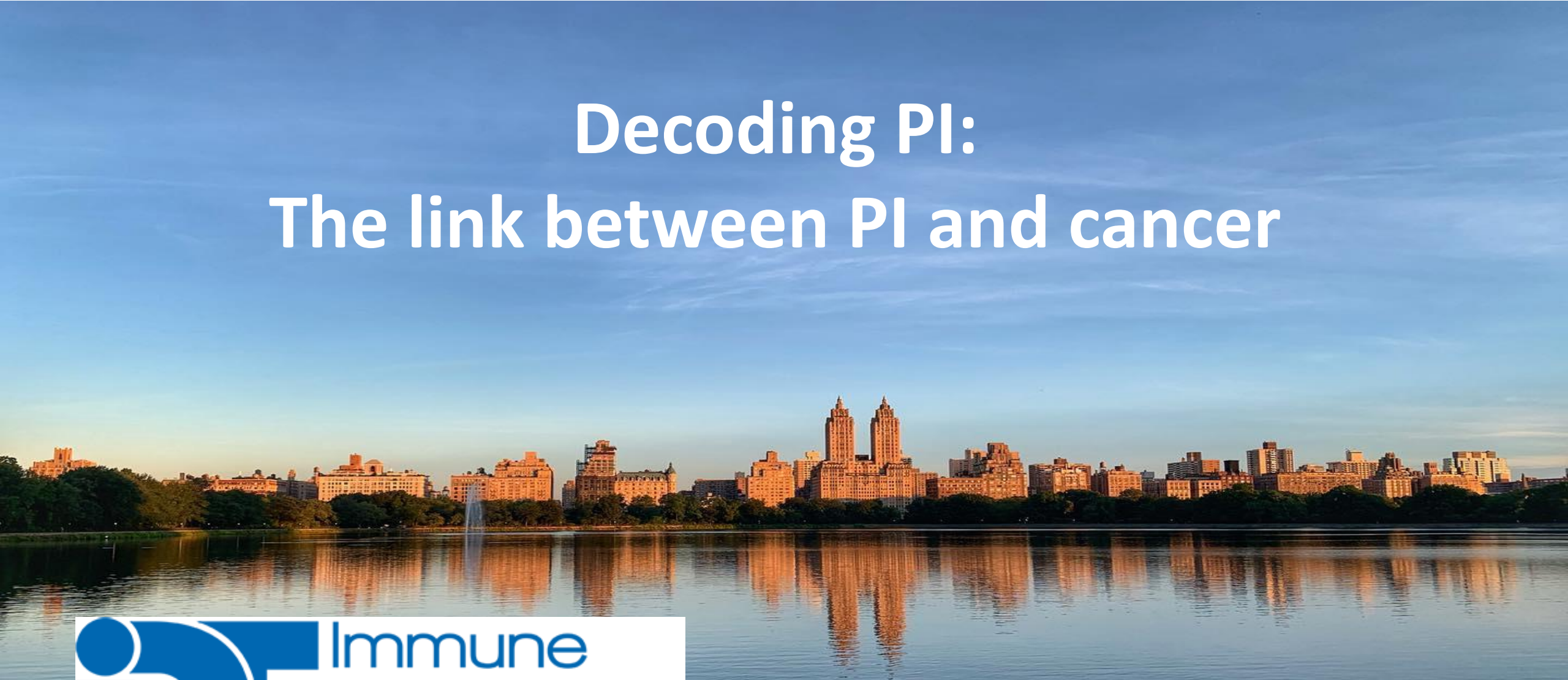
Decoding PI:
The link between PI and cancer



Charlotte Cunningham-Rundles MD PhD
Mount Sinai School of Medicine

OCTOBER 23, 2025

Disclosures

- Pharming - Consultant, Clinical trial
- Grifols - Awards committee, symposium sponsor
- Grifols - Data Safety Monitoring Board study X4 - Consultant
- Otsuka - Data Safety Monitoring Board
- Takeda - Speaker
- Sanofi – advisor and clinical trial

Immune deficiency and cancer: a long story

In 1965, Nobel laureate Sir McFarlane Burnet suggested that immunosurveillance was a central mechanism by which tumor development was kept in check and predicted that this would be confirmed.

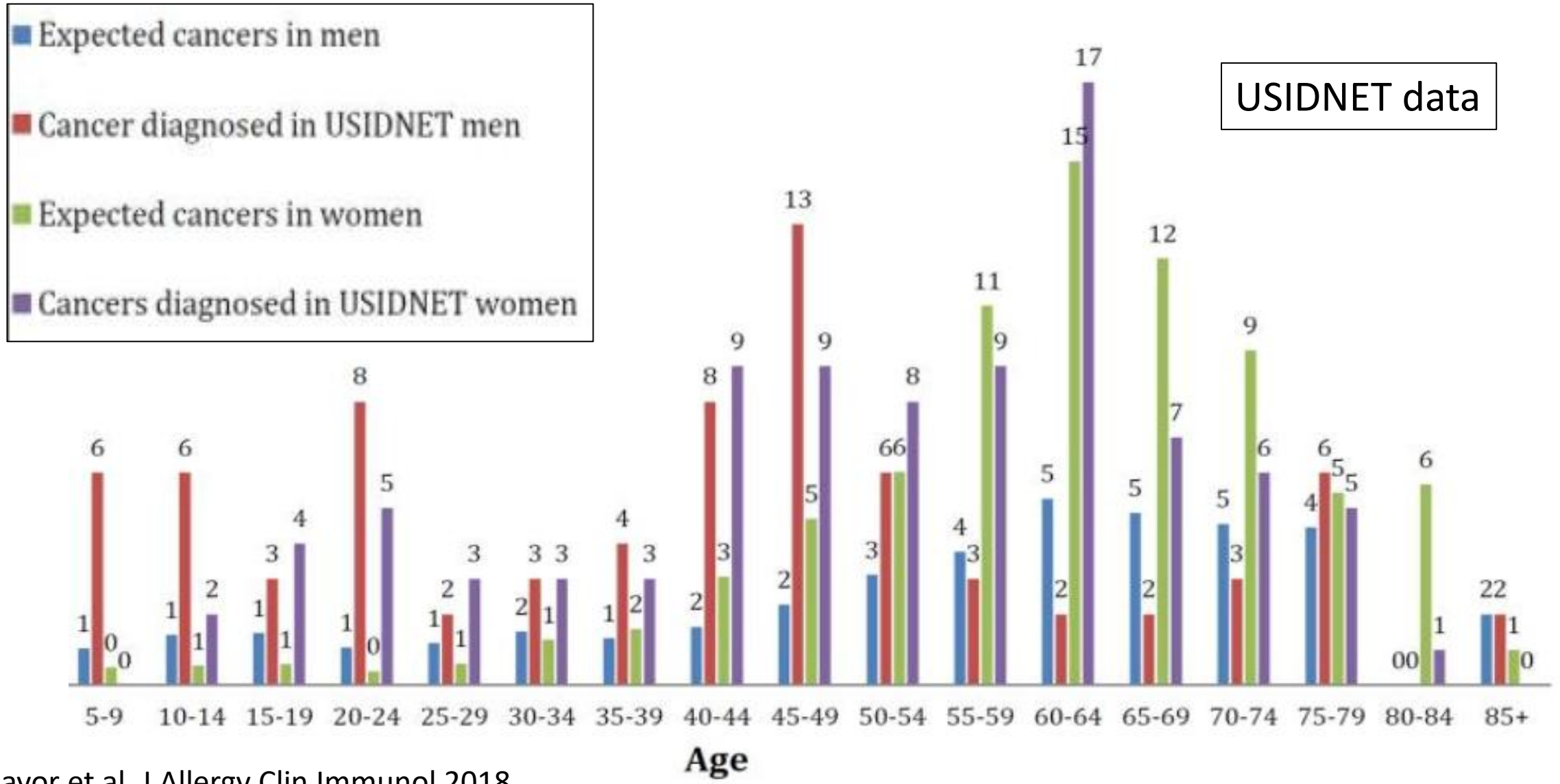
And yes, cancers do occur in:

1. **Organ and hematopoietic transplantation**
2. **Immune Suppression in general**
3. **HIV infections**
4. **Congenital immune defects**

Cancer in immune deficiency

- Why are we talking about this topic?
- Why does this occur?
- What are the difficulties in diagnosis?
- Why does Lymphoma occur in our patients?
- What have we learned?
- And what are the outcomes?

