2014 TRANSPLANT REVIEW GUIDELINES

Solid Organ and Stem Cell Transplantation
Including Selected References for Organ Transplantation and Pediatric Heart Disease

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Contraindications
(Universal for all Transplants)

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 Kasikse, 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: Severe diabetes mellitus with end-organ damage, irreversible severe pulmonary disease, with FEV1 <1 L or FVC <50%, irreversible severe hepatic disease, irreversible severe renal disease.
- Active untreated or untreatable malignancy.
- Irreversible, severe brain damage.
- Social and Psychiatric Issues - Refer for psychosocial evaluation and/or psychiatry consultation for guidance. See SPECIAL CONSIDERATIONS.
  - Active alcoholism and substance abuse. Requires 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing. For a past history of alcohol and substance use, see SPECIAL CONSIDERATIONS. (Lucey et al).
  - 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. See the SPECIAL CONSIDERATIONS section for additional information.
  - 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.
Contraindications

- 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).

References


Special Considerations
(Universal for all Transplants)

**NOTE:** The following list contains the standard special considerations for transplants. These special considerations apply to ALL types of transplants unless otherwise noted in the specific guideline content. There may be additional special considerations that apply to a specific type of transplant. Please refer to the “SPECIAL CONSIDERATIONS” section in the specific type of transplant for more information.

- Requests for liver/kidney, heart/liver, liver/lung and kidney/heart transplants: Refer to Medical Director.
- Psychological and social issues that do not meet the level of a contraindication 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. Refer for psychosocial evaluation and/or psychiatry consultation for guidance.
- Recent graft loss. If primary non-function or less than one year since the initial transplant. For Optum case managers: file Quality of Care concern through COMPASS issue management/Complex medical conditions/ COE and inform Medical Director.
- Recent history of malignancy (treated) within 5 years. Requires oncologic assessment of status of treated malignancy.
- Past history (> 6 months in the past) of alcohol, crystal meth, heroin, cocaine, methadone, narcotics, etc., requires program documentation of surveillance including but not limited to drug testing, chemical dependency/substance abuse evaluation and evaluation of hepatitis exposure. The patient should be evaluated by a Substance Abuse specialist. Refer to the specialist evaluation for guidance.
- HIV infection without AIDS and with sustained CD4 counts > 200/mm$^3$. Refer to Medical Director.
- BMI $\geq$ 35 kg/m$^2$ (may vary by type of transplant).
  - Refer to requesting program Patient Selection Criteria.
  - If outside the program’s patient selection criteria, refer to Medical Director.
- Chronic peptic ulcer disease, gastrointestinal (GI) bleeding, diverticulitis, etc. - 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.
- High-dose systemic corticosteroid use defined as > 10mg prednisone/day or equivalent. The dose may vary by type of transplant.
  - Refer to requesting program Patient Selection Criteria.
  - If outside the program’s patient selection criteria, refer to Medical Director.
- For solid organ transplants other than heart, significant, uncorrectable cardiac disease. Cardiac evaluation and clearance required.
Minimum Patient Evaluation Requirements
(Universal for all Transplants)

**NOTE:** The following list contains the standard minimum patient evaluation requirements for transplants. These requirements apply to ALL types of transplants unless otherwise noted in the specific guideline content. There may be additional requirements that apply to a specific type of transplant. Please refer to the “MINIMUM PATIENT EVALUATION REQUIREMENTS” section in the specific type of transplant for more information.

- The objective of pre-transplant assessment is to ensure that:
  - Transplantation is technically possible;
  - The recipient's chances of survival are not compromised by transplantation;
  - Graft survival is not limited by premature death (maximum benefit obtained from a limited resource);
  - Pre-existing conditions are not exacerbated by transplantation;
  - Measures are identified to minimizes peri- and post-operative complications;
  - Patients are informed of the likely risks and benefits of transplantation (Renal Association).

- Psychosocial evaluation and clearance.

- For all transplants other than heart - In the presence of known or suspected cardiac disease, the following tests are indicated:
  - For patients with evidence of left ventricular hypertrophy (LVH) or signs and symptoms of heart failure (HF) cardiology consultation is required. HF may be a contraindication to proceeding with transplantation.
  - With a prior history of ischemic heart disease (IHD): men ≥ 45 or women ≥ 55 years, IHD in a first-degree relative, current cigarette smoking, diabetes, hypertension, fasting total cholesterol > 200 mg/dL, high-density lipoprotein cholesterol < 35 mg/dL and left ventricular hypertrophy (Kasiske, et al.), cardiology consultation and clearance are required.

- Risk factor modification should be aggressively pursued.

- Patients at high risk, e.g., renal disease from diabetes, prior history of IHD, or ≥ 2 risk factors, should have a cardiac stress test.

- Patients with a positive cardiac stress test should undergo coronary angiography for possible revascularization prior to transplantation.

- Patients with critical coronary lesions should undergo revascularization prior to transplantation.
  - Electrocardiogram (EKG) with normal results OR cardiology clearance.
  - Echocardiogram or MUGA or cardiac MRI with LVEF > 40% OR cardiology clearance.
  - Arterial Blood Gases (ABG) within the normal range or pulmonary clearance.
  - Cardiopulmonary stress test – abnormal results require cardiology consultation, possibly left heart catheterization AND cardiology clearance.

- For all transplants other than lung - In the presence of known or suspected pulmonary disease the following tests are indicated. Pulmonary consultation and clearance are required when results are abnormal:
  - Chest X-ray with no active disease.
  - Pulmonary function testing (PFT) with FVC ≥ 50%, FEV1 ≥ 50% and DLCO (corrected) 40% for adults (≥ 50% in children).
• Colonoscopy (if indicated or > age 50) with removal of any polyps. Indications include history of inflammatory bowel disease, primary sclerosing cholangitis, polyps, family history of colon cancer, positive fecal occult blood test.
• HIV testing. See CONTRAINDICATIONS and SPECIAL CONSIDERATIONS.
• Testing for Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology. Immunizations up to date when indicated such as Hepatitis A and Hepatitis B.
  – Note: In the case of stem cell transplants, immunizations are updated post-transplant.
• For all transplants other than kidney, serum creatinine < 2.5 mg/dL (≤ 1.5 mg/dL in children) or GFR > 35 ml/min. If abnormal, may be eligible for a combined transplant.
• For all transplants other than liver, liver function tests (LFT) with transaminases ≤ 3x upper limit of normal and total bilirubin < 2.5mg/dL.
• Screening for peripheral artery disease (PAD) when indicated or > age 50. The possibility of PAD should be strongly considered for all diabetics. If present, intervention and/or clearance required.
• Dental examination by a Dentist. Required dental work to be completed prior to transplant.
• Mammogram (if indicated or > age 40) - Intervention and/or clearance required for abnormal findings.
• GYN examination with Pap smear (if indicated or > age 18) - Intervention and/or clearance required for abnormal findings.

