TRANSPLANT

REVIEW GUIDELINES

Solid Organ Transplantation

Effective November 1, 2017

Table of Contents

Universal Contraindications

NOTE: *The following list contains the standard contraindications for transplants. These contraindications apply to ALL types of transplants unless otherwise noted. There may be additional contraindications that apply to a specific type of transplant. Please refer to the "Contraindications" section in the specific type of transplant for more information.*

This information was obtained from multiple sources in the peer reviewed medical literature. Unless otherwise noted, the following information was obtained from literature authored by Kasiske, Kanaan, Martin et al., Orens et al., and Mehra et al.

- Infections
  - Acquired Immunodeficiency Syndrome (AIDS) or certain serious and life-threatening diseases that occur in HIV-positive people. These diseases are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS. See Appendix for a complete list of these conditions.
  - Systemic or uncontrolled infection including sepsis.
- Significant uncorrectable life-limiting medical conditions
- Severe end stage organ damage including but not limited to: Severe diabetes mellitus with end organ damage, irreversible severe pulmonary disease, with FEV_1 < 1 L or FVC < 50%, irreversible severe hepatic disease, irreversible severe renal disease
- Active untreated or untreatable malignancy
- Irreversible, severe brain damage
- Active alcohol dependency and substance abuse
  - Active alcohol dependency and/or substance abuse requires six months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing. Active alcohol and substance abuse is defined as the consumption of alcohol in someone with a prior history of active alcohol dependency or the use of any illicit substance at any time in the six months prior to the request for transplant. EXCEPTIONS:
    - Catastrophic decompensation/critical time limitation:
      - Objective failure of therapy for severe acute alcoholic hepatitis. (Mathurin et al.) See Appendix for Lille protocol.
      - Critical decompensation in cirrhotic patients as judged by MELD score predicting mortality prior to completion of required abstinence program.
      - Critical decompensation in heart or lung patients as judged by UNOS status or LAS score predicting mortality prior to completion of required abstinence program.
      - Special circumstances (directed donor, limited availability of a living donor, etc.) in kidney patients who have been adherent but have not yet completed the full abstinence program may be considered before completion of required abstinence program.

- Requires:
  - Appropriate patient and psychosocial support profile
    - Presence of close supportive social network
    - Absence of severe coexisting diseases or severe psychiatric disorders
    - Agreement by patient (with support of his social network) to post-transplant rehab and monitoring, and to lifelong alcohol/cigarette abstinence
  - Evaluation by addiction specialist indicating high likelihood of success of post-transplant rehab and abstinence
  - Approval by a medical review board that includes beside the regular members, a psychiatrist, addiction specialist and an ethicist
  - No special consideration for acute decompensation with illicit drug addiction and/or abuse

– Inactive alcohol and/or substance abuse (alcohol, crystal meth, heroin, cocaine, methadone, and/or narcotics, etc.)

- More than six months but less than two years abstinence
  - Requires program documentation of surveillance including but not limited to drug testing, chemical dependency/substance abuse evaluation and evaluation of hepatitis exposure
  - Evaluation by addiction specialist indicating high likelihood of abstinence
- More than two years abstinence
  - Evaluation by a Substance Abuse specialist (MD, PsyD, PhD or equivalent credential) may be considered

– Recreational or medicinal use of marijuana is not a contraindication

- Social and Psychiatric Issues — refer for psychosocial evaluation and/or psychiatry consultation for guidance
  - Emotional instability, significant depression or other psychiatric illness that cannot be controlled that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
  - Limited cognitive ability (memory loss, dementia, etc.) that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
  - Lack of psychosocial support as indicated by either no identified caregiver or an uncommitted caregiver. This would include the lack of transportation to and from transplant related appointments, patient and/or caregiver is unable to adhere to the requirements of transplant related treatment plan. A care contract may be needed.
  - Lack of sufficient financial means to purchase post-transplant medications.
  - History of non-adherence that has not been successfully remediated.

  - Inability to give informed consent. If the patient has an authorized representative/guardian/conservator or parent in the case of a minor, that individual must understand and support the ongoing health care needs of the patient.

- Post-transplant lymphoproliferative disease (PTLD) unless no active disease demonstrated by negative positron emission tomography (PET) scan and resolved adenopathy on computed tomography (CT) and/or magnetic resonance imaging (Blaes, Khedmat)

- Limited irreversible rehabilitative potential (Bunnapradist)

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Kidney including Kidney/Liver, Kidney/Heart & Kidney/Lung

General Information

- For multiorgan transplant, patient must meet criteria for each organ.
- Kidney transplantation is the treatment of choice for suitable patients with end-stage kidney disease.
- Preemptive living donor transplantation is encouraged whenever possible.
- Candidates should be referred to a transplant center as soon as it appears probable that renal replacement therapy (dialysis) will be needed within the next 6–12 months. (Kasiske et al.)
- Due to the very long wait times and the likely increased burden of comorbid conditions, patients over the age of 70 may not be considered for deceased donor transplantation by many kidney transplant programs. In many instances, while a member between 70–75 years of age may not be considered for a deceased donor transplant, a center may be willing to evaluate an older patient for a living donor transplant.
  - Prior to considering referral for evaluation for kidney transplant at any center, the center's policy on older patients should be clarified
  - The importance of living donation in this situation should be emphasized with the patient
- Wait times in many parts of the country can last for years, particularly for those with blood groups O and B and those who are highly sensitized.
  - Patients should be very strongly encouraged to consider living donation and to seek out potential donors
  - Double listing in another United Network for Organ Sharing (UNOS) Region with a shorter wait time should be discussed and encouraged if the patient's living situation will allow the flexibility to do this
- Candidates should be informed that placement on the cadaveric waiting list does not guarantee transplantation, since changes in their medical status may delay or preclude transplantation. (Kasiske et al.)
  - If a patient will have to be on a waiting list for a long time, the importance of maintaining transplant readiness by strict adherence to all advice from the transplant center, the treating nephrologist and the dialysis center should be emphasized
- Desensitization protocols for highly sensitized (high PRA) patients are covered
- ABO incompatible transplants are covered
- Kidney Paired Donation/Exchange (KPD) is covered
- Patients with primary oxalosis with ESRD should be considered for combined liver/kidney transplant (Eason et al.)