Patients with primary immune defects have more cancers than age matched subjects

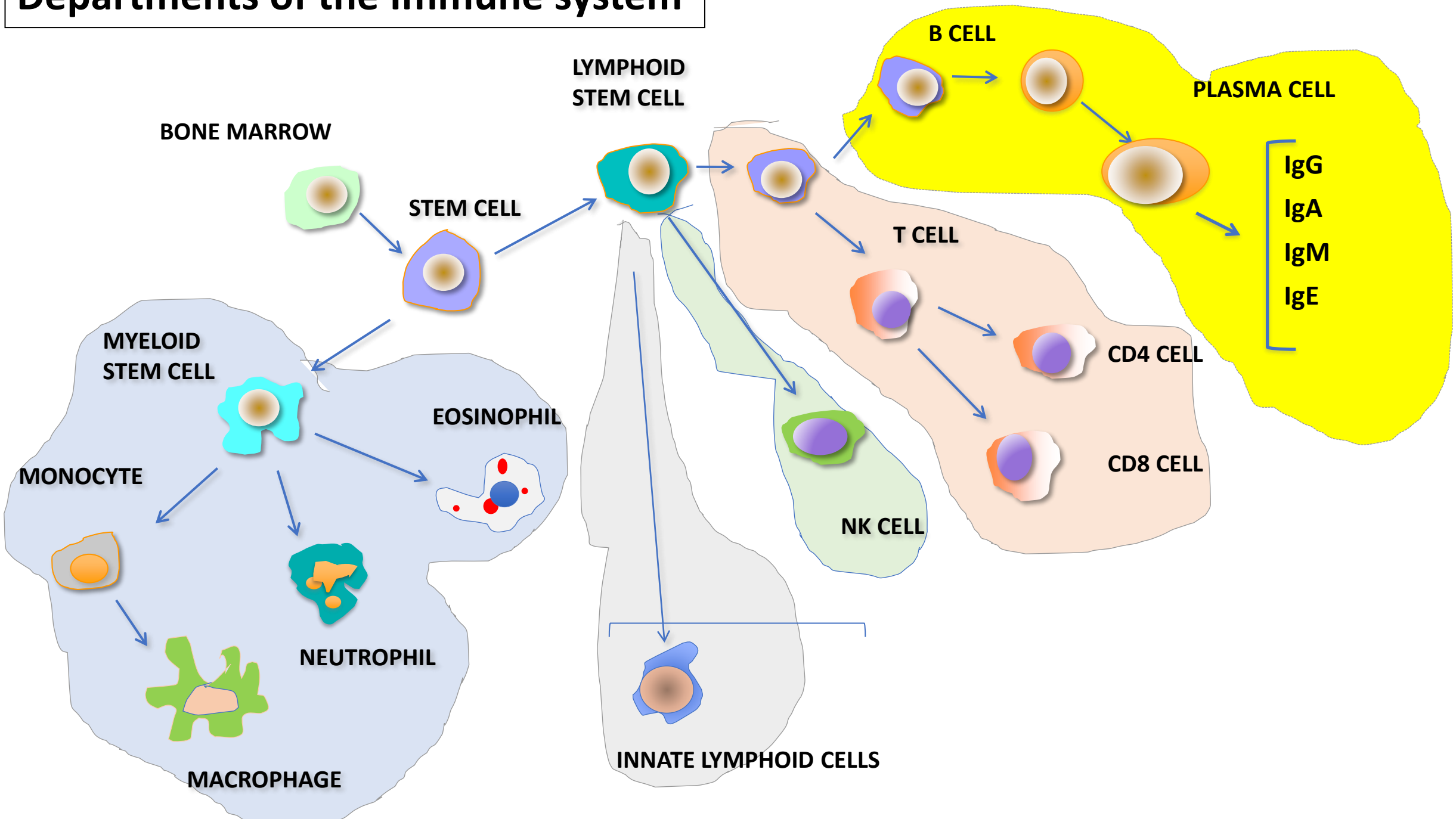


Mayor et al, J Allergy Clin Immunol 2018

How can we understand the cancer risks in our patient better?

Who is at risk?

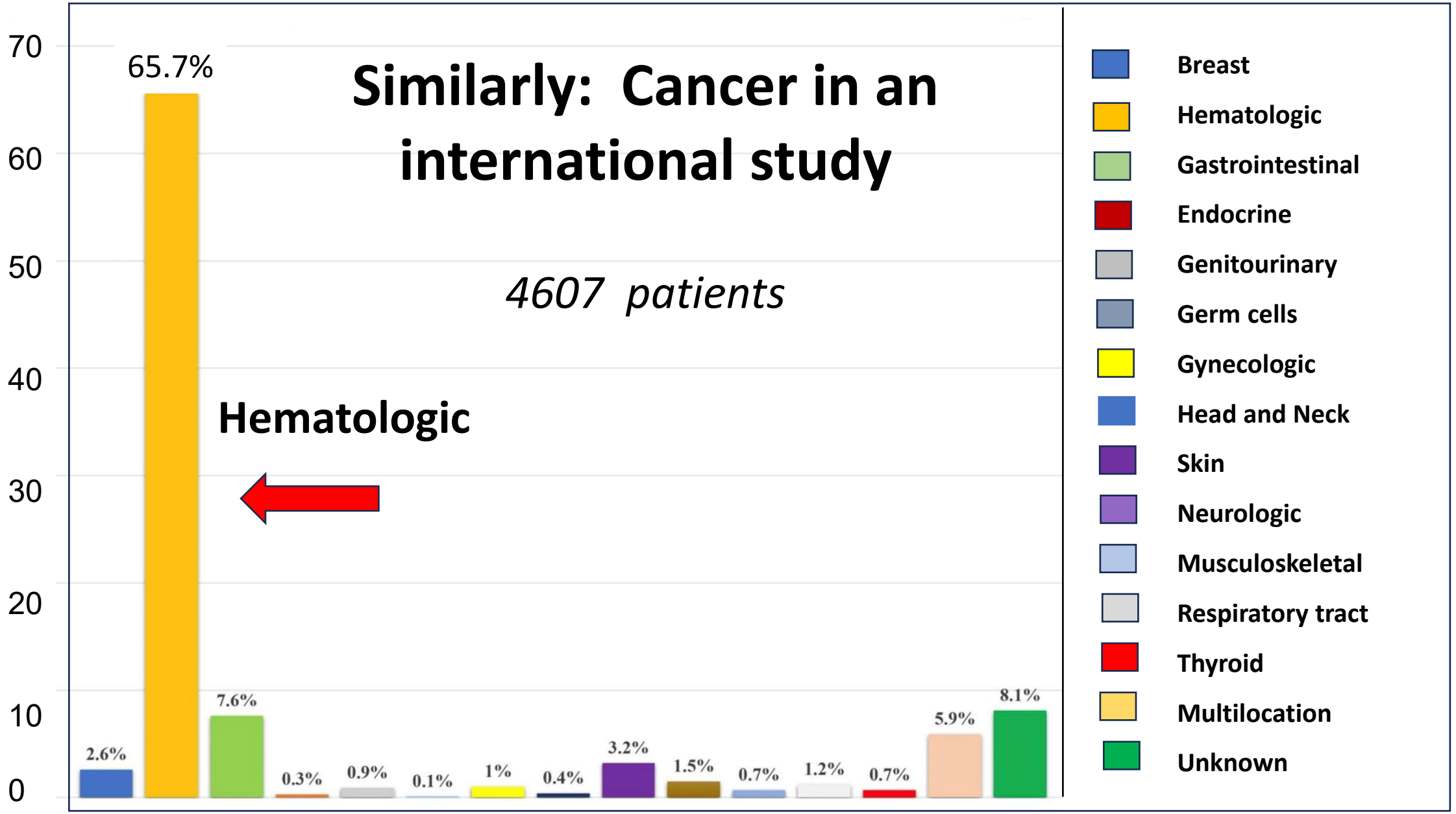
Departments of the Immune system



Classification of primary immune defects

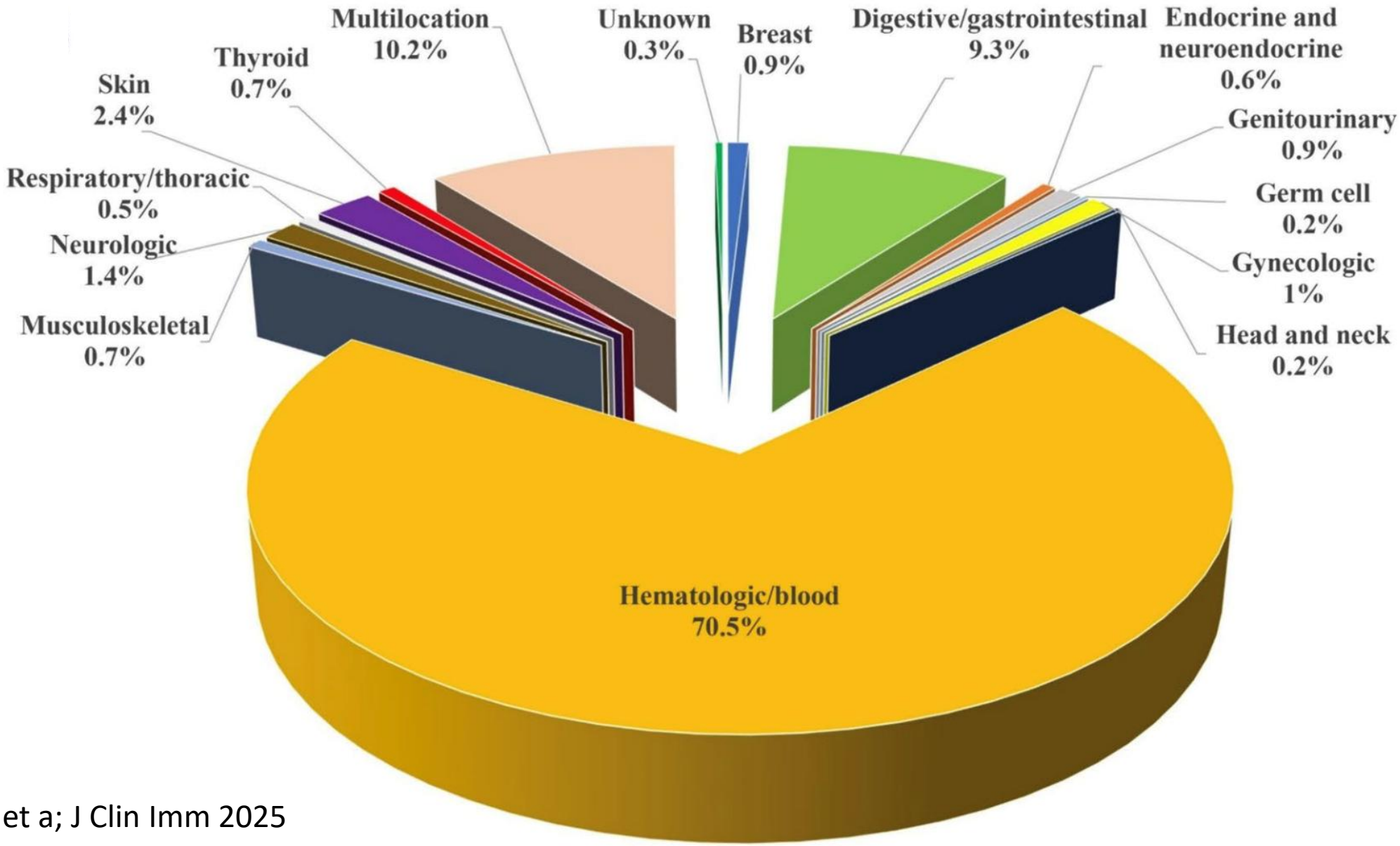
1. Immunodeficiencies affecting cellular and humoral immunity (combined)
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly Antibody Deficiencies
4. Diseases of Immune Dysregulation
5. Congenital defects of phagocytes -- number or function
6. Defects in Intrinsic and Innate Immunity
7. Auto-inflammatory Disorders
8. Complement Deficiency
9. Bone Marrow Failure Syndromes
10. Phenocopies of Inborn Errors of Immunity

Poli et al, 2025: International Union of Immunological Societies:
Diseases Committee Report on Inborn Errors of Immunity.



