

OPTN/UNOS *Ad Hoc* Disease Transmission Advisory Committee
Report to the Board of Directors
November 16-17, 2009
Orlando, Florida

Summary

I. Action Items for Board Consideration

- *To be determined based upon Executive Committee Review of HTLV-1/2 proposal.*

II. Other Significant Items

- The Committee reviewed public comment feedback on its proposal to modify HTLV-1/2 screening requirements in preparation for consideration by the Executive Committee on October 23, 2009. (Item 1, Page 3)
- The Committee discussed the potential effects of the pandemic (H1N1) 2009 influenza virus on the transplant community, and reviewed a guidance document it developed to help members prepare for the influenza season. (Item 2, Page 8)
- The Committee completed its semi-annual review of potential disease transmission events reported to the Patient Safety System. (Item 3, Page 9)
- The Committee discussed its plans to review trends and patterns noted in bacterial, TB and fungal transmissions reported to the Patient Safety System and share this information with the transplant community. (Item 4, Page 9)
- The Committee reviewed malignancy data requested during the May 2009 meeting and heard an update on the Malignancy Subcommittee efforts to develop a guidance document for the transplant community to categorize the risk of donor tumor risk transmission. (Item 6, Page 11)
- The Committee received an update from its Policy Rewrite Subcommittee regarding modifications to policy sections 2.0 and 4.0. (Item 7, Page 15)
- The Committee discussed the need to develop a follow-up survey on serology and NAT testing trends in the OPO community to better understand current practices as more testing kits are eliminated. (Item 8, Page 16)
- The Committee discussed and finalized suggested additions and revisions to the donor, candidate and recipient data collection forms that will require OMB approval. (Item 9, Page 16)
- The Committee was updated on plans to create a bi-annual newsletter to report on general concepts and trends that have been recognized as potential transmission reports as reviewed. (Item 10, Page 16)

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Michael G. Ison, MD, MS, Chair
Michael Nalesnik, MD, Vice Chair

This report reflects the work of the Ad Hoc Disease Transmission Advisory Committee (DTAC) during its September 9, 2009, meeting in Chicago, Illinois, as well as all monthly case review conference calls. Additionally, the Committee's OMB Forms Review, Policy Rewrite and Newsletter Subcommittees have met by teleconference and LiveMeeting® since the DTAC reported to the Board in June, 2009.

1. Proposal to Modify Requirements for Mandatory HTLV-1/2 Testing for All Potential Deceased Donors

The *Ad Hoc* HTLV Advisory Group was created by the Committee to address concerns in the OPO community regarding plans to retire a frequently used HTLV-I/HTLV-II EIA assay kit on December 31, 2009. Currently, testing of donors for HTLV is required for all potential deceased organ donors in the United States (OPTN Policy 2.2.8.1). This Advisory Group was asked to advise the Committee on current options regarding alternate testing methods and whether subsequent changes to policy language may be necessary. The group included members from the DTAC, OPO, Operations and Organ Availability Committees, AOPO, CDC, FDA, HRSA, experts in the field of HTLV, as well as representatives from test kit manufacturers and labs that support many OPO's testing needs.

The Committee reviewed the Advisory Group's recommendations and supported the idea of retrospective donor testing. The Committee agreed that prospective testing with the high throughput testing platform as the OPO community's only FDA-licensed option would present significant logistical and financial concerns. In light of the low prevalence of transmission and expected disease, the Committee agreed that reporting of any positive HTLV-1/2 screening results (including any confirmatory testing) and careful follow-up of recipients receiving confirmed HTLV positive organs (with this information captured in the OPTN's Patient Safety SystemSM) was an appropriate and cautious response to the situation. All data collected on donor HTLV-1/2 status, confirmatory testing (including test system used, sample type tested, and results) and recipient follow-up will be reviewed in 2 years and used to make long term decisions regarding HTLV testing requirements. Further, diagnostic companies should be encouraged to develop other HTLV assays that will lend themselves to prospective testing in the future.

The Board of Directors considered the Committee's plans to address HTLV testing requirements during its June 22-23, 2009 meeting. Board members agreed that continuing to require prospective testing when the remaining FDA-licensed test kit still does not differentiate between HTLV-1 and HTLV-2 may not be practical or feasible, considering the logistical barriers. After lengthy discussion, the Board voted to discontinue the requirement of prospective HTLV testing for deceased donors. The Board further directed that retrospective testing with confirmation shall be performed on all deceased donors. Implementation of this policy should be delayed to permit a minimum forty-five day public comment period and review by the Executive Committee and there shall be a two-year window for retrospective testing.

As a result, the Committee released its proposal to modify requirements for mandatory HTLV-1/2 testing for all potential deceased donors for public comment from August 17 through September 30, 2009 (**Exhibit A**).

The Committee reviewed committee, individual and regional public comment feedback during its September 9, 2009 meeting in Chicago and a subsequent conference call on October 1, 2009 (see **Exhibit**

A, page 14). The Committee recognized that there were several themes that emerged from the public comment:

- Strong support for removal of the requirement for prospective screening of deceased donors for HTLV-1 and 2.
- Consistent comments about several issues about the proposal for retrospective testing:
 - Concern that this represented research. The Committee feels that this does not represent research since it will be establishing a community standard and collecting data, as is currently done with most other required screening tests, on results of this screening. The Committee will then correlate these results with recipient outcomes to inform future policy.
 - Concern about informing recipients about results. Many suggested that recipients should not be informed about the results since there is no established screening, monitoring, or treatment options. The Committee is concerned that failure to inform recipients may result in legal risk if disease transmission occurs.
 - Disagreement about the need for retrospective testing as the current data suggests that there is not a significant risk of transmission. The Committee notes that there is no data to confirm whether the donors were truly infected with HTLV-1 in current OPTN data (due to high false positive rate, apparent high frequency of HTLV-2 infection in donors, and no requirements for confirmatory testing). As a result, the current assessment of the true risk of transmission is only an estimate backed with incomplete data. It was also noted that current American Association of Tissue Banks (AATB) guidelines require screening for HTLV-1/2.
 - Concerns regarding liability and the potential for litigation brought forth by recipients of organs from donors with HTLV-1 confirmed post-transplant. The Committee is sensitive to these concerns and will provide guidance regarding informing recipients and recipient follow-up in a guidance document to be presented to the Board of Directors in November if this proposal is passed. The Committee acknowledges these concerns believe that informed consent of candidates and careful explanation of the risks associated with transplant should mitigate these concerns. It was noted in the briefing paper that West Nile Virus has a higher incidence of occurrence and similar neurologic sequelae, yet donor screening is not required.
 - Concern that this would establish a precedent for retrospective screening for other uncommon infections. The Committee feels that the unique circumstances of this situation should be pointed out; i.e., that screening for HTLV-1/2 was standard procedure, and that unilateral discontinuation of the testing system necessary to support rapid screening is an unprecedented event and calls for a specific response limited only to this virus.
 - Concern that a two year period of retrospective testing will not provide adequate data to make this a worthwhile effort. The Committee agrees that the small number of cases and the limited follow-up may not capture the risk, if small, of disease transmission. This approach, though, would capture information on all donors and recipients and provide an early indicator (i.e. if several transmissions were recognized vs. no transmissions at all)

of the impact of the change in policy. The data, though limited, may allow for future evidence-based policy making regarding HTLV screening.

- Concerns from a small number of OPOs that will have prospective access to HTLV-1/2 screening. Will policy language require that they complete retrospective testing? The Committee believes that OPOs with prospective access to the FDA-licenses testing platform for HTLV-1/2 screening should certainly be able to complete this testing prior to transplant. However, confirmatory testing to differentiate between HTLV-1 and HTLV-2 will still be required on all screen positive samples. This confirmatory testing may still be completed retrospectively.

After review, it was agreed that respondents to the public comment did not specifically address issues related to the quality of the current data. There are still significant challenges:

- There are no data to confirm whether the donors were truly infected with HTLV-1 in OPTN/UNOS data (due to high false positive rate, apparent high frequency of HTLV-2 infection in donors, and no requirements for confirmatory testing). As a result, the current assessment of the true risk of transmission is only an estimate backed with incomplete data;
- No robust reporting system is in place to capture all complications related to potential transmission, as clinicians may be mistaking HTLV-related symptoms for other causes. This would mean that HTLV transmission cases might not be recognized or reported as potential transmissions to the Patient Safety System); and
- There will be logistic challenges for many OPOs with accessing the only FDA-licensed testing platform available after 1/1/2010.

Further, the Committee is concerned that there will still be some donors who have retrospective testing performed if HTLV screening is no longer required of organ donors since current policy requires such screening in tissue donors. Approximately one-third of organ donors are also tissue donors. There was apprehension that if HTLV screening was eliminated for organ donors yet still completed for tissue donors without the ability to require follow-up confirmatory testing, many more recipients could be told that they may have HTLV-1 when no risk may exist (due to the high false positive rate or HTLV-2 infection).

As a result of this, the Committee agreed that screening and confirmatory test results should be acquired to truly inform future policy decisions related to HTLV screening.

The Committee sees three approaches to address the current situation:

- Retrospective donor screening and follow-up confirmatory testing on all screen positive samples for a period of two years as outlined in the Committee's public comment proposal.
 - Public comment feedback has highlighted issues related to potential legal implications or liability issues for OPOs and transplant centers related to informing recipients of infection with an untreatable infection. Further, the small number of cases and the limited follow-up may not capture the risk, if small, of disease transmission. This approach, though, would capture information on all donors and recipients and provide an early indicator (i.e. if several transmissions were recognized vs. no transmissions at all) of the impact of the change in policy.

- Discontinue prospective donor screening and conduct a formal research study to collect data on frequency of HTLV-1 infection in donors and risk of transmission to recipients.
 - This approach would overcome many of the logistic challenges highlighted in public comment while still allowing the collection of information needed to inform future policy. Challenges of this approach would include securing funding for such a project (as there is currently no mechanism in place to facilitate and fund such a program) and a smaller number of cases would be included since, logistically, only some OPOs may be willing to participate and funds would likely not be sufficient to do a truly national study. This smaller denominator might result in a longer study period or an underestimation of impact of the potential for HTLV-1 transmission via organ donation.
- Removal of all HTLV screening requirements for deceased donors based on the available data and public comment feedback.
 - Although this is the predominate opinion from public comment, the data that is currently available (and outlined in the public comment proposal) is based on limited data and may not accurately reflect the actual number of recipients who have received HTLV-1 positive organs due to the high rate of false positive screening results, the high apparent incidence of HTLV-2 infection in organ donors, and the fact that further confirmatory testing was not required.

As such, the Committee still feels strongly that additional data needs to be collected on: (1) the frequency of confirmed HTLV-1 infection in the donor pool, (2) the identification of risk factors for HTLV-1 infection among donors, and (3) the impact of implanting organs from an HTLV-1 infected donor into an uninfected recipient (though the OPTN does not collect pre-transplant recipient HTLV data). The Committee does not feel that recognition by the physician(s) caring for an organ recipient can be depended upon because malignancies may occur late post-transplant and not be considered as a potential sequellae of HTLV-1 transmission, and that milder neurologic complications may be attributed to non-infectious causes- particularly if they are transient or self-limited. Collection of this data as part of a dedicated research project would overcome many of the legal and logistic issues raised by public comment; however, there is not a current mechanism to fund and facilitate such a study. Requiring national retrospective testing is associated with significant logistic and legal challenges but would most efficiently collect the data to potentially inform future policy.