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

**General Information**

- For multi-organ 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.).
- 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 m² (<0.5 mL/s/1.73 m²).
  - 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.
- Due to the very long wait times and the likely increased burden of comorbid conditions, patients over the age of 70 are not 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.
- Paired Kidney Donation/Exchange (PKD) is covered.
- Patients with primary oxalosis with ESRD should be considered for combined liver/kidney transplant (Eason et al.).
Indications

- **End-stage Renal Disease (ESRD):**
  - Chronic renal failure with a Glomerular Filtration Rate (GFR) < 20 ml/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:** (Eason et al., Martin et al.).
  - ESRD patients with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure with gradient > 10 mmHg.
  - ESLD and CKD with GFR ≤ 30 ml/min.
  - Patients with acute renal insufficiency including hepatorenal syndrome with creatinine ≥ 2 mg/dL and dialysis ≥ 8 weeks.
  - Patients with ESLD and evidence of CKD and kidney biopsy demonstrating > 30% glomerulosclerosis or 30% fibrosis.
- **Combined heart/kidney transplant (Russo 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.

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 also noted below.**
- **When a contraindication on this list is present, the transplant will not be approved.**
- **Refer to Medical Director.**

- Reversible renal failure (Bunnapradist).
Special Considerations

- Please review the universal Special Considerations found at the beginning of the Guidelines.
- These apply to all transplants unless otherwise noted below.
- Additional indications that are specific to a particular type of transplant are also noted below.
- Additional consultation and/or evaluation may be indicated.
- This section was previously referred to as “Relative Contraindications.”
- If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
- 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.).

- BMI $\geq 35$ 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 should have cardiac testing done when indicated. See MINIMUM PATIENT EVALUATION REQUIREMENTS.

Minimum Patient Evaluation Requirements

- Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.
- These requirements apply to all transplants unless otherwise noted below.
- Additional indications that are specific to this particular type of transplant are also noted below.
- Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.
- For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.
- Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

- There are no organ-specific medical evaluation requirements.
References


Liver

General Information

- A Model for End-Stage Liver Disease (MELD) score $\geq 15$ 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.).

- 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.
  - 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).

- 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: http://optn.transplant.hrsa.gov/resources/allocationcalculators.asp.

- Generally, patients with MELD scores $< 15$ should not be listed or transplanted unless one or more of the indications discussed below are present:
  - 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).**
    1. Not a candidate for subtotal hepatic resection.
    2. Tumor is HCC stage II (T2 one nodule 2.0–5.0 cm; two or three nodules, all $\leq 3.0$ cm).
    3. No macrovascular involvement.
    4. No identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

  - Tumors can be downstaged with hepatic artery chemoembolization (HACE) 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. See SPECIAL CONSIDERATIONS below.

  - See SPECIAL CONSIDERATIONS below for a list of other conditions that are currently eligible for MELD exception points for adults.

  - Children with the following conditions will be awarded PELD exception points:
    - Hepatoblastoma.
    - Urea cycle disorders and organic acidemia.
    - Combined liver/intestine transplant.

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

• Transplantation is indicated for patients with End-Stage Liver Disease (ESLD) with a life expectancy < 12–24 months and who have developed life-threatening complications.

• MELD score ≥ 15, either calculated or with additional MELD points awarded by Regional Review Board (RRB) following review (Carbone, Newsome et al.). Note that patients with HCC falling within the Milan criteria (T2 lesion) are automatically awarded 22 MELD points.
  – Results from A2ALL (Berg et al.) study demonstrated significant survival advantage associated with receipt of Living Donor Liver Transplant (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 live donor liver transplant (Koffron and Stein). Additional considerations may be present where liver transplantation may be appropriate in other circumstances such as familial amyloid polyneuropathy (FAP) or where quality of life considerations become paramount. See SPECIAL CONSIDERATIONS below.

• 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.

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

• Additional considerations may be present where liver transplantation may be appropriate in other circumstances where quality of life considerations become paramount. See SPECIAL CONSIDERATIONS below.
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 also noted below.
- When a contraindication on this list is present, the transplant will not be approved.
- Refer to 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.

Special Considerations

- Please review the universal Special Considerations found at the beginning of the Guidelines.
- These apply to all transplants unless otherwise noted below.
- Additional indications that are specific to a particular type of transplant are also noted below.
- Additional consultation and/or evaluation may be indicated.
- This section was previously referred to as “Relative Contraindications.”
- If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
- 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.).

- Calculated MELD score < 15. Patients with MELD < 15 will not be approved unless one or more of the following are present:
  - Hepatocellular carcinoma, T2 lesion, eligible for MELD exception points OR awarded MELD exception points by Regional Review Board (RRB) on appeal.
  - Cholangiocarcinoma.
  - Cystic fibrosis with signs of reduced pulmonary function with forced expiratory volume at one second (FEV1) 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.
The peer-reviewed literature does not support a survival advantage with liver transplantation in these situations. Refer to Medical Director.

• Hepatocellular carcinoma that has been "downstaged" (Pomfret et al., Yao et al. and Ravaioli 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. Refer to Medical Director with protocol (Centers for Medicare and Medicaid [CMS], Martin et al.).
  – 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 (CMS, 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 (CMS, Martin et al.).

• Congenital abnormalities that will preclude or prevent liver transplant.

• For patients with low MELD scores, persistent hyponatremia is an independent risk factor for death on the waiting list (Kim et al.). MELD exception points may be granted by the Regional Review Board (RRB). A MELD-Na calculator is found at http://www.mayoclinic.org/meld/mayomodel8.html. Refer to Medical Director.

• Significant, uncorrectable pulmonary disease. Pulmonary evaluation and clearance required.

• Significant pulmonary hypertension. Pulmonary evaluation and clearance required.

• Significant, uncorrectable cardiac disease. Cardiac evaluation and clearance required.

Minimum Patient Evaluation Requirements

Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.

These requirements apply to all transplants unless otherwise noted below.

Additional indications that are specific to this particular type of transplant are also noted below.

Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.

For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.

Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

These recommendations are consistent with the 2013 AASLD Clinical Practice Guidelines (Martin et al.).

• Abdominal ultrasound with Doppler to determine hepatic artery and portal vein anatomy and the presence of hepatocellular carcinoma (HCC).