Fekrvand et al, J Clin Immun 2025

4607 patients with primary immune defects - collected from electronic searches



Fekrvand et a; J Clin Imm 2025

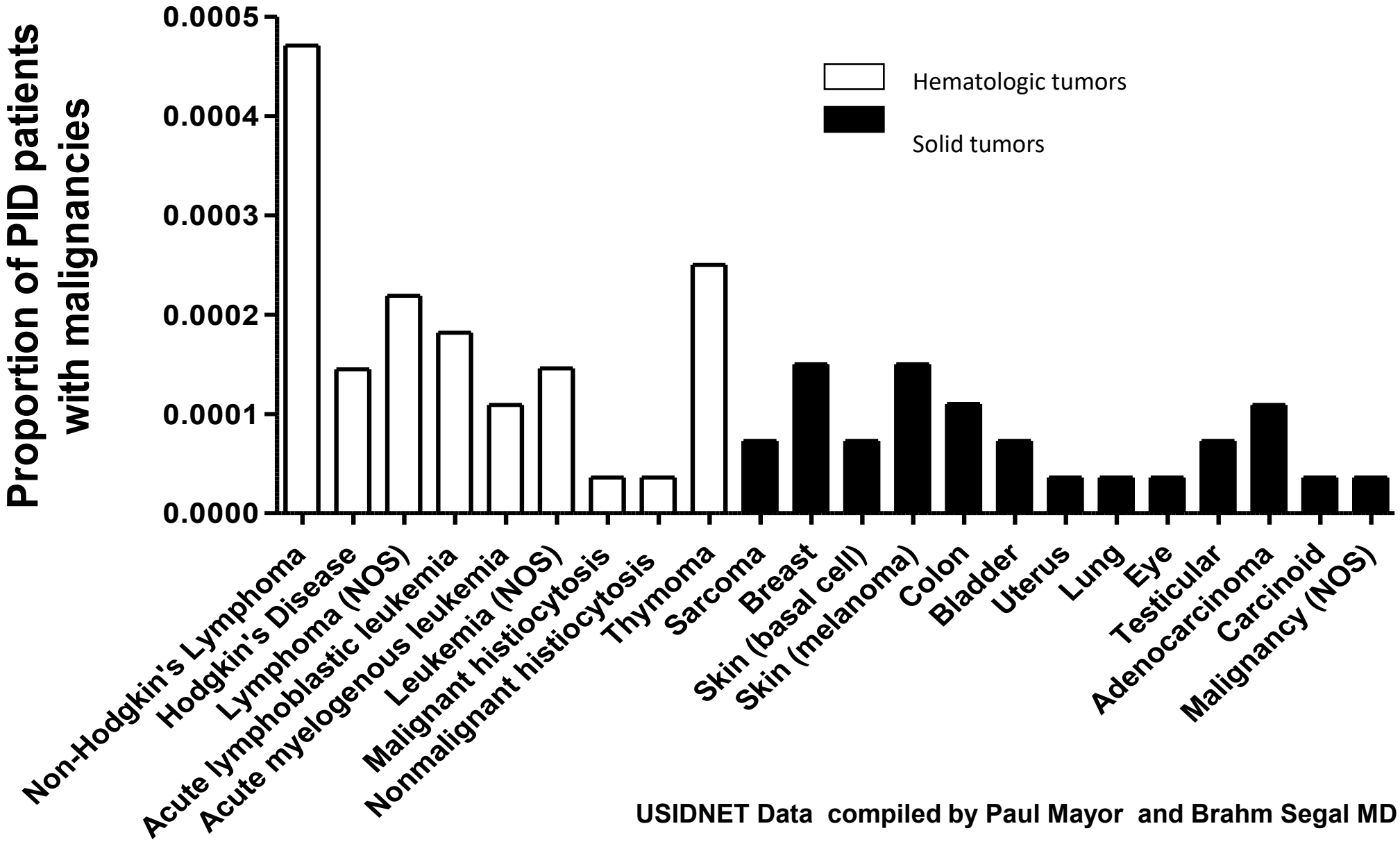
Cancers are found more in these Immune Defects

1. Immunodeficiencies affecting cellular and humoral immunity (combined)	
2. Combined immunodeficiencies with associated or syndromic features	30.3%
3. Predominantly Antibody Deficiencies	38.8%
4. Diseases of Immune Dysregulation	
5. Congenital defects of phagocytes -- number or function	
6. Defects in Intrinsic and Innate Immunity	
7. Auto-inflammatory Disorders	
8. Complement Deficiency	
9. Bone Marrow Failure Syndromes	12.7%
10. Phenocopies of Inborn Errors of Immunity	

Poli et al, 2025: International Union of Immunological Societies: Diseases Committee Report on Inborn Errors of Immunity.

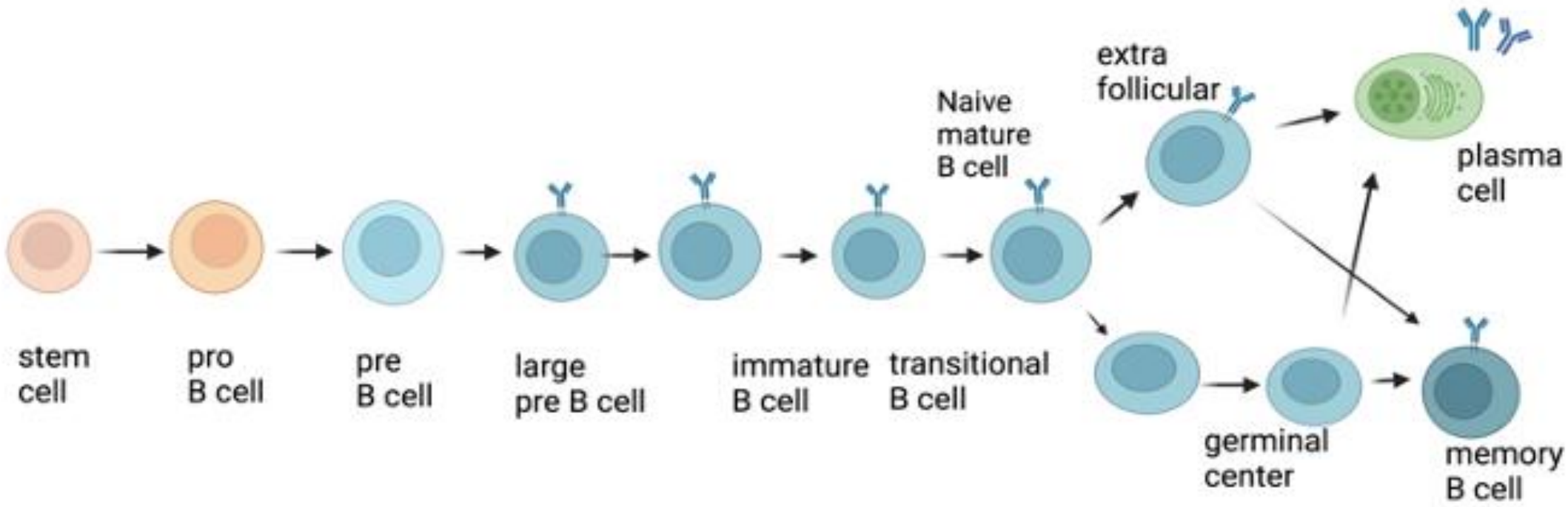
Fekrvand et a; J Clin Imm 2025

USIDNET data: What kind of cancers are found in the US?

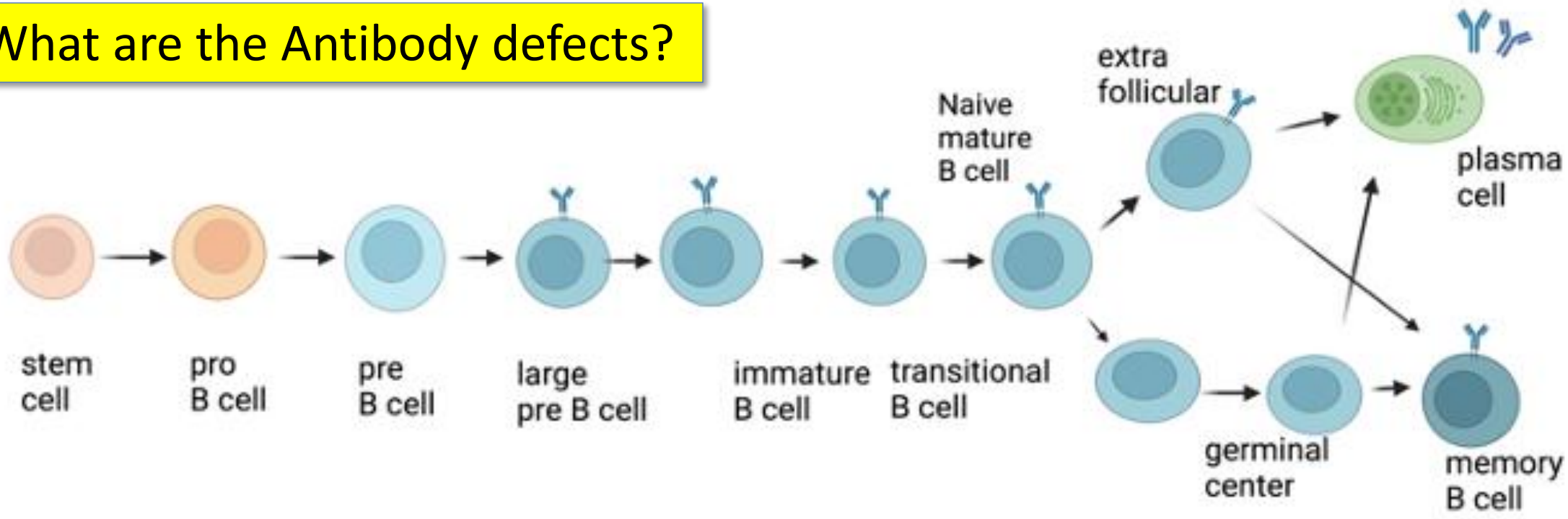


USIDNET Data compiled by Paul Mayor and Brahm Segal MD JACI 2018

Cancers in Antibody Deficiency



What are the Antibody defects?



