Understanding Hodgkin Lymphoma



Resource Center

Lymphoma Research Foundation

Overview

Hodgkin lymphoma (HL), also known as Hodgkin disease, represents about 10% of all lymphomas in the United States. It is estimated that 8,720 new cases of HL will be diagnosed in the United States in 2025. HL can occur in both children and adults, but it is most common in young adults between the ages of 20 and 29 years, with an average age of 39 years at diagnosis.
HL is often characterized by the presence of very large cells called Reed-Sternberg (RS) cells (Figure 1) and usually starts in the lymph nodes (small bean-shaped structures that help the body fight disease, Figure 2). It can spread to other lymph nodes and, rarely, to other organs.

The exact cause of HL is not fully understood, and most cases of HL are not explained by any clear cause. Certain factors may increase the risk of developing it, such as a weakened immune system, certain infections (like Epstein-Barr virus [EBV], also known as mononucleosis), genetic factors, or exposure to certain chemicals. Biological siblings of patients with HL have a slight increased risk of also developing HL.

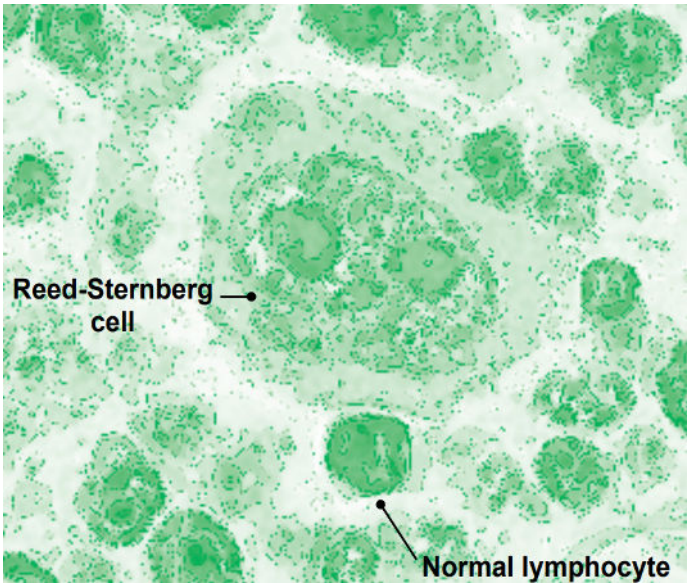


Figure 1. Example of a normal lymphocyte (a type of white blood cell that fights infection and cancer) and a Reed-Sternberg cell found in HL. HL, Hodgkin lymphoma.

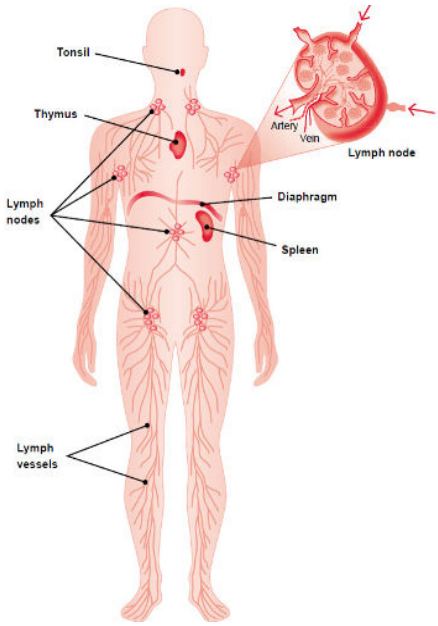


Figure 2. The lymphatic system and lymph nodes.

