

# Diagnosis and Staging of Cutaneous Lymphomas

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# Overview of the Talk

- How does my doctor diagnose a lymphoma of the skin?
  - What happens to my skin biopsy?
  - Translating a biopsy report from “medicalese” into English
- What is staging and what are the tests that need to be done?
  - The importance of a dermatologist’s eyes
  - Blood tests
  - Radiology
- Staging Mycosis Fungoides/Sezary Syndrome
- Staging other cutaneous lymphomas

# Diagnosing lymphoma

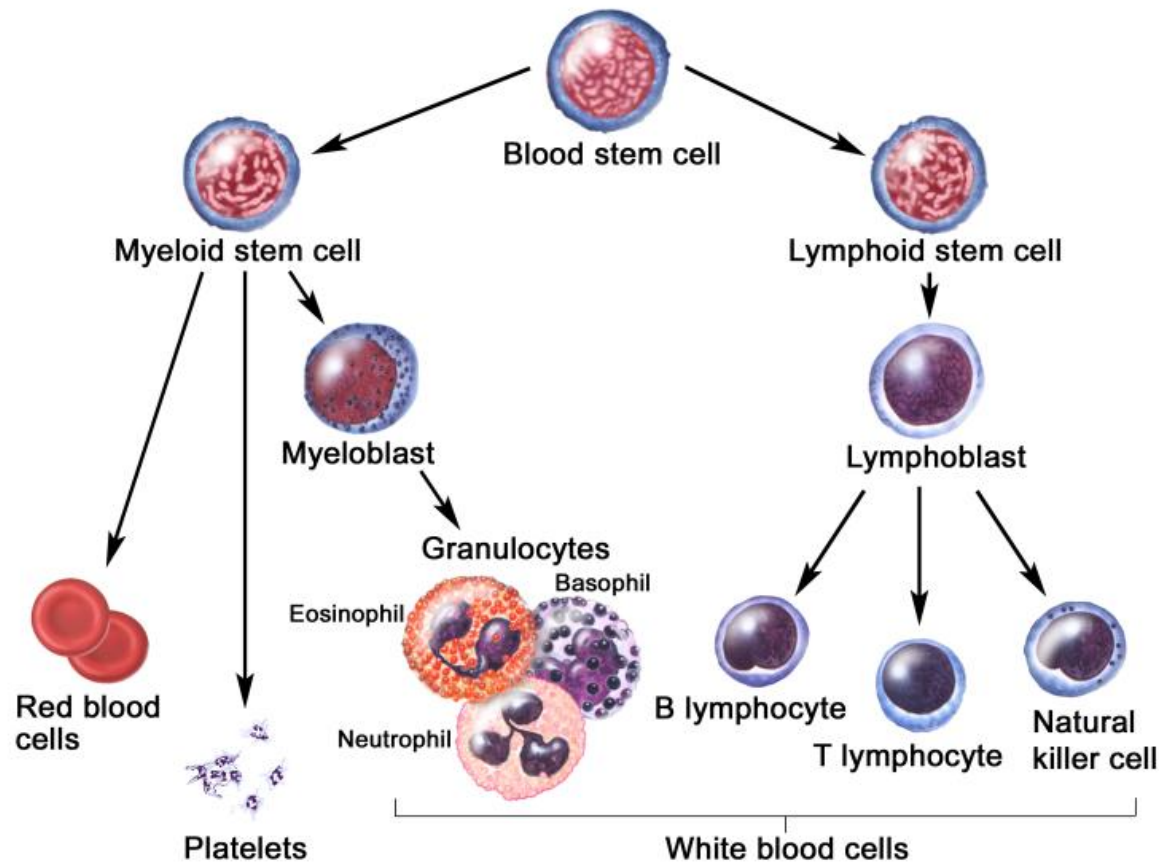
- Diagnosis= naming the problem and telling where it came from
- We name cancers by the type of cell that they come from
- Lymphoma= cancer of the lymphocytes

# Hodgkin vs Non-Hodgkin Lymphoma

- Historically, Hodgkin lymphoma was the first to be recognized under the microscope. Everything else was called “non-Hodgkin” by the process of elimination
- There will be about 82,000 new cases of lymphoma diagnosed this year in the US (American Cancer Society statistics)
  - 8,000 cases of Hodgkin’s lymphoma
  - 74,000 cases of non-Hodgkin’s lymphoma
- Virtually all cutaneous lymphomas are non-Hodgkin’s lymphoma

# Lymphocytes are a white blood cell

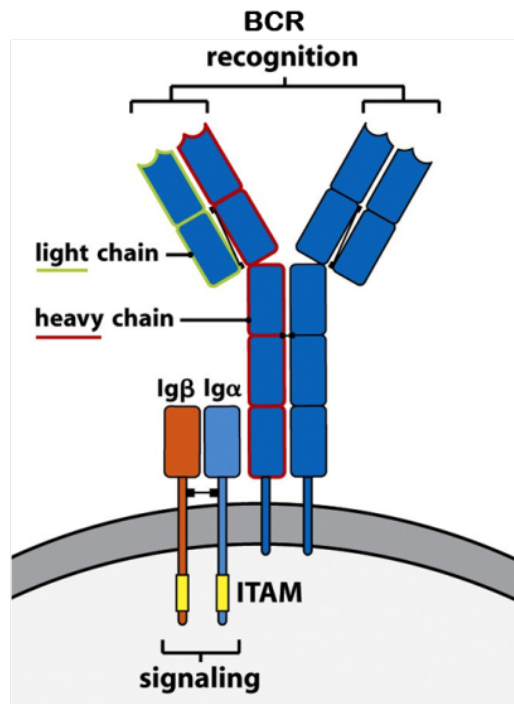
They defend us against infections and foreign invaders (cancer)



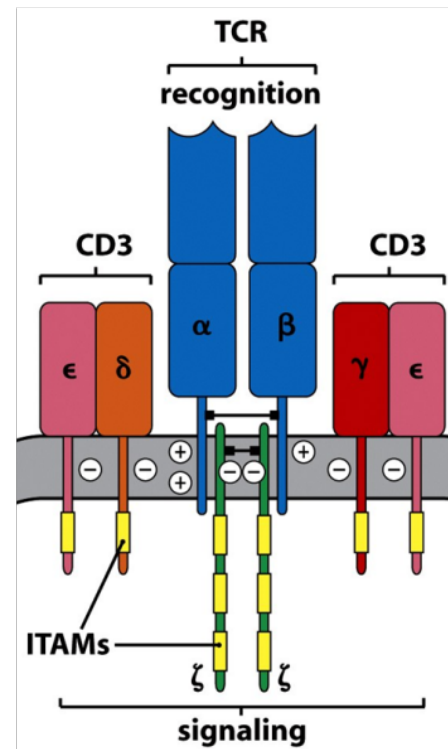
T and B lymphocytes are defined by the proteins they make (express)

