2402: Disease Classification

The Disease Classification Form is required for all transplants, including subsequent transplants on the comprehensive report form track.

All transplant centers participating in the CIBMTR must submit a Disease Classifcation Form (Form 2402) for each allogeneic (related or unrelated) hematopoietic cell transplant (HCT). The Disease Classification Form is a requirement of the SCTOD for all United States transplant centers when either the stem cell donation or the transplant occurs within the United States. For more information regarding the SCTOD, see General Instructions, Stem Cell Therapeutics Outcomes Database.

Although data regarding recipients receiving autologous HCT are not required to be submitted as part of the C.W. Bill Young Transplant Program, the CIBMTR is highly committed to collecting data on these recipients for research studies. Centers choosing to report autologous data to the CIBMTR must report on all autologous transplants performed at their center. For more information regarding data reporting for autologous HCT, see General Instructions, Autologous Hematopoietic Stem Cell Transplant.

The Disease Classification Form may be submitted to the CIBMTR up to two weeks prior to the start of the recipient's preparative regimen (see Helpful Hint below). The Disease Classification Form is due the day of the HCT (day 0), and is past due if not received by that date.

The Disease Classification Form is designed to capture important details regarding the recipient's primary disease for which the reported HCT is being given. Key reporting areas differ depending on the disease reported (question 1), but may include disease type, subtype, transformations, cytogenetic and molecular markers, disease-specific laboratory results, staging, and disease status.

Helpful Hint:
In order to avoid having to make changes to the HCT date, complete the data for the Pre-TED Disease Classification Form (in FormsNet3^{SM} or on paper), but do not submit the form until the first dose of the preparative regimen is given.

For recipients receiving a subsequent HCT:
Transplant centers must submit a Disease Classification Form for all subsequent HCTs; this includes recipients assigned to the TED Forms **and** the Comprehensive Report Forms by the form selection algorithm.

For the majority of subsequent HCTs, the recipient will remain on the original follow-up form track (TED or

CRF) assigned by the form selection algorithm. For more information regarding center type and the form selection algorithm, see Section 1 in the Center Reference Guide. A recipient may need to change tracks if enrolled on a study that requires comprehensive forms.

For recipients of multiple transplants, transplant centers are not granted access to the new Pre-TED Disease Classification Form in FormsNet3^{SM} until the Post-TED (Form 2450) or Post-Infusion Data Form (Form 2100) from the previous transplant has been completed.

Links to Sections of the Form:

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please click here or reference the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
2/	2402:	Add	Added (in red below) additional instruction for question 277:

27/ 19	Disease Classification		***Question 277: Was a PET (or combination PET / CT) scan performed? (at last evaluation prior to the start of the preparative regimen / infusion)*** *Report "Yes" and go to question 278 if a PET scan was performed within three months prior to the start of the preparative regimen / infusion. Combination PET / CT may also be reported, but a CT scan alone should not be captured here. Centers may report a PET scan performed during the most recent line of therapy so long as it is the most recent scan and was done within noted period. Report "No" and go to question 283 if a PET scan was not performed within this period.*
2/ 27/ 19	2402: Disease Classification	Add	Added (in red below) additional instruction for question 165: *Indicate the number of times the recipient has been in the disease phase reported in question 163.*
8/ 10/ 18	2402: Disease Classification	Modify	Modified (red text was added, struck out text was deleted) the instructional blue box for question 212: Myelofibrosis that develops in patients with essential thrombocythemia (ET) or polycythemia vera (PV) is considered secondary myelofibrosis. The CIBMTR forms capture disease subtype using the WHO classification of myeloid neoplasms and acute leukemia. Secondary myelofibrosis is not included as a separate category per the WHO classification. Therefore, when reporting the disease subtype **at the time of transplant** for recipients with secondary myelofibrosis, report "Primary Myelofibrosis (PMF)" to accurately capture these cases on the CIBMTR Forms. ~~Myelofibrosis that develops in patients with essential thrombocythemia (ET) or polycythemia vera (PV) is considered secondary myelofibrosis. However, effective immediately, cases of post-essential thrombocythemia myelofibrosis (post-ET MF) or post-polycythemia vera myelofibrosis (post-PV MF) will now be reported as "Primary Myelofibrosis (PMF)" at the time of HCT. In order to capture accurate data, the secondary MF cases need to be lumped in with the PMF cases, since treatment for post-ET MF and post-PV MF is the same as PMF.~~
8/9/ 18	2402: Disease Classification	Add	Added instruction for question 281-282: If the PET scan result is only documented as an 'X', report this as "Unknown" for question 281.
4/ 10/ 18	2402: Disease Classification	Modify	Updated the Common Disease Transformation Table included in the instructions for questions 1 and 2. The CLL section of the form should not be completed for a Richter's Transformation as of Revision 3 of the Form 2402.
4/9/ 18	2402: Disease Classification	Modify	Modified the following instruction for question 317: Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation. ~~A PET scan~~ Date of radiographic study (PET, MRI, CT) may be used **if** the same ~~a previous PET scan~~ radiographic study had previously been obtained and **only** in limited circumstances (e.g., plasmacytomas, lytic lesions).
3/ 22/ 18	2402: Disease Classification	Add	Added **MDS/MPN** note box below the instructions for question 256 regarding recipients who only received supportive care prior to transplant.

2/ 28/ 18	2402: Disease Classification	Add	Added the following instruction for question 283. *When a transformation has occurred (e.g., follicular lymphoma (FL) transformed to DLBCL), count the response number (CR1, REL2, etc.) beginning with the transformed lymphoma (in this case the DLBCL). Do not include the responses to the lymphoma sub-type prior to the transformation.*
2/ 27/ 18	2402: Disease Classification	Add	Added instruction for questions 281-282. *If multiple scores are documented, report the highest.*
2/ 14/ 18	2402: Disease Classification	Remove	Removed incorrect instruction (struck out below) from question 271. *If the histology reported at infusion (question 268) is a transformation from CLL, indicate "Yes," and go to question 272. ~~Also, complete the disease classification questions for CLL.~~*
1/ 30/ 18	2402: Disease Classification	Modify	Version 3 of the 2402: Disease Classification section of the Forms Instruction Manual released. Version 3 corresponds to revision 3 of the Form 2402.

Last modified: 2019/02/27

Q1-2: Primary Disease for HCT / Cellular Therapy

Disease Classification Questions
The newest versions of the TED Forms use the World Health Organization (WHO) disease classifications. The Disease Classification questions contain all of the established WHO disease types and subtypes. The "other, specify" category should be used only if the recipient's disease is not one of the listed options. For more information regarding disease classification, consult a transplant physician, contact your center's CIBMTR CRC, or visit the WHO website at: http://www.who.int/classifications/icd/en/.
Several of the Disease Classification questions ask for *"Status at Transplantation."* Although there are many interpretations of disease response criteria, **when reporting data to the CIBMTR, use the guidelines in this manual to determine disease status**. A majority of the disease response criteria are established by an international working group. Citations of resources used to define disease responses are included where applicable.
If the recipient's status is unclear, consult with the transplant physician for further information or contact your center's CIBMTR CRC.

Malignant vs. Non-Malignant
Malignant diseases involve cells dividing without control that can spread to other parts of the body through blood and lymph systems. These diseases are usually characterized by unlimited, aggressive growth, invasion of surrounding tissues, and metastasis.
Non-malignant diseases involve cell overgrowth, but lack the malignant properties of cancer.
The CIBMTR database disease codes are represented in parentheses after the disease subtype on the Disease Classification questions and can be helpful in mapping diagnosis [e.g., Myeloid Sarcoma (295)], and determining if the disease is malignant or non-malignant. Disease codes (10-299) indicate a malignant disease, with the exception of Paroxysmal Nocturnal Hemoglobinuria (PNH) (56). A disease code of (300) or above indicates a non-malignant disease, with the exception of disease code (900), which could indicate either a malignant or non-malignant disease.

If the indication for HCT is due to a combination of diseases or a transformation of one disease to another, it may be necessary to report multiple disease classifications. The tables below list how common examples of disease combinations and transformations should be reported using the Disease Classification questions.

Common Disease Combinations

Disease Combinations	Report Primary Disease as:	Report disease diagnosis date of:	Complete multiple disease sections of the Disease Classification Form?
FAN or SAA and AML	AML	AML	No
FAN or SAA and MDS	MDS	MDS	No
MYE and AMY	MYE	MYE	No

Common Disease Transformations

Disease Transformation	Report primary disease as:	Report disease diagnosis date of:	Complete multiple disease sections of the Disease Classification Form?
MDS or MPS to AML	AML	AML	Yes- AML and MDS/MPN
JMML to AML	AML	AML	Yes- AML and MDS/MPN (select questions only)
NHL to another NHL	Second NHL diagnosis	Second NHL diagnosis	No
HL to NHL*	NHL	NHL	No
CLL to NHL (i.e., Richter's Syndrome)	NHL	CLL	No

AML=Acute Myelogenous Leukemia; AMY=Amyloidosis; CLL=Chronic Lymphocytic Leukemia; FAN=Fanconi Anemia; MDS=Myelodysplastic Syndrome; MPS=Myeloproliferative Disease; MYE=Multiple Myeloma; NHL=Non-Hodgkin Lymphoma; SAA=Severe Aplastic Anemia.

*Ensure that the disease process is a transformation from Hodgkin lymphoma to Non-Hodgkin lymphoma (typically diffuse large B-cell lymphoma), rather than the distinct entity "B-cell lymphoma, unclassifiable, with features indeterminate between DLBCL and classical Hodgkin Lymphoma."

Question 1: Date of diagnosis for primary disease for HCT:

The date of diagnosis is important because the interval between diagnosis and HCT is often a significant indicator for the recipient's prognosis post-HCT.

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease. Enter the date the sample was collected for examination. If the diagnosis was determined at an outside center, and no documentation of a pathological or laboratory assessment is available, the dictated date of diagnosis within a physician note may be reported. Do not report the date symptoms first appeared.

If the recipient was diagnosed prenatally (*in utero*), report the date of birth as the date of diagnosis.

If the exact pathological diagnosis date is not known, use the process described in General Instructions, Guidelines for Completing Forms.

If this is a subsequent HCT for a new malignancy (or other new indication), report the date of diagnosis of the new malignancy.

Question 2: What was the primary disease for which the HCT was performed?

Select the primary disease for which the recipient is receiving the HCT and continue with the appropriate disease classification questions.

Last modified: 2018/05/16

Q3-89: Acute Myelogenous Leukemia

Acute Myelogenous Leukemia (AML) is a cancer of the white blood cells. It is characterized by the rapid proliferation of abnormal, immature myelocytes, known as myeloblasts, in the bone marrow. This accumulation of blasts in the marrow prevents the formation of healthy red blood cells, white blood cells, and/or platelets. Normal myeloblasts develop into neutrophils, basophils, and eosinophils, which are all white blood cells that fight infection. In AML, the leukemic myeloblasts do not fully develop and are unable to fight infection. The symptoms of AML result from a drop in red blood cell, platelet, and normal white blood cell counts caused by the replacement of normal bone marrow with leukemic cells.

Certain prognostic indicators are associated with poorer outcomes. These include advanced age (50+ years of age), AML arising from MDS or secondary/therapy-related AML, and certain genetic mutations that are described in greater detail later in this manual.

Question 3: Specify the AML classification

Indicate the disease classification at diagnosis.

Report the most specific entity that applies to the recipient. For example, if the recipient was classified using both cytogenetic data and the M5 FAB classification, the more specific cytogenetic data should be reported for classification purposes.

Question 4: Did AML transform from MDS or MPN?

AML often evolves from MDS or MPN. This transformation is typically distinguished by the percentage of blasts in the bone marrow.

AML that transforms from MDS or MPN has a lower survival prognosis because of the association with unfavorable cytogenetic abnormalities.

AML can also evolve from Juvenile Myelomonocytic Leukemia (JMML). JMML is a rare form of chronic leukemia that affects young children, usually before the age of five. JMML results from DNA mutations in cells called monocytes. Normal monocytes attack invading microorganisms and assist lymphocytes in carrying out immune functions. Abnormal monocytes in JMML accumulate in the bone marrow and interfere with the production of normal white blood cells, red blood cells, and platelets.

If AML transformed from MDS or MPN (including JMML), check “Yes” and complete both the **AML and MDS/MPN** disease classification sections. If AML did not transform from MDS or MPS, check “No.”

If MDS/MPN is suspected, but not confirmed by documented laboratory or pathologic findings, or if there is documentation of MDS/MPN **concurrent** with AML, check “No.”

Question 5: Is the disease (AML) therapy related?

Agents such as radiation or systemic therapy used to treat other diseases (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or breast cancer) can damage the marrow and lead to a secondary malignancy such as AML. If the diagnosis of AML is therapy-related, check “Yes.”

If the diagnosis of AML is not therapy-related, check “No.”

- If AML was preceded by therapy-related MDS, check “No.”
- If the recipient developed AML after an environmental exposure (e.g., exposure to benzene), check “No.”

If it is unknown whether or not the diagnosis of AML was therapy-related, check “Unknown.”

Question 6: Did the recipient have a predisposing condition?

A predisposing condition is a condition that contributes to the susceptibility of developing leukemia. Therefore, diagnosis of the condition increases the likelihood that the recipient will develop leukemia. If the recipient has a documented history of a predisposing condition, check “Yes” and continue with question 7. If there is no history of a predisposing condition or if predisposition is unknown, indicate “No” or “Unknown” and continue with question 9.

