CAR-T cell therapy differs from stem cell transplantation. Both stem cell transplantation and CAR-T cell therapy are cellular therapies, and many of the steps in the procedures are similar, such as collecting cells from the patient, conditioning chemotherapy, and reinfusion of the cells. However, CAR-T cell therapy uses patients’ own immune cells called chimeric antigen receptor (CAR) T cell therapy, an immunotherapy approach, as opposed to immune cells collected from a matched donor. The process for CAR-T cell therapy is less intense, with fewer side effects, and the side effects caused by cytokine release syndrome (CRS) are unique to CAR-T cell therapy.

Is the procedure covered by insurance? Before undergoing this procedure, check with your medical insurance provider to see what costs the provider will cover and what costs you will be responsible for paying. If there is a dispute about coverage or if coverage is denied, ask your insurance carrier about their appeals process if a claim is repeatedly denied, contact your state’s insurance agency.

How do I know that I am getting my own CAR-T cell therapy? There are several quality control checks throughout the process to make sure that you only receive your own CAR-T cells. Your T cells are labeled with a unique identifier that stays with them during the entire process, and the identifiers are carefully matched to your identity before the cells are infused.

Where can I go if I experience symptoms? You will need to seek immediate attention for any of the following:

- Signs or symptoms associated with CRS including fever, chills, rapid heartbeat, nausea, feeling short of breath, and feeling faint or dizzy upon standing.
- Signs or symptoms associated with neurologic events including altered mental state, sleepiness, memory loss, or personality changes, vision changes in your level of consciousness, difficulty writing, speech disorders, tremors, and confusion.
- Signs or symptoms associated with infection such as fever or chills.
- Signs or symptoms associated with bone marrow suppression including feeling overtired, bleeding that does not stop, or feeling faint or dizzy upon standing.
- Signs or symptoms associated with CRS including fever, chills, rapid heartbeat, nausea, feeling short of breath, and feeling faint or dizzy upon standing.
- Signs or symptoms associated with infection such as fever or chills.
- Signs or symptoms associated with bone marrow suppression including feeling overtired, bleeding that does not stop, or feeling faint or dizzy upon standing.
- Signs or symptoms associated with neurologic events including altered mental state, sleepiness, memory loss, or personality changes, vision changes in your level of consciousness, difficulty writing, speech disorders, tremors, and confusion.
- Signs or symptoms associated with infection such as fever or chills.

How long do I need to be near the certified treatment center? You will need to plan to be near the certified treatment center for at least four weeks after the infusion of your CAR-T cells. Before receiving the CAR-T cell therapy, tell your healthcare provider about all the medications, including the dosages, you currently take. Be sure to include prescription and over-the-counter medicines, as well as vitamins and herbal supplements. It is also important to tell your healthcare provider about all your medical history, including if you have or have had:

- Neurologic conditions (such as seizures, stroke, or memory loss)
- Lung or breathing conditions
- Neurologic conditions (such as seizures, stroke, or memory loss)
- Lung or breathing conditions
- Kidney conditions
- A recent or active infection

CAR-T Cell Therapy for Lymphoma

Immunotherapy enhances the power of a patient’s immune system to attack tumors. An immunotherapy approach, called chimeric antigen receptor (CAR) T cell therapy, uses patients’ own immune cells to treat their cancer.
The Process

**Leukapheresis**

The first step of CAR-T cell therapy is to obtain some of your T cells, a type of white blood cell. This process is called leukapheresis and usually takes three to four hours.

- During leukapheresis, your blood is removed through an IV.
- Your blood is washed through a machine that filters your T cells from the other blood cells.
- The rest of your blood cells are returned to your body.

**T-Cell Engineering**

Once enough of the CAR-T cells are available at the processing center, the T cells are sent to a processing center where they are genetically engineered to target your lymphoma.

- The genetically enhanced cells now have chimeric antigen receptors (CARs) that allow the T cells to better recognize your cancer cells.
- The CARs on the surface of the T cells specifically binds to a protein, for instance, CD19 on lymphoma cells.

**CAR-T Cell Infusion**

A few days after completing chemotherapy, you will receive your CAR-T cells at your certified treatment center.

- The infusion of CAR-T cells takes less than one hour.
- You may be given acetaminophen (Tylenol) and/or anti-seizure medications such as levetiracetam, if needed.
- Neurological symptoms are treated with corticosteroids and tocilizumab (Actemra), which was approved by the U.S. Food and Drug Administration (FDA) in 2017.