It was recognized that receiving retrospective results may certainly cause anxiety in recipients and concerns regarding liability for transplant professionals. Given the rapid development of disease in a small number of transplant recipients, it is evident that immunosuppression may play a part in HTLV-related disease developing more quickly than in non-immunosuppressed individuals. With this knowledge, immunosuppression may be adjusted, at the discretion of the individual transplant centers, in hopes of minimizing the impact of disease transmission; such an intervention is untested. It was also noted that related neurologic disease may be misdiagnosed without the knowledge of confirmed HTLV-1 infection. Misdiagnosis could result in incorrect and even potentially harmful treatment for recipients of HTLV-1 positive organs that may develop neurologic diseases.

A very small number of OPOs (less than ten that the Committee is aware of) will still have prospective access to the FDA-licensed platform available for HTLV-1/2 screening as of January 1, 2010. These OPOs raised concerns during regional meetings regarding the proposed policy language's strict specification for retrospective testing, and questioned whether continuing to test donors prospectively would be a potential policy violation. The Committee believed that these OPOs should still be allowed to

test prospectively if they had this access. As a result, the proposed language was modified accordingly, as noted below.

Staff recommended that the Committee should be prepared to outline to the Executive Committee what should be expected if this screening test is eliminated, as the Executive Committee will probably look to this group's expertise as it works to address this issue. Much of this information is also included in a soon to be published journal article.

After a final review of all comments received, the Committee submitted the following for consideration by the Executive Committee:

****RESOLVED**, that Policy 2.2.3.1 (For All Potential Donors) shall be amended as set forth below, effective January 1, 2010.

2.2.3 The Host OPO must perform the following pertinent FDA licensed, approved, or cleared serological screening tests and provide this information to the OPO or transplant center. In the event that such screening tests are not commercially available prior to transplant, then a FDA approved diagnostic test is permissible to assess the donor. The Host OPO must document in the donor record circumstances when such information is not available. In all cases, the transplant center will make the clinical decision whether to accept or reject the organ based on the available data or identify the need for additional information. The Host OPO may be requested to provide additional information if possible in addition to the information required on all donors. Required tests should include:

2.2.3.1 For all potential donors:

- ABO typing with sub-typing for ABO-A donors;
- FDA licensed Anti-HIV I, II;
- CBC;
- Electrolytes;
- Hepatitis screen serological testing; including HBsAg, HBcAb, and Anti-HCV;
- VDRL or RPR;
- Anti-HTLV-1/II; Prospective or Retrospective HTLV-1/2 antibody testing. Prospective testing may be completed in lieu of retrospective testing, but is not required. (Confirmatory testing to differentiate between HTLV-1 and HTLV-2 must be completed on all screen positive tests.)
- Anti-CMV;
- EBV serological testing;
- Blood and urine cultures;
- Urinalysis within 24 hours prior to cross clamp;
- Arterial blood gases;
- Chest x-ray; and
- Serum Glucose.

Additional Organ Specific information is required as follows:

[...]

If retrospective testing is passed by the Executive Committee, a guidance document to aid OPOs and transplant centers in adopting this new process will be created in cooperation with the OPO, Transplant Administrators and Organ Availability Committees for review during the November 2009 Board Meeting.

The Resource and Impact Statement for this proposal can be found in **Exhibit B**.

2. Potential Effects of the Pandemic (H1N1) 2009 Influenza Virus on the Transplant Community

The Committee reviewed a guidance document it developed regarding H1N1 and implications for transplantation (**Exhibit C**). This information is currently posted on the OPTN and UNOS websites for members.

Several members shared anecdotal information regarding patient care and even an organ offer received from a confirmed positive individual. All agreed that there is little information available to consider when making decisions on whether to accept these organs. After some discussion, members made the following suggestions of key information of which both OPO and transplant center personnel should be aware of during the organ offer process for donors with confirmed or potential H1N1:

OPO personnel should consider the following as they as evaluate potential donors:

- Did the donor present with or have during their hospital course, a febrile illness or respiratory distress?
- Does the potential donor have recent history of:
 - Documented H1N1?
 - Household exposure to febrile illness?

IF YES TO ANY, additional testing is warranted, and should be discussed with an Infectious Diseases consultant or OPO medical director.

For donors with proven or suspected influenza, the OPO should obtain the following specific information. Transplant centers should consider this information in order to make informed decisions regarding organ acceptance includes:

- Date of onset of flu-like illness
- Initial diagnosis and date
 - Collection method (nasal swab, nasal wash, throat swab, BAL, other)
 - Testing used- keep in mind that the relative sensitivities of different tests vary greatly (rapid antigen test, culture, PCR, other)
 - Results
- Was subsequent testing completed?
 - Date(s) performed
 - Collection method (nasal swab, nasal wash, throat swab, BAL, other)
 - Testing used- keep in mind that the relative sensitivities of different tests vary greatly (rapid antigen test, culture, PCR, other)
 - Results
- Management issues:
 - Drug for treatment
 - Dosage
 - Date initiated

- Duration of therapy and time of offer
- Cause of death- was it specifically flu related?

Members agreed that guidance should be available to OPOs and transplant centers, but that local infectious disease must be involved to consider all cases independently. It was questioned whether H1N1 testing should be required for all donors. Because the rapid test is not sensitive enough to be counted upon, the Committee agreed that this and/or prophylactic antiviral treatment would not necessarily be a practical approach. OPO representatives were encouraged to talk with their medical directors and consider all available resources as they plan for the pandemic.

