Instructions for X-Linked Lymphoproliferative Syndrome (XLP) Pre-HCT Data (Form 2034)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the XLP Pre-HCT Form.

E-mail comments regarding the content of the CIBMTR Forms Instruction Manual to: CIBMTRFormsManualComments@nmdp.org. Comments will be considered for future manual updates and revisions. For questions that require an immediate response, please contact your transplant center's CIBMTR CRC.

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X-Linked Lymphoproliferative Syndrome Pre-HCT Data

X-linked lymphoproliferative syndrome, also known as XLP or Duncan's syndrome, is a rare inherited immunodeficiency. It is characterized by severe immune dysregulation, which generally manifests as an exaggerated immune response to infection. XLP belongs to the group of familial hemophagocytic lymphohistiocytosis syndromes. Patients typically present in childhood or early adolescence, often following infection with Epstein-Barr virus (which causes what is commonly known as "mono," or infectious mononucleosis); up to 90% of XLP patients are seropositive for Epstein-Barr virus.[1] Following the response to the pathogen, the exaggerated proliferation of T-cells, B-cells, and macrophages may clinically manifest as hemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinemia, and/or lymphoma.

XLP is divided into two specific types that are characterized by their clinical presentation and associated genetic abnormalities. XLP1 is defined by the *SH2D1A* mutation, which affects the signaling lymphocyte activation molecule (SLAM)-associated protein (SAP).

XLP1 patients are more likely to present with fulminant infectious mononucleosis (FIM) and/or HLH following EBV, dysgammaglobulinemia, and/or lymphoma. Mutations in *BIRC4*, also known as x-linked apoptosis inhibitor protein (XIAP), define XLP2. Patients with XLP2 tend to present with colitis and/or splenomegaly; they may also present following EBV infection with or without subsequent HLH. The common presentation of HLH following EBV suggests there may be a functional or molecular link between the SAP and XIAP proteins.[2]

The X-Linked Lymphoproliferative Syndrome Pre-HCT Data Form is one of the Comprehensive Report Forms. This form captures XLP-specific pre-HCT data such as: the recipient's clinical and genetic findings at the time of diagnosis and prior to the start of the preparative regimen, pre-HCT treatments administered, and disease manifestations prior to the preparative regimen.

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track whose primary disease is reported on Form 2400, question 357 as "disorders of the immune system" and question 628 as X-Linked Lymphoproliferative Syndrome. Additional disease insert forms will be required if the recipient had lymphoma at the time of their XLP diagnosis or prior to the start of the preparative regimen.

[1]Sumegi J, Huang D, Lanyi A, et al. Correlation of mutations of the SH2D1A gene and Epstein-Barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. *Blood,* 2000;96(9):3118-25.
[2]Schmid JP, Canioni D, Moshous D, et al. Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency). *Blood,* 2011;117(5):1522-9.

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.

- Outcomes data accurately reflects appropriate transplant type and product for each transplant center.

- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other agency.

The Key Fields precede the form body and are automatically populated in the FormsNet3[SM] application based on information provided on the CRID Assignment Form 2804. If errors are noted in the key fields, correct Form 2804 and then review it for accuracy. After Form 2804 has been corrected, verify data has been updated on all completed forms. If the data has not been updated automatically, centers will need to reprocess the completed forms to correct the key field data. If errors are noted in key fields for second or subsequent transplants, contact your CRC to make any necessary corrections to the transplant or product type. Transplant and product type will not be automatically populated on product or donor specific forms (Forms 2004, 2005, and 2006) and will need to be manually reported.

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Subsequent Transplant

If this is a report of a second or subsequent transplant for the same disease subtype, and this baseline disease insert has not been completed for the previous transplant (e.g., patient was on TED track for the prior HCT, prior HCT was autologous with no consent, etc.), begin at question 1. If this is a report of a second or subsequent transplant for a different disease (e.g., patient was previously transplanted for a disease other than X-linked lymphoproliferative syndrome), begin at question 1.