Indications

- When to refer (Bunnapradist)
  - Kidney transplantation should be discussed with all patients with irreversible advanced chronic kidney disease (CKD).
  - Patients with CKD without known contraindications for transplantation should be referred to a transplant program when they approach CKD stage 4 or a glomerular filtration rate (GFR) less than 30 ml/min/1.73 m^2.
  - Early referral will improve the chances of a patient receiving a preemptive transplant, especially those with a potential living donor; referral to a kidney transplant program does not imply immediate transplantation.
- End-stage renal disease (ESRD).
  - Chronic renal failure with glomerular filtration rate (GFR) < 20ml/min
  - Chronic renal failure on dialysis
  - Symptomatic uremia
- Anticipated ESRD as defined above within next 12 months (preemptive transplantation).
- Combined liver/kidney transplant when one or more of the following are present: (Nadim et al.). See Appendix for modified RIFLE criteria and National Kidney Foundation (NKF) definition of chronic kidney disease (CKD).
  - Candidates with persistent acute kidney injury (AKI) for ≥ 4 weeks with one of the following:
    - Stage 3 AKI as defined by modified RIFLE criteria, i.e., a threefold increase in serum creatinine (Scr) from baseline, Scr ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl or on renal replacement therapy
    - eGFR ≤ 35 ml/min (MDRD-6 equation) or GFR ≤ 25 ml/min (iothalamate clearance)
  - Candidates with CKD, as defined by the National Kidney Foundation, for 3 months with one of the following:
    - eGFR ≤ 40 ml/min (MDRD-6 equation) or GFR ≤ 30 ml/min (iothalamate clearance)
    - Proteinuria ≥ 2 g a day
    - Kidney biopsy showing > 30% global glomerulosclerosis or > 30% interstitial fibrosis
    - Metabolic disease
- Combined heart/kidney transplant. (Russo et al., Hong et al. and Gill et al.)
  - Low risk patients with ESRD or CKD with eGFR < 33 ml/min. Refer to Medical Director.
- Retransplantation. Usually due to primary non-function, rejection, recurrent disease and/or immunosuppression toxicity.

Organ-specific Contraindications

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present, the transplant will not be approved. Refer to the Medical Director.

- Reversible renal failure (Bunnapradist)

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

These recommendations are consistent with the 2001 American Society of Transplantation (AST) Clinical Practice Guidelines. (Kasiske et al.)

- Requests for liver/kidney and kidney/heart transplants: Refer to Medical Director.
- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx
- Recent history of malignancy (treated) within 5 years. The 2001 Clinical Practice Guidelines (Kasiske et al.) provide detailed recommendations for a large number of malignancies and can be consulted if there are questions about the appropriateness of kidney transplantation in the presence of a history of malignancy.
  - Requires oncology clearance
- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria
- BMI ≥ 35 kg/m^2. NOTE: “There are few data to suggest which, if any, obese patients should be denied transplantation based on obesity per se. (Kasiske et al.)
  - Refer to requesting program Patient Selection Criteria
  - If outside the program’s patient selection criteria, refer to Medical Director
- Pediatric patients should have a normal history and physical, or if symptomatic heart disease, cardiac testing done that indicates an ejection fraction (EF) > 40%, normal wall motion, and left ventricular shortening fraction (SF) > 27%.

  - If the EF or SF is abnormal, consultation with a pediatric cardiologist is necessary as the abnormality may be due to chronic fluid overload and/or hypertension
- Adult patients with known heart disease including but not limited to heart failure, cardiomyopathy and coronary artery disease require cardiology consultation and completion of consultant's recommendations, if any.
- Chronic peptic ulcer disease, GI bleeding, diverticulitis.
  - GI clearance required
- Patients over the age of 70.
  - Not all programs are willing to list patients over the age of 70 for deceased donor kidney transplantation. Refer to requesting program Patient Selection Criteria.
  - If outside the program's patient selection criteria, refer to Medical Director.
- Significant, uncorrectable pulmonary disease. Pulmonary consultation and completion of consultant's recommendations if any is required.

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Liver

General Information

- A Model for End-Stage Liver Disease (MELD) score ≥ 15 or a Child-Turcotte-Pugh (CTP) score of 7 or more correlates with improved one year survival following transplant compared to survival without transplant. Patients with MELD scores < 15 will have an increased risk of death within one year with liver transplant than without. MELD scores frequently change over time. (Schaubel et al.)

Patients may be placed on the UNOS waiting list for liver transplantation without meeting these criteria. However, priority status is currently defined by the MELD score for adult recipients and the Pediatric End-Stage Liver Disease (PELD) score for pediatric recipients. PELD score is not required for listing but may be used for the purpose of assigning priority for organ allocation. Definitions and calculators for the MELD and PELD scores can be found on the OPTN website at:
https://optn.transplant.hrsa.gov/resources/allocation-calculators/

- Adults with hepatocellular carcinoma (HCC) who meet Milan criteria (Mazzaferro) will be awarded MELD exception points. OPTN Dynamic Imaging criteria apply. See “Special Considerations” below.
  - Milan Criteria (Mazzaferro)
    - Not a candidate for subtotal hepatic resection
    - Tumor is HCC stage II (T2 one nodule 2.0 – 5.0 cm; two or three nodules, all ≤ 3.0 cm)
    - No macrovascular involvement
    - No identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone
  - Tumors can be downstaged with hepatic artery chemoembolization (HACE or TACE) with or without radiofrequency ablation (RFA). If successfully downstaged to be within the Milan criteria, MELD exception points are not automatically assigned. All such candidates with HCC, including those with downsized tumors whose original or presenting tumor was greater than a stage T2, must be referred to the applicable Regional Review Board (RRB) for prospective review in order to receive additional priority.
- Children with the following conditions will be awarded PELD exception points:
  - Hepatoblastoma
  - Urea cycle disorders and organic acidemia
  - Combined liver/intestine transplant
- Living Donor Liver Transplant (LDLT). See “Indications” below.
  - Results from A2ALL (Berg et al., Olthoff et al.) study demonstrated significant survival advantage associated with receipt of LDLT in comparison to continued waiting for Deceased Donor Liver Transplant (DDLT) for candidates with low laboratory MELD scores
  - Complications of cirrhosis with low MELD score should be considered for LDLT (Koffron and Stein)

- Patients with primary oxalosis with ESRD should be considered for combined liver/kidney transplant. (Eason et al.)

Indications

- Candidate for evaluation as per the American Association for the Study of Liver Disease (AASLD) recommends the following timing for referral for transplant evaluation. (Martin et al.) This is supported by Schaubel et al. NOTE: This is NOT a recommendation to transplant low MELD patients. https://optn.transplant.hrsa.gov/resources/allocation-calculators/
  - Evaluation for liver transplant should be considered once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy or variceal hemorrhage or hepatocellular dysfunction results in MELD Score $\geq$ 15 (1-A).
  - Potential Liver transplant candidates with worsening renal dysfunction or other evidence of rapid hepatic decompensation should have prompt evaluation for liver transplant (2-B)
- Liver transplant candidate as per Organ Procurement and Transplant Network (OPTN) guidelines.
  - Transplantation is indicated for patients with End-Stage Liver Disease (ESLD) with a life expectancy < 12-24 months OR who have developed life-threatening complications or with severe liver associated debility frequently associated with sustained portal hypertension.
    - Intractable ascites usually requiring frequent paracenteses
    - Recurring variceal bleeding not well controlled with surgical banding and medical therapy
    - Recurring spontaneous bacterial peritonitis (SBP)
    - Intractable hepatic encephalopathy
    - Severe thrombocytopenia with complications
    - Intractable pruritus
    - Muscle wasting due to liver disease with other systemic illnesses excluded
    - Debilitating fatigue due to liver disease with other systemic illnesses excluded
- Polycystic liver disease with massive enlargement leading to physical impairment
- Hepatocellular carcinoma within Milan criteria determined by the OPTN Dynamic Imaging criteria and no CONTRAINDICATIONS.
  - Not a candidate for subtotal resection
  - The HCC meets the definition of a Stage T2 lesion(s) that include any of the following:
    - One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size
    - Two or three lesions greater than or equal to 1 cm and less than or equal to 3 cm in size
  - Written documentation has been submitted with the request that the lesion meets the definition of OPTN Class 5B, 5T or a combination of 5A lesions that meets the definition of tumor Stage T2

