.[90] Moreover, it is traditional for members of this

community to find spouses within the community, often by arranged marriages. As such, there is

substantial awareness of the risks of genetic conditions and significant stigma associated with

being a member of a family who has members who have these diseases. In a sense, this familial

membership is used a surrogate marker to define a presumed carrier state. This presumed carrier

state can lead to social sequela, including increased barriers to finding a spouse through the

traditional process of arranged marriages and a sense of social stigma.[91]

---

[89] See Raz and Vizner (2008) for an interesting discussion of this topic.
[90] See Hoffman et al. (2014) andMcClain, Nathanson, et al. (2005) for data regarding carrier rates in the Ashkenazi population.
[91] See Lehmann et al. (2002) and Raz and Vizner (2008).

Within the broader population, possessing a given genetic trait may result in fewer psycho-social effects. However, as people's awareness of their own genetic traits increase, through both the increased use of genetic testing for medical purposes as well as the increased use of consumer driven genetic analysis, it is possible that importance or influence of genetic traits in constituting social groups may increase.[92] In this context, the psychological and social implications of having been determined to be genetically "unfit" to receive an organ transplant may be significant.

4.4 QUALITY OF LIFE OR SAVING LIFE: HOW THE PRESENCE OF ALTERNATIVE THERAPIES SHAPES THE QUESIONTS OF JUSTICE

Within the field of organ transplantation there are two broad categories of organs: those for which a transplant is necessary to continue life, such as heart, lungs and liver, and those for which a transplant improves a patient's health and quality of life, such as kidneys and pancreas In renal transplantation, alternative life-sustaining therapy exists in the form of dialysis. However, the quality of life for those who undergo transplant and those who do not is widely divergent.[93] It is well documented that individuals suffering from chronic kidney disease have substantial improvements in their longevity and quality of life as compared to individuals who remain dialysis dependent.[94] Still, the difference in the outcomes and experiences between those

---

[92]See Lee and Crawley (2009).
[93] See Laupacis et al. (1996).
[94] See Port et al. (1993) and Simmons et al. (1984) as representative publications.

who receive a kidney transplant and those who do not is obviously less significant than among those individuals who require organ transplants to sustain life.

Nevertheless, the prospect of using genetic predictors in renal transplantation raises an additional consideration. Because the life-saving option of dialysis exists, having kidney transplantation is therefore a matter of quality of life. Therefore, it would be appropriate to be more conservative—i.e., require a greater prospect of good outcome—in the context of renal transplantation than in the context of life-saving organ transplantation. For this reason, we might be more liberal in employing genetic predictors of poor outcome to exclude potential candidates.

As an example, consider a genetic polymorphism which is associated an 85% percent likelihood of allograft failure within the first 3 years after transplantation. It may be ethically appropriate to exclude a candidate for kidney transplantation who possesses this polymorphism because a reasonable alternative therapy exists (i.e. dialysis), while if a similar candidate was being considered for a liver transplantation it would be appropriate to proceed with transplantation (despite the decreased likelihood of allograft and patient survival conferred by the genetic polymorphism), because no alternative therapy exists.

5.0 PHILOSOPHY, MEET POLICY: A PROPOSAL FOR INCORPERATION OF GENETIC RISK ANALYSIS WITHIN THE CURRENT ALLOCATION SYSTEM

As discussed in section 4, there are significant ethical and social implications which would arise if genetic risk analysis were incorporated into the decision making process regarding candidate evaluation and organ allocation. The gravity of these implications might suggest that all such consideration should be prohibited. Unfortunately, such a prohibition would be very difficult to enforce. Under the current system, individual programs are given wide latitude in determining whether a given potential recipient is an acceptable candidate. No mechanism currently exists to curtail the consideration of genetic information. Although rules could be constructed to forbid programs from performing genetic testing for the purpose of predicting transplant outcome and candidate suitability, such rules would likely be insufficient to fully enforce a ban on the use of genetic risk profiles.