Question 7-8: Specify condition:

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage and corresponding rearrangements, proportional dwarfism, and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder (trisomy 21). It is characterized by an additional chromosome 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and

leukemias.

Dyskaratosis congenita (DKC), also known as Zinsser-Engman-Cole syndrome, involves progressive bone marrow failure. Patients with DKC experience skin hyperpigmentation, nail dystrophy, and oral leukoplakia (a white patch / plaque that cannot be rubbed off).

Indicate the recipient's predisposing condition prior to the diagnosis of leukemia. If the condition was "Other condition," specify the condition in question 8.

At Diagnosis, Last Evaluation, and In Between
Questions 9-83 ask about testing performed at different time points prior to HCT. For reporting purposes, use the definitions below to determine where to report testing on the Disease Classification Form.
At Diagnosis: Any testing performed between the date of diagnosis (question 1) and the start of any treatment for AML.
In Between: Any pre-infusion testing which cannot be reported as part of "At Diagnosis" or "Last Evaluation."
Last Evaluation: Testing performed during the recipient's work-up for HCT or cellular therapy (generally within 30 days of the start of the preparative regimen or infusion).

Question 9: Were cytogenetics tested (karyotyping or FISH)? (at diagnosis)

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality which reflects the recipient's disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence in situ hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C, Cytogenetic Assessments.

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

FISH is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

Table 3. Examples of AML Cytogenetic Findings Categorized by Prognosis

Favorable	Intermediate	Poor
t(15;17) t(8;21) inv(16) or t(16;16)	Normal +8 t(9;11) *All other abnormalities*	≥ 3 abnormalities 5- or 5q- 7- or 7q- t(9;22)

Indicate whether cytogenetic studies were performed at diagnosis. Do not report any testing performed after treatment for AML has started. If cytogenetic studies were obtained at diagnosis, check “Yes” and go to question 10. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate “No” or “Unknown” respectively and go to question 21.

Question 10-11: Were cytogenetics tested via FISH?

If FISH studies were performed at diagnosis (see note box above question 9), report “Yes” for question 10 and indicate whether clonal abnormalities were detected in question 11. Do not report any testing performed after treatment for AML has started. If FISH studies were not performed at this time point, report “No” for question 10 and go to question 15. Examples of this include: no FISH study performed or FISH sample was inadequate.

Question 12-14: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH at diagnosis (see note box above question 9) in question 12. After indicating the number of abnormalities in question 12, select all abnormalities detected in questions 13-14.

If a clonal abnormality is detected, but not listed as an option in question 13, select “Other abnormality” and specify the abnormality in question 14. If multiple “Other abnormalities” were detected, report “see attachment” in question 14 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 15-16: Were cytogenetics tested via karyotyping?

If karyotyping was performed at diagnosis (see note box above question 9), report “Yes” for question 15 and indicate whether clonal abnormalities were detected in question 16. Do not report any testing performed after treatment for AML has started. If karyotyping was not performed at this time point, indicate “No” and go to question 20. Examples of this include: karyotyping was not performed or karyotyping sample was inadequate.

Question 17-19: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping at diagnosis (see note box above question 9) in

question 17. After indicating the number of abnormalities in question 17, select all abnormalities detected in questions 18-19.

If a clonal abnormality is detected, but not listed as an option in question 18, select “Other abnormality” and specify the abnormality in question 19. If multiple “Other abnormalities” were detected, report “see attachment” in question 19 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 20: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 9-19. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 21: Were tests for molecular markers performed (e.g., PCR, NGS)? (at diagnosis)

Molecular markers for disease refer to specific genetic sequences which are believed to be associated with the recipient’s primary disease. Testing for these sequences is often performed using PCR based methods; however, lower sensitivity testing, including FISH, may also be used to detect molecular markers. Once a marker has been identified, these methods can be repeated to detect minimal residual disease (MRD) in the recipient’s blood, marrow, or tissue. Molecular assessments include polymerase chain reaction (PCR) amplification to detect single specific disease markers; however, molecular methods are evolving and now include chromosomal microarray / chromosomal genomic array, Sanger sequencing, and next generation sequencing (e.g., Illumina, Roche 454, Proton / PGM, SOLiD).

If testing for molecular markers was performed at diagnosis (see note box above question 9), report “Yes” and go to question 22.

If molecular marker testing was not performed at diagnosis or it is not known if testing was done, report “No” or “Unknown” respectively and go to question 34.

Question 22-33: Specify results

For each molecular marker in questions 22-31, report whether testing was “Positive,” “Negative,” or “Not done” at diagnosis (see note box above question 9). If tests identified a molecular marker other than those listed in questions 22-31, report the result in question 32 and specify the marker in question 33.

If multiple “Other molecular marker[s]” were tested, report one instance (i.e., copy) of question 32-33 for each “Other molecular marker” tested. If greater than 3 “Other molecular marker[s]” were tested, do the following:

- report one instance of question 32-33; and
- report “Positive” if any of the “Other molecular marker[s]” were positive, otherwise, report “Negative;” and
- report “see attachment” in question 33; and
- attach any / all reports documenting the results of testing for “Other molecular marker[s].”

If CEBPA is reported as “Positive” (question 22) question 23 must be completed. If the lab report does not specify whether the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting “Unknown.”

If FLT3-ITD is reported as “Positive” (question 25) questions 26 and 27 must be completed. If the allelic ratio is known, report “Known” for question 26 and report the value in question 27. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting “Unknown.”

Table 4. Common Molecular Markers Associated with AML

Molecular Abnormality	Characteristics
CEBPA	CEBPA, *aka* CCAAT/enhancer binding protein α, is a transcription factor required for the differentiation of granulocytes. Numerous CEBPA mutations have been identified in relation to AML, with the majority of patients displaying biallelic mutations ultimately resulting in the down regulation of gene activity. Decreased gene activity results in decreased differentiation potential for immature granulocytes. An estimated 7-15% of AML patients have CEBPA mutations and CEBPA mutations are generally found in M1 and M2 subtypes in conjunction with intermediate-risk cytogenetics. Studies show an association with more favorable outcomes.[1]
FLT3-D835 point mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-D835 point mutation, *aka* FLT3-TKD, is an activating mutation impacting tyrosine-kinase domains. FLT3 mutations are found in up to 1/3 of all AML patients. The clinical significance of TKD activation remains unclear. FLT3-D385 mutations are often found in conjunction with other mutations. Overall, FLT3-D385 is not considered a favorable or poor prognostic indicator. However, in certain combinations with other mutations, there are associations with both improved and diminished survival.[23]
FLT3-ITD mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-ITD (internal tandem duplication) interferes with certain down regulation functions within receptor tyrosine kinases, leading to activation of TK activity. FLT3 mutations are found in up to 1/3 of all AML patients. FLT3-ITD is considered a poor prognostic factor. Sorafenib (Nexavar) has been shown to initially improve disease response in FLT3-ITD-positive AML.[4]
IDH1	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH1 mutations result in incorrect catalytic activity, leading to increased levels of an oncometabolite, 2-hydroxyglutarate. The pathologic activity of IDH1 mutations is still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis;

	research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH1 mutation may be a less favorable prognostic indicator.[5]
IDH2	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH2 is a mitochondrial homolog to IDH1. Much like IDH1 mutations, IDH2 mutations result in incorrect catalytic activity, leading to increased levels of (D)-2-hydroxyglutarate. The pathologic activity of IDH2 mutations are still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis; research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH2 mutation may be a more favorable prognostic indicator, unlike IDH1 mutation, though there may be differences based on where the IDH2 mutation occurs in gene.[6]
KIT	KIT encodes a receptor tyrosine kinase. The KIT mutations at exons 8 and 17 are associated with activation of encoded proteins, resulting in activation impacting tyrosine-kinase domains. Patients with t(8;21) and inv(16) cytogenetics are frequently screened for KIT mutations, which adversely affect prognosis in these patients.[7]
NPM1	NPM1 encodes a protein responsible for multiple cellular functions, including the regulation of the ARF-p53 tumor suppressor pathway. Mutations in NPM1 result in gene over-expression and subsequent inactivation of ARF-p53 tumor suppression pathway. NPM1 mutations are one of the most common molecular markers seen in AML and are associated with improved survival.[8]
Other molecular marker	Assessments for other molecular markers known or believed to be associated with AML may be performed. If these studies are performed, indicate “positive” or “negative” and specify the marker in question 56.

[1] Lin L, Chen C, Lin D, Tsay W, Tang J, Yeh Y, Shen H, Su F, Yao M, Huang S, Tien H. (2005). Characterization of CEBPA Mutations in Acute Myeloid Leukemia: Most patients with CEBPA mutations have biallelic mutations and show a distinct immunophenotype of the leukemic cells. *Clin Cancer Res*, 11, 1372-9.

[2] Mead AJ, Linch DC, Hills RK, Wheatley K, Burnett AK, Gale RE. (2007). FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 international tandem duplications in patient with acute myeloid leukemia. *Blood*, 110, 1262-70.

[3] Whitman SP, Ruppert AS, Radmacher, MD, et al. (2008). FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. *Blood*, 111, 1552-59.

[4] Man CH, Fung TK, Ho C, et al. (2011). Sorafenib treatment of FLT-ITD+ acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent non-responsiveness associated with the emergence of a D835 mutation. *Blood*, 119 (22), 5133-43.

[5] Marucci G, Maharry K, Wu YZ, et al. (2010). IDH1 and IDH2 Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. *J Clin Oncol*, 28(14), 2348-55.

[6] Green CL, Evans CM, Zhao L, et al. (2011).The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. *Blood*, 118(2), 409-12.

[7] Döhner K, Döhner H. (2008).Molecular characterization of acute myeloid leukemia. *Haematologica*, 93(7), 976-82.

[8] Varhaak RGW, Goudswaard CS, van Putten W, et al. (2005).Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. *Blood*, 106(12), 3747-54.

Question 34: Were cytogenetics tested (karyotyping or FISH)? (between diagnosis and last evaluation)

See question 9 for a description of cytogenetic tests. Indicate whether cytogenetic studies were performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note above question 9). If cytogenetic studies were obtained during this time, check “Yes” and go to question 15. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate “No” or “Unknown” respectively and go to question 46.

Question 35-36: Were cytogenetics tested via FISH?

If FISH studies were performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 9), report “Yes” for question 35 and indicate whether clonal abnormalities were detected in question 36. If multiple FISH assessments were performed, report “Abnormalities Identified” if any testing showed clonal abnormalities during this period. If FISH studies were not performed during this period, report “No” for question 35 and go to question 40. Examples of this include: no FISH study performed or all FISH samples were inadequate.

Question 37-39: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 9) in question 37. If FISH studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities in question 37, select all clonal abnormalities detected during this period in questions 38-39. This includes all clonal abnormalities detected any FISH assessment performed during this period.

If a clonal abnormality is detected, but not listed as an option in question 38, select “Other abnormality” and specify the abnormality in question 39. If multiple “Other abnormalities” were detected, report “see attachment” in question 39 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 40-41: Were cytogenetics tested via karyotyping?

If karyotyping was performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 9), report "Yes" for question 40 and indicate whether clonal abnormalities were detected in question 41. If multiple karyotypes were performed, report "Abnormalities Identified" if any testing showed clonal abnormalities during this period. If karyotyping was not performed during this period, report "No" for question 40 and go to question 45. Examples of this include: no karyotyping performed or all karyotype samples were inadequate.

Question 42-44: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 9) in question 42. If karyotype studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities in question 42, select all clonal abnormalities detected during this period in questions 43-44. This includes all clonal abnormalities detected any karyotype performed during this period.

If a clonal abnormality is detected, but not listed as an option in question 38, select "Other abnormality" and specify the abnormality in question 39. If multiple "Other abnormalities" were detected, report "see attachment" in question 39 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 45: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 34-44. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 46: Were tests for molecular markers performed (e.g., PCR, NGS)? (between diagnosis and last evaluation)

See question 21 for a description of testing for molecular markers. Indicate whether testing for molecular markers was performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note above question 9). If testing for molecular markers was performed during this time, check "Yes" and go to question 47. If cytogenetic studies were not obtained during this period or it is not known whether testing for molecular markers was performed, indicate "No" or "Unknown" and go to question 59.

Question 47-58: Specify results

For each molecular marker in questions 47-56, report whether testing was "Positive," "Negative," or "Not

done" between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 9). If tests identified a molecular marker other than those listed in questions 47-56, report the result in question 57 and specify the marker in question 58.

If multiple "Other molecular marker[s]" were tested, report one instance (i.e., copy) of question 57-58 for each "Other molecular marker" tested. If greater than 3 "Other molecular marker[s]" were tested, do the following:

- report one instance of question 57-58; and
- report "Positive" if any of the "Other molecular marker[s]" were positive, otherwise, report "Negative;" and
- report "see attachment" in question 58; and
- attach any / all reports documenting the results of testing for "Other molecular marker[s]."

If CEBPA is reported as "Positive" (question 47) question 48 must be completed. If the lab report does not specify whether the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting "Unknown."

If FLT3-ITD is reported as "Positive" (question 50) questions 51 and 52 must be completed. If the allelic ratio is known, report "Known" for question 51 and report the value in question 52. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting "Unknown."