• Chronic smokers, patients over the age of 60, and those with a clinical or family history of heart disease or diabetes should undergo evaluation for coronary artery disease. Dobutamine stress echocardiography appears to be an effective screening test in this setting; however, positive test results should be confirmed with cardiac catheterization.

• All patients undergoing evaluation for potential liver transplantation should undergo screening for pulmonary hypertension. Doppler echocardiography is an excellent screening test in this setting; however, positive test results should be confirmed with right heart catheterization.
References


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 five 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. Also, the one-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).
  - 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.) (See APPENDIX), 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 (See APPENDIX), 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. Usually due to non-function of the grafted organ(s), chronic rejection and chronic allograft pancreatitis.

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 also noted below.
- When a contraindication on this list is present, the transplant will not be approved.
- Refer to Medical Director.

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

Special Considerations

- Please review the universal Special Considerations found at the beginning of the Guidelines.
- These apply to all transplants unless otherwise noted below.
- Additional indications that are specific to a particular type of transplant are also noted below.
- Additional consultation and/or evaluation may be indicated.
- This section was previously referred to as “Relative Contraindications.”
- If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
- 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. Refer to Medical Director.
- May require an extra-contractual agreement. Contact Contracting & Network Development.
• 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.

Minimum Patient Evaluation Requirements

- Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.
- These requirements apply to all transplants unless otherwise noted below.
- Additional indications that are specific to this particular type of transplant are also noted below.
- Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.
- For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.
- Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

- Liver function tests (LFT) with transaminases ≤ 3x upper limit of normal and total bilirubin < 2.5mg/dL.
- For PTA: serum creatinine < 2.5 mg/dL (≤ 1.5 mg/dL in children) or GFR > 35 ml/min. If abnormal, may be eligible for a combined transplant (SPK or PAK). See KIDNEY.
- Carotid Doppler ultrasound (with known coronary artery disease or > age 50) – Abnormal findings evaluated further. Intervention and/or clearance required for abnormal findings.
Appendix

**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
References


Intestine including Liver/Intestine & Multivisceral

General Information

- 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 data base).

- 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).
  - Dependent on TPN with cholestatic liver disease.
    - If cholestasis is advanced, or cirrhosis is present, a combined liver/intestine transplant is performed.
    - 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 anastamoses of one or more of the separate organs problematic when compared to an en bloc dissection and transplantation that requires fewer vascular and intestinal anastamoses OR
  • Desmoid tumors.

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.

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 also noted below.
• When a contraindication on this list is present, the transplant will not be approved.
• Refer to Medical Director.

• There are no organ specific contraindications.

Special Considerations

• Please review the universal Special Considerations found at the beginning of the Guidelines.
• These apply to all transplants unless otherwise noted below.
• Additional indications that are specific to a particular type of transplant are also noted below.
• Additional consultation and/or evaluation may be indicated.
• This section was previously referred to as “Relative Contraindications.”
• If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
• Refer to Medical Director if questions remain.

• 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. Refer to Medical Director.
Minimum Patient Evaluation Requirements

- Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.
- These requirements apply to all transplants unless otherwise noted below.
- Additional indications that are specific to this particular type of transplant are also noted below.
- Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.
- For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.
- Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

- There are no organ specific medical evaluation requirements.

References


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).

- 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 > 42% according to the July 2012 report from the Scientific Registry of Transplant recipients (SRTR). The majority of these devices are VADs (Alba). See complete discussion below.

- Total Artificial Hearts
  - A total artificial heart (TAH) can maintain the life of a patient with an irreparably damaged heart.
  - Examples of artificial heart devices:
    - The SynCardia (formerly know 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 Portable Driver was approved on June 26, 2014 for use with the SynCardia temporary Total Artificial Heart as a bridge to transplantation in cardiac transplant candidates who are clinically stable. This allows patients with the SynCardia TAH to be discharged home pretransplant while they wait for a donor heart.
    - The FDA has recently approved the use of the Total Artificial Heart for Destination Therapy under a Humanitarian Use Device exception. SynCardia is in the process of developing the Humanitarian Device Exemption (HDE) protocol for FDA approval (SynCardia, Press Release, April 12, 2012).
    - AbioCor is approved by the FDA under a Humanitarian Device Exemption (HDE) for use as destination therapy for patients with end-stage heart disease (FDA-1). These are patients who have failed optimal medical therapy, who have no other reasonable medical or surgical treatment options, and who meet all of the following criteria: (NOTE some benefit plans have specific language on the use of HDE devices.)
      - Unlikely to live more than a month without an intervention.
      - Not eligible for a heart transplant.
      - Less than 75 years old.
      - Require multiple inotropic support.
      - In biventricular failure not treatable by LVAD destination therapy.
      - Unable to be weaned from biventricular support if on such support.
      - Chest volume large enough to hold the device.
Ventricular Assist Devices

Please refer to Mechanical Circulatory Support Devices Guidelines available internally on Knowledge Library or externally at www.unitedhealthcareonline.com.

Indications

- 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).

Contraindications

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- Refer to Medical Director.

Unless otherwise annotated, these recommendations are consistent with the International Society for Heart and Lung Transplantation (ISHLT) 2006 Listing Criteria for Heart Transplantation (Mehra, et al.).
- Significant peripheral vascular disease not correctable with surgery.
- Severe irreversible pulmonary hypertension with pulmonary artery systemic pressure >60 mmHg, mean transpulmonary gradient >15 mmHg, and/or pulmonary vascular resistance (PVR)>5 Wood units on maximal vasodilator therapy (Alba). However, the patient may qualify for combined heart/lung transplantation.
• 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 FEV1 <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).
• Chagas disease (Trypanosoma cruzi infection) (Bestetti).

Special Considerations

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• Refer to Medical Director if questions remain.

Unless otherwise annotated, these recommendations are consistent with the International Society for Heart and Lung Transplantation (ISHLT) 2006 Listing Criteria for Heart Transplantation (Mehra, et al.).

• Patients with renal failure should be evaluated for combined heart-kidney transplantation. See MINIMUM PATIENT EVALUATION REQUIREMENTS below and indications for KIDNEY transplant.
• 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.
• High-dose systemic corticosteroid use (> 10mg prednisone/day or equivalent).
  – Refer to requesting program Patient Selection Criteria.
  – If outside the program’s patient selection criteria, refer to Medical Director.
• BMI < 20 or > 30 kg/ m² (Jessup).
  – 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).
Minimum Patient Evaluation Requirements

• Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.
• These requirements apply to all transplants unless otherwise noted below.
• Additional indications that are specific to this particular type of transplant are also noted below.
• Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.
• For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.
• Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

Unless otherwise annotated, these recommendations are consistent with the ISHLT 2006 Listing Criteria for Heart Transplantation (Mehra, et al.).

