Introduction

The Kidney & Pancreas Transplantation Committee Continuous Distribution Workgroup (the Workgroup) met via Citrix GoToMeeting teleconference on 3/12/2021 to discuss the following agenda items:

1. Welcome & Review of Project Goals
2. Recap of 2/26 Meeting
3. Discussion: Human Leukocyte Antigen (HLA) Matching Data Request

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

1. Welcome & Review of Project Goals

The Workgroup reviewed the scope of the Continuous Distribution project, which is to change allocation from a classification-based system to a points-based system. The Workgroup is currently in the second phase of the project where they will be assigning values to the kidney and pancreas attributes and developing a concept paper.

Summary of discussion:
There was no discussion.

2. Recap of 2/26 Meeting

During the Workgroup’s last call, the Workgroup received an overview presentation on the Final Rule and discussed the impact of human leukocyte antigen (HLA) matching on the following:

- 0-ABDR mismatches
- DQ matching
- Graft life and pediatric priority
- Race and equity in access

Summary of discussion:
There was no discussion.

3. Discussion: HLA Data Request

The Workgroup continued discussing factors that should be considered in the HLA data request and categorized these factors in order to determine their feasibility in the Continuous Distribution framework, while also aligning with current policy. The Workgroup reviewed that the goal of developing a rating scale for HLA matching is to determine which matches should be prioritized over others.
The Workgroup was informed that factors that were more complex would be placed on hold for future discussion later in the development of the Continuous Distribution framework.

**Summary of discussion:**

The Workgroup was asked the following questions to help guide their discussion:

- Should the Workgroup emulate the current system and assign points to 0-ABDR mismatches and DR mismatches?
- Does the Workgroup want to have a rating scale for individual loci?
- Other options?

A member inquired if the models would be looking at survival or distribution. Staff stated that they were assuming the models would be looking at graft survival, but if the Workgroup doesn’t think that makes sense then they can consider other options.

A member stated that the impact of HLA matching in allocation on different racial groups needs to be considered moving forward and that they would be supportive of this being modeled into the permutations in order to get some data. Staff stated that, once the Workgroup has an idea of how they might implement HLA matching in the continuous distribution system, it will help to better anticipate what disparities there might be and to what degree and help the Workgroup ask more focused questions from that data.

A member inquired how far out the models can estimate graft survival. Staff stated that there would need to be a balance since the models could go as far back as there is nationally collected data; however, the Workgroup would need to determine if the transplants from that far back in time is representative of the transplants occurring today. Staff questioned if the answer to that would change Workgroup members recommendation. A member stated that it would change their recommendation, since it seems the following are the goals of creating these models:

- Help promote longer term graft survival by having better matching and, with better matching, decrease the occurrence of rejection
- For patients that do reject the organ and need another, ensure that patients needing a second or third transplant are not as sensitized as they could be – better matching limits the potential for antibodies to develop later on making it easier to transplant a second or third time.

A Scientific Registry of Transplant Recipients (SRTR) representative stated that one of the other complications has to do with the HLA matching data itself and the mismatching algorithm which changes overtime. For example, what is a 0-ABDR mismatch today is not necessarily what would have been considered a 0-ABDR mismatch in the past because the matching tables get updated and the way the data is collected changes overtime. The SRTR representative emphasized that, if the Workgroup goes too far back, the mismatches that are observed in the data set are not following the same mismatch rules as current transplants would be following.

An SRTR representative mentioned that before putting HLA matching into the kidney-pancreas simulated allocation model (KPSAM), the Workgroup will also have to decide how much priority to give HLA matching relative to other attributes. Staff explained that the results of this data request will help inform the weighting of HLA by allowing the Workgroup to see the impact of different levels of HLA matching in terms of graft survival.

A member noted that, if the Workgroup is looking at DQ and some other loci, that typing wasn’t required to be entered and it’s going to be hard to model outcomes from longer term data.
Another member mentioned that data for HLA matching is stronger for kidney than it is for pancreas and that HLA matching is probably more valuable for patients who may need more than one transplant in their lifetime to minimize future sensitization – ex. children, low Kidney Donor Profile Index (KDPI) recipients, recipients who received the kidney first followed by the pancreas or pancreas after kidney (PAK) recipients.

A member stated that the Workgroup needs to determine if there’s a significant benefit in any population from any match that the Workgroup wants to model. The member suggested starting with modeling 0-ABDR and class 2 matching since that’s what the literature currently supports. A member noted that there’s a very low percentage (4%) of kidney transplants that have a 0-ABDR mismatch. Staff inquired if the Workgroup would want to compare a 0 mismatch at specific loci versus (vs.) different levels of matches at the DR DQ loci vs. no matches at all.

A member mentioned that the OPTN Histocompatibility Committee wanted to look at all the loci independently, then the member suggested also looking at 0-ABDR mismatches and class two independently (DR loci separate, DR DQ loci together, and DQ loci separate). A member explained that a lot of literature recently has indicated that DQ matching may be more important than DR matching in class 2.

