At-a-Glance

- **Proposal to standardize MELD/PELD exception criteria and scores**
- **Policy affected: Policy 3.6.4.5 (Liver Candidates with Exceptional Cases)**
- **Liver and Intestinal Organ Transplantation Committee**

  The MELD and PELD scores estimate a candidate's likelihood of dying on the waiting list within three months without a transplant. These scores are used to prioritize offers for liver transplant candidates. These scores allow candidates to be ranked based on their relative urgency for a liver transplant. However, depending on the cause of the liver disease, a calculated MELD/PELD score may not always reflect a candidate's need for a liver transplant. The Liver and Intestinal Organ Transplantation Committee is proposing standardized criteria and MELD/PELD scores for candidates with six diagnoses: hepatopulmonary syndrome, cholangiocarcinoma, cystic fibrosis, familial amyloidosis, primary hyperoxaluria, and portopulmonary hypertension. The Committee felt that candidates with these diagnoses should be treated consistently throughout the country.

- **Affected groups**
  Pediatric and adult liver candidates, transplant surgeons, transplant physicians, transplant coordinators, OPO procurement coordinators, OPO executive directors, OPO medical directors, OPO PR/public relations/public education staff, transplant administrators, and transplant public relations/public education staff

- **Specific requests for comment**
  Transplant coordinators and physicians should consider the following questions when reviewing this proposal:

  - Will standardizing MELD/PELD exception scores disadvantage candidates in certain regions?
  - Are there any significant negative impacts on candidates as a result of this policy addition?
  - If you have concerns or objections about the proposed criteria or MELD/PELD score assignment for a **specific** diagnosis) or diagnoses) but are in favor of other aspects of the proposal, **please** note that in your comment.

  All readers should not feel limited to the questions above. They are meant only to highlight key issues within the proposal that may specifically interest some readers.

Proposal to Standardize MELD/PELD Exception Criteria and Scores

Policy affected: Policy 3.6.4.5 (Liver Candidates with Exceptional Cases)

Liver and Intestinal Organ Transplantation Committee

Summary and Goals of the Proposal:

This proposal will establish criteria and MELD/PELD scores for candidates with hepatopulmonary syndrome, cholangiocarcinoma, cystic fibrosis, familial amyloidosis, primary hyperoxaluria, and portopulmonary hypertension. This proposal should provide consistency in scores assigned to liver transplant candidates with these diagnoses.

Background and Significance of Proposal:

The MELD/PELD allocation system was implemented on February 27, 2002. The MELD and PELD scores used to prioritize offers for liver transplant candidates estimate a candidate's risk of dying on the waiting list within three months. These scores allow candidates to be ranked based on their relative urgency for a liver transplant. However, depending on the cause of their disease, the calculated MELD/PELD score may not reflect a candidate's need for a liver transplant. Policy 3.6.4.5 (Liver Candidates with Exceptional Cases) allows transplant centers to assign higher MELD or PELD scores to candidates with particular diseases, when the center applies to the Regional Review Board (RRB). The committee identified several specific diagnoses when MELD/PELD was implemented (e.g., Hepatocellular carcinoma, Hepatoblastoma, Hepatopulmonary Syndrome (HPS), Familial Amyloidosis and Primary Oxaluria); however, the Committee recognized that it could add other diagnoses as the transplant community gained experience with the MELD/PELD system.

In 2005, the Committee charged the MELD Exceptional Study Group (MESSAGE) to: "(1) to identify conditions for which a specific, objective, endpoint exists that defines need for LT such that assignment of additional priority can be automatic (without RRB peer review) and recommend the amount of additional priority so assigned, and (2) for those conditions where there is insufficient evidence, to recommend specific, objective data elements to be collected for individual conditions for which there was insufficient evidence for granting increased priority." The MESSAGE presented its work at a consensus conference held in Chicago, IL, in March 2006, where a total of 17 diagnoses were discussed[1].