If this is a report of a second or subsequent transplant for the same disease and this baseline disease insert has previously been completed, check the indicator box and continue with question 52.

Disease Assessment at Diagnosis

Question 1: Is this recipient a registered participant in the United States Immunodeficiency Network (USIDNET)?
The United Stated Immunodeficiency Network (USIDNET) is a research consortium studying primary immune deficiencies. They maintain a registry of primary immunodeficiency patients and act as a resource for clinical and laboratory research. Indicate if the recipient is a registered participant in the USIDNET. If "yes," continue with question 2. If "no," continue with question 3.

Question 2: USIDNET ID
Report the recipient's USIDNET participant identification number.

Question 3: What was the date of diagnosis?
X-linked lymphoproliferative syndrome (XLP) is characterized by multiple clinical, laboratory, and genetic features, rather than distinct pathological characteristics. Examples of testing done to confirm a diagnosis of XLP include peripheral blood sample analysis to determine the presence or absence of functional SH2D1A or BIRC4 proteins, or molecular testing for *SH2D1A* or *BIRC4* mutations. The date of diagnosis should be the date of sample collection of last assessment used to establish a diagnosis of XLP. If there is a strong family history of XLP and no testing is done to confirm the diagnosis, report the recipient date of birth.

Question 4: Was genetic testing used to confirm the diagnosis?
X-linked lymphoproliferative syndrome is known to be an inherited disorder; for that reason, genetic testing is often done to confirm the diagnosis. If there is known family history of XLP, or the mother is a known carrier, genetic testing may be done prior to the onset of symptoms or even prenatally. The presence of *SH2D1A* (XLP1/XLP) or *BIRC4* (XLP2/XIAP) mutations are associated with XLP. Other gene mutations may be present and should be reported even if their clinical significance is uncertain. Indicate if genetic testing was performed.

If genetic testing was performed, check "yes" and continue with question 5. If genetic testing was not done or it is unknown if genetic testing was performed, indicate "no" or "unknown" and continue with question 10.

Questions 5-8: Specify genetic mutation(s) present at diagnosis

If question 4 indicates that genetic testing was performed, each of questions 5-7 must be answered. Indicate "yes" if testing revealed the specified gene mutation; indicate "no" if testing was done but did not reveal the specified gene mutation. If testing for the specified gene mutation was not done or it is unknown if testing was performed, specify this. Do not leave any response blank. If a genetic mutation was found that is best classified as "other mutation," specify in question 8.

Question 9: Was documentation submitted to the CIBMTR? (e.g., pathology report)

Indicate if a copy of the genetic testing report is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the genetic report. Attaching a copy of the report may prevent additional queries.

Question 10: Was X-linked inheritance demonstrated in the recipient's maternal family members?

X-linked patterns of inheritance are caused by genetic mutations carried on the X chromosome, which is a sex chromosome (allosome). Males normally carry one copy of the X chromosome and one copy of the Y chromosome. For this reason, a faulty X chromosome will affect all men who carry it, since it is the only X chromosome they can express; men will be symptomatic for x-linked recessive patterns of inheritance. X-linked traits cannot be passed from father to son (since the father will supply the son's Y chromosome). Women carry two copies of the X chromosome. This means they will be carriers for x-linked recessive traits, but will rarely be symptomatic since they will *generally* have a normal X chromosome that is expressed. (For x-linked *dominant* patterns of inheritance, only a single mutated X chromosome is necessary for symptomatic expression. Therefore, x-linked dominant patterns of inheritance affect both men and women.)

XLP follows an x-linked recessive pattern of inheritance. Indicate if the patient's maternal family members exhibit evidence of x-linked recessive inheritance; this would be shown by a brother, male maternal cousin, maternal uncle, and/or maternal grandfather being affected by the disease. Do not report "yes" based only on known carrier status in female family members. Specify "no" if the recipient's brother(s) and/or male cousin(s) all exhibit normal X chromosome expression (no evidence of disease). Indicate "unknown" if information is not available about the recipient's family history or if the recipient is the only male child and does not have male maternal cousins.