## *T Cell and B Cell Antigen Receptors (TCR and BCR)*

### *B cell Receptor*

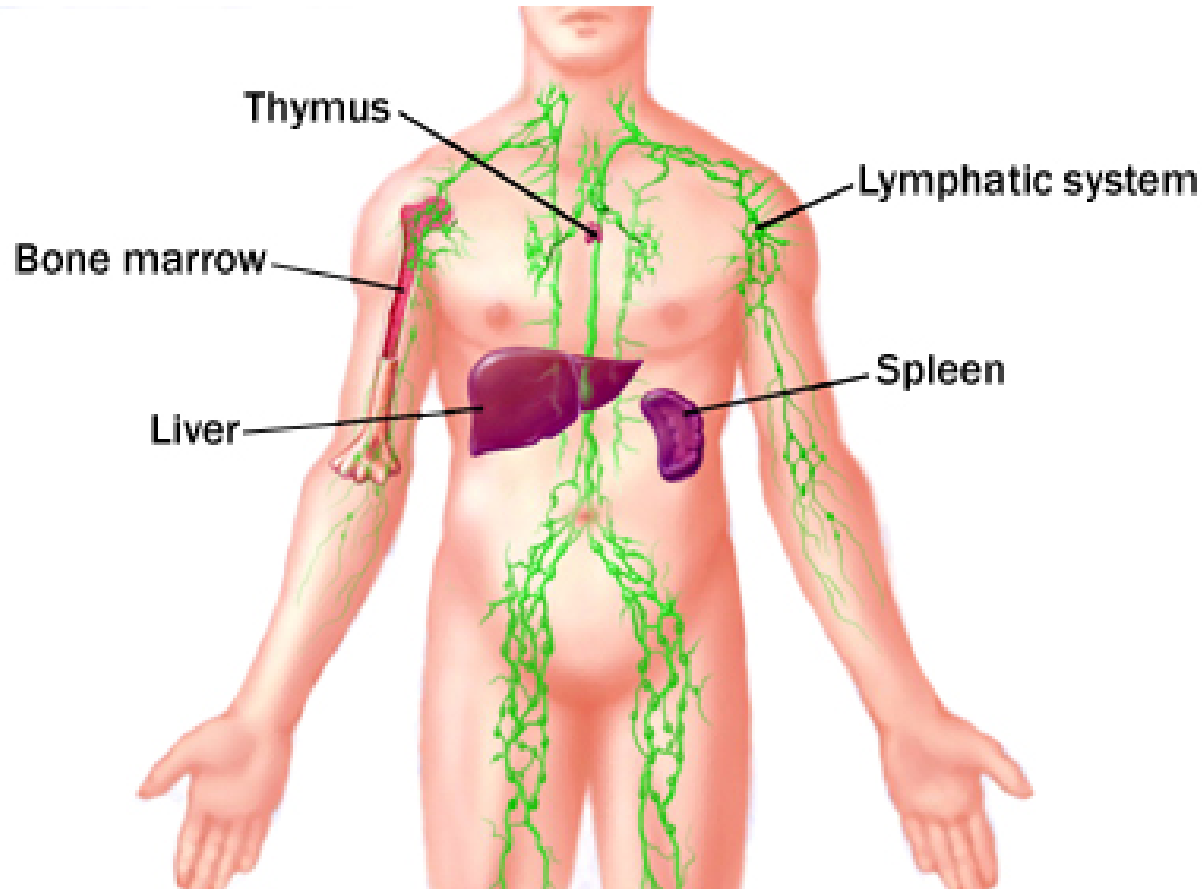


### *T cell Receptor*



# Where are lymphocytes found?

## The lymphatic system



# There are many lymphocytes in the skin as well!

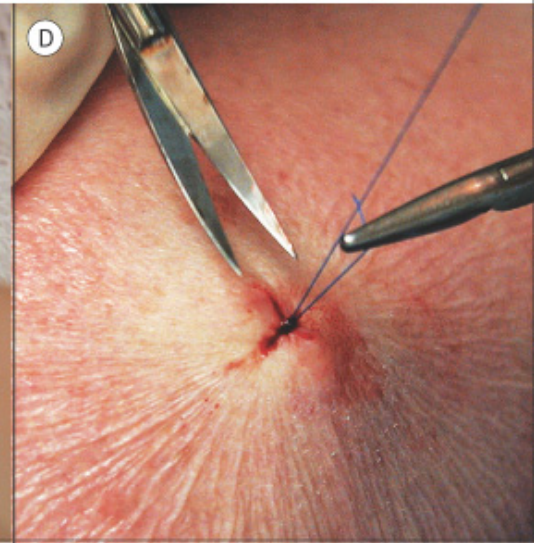
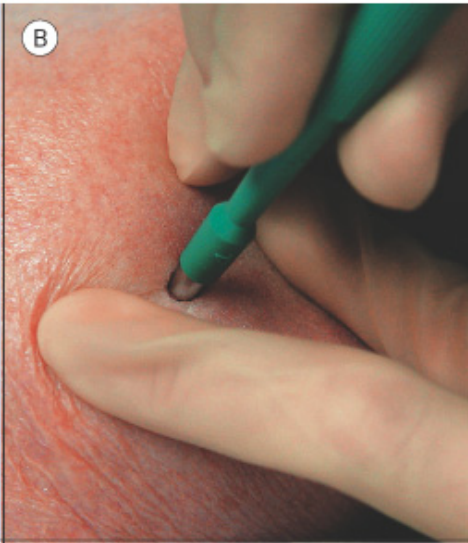
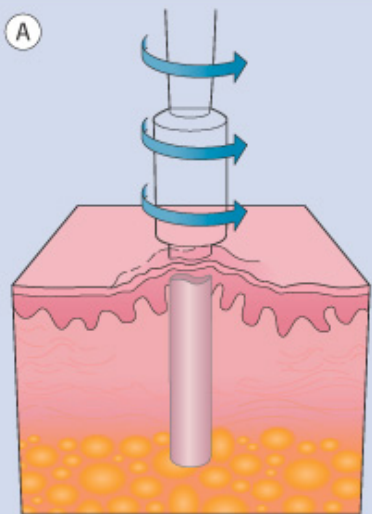
- There are more T lymphocytes in the skin than there are in the bloodstream
- They function as our police force/army, protecting us from “invaders” (germs, especially viruses) and cancers
- When the cells multiply out of control, a cancer forms





First, a dermatologist (or other doctor) decides that a rash or lesion needs a biopsy

PUNCH BIOPSY

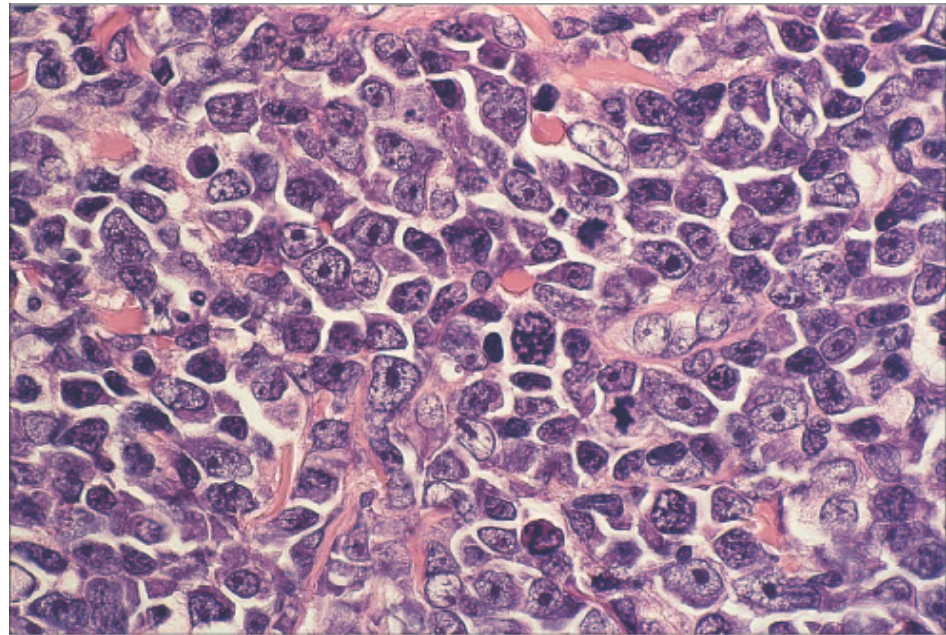


The biopsy goes to a pathologist (a doctor who studies tissues) and they do a variety of tests

- Histology
- Immunohistochemistry
- TCR (T cell receptor) gene rearrangement study