  - No macrovascular involvement
  - No identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.
- Hepatocellular carcinoma that has been “downstaged”. (Pomfret et al.) Refer to Medical Director.
  - Note: Successful downstaging does not result in an automatic award of MELD exception points. The case must be referred to the Regional Review Board with a request for exception points.
  - The inclusion criteria for downstaging should be a single tumor < 8 cm or 2 to 3 tumors, each < 5 cm, with a total tumor diameter < 8 cm and no vascular invasion by imaging criteria.
  - The criteria for successful downstaging should be as follows:
    - The tumor must meet the Milan Criteria after the downstaging procedure(s), as assessed by imaging requirements for priority listing and maintaining listing for LT (liver transplant) every 3 months.
    - Successful downstaging also requires a significant decrease in the AFP level to < 500 ng/ml for those patients with an initial AFP level > 1000 ng/ml.
  - There will be a minimum time-out or observation period of 3 months from the date on which imaging is documented to meet the Milan Criteria before eligibility for active priority listing.
  - Those with acute hepatic decompensation after downstaging procedures are not eligible for Deceased Donor Liver Transplant (DDLT) or Living Donor Liver Transplant (LDLT) unless they meet the above.
- Cholangiocarcinoma (Martin et al.). Refer to Medical Director with protocol.
  - May be approved under certain circumstances under the appropriate protocol at a center with an approved living donor liver transplant program OR a program in a region where the RRB will award MELD exception points to patients who qualify under the requesting program’s treatment protocol (Heimbach et al., Becker et al. and Gores.)
  - If donor availability (living or deceased) is in doubt due to program qualification (living donor) or RRB policy (deceased donor), the member can be educated about other available in-network programs that can satisfy one or both of the donor requirements
- Neuroendocrine tumors (NET). CMS has concluded: “It is unclear which patients could benefit in this rare disease, but some patients do appear to benefit from a transplant. Therefore, coverage of this treatment may be best considered only in carefully selected patients on a case by case basis at this time.” Refer to Medical Director. (Martin et al.)
- Hemangioendothelioma (HAE). CMS and AASLD have concluded that generally patients with HAE have a better prognosis than do patients with HCC and may not have evidence of significant underlying liver disease. Consequently, transplantation is not common, but not necessarily contraindicated. For patients with large tumors liver transplantation should be considered for patients with unresectable HAE. Refer to Medical Director. (Martin et al.)

- Hepatoblastoma: Children with hepatoblastoma may be considered for transplantation under the following circumstances. MELD rules are not applied for patient selection. The patient will have received chemotherapy as part of the initial management of the tumor prior to consideration for transplant. (National Cancer Institute, 2015)
  - Patients whose tumors remain unresectable should be considered for liver transplantation.
  - If extrahepatic disease is in complete remission after chemotherapy, and the primary tumor remains unresectable, orthotopic liver transplantation may be performed
  - If extrahepatic disease is not resectable or the patient is not a transplant candidate, additional chemotherapy, TACE, or radiation therapy
  - Liver transplantation should be considered for patients with nonmetastatic disease recurrence in the liver that is not amenable to resection

- Retransplantation is usually due to primary non-function, hepatic artery thrombosis, portal vein thrombosis, rejection, chronic cholestasis without chronic rejection and recurrent disease.

Organ-specific Contraindications

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved. Refer to the Medical Director.

Unless otherwise annotated, these recommendations are consistent with the 2013 American Association for the Study of Liver Disease (AASLD) Clinical Practice Guidelines. (Martin et al.)

- Active untreated or untreatable non-hepatic malignancy
- Hepatocellular carcinoma that exceeds University of California, San Francisco (UCSF) criteria:
  - Single lesion not exceeding 6.5 cm; OR
  - 2-3 lesions, none exceeding 4.5 cm, WITH
  - Total tumor diameter not greater than 8 cm
- Congenital abnormalities that will preclude or prevent liver transplant

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

Unless otherwise annotated, these recommendations are consistent with the 2013 American Association for the Study of Liver Disease (AASLD) Clinical Practice Guidelines. (Martin et al.)

- Requests for liver/kidney, heart/liver and liver/lung and transplants. Refer to Medical Director.
- Additional considerations may be present where liver transplantation may be appropriate in other circumstances where quality of life considerations become paramount.
  - Calculated MELD score < 15 AND ELIGIBLE FOR MELD EXCEPTION POINTS will be approved when one of the following is present:

    - Cystic fibrosis with signs of reduced pulmonary function with forced expiratory volume at one second (FEV_1) that falls below 40 percent
    - Portopulmonary hypertension
    - Hepatic artery thrombosis within 14 days of transplant
    - Hepatoblastoma (pediatric) eligible for PELD exception points
    - Urea cycle disorder or organic acidemia (pediatric) eligible for PELD exception points
    - Primary oxaluria eligible for MELD exception points
    - Hepatopulmonary syndrome eligible for MELD exception points
    - Combined liver/intestine or multivisceral transplant
    - Familial amyloidosis/familial amyloid polyneuropathy (FAP)
        - Patients may have no measurable abnormality of liver function at the time of the request for authorization.
        - Liver transplants generally are done below the age of 30 AND when the patients are clinically well.
        - Patients may be living donors for a “domino transplant.”
  - All other presentations not eligible for automatic MELD exception points including but not limited to elevated CTP score, intractable pruritus (itching), recurrent spontaneous bacterial peritonitis, bleeding, ascites, thrombocytopenia, encephalopathy, polycystic liver disease or other quality of life issues not adequately accounted for in the MELD/PELD score may be considered. Refer to Medical Director.

- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx
- Recent history of malignancy (treated) within 5 years. Requires oncologic assessment of status of treated malignancy.
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria
- BMI ≥ 35 kg/m^2.
  - Refer to requesting program Patient Selection Criteria

  - If outside the program's patient selection criteria, refer to Medical Director
- Pediatric patients should have a normal history and physical, or if symptomatic heart disease, cardiac testing done that indicates an ejection fraction (EF) > 40%, normal wall motion, and left ventricular shortening fraction (SF) > 27%.
  - If the EF or SF is abnormal, consultation with a pediatric cardiologist is necessary as the abnormality may be due to chronic fluid overload and/or hypertension
- Adult patients with known heart disease including but not limited to heart failure, cardiomyopathy and coronary artery disease require cardiology consultation and completion of consultant's recommendations if any.
- Chronic peptic ulcer disease, GI bleeding, diverticulitis.
  - GI clearance required
- Patients over the age of 70.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Significant, uncorrectable pulmonary disease. Pulmonary consultation and completion of consultant's recommendations if any is required.
- Significant uncorrectable cardiac disease. Cardiology evaluation and clearance required.