• Assessment of heart failure severity.
  – EKG
  – Echocardiogram
  – Cardiopulmonary stress test.
  – Right heart catheterization.
  – \( \text{VO}_2\text{max} \)
• Liver function tests (LFT) with transaminases ≤ 3x upper limit of normal and total bilirubin < 2.5mg/dL.
• HbA1C for diabetics.
• Serum creatinine < 2.5 mg/dL (≤ 1.5 mg/dL in children) or GFR > 35 ml/min due to intrinsic renal disease or not reversible with augmentation of cardiac output. If abnormal, may be eligible for a combined transplant. See KIDNEY.
• Carotid Doppler ultrasound when indicated or age > 50 – Abnormal findings evaluated further. Intervention and/or clearance required for abnormal findings.
### New York Heart Association (NYHF) Functional Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (feeling heart beats), dyspnea (shortness of breath) or anginal pain.</td>
</tr>
<tr>
<td>Class II</td>
<td>(Mild) - Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>Class III</td>
<td>(Moderate) - Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>Class IV</td>
<td>(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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Objective Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.</td>
</tr>
<tr>
<td>C</td>
<td>Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.</td>
</tr>
<tr>
<td>D</td>
<td>Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.</td>
</tr>
</tbody>
</table>

### American Heart Association Classification (AHA)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Presence of heart failure risk factors but no heart disease and no symptoms.</td>
</tr>
<tr>
<td>Stage B</td>
<td>Heart disease is present but there are no symptoms (structural changes in heart before symptoms occur).</td>
</tr>
<tr>
<td>Stage C</td>
<td>Structural heart disease is present AND symptoms have occurred.</td>
</tr>
<tr>
<td>Stage D</td>
<td>Presence of advanced heart disease with continued heart failure symptoms requiring aggressive medical therapy.</td>
</tr>
</tbody>
</table>
References


Canter CE. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 6-FEB-2007; 115(5): 658-76.


Johnson MR. When is retransplantation a viable option? Heart Fail Clin. 01-JAN-2007; 3(1): 97-105.


NYHF. Available at: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Accessed July 20, 2012.


Yamani MH and Taylor DO. Heart Transplantation. Cleveland Clinic: Current Clinical Medicine, 2nd ed.
Lung

General Information

• The indications for lung transplantation include a diverse array of pulmonary diseases of the airways, parenchyma, and vasculature.

• From International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update (Orens, et al.) (2006 ISHLT Guidelines): “Lung transplantation is indicated for patients with chronic, end-stage lung disease who are failing maximal medical therapy, or for whom no effective medical therapy exists. Potential candidates should be well informed and demonstrate adequate health behavior and a willingness to adhere to guidelines from health care professionals.”

• 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/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 to 120 percent 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 is recommended in peer-reviewed medical literature and many of which are taken into considered in the LAS.

• Retransplantation. 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.
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 also noted below.
- When a contraindication on this list is present, the transplant will not be approved.
- Refer to Medical Director.

Unless otherwise noted, these recommendations are consistent with the 2006 ISHLT Guidelines for the Selection of Lung Transplant Candidates (Orens, et al., Spahr 2011).

- 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

- Please review the universal Special Considerations found at the beginning of the Guidelines.
- These apply to all transplants unless otherwise noted below.
- Additional indications that are specific to a particular type of transplant are also noted below.
- Additional consultation and/or evaluation may be indicated.
- This section was previously referred to as “Relative Contraindications.”
- If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
- Refer to Medical Director if questions remain.

Unless otherwise noted, these recommendations are consistent with the 2006 ISHLT Guidelines for the Selection of Lung Transplant Candidates (Orens, et al.).

- Mechanical ventilation. Refer to Medical Director.
- HIV infection without AIDS and with sustained CD4 counts > 200/mm³.
  - Needs ID clearance. Refer to requesting program Patient Selection Criteria.
- BMI > 30 kg/m².
  - Refer to requesting program Patient Selection Criteria.
  - If outside the program’s patient selection criteria, refer to Medical Director.
- BMI < 17 kg/m².
  - Refer to requesting program Patient Selection Criteria.
  - If outside the program’s patient selection criteria, refer to Medical Director.
- 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.
• High-dose systemic corticosteroid use (> 0.3mg/kg/day prednisone or equivalent).
  – Refer to requesting program Patient Selection Criteria.
  – If outside the program’s patient selection criteria, refer to Medical Director.
• Severe or symptomatic osteoporosis.
• 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).

Minimum Patient Evaluation Requirements

• Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.
• These requirements apply to all transplants unless otherwise noted below.
• Additional indications that are specific to this particular type of transplant are also noted below.
• Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.
• For non-COE programs, documentation of ALL Minimum Patient Evaluation Requirements is required.
• Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

Unless otherwise noted, these recommendations are consistent with the 2006 ISHLT Guidelines for the Selection of Lung Transplant Candidates (Orens, et al.).
• Carotid Doppler ultrasound (with known coronary artery disease or > age 50) – Abnormal findings evaluated further. Intervention and/or clearance required for abnormal findings.

References


Heart/Lung

General Information
In 2013, 23 heart/lung transplants have been completed, 7 in children and 16 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.**

Hematopoietic Stem Cell Transplant

General Information

- “Back-up” autologous harvesting for patients in complete remission (CR) with no evidence of marrow involvement by malignancy is appropriate. For example, bone marrow or peripheral blood progenitor cell harvesting is appropriate for patients with acute myeloid leukemia (AML) or multiple myeloma in CR and who might be transplanted in the future.

- Donor lymphocyte infusion (DLI) following allogeneic stem cell transplant is appropriate for incomplete chimerism and disease relapse in the setting of incomplete chimerism. This is not a second stem cell transplant (Bacigalupo et al.).

- Repeat stem cell transplant is appropriate for primary and secondary failure to engraft and disease relapse. Primary failure is the result of slow or incomplete blood count recovery after SCT, while secondary failure is associated with decreasing blood counts following a successful SCT graft.

- Autologous stem cell transplant with or without a second autologous transplant (tandem transplant) is considered a standard of care for the treatment of multiple myeloma although controversy does exist particularly in the era of newer and more effective chemotherapy agents such as bortezomib, lenalidomide and thalidomide (Blade et al., Harousseau & Moreau, Bashey et al., Kumar et al.). As the primary and salvage treatment for multiple myeloma has become increasingly successful in recent years, it is likely that, going forward, multiple factors will need to be considered prior to making decisions regarding the use of transplantation procedures; e.g., risk stratification, age, comorbidities, etc. and that the role of transplantation may decrease for certain subgroups.