Specify if the following disorders were present at diagnosis

XLP typically presents following an exaggerated response to Epstein-Barr virus. Other common clinical presentations of XLP are dysgammaglobulinemia and/or lymphoproliferative processes. Additional clinical manifestations may include a lesser

response to EBV or other pathogen, cytopenias including aplastic anemia, autoimmune processes including vasculitis or psoriasis, lymphoma, and/or colitis. Specify if the recipient had any of the following at the time of diagnosis.

Question 11: Aplastic anemia
Aplastic anemia is a hematologic condition defined by peripheral blood cytopenia(s) and markedly hypocellular marrow with pancytopenia. Indicate if the patient had aplastic anemia at the time of XLP diagnosis.

Question 12: Colitis
Colitis refers to inflammation of the large intestine, often manifesting as diarrhea, abdominal pain and bloating, and melena (black "tarry" feces) or hematochezia (passage of fresh blood in feces). Indicate if the patient had colitis at the time of XLP diagnosis.

Question 13: Epstein-Barr Virus (EBV) infection with evidence of Hemophagocytic Lymphohistiocytosis (HLH)
Epstein-Barr viral infection is ubiquitous and rarely causes life-threatening complications. EBV generally infects the B-lymphocytes; however, in rare circumstances it may infect natural killer (NK) cells and T-lymphocytes. This unusual event is associated with aggressive lymphoproliferative manifestations, including hemophagocytic lymphohistiocytosis (HLH). HLH leads to an abnormal proliferation of macrophages and histiocytes, leading to the phagocytosis of healthy circulating blood cells. Indicate if the patient had evidence of HLH secondary to EBV at the time of diagnosis.

Question 14: EBV infection without HLH
EBV sensitivity is a common characteristic of XLP. The majority of patients present after acute EBV infection has caused an exaggerated response of the immune system and subsequent excessive proliferation of lymphocytes. Indicate if the patient had evidence of an EBV infection *without* HLH prior to or at time of diagnosis.

Question 15: Hypogammaglobulinemia
Hypogammaglobulinemia is a condition in which the body does not make enough antibodies or immunoglobulins. It is generally due to decreased numbers of B-lymphocytes. Indicate if the patient had hypogammaglobulinemia at the time of XLP diagnosis.

Question 16: Lymphoproliferative disorder
Various lymphoproliferative disorders caused by clonal lymphocyte proliferation may present with XLP due to the exaggerated, dysfunctional immune response caused by the disease. Examples of lymphoproliferative disorders include large granular lymphocytic leukemia (LGL) and lymphoplasmacytic lymphoma (also known as Waldenström's macroglobulinemia). Indicate if the patient had a lymphoproliferative disorder *other than lymphoma* at the time of XLP diagnosis.

Question 17: Lymphoma

XLP is associated with a higher incidence of lymphoma, which may be secondary to EBV infection; however, not all lymphomas in the setting of XLP exhibit EBV clonality. There is speculation that lymphoma risk is increased secondary to aberrant invariant natural killer T-cell (iNKT), NK cell, and T-cell cytotoxic function. The majority of lymphomas seen in XLP patients are T-cell lymphomas. Indicate if the patient had lymphoma at the time of XLP diagnosis. If yes, also complete Form 2018, Hodgkin and Non-Hodgkin Lymphoma Pre-HCT Data.

Question 18: Psoriasis

Psoriasis is an immune-mediated skin condition characterized by dry, thick patches of skin that are primarily red with silver-white scaling. Indicate if the patient had psoriasis at the time of XLP diagnosis.

Question 19: Vasculitis

Vasculitis refers to inflammation of the vasculature (blood vessels), including both veins and arteries. Vasculitis may impact blood vessels of any size, from capillaries and arterioles to the great truncal vessels. It is typically caused by autoimmunity. Indicate if the patient had vasculitis (any presentation) at the time of XLP diagnosis. If "yes," continue with questions 20-23. Answer each of questions 20-22 and do not leave any response blank. If "no," continue with question 24.

