

# Non-Hodgkin's Lymphoma (NHL)

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## INTRODUCTION

Non-Hodgkin's lymphoma ("NHL") is among over 200 types of cancers that originate in the lymphatic system. NHL is particularly peculiar. *The Non-Hodgkin's lymphomas represent the most complex and diverse set of cancers to fall under a single rubric. Today, there are well over 65 different kinds of NHL. These diseases represent some of the fastest, and slowest growing cancers known to medicine* (Center for Lymphoid Malignancies, 2020). NHL is not a single disease but instead a group of similarly related cancers, named lymphoid neoplasms (Center For Lymphoid Malignancies, 2020). In the 2016 review of the World Health Organization, it was estimated that there are at least 86 types of NHL. Despite their similar common characteristics, NHLs differ in certain features. There are two main types of lymphoma: Hodgkin lymphoma and non-Hodgkin's lymphoma (Center for Lymphoid Malignancies, 2020). The likelihood of NHL depends on the specific type. The majority of lymphocytes originate in your bone marrow before they exit and circulate around your body while making stops in lymph nodes in your body. This is a crucial point in the process since it is when the lymphocytes become part of your immune system, leading them to fight infections (Center for Lymphoid Malignancies, 2020).

Usually, doctors will diagnose lymphoma with *physical and blood tests, chest x-ray, and a biopsy (examining tissue). Treatments include chemotherapy, radiation therapy, targeted therapy, biological therapy, or therapy to remove proteins from the blood. Targeted therapy uses drugs or other substances that attack specific cancer cells with less harm to normal cells. Biologic therapy boosts your body's own ability to fight cancer. If you don't have symptoms, you may not need treatment right away* (Medline Plus, 2016). This disease is complex but extremely fascinating. Before discovering this disease, popular opinion was always that white blood cells were good for you, and it was an anomaly that it could lead to something as serious as cancer.

## HISTORY

Both Non-Hodgkin's and Hodgkin's lymphoma are named after Thomas Hodgkin, a physician as well as a prominent British pathologist who studied medicine in Edinburgh and Paris. Thomas also served as conservator of the pathology museum at Guy's Hospital Medical School from 1825 and studied preserved specimens of organs there. In 1832. Thomas published a paper named "On Some Morbid Appearances of the Absorbent Glands and Spleen". At that time, it was ignored as just another ordinary paper. More than thirty years later however, Hodgkin finally received the credit he deserved. Samuel Wilks, another British Physician decided to name the disease after Hodgkin when describing identical features of the disease from Thomas' paper.

Though the classification of Hodgkin's lymphoma was prompt, the classification of NHL and other types went through a series of alterations. It began in 1956 when Henry Rappaport proposed to classify lymphomas through his *The architectural arrangement of the neoplastic cells and their cytological identification* (New Medical, 2022). In 1975, another proposal was introduced by the Luke-Collins classification system which attempted to *relate cell morphology to immunologic function* (New Medical, 2022). Even though it gave us more information and understanding of the immunology of lymphoma, there was not much effect from this claim. However, in 1982, the Working Formulation for NHL quickly overruled the previous classifications by introducing three *prognostic groups: low, intermediate and high grade* (New Medical, 2022). In 1994, Hematologists from America and Europe suggested a new approach for the classification of NHL. Known as the Revised European-American Classification of Lymphoid Neoplasms (REAL classification), it took into account *immunologic, genetic and clinical characteristics of the disorders and not solely histopathologic characteristics of the tumor cells* (New Medical, 2022). This classification was somewhat successful but still had major drawbacks. However, it had been much improved and became the World Health Organization (WHO) Classification. Despite this change, scientists are still working on the classification and providing new insights.

## Symptoms

Most symptoms for NHL are more or less the same as the symptoms of Hodgkin's lymphoma. They also share similarities with those of some other diseases. These symptoms are often mild but can occasionally be severe. Since the symptoms could be common, it might not be easy to diagnose NHL straight away without extensive testing. In summary the symptoms and their associated characteristics fall into the following categories:

### Lymph Nodes

The most common sign of NHL is swollen lymph nodes. Lymph nodes are small glands that filter a *clear fluid that circulates through the lymphatic system* (Lymphoma Actions, 2022) known as lymph. In NHL, a lymphocyte in the lymph node develops a genetic mutation and causes the lymph nodes to swell. As a result, the area where the lymph nodes are will cause painless lumps. This is often the first sign of the NHL. These lymph nodes often are located on the neck, groin, or armpit and can press *against a vein (swelling of an arm or leg), a nerve (pain, numbness or tingling), or the stomach (early feeling of fullness)* (Lymphoma Actions, 2022). While some lumps are obvious, others may be hard to find.