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Pancreas & Kidney/Pancreas

General Information

- There are three variations of pancreas and kidney/pancreas transplants.
  - Both organs can be inserted during one procedure and this is referred to as Simultaneous Pancreas Kidney transplantation (SPK)
  - The pancreas can be transplanted after a kidney transplant and this is referred to as Pancreas After Kidney transplantation (PAK) OR
  - The pancreas can be transplanted alone and this is called Pancreas Transplant Alone (PTA)
- SPK, PAK or PTA may be indicated in patients with either Type 1 or Type 2 diabetes. Pancreas transplantation can provide excellent outcomes for patients with labile diabetes. (Gruessner) The outcomes of combined kidney pancreas transplants in Type 2 diabetics are comparable to the outcomes in Type 1 diabetics. (Light et al., Nath et al.)
- SPK transplant is the definitive treatment of Type 1 diabetes combined with end-stage renal disease. Long-term graft function can lead to improvement in diabetes-related complications and, in patients younger than 50 years, can lead to improved overall survival. PAK transplant and PA transplant do not result in similar improvements in patient survival, but with appropriate patient selection, they can improve quality of life by rendering patients insulin-free. (Dhanireddy)
- Data from the International Pancreas Transplant Registry indicate that most recipients have Type 1 diabetes with about 7% having Type 2 disease. A pancreas transplant may be justified on the basis that patients replace daily injections of insulin with an improved quality of life but at the expense of a major surgical procedure and lifelong immunosuppression. (White)
- Improved surgical techniques and immunosuppressive protocols have led to improved patient and graft survival. Patient survival now reaches over 95% at one year post-transplant and over 83% after 5 years. The best graft survival was found in SPK with 86% pancreas and 93% kidney graft function at one year. PAK pancreas graft function reached 80%, and PTA pancreas graft function reached 78% at one year. The 1-year immunological graft loss rate also decreased:
  - In SPK, the immunological 1-year graft loss rate was 1.8%,
  - In PAK 3.7%, and
  - In PTA 6.0% (Gruessner)
- Complications include graft thrombosis, bleeding, abdominal abscess, pancreatic leak, urinary tract infection, and early rejection. (Ablorsu) Pancreas transplant is associated with more surgical complications and higher perioperative morbidity and mortality than kidney transplant alone. (Dhanireddy) There is a high incidence of kidney graft failure in SPK recipients, following a pancreas graft loss. About 50% of the kidney graft failure occurred within three months after the loss of the pancreas graft. (Hill)

- Allogeneic Islet Cell transplantation is an experimental procedure and IS NOT covered except:
  - When performed under a clinical trial AND
  - A clinical trial benefit exists AND
  - The trial conforms to the provisions of that benefit

> Generally, since diabetes does not meet the definition of a life-threatening illness found in most commercial benefit plans, allogeneic islet cell transplants will not be covered even in patients with a life-threatening clause in their benefit plan. The benefit plan must be checked carefully for the definition of life-threatening illness and other coverage provisions for investigational, experimental and "promising but unproven" treatments.
>
> For patients with Medicare as primary coverage, allogeneic islet cell transplants may be a covered benefit if performed in a center that is participating in the current NIH sponsored trials of allogeneic islet cell transplantation that are covered by Medicare (Islet Transplantation in Type 1 Diabetes, NCT 00434811 and Efficacy of Islet After Kidney Transplantation, NCT00468117) and all other benefit provisions have been met. For participating centers, go to www.clinicaltrials.gov and search for one or both of these trials.

- Autologous Islet Cell transplantation (sometimes referred to as Islet Autologous Transplantation or IAT) following total pancreatectomy for non-malignant conditions is an accepted treatment to prevent the immediate onset of insulin dependent diabetes mellitus. This is a covered MEDICAL benefit under the UHC COC. (Bramis)

  NOTE: For Optum nurses, autologous islet cell transplant is covered under the member's medical benefit. Refer to Job Aid 22211095: TS Auto Islet Cell transplant Notification NF/EC Process.

  - There are only a handful of laboratories experienced in isolating the islets from the excised pancreas and relatively few centers in the US with extensive experience with autologous islet cell infusions and management of the patients post-infusion.
  - Reinfusion of the islets does not prevent the pancreatic exocrine insufficiency that follows total pancreatectomy. This is managed in the same way as for any patient who has undergone a total pancreatectomy.
  - Autologous islet cell transplant does not require treatment with immunosuppressive drugs. Post-infusion management of these patients is the same as the management of any other patient at risk for the development of diabetes.
  - Autologous islet cell transplantation is a laboratory and procedural add-on to the cost of a total pancreatectomy. It should not be considered to be an organ transplant.

  - Most patients will develop diabetes eventually. (Dean) Even though the islets lodge in the liver and function normally initially, this is not a normal environment for them. The pancreas they were taken from was not normal. Because of the underlying pancreatic disease and normal loss in processing, the number and quality of islets is not normal. The reinfused islets will eventually stop functioning. But, for the time that they are functioning, the patient is protected against the immediate development of diabetes following a total pancreatectomy. However, concurrent IAT enabled a significant proportion of patients to remain independent of insulin supplementation. (Bramis)

Indications

- SPK and PAK:
  - Qualifies for kidney transplant (see KIDNEY) AND the member is diabetic. The outcomes of combined kidney pancreas transplants in Type 2 diabetics are comparable to the outcomes in Type 1 diabetics. (Light et al.)
    - Since Type 2 diabetics tend to be older with a greater burden of significant comorbidities, it is particularly important to pay close attention to cardiovascular risk factors in these patients
- PTA:
  - Type 1 diabetes mellitus with one or both of the following:
    - Labile diabetes mellitus with documented life-threatening hypoglycemic unawareness and/or frequent hypoglycemic episodes despite optimal medical management, Clarke Hypoglycemic Score ≥ 4 (Geddes et al.) AND/OR
    - Inability to tolerate exogenous insulin
  - Type 2 diabetes mellitus meeting the following criteria with one of the following:
    - Labile diabetes mellitus with documented life-threatening hypoglycemic unawareness despite optimal medical management, Clarke Hypoglycemia Score ≥ 4 OR
    - Severe physical or psychological impairment that make it impossible to administer exogenous insulin safely.
  - Appropriate candidates will have all of the following characteristics: (Stratta)
    - Insulin requiring diabetes for > 5 years receiving ≤ 1 unit/kg/day, AND
    - BMI ≤ 30, AND
    - Age < 60, AND
    - No history of major vascular events such as bilateral limb amputations and disabling CVA, AND
    - Not actively smoking, AND
    - Left ventricular ejection fraction ≥ 40% with no left ventricular hypertrophy
- Retransplantation is usually due to non-function of the grafted organ(s), chronic rejection and chronic allograft pancreatitis.

Organ-specific Contraindications

Please review the Universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved. Refer to the Medical Director.