**CAR-T Cell Transport**

Once enough of the CAR-T cells are available at the processing center, the cells are flown from your treatment center.

**Chemotherapy**

A few days prior to your CAR-T cell infusion, you will receive low-dose chemotherapy.

- The chemotherapy suppresses the immune system slightly so that it does not react to your CAR-T cells.
- It gives the CAR-T cells the chance to grow and fight your lymphoma.

**Side Effects**

**Cytokine Release Syndrome (CRS)**

Cytokine release syndrome (CRS) is your body's response to the activation and growth of your CAR-T cells.

- The CAR-T cells attack the lymphoma cells, while blood cells are activated and release cytokines (chemicals in the body) that are part of the natural inflammatory response a person might have after a severe infection.
- These cytokines can cause inflammation in many areas, including fever, low blood pressure, and body aches.

**Other Side Effects**

- Hypersensitivity reactions can occur during the infusion.
- Other side effects may include severe or life-threatening infections, reactivation of hepatitis B or C infections, low oxygen blood cell counts, and low platelets. As with many anti-cancer treatments, secondary malignancies are also possible.

**Long-Term Side Effects**

In most patients, the number of CAR-T cells increases to a maximum level within two weeks to then steadily decline. However, CAR-T cell therapy is unique in that the genetically modified cells can stay in your body for years, even if all of your tumor cells are gone. Other normal healthy cells in your body can also be attacked and killed by your CAR-T cells.

- For example, healthy B cells also express CD19 and can be killed by CAR-T cells targeted to CD19. This situation is called “on-target, off-tumor” toxicity, and can result in temporarily having low blood cell counts.

**Approved CAR-T Cell Therapies**

- **Allogeneic CAR-T Cells (Westcell)**
  - Treatment targeting CD19 for patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed (cancer has returned after treatment) after at least two other kinds of treatments.
  - Only approved for patients with large B-cell lymphoma who have not responded to or who have relapsed large B-cell lymphoma (DLBCL) not otherwise specified.
  - High-grade B-cell lymphoma.

- **DLBCL arising from follicular lymphoma**
  - Primary mediastinal large B-cell lymphoma.
  - High grade B-cell lymphoma.

- **Tisagenlecleucel (Kymriah)**
  - Treatment targeting CD22 for patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed large B-cell lymphoma who have not responded to or who have relapsed (cancer has returned after treatment) after at least two other kinds of treatments.
  - Only approved for patients with large B-cell lymphoma who have not responded to or who have relapsed large B-cell lymphoma (DLBCL) not otherwise specified.

- **Tocilizumab (Actemra)**
  - Approved by the FDA in 2017.

- **Cytokine Release Syndrome (CRS)**
  - CRS usually occurs in the first few days to two weeks after the infusion of the CAR-T cells.
  - Side effects will be treated with medications and other supportive measures in the hospital.
  - One medication used to treat CAR-T cell-induced CRS is tocilizumab (Actemra), which was approved by the U.S. Food and Drug Administration (FDA) in 2017. Corticosteroids can also be given for severe symptoms.

- **Neurological Effects**
  - Neurological effects may occur between two days and three weeks after receiving the CAR-T cells, and usually follow CRS.
  - They may include:
    - Seizures
    - Changes in mental state
      - Anxiety
      - Delirium
      - Headache
      - Speech conditions
      - Tinnitus
    - Other neurological symptoms
      - Tremor
      - Numbness
      - Speech conditions
      - Headache
  - The precise cause of these symptoms is unknown, but they appear related to effects of the cytokines within the central nervous system.
  - Because of the potential of these side effects, you should not drive or engage in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least eight weeks after the procedure.
  - Neurological symptoms are treated with anti-convulsants and anti-seizure medications such as levetiracetam, if needed.

Other Side Effects

- Hypersensitivity reactions can occur during the infusion.
- Other side effects may include severe or life-threatening infections, reactivation of hepatitis B or C infections, low oxygen blood cell counts, and low platelets. As with many anti-cancer treatments, secondary malignancies are also possible.

Investigational CAR-T Cell Therapies

- **CAR-T cell therapies that target CD19, CD20, CD22, and CD200 can be in development for patients with lymphoma and certain lymphocytic leukemia (CLL).**
- **Several CAR-T cell therapies are in clinical trials, including localisation monoclonal (JCAR017).**
- **For the most recent information on approved CAR-T cell therapies, visit lymphoma.org/CART**