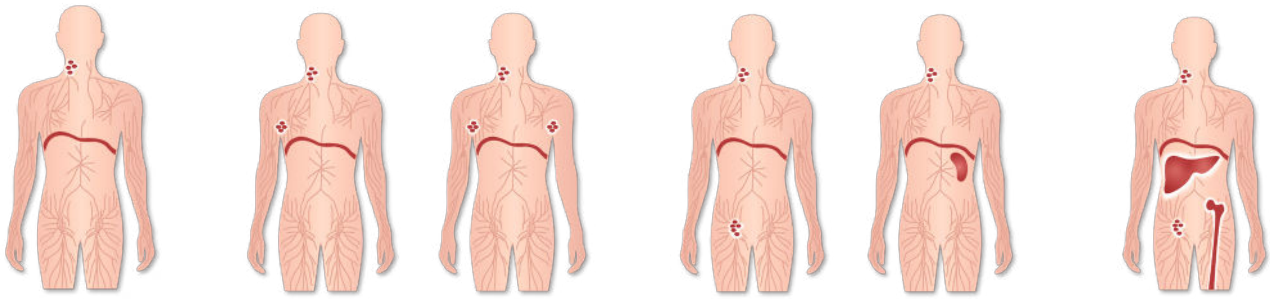
Symptoms, Staging, and Diagnostic Procedure

Common signs and symptoms of HL include:

- Swelling of the lymph nodes (usually painless).
- Recurrent fevers.
- Night sweats (drenching).
- Unexplained weight loss.
- Itching.
- Lack of energy.

While most people who have these symptoms do not have HL, anyone with persistent symptoms should see a physician to make sure that lymphoma is not present.

For staging, the results of the different tests (such as biopsies and scans) are used to determine the severity of the disease and the appropriate treatment. The Lugano staging system is used for HL and is depicted in Figure 3 below. This system categorizes HL from Stage I (limited disease) to IV (advanced disease), based on whether the disease is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs). Stage I or II is sometimes called "early stage" while Stage III and IV are considered "advanced stage". For early stage HL that affects an organ outside of the lymph system, the letter E is added to the stage (for example, stage IE or IIE).



Stage I:
Involvement of a single lymph node or group of adjacent nodes

Stage II:
Involvement of two or more groups of lymph nodes on the same side of the ***diaphragm*** (muscle that separates the chest from the abdomen)

Stage III:
- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement

Stage IV:
Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

Figure 3. Staging of HL according to the Lugano system. The Lugano system categorizes HL from Stage I (limited disease) to IV (advanced disease), based on whether the cancer is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow and/or other organs (like the liver or lungs).

Subtypes

HL is divided into two main classifications: classical HL (cHL), which accounts for the majority of cases, and nodular lymphocyte-predominant HL (NLPHL) which accounts for 5-10% of all cases. The type of HL a patient has affects their treatment options.

Nodular Sclerosis cHL is the most common subtype of cHL in the US. The involved lymph nodes contain a lot of scar tissue, which is where the name nodular sclerosis (scarring) comes from. The disease is more common in women than in men, and it usually affects adolescents and adults under the age of 50 years. The majority of patients are cured with current treatments.

Mixed Cellularity cHL is the second most prevalent form of cHL cases. The disease is more common in men than in women and primarily affects young children and is associated with EBV, and older adults and people with human immunodeficiency virus (HIV) infection. This is also more common in underdeveloped countries such as sub-Saharan Africa and is associated with EBV in these cases. These patients might present a more advanced stage (III or IV) of this subtype at diagnosis.

Lymphocyte-Rich cHL is a less common subtype of cHL. This subtype of HL is usually diagnosed at an early stage (cancer is small and has not spread) in older adults and has a low risk of relapse (disease returns after treatment).

Lymphocyte-Depleted cHL is a rare form of cHL and occurs mainly in older people and those with HIV infection. This subtype is aggressive (grows rapidly) and usually not diagnosed until it is widespread throughout the body.