- Tandem stem cell transplants require review by the Medical Director except for the following conditions: multiple myeloma, testicular germ cell tumors or neuroblastoma, pediatric brain tumors, and other conditions as part of an IRB approved clinical trial.

- Third stem cell transplants require Medical Director review.
  - If part of a sequence of high-dose chemotherapy followed by rescue stem cell infusion as is the case with some neuroblastoma, medulloblastoma and testicular germ cell tumor protocols, the entire course may be approved initially.

- Stem cell source and preparative regimens are at the discretion of the treating physician.
  - Single unit umbilical cord blood stem cell transplants are standard of care for children in many programs. Children >45kg who receive a single cord blood unit may experience prolonged time to engraftment and other post-transplant complications, therefore, a calculation of 2.5 X 10^7 nucleated cells per kilogram may improve response (de Lima & Shpall).
  - If a matched related donor is not available AND no donors have been identified through the National Marrow Donor Program (NMDP) OR there is urgency to transplant sooner than would be expected to be possible through a conventional search and harvest of an unrelated donor through the NMDP, the use of stem cells derived from umbilical cord blood or haploidentical donors cells can be authorized under certain circumstances. See SPECIAL CONSIDERATIONS.

- The stem cell transplant expert panel confirmed that the treatment of any pediatric patient under a Children’s Oncology Group (COG) protocol should be considered Standard of Care.

- Patients who have undergone stem cell transplant have altered immune systems post-transplant. In the case of allogeneic stem cell transplant, the immune system may never fully recover. These patients have unique care needs in the post-transplant period which need to be understood and managed for the rest of their lives (Rizzo et al.).

- Chimeric Antigen Receptor Therapy and/or the use of T-cells/natural killer cell protocols provide treatment of the underlying disease and are not considered to be a transplant procedure. Patients receive immune-depleting chemotherapy prior to infusion. Requests for this therapy have been received for such diseases as ALL or neuroblastoma. As it is not a transplant, the review of such requests should be completed by whoever authorizes the medical benefits for the patient and to determine if benefits for participation in a clinical trial exist (Kalos et al.).
**Indications**

If an indication is listed as “Not standard of care,” the requested service may be covered if there is a state mandate, the member has a cancer clinical trial benefit, can be covered under the CRS program, if there is a life-threatening illness clause in the benefit plan, etc. and all provisions of the applicable benefit(s) have been met.

**CHECK FOR STATE MANDATES AND THE MEMBER’S BENEFIT PLAN TO DETERMINE ELIGIBILITY.**

- ✓ = COVERED INDICATION
- N = NOT A COVERED INDICATION
- □ = If nothing is indicated, this generally means that this is not considered an indication for stem cell transplant of the type requested and we do not expect to see requests for authorization for this particular type of stem cell transplant for this indication.
  - Any requests for stem cell transplant for one of these indications will be referred to the Medical Director for review.

<table>
<thead>
<tr>
<th>Disease/Indication</th>
<th>Auto</th>
<th>Allo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphoblastic Leukemia (ALL) (Hahn et al., 2005, Oliansky et al. 2012)</td>
<td>✓</td>
<td>✓</td>
<td>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</td>
</tr>
</tbody>
</table>
| Acute Myeloid Leukemia (AML) (Oliansky et al., 2007 & 2008) | ✓ | ✓ | Intermediate and high-risk AML including but not limited to:  
• First complete response (CR1) with poor-risk cytogenetics or molecular markers.  
• AML after relapse.  
• CR2 and beyond.  
See appendix for the definition of risk markers and clinical risk factors. |
| Chronic Lymphocytic Leukemia (CLL) | N | ✓ | Lack of data supporting auto for CLL. |
| Chronic Myeloid Leukemia (CML) | N | ✓ | Minimal to no data supporting auto in CML. Allo being used much less frequently in the era of tyrosine kinase inhibitors and primarily for the relatively rare very young patients and those exhibiting less than optimal responses to targeted therapy. |
| Prolymphocytic Leukemia (Krishnan et al., Kalaycio et al.) | ✓ | ✓ |         |
### Disease/Indication