Agamma-globulinemia

Hyper IgM

Common Variable Immune deficiency

IgA deficiency

Cancers in Common Variable immune Deficiency in the USIDNET Registry

	Cancer	Number	Expected	P Value	Fold-change
CVID Males	**Lymphoma**	**16**	**1.9**	**<0.001**	**8.42**
	Skin	9	1.6	<0.001	5.63
	Thyroid	4	0.6	<0.001	6.67
	Stomach	2	0.4	0.011	5.00
	Prostate	0	6.3	0.012	0
	Bladder	3	1.1	.070	2.73
	Lung	2	2.5	0.752	0.80
	Colon	2	2.3	0.843	0.87
	Testicular	1	1.1	.924	0.91
CVID Females	**Lymphoma**	**21**	**3.0**	**<0.001**	**7.00**
	Skin	14	3.8	<0.001	3.68
	Breast	8	21	0.004	0.38
	Stomach	3	.7	.005	4.29
	Thyroid	1	5.0	.073	0.2
	Ovarian	2	2.0	1	0.1
	Uterine	2	4.2	.283	.476
	Cervix	2	1.8	.881	1.11

Mayor et al: USIDNET Data JACI 2019

Comorbidities and mortality in CVID n=972 (ESID Registry)

Condition	P-value
Lymphoma	0.001
Solid tumor	0.002
Granulomatous/lymphocytic lung disease	0.006
Splenomegaly	0.013
Autoimmunity (organ)	0.187
Enteropathy	0.493
Autoimmunity cytopenia	0.591
Bronchiectasis	0.612

Odnoletkova et al. Orphanet Journal of Rare Diseases 2018

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Mount Sinai Data

Mount Sinai

801 patients with common variable immune deficiency

33 patients (4%) -- Cancers in various organs:

- skin, breast, gall bladder, stomach, esophagus, mouth, colon, ovary. rectal, melanoma, prostate, and thyroid

66 patients (8%) -- Hematologic cancers:

- Mostly Lymphoma, also Hodgkin's disease, leukemia

Mount Sinai

66 lymphomas in 801 CVID subjects

- 37 females and 29 males
- Age diagnosed with CVID =1-77
- Age diagnosed with lymphoma =11-81
- Often extra nodal (not in a lymph node)
- Mostly EB Virus negative

Lung	10
Lymph nodes	9
Jejunum, stomach, small bowel	8
Diffuse	7
Pelvic nodes	4
Parotid	4
Abdomen	6
Liver, spleen	4
Axilla and mediastinum	3
Brain	3
Lung/ lymph nodes	2
Kidney	2
Right inguinal node	1
Mediastinum	1
Supraclavicular node / abdomen	1
Thyroid	1

Mount Sinai

updated from Smith, et al Euro J Hematology 2021

Lymphomas were found in some patients with known inflammatory features

Other Features	Numbers	Percent
Splenomegaly, lymphadenopathy	11	24
Enteropathy with or without malabsorption	9	20
Interstitial lung disease, bronchiectasis	8	18
Autoimmunity: primary biliary cirrhosis (3), pernicious anemia (2), alopecia (1), vasculitis (1), rheumatoid arthritis(1)	8	18
Other cancers (Hodgkin lymphoma, thyroid adenoma, vaginal cancer	7	16
Immune Thrombocytopenia	6	13
Granulomatous disease (lung or nodes or both)	5	11
Autoimmune hemolytic anemia	1	2

Mount Sinai

Smith, et al Euro J Hematology 2021

Why do patients with loss of antibody function develop more cancer?

The higher relative proportion of patients with loss of antibody functions and cancer is due to these two facts:

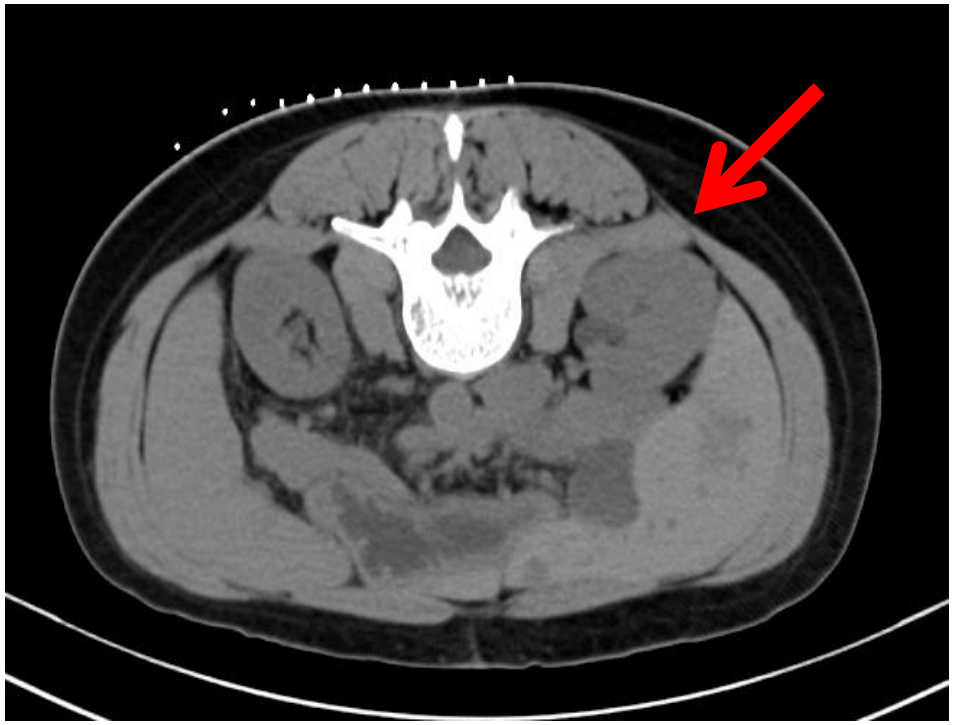
1. There are more patients with these defects overall

2. And and increased life expectancy in these immune defects, contribute to the higher detection and reporting of cancers in these patients.

44 year old woman who had long standing CVID

CVID diagnosed at the age of 24
IgG= 45; IgA= 0; IgM = 30 mg/dl

- Age 44: Chronic cough;
- Bronchoscopy
- Follicular bronchiolitis
- Pulmonary functions stable
- CT of the lungs, noted mass above the left kidney.



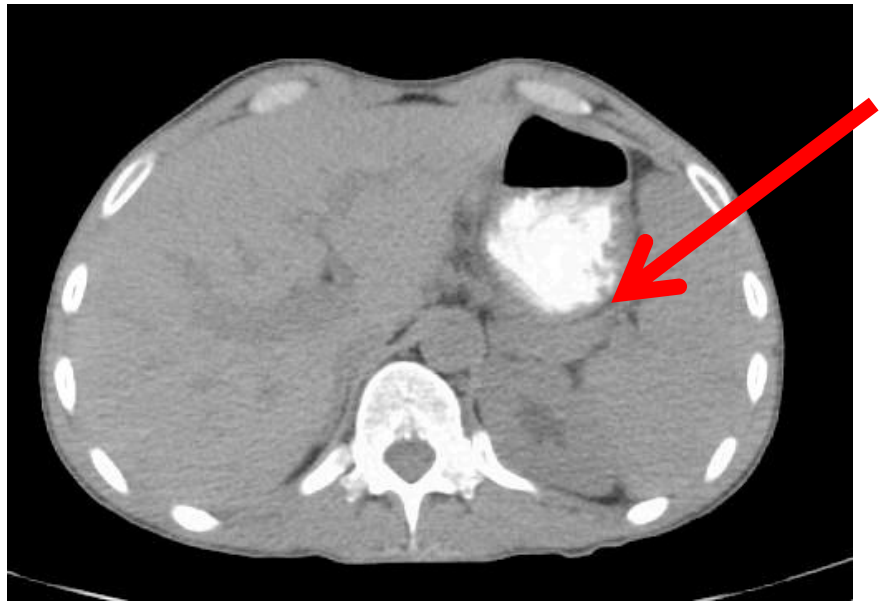
CT abdomen/Pelvis: retroperitoneal adenopathy in the left paraaortic region. In the midportion of the left kidney there is a hyperdense 2.4-cm mass.

Kidney Biopsy: Fragments of lymphoid tissue and kidney parenchyma with an atypical lymphoid infiltrate; marginal zone B-cell lymphoma.

Rituximab treatment only; currently well, age 62

45 year old man with CVID since age 20

- Age 20: IgG= 23, IgA=0 IgM=2 mg/dl
- Put on IVIG
- Age 43, had weight loss and an abdominal mass in the jejunum
- Resected, given CHOP + Rituximab
- Currently well, age 59.



Soft tissue mass located anterior/inseparable to left psoas muscle, extends superior to the left para-aortic region extending to the adjacent soft tissue plane immediately anterior to the left renal fossa and encasing the left ureter measuring 4.8 cm x 2.2 cm in greatest dimension.