Nodular Lymphocyte-Predominant HL (NLPHL), accounts for 5%-10% of all HL cases. It affects men more often than women and is usually diagnosed in young males before the age of 35 years. This subtype is characterized by the appearance of large white blood cells (lymphocytes and histiocytes, sometimes called popcorn cells) under the microscope as well as small B-cells that typically have CD20 protein on their surface. NLPHL is most often diagnosed at an early stage (>70%of patients) and is still curable even at more advanced stages (III-IV) or when it involves organs other than lymph nodes. This form of HL is indolent (grows slowly) and can relapse many years later regardless of how it is first treated. Prognosis is usually still excellent even at the time of relapse. Transformation of NLPHL to aggressive lymphoma is uncommon (<5% of patients at 10 years after initial diagnosis) and is associated with lower rates of cure and survival. Follow-up is very important because of the possibility of late relapse.



Treatment Options

Treatment is based on the severity of symptoms. When adult patients show no or few symptoms, doctors may decide to monitor the patient without treating the disease. This approach is called active surveillance, or watchful waiting. In this case, patients' overall health and disease are monitored through regular check-up visits that may include laboratory tests (like a complete blood cell count) and physical examinations (like checking for any swelling). Sometimes, patients experience symptoms due to low red blood cell count (anemia). If patients begin to have symptoms or signs of disease progression, treatment is then prescribed. Children, however, always receive treatment for cHL.

First Treatment after Diagnosis

cHL

The majority of patients with newly diagnosed cHL can be cured. While the treatment depends on the type of cHL and the patient's overall health, most patients receive as their first treatment:

Chemotherapy (drugs that stop the growth of or kill cancer cells).

- Common chemotherapy regimens used as initial treatment (frontline chemotherapy) for cHL are listed in Table 1.
- Some chemotherapy regimens include steroids (like dexamethasone or prednisone), which treat cancer and help to relieve inflammation (redness, swelling, pain, and/or a feeling of heat in an area of the body).

Radiation therapy (uses high-energy radiation to kill cancer cells) works very well against HL.

Immunotherapy (drugs that use the body's immune system to fight cancer) with antibody-drug conjugates (ADC).

- An ADC is a monoclonal antibody (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication. This targeting helps direct the chemotherapy to the cancer cells and prevent some of the killing of healthy cells in the body.
- The ADC brentuximab vedotin (Adcetris) can be used as frontline therapy for stage III or IV cHL in combination with other drugs such as doxorubicin, vinblastine, and dacarbazine (BV+AVD).

Chemoimmunotherapy is a combination of chemotherapy with immunotherapy. AVD chemotherapy combined with the checkpoint inhibitor nivolumab is used to treat patients with advanced disease.

For more information on ADCs and other types of immunotherapy, please view the Immunotherapy and Other Targeted Therapies fact sheet on the Lymphoma Research Foundation's website (lymphoma.org/publications).



Table 1. Common frontline chemotherapy regimens used to treat cHL.

Abbreviation	Description
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
AVD	Doxorubicin, vinblastine, and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BV+AVD	Brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine
BV-AVPC	Brentuximab vedotin, doxorubicin, vincristine, prednisone, cyclophosphamide
AEPA/CAPDac	Vincristine, etoposide, prednisolone, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine

cHL, classic Hodgkin lymphoma.

NLPHL

Patients with NLPHL may not require immediate treatment and can go under observation or watchful waiting if the lymphoma was removed by surgery. Treatments for NLPHL may be used alone or combined, depending on the stage of the disease (how much the cancer has grown and if it has spread in the body) and the B symptoms (fever without infection, drenching night sweats and unexplained weight loss).

The most common treatments for NLPHL are radiation therapy, chemotherapy, immunotherapy with rituximab (Rituxan), or surgery. In many situations, multiple treatment approaches are reasonable with no single "best" option, and it is appropriate for patients and families to play an active role in treatment decision-making. It is often preferable to avoid aggressive upfront treatments in NLPHL because of the cumulative side effects of such treatments over time and the curability of the disease even at relapse (>90% survival at 10 years after initial diagnosis).