Any suspected or confirmed transmissions of H1N1 from donor to recipient should be reported to the Patient Safety System per current policy. The Committee considered whether data could be collected for all recipients receiving organs from known H1N1 positive donors. Recommendations to survey members to collect this information, with the understanding that completion of these surveys would be voluntary, were made to Patient Safety staff. Because such data collection would be outside of the currently defined functions of UNOS staff, a resource analysis will be developed and taken to the executive leadership for consideration to determine if there is adequate staff to complete this request. It was recognized that programming and funding for such an effort would be difficult to obtain.

Concerns were also raised that the initial guidance document posted on the OPTN and UNOS websites may be “buried” in the list of other more recent postings. Staff will share these concerns with the Communications Department to determine if a separate link button or side bar accent can be added to the sites to carry members to all H1N1 documentation. In the interim, members asked that the current documentation be updated to include the specific information related to donor evaluation and organ selection as noted above.

An H1N1 Subcommittee, consisting of OPO and Infectious Disease representatives from the Committee will meet periodically to review current concerns and update the Guidance document as appropriate.

3. Semi-Annual Case Review

The Committee reviews information pertaining to ongoing and recently reported potential disease transmission cases during monthly case calls. This work is conducted toward building a body of evidence that will enable the Committee to assess the risk of unanticipated disease transmission involved in organ transplantation. During its September 2009 meeting, the Committee reviewed cases 1 through 71, reported during the first half of 2009 in order to agree upon classification (**Exhibit D**) for determining the likelihood of the transmission event being donor-derived based upon the information provided by the OPO and recipient transplant centers.

It was suggested that a new category be created to better capture case classification. A suggestion was made to designate an indeterminate or unlikely designation to capture those cases that cannot be specifically excluded but do not appear to involve donor transmission. A formal definition will be created for this classification after further discussion, and it will be employed for future case review.

4. Trends and Patterns in Reported Potential Disease Transmission Events

Dr. Ison discussed the need to review all cases reported to the Patient Safety System by category to consider overarching themes (**Exhibit E**). This will be helpful discussion to inform the Operations and Safety Committee on potential opportunities for improvements upon current process or systems.

Currently, a separate library for bacterial cases has been set up to streamline the review process. An overall review of all bacterial transmission cases will be led by Dr. Emily Blumberg. Dr. Blumberg noted that approximately half of the potential bacterial transmissions reported involved resistant organisms. Concerns regarding the delay in sharing culture results with recipient centers were discussed. An OPO representative on the Committee noted that such delays sometimes stem from cultures drawn by hospital staff rather than OPO staff. Going back to the hospital to collect final culture results can be difficult because the patient is deceased and records are closed before final results are reported. Electronic medical records can be difficult for OPOs to navigate, and getting access to the records can be difficult as well. Members agreed that there should be some mechanism for OPOs to be allowed access to patient records to collect accurate donor information efficiently. Log-in permissions require OPO staff to have paperwork on file with each hospital in their DSA, and that the hospitals and OPOs keep this log on information up-to-date. It was also noted that cultures drawn by an OPO might not show the full extent of infection due to treatment already underway that could cover true culture results. On a related note, members discussed frustration regarding the delay in getting autopsy results, where several potential transmissions were discovered. These may all be issues that the Operations and Safety Committee considers in the future as part of the full donation and transplantation process.

The Committee has reviewed 12 cases of potential TB transmission this year alone, a sharp spike from years past. Donor information regarding risk factors will be looked at closely, with a focus on screening for known risk factors (i.e. foreign born, prior incarceration, etc.). Dr. Ison questioned the prevalence of some of these risk factors in the total population. Similar to concerns regarding bacterial cases in general, there appears to be a delay in reporting final results after Acid Fast Bacilli (AFB) cultures are completed and *Mycobacterium tuberculosis* is identified. Delays in reporting of up to six weeks have been noted in cases reported to the Patient Safety System. Dr. Ison noted that there may be an upcoming study for Quantiferon donor testing. If this is the case, the study will be completed with several OPOs. This type of donor screening may help decrease the number of unexpected transmissions.

The Committee then discussed plans to review fungal cases reported to the Patient Safety System. Of note, there have been a number of potential transmissions of *coccidioides immitus* from donors, producing coccidioidomycosis in recipients. This fungal infection is prevalent in the southwestern United States. As a result of the number of cases in Region 5, there has been increased prophylactic therapy (fluconazole) in all recipients at a number of transplant centers. Screening tests are being considered for all recipients as well. While the problem is regional, one must account for donors that originate in that part of the country and have travelled or moved elsewhere and could be carrying the fungus. It is important for OPOs to consider this when taking medical-social histories and determine whether screening may be appropriate. This group is considering some regional data and will have a more in depth report at a future conference call. The AST has revised guidelines for coccidioidomycosis, and they are expected to be published in November 2009. It was questioned whether testing for *coccidioides immitus* should be included in DonorNet[®]. Staff outlined the process for requesting programming related to changing DonorNet[®] forms as well as donor, candidate and recipient forms that require approval every three years by the Office of Management and Budget (OMB).

The Committee will partner with the Operations and Safety Committee to consider some of these concerns from an operational standpoint and determine if policy changes may ultimately enhance patient safety in these areas.

5. Case Workflow and 45-Day Report Reviews

UNOS staff provided members with an overview of upcoming plans to further streamline the case review process during the September 2009 meeting. Staff will begin creating a case review summary for each potential disease transmission event. This document and the 45-Day Report will be posted for review

along with a brief survey for each case. This survey will help Staff in classifying each reported event using one of the categories for determining probability of donor-derived illness:

- Proven – Disease in donor and at least one recipient
- Probable – Disease in one or more recipients with suggestive data about the donor
- Possible – Evidence to suggest but not prove transmission
- Intervention without Documented Transmission – no transmission occurred, typically because antimicrobials were used.

Staff demonstrated the draft survey function that is being created in SharePoint®. Committee members will have single page to access the summary and 45-Day Report as well as this survey. Staff plans to have a list of open surveys appear on the entry for the external SharePoint® site as a reminder for members. A January 2010 start date is planned for this effort, with piloting to take place later this year.

