OPTN/UNOS Liver and Intestinal Organ Transplantation Committee
Meeting Minutes
August 28, 2018
Conference Call

Julie Heimbach, M.D., Chairman
James Trotter, M.D., Vice Chairman

Introduction

The Liver and Intestinal Organ Transplantation Committee (Committee) met via teleconference on 08/28/2018 to discuss the following agenda items:

1. Review Geography Committee Public Comment Proposal
2. Patient Affairs Constituent Council Report
3. Region 8 Variance (Potential New Project)

The following is a summary of the Committee's discussions.

1. Review Geography Committee Public Comment Proposal

The Committee reviewed and provided feedback on the Ad Hoc Geography Committee's proposal that includes three distribution frameworks identified as being in alignment with the adopted principles of geographic distribution and the OPTN Final Rule.

Summary of Discussion:

The Committee asked about spending time changing allocation according to one framework when a different framework may be the long-term goal. However, zeroing in on one framework is a long-term process and not the goal of the current efforts to change allocation to be compliant with the Final Rule by removing DSA and region. Eventually there will be a movement towards consolidating all policies under a single framework. It is important to note that the concentric circles framework could be transitioned into the continuous distribution model. Having organ committees work concurrently to address DSA/region in their respective distribution systems reflects the expedited timeline.

The Chair asked whether the Geography Committee could decide which framework to use so there will not be any conflict between allocation changes or additional work from modifying allocation in the future. There is a directive from the Board of Directors (BOD) to send the three frameworks out for public comment and get community feedback regarding which is the most supported option. Another Committee member expressed confusion over having multiple committees making separate recommendations to the BOD at the same time and felt it is likely causing confusion in other committees as well.

A Committee member commented that the borderless and circles frameworks are not necessarily conflicted. In terms of circles sized chosen, those can be thought of as pretty close in terms of patient illness. Model for End-Stage Liver Disease (MELD) score is medical acuity and distance is a discrete variable, but that does not need to be done. Those are different things that can be changed, so they should not be in conflict.

One question related to distance as a factor in the model and whether travel time factored into the equation of nautical miles. Distance is being used as a surrogate for proximity, but what really matters is the time it takes to get from point A to point B. Travel time may be a better measure than distance, but would require more work to determine due to variables such as availability of transportation, roadways, etc.

One Committee member asked about whether the Geography Committee is looking at high-risk organs to reduce discards. Organ-specific committees will be the most knowledgeable bodies about specific risks of discards for their specific organ, and therefore will guide the development of the policies as they relate to discards. This is why discussions with the Liver Committee include special consideration for donation after circulatory death (DCD) or patients over 70 years.

Liver does not have a kidney donor profile index (KDPI) equivalent, so the factors involved would probably be just MELD and distance, which could appear to favor urban centers with a lot of donors around recipients.

Another Committee member suggested considering giving patients located in rural areas a higher score. In addition, the proximity component of the total score could be the same value out to a certain distance, which would in effect be equal to creating a fixed radius circle of that distance. This is another point that demonstrates more similarity than difference mathematically between framework 1 and 3. The Chair expressed concern over the amount of work it would take to agree on point values for each of the variables. The Committee agreed that whatever point values are determined must be rationally justified.

One question was whether there was any consideration given to disparity or donor availability in terms of geography. For example, would a patient in a location that has fewer donors have equal access to an organ from a location with many donor organ? The first principle of distribution allows constraining geographic distribution for the reduction in differences in donor supply and demand, so therefore would be allowed for consideration. How to operationalize that, however, is still a subject of debate and discussion.

Next steps:

Committee members can individually provide feedback on the proposal through the link to RedCap they will receive by email.

2. Patient Affairs Constituent Council Report

Summary of Discussion:

The Patient Affairs Committee is working under a new structure called Constituent Council. The councils are designed to increase real-time communication between and within UNOS Committees. The patient rep on the Liver Committee will interact directly with the Patient Affairs Constituent Council (PACC) as an active member in all committee activities. The structure change has resulted in constituency feedback and projects and ideas earlier in the process.