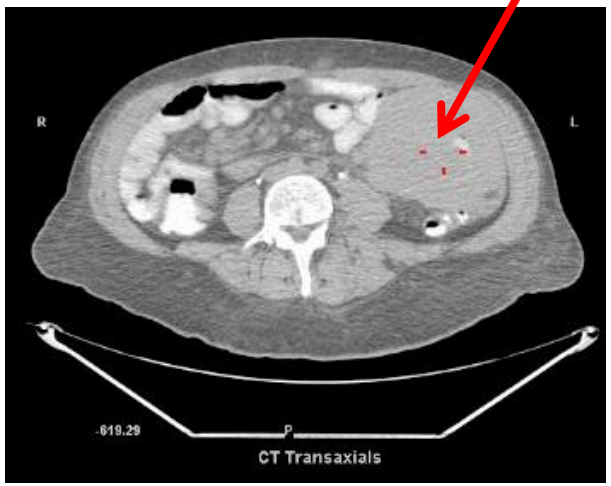
There is left-sided hydronephrosis.

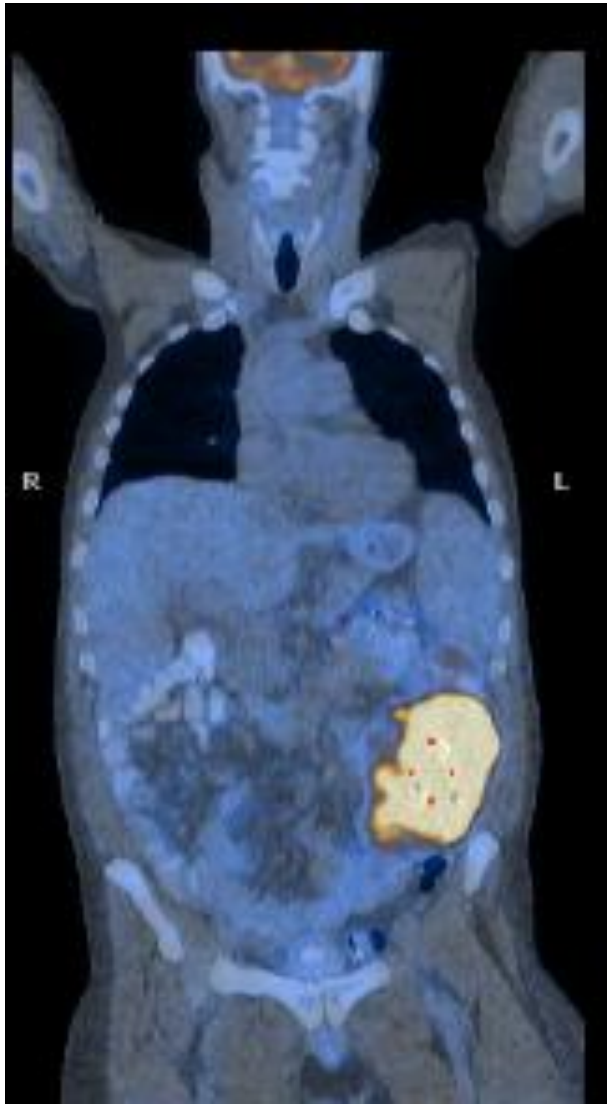
41 year old man with known CVID since age 20

- History of ITP at age 11
- IgG= 50; IgA = 0; IgM = 2; B cells 0.1%
- On IVIG
- Age 41: C/O diarrhea
- Giardia isolated
- Refractory to treatment with metronidazole
- Abdominal pain and obstruction
- CT showed a mass
- PET scan
- Lymphoma in the jejunum

IgA + Plasmablastoid lymphoma
Extensive chemotherapy,

Expired





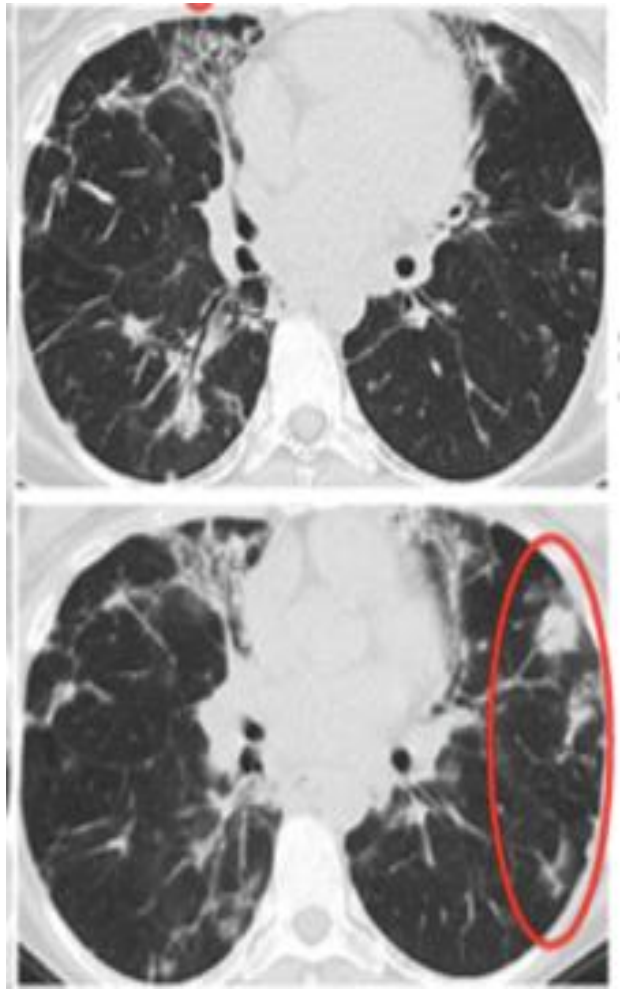
Lymphoid malignancy in CVID

- 4% - 6% of CVID patients develop lymphoma, most commonly B cell in type.
- Detection and accurate diagnosis are challenging:
  - Pre-existing lymphoid hyperplasia and lack of biomarkers lead to uncertainty about when to biopsy.
  - Accurate histologic diagnosis presents significant challenges to the pathologist.
  - Subclassifications following the updated 2016 WHO system can be difficult; this was established for immunocompetent patients.
- BUT: Differences between non-malignant lymphoproliferative disorders and overt lymphomas can be difficult to recognize.

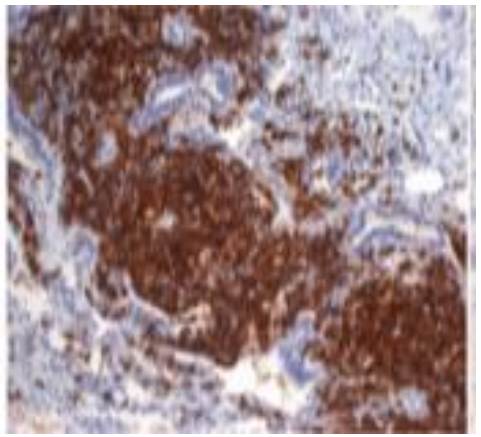
Why is the diagnosis difficult?