In cases where NLPHL is isolated in one lymph node, surgery alone can be used. In other patients with early stage disease, radiation therapy, rituximab (Rituxan) or combination chemotherapy such as ABVD or CHOP may be used. More advanced disease is usually treated with rituximab (Rituxan) in combination with chemotherapy, as listed in Table 2.

Table 2. Common frontline combination therapies used to treat NLPHL.

Regimen	Description
R-ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine + rituximab
R-CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab
R-CVbP	Cyclophosphamide, vinblastine, and prednisolone + rituximab

Relapsed and Refractory cHL

cHL

Some patients with HL respond to initial treatment and go into remission (disappearance of signs and symptoms of the disease). In other cases, the disease may relapse or become refractory (does not respond to treatment). For these patients, different therapies may result in improved treatment outcomes and may even cure the disease. For cHL, most relapses usually occur within the first three years following diagnosis, although some relapses occur much later. Patients who relapse often have the same symptoms they had when first diagnosed with HL.

A number of treatment options are available for patients with relapsed or refractory cHL. The exact treatment a doctor recommends depends on several factors, including the timing of the relapse (how long it takes to relapse after the treatment), age and overall health of the patient, disease stage, and previous therapies received.

The standard treatment (the proper treatment that is widely used by healthcare professionals and accepted by medical experts) for patients with relapsed/refractory cHL without other major health conditions consist of systemic therapy (treatment with drugs that travel in the bloodstream throughout the body), and can include:

Immunotherapy (Table 3). These can be used alone or in combination with each other:

- Monoclonal antibodies such as nivolumab (Opdivo) and pembrolizumab (Keytruda).
- The ADC brentuximab vedotin (Adcetris).

Chemotherapy regimens (see Table 4).

Chemoimmunotherapy which is a combination of chemotherapy with immunotherapy such as BvB (brentuximab vedotin [Adcetris] and bendamustine [Treanda]).



Autologous SCT (a patient's own stem cells are infused after high-dose chemotherapy). For more information on transplantation, view the Understanding Cellular Therapy publication on the Foundation's website (lymphoma.org/publications).

Radiation therapy as consolidation therapy (treatment given after cancer has disappeared following initial therapy, to kill any cancer cells that may be left in the body).

- Involved-site radiation therapy (radiation therapy that is applied to treat a specific area where the cancer is located).

Table 3. Immunotherapy drugs approved to treat relapsed or refractory cHL.

Treatment	Approved Indications
Brentuximab vedotin (Adcetris) Antibody-drug conjugate that targets the CD30 protein	• Adult patients with a) previously untreated Stage III or IV cHL (in combination with AVD), b) at high risk of relapse or progression after auto-HSCT, c) after failure of auto-HSCT, d) or after failure of ≥ 2 chemotherapy regimens (in patients who are not auto-HSCT candidates) • Pediatric patients (≥ 2 years old) with previously untreated high risk cHL (in combination with EPOCH)
Nivolumab (Opdivo) Immune checkpoint inhibitor that blocks the PD-1 receptor	• Adult patients with cHL that has relapsed or progressed after auto-HSCT and brentuximab vedotin (Adcetris) or ≥ 3 lines of systemic therapy (including auto-HSCT)
Pembrolizumab (Keytruda) Immune checkpoint inhibitor that blocks the PD-1 receptor	• Adult patients with relapsed or refractory cHL • Pediatric patients with refractory cHL, or cHL that has relapsed after ≥ 2 lines of therapy

AVD, doxorubicin, vinblastine and dacarbazine; cHL, classical Hodgkin lymphoma; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; auto-HSCT, autologous hematopoietic stem cell transplant; PD-1, programmed death receptor-1.

Table 4. Chemotherapy regimens used to treat relapsed or refractory cHL.