Staff also reviewed the latest drafts of letters to be sent to OPOs with potential disease transmission cases with members. Three letter templates (**Exhibit F**) were considered: (1) case closed, donor transmission is ruled out; (2) case closed, based upon available documentation, committee cannot determine if the transmission was clearly donor-derived; and (3) case remains open after 45 day report and additional information is requested. These three letters have been reviewed and approved by Legal Counsel and are ready to employ once the “case closing” process is finalized. A letter will be sent once a case review is complete (including the 45 day report) and assignment of a classification category is made. The Chair will review all letters before they are sent. The Committee was reminded that confirmed transmissions would not receive a letter. Legal counsel recommended that conference calls be held to discuss these cases to protect the confidential medical peer review.

6. Malignancy Subcommittee Update

The Committee was updated on the Subcommittee’s work to develop tumor transmission risk categories (**Exhibit G**). The group adopted an evidence-based approach to:

- Define an overall framework to categorize relative tumor-independent transmission risk;
- Populate risk categories with individual tumors according to the best data available; and
- Address special emphasis topics based upon DTAC cases or recent literature topics.

The Subcommittee worked to develop specific ordinaly ranked categories that would allow inclusion based on either nominal or objective data, recognizing anecdotal nature of the evidence. The Committee believes that the separation of category system from individual tumor listings facilitates updating the list regularly based upon what is learned. It was pointed out that the categories are based solely on estimated transmission risk, not tumor behavior or available therapy, and that clinical recommendations were provided without dictating practice. Categories are listed as follows:

Risk Category 0	no significant risk	use in any recipient
Risk Category 1	minimal risk	use based upon clinical judgment
Risk Category 2	low risk	use in recipients at significant risk without transplant
Risk Category 3	intermediate risk	not recommended; on occasion, life-saving transplant may be acceptable

Risk Category 4	high risk	discouraged accept in rare and extreme circumstances
Risk Category 5	unknown risk	use based on clinical judgment; evaluation incomplete or not available literature

Each of the categories was reviewed, and example tumor types were offered, with specific attention to renal cell carcinomas and central nervous system tumors.

Prostate adenocarcinomas and lung carcinomas have not yet been included in the risk categories at this time, and consideration continues. Currently, there are no recommendations for PSA screening or for whole organ frozen sections as a screen for prostate carcinoma in potential male donors. These screening practices were used in Europe, but do not seem to be practical or particularly helpful at this time.

The Subcommittee discussed a generic graded informed consent form, but felt it was outside of this group's scope. A consensus conference to consider donor tumors (U.S. and/or International) is desired, to involve the transplant community as a whole in this process. This idea will be discussed in further detail at a later date.

It was also reported that the Subcommittee's abstract "Assessment of Tumor Transmission Risk in Organ Donors with Active or Historical Malignancy" was accepted for oral presentation at the 10th ISODP and 16th European Transplant Coordinators Organization (ETCO) Organ Donation Congress in Berlin, October 4-7, 2009. The group continues to work on finalizing a manuscript for possible publication in a medical, pathology or transplant journal. This paper was originally created to be a guidance document for the transplant community in order to prevent unnecessary discard of organs that data has shown to carry little or no risk of transmission, and will ultimately require approval by the Board of Directors to be used as such once it is complete.

Incidence of Post-Transplant Malignancies and Utilization of Donors with a History of Cancer. UNOS staff presented additional data on the incidence of post-transplant malignancies and the usage of donors with a history of cancer during the September 9, 2009, meeting (**Exhibit H**). The Committee was interested in utilizing currently collected OPTN data to further investigate potential cases of donor derived and donor related malignancies in recipients.

This data included:

- Incidence of "adult" tumors reported post-transplant in pediatric recipients;
- Incidence of Post-Transplant Lymphoproliferative Disease (PTLD)/lymphoma in adult and pediatric recipients;
- Outcomes for recipients of organs from donors with or without a history of cancer; and
- Utilization of potential donors with central nervous system tumors.

The analysis of adult tumors in pediatric recipients included all deceased donor transplants in pediatric (0-17) recipients from 1999 through 2007. 12,013 transplants were performed with pediatric recipients, with the largest number of recipients receiving livers (4,452) and kidneys (3,557). Overall, 488 (or 4.1%) of these recipients developed a post-transplant malignancy. The vast majority, 386 or 3.5%, of these reports were for the development of PTLD/Lymphoma. The next largest category, including 41 cases, was recurrent tumors. Thirty-nine of the 41 cases involved liver recipients. Thirty-six recipients (0.3%) reported a post-transplant de novo tumor.

The analysis of PTLD/lymphoma included all transplants performed from 2003 through 2007. The rate of PTLD in pediatric recipients was found to be much higher than for adults across all organs and at all time points reviewed (1, 3, and 5 years post-transplant). The rate of PTLD at 3 years post-transplant on both adult and pediatric recipients was found to be lower for kidney recipients and highest for intestine recipients. Overall the five-year cumulative incidence of PTLD was much higher for pediatric recipients (3.26%) than adult recipients (0.91%).

Outcomes by donor history of cancer included an analysis of all deceased donor transplants performed from 1999 through 2007. In the case of liver and lung recipients, the percentage of recipients with any reported post-transplant malignancy was actually lower for the group receiving an organ from a donor with a history of cancer. Conversely, there was a higher percentage of heart, kidney and kidney-pancreas recipients with post-transplant malignancy in the group receiving organs from donors with a history of cancer. However, for all organs, the difference between the two groups was small.