A process has been mapped that will facilitate sharing project information between other committees and the PACC. A Committee Project Report is posted to Basecamp well in advance of Liver Committee's meetings, giving members the opportunity to review and post feedback via Basecamp. The patient rep also has the opportunity to learn more about the transplant world, and be more comfortable interacting with their home committee, as well as bringing discussion to the PACC for its input.

The Committee requested feedback from the PACC. There was strong support for a framework (in this case fixed distance) that does not prolong the allocation process, prioritizes the sickest candidate first, promotes utilization and mitigates discards, and considers recipient/graft outcomes. However, there was some confusion about the concentric circles. Additionally, many asked about time versus distance as a variable. Time would align better with ischemic times and outcomes, but can be influenced by factors such as method of travel. There were also concerns about patients in rural/isolated areas, as well as vulnerable populations such as veterans.

Feedback on communication was requested. There has been confusion as to how this is being presented in public comment and overlapping with the geography project. When information is shared is as important as how it is shared. To maintain public trust, it must be proactive, honest, and transparent. Communication strategy recommendations included collaborating with transplant centers, using social media, using plain language and layman's terms, and sharing context information, meaning the information around what is being discussed.

3. Region 8 Variance (Potential New Project)

Summary of Discussion:

The Region 8 Variance was previously discussed and supported by the Committee. Region 8 supports the opportunity to try their variance, which focuses on a center accepting a liver that they want to split to use the other lobe for another patient on the match run at their center or an affiliated center. However, since regions are no longer part of allocation, it would be difficult to go forward with this project. Under the December 2017 policy, the variance would apply if livers were recovered in Region 8 and transplanted in Region 8.

Committee members will decide if they support adding the Region 8 Variance to the list of existing variances during the special public comment. It still needs to be approved by the Policy Oversight Committee.

Next Steps:

This will be further discussed at the next meeting.

Upcoming Meetings

- September 4, 2018, Teleconference
- September 18, 2018, Teleconference
- September 25, 2018, Monthly Teleconference
- November 2, 2018, In-person Meeting in Chicago

Medicine, Health Care and Philosophy
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SHORT COMMUNICATION

Toward an accelerated adoption of data-driven findings in medicine

Research, skepticism, and the need to speed up public visibility of data-driven findings

Uri Kartoun[1]

Abstract
To accelerate the adoption of a new method with a high potential to replace or extend an existing, presumably less accurate, medical scoring system, evaluation should begin days after the new concept is presented publicly, not years or even decades later. Metaphorically speaking, as chameleons capable of quickly changing colors to help their bodies adjust to changes in temperature or light, health-care decision makers should be capable of more quickly evaluating new data-driven insights and tools and should integrate the highest performing ones into national and international care systems. Doing so is essential, because it will truly save the lives of many individuals.

Keywords Clinical informatics · Prediction modeling · Electronic medical records · Machine-learning · Data-mining · Cirrhosis · Liver transplantation

Throughout history, skepticism has played an important role in evaluating a variety of phenomena. In medicine, some scientists have occasionally been dismissed as irrational only to be proven right many years later. For instance, Galen, a second-century philosopher and physician, believed that the liver was the source of all veins and the principle organ for blood production (ElMaghawry et al. 2014). Though most of Galen's writings were incorrect, people still held strong to his beliefs even 1500 years later. Dr. William Harvey was the first to describe blood circulation to the heart, brain, and body in detail. In 1628, in his book, *De Motu Cordis* (On the Motion of the Heart and Blood), describing the structure of the heart and arteries, he posited for the first time that blood passed through the heart, not the liver as previously believed. Harvey's findings were ridiculed, and many doctors in the seventeenth century noted that they would "rather err with Galen than proclaim the truth with Harvey." (Bushak 2015).

Another example of skepticism in medicine concerns non-alcoholic fatty liver disease (NAFLD). Until a few decades ago, the scientific community was undecided about whether NAFLD is actually a clinical condition. An NAFLD diagnosis has important health and clinical implications because it is a risk factor for the development of diseases such as type 2 diabetes mellitus and an independent risk factor for cardiovascular-related mortality and all-cause mortality (Musso et al. 2011; Byrne and Targher 2015). Nonalcoholic steatohepatitis, the progressive form of NAFLD, can result in cirrhosis and hepatocellular carcinoma and is estimated to become the leading indication for liver transplant in the United States by 2020 (Charlton 2008).