Question 59: Were cytogenetics tested (karyotyping or FISH)? (at last evaluation)

See question 9 for a description of cytogenetic testing. Indicate whether cytogenetic studies were performed at the last evaluation prior to HCT / cellular therapy (see note box above question 9). If cytogenetic studies were obtained at this time point, check "Yes" and go to question 60. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate "No" or "Unknown" respectively and go to question 71.

Questions 60-61: Were cytogenetics tested via FISH?

If FISH studies were performed at the last evaluation prior to HCT / cellular therapy (see note box above question 9), report "Yes" for question 60 and indicate whether clonal abnormalities were detected in question 61. If FISH studies were not performed at this time point, report "No" for question 60 and go to question 65. Examples of this include: no FISH study performed or FISH sample was inadequate.

Question 62-64: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH at the last evaluation prior to HCT / cellular therapy (see note box above question 9) in question 62. After indicating the number of abnormalities in question 62, select all abnormalities detected in questions 63-64.

If a clonal abnormality is detected, but not listed as an option in question 63, select “Other abnormality” and specify the abnormality in question 64. If multiple “Other abnormalities” were detected, report “see attachment” in question 64 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 65-66: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to HCT / cellular therapy (see note box above question 9), report “Yes” for question 65 and indicate whether clonal abnormalities were detected in question 66. If karyotyping was not performed at this time point, indicate “No” and go to question 71. Examples of this include: karyotyping was not performed or karyotyping sample was inadequate.

Question 67-69: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping at the last evaluation prior to HCT / cellular therapy (see note box above question 9) in question 67. After indicating the number of abnormalities in question 67, select all abnormalities detected in questions 68-69.

If a clonal abnormality is detected, but not listed as an option in question 68, select “Other abnormality” and specify the abnormality in question 69. If multiple “Other abnormalities” were detected, report “see attachment” in question 69 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 70: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 59-69. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 71: Were tests for molecular markers performed (e.g., PCR, NGS)? (at last evaluation)

See question 21 for a description of testing for molecular markers. If testing for molecular markers was performed at the last evaluation prior to HCT / cellular therapy (see note box above question 9), report “Yes” and go to question 72. If molecular marker testing was not performed at this time point or it is not known if testing was done, report “No” or “Unknown” respectively and go to question 84.

Question 72-83: Specify results

For each molecular marker in questions 72-81, report whether testing was “Positive,” “Negative,” or “Not done” at the last evaluation prior to HCT / cellular therapy (see note box above question 9). If tests identified a molecular marker other than those listed in questions 72-81, report the result in question 82 and specify the marker in question 83.

If multiple “Other molecular marker[s]” were tested, report one instance (i.e., copy) of question 82-83 for each “Other molecular marker” tested. If greater than 3 “Other molecular marker[s]” were tested, do the following:

- report one instance of question 82-83; and
- report “Positive” if any of the “Other molecular marker[s]” were positive, otherwise, report “Negative;” and
- report “see attachment” in question 83; and
- attach any / all reports documenting the results of testing for “Other molecular marker[s].”

If CEBPA is reported as “Positive” (question 72) question 73 must be completed. If the lab report does not specify whether the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting “Unknown.”

If FLT3-ITD is reported as “Positive” (question 75) questions 76 and 77 must be completed. If the allelic ratio is known, report “Known” for question 76 and report the value in question 77. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting “Unknown.”

Question 84: Did the recipient have central nervous system leukemia at any time prior to the start of the preparative regimen / infusion?

Central nervous system (CNS) involvement by leukemia may be detected via pathologic examination of cerebrospinal fluid or tumor tissue as well as by radiological examinations (e.g., MRI, PET/CT, MIBG, etc.). If the recipient had documented involvement of AML in the CNS, report “Yes” for question 84. If all CNS testing was negative since the time of diagnosis, report “No.” If testing for CNS involvement was not performed from the time of diagnosis to the time of HCT / cellular therapy, report “Unknown.”

Question 85: What was the disease status (based on hematologic test results)?

Indicate the disease status of AML at the last assessment prior to the start of the preparative regimen. Refer to the AML Response Criteria section of the Forms Instructions Manual for definitions of each response. For reporting purposes, consider complete remission with incomplete hematologic recovery (CRi) a complete

remission (CR1, CR2, or CR3+).

If the recipient did not receive any treatment for AML from the time of diagnosis to the start of the preparative regimen / infusion, report “No treatment” and go to question 89.

If the recipient’s disease status is primary induction failure at the time of HCT / cellular therapy, go to question 89.

If the recipient’s disease status is CR / CRi at the time of HCT / cellular therapy, go to question 86.

If the recipient’s disease status is relapse at the time of HCT / cellular therapy, go to question 88.

Question 86: How many cycles of induction therapy were required to achieve 1st complete remission (CR)? (includes CRi)

Chemotherapy is initially given as induction therapy intended to bring the disease into remission. Recipients usually have one to two cycles of induction therapy; disease prognosis is considered less favorable if the patient fails to achieve remission with the first induction therapy and even poorer if patients fail two or more induction therapies.[1] An example of a common induction therapy for all AML subtypes (except M3) is a combination of an anthracycline and cytarabine, commonly known as “7+3.” In this regimen, cytarabine is typically administered for seven days at a dose of 100 mg/m^2/day. The anthracycline (usually daunorubicin at 45 to 60 mg/m^2/day or idarubicin at 12 mg/m^2/day) is generally given on the first three days the cytarabine is given.

The second phase of chemotherapy is known as consolidation therapy. The goal of consolidation therapy is to destroy any remaining leukemia cells and sustain remission. An example of a common consolidation therapy for all AML subtypes (except M3) is high-dose cytarabine, commonly referred to as “HiDAC.” In this regimen, cytarabine is typically administered at a dose exceeding 10 g/m^2 per cycle.

Maintenance chemotherapy may follow consolidation therapy. Maintenance chemotherapy is given in lower doses and is intended to prolong a remission. Maintenance therapy is used less commonly for the treatment of AML than other malignancies. Treatment may also be administered for relapsed disease. Much like induction therapy, treatment for relapse is intended to bring the disease back into remission. Systemic therapeutic agents used to induce remission following relapse often differ from those used in the initial induction, since the disease is often resistant to many of the agents used earlier in the disease course and is considered high-risk with a poor prognosis. Allogeneic HCT is often considered the only potential “cure” for relapsed disease.

Indicate the number of cycles of induction therapy that were required to achieve the first CR.

This question is optional for international centers.

[1] Ravandi F, Cortes J, Faderl S, et al. (2010). Characteristics and outcome of patients with acute myeloid leukemia refractory to one cycle of high-dose cytarabine-based induction therapy. Blood, 116(26):5818-23.

Question 87: Was the recipient in remission by flow cytometry?

Question 87 will only be answered if CR has been reported for question 85. Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemias is to quantify blasts in the peripheral blood or bone marrow, or to identify unique cell populations through immunophenotyping. Flow cytometry assessment may also be referred to as “MRD,” or minimal residual disease, testing.

Flow cytometric remission is a treatment response in which no blasts can be detected.

If flow cytometric abnormalities associated with the recipient’s disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate “yes.”

If flow cytometric abnormalities associated with the recipient’s disease were identified at the last evaluation prior to the start of the preparative regimen, indicate “no.”

Indicate “unknown” if flow cytometric abnormalities associated with the recipient’s disease were identified previously and no flow cytometry assessment was performed prior to the start of the preparative regimen.

Indicate “not applicable” if one of the following applies:

- No flow cytometry assessments were performed at any time prior to the start of the preparative regimen.
- Flow cytometric abnormalities were not identified on previous testing and no flow cytometric abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

This question is optional for international centers.

Question 88: Date of most recent relapse:

Enter the date of the most recent relapse prior to the start of the preparative regimen / infusion. If reporting a pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear), enter the date the sample was collected. If extramedullary disease was detected by radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place. If the physician determines cytogenetic or molecular relapse, enter the date the sample was collected for

cytogenetic or molecular evaluation. If the physician determines evidence of relapse following a clinical assessment during an office visit, report the date of assessment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, General Guidelines for Completing Forms.

Question 89: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

This question is optional for international centers.

Last modified: 2017/10/27

Q90-151: Acute Lymphoblastic Leukemia

> **Acute Lymphoblastic Lymphoma**
> Due to the aggressive nature of precursor T- and precursor B-cell lymphoblastic lymphoma (or lymphoma/leukemia), the primary disease reported for recipients with these malignancies should be acute lymphoblastic leukemia (T-cell lymphoblastic leukemia/ lymphoma or B-cell ALL, NOS {L1/L2}).

Acute Lymphoblastic Leukemia (ALL) is a cancer of the white blood cells. It is characterized by the rapid proliferation of abnormal, immature lymphocytes, known as lymphoblasts, in the bone marrow. This accumulation of blasts in the marrow prevents the formation of healthy red blood cells, white blood cells and/or platelets. Normal lymphoblasts develop into B and T lymphocytes that fight infection. In ALL, the leukemic lymphoblasts do not fully develop and therefore cannot fight infection. The symptoms of ALL are caused by the replacement of normal bone marrow with leukemic cells, resulting in a drop in red blood cells, platelets, and normal white blood cells. It is estimated that 80-85% of ALL cases occur in children, with peak incidence of pediatric ALL at age 5. Biologically, adult and pediatric ALL are very different. Pediatric cases are more often characterized by favorable prognostic indicators including a precursor B-cell population, TEL / AML1 fusion gene, and/or hyperdiploidy; adult cases are more often characterized by poor prognostic indicators including a precursor T-cell population and / or BCR / ABL fusion gene.[1]

[1] Sallan S. Myths and Lessons from the Adult/Pediatric Interface in Acute Lymphoblastic Leukemia. ASH Education Book, 1st edition. 2006:128-32.

Question 90: Specify ALL classification

Indicate the disease classification at diagnosis.

Due to the aggressive nature of precursor T- and precursor B-cell lymphoblastic lymphoma (or lymphoma / leukemia), the primary disease reported for recipients with these malignancies should be acute lymphoblastic leukemia.

If the cytogenetic or molecular abnormalities present at diagnosis are listed on the Pre-TED form, check the sub-type rather than “B-cell ALL, NOS” option.

Question 91: Did the recipient have a predisposing condition?

A predisposing condition is a condition that contributes to the susceptibility of developing leukemia. Therefore, diagnosis of the condition increases the likelihood that the recipient will develop leukemia. If the

recipient has a documented history of a predisposing condition, check “Yes” and continue with question 92. If there is no history of a predisposing condition or if predisposition is unknown, indicate “No” or “Unknown” and continue with question 94.

Question 92-93: Specify condition:

Aplastic anemia is an acquired or inherited disorder of the bone marrow characterized by pancytopenia, where the body does not produce a sufficient number of new blood cells. Inherited aplastic anemias include Fanconi anemia (specified separately on this form), Shwachman-Diamond anemia, Diamond-Blackfan anemia, and dyskeratosis congenita. Acquired aplastic anemia may develop after exposures to toxins, radiation, and/or chemotherapy, or may result from an autoimmune condition such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). The majority of presenting signs and symptoms in aplastic anemia patients are directly related to their low blood counts and include fatigue, dizziness, shortness of breath, abnormal bleeding or bruising, and frequent infections.

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage and corresponding rearrangements, proportional dwarfism, and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder (trisomy 21). It is characterized by an additional chromosome 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and leukemias.

Question 94: Were tyrosine kinase inhibitors (i.e., imatinib mestylate) given for pre-HCT therapy at any time prior to the start of the preparative regimen?

Report whether the recipient received any tyrosine kinase inhibitor from the diagnosis of ALL to the start of the preparative regimen / infusion. Examples include: Imatinib mesylate is also known as Gleevec, Glivec, STI-571, or CGP57148B.

This question is optional for international centers.

At Diagnosis, Last Evaluation, and In Between
Questions 95-145 ask about testing performed at different time points prior to HCT. For reporting purposes, use the definitions below to determine where to report testing on the Disease Classification Form.
At Diagnosis: Any testing performed between the date of diagnosis (question 1) and the start of any treatment for AML.
In Between: Any testing which cannot be reported as part of either of the two above time points.
Last Evaluation: Testing performed during the recipient's work-up for HCT or cellular therapy (generally within 30 days of the start of the preparative regimen or infusion).

Question 95: Were cytogenetics tested (conventional or FISH)? (at diagnosis)

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality which reflects the recipient's disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C, Cytogenetic Assessments.

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

FISH is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

Table 5. Examples of ALL Cytogenetic Findings Categorized by Prognosis (Adult Precursor B-cell ALL)

Favorable	Intermediate	Poor	Very Poor
High hyperdiploidy (51-65 chromosomes)	Normal 11q abnormalities del(6q) del(17p) del(9p) del(12p) -13/del(13q) t(14q32) t(10;14) Low hyperdiploidy (47-50	-7/del(7p) +8 11q23 abnormalities/ MLL t(1;19) t(17;19) t(5;14) t(9;22)	≥ 5 abnormalities t(4;11) t(8;14)

	chromosomes) Tetraploidy (> 80 chromosomes)		

[2] Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood*. 2008;111(5):2563-72.