### Fatigue

Another sign of the NHL is fatigue. Unlike being tired, fatigue does not help you feel better after sleep or rest. In lymphoma, cancer cells interfere with the regular production of blood in bone marrow, leading to anemia (deficiency of red blood cells). This then causes fatigue. However, fatigue is a symptom of a wide range of diseases, so this symptom cannot conclude that one has lymphoma unless other symptoms are also present.

### Itching

Itching, also known as pruritus, is also a symptom for many other diseases including NHL. Still, 1 in 10 people who have NHL could develop this symptom. Itching can occur in various parts of the body: the area around the lymph nodes, on patches of skin lymphoma (lymphoma that starts in the skin), the lower legs, and even the whole body. This type of itching does not produce a rash and can be extremely problematic during hot weather and is usually worse at night in bed. Frequently, symptoms are a line of defense against an underlying medical problem. Itching in NHL is caused by the immune system secreting chemicals as a response towards a change in lymphoma cells. As a result, the chemicals irritate the nerves on your skin, causing it to itch. However, this itching can also cause a "burning sensation".

### B symptoms

Most common in rapidly growing lymphomas, B symptoms can be associated with both Hodgkin's and Non-Hodgkin's lymphoma. While sometimes described as "systematic systems", it is referred to as three particular symptoms in the case of Lymphoma. The first B symptom is fever greater than 38 Celsius that occurs for three consecutive days. Another symptom is unexplained weight loss, losing 10% of body weight within six months without any explanation. The last symptom is drenching night sweats. Though its name may be misleading, these drenching "night" sweats can happen during the day as well. The presence of B symptoms also "correlates well with an elevated level of inflammatory cytokines (a signaling molecule) in body fluids." When B symptoms are present in cases of Lymphoma, they are a prognostic factor, meaning that they can be used to predict the behavior of the Lymphoma and how the doctors should deal with it. In some circumstances, B symptoms can identify if other parts of the body have lymphoma other than where it was initially discovered.

### Bruising

Another symptom of NHL is that you can be bruised easily or experience it more regularly than usual. NHL targets the white blood cells of your body, which play a significant role in healing wounds. As a result, the number of white blood cells decreases, resulting in bruises and cuts that would not appear in a slight bump. Even though this is a sign of NHL, easy bruising can also be because of your more fragile blood vessels inherited from your genes.

### Body Symptoms

The symptoms of a patient can also differ based on the infected lymph node's location. A patient with an infected lymph node on his/her abdomen may be completely different from one who has a lymph node on his/her chest. Based on these different symptoms, doctors can identify where the lymph node is and conceive a plan to treat the patient.

### Chest Symptoms

In some types of high-grade NHL, infected lymph nodes may appear on the chest, which can *press on your airways, lungs, or blood vessels* (Lymphoma Actions, 2022). Besides, they can also create a fluid build-up surrounding your lungs. These developments can cause a wide range of symptoms such as dry cough, shortness of breath, pain behind the

breastbone, and a feeling of pressure on your chest. However, these symptoms are also symptoms of other diseases such as lung diseases, therefore these chest symptoms do not necessarily mean you have NHL.

### **Tummy Symptoms**

There are also scenarios where NHL develops in the abdomen, creating abdominal symptoms. Infected lymph nodes can be found in the abdomen or lymphatic tissue located inside your liver or spleen. However, the gut is the most common place for the NHL to develop. When your spleen is swollen, you may often feel bloated quickly and feel pain behind the left side of your ribs. Your doctor may be able to feel the infected lymph nodes if this occurs. If your liver is infected, your tummy may start to swell, and a yellow tinge may begin to appear in the white area of your eyes and on your skin. You may also experience a fluid buildup in your abdomen. In the stomach, inflammation can occur which will lead to nausea, pain, and vomiting. NHL in the bowel can cause *abdominal pain, diarrhea, and constipation* (Lymphoma Actions, 2022).