The lungs and other tissues in CVID often contain unusual lymphoid infiltrates

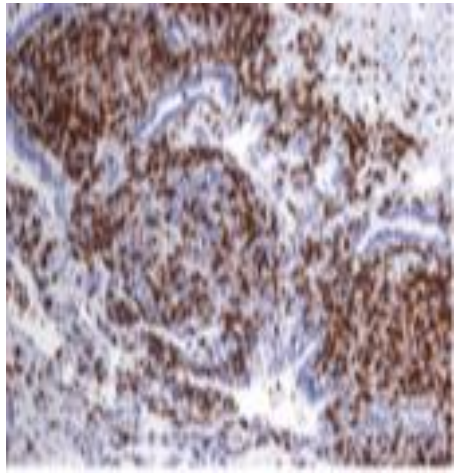
Lung



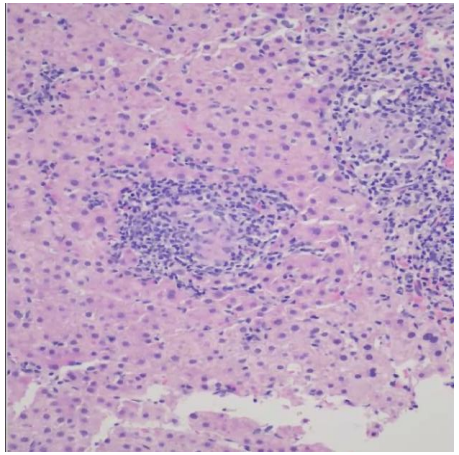
B CELLS



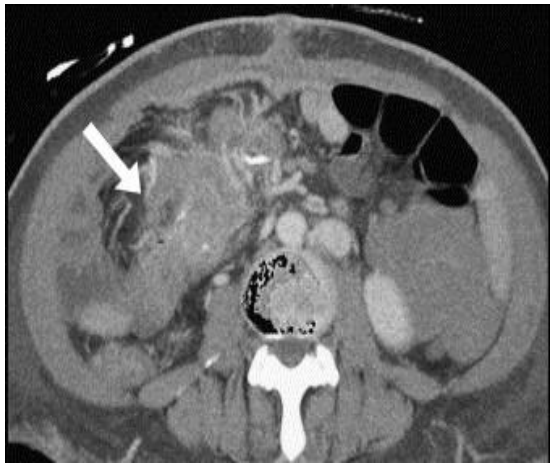
T CELLS



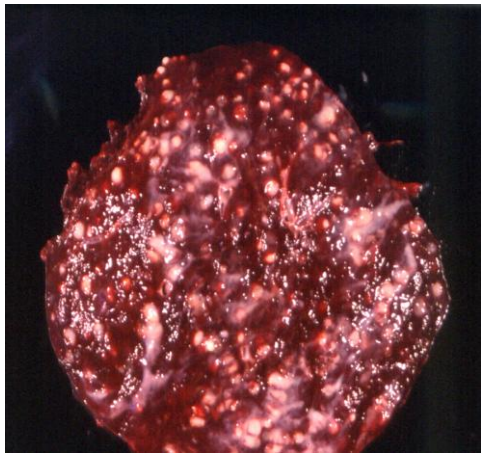
Liver



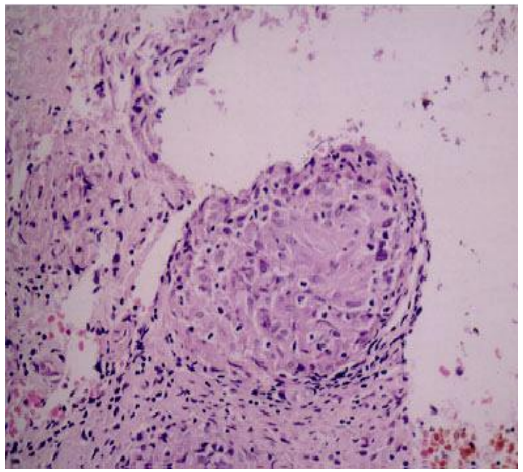
Abdomen



Spleen

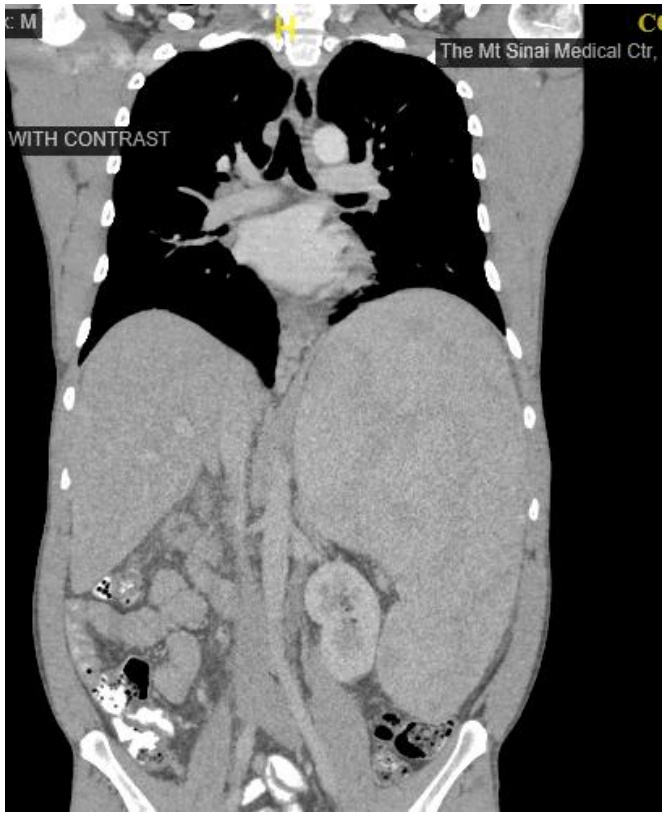


Node

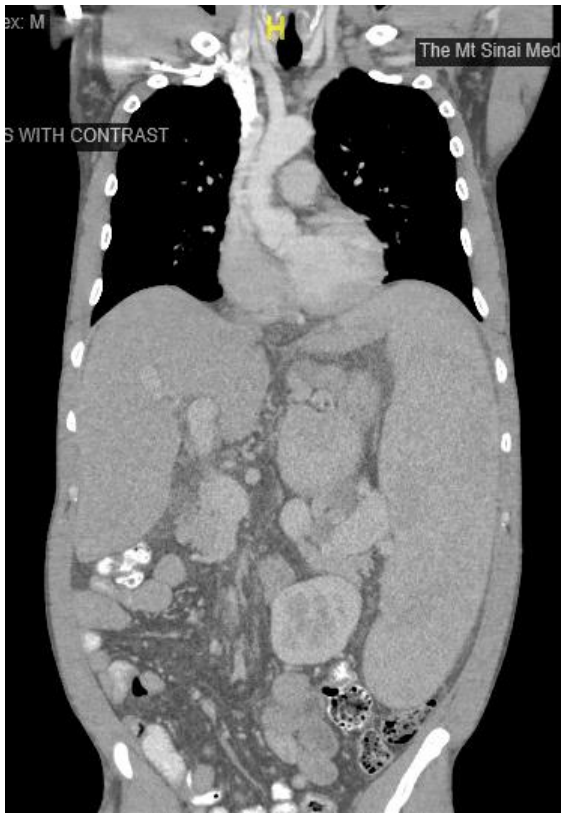


Enlarged spleen is found in 20% or more of CVID subjects, sometimes massively enlarged.

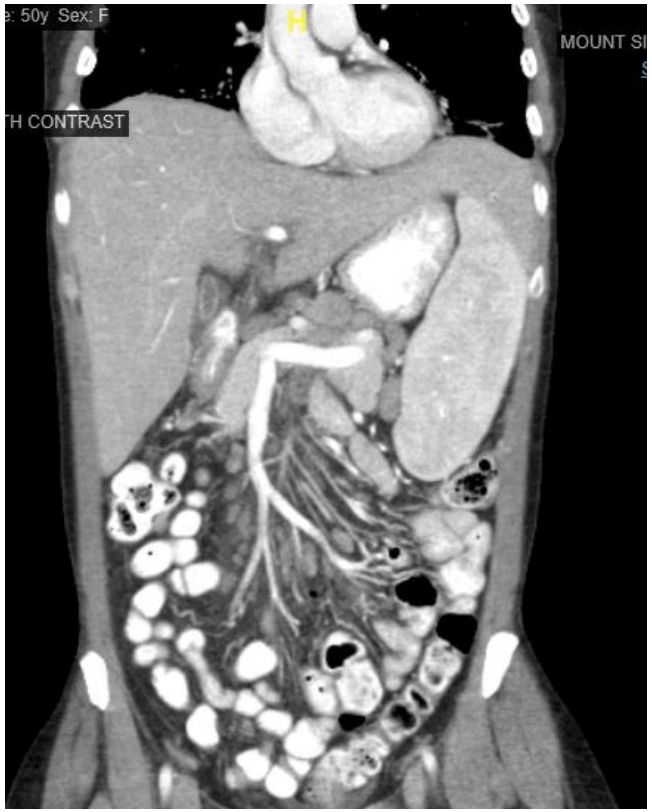
41 year old male



39 year old male



45 year old female



IgG =90; IgA= 0; Ig=15

IgG=120; IgA=6; Ig= 0

IgG=58; IgA=6; Ig=10

Six CVID patients previously diagnosed with lymphoma, did not have lymphoma!

Case	Age at CVID diagnosis in years (Gender)	Autoimmune; Lympho-proliferation features	Malignant diagnosis (Age at biopsy)	Biopsy site:	Course of Chemotherapy	Final Diagnosis
1	46 (M)	AIHA, ITP, Splenomegaly	MZL (63)	Bone marrow:	No	Monoclonal B-cell lymphocytosis
2	45 (M)	Axillary LAD Abdominal LAD	MZL (48)	Lymph node	Rituximab	Marginal zone hyperplasia
3	37 (M)	AIHA, ITP; Splenomegaly Diffuse LAD	MZL (42)	Bone marrow:	R-bendamustine, Rituximab	Normocellular bone marrow with progressive tri-lineage hematopoiesis,
4	28 (F)	AIHA, ITP; Splenomegaly Diffuse LAD	DLBCL (37)	Lymph node	Cytoxan, Prednisone and Vincristine	Reactive lymphoid hyperplasia
5	25 (F)	Lymphopenia, neutropenia, ITP; Splenomegaly	MZL (27)	Lung and node:	Rituximab	Nodular lymphoid hyperplasia, clusters of histocytes with ill-defined and poorly formed granulomas
6	43 (M)	biliary cholangitis; thyroiditis; Splenomegaly	MZL (47)	Right parotid gland and lymph node	Rituximab given only for granulomatous disease only	Atypical marginal zone hyperplasia

Confirmation of the diagnosis is essential

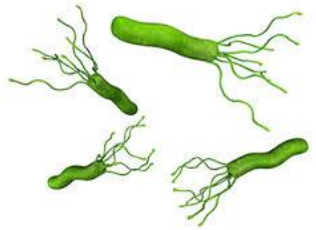
- Enlarged lymph nodes and a larger than normal spleen often occurs in antibody deficiency. This is not cancer.
- Expanded numbers of “clonal”. lymphocytes is also common and cannot be used to confirm lymphoma.

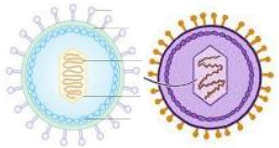
Lymphoid malignancy in CVID
Problems in diagnosis

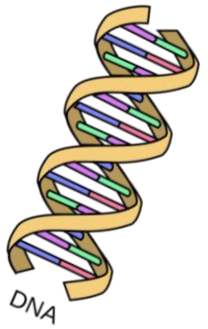
- Detection and accurate diagnosis are challenging:
  - Lymphoid hyperplasia leads to uncertainty about when to biopsy.
  - Accurate histologic diagnosis presents significant challenges to the pathologist.
  - Subclassifications of lymphoma was established for immunocompetent patients.
- Differences between non-malignant lymphoproliferative disorders and overt lymphomas can be difficult to recognize.
- B cells in CVID commonly have clonal features due to immaturity.
- PET scans may look abnormal due to chronic lymphoid activation.