Question 20: Central nervous system

CNS vasculitis refers to inflammation of the vasculature of the brain and/or spinal cord. Indicate if the patient had CNS vasculitis.

Question 21: Pulmonary system

Pulmonary vasculitis involves inflammation of pulmonary vasculature. This can range from the great vessels, such as the pulmonary arteries, to the small alveolar capillaries. Indicate if the patient had pulmonary vasculitis.

Question 22: Other vasculitis involvement

Indicate if the patient had other vasculitis involvement. Specify involvement in question 23. Examples include systemic vasculitis, urticarial vasculitis, or gastrointestinal vasculitis.

History of Epstein Barr Virus (EBV) Infection

Question 24: Is there a history of EBV infection?

Epstein-Barr virus (EBV) is one of the human herpes viruses (*Herpesviridae* family). It is the virus that causes infectious mononucleosis, commonly referred to as "mono." XLP may present as an exaggerated immune response to EBV; up to 90% of XLP patients have previously had an EBV exposure. Indicate if the recipient has a history of EBV infection, as identified by any method of detection. If the patient has not had exposure to EBV or did not have an evaluation of previous exposure, continue with question 33.

Questions 25-27: Specify results used for diagnosis of EBV

In situ hybridization refers to the use of a labeled viral probe to detect virus nucleic acids in tissue. Polymerase chain reaction (PCR) amplifies viral DNA to determine if the patient has a current primary infection or reactivation infection. Serologic testing may be used to determine the presence of EBV antigen or antibodies to EBV.

Report the method used to diagnose a current or latent EBV infection. Answer each of the questions 25-27 and do not leave any response blank. If serologic testing was used, continue with question 28. If serologic testing was not performed or was negative, continue with question 32.

Questions 28-31: Specify [serologic] results

Antibody titration to four EBV-specific markers can provide distinct information about whether a patient has a current primary or reactivated infection, recent infection, or past infection. Antibodies to EBV nuclear antigen (**EBNA**) are not seen during acute infection, but develop 2-4 months after the first presentation of infection and persist for life. **Early antigen** testing measures IgG antibodies to early antigen; this generally appears at acute onset and is only detectable for 3-6 months. **Viral capsid IgG** measures IgG antibodies to viral capsid antigen that appear 2-4 weeks after presentation and persist for life. **Viral capsid IgM** testing for IgM antibodies to viral capsid antigen indicates current or recent infection, as it is generally only detectable for 4-6 weeks following first presentation.

Specify each EBV serologic antibody test as "positive" or "negative" in questions 28-31. Do not leave any response blank unless testing failed, was inconclusive, or was not performed.

Question 32: Was documentation submitted to the CIBMTR?

Indicate if a copy of the EBV infection testing is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the laboratory report(s). Attaching a copy of the report may prevent additional queries.

Assessment of Immunologic Function at Diagnosis

Report findings from immune function studies at the time of diagnosis; if multiple studies were performed, report the initial values.

Question 33: NK cell function

Natural killer (NK) cells are cytotoxic lymphocytes implicated in viral response and tumor immunosurveillance. Patients with XLP often have normal numbers of NK cells, but the cells have functional defects. Indicate if the patient's immune studies revealed absent (≤ 10% lower limit of normal), decreased (11-50% lower limit of normal), or normal (> 50% lower limit of normal) quantity of NK cells. If NK cell function was not assessed, indicate "not done."

Questions 34-35: Invariant natural killer T-cells (iNKT)
Invariant natural killer T-cells (iNKT) are a subset of T-lymphocytes that have actions resembling mechanisms of both the innate and adaptive immune systems. They express T-cell receptors that act similarly to pattern-recognition receptors seen in the adaptive immune system. In terms of function, iNKT do not have a "memory" of previously seen antigens, similar to cells of the innate immune system. iNKT cells are absent in XLP patients with the *SH2D1A* mutation. Specify if iNKT quantification was "known" or "unknown." If "known," report the quantity of iNKT as cells/mm^3 (or cells/μL) in question 35. If "unknown," continue with question 36.