Regimen	Description
BeGEV	• Bendamustine (Treanda), gemcitabine, and vinorelbine
DHAP	• Dexamethasone, cisplatine, high-dose cytarabine
GVD	• Gemcitabine, vinorelbine, and doxorubicin
ICE	• Ifosfamide, carboplatin, and etoposide
IGEV	• Ifosfamide, gemcitabine, and vinorelbine

cHL, classical Hodgkin lymphoma.

NLPHL

Therapeutic options for relapsed or refractory NLPHL include systemic therapy with the anti-CD20 antibody rituximab (Rituxan) either alone or in combination with chemotherapy. Radiation therapy may also be used.

Treatments Under Investigation

Although many individuals diagnosed with HL are cured after treatment, researchers continue to develop new therapies that are more effective and have less side effects during therapy and for years after. New drugs being studied include immune checkpoint inhibitors (drugs that block proteins that help cancer cells evade immune response).

Investigators (experts who run clinical research) are also looking for ways to treat those patients who are not cured and in need of more treatment. These include new combinations of targeted therapies (drugs that target specific molecules that cancer cells use to survive and spread) or immunotherapies. Table 5 (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the Understanding Clinical Trials publication on the Foundation's website at lymphoma.org/publication. It is also very important that patients with HL consult with their doctor to clear up any questions they may have.

Table 5. Investigational drugs for HL.

Treatments	Class	Condition
Ipilimumab (Yervoy)	Immunotherapy; immune checkpoint inhibitor; antiCTLA-4	R/R cHL
Avelumab (Bavencio)	Immunotherapy; immune checkpoint inhibitor; antiPD-L1	Untreated cHL
Azacitidine (Vidaza)	Chemotherapy; pyrimidine nucleoside analog	Untreated NLPHL and R/R cHL
Camrelizumab (SHR-1210)	Immunotherapy; immune checkpoint inhibitor; antiPD-1	Untreated cHL and R/R cHL
Sintilimab (Tyvyt)	Immunotherapy; immune checkpoint inhibitor; antiPD-1	Untreated cHL
Mosunetuzumab (Lunsumio)	Immunotherapy; bispecific antibody; anti-CD20	Untreated NLPHL
Zimberelimab (GLS-010)	Immunotherapy; immune checkpoint inhibitor; antiPD-1	Untreated cHL

Treatments	Class	Condition
Axatilimab	Immunotherapy; monoclonal antibody; anti-CSF-1R	R/R cHL
AFM13	Immunotherapy; bispecific antibody; antiCD30/CD16A	R/R cHL
Magrolimab	Immunotherapy; monoclonal antibody; anti-CSF-1R	R/R cHL
Penpulimab	Immunotherapy; immune checkpoint inhibitor; antiPD-1	Untreated cHL and R/R cHL
Prolgolimab	Immunotherapy; immune checkpoint inhibitor; antiPD-1	R/R cHL
Ruxolitinib	Targeted therapy; JAK1/2 inhibitor	R/R cHL
Tislelizumab (BGB-A317)	Immunotherapy; immune checkpoint inhibitor; antiPD-1	Untreated cHL and R/R cHL

CD, cluster of differentiation; cHL, classical Hodgkin lymphoma; CSF-1R, colony stimulating factor-1 receptor; CTLA-4, cytotoxic Tlymphocyte-associated protein 4; JAK, Janus kinase; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PD-1, programmed death receptor-1; PD-L1, programmed death-1 ligand; R/R, relapsed/refractory.

