OPTN/UNOS Histocompatibility Full Committee Meeting
Meeting Minutes
November 13th, 2018
Conference Call

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Introduction

The Histocompatibility Committee met via Citrix GoToTraining teleconference on 11/13/2018 to discuss the following agenda items:

1. October In Person Meeting Follow Up
2. Addressing HLA Typing Errors Project Update
3. Review of HLA Table (2016) Project Update
4. Change CPRA Calculation Project Update

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

1. October In Person Meeting Follow Up

The Committee heard an update on the progress on the topics from the in person meeting last month.

Summary of discussion:

UNOS staff reminded the committee that an expense report for the in person meeting was sent out if members wanted to submit their expense report and if members have any questions to contact staff. Staff reminded the committee that a member of this (Histocompatibility) committee has been working with the Operations and Safety committee (OSC). At the in person meeting the members from the OSC joined the meeting by phone to get some input on HLA considerations for broader geographic distribution because the committee is working on their guidance for effective practices for broader geographic distribution. A member who was working with this committee updated that it was a very quick conversation and there were not a lot deliberations on the points but to expect some changes. There is a draft of the guidance document and UNOS staff will send it out to the members of the committee.

UNOS staff is in the process of finalizing draft of the Heart Allocation memo for distribution to the thoracic committee. Staff will arrange a meeting for the leadership between two committees to discuss.

Next steps:

UNOS staff will send out a draft of OSC guidance document and coordinate a meeting between Histocompatibility leadership and Thoracic leadership.

2. Addressing HLA Typing Errors Project Update

The Committee heard a brief update on the status of this project.

Summary of discussion:
UNOS staff reminded the members that during the in person meeting the final language for this proposal was voted on. The next step is for the Board Policy Group to review the proposal on 11/14/18. The Vice Chair of this committee is going to give a short presentation to the Board Policy Group to update them on any post public comment changes as well as to give them a background on the project. They will then give a recommendation on whether the proposal

should be on the consent or discussion agenda at the board meetings. UNOS staff stated that it was similar to the short presentation that several members have at their regional meetings for those whom this was unfamiliar.

UNOS staff is recommending to the Board Policy Groups that this policy goes for the consent agenda to vote at the Board meeting (12/3/2018-12/4/2018). This is due to is non-controversial nature during public comment and at regional meetings and it was positively received overall.

3. Review of HLA Equivalency Tables (2016) Project Update

The Committee heard an update about the implementation status of this project

Summary of discussion:

UNOS staff reminded the committee that this project was an update of the equivalency tables the members worked on and went to the board in December 2017. The implementation with UNOS IT is almost complete and should go live December 5th, 2018. There should be a Transplant Pro and policy notice coming out soon.

4. Change CPRA Calculation Project Update

The Committee will hear an update on the status of this project

Data Summary:

One of the researchers on this project reminded the group that the projects plan to use NMDP Stem cell registry donor HLA data in reference for CPRA calculation. A brief background of the project was given in which the member stated that they found that NMDP and UNOS donor populations have similar HLA frequency. There was a table given that showed the number of HLA typing for broad race and ethnic categories, and with future data the numbers might change; however, they believe that the current table is to be 100 times larger than the current UNOS panel which has only two years of data from deceased donors. To establish feasibility, previous data sets of 6 locus HLA haplotypes were used (in the future it is going to be expanded to 9 loci). In addition they converted a high resolution data set to UNOS antigen nomenclature mapping table and was published earlier this year.

The researcher then went on to discuss that the first manuscript that is a priority for the NMDP is the DPB1 TCE Group Match Likelihood. This manuscript is a prerequisite to publishing the 9 loci data. In this paper they wanted to show the impact of matching DPB1 T-cell epitope groups on match likelihood. Members stressed its importance for clinicians in stem cell transplant. The paper is almost ready to submit. The researcher highlighted for the committee that this data is two years old and they have been waiting to submit it. They also reminded the group that every 3 years the NMDP has to submit a report on the likelihood of patients finding a match when searching the whole registry of volunteer donors. Therefore the latest guidelines for HLA matching has changed, so UNOS will need to provide on that.

The manuscript to follow would be describing 9-locus haplotype frequency that will be the new CPRA reference panel (including DQA1 and DPA1). The researcher continued and stated that HLA-DQA and HLA-DPA are not typed for most individuals therefore the Expectation-Maximization (EM) algorithm needs more tuning to get better estimates to include the alpha data. Overall there is a lot of missing data for the alphas in this data set and we have to include all the donors so the estimates are unbiased.

Lastly the NMDP CPRA manuscript is also a priority. This project has two goals. First is to establish a validation frame work for alternative CPRA metrics. To accomplish this there are ways in which to evaluate the CPRA reference panel. The first are changes for candidates moving on the waiting list in terms CPRA point groups, CPRA as a predictor of time to offer, access-to-transplant score metric for CPRA relative to all other factors, looking at the impact

from simulated allocation models endpoints, and relationship between sample size of the panel and precision for very high CPRA candidates greater than 99.95 and why they have higher transplants rates. This could possibly be published as a case report first. The second goal is to firmly establish that NMDP stem cell donors can serve as reference panel for CPRA values for organ allocation and explain why haplotype frequency comparison between panels initially failed validation, but passed validation after re-computing UNOS haplotype frequencies.