<table>
<thead>
<tr>
<th>Disease/Indication</th>
<th>Auto</th>
<th>Allo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelodysplastic &amp; Pre-Leukemic Syndromes (Oliansky et al., 2009)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic Syndrome (MDS)</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Myelofibrosis and related conditions (e.g. PRV)</td>
<td>N</td>
<td>✓</td>
<td>Allo approved using the Dynamic International Prognostic Scoring System (DIPSS). See appendix for DIPSS scoring system.</td>
</tr>
<tr>
<td>Juvenile Myelo-Monocytic Leukemia (JMML/JCML)</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Brain Tumors</strong></td>
<td></td>
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</tr>
<tr>
<td>Anaplastic Astrocytoma</td>
<td>N</td>
<td></td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Brain stem glioma</td>
<td>N</td>
<td></td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>N</td>
<td></td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Germinoma</td>
<td>N</td>
<td></td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Glioblastoma Multiforme (GBM)</td>
<td>N</td>
<td></td>
<td>May be considered in infants.</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primitive Neuro-ectodermal Tumor (PNET)</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td><strong>Germ Cell Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular Germ Cell Tumor</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Extragonadal Germ Cell Tumor</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Seminoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Mixed Germ Cell Tumors</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Teratoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Yolk-Sac Tumor (Endodermal Sinus Tumor)</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Germ Cell Tumor of the Ovary</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Multiple Myeloma/ Plasma Cell Disorders (Hahn et al., 2003)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
<td>Refer allograft request for Medical Director Review.</td>
</tr>
<tr>
<td>a) Single auto</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>b) Tandem (auto followed by auto)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>c) Tandem (auto followed by allo)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>d) Allogeneic</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>AL-Amyloidosis</td>
<td>✓</td>
<td>N</td>
<td>Allogeneic SCT may be appropriate on clinical trial. Refer to Medical Director.</td>
</tr>
<tr>
<td>Waldenstrom Macroglobulinemia</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Monoclonal gammopathy of uncertain significance (MGUS)</td>
<td>N</td>
<td>N</td>
<td>No transplant indicated.</td>
</tr>
<tr>
<td>POEMS (Polyneuropathy Organomegaly Endocrinopathy, Monoclonal Gammopathy Skin defects Syndrome) (D’Souza et al., Ji et al., Li et al.)</td>
<td>✓</td>
<td>N</td>
<td>Autologous SCT may be appropriate. Refer to Medical Director.</td>
</tr>
<tr>
<td>Solitary Plasmacytoma</td>
<td>N</td>
<td>N</td>
<td>No transplant indicated.</td>
</tr>
<tr>
<td><strong>Hodgkin’s Disease</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>✓</td>
<td>✓</td>
<td>Tumor must be chemo-sensitive which is defined as a complete or partial response based on the Cheson criteria. See appendix for Cheson criteria.</td>
</tr>
<tr>
<td><strong>Non-Hodgkin’s Lymphoma (NHL)</strong></td>
<td></td>
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</tr>
<tr>
<td>Small B-cell lymphocytic lymphoma</td>
<td>N</td>
<td>✓</td>
<td>Auto not standard of care. This is treated in the same manner as CLL. Refer to Medical Director.</td>
</tr>
<tr>
<td>Follicle center lymphoma (Oliansky et al., 2010)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma/ immunocytoima</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Marginal zone lymphoma (mucosa-associated lymphoid tissue, splenic, nodal)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell lymphoma (mediastinal large cell, primary effusion) (Oliansky et al. 2011)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Precursor B-cell leukemia/lymphoma</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>T-cell Lymphoma</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
<td>--------------------------------------------</td>
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</tr>
<tr>
<td><strong>Other Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical teratoid Rhabdoid tumors</td>
<td>✓</td>
<td>N</td>
<td>Tandem auto may be indicated. May be appropriate as part of a clinical trial (Nikolaides et al.).</td>
</tr>
<tr>
<td>Blastic Plasmacytoid dendritic cell neoplasm</td>
<td>N</td>
<td>✓</td>
<td>Dietrich et al.</td>
</tr>
<tr>
<td>Epithelial Ovarian Cancer</td>
<td>N</td>
<td>N</td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Ewing Tumor (Ewing Sarcoma)</td>
<td>✓</td>
<td>N</td>
<td>Allogeneic not standard of care.</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>✓</td>
<td>N</td>
<td>Tandem auto can be approved.</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>N</td>
<td>N</td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>N</td>
<td>N</td>
<td>Not standard of care.</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>✓</td>
<td>N</td>
<td>Allogeneic not standard of care.</td>
</tr>
<tr>
<td>Rhabdomyosarcoma/soft tissue sarcoma</td>
<td>N</td>
<td>N</td>
<td>May be appropriate as part of a clinical trial (Stiff et al.). Refer to Medical Director.</td>
</tr>
<tr>
<td>Supratentorial Ependymoma</td>
<td>✓</td>
<td></td>
<td>Venkatramani et al.</td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>✓</td>
<td>N</td>
<td>May be appropriate in relapsed disease as part of a clinical trial (Brown et al., Campbell et al.). Refer to Medical Director.</td>
</tr>
<tr>
<td><strong>Hematological Disorders</strong></td>
<td></td>
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<tr>
<td>Aplastic Anemia</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Blackfan-Diamond Syndrome</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Chronic Granulomatous Disease</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Agranulocytosis (Kostmann Syndrome)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Amegakaryocytic Thrombocytopenia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskeratosis Congenita</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanconi Anemia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal Nocturnal Hemoglobinuria (PNH)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle Cell Anemia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalassemia Major</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<td>--------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Immunodeficiency Syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD40 Ligand Deficiency</td>
<td></td>
<td>✓</td>
<td>Patients with the non-neuropathic type may benefit from a stem cell transplant following failed enzyme replacement therapy or if significant bone pain exists in spite of enzyme replacement therapy.</td>
</tr>
<tr>
<td>Chediak-Higashi Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hemophagocytic Lymphohistiocytosis (HLH) (same as Familial Erythrophagocytic Lymphohistiocytosis - FEL)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Leukocyte Adhesion Deficiency</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ommen Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency Disease (SCIDS)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>X-linked Lymphoproliferative Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Gaucher disease type I (Pastores et al., Charrow et al., Peters &amp; Steward, Jmoudiak &amp; Futerman)</td>
<td></td>
<td>✓</td>
<td>A non-cerebral form, transplantation may effectively diminish the impact of the accumulation of metabolic byproducts in lung and liver. These patients die from lung and liver disease and are candidates for stem cell transplantation.</td>
</tr>
<tr>
<td>Niemann-Pick type B (Schuchman)</td>
<td></td>
<td>✓</td>
<td>There is little experience with transplantation for fucosidosis, a very rare entity among rare entities, but reports indicate that stem cell transplantation performed early effectively ameliorates disease progression.</td>
</tr>
<tr>
<td>Fucosidosis (Miano et al., Vellodi et al.)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lysosomal storage diseases (Heese)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Systemic Sclerosis (Scleroderma)</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Studies are ongoing. May be considered life-threatening if significant end-organ involvement, particularly kidneys and lungs. Refer to Medical Director.</td>
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### Disease/Indication

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<td><strong>Inherited Metabolic Disorders</strong></td>
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<td>Adrenoleukodystrophy</td>
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<td>Hunter Syndrome</td>
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<td>Mannosidosis</td>
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<td>Maroteaux-Lamy syndrome (MPS VI)</td>
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<td>Metachromatic Leukodystrophy</td>
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<tr>
<td>(MNGIE) Mitochondrial Neurogastrointestinal Encephalopathy (Halter et al., Filosto et al.)</td>
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<tr>
<td>Osteopetrosis</td>
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<td></td>
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<td>Rett Syndrome</td>
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<td><strong>Cardiac Conditions</strong></td>
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<td>N</td>
<td>N</td>
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<tr>
<td>Heart Disease</td>
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<td>N</td>
<td>Not standard of care. It would only be considered for approval under a clinical trial if the member's benefit plan supports participation in a clinical trial.</td>
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<td><strong>Additional Condition/Disease Indications</strong></td>
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<tr>
<td>Hematopoietic Stem Cell Transplant Reference Sheet</td>
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### 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 also noted below.
- When a contraindication on this list is present, the transplant will not be approved.
- Refer to Medical Director.

- Multi-system disease not correctable by stem cell transplantation.
Special Considerations

- Please review the universal Special Considerations found at the beginning of the Guidelines.
- These apply to all transplants unless otherwise noted below.
- Additional indications that are specific to a particular type of transplant are also noted below.
- Additional consultation and/or evaluation may be indicated.
- This section was previously referred to as “Relative Contraindications.”
- If one or more of these conditions are present, the Transplant Review Guidelines provide direction for any necessary additional evaluation and/or approval in order to understand the importance or impact of the issue in question.
- Refer to Medical Director if questions remain.