- Significant cardiac disease: (Stratta)
  - Non-correctable coronary artery disease
  - Ejection fraction (LVEF, EF) < 40%

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

- Serum C-peptide.
  - Serum C-peptide measurements are not required. Transplant candidacy is based on other considerations noted elsewhere in this document. (Stratta)
- Autologous Islet Cell transplantation. (Bramis)
  - May be indicated following total pancreatectomy for non-malignant conditions.
  - Check benefits to determine if it is covered under a particular plan.

  NOTE: For Optum nurses, autologous islet cell transplant is covered under the member's medical benefit. Refer to Job Aid 22211095: TS Auto Islet Cell Transplant Notification NF/EC Process.
- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx
- Recent history of malignancy (treated) within 5 years.
  - Requires oncology clearance.
- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria

- BMI ≥ 35 kg/m^2.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Pediatric patients should have a normal history and physical, or if symptomatic heart disease, cardiac testing done that indicates an ejection fraction (EF) > 40%, normal wall motion, and left ventricular shortening fraction (SF) > 27%.
  - If the EF or SF is abnormal, consultation with a pediatric cardiologist is necessary as the abnormality may be due to chronic fluid overload and/or hypertension
- Adult patients with known heart disease including but not limited to heart failure, cardiomyopathy and coronary artery disease require cardiology consultation and completion of consultant's recommendations, if any.
- Chronic peptic ulcer disease, GI bleeding, diverticulitis.
  - GI clearance required
- Patients over the age of 60. (Ablorsu)
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Significant, uncorrectable pulmonary disease. Pulmonary consultation and completion of consultant's recommendations if any is required.

Clarke Hypoglycemic Score

1. Check the category that best describes you: (check only one)

   ☐ I always have symptoms when my blood sugar is low (A)

   ☐ I sometimes have symptoms when my blood sugar is low (R)

   ☐ I no longer have symptoms when my blood sugar is low (R)

2. Have you lost some of the symptoms you used to have when your blood sugar was low?

   ☐ Yes (R)

   ☐ No (A)

3. In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)

   ☐ Never (A)

   ☐ Once or twice (R)

- ☐ Every other month (R)
- ☐ Once a month (R)
- ☐ More than once a month (R)

4. In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had seizure and needed glucagon or intravenous glucose)

- ☐ Never (A)
- ☐ 1 time (R)
- ☐ 2 times (R)
- ☐ 3 times (R)
- ☐ 5 times (R)
- ☐ 6 times (R)
- ☐ 7 times (R)
- ☐ 8 times (R)
- ☐ 9 times (R)
- ☐ 10 times (R)
- ☐ 11 times (R)
- ☐ 12 times (U)

5. How often in the last month have you had readings < 70 mg/dl with symptoms?

- ☐ Never
- ☐ 1 to 3 times
- ☐ 1 time/week
- ☐ 2 to 3 times/week
- ☐ 4 to 5 times/week
- ☐ Almost daily

6. How often in the last month have you had readings < 70 mg/dl without any symptoms?

- ☐ Never
- ☐ 1 to 3 times
- ☐ 1 time/week
- ☐ 2 to 3 times/week
- ☐ 4 to 5 times/week
- ☐ Almost daily

(R = answer to 5 < answer to 6, A = answer to 6 >answer to 5)

7. How low does your blood sugar need to go before you feel symptoms?

- ☐ 60 – 69 mg/dl (A)
- ☐ 50 – 59 mg/dl (A)
- ☐ 40 – 49 mg/dl (R)
- ☐ < 40 mg/dl (R)

8. To what extent can you tell by your symptoms that your blood sugar is low?

- ☐ Never (R)
- ☐ Rarely (R)
- ☐ Sometimes (R)
- ☐ Often (A)
- ☐ Always (A)

Hypoglycemic unawareness (Clarke score): R ≥ 4

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Intestine including Liver/Intestine & Multivisceral

General Information

- If no evaluation for intestinal rehabilitation has been performed, the member may be redirected to a program that has the capacity to perform these important evaluation and management services.
- Adaptation following disease or injury that leads to intestinal failure can occur over many months up to a year or more. The ability of the remaining gut to adapt to be able to support the patient with enteral nutrition alone is determined by a number of factors including the length of the remaining intestine, the segments remaining, the presence of an ileocecal valve, the presence or absence of the colon and general motility patterns. A number of medical and surgical interventions are possible to help many of these patients avoid transplant. (Centers for Medicare and Medicaid, Fryer)
- Patients with intestinal failure syndromes should be managed in centers with robust intestinal failure/rehabilitation programs to take advantage of all opportunities to regain adequate function and to avoid total parenteral nutrition (TPN) with its complications and intestinal transplantation. (Beath et al., Torres et al.)
- Timelier referral of intestinal failure patients who have not yet developed end-stage liver disease may allow for an intestine only transplant (IOT), which is associated with better outcomes. (Chungfat et al.)
- The short-term survival of pediatric intestine recipients has significantly improved in the last decade, and reached 90% at the end of the first year after transplant in high-volume intestinal transplant centers. (Avitzur & Grant)
- The hospitalization status of the intestinal transplant recipient at the time of transplantation remains a strong prognostic factor for patient survival, with an unadjusted 1-year survival rate of 83 percent for recipients not waiting in the hospital, 73 percent for recipients waiting in the hospital, and only 50 percent for recipients waiting in the intensive care unit. (SRTR database)
- Optum Transplant Center of Excellence (COE) programs are required to have intestinal failure/rehabilitation programs.

Indications

- Intestine
  - Patients with irreversible intestinal failure with associated life threatening complications (Fishbein)
  - Patients with secretory diarrhea of childhood may have high mortality/morbidity due to their underlying disease and therefore can be considered for intestine transplant evaluation in the absence of life threatening complications (Ruemmele et al.)
    - Dependent on TPN with cholestatic liver disease as defined by elevated direct bilirubin. If cholestasis is advanced, or cirrhosis is present, a combined liver/intestine transplant may be considered. (Colomb et al.)

    - Isolated intestinal transplants are performed in the presence of cholestasis only when the liver disease is felt to be reversible.
  - Inability to maintain fluid and electrolyte balance
  - Recurrent sepsis as a result of either line sepsis or intestinal stasis
  - Dependent on TPN with loss of or impending loss of (using last major vessel) vascular access
  - Non-reconstructible gastrointestinal (GI) tract
- Liver/small bowel/pancreas with or without addition of stomach or colon
  - Liver/intestine
    - One of the above AND
    - Biopsy proven fibrotic changes within the liver indicating that the TPN associated liver dysfunction is irreversible OR
    - Clinical assessment of significant portal hypertension (such as hypersplenism) where biopsy may not be available or warranted or considered safe to perform
  - Multivisceral
    - All of the above under Intestine AND
    - Technical considerations that make the anastomoses of one or more of the separate organs problematic when compared to an en bloc dissection and transplantation that requires fewer vascular and intestinal anastomoses OR
    - Desmoid tumors OR
    - Severe gastric or antroduodenal motility disorder (pseudoobstruction) (Cruz et al.) OR
    - Patients listed for multivisceral transplantation without TPN dependency require special case review (Kaufman et al.)