As discussed previously, there has already been an increased shift towards the use of whole exome and whole genome sequencing in place of targeted clinical genetic testing.[95] While such sequencing can be a powerful tool in identifying genetic variation that can contribute to a given disease, it also can identify a variety of 'incidental' findings (i.e. genetic variations which may be of clinical significance but may not be related to the original purpose of testing). Although some recommendations regarding the reporting of such incidental findings have been

---

[95] See Biesecker and Green (2014).

66

made,[96] there is variation in practices between individual laboratories and institutions. Thus, it is possible that 'incidental' findings pertinent to predicting a patient's transplant outcome may already exist and be recorded in the patient's medical record. While this may seem like a somewhat far-fetched concern, this risk may be greater than one would think. Although investigation into genes that affect transplant response is still preliminary at this stage, it is presumed that the genes identified will predominantly affect traits such as immune modulation or the response to pertinent immunosuppressant drugs. It is entirely plausible that these genes will have clinical relevance for a variety of other conditions, particularly conditions such as auto-immune disorders, which are a common cause of organ failure. As genetic testing and sequencing become more prevalent, the likelihood of genetic data pertinent to the transplant evaluation process already being available for a given potential recipient becomes more likely.

If it is not feasible to forbid the collection of pertinent genetic data, how then should it be incorporated? How should this incorporation reflect the transitional nature of scientific knowledge, wherein certain genetic markers will be suspected of predicting a poor outcome long before the strength or certainty of that prediction is clearly established? How will policies regarding the use of genetic predictors in the candidate evaluation process reflect the pre-existing incentives developed by the regulatory systems which already incentivize programs from pursuing "risky" transplants and listing "risky" candidates? Finally, how will these policies reflect the fact that research into these genetic predictors serves a legitimate purpose within the organ transplant system, both by identifying patients who are expected to have a poor outcome, thereby allowing us as a society to incorporate that information systematically into the candidate evaluation process, and by identifying populations who are ill-served by current pre- and post-

---

[96] See Green et al. (2013).

transplantation care protocols, thereby allowing us to improve the clinical care for these population sub-groups?

To address concern about transplant programs' incentives, I would recommend that patients who are found to have a genetic risk factor predicting a poor transplant outcome should be excluded from the assessment of program specific outcomes until such time that a nationwide policy on how to consider such genetic risk factors is determined. This policy change would remove the incentive that individual programs may have to avoid transplantation in patients with these genetic markers, thereby avoiding the concerns regarding justice raised in section 4 of this manuscript. It would also reduce the incentive to make clinical decisions regarding a patient's candidacy based upon published studies that identify genetic risk factors which have not been re-produced or demonstrated in relevant target populations. Absent these incentives to avoid transplantation in individuals who possess genetic risk factors associated with increased rates of poor transplant outcomes, individual transplant programs could then determine whether genetic assessments of potential transplant recipients serve either a meaningful clinical or research purpose within their institutions. This in turn may allow additional research on these topics, strengthening the quality of the findings and defining the applicability of the information obtained regarding genetic risk factors.

Further, I would recommend that UNOS establish a national database to prospectively track outcomes in patients who have been identified to have genetic polymorphisms suspected of being associated with any increased risk of poor transplant outcomes. The polymorphisms recorded within this database should be selected by a national panel of experts, based on the results published in smaller populations by individual research groups. In this way, the expert panel would identify genetic markers warranting more study, much in the way that NIH study

sections help to establish priorities for distribution of NIH research funds to topics of the greatest scientific interest. Patients found to have a polymorphism of concern should be enrolled within this database as a condition for being listed for transplantation. That patient's outcomes could then be tracked, but would be excluded from consideration within the program-specific outcome reports.