Indicate whether cytogenetic studies were performed at diagnosis. Do not report any testing performed after treatment for AML has started. If cytogenetic studies were obtained at diagnosis, check “Yes” and go to question 96. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate “No” or “Unknown” respectively and go to question 106.

Question 96-97: Were cytogenetics tested via FISH?

If FISH studies were performed at diagnosis (see note box above question 95), report “Yes” for question 96 and indicate whether clonal abnormalities were detected in question 97. Do not report any testing performed after treatment for ALL has started. If FISH studies were not performed at this time point, report “No” for question 96 and go to question 97. Examples of this include: no FISH study performed or FISH sample was inadequate.

Question 98-100: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH at diagnosis (see note box above question 95) in question 98. After indicating the number of abnormalities in question 98, select all abnormalities detected in questions 99-100.

If a clonal abnormality is detected, but not listed as an option in question 99, select “Other abnormality” and specify the abnormality in question 100. If multiple “Other abnormalities” were detected, report “see attachment” in question 100 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 101-102: Were cytogenetics tested via karyotyping?

If karyotyping was performed at diagnosis (see note box above question 95), report “Yes” for question 101 and indicate whether clonal abnormalities were detected in question 102. Do not report any testing performed after treatment for ALL has started. If karyotyping was not performed at this time point, indicate “No” and go to question 107. Examples of this include: karyotyping was not performed or karyotyping sample was inadequate.

Question 103-105: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping at diagnosis (see note box above question 95) in question 103. After indicating the number of abnormalities in question 103, select all abnormalities detected in questions 104-105.

If a clonal abnormality is detected, but not listed as an option in question 104, select “Other abnormality” and specify the abnormality in question 105. If multiple “Other abnormalities” were detected, report “see attachment” in question 105 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 106: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 95-105. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 107: Were tests for molecular markers performed (e.g., PCR)? (at diagnosis)

Molecular markers for disease refer to specific genetic sequences which are believed to be associated with the recipient’s primary disease. Testing for these sequences is often performed using PCR based methods; however, lower sensitivity testing, including FISH, may also be used to detect molecular markers. Once a marker has been identified, these methods can be repeated to detect minimal residual disease (MRD) in the recipient’s blood, marrow, or tissue. Molecular assessments include polymerase chain reaction (PCR) amplification to detect single specific disease markers; however, molecular methods are evolving and now include chromosomal microarray / chromosomal genomic array, Sanger sequencing, and next generation sequencing (e.g., Illumina, Roche 454, Proton / PGM, SOLiD).

If testing for molecular markers was performed at diagnosis (see note box above question 95), report “Yes” and go to question 108.

If molecular marker testing was not performed at diagnosis or it is not known if testing was done, report “No” or “Unknown” respectively and go to question 113.

Table 6. Common Molecular Markers Associated with ALL

Molecular Abnormality	Characteristics
BCR-ABL	BCR-ABL, *aka* Philadelphia chromosome, refers to the tyrosine kinase gene fusion resulting from the translocation of material from chromosome 9 (ABL) onto chromosome 22 (BCR).

	Molecular weight varies depending on exact location of the translocation; isoform p190 is typically seen in ALL. Tyrosine kinase inhibitor therapies such as imatinib mesylate (Gleevec) target and block ABL from fusing with BCR. Presence of BCR-ABL gene fusion is associated with poorer outcomes.[3]
TEL-AML/AML1	TEL-AML1, *aka* ETV6-RUNX1, is a fusion gene resulting from the translocation of chromosomes 12 and 21. It is the most common fusion gene seen in childhood precursor B-cell ALL. Research in murine models shows that cell lines expressing TEL-AML1 proliferate more slowly than the non-expressing cell lines, but evade inhibition of proliferation typically regulated by tissue growth factor ß (TGF-ß), ultimately leading to the growth of the leukemic cell population. TEL-AML1 is considered a favorable prognostic indicator.[4][5]
Other molecular marker	Assessments for other molecular markers known or believed to be associated with ALL may be performed. If these studies were performed, indicate “positive” or “negative” and specify the marker in question 99.

[3] Wassmann B, Pfeifer H, Scheuring UJ, et al. (2004). Early prediction of response in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) treated with imatinib. *Blood*, 103(4):1495-8.

[4] Ford AM, Palmi C, Bueno C, et al. (2009). The TEL-AML1 leukemia fusion gene dysregulates the TGF-ß pathway in early B lineage progenitor cells. *J Clin Invest*, 119(4):826-36.

[5] Jamil A, Kahwash S, Ruymann FB, Klopfenstein KJ. (2000). TEL/AML-1 fusion gene: its frequency and prognostic significance in childhood acute lymphoblastic leukemia. *Cancer Genet Cytogenet*, 122(2):73-8.

Question 108-111: Specify results

For each molecular marker in questions 108-109, report whether testing was “Positive,” “Negative,” or “Not done” at diagnosis (see note box above question 95). If tests identified a molecular marker other than those listed in questions 108-109, report the result in question 110 and specify the marker in question 111.

If multiple “Other molecular marker[s]” were tested, report one instance (i.e., copy) of question 110-111 for each “Other molecular marker” tested. If greater than 3 “Other molecular marker[s]” were tested, do the following:

- report one instance of question 110-111; and
- report “Positive” if any of the “Other molecular marker[s]” were positive, otherwise, report “Negative;” and
- report “see attachment” in question 111; and
- attach any / all reports documenting the results of testing for “Other molecular marker[s].”

Question 112: Were cytogenetics tested (karyotyping or FISH)? (between diagnosis and last evaluation)

See question 95 for a description of cytogenetic tests. Indicate whether cytogenetic studies were performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note above question 95). If cytogenetic studies were obtained during this time, check “Yes” and go to question 113. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate “No” or “Unknown” respectively and go to question 124.

Question 113-114: Were cytogenetics tested via FISH?

If FISH studies were performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 95), report “Yes” for question 113 and indicate whether clonal abnormalities were detected in question 114. If multiple FISH assessments were performed, report “Abnormalities Identified” if any testing showed clonal abnormalities during this period. If FISH studies were not performed during this period, report “No” for question 113 and go to question 118. Examples of this include: no FISH study performed or all FISH samples were inadequate.

Question 115-117: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 95) in question 115. If FISH studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities in question 115, select all clonal abnormalities detected during this period in questions 116/117. This includes all clonal abnormalities detected any FISH assessment performed during this period.

If a clonal abnormality is detected, but not listed as an option in question 116, select “Other abnormality” and specify the abnormality in question 117. If multiple “Other abnormalities” were detected, report “see attachment” in question 117 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 118-119: Were cytogenetics tested via karyotyping?

If karyotyping was performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 95), report “Yes” for question 118 and indicate whether clonal abnormalities were detected in question 119. If multiple karyotypes were performed, report “Abnormalities Identified” if any testing showed clonal abnormalities during this period. If karyotyping was not performed during this period, report “No” for question 118 and go to question 124. Examples of this include: no karyotyping performed or all karyotype samples were inadequate.

Question 120-122: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 95) in question 120. If karyotype studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities in question 120 select all clonal abnormalities detected during this period in questions 121-122. This includes all clonal abnormalities detected any karyotype performed during this period.

If a clonal abnormality is detected, but not listed as an option in question 121, select “Other abnormality” and specify the abnormality in question 122. If multiple “Other abnormalities” were detected, report “see attachment” in question 122 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 123: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 112-122. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 124: Were tests for molecular markers performed (e.g., PCR)? (between diagnosis and last evaluation)

See question 107 for a description of testing for molecular markers. Indicate whether testing for molecular markers was performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see note above question 95). If testing for molecular markers was performed during this time, check “Yes” and go to question 125. If cytogenetic studies were not obtained during this period or it is not known whether testing for molecular markers was performed, indicate “No” or “Unknown” respectively and go to question 129.

Question 125-128: Specify results

For each molecular marker in questions 125-126, report whether testing was “Positive,” “Negative,” or “Not done” between diagnosis and the last evaluation prior to HCT / cellular therapy (see note box above question 95). If tests identified a molecular marker other than those listed in questions 125-126, report the result in question 127 and specify the marker in question 128.

If multiple “Other molecular marker[s]” were tested, report one instance (i.e., copy) of question 127-128 for each “Other molecular marker” tested. If greater than 3 “Other molecular marker[s]” were tested, do the following:

- report one instance of question 127-128; and

- report “Positive” if any of the “Other molecular marker[s]” were positive, otherwise, report “Negative;” and
- report “see attachment” in question 128; and
- attach any / all reports documenting the results of testing for “Other molecular marker[s].”

Question 129: Were cytogenetics tested (karyotyping or FISH)? (at last evaluation)

See question 95 for a description of cytogenetic testing. Indicate whether cytogenetic studies were performed at the last evaluation prior to HCT / cellular therapy (see note box above question 95). Do not report any testing performed after treatment for ALL has started. If cytogenetic studies were obtained at this time point, check “Yes” and go to question 130. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate “No” or “Unknown” respectively and go to question 141.

Question 130-131: Were cytogenetics tested via FISH?

If FISH studies were performed at the last evaluation prior to HCT / cellular therapy (see note box above question 95), report “Yes” for question 130 and indicate whether clonal abnormalities were detected in question 131. If FISH studies were not performed at this time point, report “No” for question 130 and go to question 135. Examples of this include: no FISH study performed or FISH sample was inadequate.

Question 132-134: Specify cytogenetic abnormalities (FISH)

Report the number of abnormalities detected by FISH at the last evaluation prior to HCT / cellular therapy (see note box above question 95) in question 132. After indicating the number of abnormalities in question 132, select all abnormalities detected in questions 133-134.

If a clonal abnormality is detected, but not listed as an option in question 133, select “Other abnormality” and specify the abnormality in question 134. If multiple “Other abnormalities” were detected, report “see attachment” in question 134 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 135-136: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to HCT / cellular therapy (see note box above question 95), report “Yes” for question 135 and indicate whether clonal abnormalities were detected in question 136. If karyotyping was not performed at this time point, indicate “No” and go to question 141. Examples of this include: karyotyping was not performed or karyotyping sample was inadequate.

Question 137-139: Specify cytogenetic abnormalities (karyotyping)

Report the number of abnormalities detected by karyotyping at the last evaluation prior to HCT / cellular therapy (see note box above question 95) in question 137. Only consider clonal abnormalities associated with the recipient's AML when completing questions 137-139. After indicating the number of abnormalities in question 137, select all abnormalities detected in questions 138-139.

If a clonal abnormality is detected, but not listed as an option in question 138, select "Other abnormality" and specify the abnormality in question 139. If multiple "Other abnormalities" were detected, report "see attachment" in question 139 and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 140: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 129-139. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 141: Were tests for molecular markers performed (e.g., PCR)? (at last evaluation)

See question 107 for a description of testing for molecular markers. If testing for molecular markers was performed at the last evaluation prior to HCT / cellular therapy (see note box above question 95), report "Yes" and go to question 142. If molecular marker testing was not performed at this time point or it is not known if testing was done, report "No" or "Unknown" respectively and go to question 146.

Question 142-145: Specify results

For each molecular marker in questions 142-145, report whether testing was "Positive," "Negative," or "Not done" at the last evaluation prior to HCT / cellular therapy (see note box above question 95). If tests identified a molecular marker other than those listed in questions 142-143, report the result in question 144 and specify the marker in question 145.

If multiple "Other molecular marker[s]" were tested, report one instance (i.e., copy) of question 144-145 for each "Other molecular marker" tested. If greater than 3 "Other molecular marker[s]" were tested, do the following:

- report one instance of question 144-145; and
- report "Positive" if any of the "Other molecular marker[s]" were positive, otherwise, report "Negative;" and
- report "see attachment" in question 145; and
- attach any / all reports documenting the results of testing for "Other molecular marker[s]."

Question 146: Did the recipient have central nervous system leukemia at any time prior to the start of the preparative regimen / infusion?

Central nervous system (CNS) involvement by leukemia may be detected via pathologic examination of cerebrospinal fluid or tumor tissue as well as by radiological examinations (e.g., MRI, PET/CT, MIBG, etc.). If the recipient had documented involvement of ALL in the CNS, report "Yes" for question 84. If all CNS testing was negative since the time of diagnosis, report "No." If testing for CNS involvement was not performed from the time of diagnosis to the time of HCT / cellular therapy, report "Unknown."

Question 147: What was the disease status (based on hematological test results)?

Indicate the disease status of ALL at the last evaluation prior to the start of the preparative regimen. Refer to the ALL Response Criteria section of the Forms Instructions Manual for definitions of each response. For reporting purposes, consider complete remission with incomplete hematologic recovery (CRi) a complete remission (CR1, CR2, or CR3+).

If the recipient did not receive any treatment for ALL from the time of diagnosis to the start of the preparative regimen / infusion, report "No treatment" and go to question 151.

If the recipient's disease status is primary induction failure at the time of HCT / cellular therapy, go to question 151.

If the recipient's disease status is CR / CRi at the time of HCT / cellular therapy, go to question 148.

If the recipient's disease status is relapse at the time of HCT / cellular therapy, go to question 150.

Question 148: How many cycles of induction therapy were required to achieve CR?