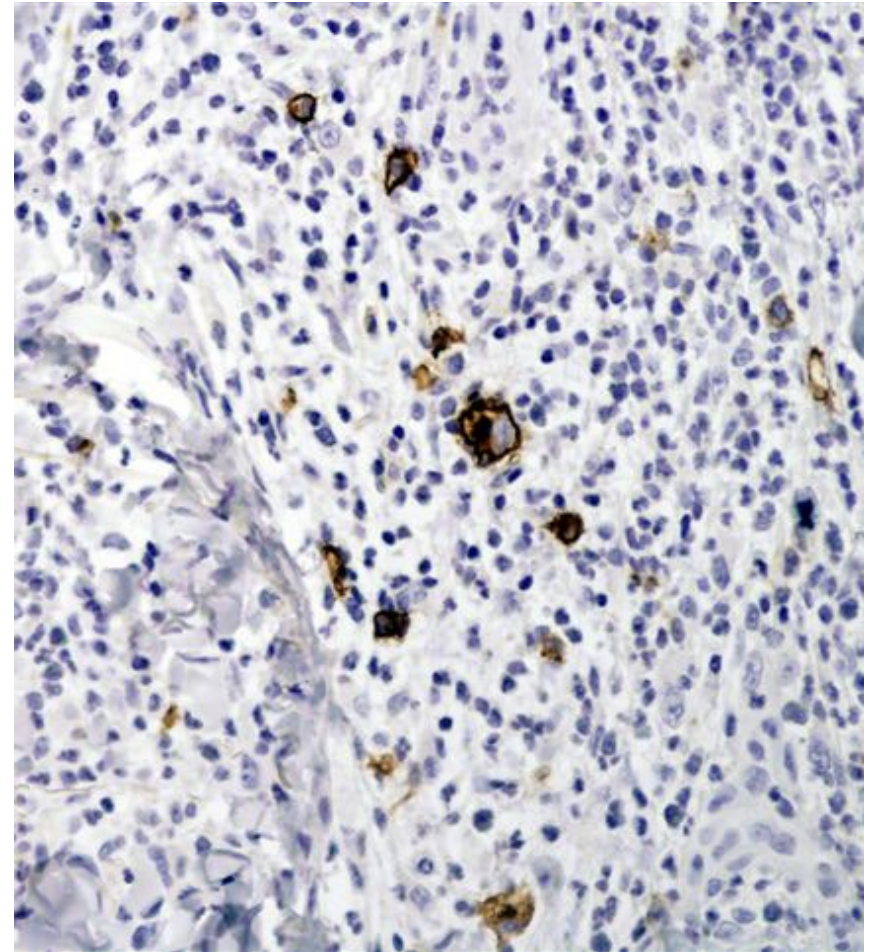
# Histology/Pathology

- Histology: The study of tissue characteristics
- Pathology: The study of abnormalities of tissue
- The pathologist identifies abnormal features of cells and abnormal arrangements (architecture)



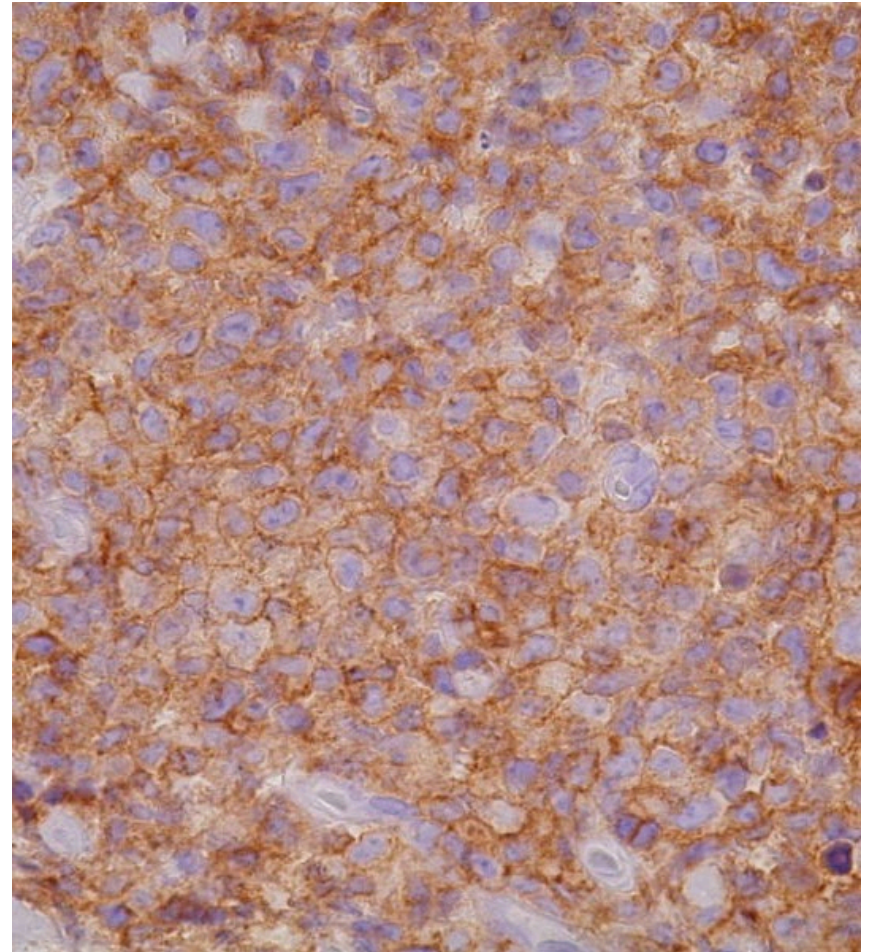
# Immunohistochemistry

- Using antibodies to label cells that express certain proteins on their surface
- Many of these proteins are named “CD and then a number”
- CD19 and CD20= B lymphocytes
- CD3, CD4, CD8= T lymphocytes
- The presence or absence of certain proteins helps us decide what type of cells are present and if they are normal or abnormal



# CD30: Can help with diagnosis *and* treatment decisions

- A protein made by activated T and B lymphocytes
- Present in CD30 lymphoproliferative disorders (lymphomatoid papulosis, anaplastic large cell lymphoma), some cases of mycosis fungoides, and Hodgkin's lymphoma
- Brentuximab vedotin is a chemotherapy medication that kills cells that express CD30



T cell receptor gene rearrangement:  
the search for a clone

# Clones in Cancer

A clone is an exact copy or replica  
(of a cell or an entire organism)



In many cases, all cancer cells are descendants of a  
single abnormal cell

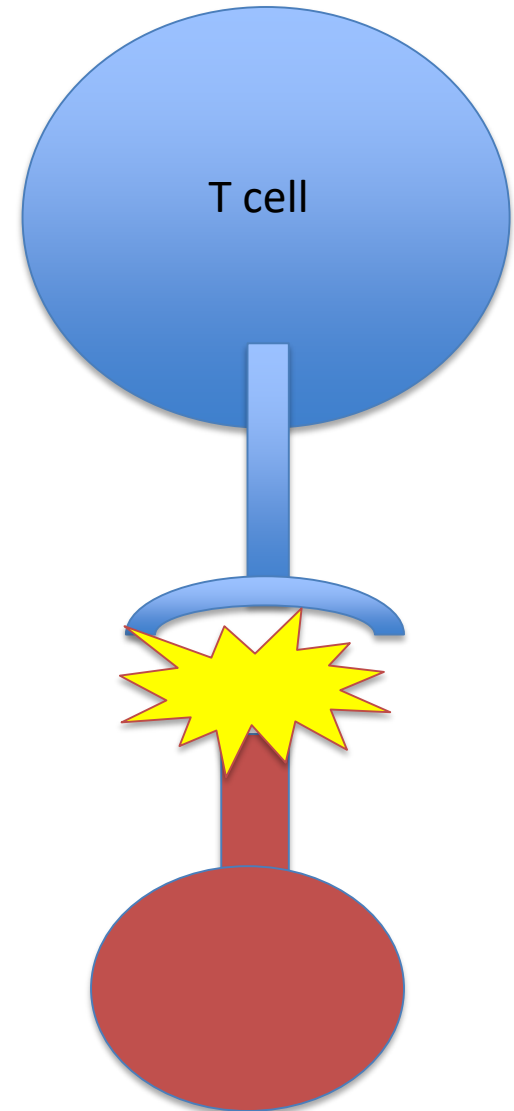


**All cancers are clones, but not all clones are cancer...**

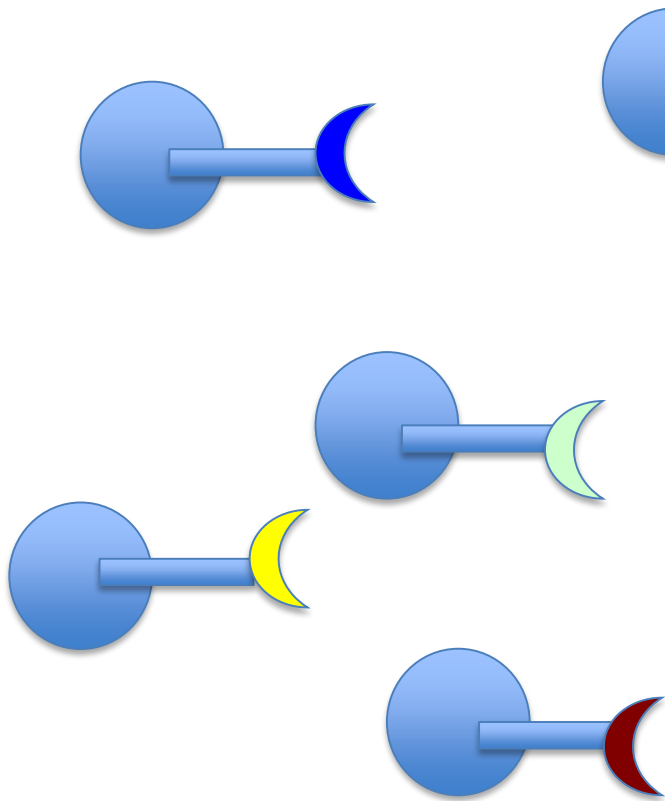
Other benign skin diseases such as drug reactions, eczema, and other rashes MAY contain clonal lymphocytes