Questions 36-39: Mucosal-associated invariant T-cells (MAIT)
Mucosal-associated invariant T-cells (MAIT) are a subset of T-lymphocytes that act as part of the innate immune system. MAIT are decreased in XLP patients with the *SH2D1A* mutation. Specify if MAIT quantification was "known" or "unknown." If "known," report the quantity of MAIT as cells/mm^3 (or cells/μL) in question 37; report the laboratory upper and lower limits of normal in questions 38-39 respectively. If "unknown," continue with question 40.

Question 40: Signaling lymphocyte activation molecule (SLAM)-associated protein (SAP) expression
Signaling lymphocyte activation molecule-associated protein (SAP) is encoded for by *SH2D1A* and is expressed in T-cells and NK cells. SAP is implicated in the development of iNKT cells, as well as in the regulation of NK and T-lymphocytes. Indicate if SAP was or was not expressed. If protein expression was not evaluated, report "not done."

Question 41: XIAP protein expression
X-linked inhibitor of apoptosis (XIAP) is encoded for by *BIRC4* and is part of an apoptosis inhibitor protein family. It is believed to be one of the more powerful inhibitors of apoptosis through its action blocking certain apoptosis cascade enzymes. Indicate if XIAP was or was not expressed. If protein expression was not evaluated, report "not done."

Question 42: Did the recipient receive supplemental intravenous immunoglobulins (IVIG)?
IVIG is a product made from pooled human plasma that primarily contains IgG. It is used to provide immune-deficient recipients with antibody function to prevent infection.

Indicate whether the recipient received IVIG at diagnosis. If "yes," continue with question 43. If "no," continue with question 44.

Question 43: Was therapy ongoing within three months of immunoglobulin testing?
Indicate whether the recipient received IVIG within three months prior to the immunoglobulin testing done at diagnosis. Patients exhibiting signs of a compromised or dysfunctional immune system may have received IVIG prior to a diagnosis being

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made. If IVIG is given within three months of immunoglobulin testing, the IgG level would not represent the recipient's native IgG.

Questions 44-45: IgG
Indicate whether IgG level was "known" or "unknown" at diagnosis. If "known," report the laboratory value and unit of measure in question 45. If "unknown," continue with question 46.

Questions 46-47: IgM
Indicate whether IgM level was "known" or "unknown" at diagnosis. If "known," report the laboratory value and unit of measure in question 47. If "unknown," continue with question 48.

Questions 48-49: IgA
Indicate whether IgA level was "known" or "unknown" at diagnosis. If "known," report the laboratory value and unit of measure in question 49. If "unknown," continue with question 50.

Questions 50-51: IgE
Indicate whether IgE level was "known" or "unknown" at diagnosis. If "known," report the laboratory value in question 51. If "unknown," continue with question 52.

Disease Assessment between Diagnosis and the Start of the Preparative Regimen

Question 52: Was HLH present?
HLH is an abnormal proliferation of macrophages and histiocytes that leads to the phagocytosis of healthy circulating blood cells. Indicate if the patient developed HLH at any time after diagnosis but prior to the start of the preparative regimen; include HLH persisting from diagnosis. If "yes," continue with question 53. If "no," continue with question 89.

Question 53: Was the HLH triggered by an acute EBV infection?
HLH may present as an exaggerated response to EBV infection. Epstein-Barr viral infection is ubiquitous and rarely causes life-threatening complications. EBV generally infects the B-lymphocytes; however, in rare circumstances it may infect natural killer (NK) cells and T-lymphocytes. This unusual event is associated with aggressive lymphoproliferative manifestations, including hemophagocytic lymphohistiocytosis (HLH). Indicate if the patient's HLH was associated with EBV infection. If "yes," continue with question 63. If "no" or "unknown," continue with question 54.