Chemotherapy is initially given as induction therapy intended to bring the disease into remission. Recipients usually have one to two cycles of induction therapy. An example of a common induction therapy for precursor B-cell ALL in children with higher-risk prognostic indicators is a combination of vincristine, prednisone, an anthracycline, and *L-asparaginase* given over 4-6 weeks. Patients with a rapid response, defined as < 5% blasts within 7 to 14 days of starting induction, have improved outcomes.[1]

[1] Gaynon PS, Desai AA, Bostrom BC, et al. Early response to therapy and outcome in childhood acute lymphoblastic leukemia: a review. Cancer. 1997;80(9):1717-26.

The second phase of chemotherapy is known as consolidation therapy. The goal of consolidation therapy is to destroy any remaining leukemia cells and sustain remission. An example of a consolidation therapy for

precursor B-cell ALL in children is daunorubicin and cytarabine; several studies support the use of consolidation therapy in ALL.

Maintenance therapy typically involves daily doses of mercaptopurine and weekly doses of methotrexate. Treatment continues for 2-3 years for most children with ALL. Treatment may also be administered for relapsed disease. Much like induction therapy, treatment for relapse is intended to bring the disease back into remission. Systemic therapeutic agents used to induce remission following relapse often differ from those used during initial induction, since the disease is considered high-risk with a poor prognosis and is often resistant to many of the agents used earlier in the disease course. Allogeneic HCT is often considered the only potential “cure” for relapsed disease, if the patient has not already been transplanted.

Indicate the number of cycles of induction therapy that were required to achieve the first CR.

Question 149: Was the recipient in remission by flow cytometry?

Question 149 will only be answered if CR has been reported for question 147. Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemias is to quantify blasts in the peripheral blood or bone marrow, or to identify unique cell populations through immunophenotyping. Flow cytometry assessment may also be referred to as “MRD,” or minimal residual disease, testing.

Flow cytometric remission is a treatment response in which no blasts can be detected.

If flow cytometric abnormalities associated with the recipient’s disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate “yes.”

If flow cytometric abnormalities associated with the recipient’s disease were identified at the last evaluation prior to the start of the preparative regimen, indicate “no.”

Indicate “unknown” if flow cytometric abnormalities associated with the recipient’s disease were identified previously and no flow cytometry assessment was performed prior to the start of the preparative regimen.

Indicate “not applicable” if one of the following applies:

- No flow cytometry assessments were performed at any time prior to the start of the preparative regimen.
- Flow cytometric abnormalities were not identified on previous testing and no flow cytometric abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 150: Date of most recent relapse:

Enter the date of the most recent relapse prior to the start of the preparative regimen. If reporting a pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear), enter the date the sample was collected. If extramedullary disease was detected by radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place. If the physician determines cytogenetic or molecular relapse, enter the date the sample was collected for cytogenetic or molecular evaluation. If the physician determines evidence of relapse following a clinical assessment during an office visit, report the date of assessment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 151: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Last modified: 2017/07/28

Q152-155: Acute Leukemias of Ambiguous Lineage and Other Myeloid Neoplasms

Questions 152-153: Specify other acute leukemia classification

Indicate the other acute leukemia disease classification at diagnosis. If the subtype is not listed, report as "other leukemia" and specify the reported disease.

- Acute undifferentiated leukemia is a type of AML characterized by immature predominating cells that cannot be classified.
- Biphenotypic, bilineage, or hybrid leukemias have characteristics representative of both myeloid and lymphoid lineages.
- Mast cell leukemia is characterized by an increased number of tissue mast cells in the peripheral blood.

Question 154: What was the disease status (based on hematological test results)?

Indicate the disease status of acute leukemia at the last evaluation prior to the start of the preparative regimen.

Table 7. Disease Status of Acute Leukemia

Disease Status	Definition
Primary Induction Failure (PIF)	The patient received treatment for acute leukemia **but never achieved complete remission at any time**. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have *never been in complete remission.*
Complete Remission (CR)	Hematologic complete remission is defined as meeting **all** of the following response criteria for at least four weeks. • < 5% blasts in the bone marrow • Normal maturation of all cellular components in the bone marrow • No extramedullary disease (e.g., CNS, soft tissue disease) • Neutrophils ≥ 1,000/µL • Platelets ≥ 100,000/µL • Transfusion independent In some cases, there may not be a four-week interval between completion of therapy and the pre-transplant disease assessment; in this case, CR should still be reported as

	the status at transplant, since it represents the “best assessment” prior to HCT. This is an exception to the criteria that CR be durable beyond four weeks; the pre-transplant disease status should not be changed based on early relapse or disease assessment post-transplant. Include recipients with persistent cytogenetic or molecular abnormalities who meet the above CR criteria for hematologic CR. Include recipients meeting the above CR criteria regardless of how many courses of therapy were required to achieve CR. The number of this complete remission can be determined by using the following guidelines: • 1st CR: no prior relapse • 2nd CR: one prior relapse • 3rd or higher: two or more prior relapses
Relapse (REL)	Relapse is defined as the recurrence of disease after CR, meeting the following criteria: • ≥ 5% blasts in the marrow or peripheral blood • Extramedullary disease • Reappearance of cytogenetic and/or molecular abnormalities associated with diagnosis that, in the judgment of a physician, are at a level representing relapse • Disease presence determined by a physician upon clinical assessment The number of this relapse can be determined by using the following guidelines: • 1st relapse: one prior CR • 2nd relapse: two prior CRs • 3rd or higher: three or more CRs Do not include a partial response (PR) when determining number of relapse. Recipients who achieve a PR to treatment should be classified as either PIF or relapse; PR in acute leukemia is generally of short duration and is unlikely to predict clinical benefit.
No Treatment	The recipient was diagnosed with acute leukemia and never received therapeutic agents; include patients who have received only supportive therapy, including growth factors and/or blood transfusions.

Question 155: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

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Q156-166: Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a slow-progressing cancer of the myeloid white blood cells. It is characterized by increased proliferation of immature white blood cells (granulocytes) with damaged DNA, or blasts, which accumulate in the blood and bone marrow. Normal blasts develop into white blood cells that fight infection. The symptoms of CML are caused by the replacement of normal bone marrow with leukemic cells, resulting in fewer red blood cells, platelets, and normal white blood cells.

Question 156: Was therapy given prior to this HCT?

If the recipient received therapy to treat CML prior to this HCT, check “yes” and go to question 157. Do not report a prior HCT or cellular therapy as these are captured separately on the Pre-TED Form (Form 2400). If the recipient did **not** receive therapy to treat CML, check “no” and go to question 163.

Question 157-162: CML treatment

Indicate the therapy the recipient received to treat CML prior to this HCT. If the recipient’s treatment consisted of a combination of chemotherapeutic agents, check the “combination chemotherapy” box **and** each drug included in the combination from the list provided. The “other, specify” category should only be used if the drug is not one of the listed options. For example, if the recipient received a combination of interferon and cytarabine, check all of the following: “combination chemotherapy,” “interferon,” and “other, specify: cytarabine.”

Question 163: What was the disease status?

Indicate the disease status of CML at the last evaluation prior to the start of the preparative regimen (or infusion if no preparative regimen was given). Refer to the CML Response Criteria section for a description of each disease response.

If the recipient is in complete hematologic response or chronic phase at the start of the preparative regimen, go to question 164. Otherwise, go to question 165.

Question 164: Specify level of response

If the recipient’s disease status (question 163) is “complete hematologic remission” or “chronic phase,” specify the cytogenetic / molecular response. Refer to the below definitions of cytogenetic and molecular responses.

Definitions of Cytogenetic and Molecular Responses to Therapy

Response	Definition
Complete molecular remission *(most favorable)*	0% BCR / ABL transcripts detected in peripheral blood or bone marrow
Major molecular remission	> 0 – 0.1% BCR / ABL transcripts detected in peripheral blood or bone marrow
Complete cytogenetic response	0% Ph+ cells detected in bone marrow
Partial cytogenetic response	> 0 – 35% Ph+ cells in bone marrow
Minor cytogenetic response	> 35 – 65% Ph+ cells in bone marrow
Minimal cytogenetic response	> 65 – 95% Ph+ cells in bone marrow
No cytogenetic response *(least favorable)*	> 95% Ph+ cells in bone marrow.

Definitions taken from Hughes, T. P., Ross, D. M. & Melo, J. V. Handbook of chronic myeloid leukemia. (Adis, 2014).

The above responses are listed from most favorable (complete molecular remission) to least favorable (no cytogenetic response). Centers should report the most favorable response achieved. For example, if a recipient has achieved a major molecular remission by PCR testing as well as a complete cytogenetic response by karyotyping / FISH, the center should report “major molecular remission” for question 164.

Question 165: Number

Indicate the number of times the recipient has been in the disease phase reported in question 163.

Question 166: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Last modified: 2019/02/27

Q167-260: Myelodysplastic / Myeloproliferative Diseases

Transformation to AML
If the recipient is being transplanted for AML that has transformed from MDS, the primary disease for HCT must be reported as AML. Disease Classification questions must be completed for both AML and MDS.

Transformation to Myelofibrosis
Recipients transplanted for post-essential thrombocythemia myelofibrosis (post-ET MF) or post-polycythemia vera myelofibrosis (post-PV MF) will be reported as ET or PV at diagnosis (Q167). Question 212: 'Did the recipient progress or transform to a different MDS/MPN subtype between diagnosis and the start of the preparative regimen?' must be answered "Yes".

The **myelodysplastic syndromes (MDS)** are a group of clonal hematopoietic stem cell diseases characterized by cytopenia(s), dysplasia (abnormal growth or development leading to an alteration in size, shape, and organization of the cell) in one or more of the major myeloid cell lines (WBC, RBC, and/or platelets), ineffective hematopoiesis, and an increased risk of developing acute myelogenous leukemia (AML). MDS occurs primarily in older adults, with a median age of 70 years. The majority of patients present with symptoms related to cytopenias. Most patients present with anemia requiring RBC transfusions.

Primary or *de novo* MDS occurs without a known history of chemotherapy or radiation exposure. Some inherited hematologic disorders, such as Fanconi anemia, dyskeratosis congenita, Shwachmann-Diamond syndrome, and Diamond-Blackfan syndrome are associated with an increased risk of MDS.

Myeloproliferative Neoplasms (MPN) are characterized by the overproduction of blood cells (red blood cells, white blood cells, and/or platelets) or collagen in the bone marrow. Often the MPN will be identified because of a blood test for another condition, as some patients are asymptomatic. Common symptoms found in the array of myeloproliferative disorders include fatigue and the enlargement of the spleen (splenomegaly).

Question 167: What was the MDS/MPN subtype?

Please indicate the MDS/MPN subtype **at diagnosis**. For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix H.

If the MDS/MPN subtype at diagnosis was “atypical chronic myeloid leukemia,” continue to the signature line.

Question 168: Was the disease (MDS/MPN) therapy-related?

Agents such as radiation or systemic therapy used to treat other diseases (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or breast cancer) can damage the marrow and lead to a secondary malignancy, such as MDS/MPN. If the diagnosis of MDS/MPN is therapy-related, select “yes.” If the diagnosis of MDS/MPN is not therapy-related, select “no.” If it is unknown if the MDS/MPN is therapy-related, select “unknown.”

Do not answer this question “yes” if the recipient developed MDS/MPN after an environmental exposure (e.g., exposure to benzene).

Question 169: Did the recipient have a predisposing condition?

A predisposing condition is a condition that contributes to the susceptibility of developing MDS/MPN. If the recipient has a documented history of a predisposing condition, select “yes” and continue with question 170. If there is no history of a predisposing condition or if predisposition is unknown, indicate “no” or “unknown” and continue with question 172.

Question 170-171: Specify condition:

Aplastic anemia may progress to MDS and/or AML. Aplastic anemia is a broad classification referring to bone marrow failure characterized by pancytopenia and marrow hypoplasia.

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage, with corresponding rearrangements. It is characterized by proportional dwarfism and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder. It is characterized by an additional chromosome 21, also referred to as trisomy 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and leukemias.

If the recipient had a predisposing condition not listed above, select “other condition” and specify the

condition in question 171.

Question 172-173: WBC

Indicate whether the white blood cell (WBC) count was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 173. If “unknown,” continue with question 174.

Question 174-175: Hemoglobin

Indicate whether the hemoglobin was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 175. If “unknown,” continue with question 177.

Question 176: Were RBCs transfused ≤ 30 days before the date of test?

Transfusions temporarily increase the red blood cell count. It is important to distinguish between a recipient whose body is creating these cells and a recipient who requires transfusions to support the counts.

Indicate if red blood cells were transfused less than or equal to 30 days prior to the testing reported in question 175.

Question 177-178: Platelets

Indicate whether the platelet count was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 178. If “unknown,” continue with question 180.

Question 179: Were platelets transfused ≤ 7 days before date of test?

Transfusions temporarily increase the platelet count. It is important to distinguish between a recipient whose body is creating the platelets and a recipient who requires transfusions to support the counts.

Indicate if platelets were transfused less than or equal to 7 days prior to the testing reported in question 178.

Question 180-181: Neutrophils

Indicate whether the neutrophil percentage in the blood was “known” or “unknown” at diagnosis. If “known,” report the value documented on the laboratory report in question 181. If “unknown,” continue with question 182.

Question 182-183: Blasts in bone marrow

If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
If the report states > n% blasts, enter (n +1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
If the report states < n% blasts, enter (n -1)% on the form. For example, if the laboratory report indicates < 5% blasts, report 4%.