# What is the T cell receptor?

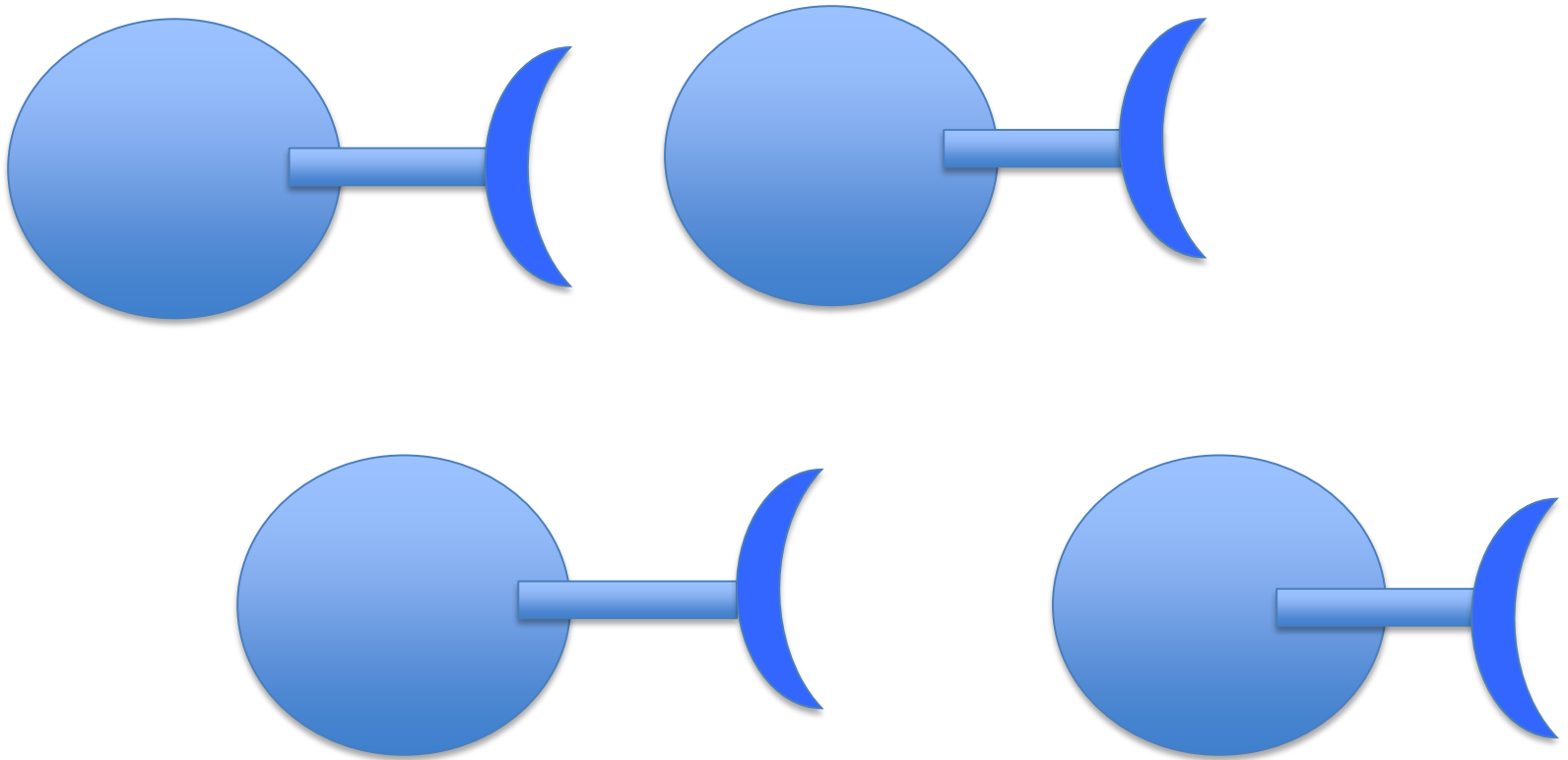
- A molecule on the surface of T cells
- It is responsible for binding to parts of viruses and other abnormal cells and then activating the immune system to destroy them



T cells all have slightly different receptors so they can identify many different things