The immediate research benefits of this program would be twofold. First, by removing disincentives for individual programs to use genetic risk analysis to reject risky transplant candidates, we would likely be able to increase the size of the population studied in relation to any single presumed genetic risk factor. This would increase the quality of the data obtained and may serve to either confirm or disprove the associations identified in smaller preliminary studies. Second, by nationalizing the study population within the United States, we would increase the likelihood that any identified associations between outcomes and genetic risk factors would be applicable across the broad US population, an important determination prior to considering the more routine clinical use of these genetic markers. Ideally, this process of data aggregation would eventually result in a sufficiently comprehensive understanding of the risks associated with a given genetic marker to then consider this marker within a national context. As I have discussed in previous sections, if a genetic marker is associated with a substantial risk of a poor transplant outcome it is not inherently unjust to consider it within the candidate evaluation process (although it is problematic). Moreover, the harms which arise from incorporation of such markers can be minimized if it is instituted in a uniform manner, ideally after having achieved a degree of societal agreement.

This is not to say that establishment of such a database is not without its own potential risks. There would be a powerful incentive to conduct research on the genetic markers deemed

'of interest' within the database. While this would likely strengthen the science aimed at understanding the usefulness of those particular genetic markers, it would run the risk of stifling research creativity with regard to other factors relevant to poor transplant outcomes. Resources may be diverted to investigate those markers selected by the relatively small cadre of experts. While it is true that this already happens to a certain extent within medical research, given the reliance that many researchers have on government funding for projects, the wide variety of funding sources available increases the diversity of scientific research somewhat. Moreover, the establishment of such a database would almost necessarily result in a move towards a consortium model of research, in which many institutions pool aggregate data in order to strengthen the resulting analysis and conclusions. While this model of research has many strengths, it does not correspond well with the prevailing model of individualized research grant assignment or academic hierarchies based on individualized academic achievements. Such concerns may need to be addressed in order to enhance the appeal that a unified research database might have to individual programs and institutions.

Despite these limitations, I feel that enacting this proposal would be beneficial both to the patients who might otherwise be rejected as transplant candidates without sufficient scientific justification and to the research mission of the medical field as a whole. It is a model which could be easily extended to other important questions of prognosis, in which the possibility that a given recipient could have a poor outcome would adversely affect his or her likelihood of inclusion within the transplant allocation process, prior to there being a broad scientific and social consensus regarding the appropriateness of considering the prognosis predictor.

One could also consider the value of extending the proposed model (data-sharing and exclusion from program specific reports) to research into therapeutic regimens, such as

immunosuppressant therapy. This may allow for more multi-center comparative research into the efficacy of given therapeutic regimens, in contrast to the common practice of individual programs publishing case series as a means of such assessment.[97] It is important to note that extension of this model to encompass clinical interventions may bring additional problems that observational studies may not. The current method of outcome assessment used in the program specific reports provides a powerful incentive to maintain the status quo for programs that are deemed "acceptable". This current method has two likely effects: research into new modalities or protocols may be somewhat discouraged, while treatment consistent with the "standard of care" (or, more realistically in transplant, one of many standards of care) is reinforced. Liberating programs from the potentially devastating financial effects associated with a poor program specific report would allow them to pursue more novel therapies, but these novel therapies have the potential to result in poorer outcomes than the status quo. Nevertheless, the ability to pursue novel therapies and protocols will likely be necessary to glean the maximal benefit from the identification of genetic predictors of transplant outcomes, by allowing our emerging understanding of interconnectedness between genetic markers and immune response to inform personalized and tailored therapeutic regimens.

---

[97]See Nehus et al. (2015) or Axelrod et al. (2016).