A member inquired, since DQ matching is a relatively recent phenomenon, how far back could the Workgroup go with the data to model this while being mindful that the immunosuppression regimens offered today are not what was offered 10 years ago and won’t be offered 2-3 years from now when this continuous distribution is implemented. Staff stated that their understanding is that the Workgroup can’t go back much further than the last major change to the kidney allocation system, so probably around 2015. Staff explained that this limits the Workgroup’s ability to look at long-term survival but would allow them to look at 5-year survival.

A member suggested that, if the Workgroup looked at data from 10 years ago, they wouldn’t have DQ data but could limit the cohort to patients who were discharged from their initial hospitalization on a steroid based regimen and stratify by rapid steroid withdrawal. The member explained that then, from that cohort, a propensity score could be developed and modeled to compare the two cohorts as opposed to a regular COX time 2 event. Staff asked the member to further explain the purpose of this analysis. The member explained that old cyclosporine data showed that the six antigen match, which is not exactly the same as the 0 antigen mismatch, performed much better than all increasing levels of mismatches. If the Workgroup wants to know the performance in the modern era, they’d want to create a cohort that most closely mimics what the majority of centers are doing and tacrolimus (TAC) is the most common immunosuppression based regimen now, so the cohort should be limited to patients using TAC. Staff summarized by stating it seems there has been a change in what medications are being used, so if the Workgroup can limit the cohort to patients using medications that are commonly used today and in the past, just maybe not as prevalently, then the Workgroup can compare data from further back in time.

A member emphasized that by looking at patients on the following immunosuppression regimens the Workgroup will be able to analyze more long-term follow up:

- TAC
  - Predominant calcineurin inhibitor since 2001, more than 80% of people discharged on immunosuppression regimens are on TAC
- Mycophenolates
  - Contemporary standard and 60% of programs do steroid containing regimens
- Rapid steroid withdrawal
A member stated that if the Workgroup wanted to look at causality, they could do propensity matching of patients who got a 0 antigen mismatch vs. all other matches and then the Workgroup could also account for any of the other characteristics, like age and comorbidities, but that’s more complicated.

An SRTR representative stated that it sounds like the member wants to limit the data to modern types of immunosuppression so TAC, prednisone, mycophenolate mofetil (MMF) and questioned if the member would include induction. A member suggested that for comparison the Workgroup would probably want to limit one cohort to patients who got depleting antibody vs. non-depleting antibody because that will impact the risk of rejection. An SRTR representative stated that they would have to review how good the data is on induction, in terms of Thymoglobulin vs. Simulect. The SRTR representative explained that they would also just be looking at the patients that started on those immunosuppression regimens initially since some patients switch if they have side effects.

A member emphasized that they proposed propensity matching as an analysis option in order to isolate the effect and mimic a randomized control trial which would randomly group patients into one of two cohorts – getting a 0 antigen mismatch vs. all other options. An SRTR representative inquired if the Workgroup would feel comfortable using the proposed cohort to generalize to the rest of the population, who may not use these immunosuppression regimens. Members thought that this data could be generalized.

An SRTR representative inquired if the Workgroup would like to analyze the impact of HLA ABDRDQ mismatch (eight antigen mismatch) vs. none, or if there are other categories that would be of interest. A member stated that the following would be the easiest categories to compare to the general population:

- 0-ABDR mismatch
- 0-DR
- 0-DQ
- Non-0 mismatch

An SRTR representative inquired what the member meant by general population. A member stated that picking the general population by immunosuppression regimen may be more difficult and they would trust the SRTR modeling group to make the decision on the cohort used for the general population.

Members agreed that that’s a good place to start. A member emphasized that it also might be worthwhile to separate out each individual loci just to show that it doesn’t really have that much impact on graft survival. Staff stated that it seems like there’s also interest in including a total zero antigen mismatch and class two matches independently.

A member suggested that the only other stratification that might be useful is DRDQ loci together, in addition to looking at them separately. The member explained that the linkage between DR loci and DQ loci is pretty tight, but there are some scenarios where they aren’t tightly linked so it would be interesting to look at them together.

Staff stated that from a practical standpoint, the Workgroup should look at some data for class 1 matching because it is currently in allocation.

A member noted that DQ typing is not universal among recipients so some subjects/patients will be lost in the analysis including DQ matching. Staff mentioned that, for this analysis, SRTR can run a report to see if there’s a systematic difference between those who have DQ typing and those who don’t, so if the data is missing a population the Workgroup will be able to identify that and use that as they consider the model.
A Workgroup Chair stated that, if the Workgroup is doing the modeling to see what the long-term outcomes are for matching, it could be argued that modeling with the patients with the highest estimated post-transplant survival (EPTS) score isn’t going to be informative. It was explained that, currently, kidneys aren’t allocated separately based on a patient’s EPTS for 0-ABDR mismatch or 0-DR mismatch.