Recent remarkable advancements in computer hardware and software and the growing accessibility of electronic medical records (EMRs) have accelerated research on predicting patient outcomes. Such advances have allowed the rapid development of massive-scale predictive models—powerful resources to study disease complications at the population level. Such models have proved highly useful to discovering or confirming disease correlations, sub-categories of diseases, and adverse drug events. The model of the end-stage liver disease (MELD) risk score, for instance, is one of the most important and widely used risk prediction scores in medicine. Unlike in the case of other scores, a patient's MELD score may indicate the likelihood of a major clinical event for the patient. MELD determines the patient's rank on the organ allocation waiting list; notably, since 2002, MELD has played a crucial role in determining

✉ Uri Kartoun
uri.kartoun@ibm.com

[1] Center for Computational Health, IBM Research, Cambridge, MA, USA

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which patient on a waiting list will be the next to receive a liver transplant (Kamath and Kim 2007).

Combining the ability to store and rapidly process the records of millions of individuals by accessing the repositories of Massachusetts General Hospital (MGH), Brigham and Women's Hospital (BWH), and the IBM Explorys Platform using machine-learning algorithms has helped us create a new and highly accurate score to predict short-term mortality in cirrhosis patients (Kartoun et al. 2017). We took an unbiased approach to the discovery of biomarkers. In this approach, we filtered a large collection of medical records through a feature-selection algorithm and identified a small set of variables that could serve as the most efficient predictors for a given medical outcome. We used the traditional supervised-learning paradigm to assess accuracy and applied standard statistical methods to assess the validity of our approach. We realized that combining the components of MELD with several easily accessible variables would enable us to construct a new score that would be approximately 10% more accurate. We named our new score MELD-Plus. MELD-Plus is an attempt to create a new mortality prediction risk score in cirrhosis. Our unbiased data-driven approach, which involves the use of an algorithm to select predicting variables as well as the large and independent databases used for validation, makes our score a useful tool that could truly save lives. Furthermore, the fact that MELD-Plus's variables are available for any patient (including total bilirubin, creatinine, albumin, INR, WBC, sodium, total cholesterol, length of stay, and age) makes it easy to calculate the patient's mortality risk using Excel or to deploy on any digital health repository.

Our preceding manuscript drafts, in which we outlined a better scoring system than MELD, raised significant skepticism from reviewers and editors. Although we were invited to present our earlier findings at a medical informatics conference (Kartoun et al. 2016), leading medical journals repeatedly criticized our work. The criticism always had a reasonable rationale, but our findings and the proposition for an alternative score did not change throughout our resubmissions and were, therefore, kept out of the public eye. Eventually we successfully published our study in October 2017 in PLoS ONE, a peer-reviewed journal.

The main criticism of our initial manuscript was valid: until 2016 we had access to only one source of data (MGH/BWH), and our claim of generalizability was indeed weak. Another criticism was that the interest in such scores might be limited to individual clinicians who are making decisions. This claim, however, may rule out the usefulness of any other type of risk score as well. Another concern was that our predictive model contained too many variables, reducing its practicability in day-to-day use. Such criticism was valid if powerful computers capable of instantaneously processing tremendous collections of EMRs were not in such broad use, as they are today. Future risk scores will likely be composed of tens of thousands of patient characteristics and be calculated automatically as an integrated component of an EMR system to provide real-time decision support to monitor a disease or to prioritize organ transplant candidacy.

Finally, we faced criticism that several of the variables that we used (all selected by a feature-selection algorithm) were associated with cardiovascular risk rather than liver-related mortality. Strikingly, researchers from the Cleveland Clinic validated another of our liver-related studies in which we strengthened the existing knowledge and discovered new biomarkers regarding the interplay between cardiovascular risk and liver disease. Both studies were published in *The American Journal of Gastroenterology* (Corey et al. 2016; Mehta et al. 2016). Medical publications that describe unbiased approaches to feature selection for developing new scores or to classifying diseases more accurately are rare. A few, however, have been published, including, for instance, a prediction model for 30-day readmission for heart failure patients (Kartoun et al. 2015) and models to classify rheumatoid arthritis (Liao et al. 2010), Crohn's disease, and ulcerative colitis (Ananthakrishnan et al. 2013). Although we were not criticized explicitly for favoring a data-driven unbiased approach rather than relying on domain expertise, it could have been our use of an approach not yet broadly accepted that have raised further criticism.