Question 54: Was the HLH triggered by any other known condition(s)?
HLH may also present as a response to malignancy or pathogen other than EBV. Indicate if the patient's HLH was associated with another known condition. If "yes," continue with question 55. If "no" or "unknown," continue with question 63.

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Questions 55-62: Specify other known condition(s)
Report condition or conditions believed to have triggered HLH. Each of the questions 55-58 and 61 must be answered as "yes" or "no"; do not leave any response blank. If the HLH was in response to a viral infection other than EBV, specify the virus in question 59. If it was a response to a virus not listed, specify in question 60. Questions 59-60 may be repeated to report multiple viral triggers. If the cause of HLH response is best classified as "other," specify in question 62.

Questions 63-69: Specify site(s) where HLH was present
Indicate "yes" or "no" for each site specified in questions 63-68. Do not leave any response blank. If "yes" is indicated for "other site," specify the site in question 69. At least one of questions 63-68 must be answered "yes."

Question 70: Was therapy given for HLH?
Indicate if the recipient received treatment for HLH after the diagnosis and before the start of the preparative regimen. If "yes," continue with question 71. If "no," continue with question 89.

Questions 71-72: Date therapy started
Indicate "known" if the therapy start date is documented and specify the first date of therapy in question 72. If the date is unknown, indicate this and continue with question 73.

Questions 73-74: Date therapy stopped
Indicate "known" if the therapy stop date is documented and specify the date therapy stopped using question 74. If the patient received systemic therapy in cycles, specify the first day of the last cycle of systemic therapy. If the patient received a single line or single administration, indicate the last day therapy was administered.

If the date is unknown, indicate this and continue with question 75.

Questions 75-88: Specify therapeutic agents
Allogeneic stem cell transplant is considered the only curative treatment for XLP. However, therapeutic agents may be given in settings where allogeneic HCT is not a viable treatment option or to maintain the patient in the pre-transplant period. Therapy may vary depending on disease presentation. Most therapeutic agents given in the setting of XLP are intended to suppress the patient's over-responsive, dysfunctional immune system. There is some evidence that cytotoxic therapy, particularly etoposide, may be beneficial in controlling lymphocyte proliferation. B-cell therapy, such as rituximab, may be given to treat EBV infection, since it generally infects B-lymphocytes. Other agents, such as IVIG, may be given to supplement the patient's immune system and provide artificial immune response.

Indicate "yes" or "no" for each therapeutic agent listed. Do not leave any response blank. If the recipient received an agent that is not listed, check "yes" for "other systemic therapy" and use question 88 to specify the treatment.

Question 89: Did colitis develop?

Colitis refers to inflammation of the large intestine, often manifesting as diarrhea, abdominal pain and bloating, and melena or hematochezia. Indicate if the patient developed colitis at any time after diagnosis but prior to the start of the preparative regimen; include colitis persisting from diagnosis.

Question 90: Did vasculitis develop?

Vasculitis refers to inflammation of the vasculature, including both veins and arteries. Vasculitis may impact blood vessels of any size, from capillaries and arterioles to the great truncal vessels. It is typically caused by autoimmunity. Indicate if the patient had vasculitis (any presentation) at any time after diagnosis but prior to the start of the preparative regimen; include vasculitis persisting from diagnosis. If "yes," continue with questions 91-94. Answer each of questions 91-93 and do not leave any response blank. If "no" or "unknown," continue with question 95.

Question 91: Central nervous system

CNS vasculitis refers to inflammation of the vasculature of the brain and/or spinal cord. Indicate if the patient had CNS vasculitis at any time after diagnosis but prior to the start of the preparative regimen; include vasculitis persisting from diagnosis.

Question 92: Pulmonary system

Pulmonary vasculitis involves inflammation of pulmonary vasculature. This can range from the great vessels, such as the pulmonary arteries, to the small alveolar capillaries. Indicate if the patient had pulmonary vasculitis at any time after diagnosis but prior to the start of the preparative regimen; include vasculitis persisting from diagnosis.