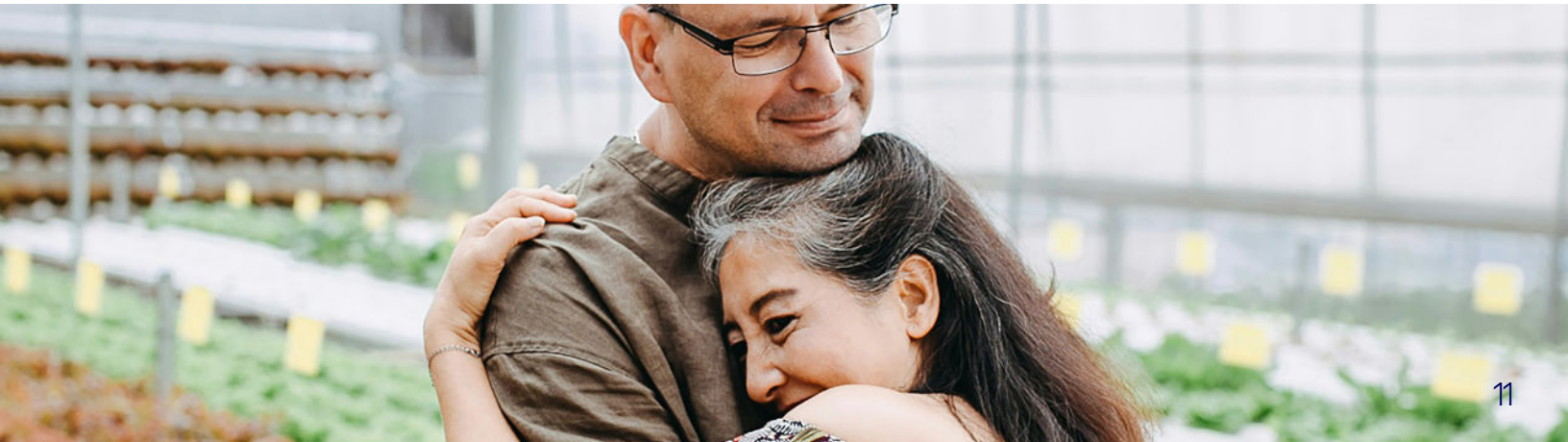
It is critical to remember that scientific research is always changing. Treatment options may change as new treatments are discovered, and current treatments are improved. Therefore, it is important that patients check with their physician or with The Foundation for any treatment updates that may have recently appeared.



How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience. It may help patients regain a sense of control that they may have lost following the lymphoma diagnosis by making sure patients receive the best care. Patients and care partners should remember they are partners in their treatment plan.

- Do not be afraid to ask your doctors or nurses questions about your care. An educated patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about lymphoma by asking your doctor for information and visiting reliable websites, such as the Foundation's at **www.lymphoma.org.**
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining the Foundation's Lymphoma Support Network, a nationwide peer support program that matches patients and care partners with people who have had similar experiences. For information about the program, call **(800) 500-9976** or email **connect@lymphoma.org.**
- Finally, it is important that patients not be afraid to talk with the healthcare team about nonmedical issues such as transportation, finances, insurance, working through treatment or taking time off, and childcare. There are nurses, social workers, and physician's assistants that are able to provide the support and resources to help.



Clinical Trials



Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. They are not a "last resort" for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments. There are four main types or phases of clinical trials. The phase is based on the study's objective and the number of participants.

Phase I

- To identify a safe dose of a new drug
- To decide on a dosing schedule for the drug
- To see what side effects are related to the therapy

Phase II

- To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I
- To confirm and learn more about the side effects identified in Phase I

Phase III

- To compare the new treatment or new use of an existing treatment with the current standard treatments
- To obtain detailed information about how well the treatment works and the types and severity of side effects it causes

Phase IV

- To look at long-term safety and effectiveness that take place after a new treatment has been approved by the FDA and is available to the public.



Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on the Foundation's website (visit **lymphoma.org/publications**), and the Clinical Trials Search Request Form at **lymphoma.org,** talk to their physician, or contact the Foundation's Resource Center for an individualized clinical trial search by calling **(800) 500-9976** or emailing **connect@lymphoma.org.**

Follow-Up

Survivorship

As a cancer survivor, it is important that you practice self-care regularly to reset your physical and emotional well-being. Adopting routines of self-care will help you recharge your batteries and stay healthy. Talk with your healthcare team about developing a wellness plan to help you stay physically and emotionally healthy and improve your mood. Consider the following suggestions:

- Watch your health. Stay up-to-date with your own medical appointments and take any medications as prescribed.
- Exercise. Stay active with short periods of daily exercise (30 minutes of power walking, jogging or biking). If not possible, take the stairs instead of the elevator or park farther away than usual.
- Eat well. Include fruits and vegetables in your meals and maintain a balanced diet.
- Cut down on risk factors. Quit smoking and reduce alcohol intake.
- Sleep. Try to get 7 hours of sleep per night, or take naps when needed.
- Rest. Meditation, deep breathing and stretching can help you relax and reduce stress.
- Write it down. Keeping a journal with thoughts and feelings may help to let go of worries and fears.

View the Foundation's Survivorship Series fact sheet on the Foundation's website at lymphoma.org/publication for more info.

Care Partners

There are many ways you can help a loved one with lymphoma, as follows:

- Be present. The most important thing that a care partner can do is to "just show up."
- Be prepared. Talk with the healthcare team so that you know what to expect throughout the treatment, how to manage symptoms and when to ask for help.
- Listen. Each person asks for help in different ways, verbally (through words) and nonverbally, and some may require more comfort while others are more action oriented.
- Avoid "cheerleading". Do not disregard your love one's negative feelings (sadness, anger or worry).
- Organize the help. A rush of sudden help upon diagnosis can make the situation harder to manage and create unproductive tension.
- Set up remote access with computer and/or phone access. This is helpful for regular communication with your loved one.
- Offer rides. This is important for people with decreased mobility or limited resources.
- Take notes. If you go into the appointments, write down notes with the doctor's plan, medications, potential side effects and other relevant information.

Patients and their care partner are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation can help patients manage this documentation.

View the Care Partners fact sheet on the Foundation's website at lymphoma.org/publication for more info.

Questions to Ask Your Healthcare Team

- What is my exact diagnosis? What subtype of lymphoma do I have? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area of the body is it specifically located?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment later on? How are the different treatments administered?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of lymphoma? Would a clinical trial be appropriate for me? How would I benefit? Are there any drawbacks of participating in a clinical trial?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?



The Foundation's Programs and Services

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs.**

Lymphoma Resource Center (LRC)

The LRC staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Treatment Navigation Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the Foundation's Lymphoma Resource Center at **800-500-9976** or **connect@lymphoma.org.**

Lymphoma Support Network

The Foundation's one-to-one peer support program – Lymphoma Support Network – connects patients and care partners with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission. For more information about this program, please contact the Foundation's Lymphoma Resource Center at **800-500-9976** or visit **lymphoma.org/resources/supportservices/lsn.**

Treatment Navigation Service

The Foundation provides a "Treatment Navigation Service" to increase awareness about trials being conducted at cancer treatment centers nationwide. Upon request, our Lymphoma Resource Center staff can conduct a customized search for potential lymphoma treatment trials in a patient's area. Trial search results can be mailed or emailed so that they may be discussed with the patient's treating healthcare team and loved ones. Individuals interested in having a trial search conducted for them can contact the Lymphoma Resource Center at **800-500-9976** or **connect@lymphoma.org** or complete a trial search request form on our website at **lymphoma.org/ctis**.

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Co-Chair: Leo I. Gordon, MD, FACP
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For individuals outside of the U.S. seeking information, the Foundation recommends the Lymphoma Coalition. The Lymphoma Coalition is a global network of worldwide nonprofit/NGO lymphoma patient organizations with information appropriate for non-U.S.-based audiences. Additional information can be found by visiting their website at https://lymphomacoalition.org/.

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Lymphoma Research Foundation

Contact the Lymphoma Research Foundation

Resource Center:
(800) 500-9976
connect@lymphoma.org

Stay Connected through our social media

Website: www.lymphoma.org
Email: Lymphoma@lymphoma.org

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