### **Skin Symptoms**

When NHL starts on the skin, it is known as cutaneous (skin) lymphoma. There are two types of skin lymphoma: cutaneous T cell lymphoma (CTCL) which starts in the T cells of the skin and cutaneous B cell lymphoma (CBCL) which starts in the B cells of the skin. CTCL is the more common type. If diagnosed with it, symptoms such as flat red patches, lumps, and *raised plaques with a scaly surface* (Lymphoma Actions, 2022) can appear. Skin lymphoma can be similar to many other skin conditions such as eczema and psoriasis. Oftentimes, skin lymphoma is low-grade lymphoma and usually does not spread past the skin.

### **Brain/Nerve Symptoms**

Though uncommon, NHL can start or spread into the brain or nervous system. Specifically, this type of NHL is known as the primary central nervous system lymphoma (PCNSL). Generally, it is diagnosed in older people at an average age of 65. This will cause *headaches, seizures, memory problems, dizziness, sight problems, numbness, tingling or weakness in a limb* (Lymphoma Actions, 2022). However, these symptoms can also appear in other conditions such as migraine or stroke.

### **Conclusion for the symptoms**

Even though most of these symptoms are common and the likelihood of one single set of symptoms being linked to NHL is low, you should be aware and careful when more than one type of symptoms starts to appear. If you have more than one of these symptoms, it is recommended that you quickly find an expert to determine your problem. It is always better to discover nothing than to detect the NHL at its late stages.

### **Treatment**

Traditionally, NHL is cured through Chemotherapy or Radiotherapy. However, new treatments such as CAR T cell therapy have also proved successful. Sometimes, patients may not need immediate treatment. If the cancer is small, a biopsy could be performed to completely cure the disease (a few cases only).

### **How are treatments decided?**

The patient's treatment will be determined by a group of medical professionals known as a multidisciplinary team (MDT). (Lymphoma Actions 2, 2022) To decide the patient's treatment, the patient's MDT must consider various lymphoma-specific factors such as:

- *The type of lymphoma you have* (Lymphoma Actions 2, 2022)
- *The stage of your disease* (Lymphoma Actions 2, 2022)
- *How fast is your lymphoma growing* (Lymphoma Actions 2, 2022)
- *The size of any lumps of lymphoma* (Lymphoma Actions 2, 2022)
- *Your symptoms* (Lymphoma Actions 2, 2022)
- *Result of genetic tests on your lymphoma, which can tell the doctor if you are likely to respond to certain treatments* (Lymphoma Actions 2, 2022)

In addition to these factors, the patients MDT will also consider individual factors, including:

- *Age of the patient* (Lymphoma Actions 2, 2022)
- *Your general health* (Lymphoma Actions 2, 2022)
- *Any other medical conditions you have* (Lymphoma Actions 2, 2022)
- *Any other medications you need* (Lymphoma Actions 2, 2022)

- Any other factors that are important to you (Lymphoma Actions 2, 2022)

### **CAR (Chimeric Antigen Receptor) T-cell therapy:**

Recently, a discovery known as CAR T-cell therapy was introduced. Currently, CAR T-cell therapy can only be applied to B cell NHL, which comprise 85% of NHL cases. This usually occurs when the B lymphocyte gets out of control and becomes cancer cells. As a result, the doctors modify the patient's T cell to attack the cancer cells. Specific for NHL, this is known as Anti-CD19 CAR T Cell Therapy. According to the article "Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors" from the New England journal of medicine (2020), Anti-CD19 CAR T Cell therapy *has shown remarkable clinical efficacy in B-cell cancers* (New England Journal of Medicine, 2020). The authors proved the efficacy of Anti CAR T Cell Therapy through vigorous and meticulous experiments by modifying Natural Killer (NK) cells.