An analysis of the utilization of potential donors with CNS tumors included eligible death data collected January 2008 through May 2009. During this time period, 92 (0.7%) eligible deaths had a reported cause of death of CNS tumor. This was the smallest category of both eligible deaths and recovered donors. The consent rate for this group (66.3%) and conversion rate (62.0%) for this group was lower than the overall consent (69.8%) and conversion (67.3%) rates respectively. It was noted that eligible deaths due to head trauma had the highest rates of consent and conversion. However, CNS tumors did have the second highest rate of organs transplanted per donor (OTPD), at 3.2. This was higher than the overall OTPD, and second only to head trauma deaths, at 3.8. Of note, most donor service areas (DSAs) did not recover more than one CNS tumor donor during the period of review, but one DSA recovered eight, making up 5.4% of their total recoveries.

After review, the Committee requested some additional data to clarify a few questions that were raised during the discussion. This information will be presented at the Committee's April 2010 meeting.

- Provide additional data on the incidence of "adult" tumors reported post-transplant in pediatric recipients.
 - Include information on the HCV status of the liver recipients with liver tumors.
 - Stratify results by donor age group and time from transplant to diagnosis of malignancy.
- Update the data on the incidence of PTLD in adult and pediatric recipients and stratify the results by different induction drugs.
- Additional data on patient survival rates and the incidence of post-transplant malignancies in recipients of organs from donors with and without a history of cancer.
 - Stratify results by recipient malignancy history.
 - Stratify results of transplants from donors with a history of cancer by the reported donor cancer free interval.
 - Provide data on recipient causes of death in each group.
 - Stratify results by adult versus pediatric recipients.
 - Examine incidence of post-transplant malignancies both including and excluding PTLD.

Post-Transplant Malignancies in Multiple Recipients of Organs From the Same Deceased Donor.

Additional descriptive information was presented on deceased donors from 2000 through 2007 where

more than one recipient of a donor's organs was reported to have a post-transplant malignancy at any time point after transplant (**Exhibit I**). This analysis included:

- Stratification of results by donor history of malignancy;
- Results both including and excluding PTLD/lymphoma cases;
- Additional information comparing donor age in this group as compared to those without post-transplant malignancy;
- Follow-up on cases with at least one donor-related tumor and additional de novo tumors reported on other recipients; and
- Determination of the size of recipient/donor subset that was reported to DTAC following the initiation of reporting guidelines in Policy 4.0.

During the analysis period, there were 157,443 transplants performed from 52,407 deceased donors. After accounting for transplants where one recipient received multiple organs from the same donor, a total of 153,702 transplant recipients were reviewed during this eight year period. The number of recipients per deceased donor ranged from one to eight. Three recipients per donor accounted for 32% of the donors. Only 11% of the donors had more than four organ recipients.

Including PTLD/lymphoma reports, 8,938 recipients (5.8%) reported at least one post-transplant malignancy. Excluding PTLD/lymphoma, 7,659 recipients or 5.0% reported post-transplant malignancies. Of these 7,659 recipients, the recipients of donors < 18 years of age had the smallest rate of post-transplant malignancy. No real difference was noted when comparing donor age groups of 18-29 with ages up to 69; however, recipients of donors ≥ 70 years of age reported the highest incidence of non-PTLD/lymphoma post transplant malignancies (6.7%).

Just over 15% of the donors transplanted in the analysis resulted in at least one recipient with a reported post-transplant malignancy. When PTLD/lymphoma cases were excluded, the total dropped to 13%.

When reviewing the group where PTLD/lymphoma was included, only 1.5% (776) of the 52,407 donors resulted in more than one recipient with a malignancy reported post-transplant. Conversely, when PTLD/lymphoma was excluded, the total dropped to 1.2% (598). Staff then explained her closer examination of these groups.

There were 37 cases of donors with two or more recipients where all recipients reported a post-transplant malignancy. This number drops to 30 when PTLD/lymphoma cases are excluded. In seven of the 37 cases, there were three or more recipients for a donor. When the PTLD/lymphoma cases are excluded, there appears to be a trend towards older donors in cases with more recipients having post-transplant malignancies. In the cases where 3 recipients were transplanted (the largest category), the median donor age increased in each category of increasing number of recipients with post-transplant malignancies. This increase went from a median age of 42 years in those cases with no recipients reporting malignancies, to 49 years in the five cases where all three recipients reported a post-transplant malignancy.

Staff provided details on the donors' gender, age, history of cancer and time to recipients' first reported malignancy for those donors resulting in two or more recipients with a reported post-transplant malignancy. The group of donors with a first malignancy reported 2+ years post-transplant accounted for 31.6% of the cases examined when PTLD/lymphoma was included and 34.6% of those where PTLD/lymphoma was excluded. When continuing to exclude PTLD/lymphoma, there were 111 cases (18.6%) with first reporting within six months of transplant, and another 108 (18.1%) reported within one year post-transplant.

Of the 598 donors with more than one recipient reporting a non-PTLD/lymphoma post-transplant malignancy, the most common donor age group was 18-29 (35.1%), followed by 40-49 (18.1%), and 30-39 (15.9%). Donors age 60 or older accounted for only 30 of the cases examined. It was noted that two-thirds of the cases involved male donors, and less than 2% of the donors had a reported history of cancer.

A total of 52 post-transplant malignancies were reported as donor-related tumors on the Post-Transplant Malignancy forms between January 2006 and May 2009. Of these reports, 16 (30.8%) had also been reported as potential donor transmission events through the Patient Safety System. Of note, those not reported to the Patient Safety System had a median time to diagnosis of 2.6 years as compared to only 214 days for those that had been reported. Members requested that this information be updated and presented at each face-to-face meeting in the future.

After review, members questioned whether cases not reported to the Patient Safety System should be evaluated to confirm donor-related tumor growth. There was great concern as to the number of cases being reported on follow-up forms and NOT reported through the Patient Safety System, and a suggestion was made to include a pop-up to remind centers to report to the Patient Safety System if donor transmission is suspected, per policy. Some additional information was requested to examine this issue. As a result, staff was asked to provide additional data on those cases reported as donor related post-transplant malignancies and not reported to the Patient Safety System during the April 2010 meeting.