6.0 CONCLUSIONS

Ultimately, the means by which we evaluate transplant candidates, as well as the protocols which we use to treat patients after they receive transplanted organs must improve and evolve. Long term renal allograft outcomes have not substantially improved since the 1990's with the median life-span of the transplanted kidneys being approximately 8 years for deceased donor kidneys and approximately 12 years for living donor kidneys.[98] Although improvements in other solid organ transplants have fared somewhat better, improving from 5.8 to 8.5 years for liver, 1.7 to 5.2 for lung, 8.8 to 11 for heart and 2.1 to 3.6 for intestine, all remain well short of the amount of time necessary to prolong many patient's lives to a "near normal" lifespan.[99]

Moreover, a severe shortage of organs available for transplant remains. While 30,970 organ transplants were performed in 2015, 121,416 people remained on the waiting list.[100] The identification of genetic predictors of poor transplant outcomes and poor response to existing transplant therapies may help us determine if there are individuals who should not be considered for transplant due to excessively high risk, as well as individuals who would benefit from closer post-transplant monitoring. Identification of these genetic markers may even lead to other crucial advances in transplant medicine by affording a greater understanding of the process by which

---

[98] See Lamb et al. (2011).
[99] See Lodhi et al. (2011).
[100] Data obtained from the OPTN website < https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/> accessed 3/7/16.

transplanted organs are rejected. Despite this importance however, emerging data regarding

genetic predictors has the potential to be misunderstood, misused, or simply disregarded due to

the complex ethical and social issues that can arise. In order to provide the optimal care for

potential transplant recipients, regardless of the transplant center at which they will receive care,

we should develop a unified and systematic approach to studying genetic predictors of poor

transplant outcome, an approach that is enhanced by my proposal to exclude those patients with

genetic polymorphism undergoing study from inclusion in the program specific reports.

Simultaneously with the process of identifying genetic predictors of poor transplant outcome, we

should engage in the process of seeking a broad societal consensus regarding the degree to which

they should be used in candidate evaluation and other aspects of transplantation policy. This

consensus is necessary to ensure that candidate evaluation and organ allocation policies continue

striving to be both just and efficacious, despite the tension that currently and will continue to

persist between those two goals.

BIBLIOGRAPHY

Abraham, G., and M. Inouye. 2015. "Genomic risk prediction of complex human disease and its clinical application." *Curr Opin Genet Dev* 33:10-6.

Almoguera, B., et al. 2014. "Transplantation genetics: current status and prospects." *Am J Transplant* 14 (4):764-78.

Anonymous. 1992. "Attitudes of critical care medicine professionals concerning forgoing life-sustaining treatments. The Society of Critical Care Medicine Ethics Committee." *Crit Care Med* 20 (3):320-6.

Ashby, V. B., et al. 2011. "Transplanting Kidneys Without Points for HLA-B Matching: Consequences of the Policy Change." *American Journal of Transplantation* 11 (8):1712-1718.

Axelrod, DA, et al. 2010. "Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization." *American Journal of Transplantation* 10 (4):837-845.

Axelrod, David, et al. 2016. "National variation in use of Immunosuppression for kidney transplantation: A call for evidence-based regimen selection." *American Journal of Transplantation*:n/a-n/a.

Barberis, Nicholas C. 2012. Thirty years of prospect theory in economics: A review and assessment. National Bureau of Economic Research.

Barshes, Neal R, et al. 2006. "Justice, administrative law, and the transplant clinician: the ethical and legislative basis of a national policy on donor liver allocation." *J. Contemp. Health L. & Pol'y* 23:200.

Beauchamp, Tom L., and James F. Childress. 2013. *Principles of biomedical ethics*. 7th ed. New York: Oxford University Press.

Biesecker , Leslie G., and Robert C. Green 2014. "Diagnostic Clinical Genome and Exome Sequencing." *New England Journal of Medicine* 370 (25):2418-2425.

Bostrom, Nick, and Toby Ord. 2006. "The Reversal Test: Eliminating Status Quo Bias in Applied Ethics." *Ethics* 116 (4):656-679.

Bunnapradist, Suphamai, and Gabriel M Danovitch. 2007. "Evaluation of adult kidney transplant candidates." *American Journal of Kidney Diseases* 50 (5):890-898.

Bunzel, B., and K. Laederach-Hofmann. 2000. "Solid organ transplantation: are there predictors for posttransplant noncompliance? A literature overview." *Transplantation* 70 (5):711-6.