Furthermore, our approach also relied on a new text-processing method that we developed to accurately extract concepts from clinical narrative notes. The method, text nailing (TN), raised skepticism in reviewers of medical informatics journals who claimed that TN "relies on simple tricks to simplify the text," and "leans heavily on human annotation." TN indeed may seem just like a trick of the light at first glance, but it is actually a fairly sophisticated method that finally caught the attention of more adventurous reviewers and editors who ultimately accepted it for publication (Kartoun 2017a, b). We found TN to be highly accurate, outperforming traditional machine-learning algorithms in multiple scenarios, such as extracting family history of coronary artery disease (Corey et al. 2016), classifying patients with sleep disorders (Beam et al. 2017; Kartoun et al. 2018), and improving the accuracy of the Framingham risk score for patients with NAFLD (Simon et al. 2017).

As for the historical trajectory of adopting liver allocation scores, in 1998, the Committee on Organ Procurement and Transplantation Policy of the Institute of Medicine (currently called "The National Academy of Medicine") published "The Final Rule," calling for "…standardized medical criteria to be used to determine the status of a person's illness and when that person can be placed on a waiting list" and further stating "…Minimum listing criteria for including transplant candidates on the national list shall be standardized and, to the extent possible, shall contain explicit thresholds for listing a patient and be expressed through objective and measurable medical criteria" (Institute of Medicine 1999). Independently, scientists reported in 2000 on a well-validated model and on the creation of a new equation to calculate survival probabilities for patients following a transjugular intrahepatic portosystemic shunt placement (Malinchoc et al. 2000). In February 27, 2002, this equation was selected to serve as the basis for the new allocation policy (Freeman et al. 2002). The equation, forming MELD, has become the standard by which priorities are determined in donor liver allocation, and as expected, implementation of MELD led to an immediate reduction in liver transplant waiting list registrations for the first time in the history of liver transplantation (with a 12% decrease in 2002) (Kamath and Kim 2007). In subsequent years, multiple studies proposed that the incorporation of sodium into the original MELD equation could significantly improve prediction accuracy for liver disease. For instance, a study published in the *New England Journal of Medicine* in 2008 estimated that using an extended version of MELD, one that incorporated serum sodium levels, would save 90 lives in the period from 2005 to 2006 (Kim et al. 2008). Additional studies supported the usefulness of sodium to improve prediction performance for liver disease (Ruf et al. 2005; Londoño et al. 2007; Luca et al. 2007). The MELD-Na score, an equation that incorporates sodium into MELD, was finally adopted in 2014 (Mulligan and Hirose 2014).

Why did it take many years to adopt MELD-Na, a score that was created by using a data-driven approach, instead of starting to use it, say, in 2008, right after multiple studies demonstrated the advantage of using sodium to improve the prediction accuracy of MELD? The lives of hundreds would have been saved if MELD-Na was in use starting in 2008 rather than in 2014. The reason for the delay was most likely to let the scientific community assess and discuss further the combination's potential usefulness as well as its drawbacks, a consideration undertaken by a large number of independent investigators and through the use of patient data captured at multiple health systems. Only after broad scientific evidence had been accumulated, was the United Network for Organ Sharing (UNOS) convinced to extend MELD to MELD-Na. Furthermore, UNOS estimated that MELD-Na was expected to save between 50 and 60 lives per year (Mulligan and Hirose 2014), and relevant to MELD-Plus, our experiments demonstrate that while MELD-Na performed slightly better than MELD, MELD-Plus performed significantly better than MELD (> 10% better) (Kartoun et al. 2017). Thus, MELD-Plus, if incorporated into hospital systems, could save hundreds of patients every year in the United States alone. Furthermore, as an encouraging first step toward adoption, a very recent study reported that MELD-Plus plays a predictive role in the occurrence of post-liver transplantation acute kidney injury, proposing a broader usefulness beyond mortality prediction (Tudoroiu et al. 2018).