Question 93: Other vasculitis involvement

Indicate if the patient had other vasculitis involvement. Specify involvement in question 94. Examples include systemic vasculitis, urticarial vasculitis, or gastrointestinal vasculitis at any time after diagnosis but prior to the start of the preparative regimen; include vasculitis persisting from diagnosis.

Question 95: Did the recipient develop lymphoma?

XLP is associated with a higher incidence of lymphoma, which may be secondary to EBV infection; however, not all lymphomas in the setting of XLP exhibit EBV clonality. There is speculation that lymphoma risk is increased secondary to aberrant iNKT, NK, and T-cell cytotoxic function. The majority of lymphomas seen in XLP patients are T-cell lymphomas. Indicate if the patient had lymphoma at any time after diagnosis but prior to the start of the preparative regimen. If the patient had lymphoma, continue with questions 96-98; also complete Form 2018, Hodgkin and Non-Hodgkin Lymphoma Pre-HCT Data.

Question 96: Was the lymphoma associated with an EBV infection?

Indicate if the patient's lymphoma was associated with an EBV infection. If the patient's EBV status was not assessed, indicate "unknown."

Question 97: Is the tumor EBV positive?

If the patient's lymphomatous tumor was evaluated for EBV clonality, indicate if it was or was not EBV positive. If the tumor was not evaluated for EBV clonality, indicate "unknown."

Question 98: Was documentation submitted to the CIBMTR? (e.g., pathology report)

Indicate if a copy of the pathology report and/or immunohistochemistry results are attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the pathology and/or laboratory report(s). Attaching a copy of the report may prevent additional queries.

Question 99: Did the recipient develop hypogammaglobulinemia?

Hypogammaglobulinemia is a condition in which the body does not make enough antibodies or immunoglobulins. It is generally due to decreased numbers of B-lymphocytes. Indicate if the patient had hypogammaglobulinemia at any time after diagnosis but prior to the start of the preparative regimen; include hypogammaglobulinemia persisting from diagnosis.

Question 100: Did the recipient develop aplastic anemia?

Aplastic anemia is a hematologic condition defined by peripheral blood cytopenia(s) and markedly hypocellular marrow with pancytopenia. Indicate if the patient had aplastic anemia at any time after diagnosis but prior to the start of the preparative regimen; include aplastic anemia persisting from diagnosis.

Questions 101-104: Specify therapy given for aplastic anemia

Indicate therapies the recipient received for aplastic anemia after the time of diagnosis and before the start of the preparative regimen. Each of questions 101-103 should be answered as "yes" or "no"; do not leave any response blank. If therapy is best categorized as "other therapy," specify in question 104.

Disease Status at Last Evaluation Prior to the Start of the Preparative Regimen

Question 105: Specify the status of HLH

If the patient previously had HLH at any time during their disease course, specify if it was "active" or "inactive" (quiescent) at the last evaluation prior to the start of the preparative regimen. If the patient never had HLH at any time during their disease course, indicate "not applicable."

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Question 106: Was colitis active?
If the patient previously had colitis at any time during their disease course, specify if it was active at last evaluation prior to the start of the preparative regimen. If the colitis was inactive, status of colitis is unknown, or the patient never had colitis at any time during their disease course (not applicable), continue with question 108.

Question 107: Was the recipient receiving therapy for colitis?
Indicate if the patient was receiving treatment for active colitis at time of last evaluation prior to the start of the preparative regimen.

Question 108: Was the CNS vasculitis active?
If the patient previously had CNS vasculitis at any time during their disease course, specify if it was active at last evaluation prior to the start of the preparative regimen. If the CNS vasculitis was inactive, status of CNS vasculitis is unknown, or the patient never had CNS vasculitis at any time during their disease course (not applicable), continue with question 110.

Question 109: Was the recipient receiving therapy for CNS vasculitis?
Indicate if the patient was receiving treatment for active CNS vasculitis at time of last evaluation prior to the start of the preparative regimen.