Bunzel, B., and G. Wollenek. 1994. "Heart transplantation: are there psychosocial predictors for clinical success of surgery?" *Thorac Cardiovasc Surg* 42 (2):103-7.

Burke, W., et al. 2013. "Recommendations for returning genomic incidental findings? We need to talk!" *Genet Med* 15 (11):854-9.

Campbell, C. D., et al. 2005. "Demonstrating stratification in a European American population." *Nat Genet* 37 (8):868-72.

Carbone, Marco, et al. 2014. "Implications of genome-wide association studies in novel therapeutics in primary biliary cirrhosis." *European Journal of Immunology* 44 (4):945-954.

Centers for Medicare and Medicaid Services. 2007. 42 CFR Parts 405, 482, 488, and 498 Medicare Program; Hospital Conditions of Participation: Requirements for Approval and

Re-Approval of Transplant Centers To Perform Organ Transplants; Final Rule edited by Department of Health and Human Services.

Chen, H., et al. 2016. "Control for Population Structure and Relatedness for Binary Traits in Genetic Association Studies via Logistic Mixed Models." *Am J Hum Genet* 98 (4):653-66.

Clarke, Oscar W, et al. 1995. "Ethical considerations in the allocation of organs and other scarce medical resources among patients." *Archives of Internal Medicine* 155 (1):29-40.

Clarke, R., et al. 2012. "Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias." *PLoS Med* 9 (2):e1001177.

Coulson, A. S., et al. 1976. "Lymphocyte tissue culture studies on human heart transplant recipients. III. Prediction of outcome of transplantation based on immunologic studies." *Clin Exp Immunol* 26 (3):623-31.

Cutting, G. R. 2015. "Cystic fibrosis genetics: from molecular understanding to clinical application." *Nat Rev Genet* 16 (1):45-56.

Daniels, Norman. 1985. *Just health care*, *Studies in philosophy and health policy*. Cambridge; New York: Cambridge University Press.

Davis, Dan, and Rebecca Wolitz. 2006. "The Ethics of Organ Allocation." https://bioethicsarchive.georgetown.edu/pcbe/background/davispaper.html.

Dixon, J., and H. G. Welch. 1991. "Priority setting: lessons from Oregon." *The Lancet* 337 (8746):891-894.

Fan, P. Y., et al. 2010. "Access and Outcomes Among Minority Transplant Patients, 1999–2008, with a Focus on Determinants of Kidney Graft Survival." *American Journal of Transplantation* 10 (4p2):1090-1107.

Faure, Stéphanie, et al. 2012. "Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication." *Journal of Hepatology* 57 (2):306-312.

Feng, Jing, et al. 2010. "The built environment and obesity: A systematic review of the epidemiologic evidence." *Health & Place* 16 (2):175-190.

Fernández-Ruiz, M., et al. 2015. "Association Between Individual and Combined SNPs in Genes Related to Innate Immunity and Incidence of CMV Infection in Seropositive Kidney Transplant Recipients." *American Journal of Transplantation* 15 (5):1323-1335.

Foster, Morris W. 2009. "Looking for race in all the wrong places: analyzing the lack of productivity in the ongoing debate about race and genetics." *Human Genetics* 126 (3):355-362.

Foster, Morris W., and Richard R. Sharp. 2002. "Race, Ethnicity, and Genomics: Social Classifications as Proxies of Biological Heterogeneity." *Genome Research* 12 (6):844-850.

George, Sheba, et al. 2013. "A Systematic Review of Barriers and Facilitators to Minority Research Participation Among African Americans, Latinos, Asian Americans, and Pacific Islanders." *American Journal of Public Health* 104 (2):e16-e31.

Glannon, Walter. 1998. "Responsibility, Alcoholism, and Liver Transplantation." *Journal of Medicine and Philosophy* 23 (1):31-49.

Golshayan, Déla, et al. 2016. "Polymorphisms in the lectin pathway of complement activation influence the incidence of acute rejection and graft outcome after kidney transplantation." *Kidney International* 89 (4):927-938.