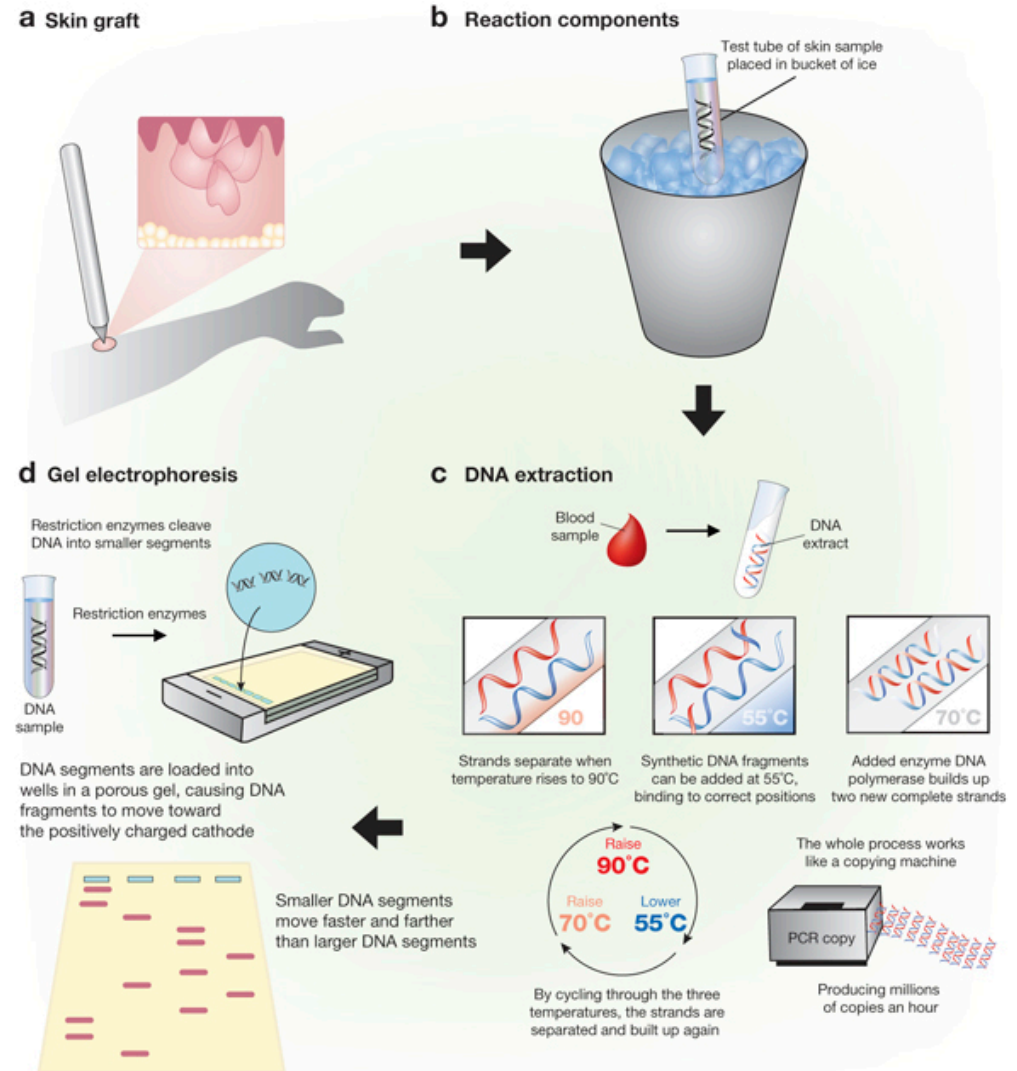


T cell clones all have exactly the same receptor



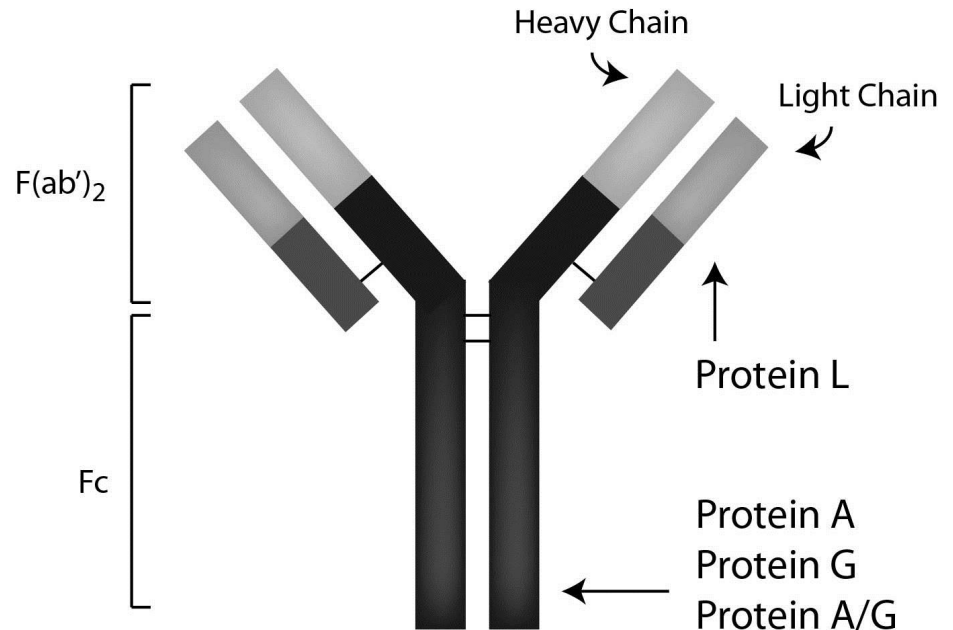
# T cell receptor gene rearrangement: the search for a clone

- DNA can be removed from lymphocytes from a blood sample or skin sample
- A process called PCR can be used to see if there is a clone of lymphocytes present



# What about B cell lymphomas?

- B cells have immunoglobulins (antibodies) instead of a T cell receptor, and we can look for clones that have identical immunoglobulin heavy chains



When the cells look like cancer, the immunohistochemistry is typical of a cutaneous lymphoma, and there is a clone, the diagnosis of a cutaneous lymphoma is made

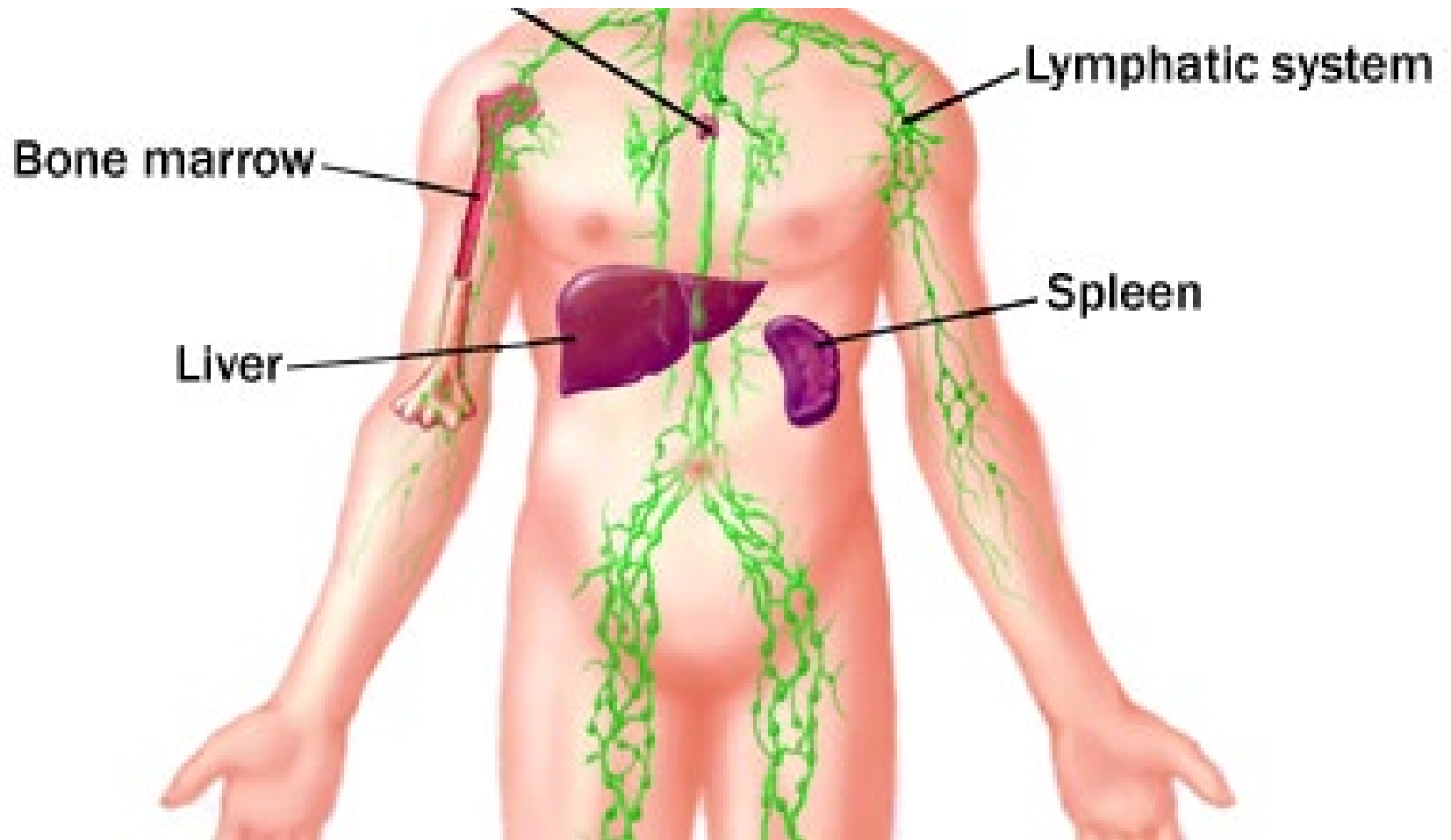
Many cases are not this straightforward and require multiple biopsies over time to make the diagnosis

# Now that the diagnosis is made, staging starts

Staging assesses the extent of the lymphoma, which is critical for defining prognosis and determining appropriate treatment



# Staging a lymphoma



# Staging Lymphomas

- TNMB system
  - T=tumor
  - N=lymph nodes
  - M=metastasis (tumor that has spread to a different organ)
  - B=blood

# Staging mycosis fungoides and Sezary Syndrome

# T: done by the eyes of a dermatologist

- T1: patches (flat skin lesions) or plaques (slightly elevated skin lesions) covering less than 10% of the skin surface
- T2: patches or plaques covering more than 10% of the skin surface
- T3: A cutaneous tumor, at least 1 cm in size
- T4: Erythroderma—redness and scaling covering at least 80% of the skin



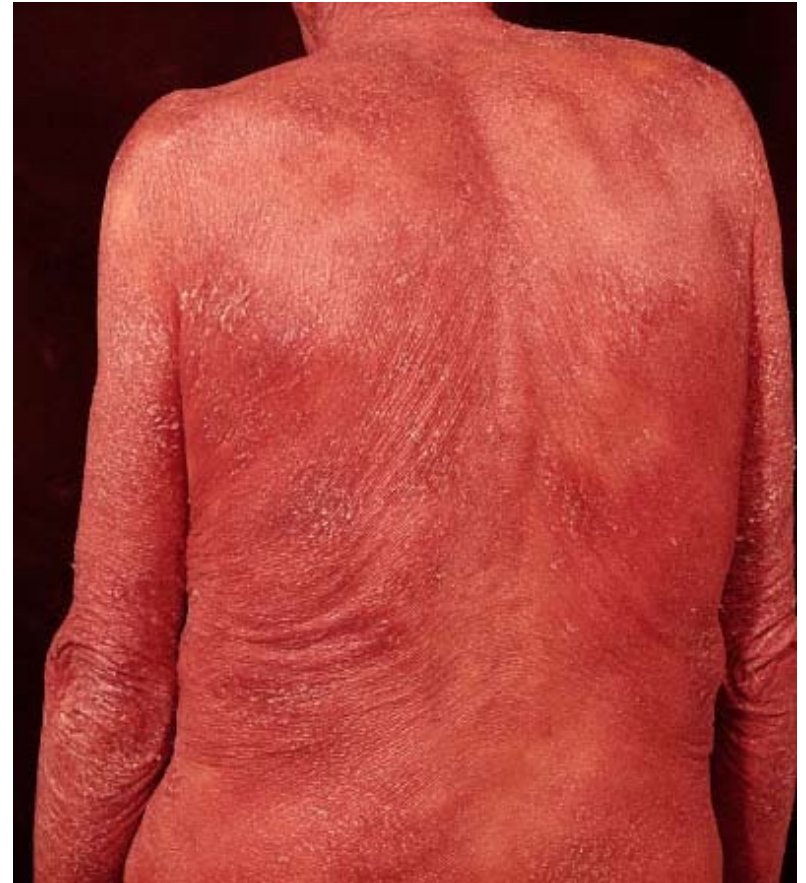
T1: Patches or plaques covering less than 10% Body Surface Area (BSA)