- Cord blood transplants in adults.
  - As there may be no reasonable alternative to the use of cord blood units in this situation and the available literature supports this approach, under this circumstance umbilical cord blood SCTs may be approved as standard of care. There is no discrimination between single or double transplants. Approval may be based on an urgent need (Brunstein et al.).
    - If participation in a clinical trial is requested, all clinical trial authorization rules will apply.
  - Request letter of medical necessity or similar documentation and refer to Medical Director for review.

- Haploidentical stem cell transplant.
  - Haploidentical SCT can be approved at a Center of Excellence (COE) (Klingebiel et al.).
    - If participation in a clinical trial is requested, all clinical trial authorization rules will apply.
  - At a non-COE program, haploidentical stem cell transplant will only be approved under a clinical trial if the member's benefit plan supports participation in clinical trials.
    - Request letter of medical necessity or similar documentation and refer to Medical Director for review.

- Allogeneic stem cell transplant for multiple myeloma is controversial either as a single allogeneic transplant as initial therapy with curative intent or as the second stage of a planned tandem transplant proceeded by an autologous transplant. The following recommendations are consistent with the evolving practice and recognize the expertise of treating physicians within network programs. This position is consistent with the recent reports from Europe and Seattle Cancer Care Alliance (Bensinger, Attal et al., Bruno et al.). This recommendation may change as additional experience is gained with the newer disease modifying agents for the treatment of myeloma and as more experience is gained with reduced intensity allogeneic stem cell transplant for this disease.
  - Reduced intensity matched related donor (MRD) and matched unrelated donor (MUD) allogeneic SCT as the second transplant can be approved as standard of care at a COE or TAP with experience with this procedure (Bruno et al. (1-4), Rotta et al.). The increased risk of treatment-related mortality (TRM), acute graft versus host disease (GVHD) and chronic GVHD must be weighed against the possible benefit of graft versus myeloma effect (GVME) and possible long-term survival (greater than three years) for those patients who do not succumb to the early complications of an allogeneic transplant. Participation in a clinical trial is not a requirement if performed at a COE or TAP program.
    - If participation in a clinical trial is requested, all clinical trial authorization rules will apply.
  - Request letter of medical necessity or similar documentation and refer to Medical Director for review.
  - MRD or MUD allogeneic SCT as initial therapy can be approved for young patients (< 50 years old) in otherwise good health with aggressive, high-risk disease refractory to conventional approaches (Georges et al.). Participation in a clinical trial is not a requirement at a COE or TAP program with experience with this procedure.
    - If participation in a clinical trial is requested, all clinical trial authorization rules will apply.
– With the exception of the younger patients described above, fully ablative allogeneic SCT is not indicated except under clinical trial.

- **HIV infection.**
  - Patients should have a formal infectious disease consult indicating adequate CD-4 count (200 or greater), RNA negativity and no active AIDS defining illness.

- **Persisting CNS involvement by malignancy except for primary CNS tumors such as those referenced under brain tumor indications.**
  - Refer to Medical Director.

- **Refer to requesting program Patient Selection Criteria for age specific criteria.**
  - If outside the program’s patient selection criteria, refer to Medical Director.

### Minimum Patient Evaluation Requirements

- Please review the universal Minimum Patient Evaluation Requirements found at the beginning of the Guidelines.

- These requirements apply to all transplants unless otherwise noted below.

- Additional indications that are specific to this particular type of transplant are also noted below.

- Center of Excellence (COE) programs are assumed to have performed all of these necessary tests and consultations. Therefore, documentation is not required.

- For non-COE programs, documentation of **ALL** Minimum Patient Evaluation Requirements is required.

- Refer to Medical Director if results are questionable or abnormal results are not further addressed in the evaluation process.

- **Serum creatinine < 2.5 mg/dL (≤ 1.5 mg/dL in children) or GFR > 50 ml/min.**
  - Serum creatinine may be higher in patients with multiple myeloma or other plasma cell dyscrasias. Patients with multiple myeloma with reduced renal function are not prohibited from undergoing autologous BMT when the decreased renal function is related to the multiple myeloma (myeloma kidney). This includes patients on hemodialysis with no other contraindications.

- **Pediatric patients should have a Lansky score > 50. Adult patients should have a Karnofsky score > 70.**
Hematopoietic Stem Cell Transplant Reference Sheet

The following is a list of rare and unusual conditions where allogeneic transplant may be indicated. The list was reviewed and accepted by the 2014 Optum Hematopoietic Stem Cell Transplant Expert Panel. If there is a condition found on this list that is not included in the INDICATIONS section above, refer to Medical Director.

1. Lymphocyte Immunodeficiencies (many of these fall under “severe combined immunodeficiency” classification)
   - Adenosine deaminase deficiency
   - Artemis deficiency
   - Calcium channel deficiency
   - Cernunnos-XLF immunodeficiency
   - CHARGE syndrome with immune deficiency
   - Common gamma chain deficiency
   - Deficiencies in CD 45, CD3, CD8
   - DiGeorge syndrome
   - DNA ligase IV
   - Interleukin-7 receptor alpha deficiency
   - Janus-associated kinase 3 (JAK3) deficiency
   - Major histocompatibility class II deficiency
   - Purine nucleoside phosphorylase deficiency
   - Recombinase-activating gene (RAG) 1/2 deficiency
   - Reticular dysgenesis
   - Winged helix deficiency
   - Zeta-chain-associated protein-70 (ZAP-70) deficiency

2. Phagocytic Deficiencies
   - Chediak-Higashi syndrome
   - Griscelli syndrome, type 2
   - Interferon-gamma receptor deficiencies
   - Leukocyte adhesion deficiency
   - Shwachman-Diamond syndrome*

   *may be considered as marrow failure syndrome rather than immunodeficiency

3. Other Immunodeficiencies
   - Autoimmune lymphoproliferative syndrome
   - Cartilage hair hypoplasia
   - CD25 deficiency
   - Familial hemophagocytic lymphohistiocytosis
   - Hyper IgD and IgE syndromes
   - ICF syndrome
   - IPEX syndrome
   - NEMO deficiency
   - NF-κB inhibitor, alpha (κB-alpha)
References


Hematopoietic Stem Cell Transplant Appendix –
Timing for Stem Cell Transplant Consultation

RECOMMENDED TIMING FOR STEM CELL TRANSPLANTATION CONSULTATION
(National Marrow Donor Program®/Be The Match® and the American Society for Blood
and Marrow Transplantation)

These guidelines for transplant consultation were developed jointly, and updated for 2013, by the National
Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT).
They are based on current clinical practice and the medical literature, including comprehensive evidence-based
reviews. One critical factor in the outcome of hematopoietic cell transplantation is the appropriate planning
and timing of the transplant. The intent of these guidelines is to identify patients at risk of disease progression
and, therefore, which patients should be evaluated for transplantation.