Green, R. C., et al. 2013. "ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing." *Genet Med* 15 (7):565-74.

Grosso, G., et al. 2012. "Predictive Value of the Charlson Comorbidity Index in Kidney Transplantation." *Transplantation Proceedings* 44 (7):1859-1863.

Gupta, A., et al. 2015. "Program-specific Reports: A Guide to the Debate." *Transplantation* 99 (6):1109-12.

Ho, Dien. 2008. "When good organs go to bad people." *Bioethics* 22 (2):77-83.

Hoffman, J. D., et al. 2014. "The Ashkenazi Jewish carrier screening panel: evolution, status quo, and disparities." *Prenat Diagn* 34 (12):1161-7.

Ioannidis, J. P., et al. 2014. "Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention." *Trends Cogn Sci* 18 (5):235-41.

Ioannidis, J. P., et al. 2001. "Replication validity of genetic association studies." *Nat Genet* 29 (3):306-9.

Jelizarow, M., et al. 2016. "A Cochran-Armitage-type and a score-free global test for multivariate ordinal data." *Stat Med* 35 (16):2754-69.

Kahneman, Daniel, and Amos Tversky. 1979. "Prospect theory: An analysis of decision under risk." *Econometrica: Journal of the Econometric Society*:263-291.

Kemmer, N., and G. W. Neff. 2010. "Liver transplantation in the ethnic minority population: challenges and prospects." *Dig Dis Sci* 55 (4):883-9.

Kilic, A., et al. 2015. "Racial disparities in outcomes of adult heart transplantation." *Circulation* 131 (10):882-9.

King, M., et al. 2014. "Population-based screening for brca1 and brca2: 2014 lasker award." *JAMA* 312 (11):1091-1092.

Lacour, A., et al. 2015. "Novel genetic matching methods for handling population stratification in genome-wide association studies." *BMC Bioinformatics* 16:84.

Lamb, K. E., et al. 2011. "Long-term renal allograft survival in the United States: a critical reappraisal." *Am J Transplant* 11 (3):450-62.

Lamont, Julian and Favor, Christi. 2014. Distributive Justice. In *The Stanford Encylcopedia of Philosophy*, edited by Edward N. Zalta.

Laupacis, Andreas, et al. 1996. "A study of the quality of life and cost-utility of renal transplantation." *Kidney Int* 50 (1):235-242.

Lee, Sandra Soo-Jin, and LaVera Crawley. 2009. "Research 2.0: social networking and direct-to-consumer (DTC) genomics." *The American Journal of Bioethics* 9 (6-7):35-44.

Lee, Sandra Soo-Jin, et al. 2001. "Meanings of Race in the New Genomics: Implications for Health Disparities Research, The." *Yale J. Health Pol'y L. & Ethics* 1:33.

Lehmann, Lisa Soleymani, et al. 2002. "A population-based study of Ashkenazi Jewish women/'s attitudes toward genetic discrimination and BRCA1/2 testing." *Genet Med* 4 (5):346-352.

Lim, Joseph K., and Emmet B. Keeffe. 2004. "Liver transplantation for alcoholic liver disease: Current concepts and length of sobriety." *Liver Transplantation* 10 (S10):S31-S38.

Lodhi, S. A., et al. 2011. "Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success." *Am J Transplant* 11 (6):1226-35.

Lowe, Michael, et al. 1995. "'These sorts of people don't do very well': race and allocation of health care resources." *Journal of medical ethics* 21 (6):356-360.

Lucey, Michael R. 2011. "Liver transplantation in patients with alcoholic liver disease." *Liver Transplantation* 17 (7):751-759.

Mathurin, Philippe, et al. 2011. "Early Liver Transplantation for Severe Alcoholic Hepatitis." *New England Journal of Medicine* 365 (19):1790-1800.

McClain, M. R., et al. 2005. "An evaluation of BRCA1 and BRCA2 founder mutations penetrance estimates for breast cancer among Ashkenazi Jewish women." *Genet Med* 7 (1):34-9.

