FONDAZIONE ITALIANA LINFOMI

Errori congeniti dell'immunità e linfomi (nell'età adulta)

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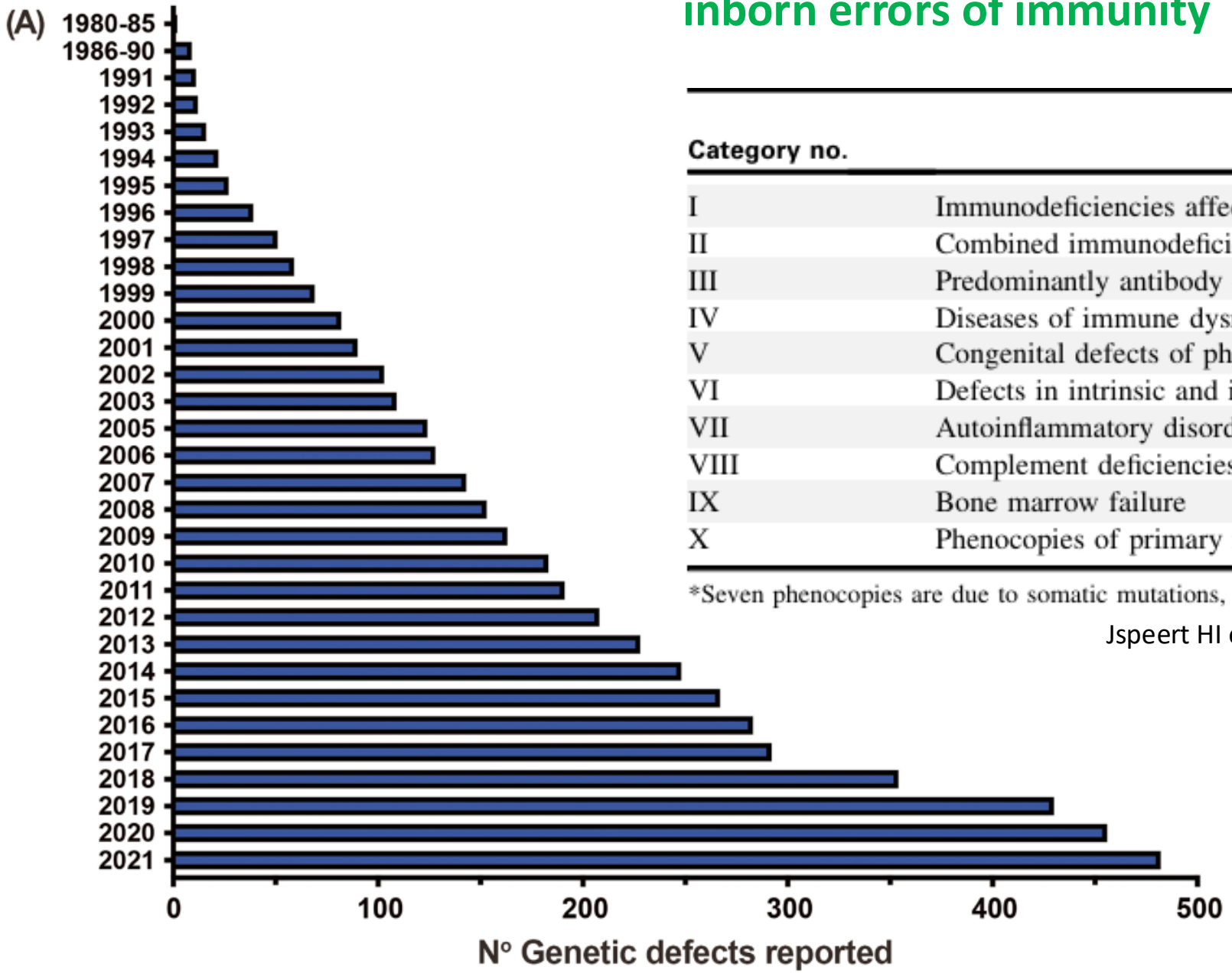
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gentili					x		
Lilly					x		
Janssen						x	
Incyte					x		
Takeda						x	
Sanofi					x		
Kiowa Kyrin					x		
Abbvie					x		

Accumulative discovery of novel genetic defects underlying inborn errors of immunity