The Liver Committee formed a subcommittee in 2007 to recommend which of these diseases/diagnoses would be appropriate to include in policy as automatic MELD/PELD exceptions, and to determine the score that they should assign to each. UNOS Research staff presented data at the March 4, 2008, Liver and Intestine Committee meeting showing that between November 1, 2006 and October 31, 2007, seven diagnoses accounted for 10.7% of all exceptional point requests (with HCC cases representing 48% of the exceptional case requests receiving automatic points for HCC). These diagnoses included cholangiocarcinoma, cystic fibrosis, familial amyloidosis, hepatopulmonary syndrome, portopulmonary hypertension, primary hyperoxaluria, and small for size syndrome. If the HCC exceptions are excluded, these seven diagnoses make up 21% of the cases that transplant centers submit to the RRBs.

[1] Freeman RB Jr, Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, Klintmalm G, Blazek J, Hunter R, Punch J. Model for end-stage liver disease (MELD) exception guidelines: Results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transpl. 2006 Dec;12 Suppl 3:S128-36

There was considerable discussion about whether to assign points based on waitlist mortality risk for each region, versus establishing a standard score across all regions. The Committee agreed that, since the precedent has already been set with exception scores for candidates with HCC, a standardized score should be used across all UNOS regions. As was the case with the changes to the HCC policy, the scores and waiting times will be monitored and adjusted if necessary. The subcommittee was charged with providing specific recommendations for standard MELD scores for the seven diagnoses, with a synopsis of the data that supports it, and to also determine whether there should be incremental increases every three months. As noted in the MESSAGE paper,

> "For many of these cases, there may be enough occurrences where mortality risk may serve as a reasonable prioritization endpoint and could be easily equated to the MELD/PELD score mortality risk estimates employed for the standard cases. Unfortunately, there is a near complete lack of data from which risk factors that would accurately define the mortality risk, or wait list removals for progressive disease, for these various conditions might be developed and validated."

Using the framework provided in the MESSAGE guidelines, the subcommittee recommended six diagnoses that could be considered for automatic MELD/PELD exception points. In most cases, the Committee felt that an initial MELD/PELD score of 22 would be appropriate, with a 10 percentage point increase (abbreviated to "10% increase") every three months.

Cholangiocarcinoma. The subcommittee agreed that the recommended MELD score should be 22 (equivalent to a 15% mortality risk), with a 10% increase every three months. The subcommittee also agreed that liver transplant candidates with cholangiocarcinoma should meet the criteria listed in **Table 1** of the MELD supplement in order to receive additional priority[2]. Candidates who do not meet these criteria will require prospective review by the RRB. The Committee supported the recommendations by a vote of 21 in favor, 0 opposed, and 0 abstentions.

TABLE 1. Criteria for MELD Exception for Liver Transplant Candidates With Cholangiocarcinoma

- Centers must submit a written protocol for patient care to the UNOS Liver and Intestinal Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by UNOS.
- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and biopsy or cytology results demonstrating malignancy, carbohydrate antigen 19-9 >100 U/mL, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (e.g., PSC).
- If cross-sectional imaging studies (CT scan, ultrasound, MRI) demonstrate a mass, the mass should be <3 cm.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.
- Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before LT. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

Abbreviations: MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing; CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis; CT, computed tomographic; MRI, magnetic resonance imaging; LT, liver transplantation.

[2] Gores GJ, Gish RG, Sudan D, Rosen CB. Model for End-Stage Liver Disease (MELD) Exception for Cholangiocarcinoma or Biliary Dysplasia. Liver Transplantation, Vol. 12, No 12, Suppl 3 (December) 2006: pp S95-S97.

Cystic Fibrosis. The subcommittee agreed that candidates who do not have reduced pulmonary function (FEV_1 of > 40%) should be listed at their calculated MELD/PELD score. However, once a candidate begins having pulmonary problems, especially if the FEV_1 falls below 40%, then their pulmonary function usually deteriorates and these patients can improve by liver transplant alone. There was some discussion about how to identify a patient that is too sick for transplantation, but the committee decided to leave this decision with the transplant centers rather than identify specific exclusionary criteria.

The subcommittee proposed a starting point at a MELD score of 22 and a PELD score of 32 (15% mortality risk) to keep consistent with the other exceptions. Candidates should receive a 10% point increase every three months. The Committee agreed with the recommendations by a vote of 20 in favor, 0 opposed, and 0 abstentions.