### **METHODS**

During their Phase 1 and 2 trials, 11 patients NHL or Chronic Lymphocytic Leukemia (CLL) had their cord blood tested through HLA mismatching using their anti-CD19 CAR-NK cells. The "*K cells were transduced with a retroviral vector expressing genes that encode anti-CD19 CAR, interleukin-15, and inducible caspase 9 as a safety switch. The cells were expanded ex vivo and administered in a single infusion at one of three doses (1×10<sup>5</sup>, 1×10<sup>6</sup>, or 1×10<sup>7</sup> CAR-NK cells per kilogram of body weight) after lymphodepleting chemotherapy.*"(New England Journal of Medicine, 2020)

### **RESULTS**

After the experiment, 8 (73%) of the 11 responded to the treatment and 7 were completely healed. Within 30 days, there were clear signals of response at every dose level. These genetically modified CAR-HK T cells still existed at low levels for the next 12 months (New England Journal of Medicine, 2020).

### **Conclusion for CAR T Cell therapy**

Out of the 11 patients, the majority healed without any major side effects. Currently, CAR T cell therapy requires only a single infusion and is usually treated within two weeks.

### **Chemotherapy**

For NHL, chemotherapy is usually the standard treatment, consisting of 4 drugs: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in addition to rituximab. This is also known as R-CHOP. It is often given every 3 weeks (Healthline, 2018). However, people with heart problems are encouraged to use other chemotherapies because of the damaging effects doxorubicin has on the heart. Usually, this treatment will take 18 weeks (Healthline, 2018). *Individual treatments can take several hours, and a healthcare provider will administer the drugs intravenously, meaning through a vein in your arm* (Healthline, 2018).

### **Side effects**

Even though Chemotherapy destroys cancer cells, they also kill healthy cells in the body. This results in many different side effects, and it is rare to have them all. Here are some common side effects:

- Irritation around the intravenous or port site (Healthline, 2018)
- Red or pink urine for a few days due to doxorubicin (Healthline, 2018)
- Appetite changes (Healthline, 2018)
- Weight changes (Healthline, 2018)
- Indigestion (Healthline, 2018)
- Nausea (Healthline, 2018)
- Vomiting (Healthline, 2018)
- Fatigue (Healthline, 2018)
- Sleeping difficulties (Healthline, 2018)
- Low blood counts (Healthline, 2018)
- Anemia (Healthline, 2018)
- Nose bleeds (Healthline, 2018)
- A runny nose (Healthline, 2018)
- Bleeding gums (Healthline, 2018)
- Mouth sores (Healthline, 2018)
- Mouth ulcers (Healthline, 2018)

- Hair loss (Healthline, 2018)
- A loss of menstruation, or amenorrhea (Healthline, 2018)
- A loss of fertility (Healthline, 2018)
- Early menopause (Healthline, 2018)
- Skin sensitivity (Healthline, 2018)
- Nerve problems, or neuropathy (Healthline, 2018)

Chemotherapy drugs can kill cancer cells throughout the body to cure cancer but also can cause pain and suffering during the process.

### Interview

The purpose of this interview is to discover insights on artificial intelligence (AI), telemedicine, and/or any other technologies that could help diagnose, prevent, or perhaps even cure non-Hodgkin's lymphoma. To that end, the study was able to secure the expert opinion of Dr. Jay H. Sanders, a preeminent expert on those matters.

### Background of Dr. Jay Sanders

Dr. Sanders is an expert on telemedicine and is often referred to by other field experts or in the media as the "Father of Telemedicine". (An Exploration into the Benefits, Challenges, and Potential of Telehealth in the United States: A Mississippi Case Study, 2019) After earning his medical degree from Harvard Medical School Magna Cum Laude, Dr. Sanders has spent over 30 years applying the latest telecommunication and information technologies to address the problems relating to the quality, cost, and access to our healthcare system. Dr. Sanders is President and CEO of The Global Telemedicine Group, Professor of Medicine at Johns Hopkins University School of Medicine (Adjunct), and a founding board member of the American Telemedicine Association where he serves as its President Emeritus.

### Are there any breakthroughs in new drugs or treatment methods besides chemotherapy with respect to non-Hodgkin's lymphoma?

The prior standards for therapy are chemotherapy and radiation therapy, but today there is beginning to be very exciting work in this area. As you know, the majority of non-Hodgkin's lymphomas are B cells and T cells. With respect to B cell lymphoma, basically what you have is a B lymphocyte that makes antibodies and gets out of control for other reasons whatever the stimulus whether it was internal or external. As a result, the doctors modify a patient's T cell so they will attack cancer cells. This is known as CAR T - cell therapy. They're now finding that in some of these patients they're able to take out their T lymphocytes and modify them to recognize the tumor cell as foreign so the T lymphocytes are attacking the tumor.