The study cohort that the NMDP CPRA manuscript is using to compare UNOS CPRA metric and NMDP CPRA metrics includes kidney transplant candidates added to the wait list between December 4, 2014, and December 31, 2016. They were selected from the UNOS registry with certain criteria; no multi-organ transplants (MOT) and at least one set of unacceptable human leukocyte antigens entered during listing with active time.

The researchers worked on how CPRA should be measured. It can be measured in different ways such as the minimum CPRA for all registration events, the maximum, or the average. Analysis was done and the longest duration made the most sense. This means that it was decided to go with the listing where the unacceptable antigens stay the same the longest. A member presented a figure that showed the distribution of UNOS's CPRA value with the longest duration while listed for each candidate in the study cohort. This distribution gives us the levels of sensitization based on UNOS's CPRA.

Next the researcher showed the validation in the shortcomings of the current UNOS CPRA in terms of linkage disequilibrium values. The right panel showed the recomputed haplotype frequency using the UNOS HLA data in star database which gave similar results to NMDP data. This showed that errors were in haplotype estimating/phasing, not in HLA data collected by UNOS. Also shows that the NMDP data set can be substituted for UNOS data in commuting CPRA values.

A member then presented a plot of the 10 most frequent HLA haplotypes for Caucasians in 3 panels. A: Standard UNOS reference panel B. NMDP reference panel C: recomputed UNOS reference panel. It was concluded that B and C haplotypes are very similar. The A panel haplotypes is unusual. Members were stressing that A is incorrect and B and C is better. This is because for B it is using a larger data set of approximately 4 million donors from NMDP and C is re-computing the 5 locus haplotype using UNOS antigens in the star database. Overall UNOS CPRA frequencies are different than NMDPs and a recomputed reference panel. To the show the differences in CPRA differently it was broken down by loci of the listed unacceptable HLAs of candidates.

The next figure was a scatterplot of CPRA NMDP and CPRA UNOS values for each candidate (using the UNOS CPRA value with the longest duration while listed). Overall it showed a systematic over estimation of CPRA while using UNOS frequencies. This was also showed in a heat map format. It illustrated how many individuals would be switching CPRA point group when comparing UNOS to NMDP CPRA data. The greatest difference is in 95 to 99 CPRA range. Member made a note that this data does not include HLA-DP. This is just describing the data from the NMDP CPRA manuscript. It shows how to compare the CPRA metric and will have to be done again when the DP data is received. Member and the research group wanted to establish a scheme for validating the metrics and measuring the impact.

In terms of CPRA as a predicator of time to offer there are no updates on this. Only a reminder that the original model showed that NMDP CPRA was a statically significant predictor of time to transplant on pre-KAS cohort but UNOS CPRA was not for highly sensitized patients above 80% CPRA.

The researcher then informed the committee that they have IRB approval to get simulation allocation model software.

The researcher also informed the committee that they were going to get help from a subject matter expert to help re-compute access- to-transplant score with alternative CPRA metrics. They will also look at what contributions CPRA will have on disparity if a different

measure of CPRA is used. The researcher believes that the disparity could be higher than geography if HLA-DP is included.

Lastly the research group are in the process of developing a new calculator to be able to compare a genotype based panel to a haplotype based panel. The idea is that they will get a deeper, more effective sampling with haplotype frequencies because they can predict frequencies of unobserved multi locus genotypes because of how the EM algorithm works which resolves allelic and phase ambiguity at the same time the data will be similar. EM is essential to get a haplotype panel to then derive a genotype panel from that.

Summary of discussion:

The researcher reminded the committee that their research group is looking to submit two more papers by the end of this year. The first being the NMDP versus UNOS CPRA at 5 locus and the second will be the match likelihood model for stem cell transplant which is a prerequisite for the 9 locus frequency paper.

While the researcher was presenting the idea about the 9 locus frequency paper, a committee member asked about sampling size and the researcher responded by saying there is a deep sample size and it will be reliable for 9 locus. The researcher also added that in the next update they will include counts and frequencies so members have an idea. In addition they will make the complete frequency data set available when the frequency data is published.

At the end of the update several members had questions. The first member asked if there is a discord between the current calculator and the new possible calculator, and are there differences with the current calculator that the committee should try to correct while we are waiting for the 9 locus paper. The researcher responded by saying that the timeline on making changes to these systems is long so it would be better to make one big change. UNOS staff responded that before the next meeting, staff will create a timeline for this project and will discuss how to get the project moving.

Another member asked about the longevity of the current typing data. They went on to say that right now there is more and more next generation testing being rolled out, therefore more patients are having a complete HLA typing performed. The member was concerned about the relevance of this data long term and asked if the data sets from NMDP would need to be periodically updated. The researcher responded by saying that HLA frequencies don't change that much over time in populations because haplotypes are inherited between generations and there is not enough selection pressure on the population to change the frequencies that much. However, they did suggest that it is worth updating every 5 years as the field gets more advanced, there will be high resolution matching for stem cell transplants.

The same member suggested another project using next-generation sequencing (NGS) based data for matching and molecular typing data in the match run in and the allocation system. They stressed that it would have a lot of impact especially with several people looking at HLA matching paradigms based on epitopes. People looking at outcome data at SRTR only have the antigen level data, even though a lot more detailed information is captured at the labs that is not making it into the system. This information is not used for matching and is not used to study outcomes on a large scale.

Upcoming Meeting

January 8, 2019