T2: Patches of plaques covering more than 10% BSA



T3: Tumor, measuring  
at least 1 cm



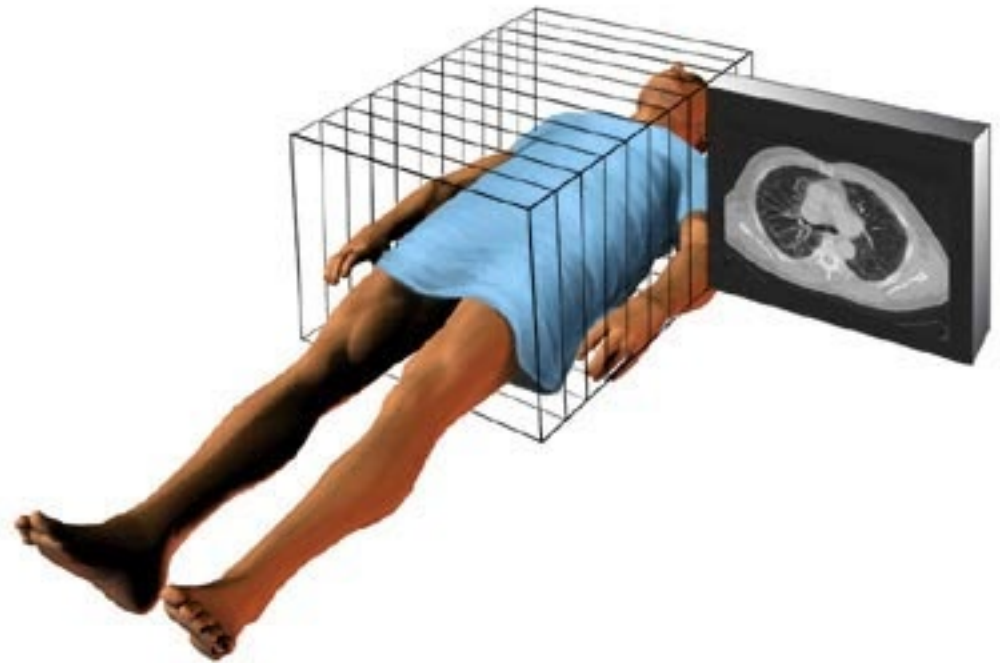
T4: Erythroderma,  
over 80% BSA

# N (lymph nodes) and M (metastases)

- Physical examination (feeling for enlarged lymph nodes, liver, spleen)
- CT scans
- PET scans
  
- Biopsies may be done if abnormalities are found.

# CT scan (or CAT scan)

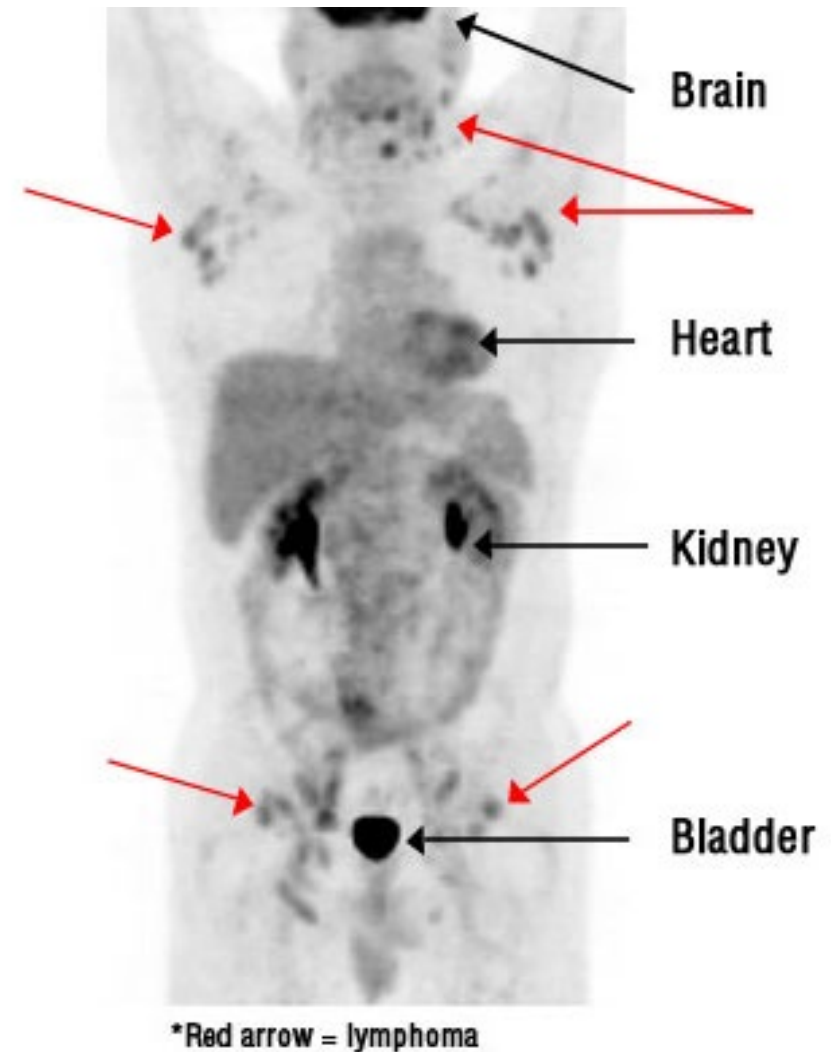
- Computerized axial tomography
- A test that uses Xrays and a computer to generate detailed pictures of the inside of the body





# PET Scan

- Positron Emission Tomography
- A test that uses radioactive sugar (glucose) to identify the extent of cancer in the body
- Information on metabolism
- Glucose is the fuel that all cells need to survive
- Cancer cells are more active and take up more glucose than most normal cells



# N: Lymph node involvement

Typically requires a biopsy of a lymph node

- N0: No abnormal lymph node involvement
- N1: Clinically enlarged lymph nodes (>1.5 cm) but pathology doesn't definitively show lymphoma
- N2: Small clusters of abnormal cells in lymph node
- N3: Lymph node replaced with lymphoma cells

# M: Metastases

- M0: No other organs involved
- M1: Other organs involved (liver, spleen, lungs, brain, bone marrow, etc.)

# Bone marrow biopsy: done in some, but not all cases



Bone marrow aspiration

# B: Blood work

- CBC or complete blood count: tells us if there is an increased number of lymphocytes in the blood (also red blood cells, platelets, and other leukocytes—white blood cells)
- LDH (lactate dehydrogenase)
- Flow cytometry—counting and sorting lymphocytes

# B: Blood involvement

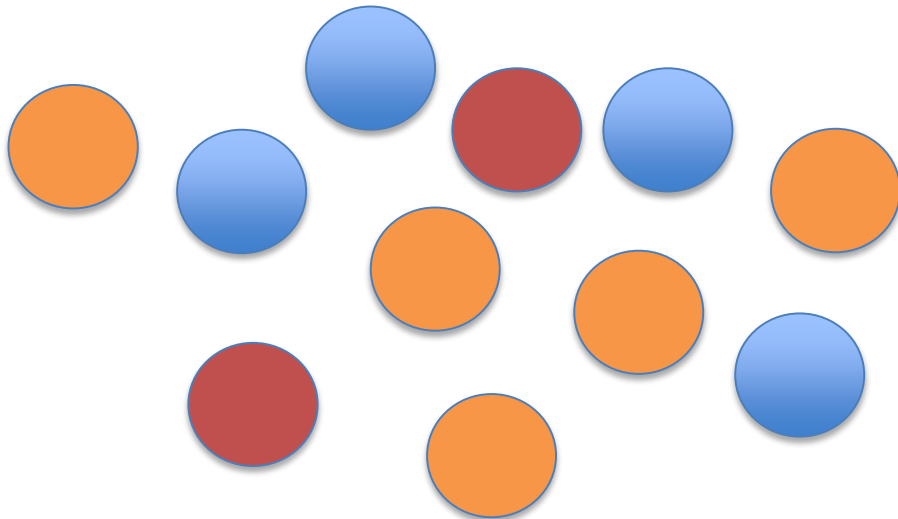
- B0: No blood involvement
- B1: Small numbers of abnormal cells in the blood (>5% atypical cells)
- B2: Significant blood involvement (Sezary Syndrome)