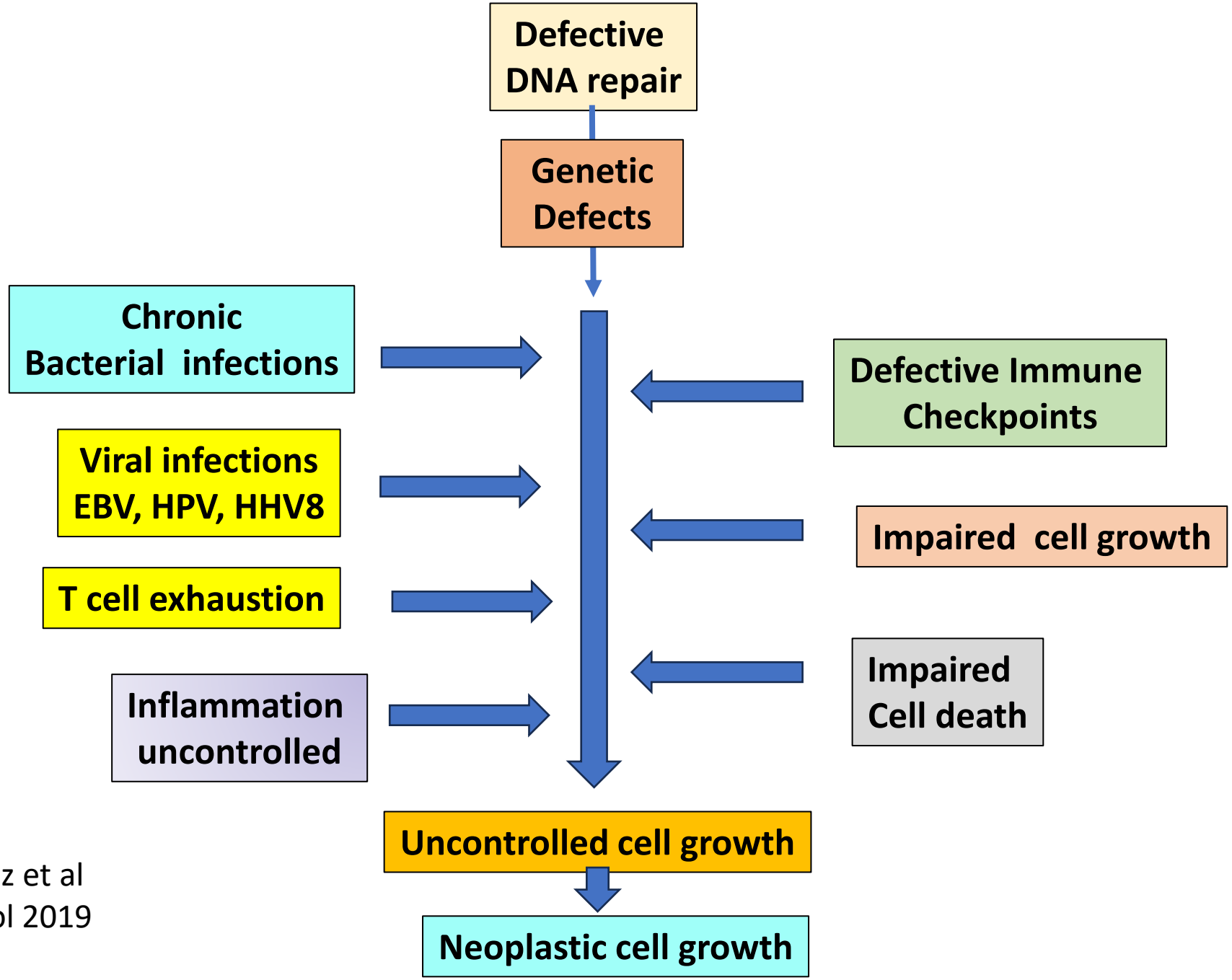
Reasons for Cancer in Primary Immune Deficiency

- Defects in cell-mediated immunity which control cancer
- Reduced cytotoxic T lymphocytes able to recognize tumor cells
- Chronic infections leading to persistent inflammation
- Lack of control of Helicobacter pylori
- Lack of control of oncogenic viruses (Epstein-Barr virus, Papilloma Virus)
- Selected Genetic mutations,
  - DNA damage repair defects
  - Cell death defects
  - Cell cycle check-points (Cartilage-hair hypoplasia)
  - Cell division defects







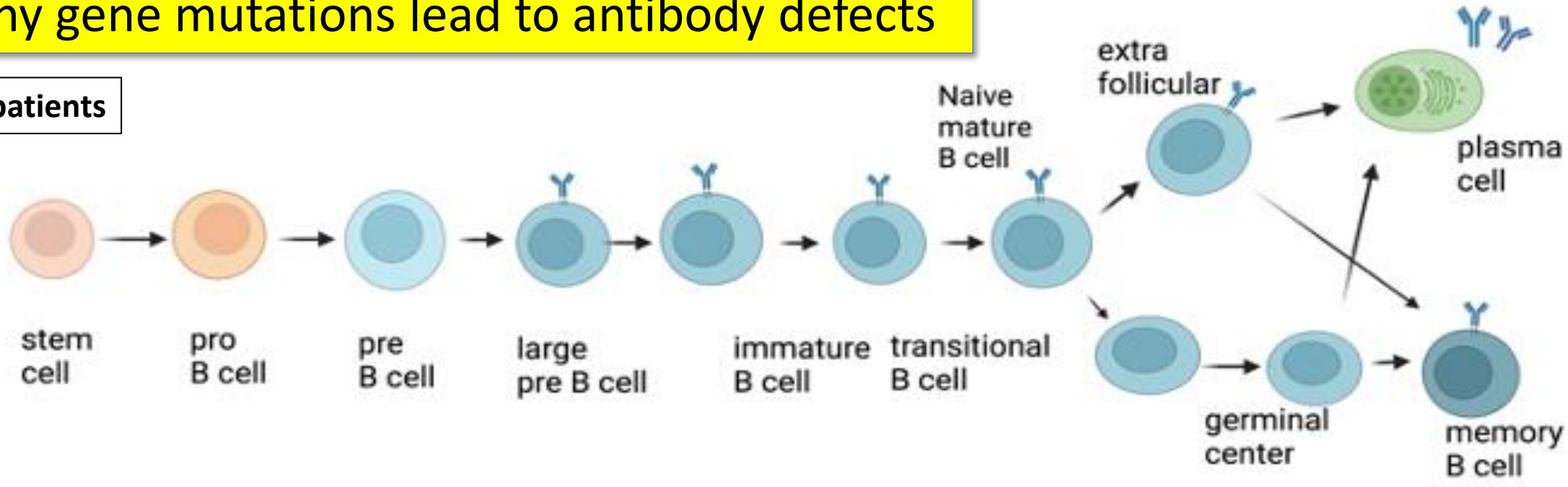


Adapted from Riaz et al
Frontiers Immunol 2019

So what about genetics?

Many gene mutations lead to antibody defects

571 patients



TOP2B

IKZF1
TCF3
RAG1
RAG2

IGHM
CD79A
CD79B
BLINK
IGLL1
SLC39A7
RAC2
PIK3CD
PIK3R1
TRNT1
PU.1
BTK

TWEAK
BAFF R

CD19
CD81
CD20
CD21
CD81
SH3KBP1
ATP7AP1

CD20
CARD11
TRNT1

CD40
CD40L
ICOS
ICOSL
TACI
PLCg

AICDA
UNG
IN080
MSH6
PIK3CD
PIK3R1
PTEN
ARHGEF1
NFKB1
NFKB2
IRF2BP2

SEC61A1
UNG
IRFBP2
TNFFSF13
MOGC
APRIL

LRBA CTLA4 STAT

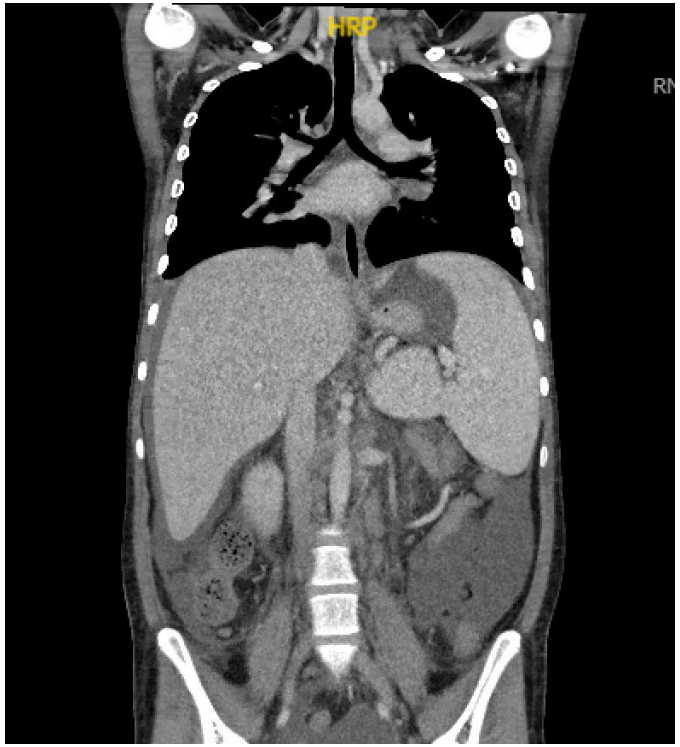
ICOS IL21 IL21R

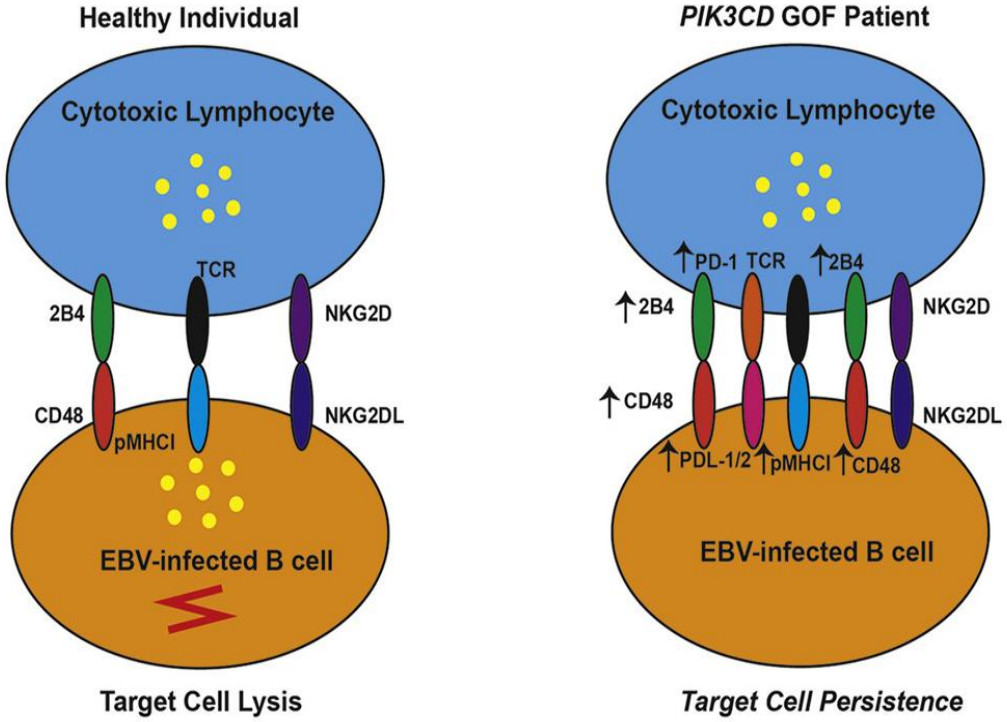
CXCR4

Abolhassani et al 2020

Gene Defect = activated phosphoinositide 3-kinase δ

- 20 year old girl, followed from age 5 with hypogammaglobulinemia, also enteropathy, interstitial lung disease, splenomegaly, lymphadenopathy.
- She had a mutation in phosphoinositide 3-kinase δ (*PIK3CD gene*) and has “APDS”
- At age 18 she developed B cell lymphoma, EBV+,
- Treated with Rituximab and T cell therapy, bone marrow transplant,
- Expired.