      Subsequent recovery of hyperbilirubinemia with nutritional and medical management may allow for “delisting” or consideration of isolated intestine transplant if the liver has improved despite initial biopsy findings.
- Retransplantation
  - May occur when there is a failed prior intestinal transplantation, including non-function of the grafted organ, acute rejection requiring enterectomy, or chronic rejection.

Organ-specific Contraindications

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved, refer to the Medical Director.

- There are no organ specific contraindications

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx
- Recent history of malignancy (treated) within 5 years.
  - Requires oncology clearance
- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria
- BMI ≥ 35 kg/m^2.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Pediatric patients should have a normal history and physical, or if symptomatic heart disease, cardiac testing done that indicates an ejection fraction (EF) > 40%, normal wall motion, and left ventricular shortening fraction (SF) > 27%.
  - If the EF or SF is abnormal, consultation with a pediatric cardiologist is necessary as the abnormality may be due to chronic fluid overload and/or hypertension
- Adult patients with known heart disease including but not limited to heart failure, cardiomyopathy and coronary artery disease require cardiology consultation and completion of consultant's recommendations, if any.
- Chronic peptic ulcer disease, GI bleeding, diverticulitis.
  - GI clearance required
- Patients over the age of 60. (Ablorsu)
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Significant, uncorrectable pulmonary disease. Pulmonary consultation and completion of consultant's recommendations if any is required.

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Heart

General Information

- Cardiac transplantation is an option for patients with end-stage heart disease. “About 2,000 heart transplants are performed each year in the United States. This number has remained relatively stable due to a lack of donors. The major indications for cardiac transplant were coronary artery disease and dilated cardiomyopathy, but over the past 20 years, dilated cardiomyopathy has supplanted coronary artery disease as the major cause. Survival rates have improved with the advent of newer immunosuppressive agents (tacrolimus and mycophenolate). The median survival for 43,906 heart transplants was approximately 9 years. At 20-years the survival rate continued to decline to reach < 10%. Seven-year survival rates for heart transplant recipients transplanted between 1998-1994, 1995-2000, and 2000-2007 were 59%, 62% and 65%, respectively. Infant heart recipients (less than one year old) had poor survival rates during the first post-transplant year (74% compared to > 85% for all other age groups), but those who survived had better long-term outcomes than adults. Elderly recipients (aged 65 or older) had survival rates comparable to younger patients through about 8 years, when survival rates began to fall more rapidly.” In spite of these statistics, the long-term success of cardiac transplants still has room for improvement. (Everly)
- In prior guideline, Chagas disease was identified as a contraindication to heart transplantation. The International Society for Heart and Lung Transplantation (ISHLT) has since identified heart transplantation as an accepted treatment of choice for heart failure caused by Chagas disease, despite the risks of reactivation of Trypanosoma cruzi infection. (Mehra et al.)
- Due to the limited availability of suitable hearts for transplant, mechanical support devices have been developed. These surgically implanted devices are intended as a bridge to transplantation (BTT) for heart-transplant-eligible candidates with nonreversible biventricular failure and who are at risk of imminent death and for destination therapy (DT) for those patients who are not eligible for heart transplant at the time of implantation.
- The proportion of patients receiving a heart transplant with a mechanical circulatory support device (MCSD) in place at the time of transplant has risen to 50.6% according to the July 2015 report from the Scientific Registry of Transplant recipients (SRTR). The majority of these devices are VADs. (Alba) See complete discussion below.
- Ventricular Assist Devices.

  Please refer to Mechanical Circulatory Support Devices Guidelines available internally on Knowledge Library or externally at: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Clinical%20Guidelines/Mechanical_Circulatory_Support_Devices_Clinical_Guideline.pdf.
- SynCardia Total Artificial Heart.
  - A total artificial heart (TAH) can maintain the life of a patient with biventricular heart failure.
  - The SynCardia (formerly known as the CardioWest) Total Artificial Heart (TAH) is available in 34 centers in the US with 13 more in the process of certification by the manufacturer as of July 22, 2012.

  - The Freedom Driver is approved for use under a clinical trial in the United States. This allows patients with the TAH to be discharged home pretransplant for the first time. This device is used as BTT for patients with severe right heart failure in addition to left heart failure. A DT trial has recently been opened.
  - The FDA has recently approved the use of the Total Artificial Heart for Destination Therapy under a Humanitarian Use Device Exception (HDE).
  - Please refer to Total Artificial Heart Medical Policy available internally on Knowledge Library or externally at: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Total_Artificial_Heart.pdf.

Indications

- Likelihood of death from heart disease within 12 - 24 months without transplant.
- Heart failure with severe cardiac disability despite optimal medical therapy, New York Heart Association Class III or IV or American Heart Association Stage D AND objective evidence of impaired functional capacity (peak oxygen consumption < 14 ml/kg/min). See Appendix for specific description of heart failure categories. (Acker, Jessup, Canter)
- Valvular heart disease with left ventricular dysfunction (not correctable with valve replacement or repair).
- Recurrent life-threatening arrhythmias not otherwise correctable despite maximal antiarrhythmic and all appropriate conventional medical and surgical modalities (including implantable devices and multiple firings from an ICD for documented VT and VF). (Cleveland Clinic, Acker)
- Intractable angina with coronary artery disease despite maximal medical therapy that is not amenable to revascularization. (Yamani and Taylor)
- Primary cardiac tumors confined to the myocardium, with a low likelihood of metastasis at time of transplantation. (Yamani and Taylor)
- Refractory heart failure requiring continuous inotropic (medications that support cardiac muscle contraction) support.
- Severe hypertrophic or restrictive cardiomyopathy, with NYHA Class IV symptoms. (Yamani and Taylor)
- Congenital Heart Disease (CHD) that is not amenable to surgical therapy or that has failed previous surgical correction. (Patel)
- Retransplantation due to primary graft failure, rejection refractory to immunosuppressive therapy and graft coronary artery disease with severe ischemia of the heart graft. Retransplantation appears most appropriate for those patients more than 6 months following original heart transplantation, who have severe cardiac allograft vasculopathy and associated left ventricular dysfunction, or allograft dysfunction and progressive symptoms of heart failure in the absence of acute rejection. (Johnson)
- Combined heart/kidney transplant. (Russo et al., Hong et al. and Gill et al.)

  - Low risk patients with ESRD or CKD with eGFR < 33 ml/min. Refer to Medical Director.

Organ-specific Contraindications

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved. Refer to the Medical Director.

Unless otherwise annotated, these recommendations are consistent with the 2016 International Society for Heart Lung Transplantation (ISHLT) Listing Criteria for Heart Transplantation: A 10-year update. (Mehra et al.)

