Understanding Cutaneous T-cell Lymphomas



Resource Center

Lymphoma Research Foundation

Overview

Lymphomas that arise in tissues or organs outside of the lymphatic system (tissues and organs that produce, store, and carry white blood cells) are called extranodal lymphomas. Extranodal lymphomas that arise and manifest primarily in the skin are called cutaneous lymphomas. When lymphomas start in the skin and there is no evidence of disease outside of the skin when the disease is first diagnosed, they are called primary cutaneous lymphomas. Primary cutaneous lymphomas are a form of non-Hodgkin lymphoma (NHL)

Cutaneous T-cell lymphoma (CTCL) starts in the T-cells of the skin and is the most common type of primary cutaneous lymphoma. Most forms of CTCL begin as indolent (slow growing) diseases and involve only skin symptoms, although some more aggressive forms of CTCL can involve the blood, lymph nodes, and other organs. CTCL affects men more often than women and usually occurs in people in their
50s and 60s.

Symptoms, Staging, and Diagnostic Procedure

CTCL lesions often look red and dry, can be of any size, and can affect any part of the body, although more often they arise on the trunk, buttocks, and thighs. Aside from the skin, CTCL can also affect the blood, lymph nodes (small bean-shaped structures that help the body fight disease), and other internal organs. Symptoms can include:

- Red rash or skin discoloration.
- Dry skin.
- Itching (which can be severe) sometimes with a burning sensation.
- Swelling (due to enlarged lymph nodes).
- Hair loss.
- Nail changes.

The type of treatment used also depends on the subtype of CTCL, skin symptoms and appearance.



Blood flow cytometry (a technique that detects and counts different types of blood cells, according to their physical and chemical characteristics and the surface markers they express) is essential to diagnose and stage CTCL, and whole-body imaging is often needed to determine if the cancer has spread to the lymph nodes or other organs. These tests may include a computed tomography (CT) scan, a positron emission tomography (PET, a form of imaging that uses a special dye to locate cancer cells in the body) scan, and/or magnetic resonance imaging (MRI, a procedure that takes detailed pictures of areas inside the body using a powerful magnet and radio waves). Swollen lymph nodes can be positive on a PET scan so a biopsy (a procedure in which a piece of the abnormal tissue is removed from the body and examined under a microscope) is necessary to confirm if cancer cells are present in the lymph node. A bone marrow biopsy (a procedure to collect small samples of the spongy tissue inside the bone) may also be performed but is not always necessary.

Once the diagnosis is made, patients undergo exams to assess the disease stage (how much the cancer has grown, what is the extent and pattern of growth in the skin [patch, plaque or tumor], and if it has spread to other parts of the body). The clinical stages of CTCL are detailed in Table 1.

Table 1. Clinical Stages of CTCL

Stages	A	B
I (disease limited to the skin)	Skin: Less than 10% covered in patches or plaques. Lymph nodes, blood, and internal organs not involved.	Skin: 10%-79% covered in patches or plaques. Lymph nodes, blood, and internal organs not involved.
II (disease limited to the skin)	Skin: 10-79% covered with patches or plaques. Lymph nodes enlarged but not involved on biopsy.	Skin: 10-79% covered with patches, plaque, and/or tumors. Lymph nodes enlarged but not involved on biopsy.
III (patients with erythroderma but without significant blood involvement)	Skin: >80 covered with patches or plaques, with or without tumors. Lymph nodes may be enlarged or not but are not involved on biopsy. Blood and internal organs are not involved.	Skin: >80 covered with patches or plaques, with or without tumors. Lymph nodes may be enlarged or not but are not involved on biopsy. Blood and internal organs are not involved.
IV (disease has spread to the lymph nodes and/or the bloodstream)	**IVA1:** Skin: Covered to any degree with patches, plaques, or tumors; blood is involved. Lymph nodes and internal organs are not involved. **IVA2:** Skin: Covered to any degree with patches, plaques, or tumors. Blood may or may not be involved. Biopsy-proven lymph node involvement. Internal organs are not involved.	Skin: Covered to any degree with patches, plaques, or tumors. Blood may or may not be involved. Lymph nodes may or may not be involved. Internal organs, including the bone marrow (the spongy tissue inside the bones), are involved.

Because it is a rare disease, patients with CTCL should be referred to a health care team that specializes in this type of lymphoma. The patients' clinical stage is important to select the best treatment. The treatment is individually chosen for each patient and may be adjusted frequently depending on how effective the treatment is and how well the patient tolerates it.

The clinical stage is also important to determine the prognosis (how well the patient will do with standard treatment) and treatment options. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret these statistics and understand how well they apply to a patient's particular situation.