Familial Amyloid Polyneuropathy (FAP). The subcommittee felt that there should be a clear diagnosis for this condition, which would include an echocardiogram to show the candidate has an ejection fraction > 40%, ambulatory status, identification of TTR gene mutation (Val30Met vs. non-Val30Met) and/or a biopsy proven amyloid in the involved organ. Additionally, if the information about the type of gene mutation is available, it would be useful to collect that information for future evaluation. The subcommittee agreed the recommended MELD score should be 22 (equivalent to a 15% mortality risk) with a 10% increase every three months. The Committee agreed with the recommendations by a vote of 20 in favor, 0 opposed, and 0 abstentions.

Hepatopulmonary Syndrome. The subcommittee agreed the recommended MELD score should be 22 for the initial application. If the candidate's PaO_2 stays below 60 mmHg, he/she will receive a 10% increase every three months. The stratified MELD score recommendations in the MESSAGE paper[3] would complicate the programming and not take into account the variability of arterial blood gas results, so the subcommittee proposed this solution in contrast to the MESSAGE recommendation. The Committee agreed with the recommendations by a vote of 20 in favor, 0 opposed, and 0 abstentions.

Portopulmonary Syndrome. The criteria for this diagnosis should include initial mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR) levels, documentation of treatment, and post-treatment MPAP < 35 mmHg and PVR < 400 dynes/sec/cm^{-5}. There was some discussion about whether 12 weeks of treatment should be required. It was determined that 12 weeks is just a guideline and not a requirement. As long as the patient responds to treatment and falls within the criteria, it should be left to the discretion of the transplant center. Additionally, transpulmonary gradient should be required for the initial diagnosis to correct for volume overload.

The subcommittee agreed the recommended MELD score should be 22 (equivalent to a 15% mortality risk) with a 10% increase every three months. The subcommittee discussed whether a repeat right heart catheterization should be required every three months to confirm the MPAPs are still below 35 mm Hg, and decided that this should be required to receieve a 10% increase in the score. The Committee agreed with the recommendations by a vote of 20 in favor, 0 opposed, and 0 abstentions.

Primary Hyperoxaluria. The subcommittee reviewed the MESSAGE recommendations that candidates meeting the following criteria will be granted a MELD score exception: AGT deficiency proven by liver biopsy sample analysis and/or genetic analysis.

[3] Krowka MJ, Fallon MB, Mulligan DC, Gish RG. Model for End-Stage Liver Disease (MELD) Exception for Portopulmonary Hypertension. Liver Transplantation 2006: 12:S114-S116.

The subcommittee agreed that exception points should only be granted for candidates listed for a combined liver-kidney transplant. The criteria should include: being on dialysis or the usual criteria for a kidney transplant. The subcommittee agreed that the creatinine clearance should match the proposed policy language drafted by the joint liver-kidney subcommittee (i.e., GFR<= 25 ml/min for 6 weeks or more by MDRD6 or direct measurement (Iothalamate or iohexol).

The subcommittee agreed the recommended MELD score should be 28 (equivalent to a 35% mortality risk) or a PELD score of 41 (equivalent to a 35% mortality risk) with a 10% increase every three months. The Committee agreed with the recommendations and agreed to circulate the proposal for public comment. Committee vote: 20 in favor, 0 opposed, and 0 abstentions.

Supporting Evidence and/or Modeling:

The specific recommendations of the MESSAGE conference can be found in the following articles:

Gores GJ, Gish RG, Sudan D, Rosen CB. Model for End-Stage Liver Disease (MELD) Exception for Cholangiocarcinoma or Biliary Dysplasia. Liver Transplantation, Vol. 12, No 12, Suppl 3 (December) 2006: pp S95-S97.

Krowka MJ, Fallon MB, Mulligan DC, Gish RG. Model for End-Stage Liver Disease (MELD) Exception for Portopulmonary Hypertension. Liver Transplantation 2006: 12:S114-S116.

Horslen S, Sweet S, Mulligan DC, Gish RG, Shepard R. Model for End-Stage Liver Disease (MELD) Exception for Cystic Fibrosis. Liver Transplantation 2006: 12:S98-S99.