### Are these new breakthroughs successful and safer than chemotherapy?

A very recent study in the New England Journal of Medicine dated February 6th states "the use of CAR transduced natural killer cells (T cells)".

### What role can telemedicine play in the prevention, treatment and post - treatment care of non-Hodgkin's lymphoma?

Here is an excerpt from an interview with Dr. Sanders, an expert in telemedicine:

*"Prior to telemedicine, the doctors used phones. If you go back to the history of when telemedicine began, my professor of medicine back in the Massachusetts General Hospital in 1969 came up with the term telemedicine. The reason for that was that we were using 2 black and white TV cameras in 1969, and he didn't want to call it television medicine so he said let's call it telemedicine. Let's assume you're a primary care physician and you have patient with non Hodgkin's lymphoma and you are trying to learn the latest therapy for it, you've called me either on a regular phone or we are looking at each other on our android or iPhone, and I'm telling you about this new therapy where you can try on your patient. That fundamentally is telemedicine."*

### Are the new breakthroughs and research all zoomed in on telemedicine?

Let me give you another classic example: in rural America, most of the hospitals don't have specialists, they have general practitioners and family practitioners. But if you as a patient came in with a stroke, they won't have a neurologist. Therefore, one of the great applications for telemedicine today is the fact that I as a primary care physician can with my telemedicine system go back to any major hospital system whether it is a secondary care facility or a tertiary care facility. You could go to the mass general and they could have a neurologist at the mass general with telemedicine looking at your cat cam and your MRI to see where the blood clot is and make a decision to tell me as your primary care doctor in a rural town in Connecticut that they need to give you a certain medicine to break up the

clot. That's the way telemedicine is working, it basically transfers the information of a specialist at one location to another doctor or nurse or a nurse practitioner at another location who may not have that information. So, it transfers that information and one important thing you may want to mention in your report: If I as a specialist at the mass general are interacting with you as a primary doctor taking care of this patient, and we have these interactions multiple time throughout the years, it has actually turned out that telemedicine is not only good for the patient, but it is also good for the primary care physician because now I'm teaching the primary care physician what he or she needs to do. And after some time, their educational level goes up. So, two of telemedicine's great strengths are that it brings immediate expertise to the patient wherever they are whether it is a hospital or in a home and it elevates the educational level of the primary care physician who is taking care of that patient.

#### **What about other forms of technology such as AI?**

You'll be sorry you asked. So, my vantage point, out of the knowledge that exists out there today and that is being discovered daily is so huge that no single individual, no single doctor (I don't care how good he or she is), no single physician can retain all of the information. Since knowledge is information-based, it is very disparate. In other words, if there's a neurology consult, and you came to a neurology specialist with a cardiological problem, he would have to send you to a cardiologist. There is so much new data that is coming out of research laboratories and clinical trials that there is not a single physician in the world that is up to date. So, let's think of this: let's assume you are a primary care doctor and you called me and I'm acting as a specialist and you ask me for some information about your patient with non-Hodgkin's lymphoma, I start talking to you about all the different chemotherapeutic protocols there are and all the radiation protocols, but I haven't kept up to date with respect to CAR T cells and all of the new work that is going on in the national institute of health. So, I will tell you about chemotherapy when there is much better info out there now so instead of chemo you can do XYZ therapy. Even though I'm hooked up to you with a telemedicine system, if the info I'm giving up is out of date, it doesn't matter how good telemedicine is. All the telemedicine does is to transmit a message. If the message is wrong, telemedicine is dangerous. AI, machine learning, will bring collective expertise, not just a single physician. Transmitting the wrong message is not good. Transmitting the right message with telemedicine is what you want, and what AI will do and the areas it will impact the most will be what we call the image specialties: radiology, pathology, geratology as machine learning adapts exceedingly well to image analyses.

#### **Have doctors tried to ensure that telemedicine is 100% safe?**

No, these doctors think they know everything, or if they feel uncomfortable, they will send you to another specialist. Getting info from one specialist and another specialist as opposed to getting the collective expertise. Let me give you one example: it's now been shown that machine learning aka AI reads just X rays much quicker and with specificity than most radiologists. There is now an AI machine learning capability, and this is important because it's the first one: it is a technology that reads a diabetic patient's retina to determine whether or not they have what's called diabetic retinopathy, which is the most common causes of blindness of an adult in the US.