Staff stated that that’s an idea the Workgroup could explore once they get some of this preliminary modeling back. A member inquired if this could be solved by restricting the cohort based off of an age, potentially under the age of 65. A Workgroup Chair stated that that would be interesting and possibly more informative about the true benefit of these types of HLA matching.

A member emphasized that there’s going to be very few patients above 65 that are going to be getting a pancreas.

A member explained that, once the Workgroup decides what matches they want to look at for graft survival, they can stratify the groups by age, race, and other factors to make sure that there are no unintended consequences of those matches. A member inquired if the Workgroup was thinking of doing step-wise modeling, so just modeling matches and then breaking them into further stratifications if the Workgroup sees that it makes a difference. Staff stated that the idea would be to adjust for those factors in the model, so the Workgroup would also need to decide, in a multi-variable model, what needs to be accounted for in order to distill out this HLA affect.

An SRTR representative stated that an adjusted analysis for all the baseline factors that we have would answer the question of what is the impact of HLA independent of all these other things. It was explained that stratifying by immunosuppression could also help, but that could simply be adjusted as a baseline factor as well.

A member emphasized that the Workgroup is making a distinction between (1) trying to estimate the impact of HLA matching on graft survival (what they’ll get out of this multi-variable model adjusting for other factors) and (2) trying to see if there’s a correlation between likelihood of getting a well matched transplant and other factors (race/ethnicity) and the potential consequences of these matches.

Members agreed that this information will be needed if the Workgroup decides matching is important enough to assign points to it in a continuous distribution system.

An SRTR representative stated that the duration of data makes an impact. If the Workgroup looks at one year survival, then age doesn’t make that much of an impact; however, if they look at longer-term survival then they may see age has a greater impact.

Members agreed to look at graft survival rather than patient survival for HLA matching. A member noted that pancreas graft survival is defined for a shorter time (only have good data over about two years), so that would be a much shorter follow up period compared to the kidney data. An SRTR representative stated that they weren’t sure how much graft survival they had for pancreas.

An SRTR representative inquired if the Workgroup was planning on including solitary pancreas in the data request. The SRTR representative explained that the HLA matching data for pancreas is quite limited and, for solitary pancreas, B-locus was the only loci found to be significant with 0 mismatches offering an advantage. The SRTR representative further explained another issue with HLA matching with pancreas is how to reconcile pancreas-after-kidneys (PAKs). Are shared mismatches allowable from the previous kidney? And if so, is the kidney HLA fully taken into account as a match if the patient still had rejection?

A member stated that, if finding something to apply to pancreas alone candidates would be a completely different discussion, it sounds like the Workgroup should limit this modeling to kidney for
now. Staff inquired if KP transplants could be looked at in conjunction with the kidney alone transplants. An SRTR representative stated the problem with that is there’s no pancreas graft survival data, the kidney graft survival data would have to be used.

A Workgroup Chair stated that the source of confusion in this discussion is that, since the Workgroup has combined kidney and pancreas together, there are multiple scenarios – kidney alone, simultaneous pancreas kidney (SPK), PAK, pancreas alone – and each needs to have their own conversation. The Chair suggested that, the next time the Workgroup discusses HLA, it needs to be very clear which organ or organ combinations the Workgroup should be talking about.

An SRTR representative suggested a simple data request from the OPTN to look at the frequency of matches across the different organ combinations. The SRTR representative commented it might be interesting for the Workgroup to see how matches differ across the organ combinations and it could help discussion. Members agreed and believed that this would help their next conversation.

**Next Steps:**
The Workgroup will continue this discussion during the next meeting.

**Upcoming Meetings**
- March 26, 2021 (Teleconference)
Attendance

- **Committee Members**
  - Vincent Casingal
  - Silke Niederhaus
  - Martha Pavlakis
  - Rachel Forbes
  - Alejandro Diez
  - Arpita Basu
  - Caitlin Shearer
  - Cathi Murphy
  - Deirdre
  - John Lunz
  - Loren Gragert
  - Parul Patel
  - Pete Lalli
  - Peter Stock
  - Pradeep Vaitla
  - Todd Pesavento

- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
  - Raelene Skerda

- **SRTR Staff**
  - Ajay Israni
  - Bryn Thompson
  - Jon Miller
  - Nick Salkowski
  - Raja Kandaswamy

- **UNOS Staff**
  - Joann White
  - Lindsay Larkin
  - Rebecca Brookman
  - Kayla Temple
  - Ross Walton
  - Alison Wilhelm
  - Amanda Robinson
  - Ben Wolford
  - James Alcorn
  - Joel Newman
  - Kaitlin Swanner
  - Kelsi Lindblad
  - Lauren Motley
  - Matthew Prentice
  - Melissa Lane
  - Nang Thu Thu Kyaw