Subtypes

There are different subtypes of CTCL, and the most common ones are mycosis fungoides (MF), CD30-positive lymphoproliferative disorders, and Sézary syndrome (SS). Other subtypes of CTCL are less frequent and can be more aggressive (fast-growing).

The most common subtype of CTCL is MF and represents around half of all skin lymphomas. Most patients with MF experience only skin symptoms. This type of CTCL is usually indolent. In many patients, the disease is limited to the skin. However, MF may progress (become worse or spread in the body) more rapidly in some patients and spread to the lymph nodes, blood, and/or internal organs.

MF may look different in each patient as skin symptoms can appear in different forms.

Potential Symptoms of MF

- Patches (usually are flat, sometimes scaly, and look like a rash).
- Plaques (thick, raised, and often itchy lesions that can be mistaken for other skin conditions like eczema, psoriasis, or dermatitis).
- Tumors (raised bumps or nodules with a diameter or height ≥ 1 cm (half the size of a penny), that may become an open sore or ulcer).
- Erythroderma (reddening and scaling of more than 80% of the skin).

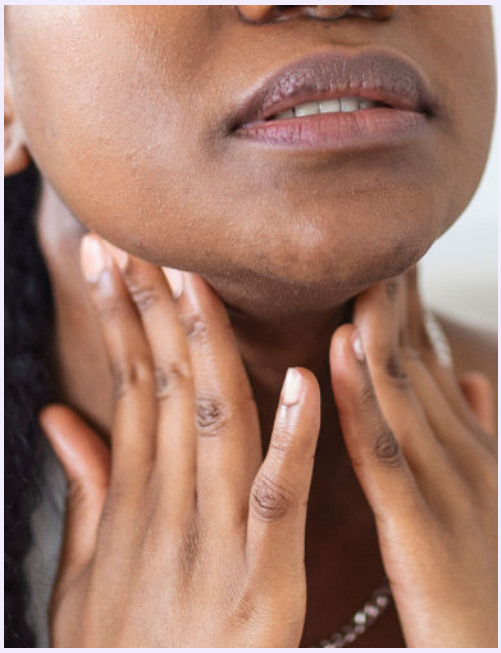
It is possible to have more than one type of skin symptom. For instance, patients with erythrodermic MF also have scaly red skin lesions that can be very itchy but also have tumors.

A medical history, physical examination, and skin biopsy (a procedure to collect small samples of the affected skin) are needed for diagnosis. A physician will examine lymph nodes, order various blood tests, and may conduct other screening tests, such as blood flow cytometry or a whole-body imaging study (such as a CT or PET scan).

MF is difficult to diagnose in its early stages because of the symptoms and the skin biopsy findings can be similar to those of other skin conditions.

SS is more aggressive and harder to treat than MF. Patients with SS by definition have stage IV lymphoma, and may experience the following signs and symptoms:

- Erythroderma.
- Sézary cells (large T-cells with an abnormal shape) in the blood.
- Enlarged lymph nodes.
- A red and itchy skin rash, often with shedding of the outer layer of the skin (exfoliation).
- Feeling cold (loss of temperature control by the skin).
- Patches and tumors (in some patients).
- Severe itching.
- Frequent skin infections (for instance, with Staphylococcus aureus).
- Keratoderma (the skin of the hands and feet becomes very thick and cracked).
- Changes in the nails, hair, or eyelids.



Treatment Options

First Treatment after Diagnosis

For MF, treatment is directed either at the skin (skin directed therapy) or at the entire body (systemic therapy, treatment with drugs that travel through the bloodstream and reach all parts of the body). Skin directed therapy can be topical (treatment applied to the skin in the form of creams, ointments, or gels) or full skin (ultraviolet light, skin radiation). The disease is not considered curable and follows a chronic course (lasting for a long period of time), but it can be managed with treatment and sometimes becomes undetectable (remission). Some patients with early-stage MF are able to remain in remission for long periods of time.

Since SS is systemic (cancer has spread to the bloodstream), it is not treated with skin-directed therapies alone. The remaining treatments approved for SS may be prescribed alone or in combination to achieve the best long-term treatment response.

Topical therapies generally are used for earlier-stage disease and are useful to treat patients who have patches and limited plaques. These therapies include:

- Topical corticosteroids (most frequently used topical therapy).
- Topical chemotherapy (drugs that stop the growth of or kill cancer cells) with, for example, mechlorethamine (Valchlor).
- Topical retinoids like bexarotene (Targretin).
- Topical immunotherapy (drugs that use the body's immune system to fight cancer) with imiquimod (Zyclara).
- Local or total skin radiation therapy.
- Phototherapy (with ultraviolet light).

Corticosteroids are the most commonly used topical treatment for CTCL. Bexarotene gel (Targretin) and mechlorethamine gel (Valchlor) have been approved by the U.S. Food and Drug Administration (FDA) as a topical treatment for Stages 1A and 1B CTCL in patients who have received previous skin treatment.