Germline Gene variants found in 405 of our CVID patients who developed cancer or lymphoid malignancy

GENE	Consequence	Cancer	Lymphoma/Leukemia
BTK	p.Tyr418His	Esophagus	
CD40L	indel-frameshift	Bladder	
IKZF1	p.Ser385*		T cell leukemia
LRBA	p.Ile2232Thr/p.Ala892Thr	Mouth	
NFKB2; **TACI**	p.His98Asn p.Cys104Arg		Gastric Maltoma
NFKB2 **TACI**	p.Gly719Glu p.Leu69fs		Gastric Maltoma
PI3KCD	p.Glu1021Lys		Lymphoma
PI3KCD	p.Glu1021Lys	Ovary	
PIK3R1 **DCLRE1C**	start gained/ start gained del exon 1-3		MALT Lymphoma
RAB27A **PMS2**	del exon 2 p.Ile18Val/p.Arg563Leu	Gall Bladder	
TACI	p.Cys104Arg		Plasmablastic Lymphoma
TACI	p.Cys104Arg	Rectal	
TACI	p.Ala181Glu		MALT Lymphoma
TCF3 **TACI**	p.Ile562Val p.Leu69fs/Cys104Arg		Lymphoma
TACI **TMPRSS15** **NBAS** **IL10RA**	p.Ala181Glu p.Ser712* Del exons 45-52 p.Arg147Pro fs*4		Lymphoma

Other questions….

- What is the best treatment for the cancer?
- How do patients do with treatment ?
- When cancer is diagnosed first and treated, how can we know if there was a primary immune defect?

Principles of treatment of cancer in patients with immune defects

- In general, standard treatment is recommended.
  - *Radiation sensitive patients (eg, ataxia telangiectasia, DNA repair defects) require dose reduction or omission of alkylating agents and radiation.)*
- As immunosuppressive pre dispose to infections, antibiotic prophylaxis and steady replacement of immunoglobulins can be critical
- Correction with with stem cell transplant can be considered in some cases.
- **In general patients with immune defects respond well to standard treatment.**

Other question

When the lymphoma or cancer comes first and chemotherapy leads to immune suppression, how can you decide if the patient actually has a primary immune defect?

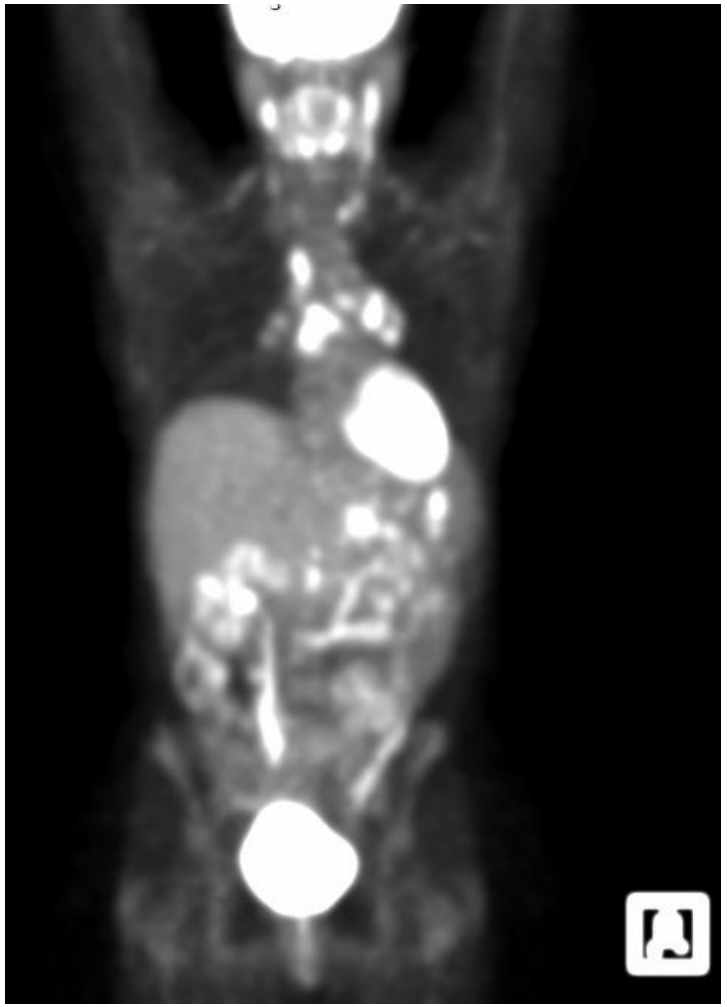
Clues that the primary immune defect was present - before the cancer

- History of significant infections in the past.
- History of enlarged spleen or lymph nodes.
- Genetic mutation found in immune deficiency is found.
- Family history of immune deficiency.

43 year old woman recent dx “CVID”

- 2011, profound fatigue, diarrhea, abdominal pain. CT scan revealed a mass on her left kidney.
- Partial nephrectomy = MALT lymphoma.
- 2012, Rituximab.
- 2013, IgG 253 mg/dL, IgA 16 mg/dL, IgM 47 mg/dL.
- Diagnosed with CVID.
- 2015, feeling poorly with fatigue and itching;
- PET scan several positive lymph nodes. Treated with bendamustine and rituximab
- 2017, worsening symptoms of itching and bruising. PET scan positive lymph nodes.
- 2017, Night sweats.
- A mediastinal lymph node biopsy: necrotizing granulomas.
- Treated with rituximab again.

- Now 49 and well, working as a teacher



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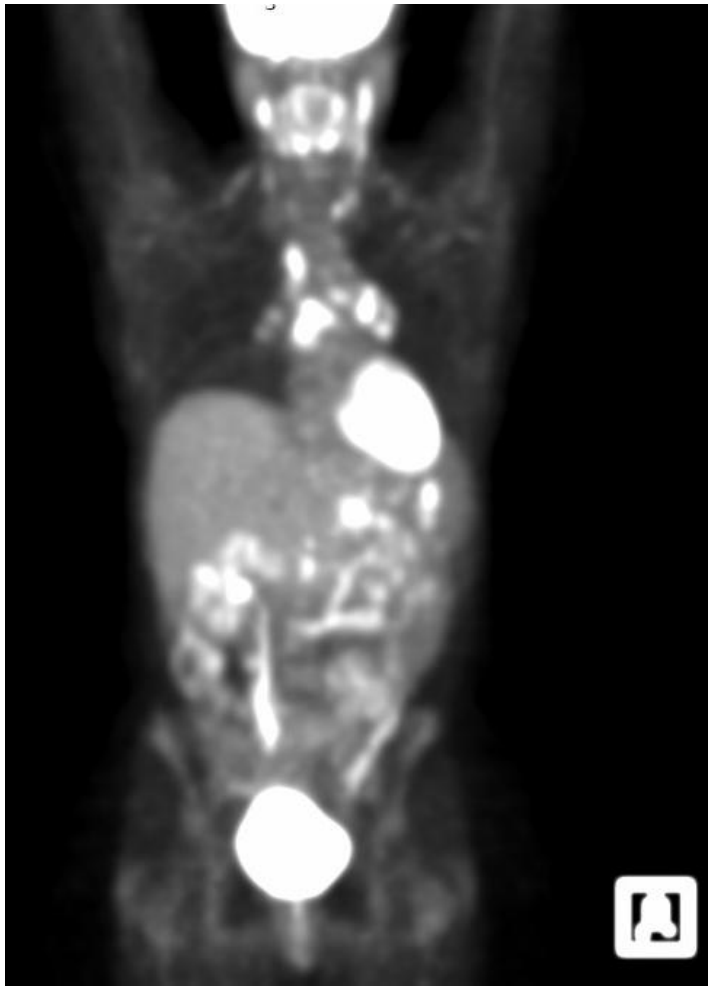

We will not be able to determine if she had the immune defect before the lymphoma

Conclusions

- Patients with primary immune defects have an increased in cancers overall.
- This is due to a number of reasons, defective immune surveillance, reduced clearance of abnormal cells, genetic defects.
- Patients with defects of antibody production have an increased incidence of lymphoma.
- Most are B cell in type, only a few are EBV+.
- Lymphoma leads to both morbidity and mortality.
- They may be more likely in subjects with other inflammatory conditions.
- Genetic defects are noted in about 30% of CVID subjects but aside from *PI3KCD*, none are clearly associated with lymphoma.
- If a lymphoma is noted first and treated, it can be difficult, or impossible, to decide if a patient has underling CVID.
- Many patients do well with standard chemotherapy including rituximab.

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