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” at diagnosis. If “known,” report the percentage documented on the laboratory report in question 183. If “unknown,” continue with question 184.

Question 184: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C.

Indicate if cytogenetic studies were obtained at diagnosis. If cytogenetic studies were obtained, select “yes” and continue with question 185.

If no cytogenetic studies were obtained or it is unknown if chromosome studies were performed, select “no” or “unknown” and continue with question 212.

Question 185: Results of test:

If cytogenetic studies identified abnormalities, indicate “abnormalities identified” and continue with question 186.

If cytogenetic studies yielded “no evaluable metaphases” or there were “no abnormalities” identified, continue with question 212.

Question 186: Specify the number of distinct cytogenetic abnormalities:

Indicate the total number of abnormalities at diagnosis.

Questions 187-211: Specify abnormalities identified at diagnosis:

Report all abnormalities identified by all methods of cytogenetic assessment at diagnosis by selecting “yes” or “no” for each question. Do not leave any response blank. If one or more abnormalities are best classified as “other abnormality,” select “yes” for question 210 and specify the abnormality in question 211.

Question 212: Did the recipient progress or transform to a different MDS/MPN subtype between diagnosis and the start of the preparative regimen?

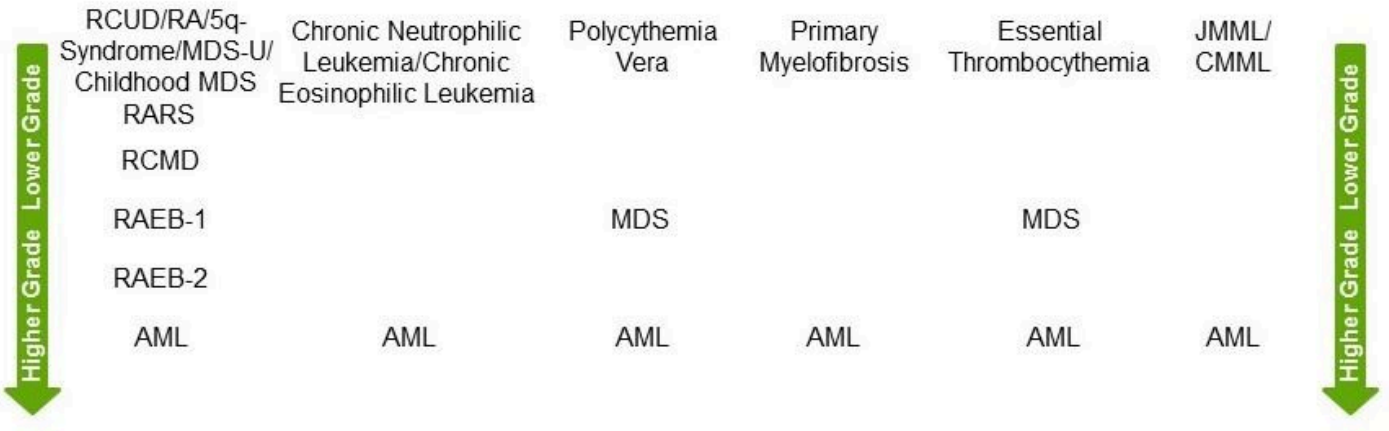
Transformation to Myelofibrosis
Myelofibrosis that develops in patients with essential thrombocythemia (ET) or polycythemia vera (PV) is considered secondary myelofibrosis. The CIBMTR forms capture disease subtype using the WHO classification of myeloid neoplasms and acute leukemia. Secondary myelofibrosis is not included as a separate category per the WHO classification. Therefore, when reporting the disease subtype **at the time of transplant** for recipients with secondary myelofibrosis, report “Primary Myelofibrosis (PMF)” to accurately capture these cases on the CIBMTR Forms.

Indicate if the recipient’s disease progressed to AML or transformed into a different MDS/MPN subtype between initial diagnosis and the start of the preparative regimen. Approximately one third of MDS cases transform into AML, signifying a poorer prognosis. Progression to AML is defined by an increase in blood or bone marrow blasts equal to or greater than 20%.

MDS/MPN subtypes may also transform/progress from one into another. A progression from one subtype of MDS to another indicates that the number of cytopenias, number of blasts, and/or morphology of marrow sufficiently qualified them for a higher grade (i.e., more severe) MDS. For example, an MDS classified as RCUD at diagnosis whose blast count rises to 8% as documented on bone marrow aspirate would have progressed to RAEB-1.

Conversely, do not report a progression/transformation if the recipient’s assessments after diagnosis show that they qualify for a lower grade (i.e., less severe MDS). For example, a recipient who is diagnosed with RAEB-2, but whose assessments show that they meet the criteria for RAEB-1 as a response to treatment, would not qualify as a progression or transformation. In this example, the disease is lower grade (i.e., less severe), rather than a higher grade (i.e., more severe) so it should not be reported as a progression/transformation. See the table below for guidance in determining the severity of MDS/MPN progressions and transformations.

Grade of MDS Progression/Transformations



Indicate if the recipient's disease progressed to AML or transformed from one MDS/MPN subtype to another. If the recipient's disease did transform or progress, select "yes" and continue with question 213. If there was no documented transformation or progression, select "no" and continue with question 216.

If there was no documented transformation or progression and the disease subtype is JMML, continue to the signature line.

Question 213: Specify the MDS/MPN subtype after transformation:

Indicate the recipient's current MDS/MPN subtype after transformation. If the recipient experienced more than one transformation after diagnosis, report the most recent subtype. For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix H.

Unless the recipient transformed to AML, continue with question 214.

If the disease transformed to AML, go to question 215.

Question 214: Specify the date of the most recent transformation:

Report the date of assessment that determined the ***most recent*** disease transformation (i.e., if there were multiple transformations, report the most recent). Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 215: Date of MDS Diagnosis

If the recipient's MDS / MPN transformed to AML prior to HCT, report the date of diagnosis of MDS / MPN. If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Ensure the date of diagnosis for AML has been reported in question 1, AML is reported as the primary disease for HCT in question 2, and the AML section of the Disease Classification Form has been complete appropriately. Go to the signature line.

Question 216-217: WBC

Indicate whether the white blood cell (WBC) count was "known" or "unknown" at the last evaluation prior to the start of the preparative regimen. If "known," report the laboratory count and unit of measure documented on the laboratory report in question 217. If "unknown," continue with question 218.

Question 218-219: Hemoglobin

Indicate whether the hemoglobin was "known" or "unknown" at the last evaluation prior to the start of the preparative regimen. If "known," report the laboratory count and unit of measure documented on the laboratory report in question 219. If "unknown," continue with question 221.

Question 220: Was RBCs transfused < 30 days before the date of test?

Transfusions temporarily increase the red blood cell count. It is important to distinguish between a recipient whose body is creating these cells and a recipient who requires transfusions to support the counts.

Indicate if red blood cells were transfused less than or equal to 30 days prior to the testing reported in question 219.

Question 221-222: Platelets

Indicate whether the platelet count was "known" or "unknown" at the last evaluation prior to the start of the preparative regimen. If "known," report the laboratory count and unit of measure documented on the laboratory report in question 222. If "unknown," continue with question 224.

Question 223: Were platelets transfused < 7 days before date of test?

Transfusions temporarily increase the platelet count. It is important to distinguish between a recipient whose body is creating the platelets and a recipient who requires transfusions to support the counts.

Indicate if platelets were transfused less than or equal to 7 days prior to the testing reported in question

222.

Questions 224-225: Neutrophils

Indicate whether the neutrophil percentage in the blood was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the value documented on the laboratory report in question 225. If “unknown,” continue with question 226.

Questions 226-227: Blasts in bone marrow:

If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
If the report states > n% blasts, enter (n+1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
If the report states < n% blasts, enter (n-1)% on the form. For example, if the laboratory report indicates < 5% blasts, report 4%.

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the percentage documented on the laboratory report in question 227. If “unknown,” continue with question 228.

Question 228: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C.

Indicate if cytogenetic studies were obtained at the last evaluation prior to the start of the preparative regimen. If cytogenetic studies were obtained, select “yes” and continue with question 229.

If no cytogenetic studies were obtained or it is unknown if chromosome studies were performed, select “no” or “unknown” and continue with question 256.

Question 229: Results of test:

If cytogenetic studies identified abnormalities, indicate “abnormalities identified” and continue with question 230.

If cytogenetic studies yielded “no evaluable metaphases” or there were “no abnormalities” identified,

continue with question 256.

Question 230: Specify the number of distinct cytogenetic abnormalities:

Indicate the total number of abnormalities at the last evaluation prior to the start of the preparative regimen.

Question 231-255: Specify abnormalities identified at the last evaluation prior to the start of the preparative regimen:

Report all abnormalities identified by all methods of cytogenetic assessment at the last evaluation prior to the start of the preparative regimen by selecting “yes” or “no” for each question. Do not leave any response blank. If one or more abnormalities are best classified as “other abnormality” select “yes” for question 254 and specify the abnormality in question 255.

Question 256: What was the disease status?

Indicate the disease status of MDS/MPN at the last assessment prior to the start of the preparative regimen. **Refer to the MDS/MPN Response Criteria section of the Forms Instructions Manual for definitions of each disease response.**

> ✻ “Never Treated” is not an option choice on the current revision of the Pre-TED: Disease Classification Form. When completing this form, centers should report “No Response (NR) / Stable Disease (SD)” for recipients who have only received supportive care prior to transplant.

Question 257: Specify the cell line examined to determine HI status:

Indicate the cell line examined to determine hematologic improvement. To determine the cell line, review the Hematologic Improvement criteria listed in the MDS/MPN Response Criteria section of the Forms Instructions Manual.

Question 258: Date of progression

Enter the assessment date that progression from hematologic improvement was established prior to the start of the preparative regimen. Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations. If extramedullary disease was detected upon radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 259: Date of relapse:

Enter the assessment date that relapse from complete remission was established prior to the start of the preparative regimen. Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations. If extramedullary disease was detected on radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 260: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Last modified: 2018/08/10

Q261-267: Other Leukemia

CLL, or chronic lymphocytic leukemia, is characterized by ≥ 5 × 10^9/L monoclonal lymphocytes with a CLL phenotype (usually co-expressed CD5 and CD23). The term SLL, or small lymphocytic lymphoma is used for non-leukemic cases with the tissue morphology and immunophenotype of CLL.

Hairy cell leukemia is characterized by the presence of abnormal B-lymphocytes in the bone marrow, peripheral blood, and spleen.

PLL, or prolymphocytic leukemia, is a type of CLL and is characterized by increased presence of immature prolymphocytes in the bone marrow and peripheral blood.

Question 261-262: Specify the other leukemia classification

Indicate the other leukemia disease classification at diagnosis. If the subtype is not listed, report as “other leukemia” and specify the reported disease.

Question 263: Was any 17p abnormality detected?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C.

Indicate if cytogenetic studies detected any 17p abnormality at any time prior to the start of the preparative regimen.

If “yes” and the disease classification is CLL, continue with question 264. If “yes” and the disease classification is PLL, continue with question 266.

If cytogenetic studies did not detect any 17p abnormality at any time prior to the start of the preparative regimen, select “no” and continue with question 264.

Question 264: Did a histologic transformation to diffuse large B-cell lymphoma (Richter syndrome) occur at any time after CLL diagnosis?

Histologic transformation may occur after CLL diagnosis. Indicate if CLL transformed into diffuse large B-cell lymphoma (known as Richter’s transformation or Richter’s syndrome). If CLL transformed, select “yes” and continue with question 271. If CLL did not transform, select “no” and continue with question 266.

Question 265: What was the disease status? (Atypical CML)

Indicate the disease status for atypical CML at the last evaluation prior the start of the preparative regimen (or infusion of no preparative regimen was given). If no treatment was given prior to HCT, go to the signature line. Otherwise, continue with question 267.

Disease Status of Atypical CML

Primary Induction Failure (PIF)
The patient received treatment for atypical CML **but never achieved complete remission at any time**. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have_ never been in complete remission._

Complete Remission (CR)
All of the following criteria are met and maintained for four or more weeks:

- Marrow with normal maturation of all cellular components
- ≤ 5% blasts in the marrow
- No signs or symptoms of the disease
  If the timeframe between achieving CR and the start date of the HCT (i.e., day 0) is less than four weeks, and the recipient is believed to be in CR, report the status at transplantation as CR.

*Important: if within four weeks following transplant the recipient's status is determined to **not be CR**, an Error Correction Form must be submitted to change the pre-HCT status.*

Include recipients with persistent cytogenetic abnormalities who otherwise meet all the criteria of CR.

Report that the recipient is in CR at the time of transplant no matter how many courses of therapy it may have taken to achieve that CR.

The number of this complete remission can be determined by using the following guidelines:

- 1st CR: no prior relapse
- 2nd CR: one prior relapse
- 3rd or higher: two or more prior relapses

Relapse (REL)
Recurrence of disease after CR. Relapse is defined as:

- > 5% blasts in the marrow
- Extramedullary disease
- Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis at levels that, as determined by a physician, represent relapse.

The number of this relapse can be determined by using the following guidelines:

- 1st relapse: one prior CR
- 2nd relapse: two prior CRs
- 3rd or higher: three or more CRs

No treatment
The recipient was diagnosed with atypical CML and never treated.