Systemic treatment may be used in more advanced-stage disease and in patients with earlier stage disease who did not respond to or did not tolerate topical therapies.

Systemic treatments include:

Chemotherapy, including:

- Methotrexate
- Pralatrexate
- Pegylated liposomal doxorubicin
- Fludarabine
- 2chlorodeoxyadenosine
- Pentostatin
- Chlorambucil
- Folate analogues, like pralatrexate (Folotyn)

Immunotherapy:

- Immunomodulatory agents (drugs that work on the immune system directly by regulating [activating or slowing down] the activity of specific proteins) such as interferon alfa or gamma (with or without topical therapies)
- Antibody-drug conjugate (ADC) such as brentuximab vedotin (Adcetris) which is a monoclonal antibody (a protein made in the laboratory that bind to cancer cells and help the immune system destroy them) attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein called CD30 on the cancer cell surface.
- Monoclonal antibodies such as mogamulizumab (Poteligeo).

Oral retinoids like bexarotene (Targretin).

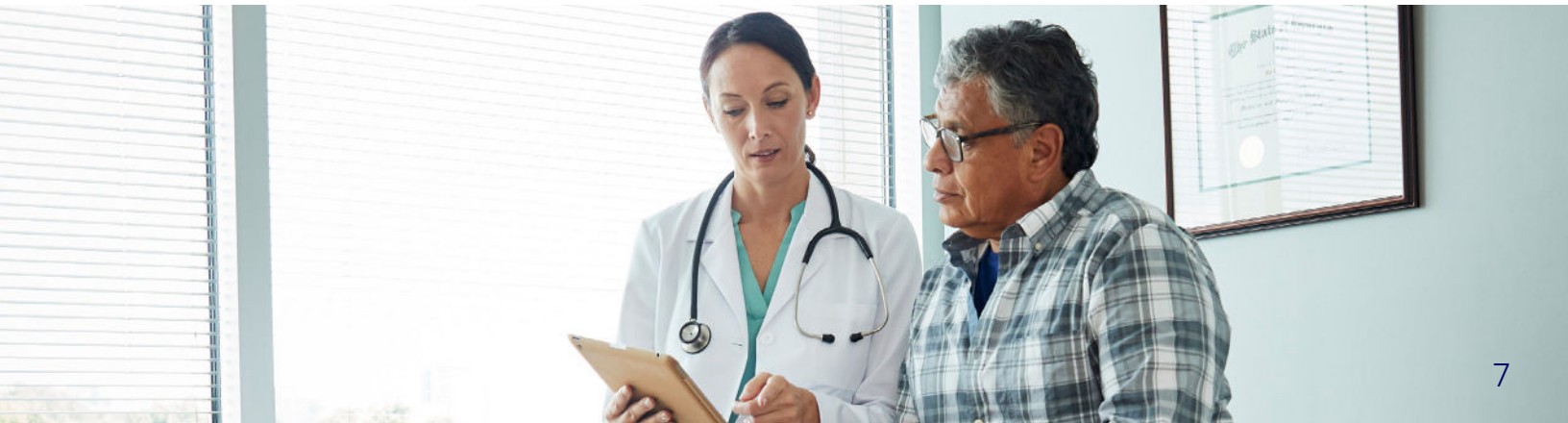
Targeted therapy (drugs that target molecules that the cancer cells use to grow and spread) with histone deacetylase (HDAC) inhibitors such as vorinostat (Zolinza) or romidepsin (Istodax).

Extracorporeal photopheresis (the blood of the patient is removed, and the white blood cells are isolated, exposed to UV radiation and returned to the patient).

Stem cell transplantation (SCT), the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells and then receives healthy stem cells to restore the bone marrow's ability to make new blood cells. There are two types of SCT:

- Autologous: The patient receives his/her own stem cells after high dose chemotherapy and/or radiation.
- Allogeneic: The patients receive stem cells from a donor, usually a family member or an unrelated donor). Allogeneic SCT not only restores the bone marrow's ability to make new blood cells but also transplant a new donor-derived immune system.

Patients with more advanced-stage MF often require systemic therapies.



Relapsed and Refractory CTCL

Some patients with cutaneous lymphoma respond to initial treatment and go into remission. In other cases, the disease may relapse (disease returns after treatment) or become refractory (does not respond to treatment). For these patients, different therapies may result in improved treatment outcomes.

Patients with high-risk disease (advanced disease that has failed to adequately respond to multiple forms of systemic therapy) may receive an allogeneic SCT. To know more about stem cell transplantation, please view the Understanding Cellular Therapy guide at the Foundation's website (lymphoma.org/publications).