This is determined by flow cytometry

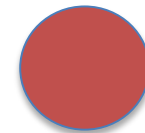
# Flow cytometry

Sorting cells based on proteins they express

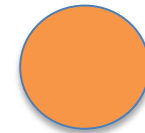
Lymphocytes from patient with  
Sezary Syndrome



Normal CD4 T cell



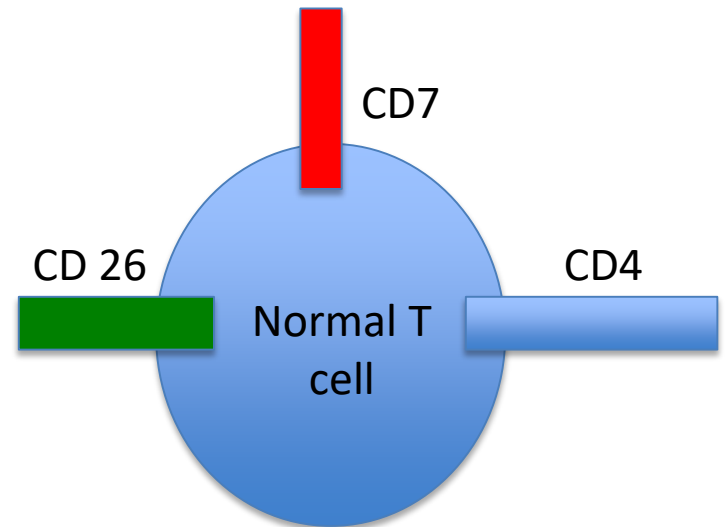
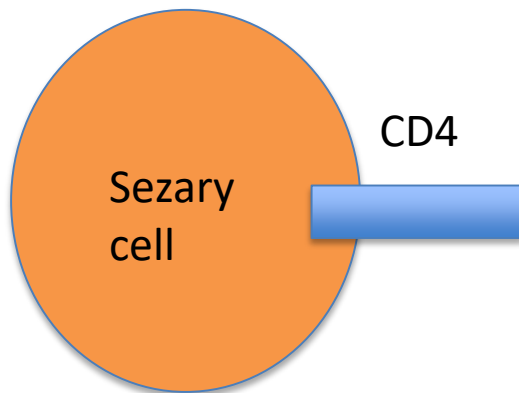
Normal CD8 cell



Cancer (Sezary)  
cell

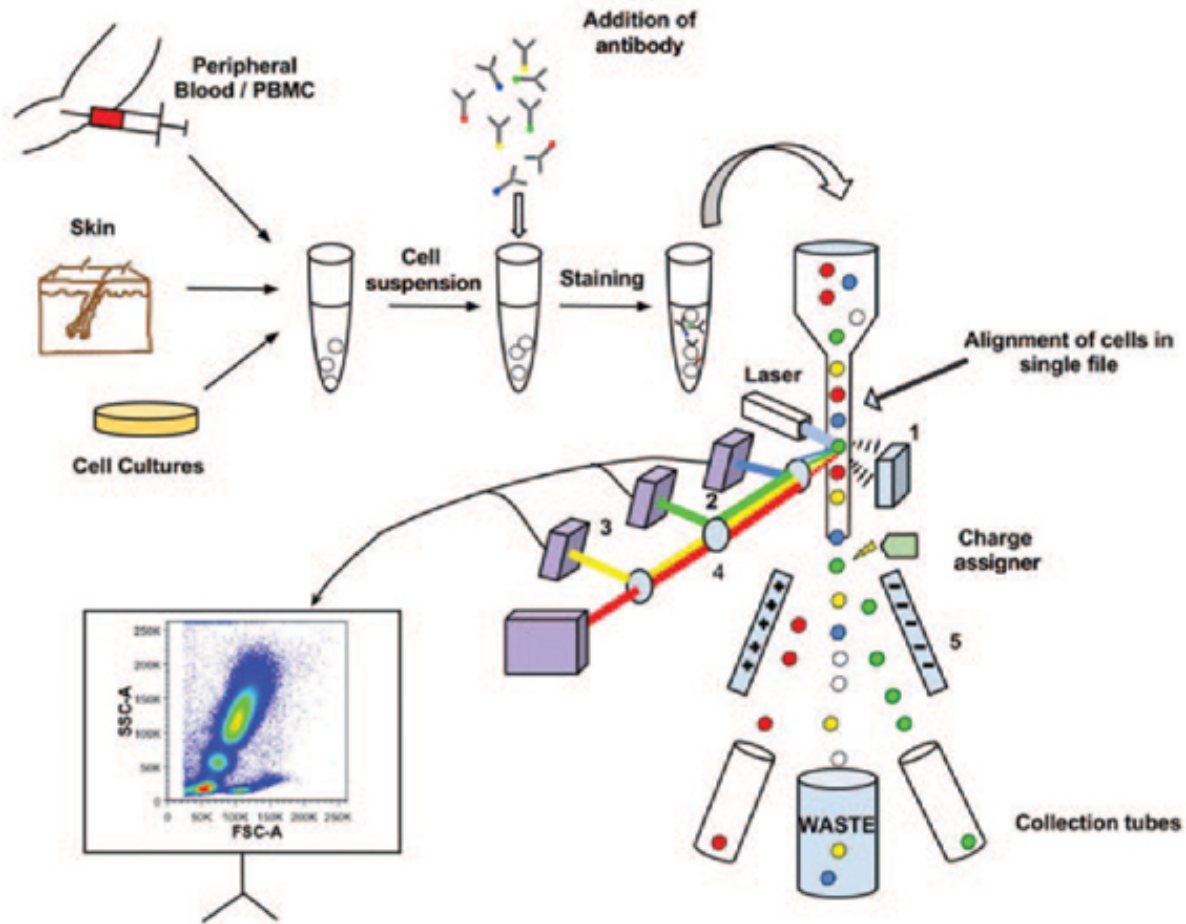
# How we do this

- Normal T cells have proteins that they make and are attached to their surface
- Cancer cells will stop making some of these normal proteins (CD7, CD26)
- We can use flow cytometry to find the abnormal cells

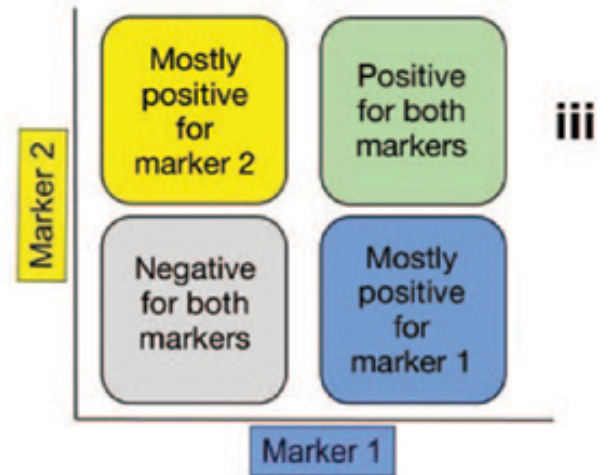
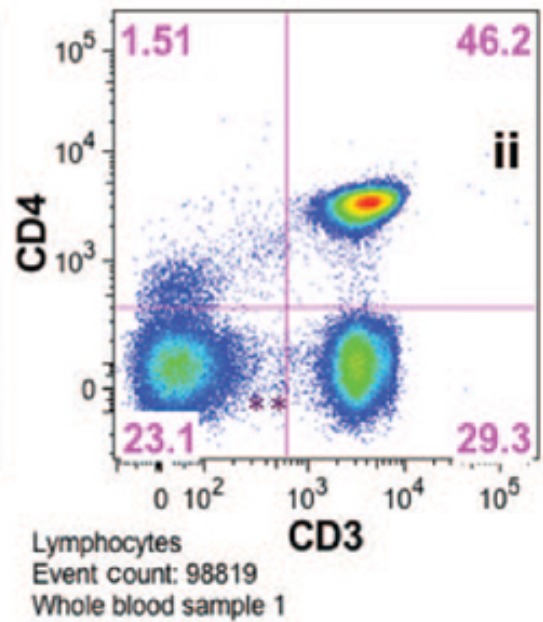
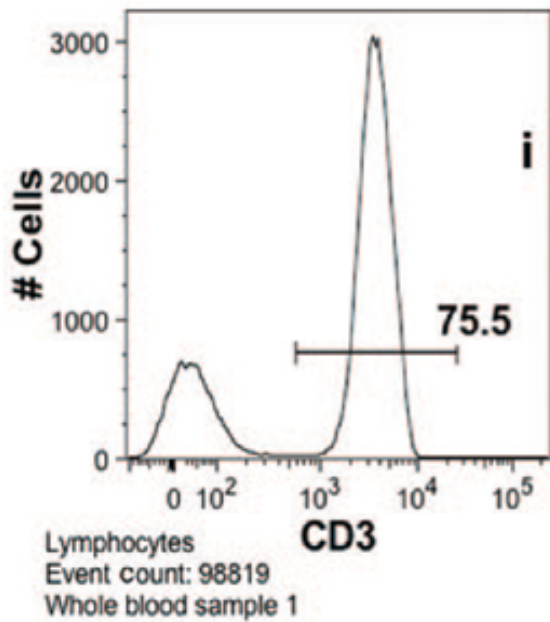