Question 266: What was the disease status? (CLL, PLL, Hairy cell leukemia)

Indicate the disease status for CLL/SLL, PLL, or hairy cell leukemia at the last evaluation prior the start of the preparative regimen (or infusion if no preparative regimen was given) and continue with question 267.

If reporting **CLL / SLL** or **PLL**, refer to the CLL Response Criteria section of the Forms Instructions Manual for definitions of each response.

Disease Status of Hairy Cell Leukemia[1]

Untreated
The recipient was diagnosed with hairy cell leukemia and never treated.

Complete Remission (CR)
Disappearance of all evidence of disease.
Requires **all** of the following:

- Neutrophils ≥ 1.5×10^9
- Hemoglobin ≥ 12.0 g/dL
- Platelets ≥ 100×10^9/L
- Absence of hairy cells on peripheral blood smear
- No palpable lymphadenopathy or hepatosplenomegaly

Partial Remission (PR)
Requires **all** of the following:

- ≥ 50% reduction in the absolute hairy cell count in the peripheral blood and the bone marrow
- ≥ 50% improvement of all cytopenias
- ≥ 50% reduction in abnormal lymphadenopathy or hepatosplenomegaly

Stable Disease (SD)
Not applicable for hairy cell leukemia.

Progressive Disease
Not applicable for hairy cell leukemia.

Relapse (untreated)
Relapse after CR:

- Reappearance of hairy cells in the peripheral blood smear and/or bone marrow (regardless of the degree of infiltration)
- Development of peripheral blood cytopenias
- Splenomegaly

Relapse after PR:

- ≥ 50% increase of residual hairy cells in the marrow
- Development of cytopenias
- Splenomegaly insufficient to qualify as PR
  OR
- Reappearance of hairy cells in the bone marrow of those patients who had been classified as partial responders based on residual splenomegaly only

[1] Saven, A., Burian, C., Koziol, J. A., & Piro, L. D. (1998). Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood*, 92(6), 1918-1926.

Other leukemia:

To determine the disease status, use the criteria for the leukemia that most closely resembles the disease for which this form is being completed. For questions, contact your transplant center's CIBMTR CRC.

Question 267: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Last modified: 2017/10/23

Q268-285: Hodgkin and Non-Hodgkin Lymphoma

Hodgkin lymphoma (HL or Hodgkin disease) is a cancer of the immune system that is marked by the presence of a type of cell called the Reed-Sternberg cell. The two major types of Hodgkin lymphoma are classical Hodgkin lymphoma (90-95% of cases) and nodular lymphocyte-predominant Hodgkin lymphoma (5-10% of cases).

Classical Hodgkin lymphoma can be further subdivided into four histologic subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte deplete (LD), and lymphocyte rich (LR). Symptoms include the painless enlargement of lymph nodes, spleen, or other immune tissue. Generalized pruritus is also common and may precede the diagnosis by months. The most common sites of involvement include cervical, supraclavicular, and mediastinal lymph nodes. Central nervous system involvement may occur in rare cases. Other symptoms include fever, weight loss, fatigue, and/or night sweats.

Non-Hodgkin lymphoma (NHL) is a large group of cancers derived from lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and are often marked by enlarged lymph nodes, fever, night sweats and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing), intermediate, or indolent (slow-growing) and can develop from either B-cells or T-cells. See Table 10.

Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas and are collectively known as **post-transplant lymphoproliferative disorders (PTLD)**.

> **Acute Lymphoblastic Leukemia / Lymphoma**
> Due to the aggressive nature of precursor B- and precursor T-cell lymphoblastic lymphoma (or lymphoma / leukemia), the primary disease to report for recipients with these malignancies should be acute lymphoblastic leukemia (B-cell lymphoblastic leukemia/ lymphoma or early T-cell precursor lymphoblastic leukemia.

Hodgkin Lymphoma (HL) and non-Hodgkin Lymphoma (NHL) are WHO disease classification subtypes of lymphoma. HL and NHL can transform into other disease subtypes. NHL can transform into other NHL subtypes, or into HL subtypes, but HL will rarely transform into NHL. Additionally, HL and NHL can occur at the same time and most likely classified as “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma”.

In order to complete the correct Disease Classification questions for a recipient who has a history of both HL and NHL, **it is important to determine which disease is active prior to the start of the preparative regimen. A physician must make this determination.**

The following two scenarios are examples of the data reporting practice for recipients with a combination of HL and NHL.

> **Scenario 1:** A recipient is being transplanted for active NHL, but has a history of HL that is in remission at the start of the preparative regimen. Report the active NHL on the Disease Classification questions, and report HL as a prior malignancy on the Pre-TED Form (Form 2400).
>
> **Scenario 2:** A recipient is being transplanted for both active NHL and active HL. Report this as NHL using "Other B-cell Lymphoma" and specify in question 269. Complete the Disease Classification questions for NHL. This only applies when the NHL and HL have been diagnosed at different times (i.e., two primaries).

Question 268-269: Specify the lymphoma histology (at infusion)

Indicate the histology for which the recipient is receiving a transplant or cellular therapy. If the histology is "Other B-cell lymphoma" or "Other T-cell / NK-cell lymphoma," specify the histology in question 269.

Go to question 270 if either of the following histologies were reported in question 268:

- Diffuse, large B-cell lymphoma – Activated B-cell type (non-GCB)
- Diffuse, large B-cell lymphoma – Germinal center B-cell type

Otherwise, go to question 271.

Question 270: Assignment of DLBCL subtype:

DLBCL subtypes may be identified using different techniques including immunohistochemistry (IHC) and gene expression profiling. IHC involves staining a tissue sample and determining the presence of cell surface markers via microscopy. Gene expression profiling utilized molecular techniques.

Report the method used to determine the DLBCL subtype. Indicate "Unknown" if the method cannot be determined from the available source documentation.

Question 271: Is the lymphoma histology reported at transplant a transformation from CLL?

In some cases, CLL may evolve to a more aggressive diffuse large B-cell lymphoma (DLBCL). This is

commonly referred to as Richter's syndrome or Richter's transformation. In a sub-set of CLL cases, the transformation may be to Hodgkin lymphoma (HL).

If the histology reported at infusion (question 268) is a transformation from CLL, indicate "Yes," and go to question 272.

If the histology reported at infusion is not a transformation from CLL, indicate "No" and go to question 273.

Question 272: Was any 17p abnormality detected?

Report "Yes" if an abnormality was ever detected (by any method) on the short arm of chromosome 17 since the date of diagnosis of CLL. This includes any 17p abnormality detected after transformation to lymphoma and go to question 277. Report "No" if a 17p abnormality was not detected and go to question 277.

Question 273: Is the lymphoma histology reported at transplant a transformation from a different lymphoma histology (not CLL)?

Transformation may occur when a slow-growing lymphoma with an indolent clinical history changes to a more aggressive lymphoma histologically and clinically. An example of a common transformation would include follicular lymphoma evolving to a diffuse large B-cell lymphoma (DLBCL).

If a histologic transformation occurred after or concurrently with diagnosis, indicate "Yes" and go to question 274 If a histologic transformation did not occur, indicate "No" and go to question 277.

Question 274-275: Specify the original lymphoma histology (prior to transformation)

Report the histology of the recipient's primary disease at diagnosis. If the histology is "Other B-cell lymphoma" or "Other T-cell / NK-cell lymphoma," specify the histology in question 275.

Question 276: Date of original lymphoma diagnosis

Report the date of diagnosis for the histology specified in questions 274-275. If the exact pathological diagnosis date is not known, use the process described in General Instructions, General Guidelines for Completing Forms.

Question 277: Was a PET (or combination PET / CT) scan performed? (at last evaluation prior to the start of the preparative regimen / infusion)

Report "Yes" and go to question 278 if a PET scan was performed within three months prior to the start of the preparative regimen / infusion. Combination PET / CT may also be reported, but a CT scan alone should not be captured here. Centers may report a PET scan performed during the most recent line of therapy so long as it is the most recent scan and was done within noted period. Report "No" and go to question 283 if a

PET scan was not performed within this period.

Question 278: Was the PET (or PET / CT) scan positive for lymphoma involvement at any disease site?

Report “Yes” if the most recent PET scan prior to the start of the preparative regimen / infusion detected the recipient’s primary disease. Otherwise, report “No.”

Question 279-280: Date of PET scan

Questions 279-280 refer to the PET scan used to answer question 278. If the date of this PET scan is known, report “Known” and specify the date in question 280. If the date is only partially known (e.g., the month and year are known, but not the day) report “Known”, and use the process described in General Instructions, General Guidelines for Completing Forms to complete question 280. If the date cannot be determined / estimated, report “Unknown” and go to question 281.

Question 281-282: Deauville (five-point) score of the PET (or PET/CT) scan

Questions 281-282 refer to the PET scan used to answer question 278. Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If “Known,” report the score in question 282. Otherwise, report “Unknown” for question 281 and go to question 283. If the PET scan result is only documented as an ‘X’, report this as “Unknown” for question 281.

If multiple scores are documented, report the highest.

Question 283: What was the disease status?

The recipient’s pre-HCT disease status may be evaluated by a PET scan, CT scan, or both. If possible, complete question 283 using the metabolic (PET) criteria provided in the Lymphoma Response Criteria section of the manual. If it is not possible to use metabolic criteria to report the recipient’s disease (e.g., insufficient PET scan(s), non-PET-avid disease), use the radiographic criteria instead.

Indicate the disease status at the last evaluation prior to the start of the preparative regimen. When determining the disease status, compare the restaging assessments immediately prior to the preparative regimen to the assessments at baseline. “Baseline” is defined as the disease at diagnosis or at relapse/ progression. When a transformation has occurred (e.g., follicular lymphoma (FL) transformed to DLBCL), count the response number (CR1, REL2, etc.) beginning with the transformed lymphoma (in this case the DLBCL). Do not include the responses to the lymphoma sub-type prior to the transformation.

Question 284: Total number of lines of therapy received (between diagnosis and HCT / infusion)

A single line of therapy refers to any agents administered during the same time period with the same intent

(induction, consolidation, etc.). If a recipient's disease status changes resulting in a change to treatment, this should be considered a new line of therapy. Additionally, if therapy is changed because a favorable disease response was not achieved, this should be considered a new line of therapy.

Indicate how many lines of therapy the recipient received prior to the start of the preparative regimen / infusion.

Question 285: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date imaging took place for the radiographic assessment (CT, MRI, PET, or PET/CT). Report the date the sample was collected for pathological evaluation (e.g., bone marrow biopsy). If no radiographic or pathologic assessment was performed within one month prior to transplant, report the most recent office visit in which the physician evaluated the recipient's disease status.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, General Guidelines for Completing Forms.

Last modified: 2019/02/27

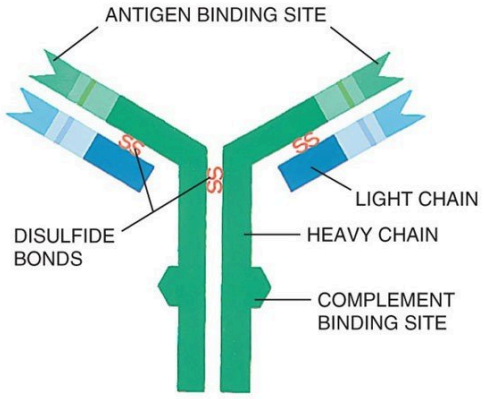
Q286-317: Multiple Myeloma / Plasma Cell Disorder

One kind of white blood cell, the plasma cell (also called plasma B cells, plasmocytes, or effector B cells), produces proteins called antibodies or immunoglobulins (Igs) that are part of our defense system against foreign substances (called antigens). Antibodies are produced in response to such things as viruses, bacteria, and other infectious agents.

Multiple myeloma is a cancer that leads to the proliferation of malignant plasma cells (myeloma cells). Myeloma cells usually proliferate in the bone marrow. When myeloma cells grow into isolated masses in other sites, these masses are called plasmacytomas. Health problems caused by multiple myeloma can affect the bones, immune system, kidneys, and red blood cell count.

The immunoglobulins (antibodies) produced by healthy plasma cells are composed of pairs of heavy chains and light chains (see graphic below). Healthy plasma cells create many different kinds of immunoglobulins that are classified by their heavy chain type into five categories (IgG, IgA, IgM, IgD, or IgE). The light chain types are designated kappa (κ) or lambda (λ). The whole Ig molecule is then labeled IgG kappa, IgG lambda, IgA kappa, IgA lambda, etc. These protein levels can be measured in blood serum and/or urine.

Structure of an Immunoglobulin (Antibody)



Secretory Multiple Myeloma:

Healthy plasma cells make immunoglobulins (antibodies) of all types. With the proliferation of malignant plasma cells, the level of one immunoglobulin type increases in the blood and/or urine. This abnormal immunoglobulin type is called the monoclonal immunoglobulin, monoclonal protein (M-protein/M-spike/M-component), or paraprotein. In most cases, the normal immunoglobulins are reciprocally depressed.

Patients with this condition are said to have *secretory myeloma*.

Some myeloma patients make only an excess of the light chain portion of the immunoglobulin molecule (i.e., only monoclonal kappa or lambda light chains). The light chain is also called Bence Jones protein. In most patients whose myeloma cells only make light chains, this paraprotein may not be detectable in the blood, but only in the urine. These patients are said to have *light-chain-only disease*. Ninety-seven percent of patients diagnosed with multiple myeloma have a detectable paraprotein in the blood serum and/or urine.