- Update the table provided previously looking at the number of cases reported to each system.
- Contact transplant centers to validate the information provided on donor related tumors reported on the follow-up forms but not included in the Patient Safety System. Provide the results of this validation to the committee

7. Modifications to Policies 2.0 and 4.0 - Proposal Timeline and Discussion

The Committee received an update on efforts to rewrite policies 2.0 and 4.0 by the Policy Rewrite Subcommittee. The overall rewrite effort is meant to move language related to OPO donor evaluation and up to the point of recovery to section 2.0 and language related to reporting and potential disease transmission in policy 4.0. Due to unforeseen time constraints related to the Committee's efforts with HTLV and H1N1, this project has been delayed. It was agreed that additional input from both the OPO and the Operations and Safety Committees will be beneficial, as much of policy 2.0 covers OPO process. The Committee anticipates this proposal going out for public comment in early 2010. Staff noted that a complete re-write of all current policy language is underway by staff. These particular sections will be the first sections that go through the rewrite process to include plain language.

The Committee discussed the need for creating a Patient Safety Contact at all OPOs and transplant centers. This position would make communication of important information related to potential transmission more efficient and may be included in both bylaw and policy language.

Committee members also want to redefine the 45-day follow-up period for potential malignancy transmissions. This amount of time is not helpful in following recipients, and the topic will be re-visited by the Malignancy Subcommittee to determine whether 6 months or a year may be more appropriate.

The Committee then discussed the time interval related to reporting potential transmission events. Current policy requires that reports be made to the Patient Safety System within one working day. Members were concerned that a 24 hour reporting requirement would be more appropriate in instances where a case was acknowledged on a Friday, but not reported until the next week. Staff noted that there were a small number of members that are not reporting or are reporting events beyond a working day. An

example of a positive blood culture found on a Friday and reported four days later due to a holiday weekend would not be a policy violation but could be detrimental to recipient safety. Members agreed that a 24 hour period appears to be a reasonable expectation for all reports. Members discussed whether member education would also help resolve concerns in this area, but were supportive of incidents involving late reporting going to the Membership and Professional Standards Committee to be considered as potential policy violations.

8. Serology and NAT Updates

The Committee surveyed all OPOs regarding serology testing in October 2008 to learn more about current testing practices. The need for a follow-up survey of OPOs was discussed as a tool to re-evaluate how members were addressing the current and upcoming changes to testing platform availability. Members agreed that questions regarding nucleic acid testing (NAT) should also be included this time. The OPO Committee surveyed members on this last year, so NAT-related questions were not included on this Committee's October 2008 survey.

The survey did not have a 100% response rate, so members agreed that it would be important to partner with AOPO. Plans to revamp the survey format in order to be more user friendly were discussed. The last version included many write in fields that required a great deal of fact checking and clarification. Drop down selections will be included to lessen the burden for OPO members completing the form and also to make data extraction and review easier for staff.

The Committee discussed sending out the survey in spring 2010, but a recommendation was made to hold this effort until a manuscript regarding NAT testing is published by AJT. This publication is expected later in 2010. It was agreed that it would be wise to wait and see if this paper changes testing practices before surveying the community.

A new Survey Subcommittee will be named to begin developing the survey in 2010.

9. OMB Donor, Candidate and Recipient Forms Review Subcommittee Update

The Committee received a brief update on forms revisions, the Office of Management and Budget (OMB) review and approval process, and progress made by this Committee to date during the September 9, 2009, meeting (**Exhibit J**). The Committee reconvened by teleconference on September 21, 2009 for a final review of recommended revisions and rationale for each of these recommended changes to the current Deceased Donor Registration (DDR), Transplant Candidate Registration (TCR), Transplant Recipient Registration (TRR), Transplant Recipient Follow-Up (TRF), Living Donor Registration (LDR), and Post-Transplant Malignancy (PTM) forms used to follow organ donors, transplant candidates and transplant recipients. The Committee was asked to focus their expertise on serology and malignancy data. After considering additional feedback and comments from other organ specific and constituent committees, members finalized their recommendations.

UNOS staff will forward all recommendations on to the Ad Hoc Data Management Group and the Policy Oversight Committee for review before public comment and review by the Board of Directors.

10. Newsletter Subcommittee

The Committee was updated on the status of this project. Several articles have been turned in, and are now being reviewed and/or revised. The group hopes to publish its first electronic newsletter in late fall, sending it to all members. The first newsletter will focus on introducing the document to members and some brief general articles on TB and bacterial transmissions.

It was questioned whether the newsletter could be set with a counter to track the number of readers. This would get a metric of how many people are considering the information. Staff will talk with the Communications Department to determine if this can be done. A second recommendation was made to include a brief survey asking for job title and whether the reader found the information to be helpful and/or interesting.

11. Review of Policies and Bylaws Issued for Public Comment

The Committee reviewed the seven proposals released for public comment on July 10, 2009, during its September 9, 2009, meeting.

1. Proposal to Include Non-Directed Living Donors and Donor Chains in the Kidney Paired Donation Pilot Program *Kidney Transplantation Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

2. Proposal to Improve the ABO Verification Process for Living Donors (Affected Policies: Policy 12.3.1 (ABO Identification) and 12.8.1 (Reporting Requirements)) *Living Donor Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

3. Proposed Guidance for the Medical Evaluation of Living Liver Donors *Living Donor Committee*

- After reviewing the proposal, Committee members shared general concerns that there are no specific policy requirements for living donor testing, only recommendations. Several members agreed that minimum testing requirements for living donors should be the same as that for deceased donors, if not more stringent for living donors, because there is more time available for testing.