- Significant peripheral vascular disease not correctable with surgery
- Significant uncorrectable life-limiting medical conditions such as severe end stage organ damage including: Severe diabetes mellitus with end organ damage, irreversible severe pulmonary disease, with FEV_1 < 1 L or FVC < 50%, irreversible severe hepatic disease, irreversible severe renal disease etc. (Acker)
- Active systemic and/or uncontrolled infection associated with left ventricular assist device.
- Ongoing tobacco use. (Acker)

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

Unless otherwise annotated, these recommendations are consistent with the 2016 International Society for Heart Lung Transplantation (ISHLT) Listing Criteria for Heart Transplantation: A 10-year update. (Mehra et al.)

- Severe irreversible pulmonary hypertension:
  - Pulmonary artery systemic pressure > 60 mm Hg, mean transpulmonary gradient > 15 mm Hg, and/or pulmonary vascular resistance (PVR) > 5 Wood units on maximal vasodilator therapy. (Alba) However, the patient may qualify for combined heart/lung transplantation.
  - Elevated PVR defined as a PVR > 5 Woods units, a PVR index >6, or a transpulmonary pressure gradient 16 to 20mmHg, should be considered as relative contraindications to isolated cardiac transplantation. If the pulmonary artery systolic pressure is >60 mmHg in conjunction with any of these 3 variables, the risk of right heart failure and early death is increased. If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls to <85 mmHg, the patient remains at high risk of right heart failure and mortality after isolated cardiac transplantation. (Weill et al.)

  - The current recommended practice is to perform right heart catheterization, treat with vasodilator, intraaortic balloon pump (IABP) and/or mechanical circulatory support device and follow with serial right heart catheterization. If the PA pressure and PVR do not respond to these interventions after 3 to 6 months it is reasonable to conclude that pulmonary artery hypertension is irreversible. (Mehra et al.)
  - Refer to program patient selection criteria
- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx.
- Patients with renal failure can be evaluated for combined heart-kidney transplantation.
  - Requests for heart/liver and kidney/heart transplants: Refer to Medical Director.
- Significant chronic pulmonary disease defined as FVC < 50%, non-reversible FEV1 < 50 % and DLCO (corrected) < 40 % for adults (< 50 % in children).
  - Pulmonary clearance required
- Diabetes with end-organ damage other than nonproliferative retinopathy or poor glycemic control ($HgbA_{1C}$ > 7.5 or 55 mmol/mol) despite optimal effort is a relative contraindication for transplant.
- Recent history of malignancy (treated) within 5 years.
  - Requires oncology clearance
- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria
- BMI > 35 kg/m^2.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Patients over the age of 70.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Recent stroke - unless associated with left ventricular assist device. (Jessup)
- Active pulmonary embolism (< 6 weeks). (Jessup)

Heart Failure Classification

New York Heart Association (NYHA) Functional Classification

Class	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation feeling heart beats), dyspnea (shortness of breath) or anginal pain.
Class II	(Mild) - Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	(Moderate) - Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	(Severe) - Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present at rest. If any physical activity is undertaken, discomfort is increased.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

American Heart Association Classification (AHA)

Stage	Definition
Stage A	Presence of heart failure risk factors but no heart disease and no symptoms
Stage B	Heart disease is present but there are no symptoms (structural changes in heart before symptoms occur)
Stage C	Structural heart disease is present AND symptoms have occurred
Stage D	Presence of advanced heart disease with continued heart failure symptoms requiring aggressive medical therapy

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FDA-3 Food and Drug Administration (FDA). HeartWare VAS . Panel reviewed on April 25, 2012. August 2017. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100047a.pdf

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Yamani MH, Taylor DO. Heart Transplantation. In: Cleveland Clinic. Current Clinical Medicine, 2nd ed. Philadelphia, PA: Saunders;2010.

Lung

General Information

- The indications for lung transplantation include a diverse array of pulmonary diseases of the airways, parenchyma, and vasculature.
- From the International Society for Heart and Lung Transplantation (ISHLT) Consensus Document for the Selection of Lung Transplant Candidates: 2014 — An Update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation (Weill et al.): "Lung transplant should be considered for adults with chronic, end-stage lung disease who meet all of the following criteria: High (50%) risk of death from lung disease within 2 years if lung transplantation is not performed; High (80%) likelihood of surviving at least 90 days after lung transplantation; and High (80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."
- The patient selection criteria, timing of listing and choice of procedure type are critically important steps in optimizing the outcome of lung transplantation.
- "In general, referral for transplantation assessment is advisable when patients have a less than 50%, 2 to 3 year predicted survival or New York Heart Association (NYHA) class III or IV level of function, or both." (Orens et al.)
- The Lung Allocation Score (LAS) is used to place patients on the lung waiting list. This is similar to the MELD system for liver transplantation. The LAS takes into account the severity of the illness pre-transplant including the likelihood of death on the waiting list and the likelihood of survival one year post-transplant. The LAS is a dynamic measurement that is updated on a regular basis according to a follow-up schedule determined by UNOS. Waiting time on the list is no longer an important criterion. Information about the LAS and the LAS Calculator can be found at: http://optn.transplant.hrsa.gov/converge/resources/allocationcalculators.asp?index=88.
- Unique to lung transplantation, decisions must often be made about whether to replace one or both lungs. (Kreider et al.) The choice of single or double lung transplantation is a clinical decision that is left to the treating physicians.
- Double lung transplantation is indicated for cystic fibrosis and other lung diseases characterized or complicated by chronic infections.

Indications

- Any ambulatory patient with end-stage pulmonary disease.
  - Clinically and physiologically severe disease
  - Medical therapy ineffective or unavailable
  - Limited life expectancy, usually less than two to three years
  - Ambulatory, with rehabilitation potential
  - Acceptable nutritional status, usually 80 – 120 % of ideal body weight

  - Satisfactory psychosocial profile and support system
  - Adequate coverage for the procedure and for post-transplantation care
  - Age < 65 or in well selected patients with end-stage pulmonary disease who are > 65 years old (Machuca)
- Typical patient selection criteria are recommended in peered reviewed medical literature and many of which are taken into considered in the LAS.
- Retransplantation is usually due to non-function of the grafted organ, rejection refractory to immunosuppressive therapy, bronchiolitis obliterans (chronic rejection) and airway complications not correctable by other measures.

Organ-specific Contraindications

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved. Refer to the Medical Director.

Unless otherwise annotated, these recommendations are consistent with the International Society for Heart and Lung Transplantation (ISHLT) Consensus Document for the Selection of Lung Transplant Candidates: 2014 — An Update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. (Weill)

- Significant chest wall/spinal deformity. (Moreno)
- Active or recent history of smoking including tobacco or marijuana. Requires 6 months of documented abstinence through participation in a structured smoking cessation program and, in the case of marijuana, participation in a substance abuse program with regular meeting attendance and negative random drug testing. This may be part of an overall smoking cessation program for those who use both tobacco and marijuana.