Pomfret EA, Gish RG, Brandhagen D. Model for End-Stage Liver Disease (MELD) Exception for Familial Amyloidotic Polyneuropathy. Liver Transplantation 2006: 12:S100-S101.

Fallon MB, Mulligan DC, Gish RG, Krowka MJ. Model for End-Stage Liver Disease (MELD) Exception for Hepatopulmonary Syndrome. Liver Transplantation 2006: 12:S105-S107.

Horslen S, Gish RG, McDonald R. Model for End-Stage Liver Disease (MELD) Exception for Primary Hyperoxaluria. Liver Transplantation 2006: 12:S117-S118.

Expected Impact on Program Goals, Strategic Plan, and Adherence to OPTN Final Rule:

As described above, this proposal will address “Challenge 3 - Reduce Variation in Access to Transplantation, “which was one of the OPTN/UNOS September 2006-2007 Strategic Plan goals.

Plan for Evaluating the Proposal:

The Liver and Intestinal Organ Transplantation Committee will review MELD/PELD exception data to ensure that this change serves its intended purpose without having a negative impact on liver transplant candidates.

The proposal should:

- Reduce the regional variation in the MELD/PELD scores assigned for these diagnoses; and
- Increase consistency in the critera used to assign MELD/PELD scores for these diagnoses

Policy Performance Measures: The following data will be provided to the Committee to evaluate the effects from this policy modification:

- The OPTN will monitor the number of exceptional case requests for each diagnosis by region. This will include the number of cases submitted that do not meet the criteria and/or those where the requested MELD/PELD score is higher than assigned in policy.
- The OPTN will monitor listing, death and transplant rates as well as post-transplant outcomes for these diagnoses.

Time Line for Evaluation

- If the board approves this policy change, the committee will evaluate it every 6 months after UNOS implements the change.

Additional Data Collection:

UNOS will need to add fields to the MELD/PELD exception forms to determine if the candidate meets the requirements for automatic points without requiring prospective RRB review. This meets the first OPTN Principle of Data Collection "Develop transplant, donation, and allocation policies"

Expected Implementation Plan:

UNOS IT staff will need to reprogram UNet^{SM} to modify the MELD/PELD exception applications. The Liver and Intestinal Organ Transplantation Committee will work with UNOS IT to implement this policy modification.

Communication/Education Plan:

Communication Activities			
Type of Communication	**Audience(s)**	**Deliver Method(s)**	**Timeframe**
Policy Notice following Board Approval	Pediatric and adult liver candidates, transplant surgeons, transplant physicians, transplant coordinators, OPO procurement coordinators, OPO executive directors, OPO medical directors, OPO PR/public education staff, public, transplant administrators, and transplant public relations/public education staff	Blast e-mail, OPTN and UNOS websites	1 month after Board approval
System Notice upon implementation	All UNet^{SM} Users	Blast e-mail, UNet^{SM} notice	TBD

Monitoring and Evaluation:

If this change is approved, the computer match system operated by the OPTN will be updated to require transplant centers to enter the appropriate information into the MELD/PELD exception application. Transplant centers are expected to enter accurate and updated information into the MELD/PELD exception applications. The UNOS Department of Evaluation and Quality (DEQ) verifies the information included on the MELD/PELD exception application during on-site surveys of liver transplant programs.

UNOS staff forwards potential policy violations to the OPTN/UNOS Membership and Professional Standards Committee (MPSC) for review.

Policy Proposal:

The Liver and Intestinal Organ Transplantation Committee request your consideration and feedback on the recommended modifications to policies 3.6 (Allocation of Livers) as drafted below:

3.6.4.5 Liver Candidates with Exceptional Cases. Special cases require prospective review by the Regional Review Board. The center will request a specific MELD/PELD score and shall submit a supporting narrative. The Regional Review Board will accept or reject the center's requested MELD/PELD score based on guidelines developed by each RRB. Each RRB must set an acceptable time for Reviews to be completed, within twenty-one days after application; if approval is not given within twenty-one days, the candidate's transplant physician may list the candidate at the higher MELD or PELD score, subject to automatic referral to the Liver and Intestinal Organ Transplantation Committee for review; this review by the Liver and Intestinal Organ Transplantation Committee may result in further referral of the matter to the Membership and Professional Standards Committee for appropriate action in accordance with Appendix A of the Bylaws. Exceptions to MELD/PELD score must be reapplied every three months; otherwise the candidate's score will revert back to the candidate's current calculated MELD/PELD score. If the RRB does not recertify the MELD/PELD score exception, then the candidate will be assigned a MELD/PELD score based on current laboratory values. Centers may apply for a MELD/PELD score equivalent to a 10% increase in candidate mortality every 3 months as long as the candidate meets the original criteria. Extensions shall undergo prospective review by the RRB. A candidate's approved score will be maintained if the center enters the extension application more than 3 days prior to the due date and the RRB does not act prior to that date (i.e., the candidate will not be downgraded if the RRB does not act in a timely manner). If the extension application is subsequently denied then the candidate will be assigned the laboratory MELD score.

3.6.4.5.1 Liver Candidates with Hepatopulmonary Syndrome (HPS). Candidates with a clinical evidence of portal hypertension, ~~evidence of a shunt,~~ and a PaO_2 < 60 mmHg on room air will be listed at a MELD score of 22 without RRB review with a 10% increase in points every three months if the candidate's PaO_2 stays below 60 mmHg. ~~referred to the RRB for consideration of a MELD score that would provide them a reasonable probability of being transplanted within 3 months. Candidates should have no significant clinical evidence of underlying primary pulmonary disease.~~

~~3.6.4.5.2 Liver Candidates with Familial Amyloidosis or Primary Oxaluria. Candidate with familial amyloidosis or primary oxaluria may be referred to the RRB for consideration of a MELD score that would allow them to be transplanted within 3 months.~~

3.6.4.5.2 Liver Candidates with Cholangiocarcinoma. Candidates meeting the criteria listed in Table 4 will be listed at a MELD score of 22 without RRB review with a 10% increase every three months.

3.6.4.5.3 Liver Candidates with Cystic Fibrosis. Liver candidates with signs of reduced pulmonary function, defined as having an FEV_1 that falls below 40%, will be listed at a MELD score of 22/PELD score of 32 without RRB review with a 10% increase every three months.

3.6.4.5.4 Liver Candidates with Familial Amyloid Polyneuropathy (FAP). Candidates with a clear diagnosis, to include an echocardiogram showing the candidate has an ejection fraction > 40%, ambulatory status, and identification of TTR gene mutation (Val30Met vs. non-Val30Met) and/or a biopsy proven amyloid in the involved organ, will be listed at a MELD score of 22/PELD score of 32 without RRB review with a 10% increase every three months.

3.6.4.5.5 Liver Candidates with Primary Hyperoxaluria. Candidates with AGT deficiency proven by liver biopsy (sample analysis and/or genetic analysis), and listed for a combined liver-kidney transplant will be listed at a MELD score of 28/PELD score of 41 without RRB review with a 10% increase every three months. Candidates must have a GFR<= 25 ml/min for 6 weeks or more by MDRD6 or direct measurement (Iothalamate or iohexol).

3.6.4.5.6 Liver Candidates with Portopulmonary Syndrome. Candidates that meet the following criteria will be listed at a MELD score of 22 points with a 10% increase every three months if the mean pulmonary arterial pressure (MPAP) stays below 35 mmHg (confirmed by repeat heart catheterization).

- Diagnosis should include initial MPAP and pulmonary vascular resistance (PVR) levels, documentation of treatment, and post-treatment MPAP < 35 mmHg and PVR < 400 dynes/sec/cm^{-5}.
- Transpulmonary gradient should be required for initial diagnosis to correct for volume overload.

TABLE 4. Criteria for MELD Exception for Liver Transplant Candidates With Cholangiocarcinoma (CCA)

- Centers must submit a written protocol for patient care to the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN/UNOS.
- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and biopsy or cytology results demonstrating malignancy, carbohydrate antigen 19-9 100 U/mL, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (e.g., primary sclerosing cholangitis).
- If cross-sectional imaging studies (CT scan, ultrasound, MRI) demonstrate a mass, the mass should be 3 cm.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.
- Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.