It was noted that insurance coverage for testing living donors can be difficult. These tests are often not covered under the potential recipient's insurance. If a potential living donor is ultimately ruled out, he or she could be left to cover the expenses of additional testing. The Committee discussed whether expense should be considered over patient safety. Members questioned whether additional testing could be requested as a last step in the living donor evaluation process. Concerns were voiced that the presence of longstanding latent pathogens in potential living donors might not be suspected, even after careful evaluation over a long period of time.

After discussion, the Committee voted to support the proposed guidance document (10 in favor, 0 opposed, 0 abstentions) with the following recommendations:

- Appropriate questions be included as part of the medical-social evaluation to determine whether a potential living donor may fall into a high risk category. There is no mention of questions related to sexual activity, etc. in the Social History section of the guidance document.
- There are no current FDA-licensed HTLV-1/2 screening tests that differentiate between HTLV-1 and HTLV-2. For this reason, the "HTLV 1" notation under Transmissible Disease Testing header should be edited to read "HTLV-1/2."

- EBV and TB testing should be moved to the section of typically included screening tests and out of the section that suggests tests depending on transplant program preference.
- Coccidioidomycosis testing (cocci titer) should be added to the list of tests based upon transplant program preference and donor risk profile due to its high prevalence in the Southwest U.S. and the difficulty to discern its presence in living or deceased donors without testing.

The Committee believes that minimum standards for living donor testing should be established, and is happy to partner with the Living Donor Committee and provide guidance in the development of such policy requirements.

4. Notification Requirements for OPOs, Transplant Hospitals, and Histocompatibility Labs When Faced with an Adverse Action Take by Regulatory Agencies (Affected Bylaws: Appendix B (Sections I, II, III): Criteria for OPO, Transplant Hospital, and Histocompatibility Laboratory Membership) *Membership and Professional Standards Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

5. Proposal to Change the Bylaws to Reconcile Discrepancies in Patient Volume Requirements for Full and Conditional Program Approval when Qualifying Kidney, Liver and Pancreas Primary Transplant Physicians (Affected Bylaw: Appendix B, Attachment I) *Membership and Professional Standards Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

6. Proposal to Add Language to the Bylaws Requiring Transplant Center and OPO Members to Follow State Law Regarding Anatomical Gifts (Affected Bylaws/Policies: Article I, Sex 1.10, Appendix B, Section I and II, and Policy 3.4 (Organ Procurement, Distribution and Alternative Systems for Organ Distribution or Allocation) *Membership and Professional Standards Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

7. Proposal to Change Requirements for Labeling and Packaging Organs Procured by Visiting Transplant Center Teams and for OPO Labeling of Tissue Typing Materials (Affected Policy: 5.0 (Standardized Packaging, Labeling and Transporting of Organs, Vessels and Tissue Typing Materials) *Organ Procurement Organization (OPO) Committee*

- Upon review, the Committee determined that it had no comment regarding this issue.

The Committee's proposal to modify requirements for mandatory HTLV-1/2 screening was released for public comment on August 17, 2009. The Committee reviewed proposal feedback (see **Exhibit A**) during its September 9, 2009, meeting in Chicago and during a follow-up conference call on October 1, 2009. Please see item one in this report for additional detail.

12. Welcome to New Members and Orientation

The Committee welcomed three new members. After introductions, staff then provided a brief orientation, including the Committee's charge, background on the case review process and an introduction of the

Committee's goals for 2009-2010 (**Exhibit K**). Additional detail was provided to members in two general orientations sessions hosted by staff via teleconference.

All Committee members were encouraged to share ideas for presenting or sharing information with professional societies and other groups with the Chair or staff. This provides an excellent opportunity for sharing findings and ultimately helping improve upon patient safety practices.

AD HOC DISEASE TRANSMISSION ADVISORY COMMITTEE

		07/09/2009	08/13/2009	09/09/2009	09/17/2009
NAME		Live Meeting/ Teleconference	Live Meeting/ Teleconference	In Person	Teleconference
Michael Ison, MD	Chair	X	X	X	X
Michael Nalesnik, MD	Vice Chair	X	X	X	X
Emily Blumberg, MD	At Large		X	X	X
Kevin Carney, RN, CCTC	At Large				
Peter Chin-Hong, MD	At Large	X		X	
J. Michael DiMaio, MD	At Large			X	X
Jon Gockerman, MD	At Large	X			X
Michael Green, MD, MPH	At Large	X		X	
Richard Hasz, Jr., MFS	At Large		X	X	X
Bernard Kubak, MD, PhD	At Large	X		X	X
Daniel Lebovitz, MD	At Large		X	X	X
Timothy Pruett, MD	At Large	X			X
Alison Ballew Smith, RN, BSN	At Large	X	X	X	
Lewis Teperman, MD	At Large		X	X	
Brahm Vasudev, MD	At Large	X		X	
James Bowman III, MD	HRSA Ex Officio			X (PHONE)	
Elizabeth Ortiz-Rios, MD	HRSA Ex Officio		X	X	
Bernard Kozlovsky, MD, MS	HRSA Ex Officio	X		X (PHONE)	
Matthew Kuehnert, MD	CDC Ex Officio	X			
Shandie Covington, BS	Committee Liaison	X	X	X	
Kimberly Parker, BS	Support Staff	X		X	X
Sarah Taranto	Support Staff	X	X	X	X
Kimberly Taylor, RN	Support Staff	X	X	X	X
Lin McGaw, RN, MEd	Support Staff				
Stacey Burson	Support Staff	X	X	X (PHONE)	
Mary D Ellison, PhD, MSHA	Support Staff			X	
Robert Metzger, MD	Support Staff	X		X	
William Bower, MD	CDC	X	X	X	X
Debbie Seem	CDC	X	X		