The adoption of MELD-Na would had been faster if the scientific community had been able to publish convincing studies earlier to assess the contribution of sodium to MELD. Organizations such as The American Medical Information Association (AMIA) have encouraged universities as well as commercial companies to form "Challenges," such as the de-identification and the smoking status challenges (Uzuner et al. 2007, 2008). Such challenges have resulted in a variety of high-impact papers that have significantly enhanced the medical informatics subdomain, as well as the entire health-care domain. If UNOS had worked more collaboratively with AMIA, as well as with The Institute of Electrical and Electronics Engineers (IEEE)'s Engineering in Medicine and Biology Society, new challenges could have been formed, with titles such as "The MELD-Plus Challenge" or "The Liver Disease Challenge," inviting investigators from all around the globe to assess current scores and propose new scores that might even outperform MELD-Plus. Additional associations, such as the Association for Computing Machinery (ACM), might be encouraged to be involved in such efforts focused on computational assessments of health. Such initiatives could help accelerate the adoption of health-related data-driven findings, as these challenges are expected to produce scientific papers faster and thus support or rule out the usefulness of the newest findings.

In a desirable future scenario, UNOS may decide to replace MELD (or its subsequent score, MELD-Na) with MELD-Plus or even with more advanced futuristic scores that may be developed by other researchers that incorporate, for instance, additional behavioral and genetic aspects. Hypothetically, we can imagine a patient a decade from now who is in need of a liver replacement. That patient might feel encouraged if MELD-Plus was in use, determining more accurately his or her rank on the waiting list. MELD-Plus will not cure that patient, of course, but its ability to assess the severity of a condition more precisely could mean that the patient might wait 2 months less for a new liver than if the original MELD was in use. MELD-Plus, therefore, could save the patient's life.

On the one hand, skeptics are often proven wrong as science advances. For instance, it took years for the mainstream scientific community to accept Harvey's contributions over Galen's. On the other hand, skepticism in medicine is essential, especially regarding questionable treatments and methods and the potential effects of using new medicines. Advances in medicine that have raised significant skepticism include, for example, a human head transplant operation proposed by neurosurgeon Dr. Sergio Canavero (former director of the Turin Advanced Neuromodulation Group, Italy) or a new approach to slow the progression of Alzheimer's disease proposed by Dr.

Dale Bredesen (University of California, Los Angeles). The development of new risk scores, by contrast, and especially those that are based on components of similar widely used scores, such as MELD, should not be interpreted as questionable and thus should be expected to raise only minor levels of skepticism. Regardless of any specific disease, when a new score is introduced publicly in a peer-reviewed scientific journal, the scientific community would benefit from the availability of mechanisms that could evaluate the scores more rapidly, considering data derived from multiple health-care systems. Especially, official organizations that rely on the scores (e.g., the American Diabetes Association, the American Heart Association, UNOS) would benefit from such mechanisms. Combining the most advanced data-driven algorithms with human expertise is expected to achieve a desirable increase in knowledge, and this could potentially affect decisions to either replace or extend current scoring methods. Incorporating data-driven scores adjusted by human expertise is essential, especially within the context of medical ethics, and will help in deciding which research findings may be worth accelerating and what safeguards need to be provided. For instance, a better scoring system might result in some patients being pushed up the queue for transplantation, but it would result in other patients being pushed down. Additional components coming into play regarding medical scoring systems must consider the ability to assess the true risk of learning algorithms (Kartoun 2018) and the potential for sociological biases at the individual level, as well as at the social level. An algorithm favoring a candidate for transplant based on his or her political views, family status, or sexual preference are just a few examples for such potential biases.

To accelerate the adoption of a new method with a high potential to replace or extend an existing, presumably less accurate, medical scoring system, evaluation should begin days after the new concept is presented publicly, not years or even decades later. Metaphorically speaking, as chameleons capable of quickly changing colors to help their bodies adjust to changes in temperature or light, healthcare decision makers should be capable of more quickly evaluating new data-driven insights and tools and should integrate the highest performing ones into national and international care systems. Doing so is essential, because it will truly save the lives of many individuals.

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Compliance with ethical standards

Conflict of interest The author has declared that no competing interests exist. The author confirms that the commercial affiliation with IBM does not alter his adherence to all Medicine, Health Care and Philosophy policies.

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