While transplant may be immediately indicated for some patients with these factors, it may not be for all
patients. The consultation helps ensure there are plans in place for the patient to move quickly to transplant,
if needed, before disease progresses or complications develop. If allogeneic transplant is a possibility, it helps
provide adequate time for an unrelated donor or cord blood search.

Adult Leukemias and Myelodysplasia

Acute Myelogenous Leukemia (AML)
- High-risk AML including:
  - Antecedent hematological disease [e.g., myelodysplasia (MDS)].
  - Treatment-related leukemia.
  - Induction failure.
- CR1 with poor-risk cytogenetics or molecular markers.
- AML after relapse.
- CR2 and beyond.

Acute Lymphoblastic Leukemia (ALL)
- CR1 standard or high-risk, including:
  - Poor-risk cytogenetics (e.g., Philadelphia chromosome positive, t(9;22) or 11q23 rearrangements).
  - High WBC (>30,000 - 50,000) at diagnosis.
  - CNS or testicular involvement.
  - No CR within 4 weeks of initial treatment.
  - Induction failure.
- ALL after relapse.
- CR2 and beyond.
Myelodysplastic Syndromes (MDS)
- Intermediate-1 (INT-1), intermediate-2 (INT-2) or high IPSS score.
- Any MDS with poor prognostic features, including:
  - Older age.
  - Refractory cytopenias.
  - Adverse cytogenetics.
  - Transfusion dependent.

Chronic Myelogenous Leukemia (CML)
- No hematologic response post-tyrosine kinase inhibitor (TKI) initiation.
- No complete cytogenic response post TKI initiation.
- Disease progression.
- Intolerance to TKI.
- Accelerated phase.
- Blast crisis (myeloid or lymphoid).

Chronic Lymphocytic Leukemia (CLL)
- High-risk cytogenetics or molecular features (e.g., 11q or 17p deletions, un-mutated Ig VH mutational status).
- Short initial remission.
- Poor initial response.
- Fludarabine-resistant.

Pediatric Acute Leukemias

Acute Myelogenous Leukemia (AML)
- Monosomy 5 or 7.
- Age <2 years at diagnosis.
- Induction failure.
- CR1 with HLA matched sibling donor.
- AML after relapse.
- CR2 and beyond.

High-Risk Acute Lymphoblastic Leukemia (ALL)
- Induction failure.
- Philadelphia chromosome positive.
- WBC > 100,000 at diagnosis.
- 11q23 rearrangement.
- Mature B cell phenotype (Burkitt's lymphoma).
- Infant at diagnosis.
- CR1 duration < 18 months.
- ALL after relapse.
- CR 2 and beyond.
Lymphomas
Non-Hodgkin's Lymphoma
  • Follicular.
    – Poor response to initial treatment.
    – Initial remission duration <12 months.
    – Second relapse.
    – Transformation to diffuse large B-cell lymphoma.
  • Diffuse Large B-Cell or High-Grade Lymphoma.
    – At first or subsequent relapse.
    – CR1 for patients with high or high-intermediate IPI risk.
    – No CR with initial treatment.
  • Mantle Cell.
    – Following initial therapy.
Hodgkin's Lymphoma
  • No initial CR.
  • First or subsequent relapse.

Multiple Myeloma
Multiple Myeloma
  • After initiation of therapy.
  • At first progression.
2014 Selected References Document


Bensinger WI. (2) Reduced intensity allogeneic stem cell transplantation in multiple myeloma. *Front Biosci*. 2007 May 1,12:4384-4392.


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Appendix

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 jirovecii 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].)

Clinical, Cytogenetic and Mutational Risk Stratification for AML

Favorable risk:
- Cytogenetics.
  - t(8;21).
  - inv(16) or t(16;16).
- Mutations.
  - Kit.

Intermediate risk (one or more of the following):
- Cytogenetics.
  - Normal.
  - +8.
- Mutations.
  - Flt3 ITD-positive.
  - Mutant TET2, MLL-PTD, DNMT3A, ASXL1, PHF6.

Unfavorable (high) risk (one or more of the following):
- Cytogenetics.
  - -5/-7.
  - 11q23, 20q.
  - 3 or more.
- Clinical features:
  - CR2 and beyond.
  - Age > 70.
  - Refractory to induction chemotherapy.
  - Persistence of minimal residual disease following induction.

The Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis (PMF)

The DIPSS for PMF uses five risk factors to predict survival. Values for score calculation are as follows:

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<tr>
<td>Age &gt; 65</td>
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</tr>
<tr>
<td>Hemoglobin level &lt; 10 g/dL</td>
<td>2</td>
</tr>
<tr>
<td>White blood cell count (WBC) &gt; 25 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral blood blasts ≥ 1%</td>
<td>1</td>
</tr>
<tr>
<td>Presence of constitutional symptoms</td>
<td>1</td>
</tr>
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</table>

Risk categories: Low (score 0), intermediate-1 (score 1 or 2), intermediate-2 (score 3-4), high (score 5-6).


Complete Remission (CR): Disappearance of all evidence of disease.

Nodal masses
- FDG-avid or PET positive prior to therapy: mass of any size permitted if PET negative.
- Variably FDG-avid or PET negative: regression to normal size on CT.

Spleen, Liver
- Not palpable, nodules disappeared.

Bone marrow
- Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative.

Partial Remission (PR): Regression of measurable disease and no new sites.

Nodal masses
- Greater than 50% decrease in sum of the products of diameters (SPD) of up to 6 largest dominant masses; no increase in size of other nodes.
  - FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site.
  - Variably FDG-avid or PET negative; regression on CT.

Spleen, Liver
- Greater than 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.

Bone marrow
- Irrelevant if positive prior to therapy; cell type should be specified.

Note: Reader is advised to refer to the following for full detail:
The following are approved changes incorporated into the revision numbers indicated below.

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<td>08/14/2012: Approved by National Medical Care Management Committee.</td>
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<td>10/10/2013: Revised and updated. Lynn Wetherbee. Approved by Medical Technology Assessment Committee.</td>
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