Question 110: Was pulmonary vasculitis active?
If the patient previously had pulmonary vasculitis at any time during their disease course, specify if it was active at last evaluation prior to the start of the preparative regimen. If the pulmonary vasculitis was inactive, status of pulmonary vasculitis is unknown, or the patient never had pulmonary vasculitis at any time during their disease course (not applicable), continue with question 112.

Question 111: Was the recipient receiving therapy for pulmonary vasculitis?
Indicate if the patient was receiving treatment for active pulmonary vasculitis at time of last evaluation prior to the start of the preparative regimen.

Question 112: Was the other vasculitis active?
If the patient previously had other vasculitis at any time during their disease course, specify if it was active at last evaluation prior to the start of the preparative regimen. If the other vasculitis was inactive, status of other vasculitis is unknown, or the patient never had other vasculitis at any time during their disease course (not applicable), continue with question 114.

Question 113: Was the recipient receiving therapy for other vasculitis?
Indicate if the patient was receiving treatment for active other vasculitis at time of last evaluation prior to the start of the preparative regimen.

Specify the clinical and laboratory features assessed at last evaluation prior to the preparative regimen: These questions are intended to determine the immunological status of the recipient prior to the preparative regimen. Testing may be

performed multiple times within the pre-transplant work-up period (approximately 30 days) prior to the start of the preparative regimen; report the most recent laboratory value. Laboratory values obtained on the first day of the preparative regimen may be reported as long as the sample was taken before any radiation or systemic therapy was administered.

Questions 114-116: Serum ferritin

Indicate whether serum ferritin level was "known" or "unknown" immediately prior to the start of the preparative regimen. If "known," report the value and unit of measure documented on the laboratory report in question 115; indicate the date sample was collected in question 116. If "unknown," continue with question 117.

Questions 117-119: Soluble interleukin-2 receptor (sIL-2R)

Indicate whether soluble interleukin-2 receptor levels were "known" or "unknown" immediately prior to the start of the preparative regimen. If "known," report the value and unit of measure documented on the laboratory report in question 118; indicate the date sample was collected in question 119. If "unknown," continue with question 120.

Questions 120-122: Triglycerides

Indicate whether triglyceride levels were "known" or "unknown" immediately prior to the start of the preparative regimen. If "known," report the value and unit of measure documented on the laboratory report in question 121; indicate the date sample was collected in question 122. If "unknown," continue with question 123.

Questions 123-125: Fibrinogen antigen assay (factor I; fibrinogen activity; functional fibrinogen; fibrinogen antigen)

Indicate whether fibrinogen antigen levels were "known" or "unknown" immediately prior to the start of the preparative regimen. If "known," report the value and unit of measure documented on the laboratory report in question 124; indicate the date sample was collected in question 125. If "unknown," continue with question 126.

Question 126: Bone marrow aspirate/biopsy evidence of hemophagocytosis

Bone marrow aspirate and biopsy evidence of hemophagocytosis typically includes hypercellularity with markedly increased histiocytes and cytotoxic T-cells. Indicate if the pathologist interpretation of the marrow indicated the presence or absence of findings consistent with hemophagocytosis. If bone marrow evaluation was not performed, indicate "not done."

Questions 127-128: Specify the cerebrospinal fluid (CSF) findings

Indicate if protein and WBC count were elevated or normal in questions 127 and 128, respectively. If CSF evaluation was not performed, indicate "not done."

Question 129: Was donor testing for XLP done prior to HCT?

Indicate if the donor was tested for XLP during their donor selection work-up. This is most applicable for related male donors. If the donor was tested, continue with question

130. If the donor was not tested for XLP or testing is not applicable because the donor is unrelated or female, continue with the signature section.

Question 130: Was there evidence of XLP?
Indicate if testing revealed evidence of XLP in the donor.

Signature
The FormsNet3^{SM} application will automatically populate the signature data fields, including name and email address of person completing the form and date upon submission of the form.

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