McClain, Monica R., et al. 2005. "Adjusting the estimated proportion of breast cancer cases associated with BRCA1 and BRCA2 mutations: Public health implications." *Genet Med* 7 (1):28-33.

Melotti, Roberto, et al. 2011. "Adolescent Alcohol and Tobacco Use and Early Socioeconomic Position: The ALSPAC Birth Cohort." *Pediatrics* 127 (4):e948-e955.

Moss, Alvin H, and Mark Siegler. 1991. "Should alcoholics compete equally for liver transplantation?" *Jama* 265 (10):1295-1298.

Moyer, Virginia A. 2014. "Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: US Preventive Services Task Force recommendation statement." *Annals of internal medicine* 160 (4):271-281.

Muller, B., et al. 2016. "Improved prediction of complex diseases by common genetic markers: state of the art and further perspectives." *Hum Genet* 135 (3):259-72.

Mytilineos, Joannis, et al. 2004. "Relevance of IL10, TGFβ1, TNFα, and IL4Rα Gene Polymorphisms in Kidney Transplantation: A Collaborative Transplant Study Report." *American Journal of Transplantation* 4 (10):1684-1690.

Nehus, E., et al. 2015. "Clinical Practice of Steroid Avoidance in Pediatric Kidney Transplantation." *Am J Transplant* 15 (8):2203-10.

Nelson, H. D., et al. 2014. "Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation." *Ann Intern Med* 160 (4):255-66.

Neuberger, James, et al. 1998. *Assessing priorities for allocation of donor liver grafts: survey of public and clinicians*. Vol. 317. Journal Article.

Nsengimana, Jérémie, and D. Timothy Bishop. 2012. "Design Considerations for Genetic Linkage and Association Studies." In *Statistical Human Genetics: Methods and Protocols*, edited by C. Robert Elston, M. Jaya Satagopan and Shuying Sun, 237-262. Totowa, NJ: Humana Press.

O'Rahilly, Stephen, and I.Sadaf Farooqi. 2006. *Genetics of obesity*. Vol. 361. Journal Article.

Orentlicher, D. 1996. "Psychosocial assessment of organ transplant candidates and the Americans with Disabilities Act." *Gen Hosp Psychiatry* 18 (6 Suppl):5S-12S.

Organ Procurement and Transplantation Network. 2016. "Strategic Plan Goal 2: Provide equity in access to transplants." Accessed 1-19-2016. https://optn.transplant.hrsa.gov/governance/strategic-plan/goal-2/.

Port, F. K., et al. 1993. "Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients." *JAMA* 270 (11):1339-1343.

Qin, Huaizhen, et al. 2010. "Interrogating local population structure for fine mapping in genome-wide association studies." *Bioinformatics* 26 (23):2961-2968.

Qin, Huaizhen, and Xiaofeng Zhu. 2012. "Allowing for Population Stratification in Association Analysis." In *Statistical Human Genetics: Methods and Protocols*, edited by C. Robert Elston, M. Jaya Satagopan and Shuying Sun, 399-409. Totowa, NJ: Humana Press.

Ratcliffe, Julie. 2000. "Public preferences for the allocation of donor liver grafts for transplantation." *Health Economics* 9 (2):137-148.

Raz, Aviad E., and Yafa Vizner. 2008. "Carrier matching and collective socialization in community genetics: Dor Yeshorim and the reinforcement of stigma." *Social Science & Medicine* 67 (9):1361-1369.

Roberts, John P., et al. 2004. "Effect of Changing the Priority for HLA Matching on the Rates and Outcomes of Kidney Transplantation in Minority Groups." *New England Journal of Medicine* 350 (6):545-551.

Rodrigue, J. R., et al. 2013. "The Alcohol Relapse Risk Assessment: a scoring system to predict the risk of relapse to any alcohol use after liver transplant." *Prog Transplant* 23 (4):310-8.