#### **Do the doctors still side with the traditional methods when treating non-Hodgkin's lymphoma patients?**

Still traditional, but soon the pathologist who is reading the lymph node biopsy to determine whether it is Hodgkin's lymphoma or non-Hodgkin's lymphoma and if it is non-Hodgkin's lymphoma, what kind of non-Hodgkin's lymphoma it is. Pretty soon, the machine learning algorithm will read that pathology slide.

#### **Roleplay:**

"Lauren, your son has been diagnosed with large B cell non-Hodgkin's lymphoma". I still vividly remember the petrified look on Lauren's face before she broke down sobbing, holding her son Liam tightly in her arms. The 5-year-old was bewildered and scared, not knowing how much pain he will have to suffer for the following years. At this point, I didn't know what to do. Thoughts began racing through my mind. Was I supposed to comfort her? Or was I supposed to wait? I was never the type of guy who dealt with patients, it was usually my professor who dealt with this situation. I quickly stood up and asked one of the nurses behind me to escort them out so I could think of a solution.

It's only been a week since my professor passed away. Even now I recall the day he found me on the streets. He was the best mentor anyone could ask for. I always looked up to him as a father figure. From an early age, He always brought me to his lab and taught me everything I learned now. I had always been his assistant in his projects and experiments. We often studied ways to improve the treatment of non-Hodgkin's lymphoma known as CAR T cell therapy.

However, his death changed everything.

That day, I arrived home depressed and frustrated, lost in thought as I had no idea what to do. The sudden death of my professor honestly took a toll on me. I quickly stumbled on to the couch and passed out.

“Ready for another day of work?” My professor Lee pulled me out for bed before I could complain. For a 30-year-old, He was full of energy. He always made me feel like I was ten years older than him. Within thirty minutes we were examining T cells and then... CRASH! The ceiling above me began crashing down from above before our Petri dishes set on fire. Bewildered, I turned around to look for my professor. He was stuck under a rock, blood slowly gushing out of his mouth as he began coughing out a few words. “...knowledge....is..po..w.e...r....” His face turned pale before his eyes rolled over. “Professor! Wai..!”

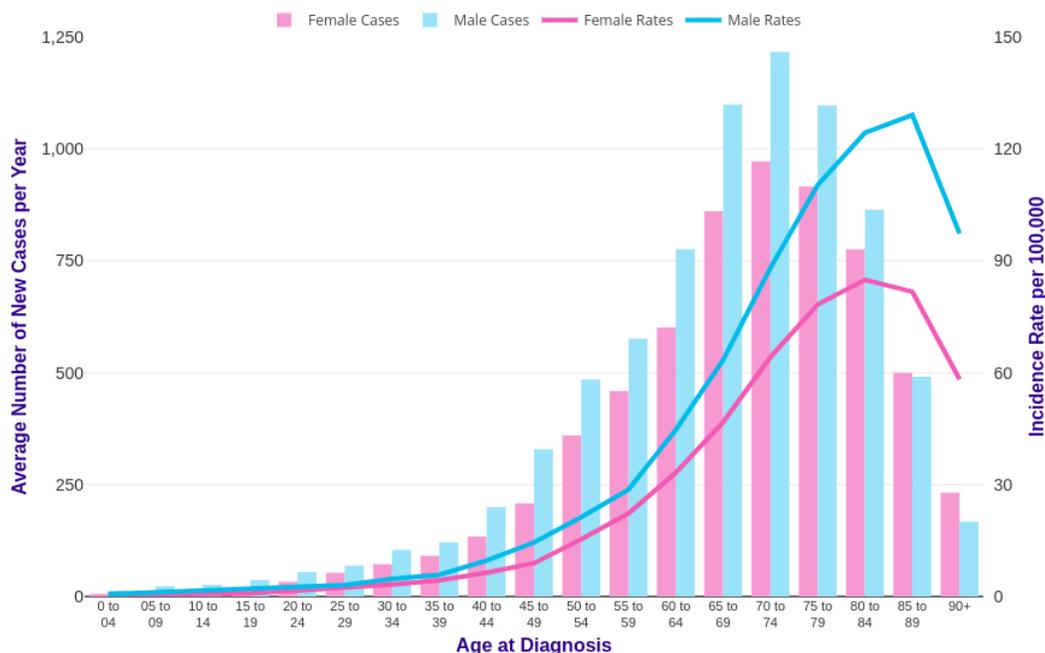
I leaped out of bed with my professor’s last words in my head. “Knowledge is power”. I knew I could not let him down. When he was around, I could slack off and stay at home instead of learning and perfecting myself. However, all the patient’s lives now are in my hands. My professor had a twin brother called Harry. He lived on the south side of the city. I have only seen him a couple of times when he came to my professor’s lab for information. Through my observations, she was quiet and didn’t like to talk. According to Lee, Harry was a professor of non-Hodgkin’s lymphoma in the University. Knowing that he was the only option left, I decided to visit him.