Distribution of Monoclonal Proteins in Secretory Multiple Myeloma[12]

Monoclonal Proteins at Diagnosis	Percent
Source of monoclonal proteins	
Serum monoclonal proteins	80%
Urine monoclonal proteins	75%
Type of monoclonal proteins	
IgG	50-54%
IgA	20%
Monoclonal light chain (light-chain-only disease)	20%
IgD	2%

[1] Kyle RA, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78(1):21-33.

[2] International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haem*. 2003;121(5):749-57.

Nonsecretory Multiple Myeloma:
In some myeloma patients, the malignant plasma cells do not produce an excess of the heavy chain or light chain portion of the immunoglobulin molecule; therefore, a paraprotein is not detectable in the serum or urine. These patients are said to have nonsecretory myeloma (i.e., the absence of a paraprotein on immunofixation). Immunofixation detects the specific immunoglobulins after separating the proteins into bands on an electrophoresis gel. Nonsecretory myeloma accounts for 3% of myeloma cases.

Amyloidosis:
Amyloidosis is a disease in which abnormally folded proteins build up in different tissues of the body. In the most common amyloidosis, AL amyloidosis, the abnormally folded protein is the light chain component of an

immunoglobulin. These light chains may build up in a variety of tissues, but the most common sites of build-up are the heart, kidneys, liver and nerves. According to the Amyloidosis Foundation, AL Amyloidosis is a relatively rare disorder, with 1200-3200 new cases reported each year in the United States. The disease mostly impacts men and people over 40.[3]

[3] Amyloidosis Foundation. Amyloidosis – Primary AL. 15 Apr. 2013. Accessed at: http://www.amyloidosis.org/TreatmentInformation/primaryAL.html
Accessibility verified on October 21, 2013.

Question 286-287: Specify the multiple myeloma/plasma cell disorder (PCD) classification:

Indicate the multiple myeloma/plasma cell disorder (PCD) disease classification at diagnosis. If the subtype is not listed, report as "other plasma cell disorder" and specify the reported disease.

Plasma Cell Disorders and Characeristics

Multiple Myeloma (symptomatic)[4]
Diagnostic criteria for symptomatic multiple myeloma requires clonal bone marrow plasma cells in ≥ 10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

1. Evidence of end organ damage (i.e., CRAB features) that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >1 mg/dL (> 0.25 mmol/L) higher than the ULN or > 11 mg/dL (> 2.75 mmol/L)
- Renal insufficiency: creatinine clearance < 40 ml/min or serum creat >2 mg/dL (> 177 µmol/L)
- Anemia: hemoglobin > 2 g/dL (> 20 g/L) below the LLN or a hemoglobin <10 g>
- Bone lesions: one or more osteolytic lesions on skeletal x-ray, CT or PET-CT

2. Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma percentage ≥ 60%
- Involved **:** uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesion on MRI studies (each lesion must be ≥ 5 mm in size)

[4] (2015, October 29). International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. Retrieved February 15, 2017, from http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/

Plasma Cell Leukemia

- Peripheral blood absolute plasma cell count of at least 2.0 × 10^9/L (2,000 cells/mm^3)
- ≥ 20% plasma cells in the peripheral differential white blood cell count.[5]

Solitary Plasmacytoma (in absence of bone marrow findings diagnostic for multiple myeloma or plasma cell leukemia)

Extramedullary:

- No M-protein in serum and/or urine
- Extramedullary tumor of clonal plasma cells
- Normal bone marrow
- Normal skeletal survey
- No related organ or tissue impairment (end organ damage including bone lesions)

Bone Derived

- No M-protein in serum and/or urine
- Single area of bone destruction due to clonal plasma cells
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey (and MRI of spine and pelvis if done)
- No related organ or tissue impairment (no end organ damage other than solitary bone lesion)[5]

Note: if the recipient has greater than one plasmacytoma, but has not been diagnosed with another plasma cell disorder, select "other plasma cell disorder" and specify how many plasmacytomas are present and if each is bone derived or extramedullary.

Amyloidosis

Amyloidosis is the buildup of abnormally folded proteins in various tissues of the body. Affected tissues may include the kidneys, heart, liver, gastrointestinal tract, etc. In the most common type of amyloidosis, "AL amyloidosis," light chains from antibodies function as the amyloid protein, building up within organs and disrupting organ function. Serum and urine tests are useful for evaluating amyloidosis, but a tissue biopsy is the best way to diagnose the condition.

Osteosclerotic myeloma/ POEMS Syndrome

POEMS syndrome is poorly understood, but generally refers to **p** olyneuropathy, **o** rganomegaly, **e** ndocrinopathy, **M** protein, and **s** kin changes. Diagnosis may be made using the presence of the major

criteria and one minor criteria below:

Major Criteria (both of the following):

- Polyneuropathy
- Monoclonal plasmaproliferative disorder

Minor Criteria (at least one of the following):

- Sclerotic bone lesions[6]
- Castleman disease[6]
- Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)
- Edema (edema, pleural effusion, or ascites)
- Endocrinopathy (adrenal, thyroid[7], pituitary, gonadal, parathyroid, pancreatic[7])
- Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)
- Papilledema

Light Chain Deposition Disease

Similar to amyloidosis, light chain deposition disease is characterized by the overproduction and deposition of light chains in organs throughout the body; however, the organ most often affected is the kidneys. Under microscopy, the pattern of deposition and the use of staining techniques help pathologists differentiate between amyloidosis and light chain deposition disease.[8]

[5] The International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma, and related disorders: a report of the international myeloma working group. *Brit J Haematol*. 2003;121(5):749-57.

[6] Osteosclerotic lesion or Castleman disease is usually present.

[7] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101(7):2496-506.

[8] UNC Kidney Center, University of North Carolina. Light Chain Deposition Disease. 5 Apr. 2013. Accessed at: http://unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/light-chain-deposition-disease Accessibility verified on January 30, 2017

For recipients diagnosed with more than one PCD, either sequentially or concurrently, ensure that all

applicable questions are completed.

If the recipient's disease classification is one of the following, continue with question 288.

- Multiple myeloma – IgG
- Multiple myeloma – IgA
- Multiple myeloma – IgD
- Multiple myeloma – IgE
- Multiple myeloma – IgM (not Waldenstrom macroglobulinemia)
- Multiple myeloma – light chain only

If the recipient's disease classification is the following, neither kappa nor lambda light chains will be present; therefore, continue with question 289.

- Multiple myeloma – non-secretory

If the recipient's disease classification is one of the following, continue with question 294.

- Plasma cell leukemia
- Solitary plasmacytoma (no evidence of myeloma)
- Amyloidosis
- Osteosclerotic myeloma/POEMS syndrome
- Light chain deposition disease

If the recipient's disease classification is the following, continue with question 287.

- Other Plasma Cell Disorder

Question 288: Light Chain

Indicate the presence of light chains as either kappa or lambda.

Question 289-290: What was the Durie-Salmon staging (at diagnosis)?

Indicate Durie-Salmon stage and sub-classification at diagnosis. If this is not documented in the medical record, see the table below to determine the appropriate stage and sub-classification. If "unknown," continue with question 291.

Durie-Salmon Staging System for Multiple Myeloma[8]

Stage	Criteria
I	All of the following: • Hemoglobin > 10 g/dL • Serum calcium normal (< 10.5 mg/dL) • On radiograph, normal bone structure or solitary bone plasmacytoma only • Low M-component production rate (IgG < 5 g/dL, IgA < 3 g/dL), Urinary light chain M-component on electrophoresis (< 4 g/24 hr)
II	Fitting neither stage I nor stage III
III	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Advanced lytic bone lesions (three or more lytic lesions) • High M-component product rate (IgG > 7 g/dL, IgA > 5 g/dL), Urinary light chain M-component on electrophoresis (> 12 g/24 hr)
Sub-classification	(either A or B) A: Relatively normal renal function (serum creatinine < 2.0 mg/dL) B: Abnormal renal function (serum creatinine ≥ 2.0 mg/dL)

[8] Adapted from Durie BG, Salmon SE: A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36:842-54.

Question 291-293: Stage at Diagnosis: I.S.S.

Report the recipient's lab values from diagnosis and the ISS stage of myeloma.

I.S.S. Staging System for Multiple Myeloma[9]

Stage	Description
Stage I	Serum β2-microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
Stage II	Serum β2-microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL OR Serum β2-microglobulin 3.5 to <5.5 mg/dL irrespective of serum albumin level
Stage III	Serum β2-microglobulin ≥ 5.5 mg/L irrespective of serum albumin level

[9] Greipp, P. R., San Miguel, J., Durie, B. G., Crowley, J. J., Barlogie, B., Bladé, J., … & Westin, J. (2005).

International staging system for multiple myeloma. *Journal of Clinical Oncology*, 23(15), 3412-3420.

Question 294: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient's disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix C.

Indicate if cytogenetic studies were obtained at any time prior to the start of the preparative regimen. If cytogenetic studies were obtained, select "yes" and continue with question 295.

If no cytogenetic studies were obtained or if it is unknown if chromosome studies were performed, select "no" or "unknown" and continue with question 316.

Question 295: Results of test:

If cytogenetic studies identified abnormalities, indicate "abnormalities identified" and continue with question 296.

If cytogenetic studies yielded "no evaluable metaphases" or there were "no abnormalities" identified, continue with question 316.

Question 296-315: Specify abnormalities identified at any time prior to the start of the preparative regimen:

Report all abnormalities identified by all methods of cytogenetic assessment at any time prior to the start of the preparative regimen by selecting "yes" or "no" for each question. Do not leave any response blank. If one or more abnormalities are best classified as "other abnormality" select "yes" for question 314 and specify the abnormality in question 315.

Question 316: What was the disease status?

Amyloidosis
If the recipient's primary disease is amyloidosis (without evidence of myeloma), report Complete Remission (CR) if the CR criteria for all involved organs are met (see Amyloidosis Response Criteria). If the disease status at transplant is anything other than CR, report "Not applicable." This is a change from the previous instruction which asked centers to report "Not applicable" for all amyloidosis cases, regardless of disease response.

Indicate the disease status of the PCD at the last evaluation prior to the start of the preparative regimen. If

the primary disease is POEMS, report “Not applicable” and go to the signature line. See the Multiple Myeloma Response Criteria section for multiple myeloma and solitary plasmacytoma disease status definitions. See Plasma Cell Leukemia Response Criteria for plasma cell leukemia disease status definitions.

Question 317: Date Assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation. Date of radiographic study (PET, MRI, CT) may be used ***if*** the same radiographic study had previously been obtained and ***only*** in limited circumstances (e.g., plasmacytomas, lytic lesions).

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Last modified: 2018/04/09

Q318-319: Solid Tumors

Question 318-319: Specify the solid tumor classification:

Indicate the solid tumor disease classification at the time of diagnosis. Germ cell tumors that originate in the ovary or testes should be reported as *ovarian* or *testicular*, respectively. If the subtype is not listed, report as "Other solid tumor" and specify the reported malignancy in question 310. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q320-321: Severe Aplastic Anemia

Questions 320-321: Specify the severe aplastic anemia classification:

Indicate the severe aplastic anemia disease classification at diagnosis. If the subtype is not listed, report as “other acquired cytopenic syndrome” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q322-324: Inherited Abnormalities of Erythrocyte Differentiation or Function

Questions 322-324: Specify the inherited abnormalities of erythrocyte differentiation or function classification

Indicate the inherited abnormalities of erythrocyte differentiation or function disease classification at diagnosis. If the subtype is not listed, report as “other constitutional anemia” or “other hemoglobinopathy” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q325-327: Disorders of Immune System

Questions 325-327: Specify disorder of immune system classification:

Indicate the disorder of the immune system's disease classification at diagnosis. If the subtype is not listed, report as "other SCID" or "other immunodeficiency" and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q328-329: Inherited Abnormalities of Platelets

Questions 328-329: Specify inherited abnormalities of platelets classification:

Indicate the inherited abnormalities of platelets disease classification at diagnosis. If the subtype is not listed, report as “other inherited platelet abnormality” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q330-331: Inherited Disorders of Metabolism

Questions 330-331: Specify inherited abnormalities of metabolism classification:

Indicate the inherited abnormalities of metabolism disease classification at diagnosis. If the subtype is not listed, report as “inherited metabolic disorder, not otherwise specified” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q332-333: Histocytic Disorders

Questions 332-333:: Specify the histiocytic disorder classification:

Indicate the histiocytic disorder disease classification at diagnosis. If the subtype is not listed, report as “other histiocytic disorder” and specify the reported disease in question 333. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q334-341: Autoimmune Diseases

Questions 334-341: Specify autoimmune disease classification:

Indicate the autoimmune disease classification at diagnosis. If the subtype is not listed, report as “other arthritis,” “other connective tissue disease,” “other vasculitis,” “other autoimmune neurological disorder,” “other autoimmune cytopenia,” or “other autoimmune bowl disorder,” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Last modified: 2018/01/30

Q342: Other Disease

Question 342: Specify other disease:

Before using this category, check with a transplant physician to determine whether the disease can be classified as one of the listed options in the Disease Classification questions. Examples include: erythropoietic protoporphyria (EPP), and dystrophic epidermolysis bullosa (DEB).

Last modified: 2018/01/30