# Flow cytometry



# Flow cytometry



# Staging MF/SS

	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2	0	0, 1
IIB	3	0-2	0	0, 1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

# Staging cutaneous lymphomas other than MF/SS

## **Cutaneous T-cell and NK-cell lymphomas**

Primary cutaneous CD30+ lymphoproliferative disorders

Primary cutaneous anaplastic large-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal-type

Primary cutaneous peripheral T-cell lymphoma, unspecified

    Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

    Cutaneous  $\gamma/\delta$  T-cell lymphoma

    Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma

    Primary cutaneous peripheral T-cell lymphoma, unspecified, other

## **Cutaneous B-cell lymphomas**

Primary cutaneous marginal zone B-cell lymphoma

Primary cutaneous follicle center lymphoma

Primary cutaneous diffuse large B-cell lymphoma, leg-type

Primary cutaneous diffuse large B-cell lymphoma, other

Intravascular large B-cell lymphoma

Precursor hematologic neoplasm: CD4+/CD56+ hematodermic neoplasm, blastic NK-cell lymphoma

# Staging other cutaneous lymphomas : the problems

- Many different types of cutaneous lymphomas
- Most are rare
- Different prognosis and clinical course

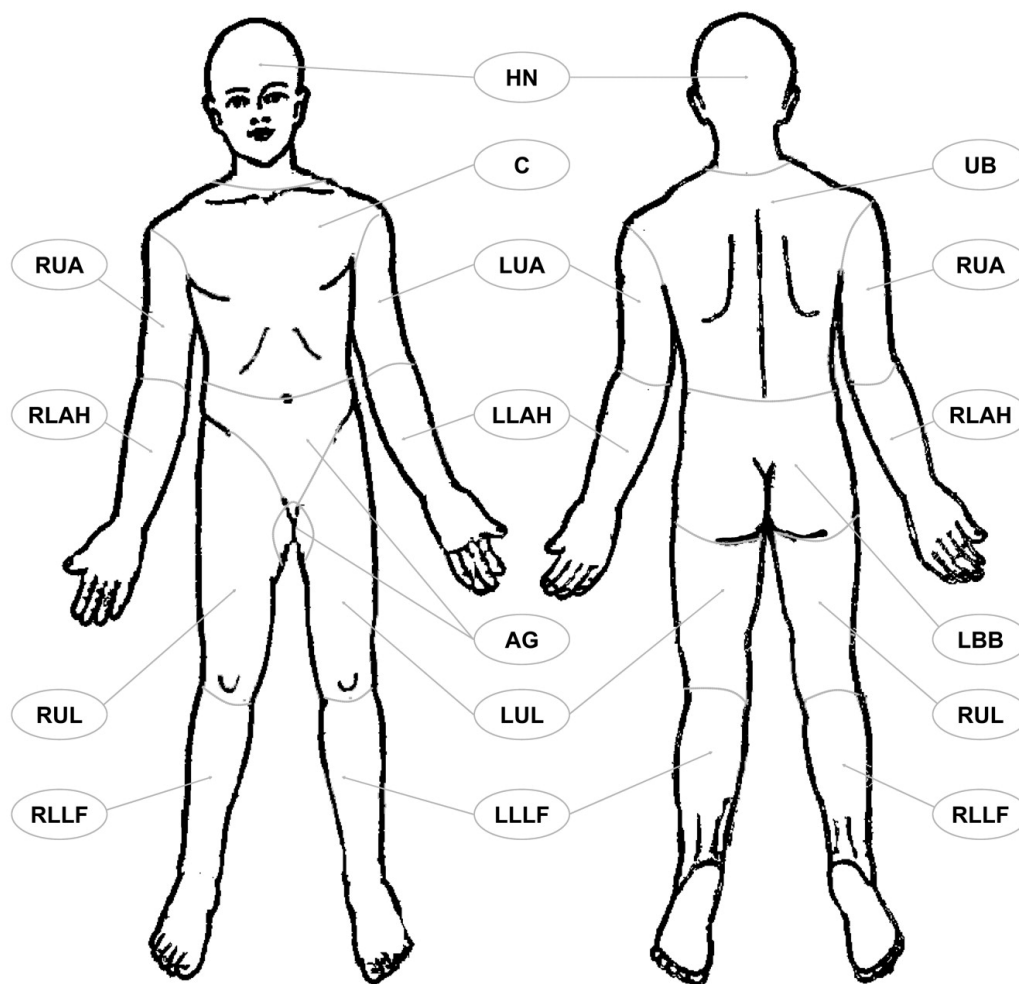
# Staging other cutaneous lymphomas

- Traditional system for staging non-Hodgkins lymphoma (Ann Arbor system) only classifies cutaneous lymphomas as Stage IE (one site) or Stage IVD+ (multiple skin sites)
- In 2007, a staging system was developed for all other cutaneous lymphomas that describes the extent of the lymphoma (using TNM classification) but DOES NOT give any prognostic information

# T

- T1: Solitary skin involvement
  - T1a: a solitary lesion <5 cm diameter
  - T1b: a solitary lesion >5 cm diameter
- T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions
  - T2a: all-disease-encompassing in a <15-cm-diameter circular area
  - T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area
  - T2c: all-disease-encompassing in a >30-cm-diameter circular area
- T3: Generalized skin involvement
  - T3a: multiple lesions involving 2 noncontiguous body regions
  - T3b: multiple lesions involving  $\geq 3$  body regions

## Body regions as defined in the proposed TNM system for the designation of T (skin involvement) category.



HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock

Kim Y H et al. Blood 2007;110:479-484



# N and M

- N0: No clinical or pathologic lymph node involvement
- N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
- N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
- N3: Involvement of central lymph nodes
  
- M0: No evidence of extracutaneous non-lymph node disease
- M1: Extracutaneous non-lymph node disease present

# Staging other cutaneous lymphomas

- Current staging system helps doctors to classify patients in a uniform fashion
- Our hope is that over time we will be able to better define prognosis for the different types of cutaneous lymphomas
- Currently, it is easier to define prognosis based on the growth pattern of the lymphoma

# Types of Lymphoma

- Indolent
  - Grows slowly
  - Treatment may not be necessary unless causing symptoms
  - Usually not curable
- Aggressive
  - Grows rapidly
  - Treatment necessary for survival
  - Often curable

# Indolent Lymphomas

- Mycosis Fungoides
- Granulomatous Slack Skin
- Subcutaneous panniculitic T-cell lymphoma
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous CD4+ small/medium pleomorphic T cell lymphoproliferative disorder
- Primary cutaneous marginal zone lymphoma
- Primary cutaneous follicle center cell lymphoma

# Aggressive Lymphomas

- Sezary Syndrome
- Primary cutaneous NK/T cell lymphoma, nasal type
- Primary cutaneous aggressive CD8+ T cell lymphoma
- Primary cutaneous  $\gamma/\delta$  lymphoma
- Primary cutaneous peripheral T cell lymphoma, NOS
- Primary cutaneous diffuse large B cell lymphoma

Thank you for your attention!

Questions?