Rojas, L., et al. 2015. "Effect of CYP3A5[ast]3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies." *Pharmacogenomics J* 15 (1):38-48.

Sandel, Michael J. 2007. *Justice : a reader*. Oxford ; New York: Oxford University Press.

Santiago-Delpin, E. A., et al. 1983. "Pretransplant predictors in renal transplantation." *Am J Surg* 146 (5):586-8.

Schold, J. D., et al. 2010. "Significant alterations in reported clinical practice associated with increased oversight of organ transplant center performance." *Prog Transplant* 20 (3):279-87.

Sears Jr, Samuel F., et al. 2000. "The role of patients' ability to pay, gender, and smoking history on public attitudes toward cardiac transplant allocation: An experimental investigation." *Health Psychology* 19 (2):192-196.

Sham, Pak C., and Shaun M. Purcell. 2014. "Statistical power and significance testing in large-scale genetic studies." *Nat Rev Genet* 15 (5):335-346.

Shaw, David, et al. 2013. "Lessons from the German Organ Donation Scandal." *Journal of the Intensive Care Society* 14 (3):200-201.

Simmons, R. G., et al. 1984. "Comparison of quality of life of patients on continuous ambulatory peritoneal dialysis, hemodialysis, and after transplantation." *Am J Kidney Dis* 4 (3):253-5.

Stephan, J., et al. 2015. "A random forest approach to capture genetic effects in the presence of population structure." *Nat Commun* 6:7432.

Suthanthiran, Manikkam. 2000. "Renal transplantation: reaping the rewards of biomedical research." *Current opinion in nephrology and hypertension* 9 (6):597-598.

Taber, D. J., et al. 2015. "African-American race modifies the influence of tacrolimus concentrations on acute rejection and toxicity in kidney transplant recipients." *Pharmacotherapy* 35 (6):569-77.

Tabor, Holly K., et al. 2002. "Candidate-gene approaches for studying complex genetic traits: practical considerations." *Nat Rev Genet* 3 (5):391-397.

Tang, Hua, et al. 2005. "Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies." *The American Journal of Human Genetics* 76 (2):268-275.

Tian, Chao, et al. 2008. "Accounting for ancestry: population substructure and genome-wide association studies." *Human Molecular Genetics* 17 (R2):R143-R150.

Tognazzini, Neal and Coates, D. Justin. 2014. Blame. In *The Stanford Encyclopedia of Philosophy*, edited by Edward N. Zalta.

Tong, Allison, et al. 2010. "Community Preferences for the Allocation of Solid Organs for Transplantation: A Systematic Review." *Transplantation* 89 (7):796-805 10.1097/TP.0b013e3181cf1ee1.

U.S. Renal Data System. 2013. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Ubel, Peter A, et al. 1999. "Social Acceptability, Personal Responsibility, and Prognosis in Public Judgments and Transplant Allocation." *Bioethics* 13 (1):57-68.

United Network of Organ Sharing. 2015. "Organ Procurement and Transplantation Network-Policies." Accessed Jan 21st, 2015. http://optn.transplant.hrsa.gov/governance/policies/.

Vladeck, Bruce C, et al. 2012. "Rationing livers: the persistence of geographic inequity in organ allocation." *Virtual Mentor* 14 (3):245.

Volk, M. L., et al. 2011. "Variation in Organ Quality between Liver Transplant Centers." *American Journal of Transplantation* 11 (5):958-964.

Wiggins, David. 2004. "Neo-Aristotelian Reflections on Justice." *Mind* 113 (451):477-512.

Wray, N. R., et al. 2013. "Pitfalls of predicting complex traits from SNPs." *Nat Rev Genet* 14 (7):507-15.

Xu, Chun-Fang, and Ellen Solomon. 1996. "Mutations of theBRCA1gene in human cancer." *Seminars in Cancer Biology* 7 (1):33-40.

Zhu, Mengjin, and Shuhong Zhao. 2007. "Candidate gene identification approach: progress and challenges." *Int J Biol Sci* 3 (7):420-427.