50 minutes later, I was sitting next to a bearded man who was on a rant about Lymphoma. I was like I was taking another course of lymphoma again. “Most symptoms for NHL are more or less the same as the symptoms of Hodgkin’s lymphoma. They also share similarities with those of some other diseases. These symptoms are often mild but can occasionally be severe. Since the symptoms could be common, it might not be easy to diagnose NHL straight away without extensive testing. In summary, the symptoms and their associated characteristics fall into the following categories....” He then started lecturing me about the cure and how I should treat patients. “CAR T cell therapy is the quickest and the best way to deal with your patient right now. First, you will have to remove an individual’s T cells. Next, you must alter the T cell so that the T cell can eliminate cancer from the body. You will have to monitor the patient for a few weeks before declaring cancer. Beware that there will be side effects such as fever, joint and muscle aches, shortness of breath, low blood pressure, confusion, and seizures.”

**One month later:**

“Thanks a lot!” Lauren was overjoyed when I finally told her Liam is successfully cured and will no longer have further complications. It was the best day of my life. Seeing someone being overjoyed and delighted is the best feeling you can have, especially when you are the cause of it. Of course, I will also have to thank my Professor Harry and Lee for the outcome.

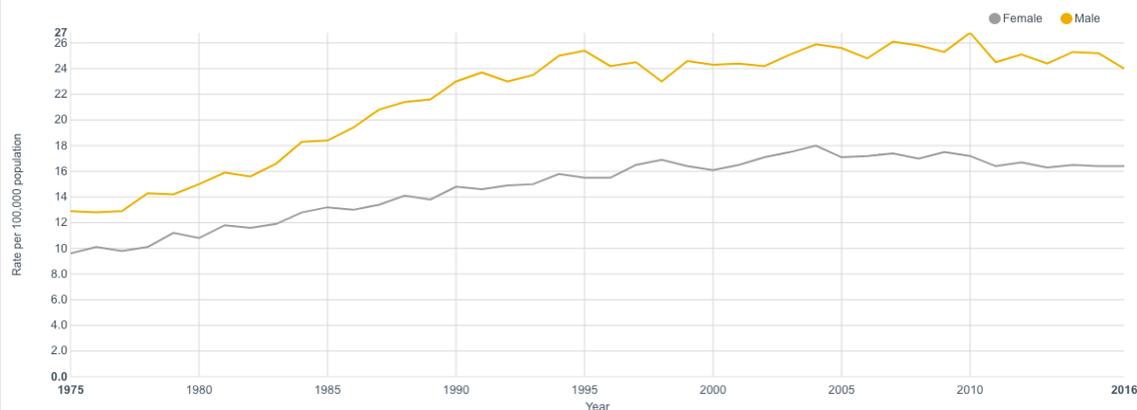
**Additional Information**



**Figure 1: Graph of cases for age groups from 2015 – 2017 Cancer Research UK (2022)**

### Trends in incidence rates, 1975-2016

Non-Hodgkin lymphoma, by sex



Per 100,000, age adjusted to the 2000 US standard population.

Data sources: Surveillance, Epidemiology, and End Results (SEER) 9 registries, National Cancer Institute, 2019

**Figure 2: Graph of cases for Male and Females from 1975 to 2016 Cancer Statistics (2022)**

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