Combination chemotherapy regimens are for those with refractory or advanced disease or that have spread from the skin to other parts of the body. Some of the systemic therapies can be combined to improve the response. Patients also often use skin directed treatments in conjunction with systemic therapies.





Treatments Under Investigation

Many yet-to-be-approved treatments (also referred to as investigational drugs) are currently being tested in clinical trials for CTCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by health care professionals and accepted by medical experts). The table below lists some of these treatments that can be accessed through a clinical trial. For more information about clinical trials, view the Understanding Clinical Trials publication on the Foundation's website **(lymphoma.org/publications)**.

Table 2. Selected Agents Under Investigation for CTCL in Phase 2 or 3 Clinical Trials

Agent (drug)	Class (type of treatment)	Type of Lymphoma
AFM13	Immunotherapy; bispecific antibody, anti-CD30 & -CD16A	R/R CTCL
CD30 biAb-AATC	Immunotherapy; bispecific antibody, anti-CD30 & -CD3	R/R CTCL
Cemiplimab (Libtayo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	R/R CTCL
DR-01	Immunotherapy; monoclonal antibody, anti-CD94	Untreated CTCL
Durvalumab (Imfinzi)	Immunotherapy; immune checkpoint inhibitor, anti-PD-L1	R/R CTCL
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti- KIR3DL2	R/R CTCL
Lenalidomine (Revlimid)	Immunotherapy; immunomodulatory drug	Untreated CTCL and R/R CTCL
Linperlisib	Targeted therapy; PI3K inhibitor	R/R CTCL

Agent (drug)	Class (type of treatment)	Type of Lymphoma
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	R/R CTCL
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	R/R CTCL
Ritlecitinib	Targeted therapy; JAK3 inhibitor	R/R CTCL
Talimogene laherparepvec (Imlygic)	Immunotherapy; oncolytic viral therapy	R/R CTCL

CD, cluster of differentiation; CTCL, cutaneous T-cell lymphoma; JAK3, Janus kinase 3; KIR3DL2, killer cell immunoglobulin like receptor three Ig domains and long cytoplasmic tail 2; PD-1, programmed cell death protein 1; PDL1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; R/R, relapsed and/or refractory.

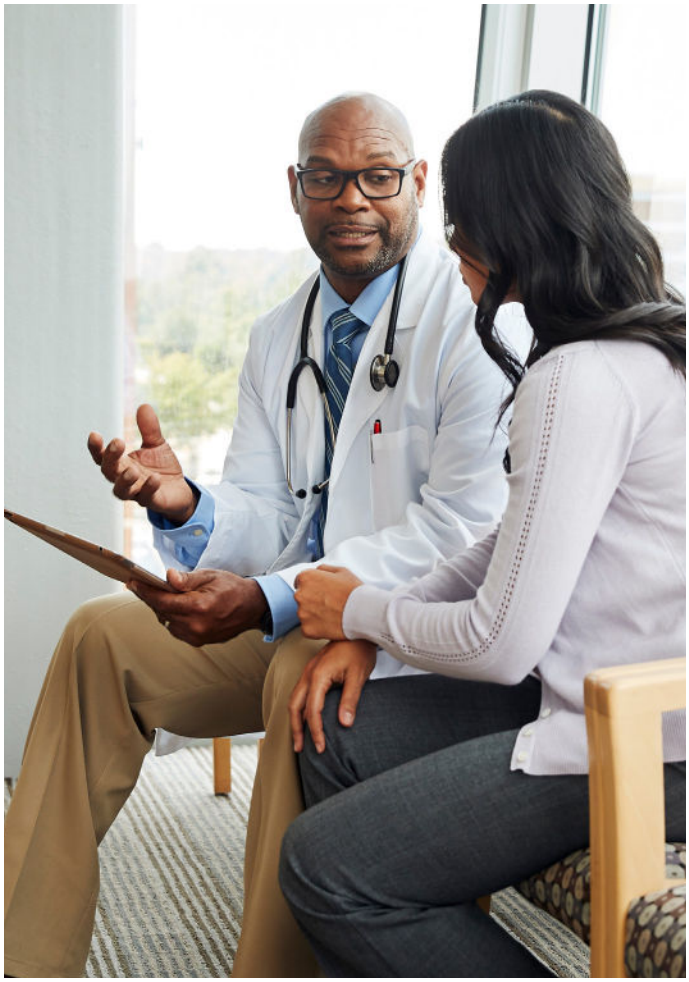
It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered, and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients with CTCL consult a specialist to clear up any questions.

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 caregivers 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 caregivers with people who have had similar experiences.
  For information about the program, call (800) 500-9976 or email helpline@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, physician's assistants that are be able to provide the support and resources to help.

Clinical Trials



Clinical trials are important in finding effective drugs and the best treatment doses for patients with cutaneous lymphomas. 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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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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