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

Unless otherwise annotated, these recommendations are consistent with the International Society for Heart and Lung Transplantation (ISHLT) Consensus Document for the Selection of Lung Transplant Candidates: 2014 — An Update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. (Weill)

- Primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS Issues Management/Submit a member complaint/Complex Medical Conditions and inform Medical Director. http://optumcrt.uhc.com/sites/issuesmgmt/Pages/SubmitMCC.aspx.
- Recent history of malignancy (treated) within 5 years.
  - Requires oncology clearance

- Social and psychiatric issues. Refer for psychosocial evaluation and/or psychiatry consultation for guidance. May require substantial investment of time and energy to create the proper arrangements that will allow a successful transplant. A formal Care Contract may be indicated.
  - Significant depression or other treatable psychiatric illness
  - Insufficient social (caregiver) support
  - Inadequate funding to pay for immunosuppressive medications post-transplant
- Mechanical ventilation. Refer to Medical Director.
- HIV infection without AIDS and with sustained CD4 counts > 200/mm^3.
  - Needs ID clearance
  - Refer to requesting program Patient Selection Criteria
- BMI ≥ 30 kg/m^2.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- BMI < 17 kg/m^2.
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- Chronic peptic ulcer disease, GI bleeding, diverticulitis.
  - GI clearance required
- Severe or symptomatic osteoporosis.
  - Refer to requesting program Patient Selection Criteria
- Patients over the age of 65. (Weiss)
  - Refer to requesting program Patient Selection Criteria
  - If outside the program's patient selection criteria, refer to Medical Director
- The presence of other medical comorbidities such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease must be assessed individually based on severity of disease, presence of end-organ damage, and ease of control with standard therapies. (Lee)

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Heart/Lung

General Information

In 2015, 15 heart/lung transplants were completed, 3 in children and 12 in adults.

Indications

- Patients with end-stage pulmonary vascular disease with end-stage non-reversible cardiac disease secondary to one of the following:
  - Primary pulmonary hypertension
  - Eisenmenger syndrome with a cardiac defect not correctable by surgical repair
  - Patients who are appropriate for single or double lung transplantation and who have severe cardiac disease not otherwise treatable
- Retransplantation. Usually due to primary graft failure (non-function of the grafted organ), rejection refractory to immunosuppressive therapy, bronchiolitis obliterans (chronic rejection) and coronary artery disease (graft vasculopathy).

EVALUATION AND MANAGEMENT GUIDELINES FOR PATIENTS WHO ARE POTENTIAL CANDIDATES FOR COMBINED HEART/LUNG TRANSPLANTATION ARE THOSE FOR HEART AND LUNG TRANSPLANTATION. SEE HEART and LUNG.

Reference

United Network for Organ Sharing: https://www.unos.org/about/annual-report/. Accessed August 2017.

Appendix

Lille Protocol

Severe acute alcoholic hepatitis (AAH) with Maddrey's discriminant function > 32 (4.6 × (patient's prothrombin time in seconds – matched control's prothrombin time in seconds) + patient's serum bilirubin level in milligrams per deciliter).

- Nonresponsive to medical therapy (associated with 6-month survival of ~ 30%)
  - Lille score[1] > 0.45 after seven days of standard medical care for severe liver insufficiency and use of glucocorticoids (40 mg per day of prednisolone for at least 7 days) OR
  - Continuous increase in MELD score
- Severe AAH as the first liver-decompensating event
- Presence of close supportive family members
- Absence of severe coexisting or psychiatric disorders
- Agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence.
- Selection is done four medical teams who independently meet the patient and family members
  - Team 1 (closest to the patient): nurses, one resident and one fellow
  - Team 2: specialist in addiction,
  - Team 3: senior hepatologists
  - Team 4: Anesthesiologist and transplant surgeons.
- All of the evaluating teams have to reach complete consensus.

Lille Score: 6-month survival probability of patients with a Lille model above 0.45 is about 25% contrary to patients with a Lille model below this cutoff (85%).

Louvet A., Naveau S., Abdelnour M et al. The Lille Model: A New Tool for Therapeutic Strategy in Patients with Severe Alcoholic Hepatitis Treated With Steroids. *Hepatology*. 2007;45(6):1348-54.

Lille score can be calculated at http://www.lillemodel.com/score.asp.

Modified RIFLE Criteria (Nadim et al.)

Table 2: Modified RIFLE/acute kidney injury network (AKIN) criteria for the definition and classification of acute kidney injury (AKI) (Mehta et al.)

AKI stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase Scr of ≥ 0.3 mg/dl within 48 h or a 1.5- to 2-fold increase from baseline	<0.5 ml/kg/h for >6 h
2 (Injury)	Increase Scr > 2 to 3-fold from baseline	<0.5 ml/kg/h for >12 h
3 (Failure)	• Increase Scr > 3-fold from baseline OR • Scr ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl OR • initiation of renal replacement therapy	<0.3 ml/kg/h for 24 h or anuria for 12 h

Nadim MK, Sung RS, et al. Simultaneous liver–kidney transplantation summit: current state and future directions. *Am J Transplant*. 2012;12:2901-2908.

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National Kidney Foundation Definition of Chronic Kidney Disease (CKD)

- Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
  - Pathological abnormalities; or
  - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
- GFR < 60 ml/min/1.73 m^2 for ≥ 3 months, with or without kidney damage

AIDS-defining Conditions

Certain serious and life-threatening diseases that occur in HIV-positive people are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS.

The Centers for Disease Control and Prevention (CDC) has developed a list of these conditions (see below). No single patient is likely to have all of these problems. Some of the conditions are rare.

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary,†§ disseminated,† or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- *Pneumocystis jiroveci* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†

- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged 18 Months and for HIV Infection and AIDS Among children Aged 18 Months to <13 Years—United States 2008. Morbidity and Mortality Weekly Report, December 5, 2008/57 (RR-10).

The following are approved changes incorporated into the revision numbers indicated below.	
Revision	**Date, Description of Change, and Name**
1.0	07/19/2012: New. Lynn Wetherbee. Approved by Medical Technology Assessment Committee
1.0	08/14/2012: Approved by National Medical Care Management Committee
2.0	10/10/13: Revised and updated. Lynn Wetherbee Approved by Medical Technology Assessment Committee
2.0	10/16/2013: Approved by Complex Medical Conditions Policy Committee
2.0	11/12/13: Approved by the National Medical Care Management Committee
3.0	08/07/2014: Approved by Medical Technology Assessment Committee
3.0	09/09/2014: Approved by National Medical Care Management Committee
4.0	8/25/2015: Revised and updated: Lorraine Staver
4.0	09/03/2015: Approved by Medical Technology Assessment Committee
4.0	10/13/2015: Approved by National Medical Care Management Committee
5.0	08/16/2016: Revised and updated. Transplant Review Guidelines separated into two documents: Hematopoietic Stem Cell Transplantation and Solid Organ Transplantation.
5.0	09/01/2016: Approved by Medical Technology Assessment Committee
5.0	09/13/2016: Approved by National Medical Care Management Committee

5.0	10/10/2016: Removed Chagas disease as a contraindication to heart transplantation. Updated special considerations for BMI and poor glycemic control for heart transplantation.
6.0	09/07/2017: Approved by Medical Technology Assessment Committee.
6.0	9/12/2017: Approved by National Medical Care Management Committee.
6.0	9/20/2017: Approved by Optum Policy and Guideline Committee.

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