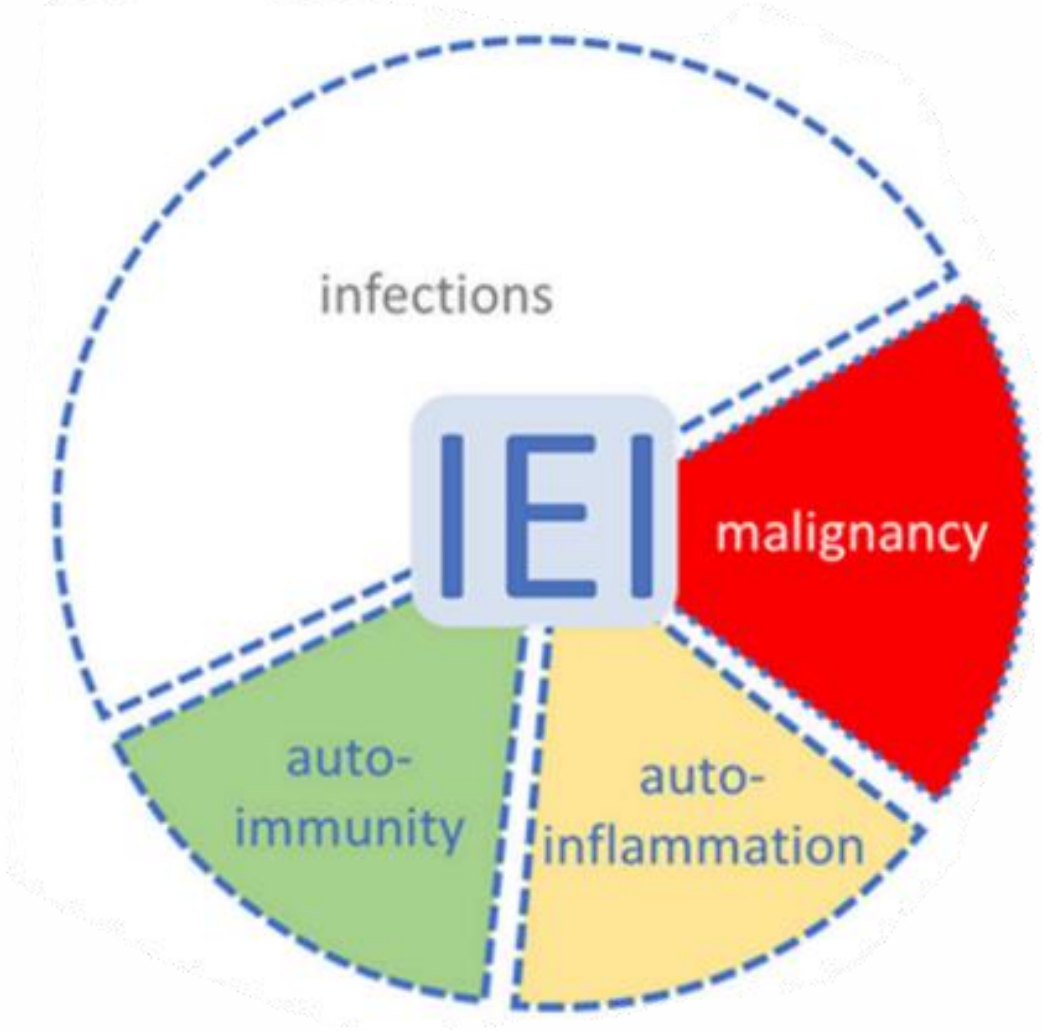
Category no.	Category
I	Immunodeficiencies affecting cellular and humoral immunity
II	Combined immunodeficiencies with associated or syndromic features
III	Predominantly antibody deficiencies
IV	Diseases of immune dysregulation
V	Congenital defects of phagocyte number, function, or both
VI	Defects in intrinsic and innate immunity
VII	Autoinflammatory disorders
VIII	Complement deficiencies
IX	Bone marrow failure
X	Phenocopies of primary immunodeficiencies

*Seven phenocopies are due to somatic mutations, with remaining 8 due to autoantibodies.

Jspeert HI et al. J All Clin Immunol 2025; 155: 740

Tangye SG et al. J Clin Immunol 2022; 42:1473–1507

Clinical challenging in Inborn Errors of Immunity



Bomken S et al. Front. Immunol. 2018; 9:2912

United States Registry

Cancers Type	Men	Women	Totals
Lymphoid cancer	41	41	82
Genitourinary cancer	7	7	14
Gastrointestinal cancer	9	5	14
Endocrine cancer	4	5	9
ENT cancer	5	1	6
Skin (NOS*)	10	15	25
Lung (NOS*)	2	3	5
Bone Cancer (NOS*)	1	1	2
Breast Cancer (NOS*)	0	10	10
Unspecified Primary	1	3	4
Totals	80	91	171

10-fold excess relative risk of **lymphoma** in men and 8-fold excess relative risk in women ($p<0.001$)

The age of onset/diagnosis of lymphoma ranged from 7 months to 76 years (median age: 12 years)

Mayor PC et al, J Allergy Clin Immunol. 2018; 141(3): 1028–1035

Articles selected for individual cases
N= 182
case series 32 ; individual cases 150
(corresponding to 386 patients)

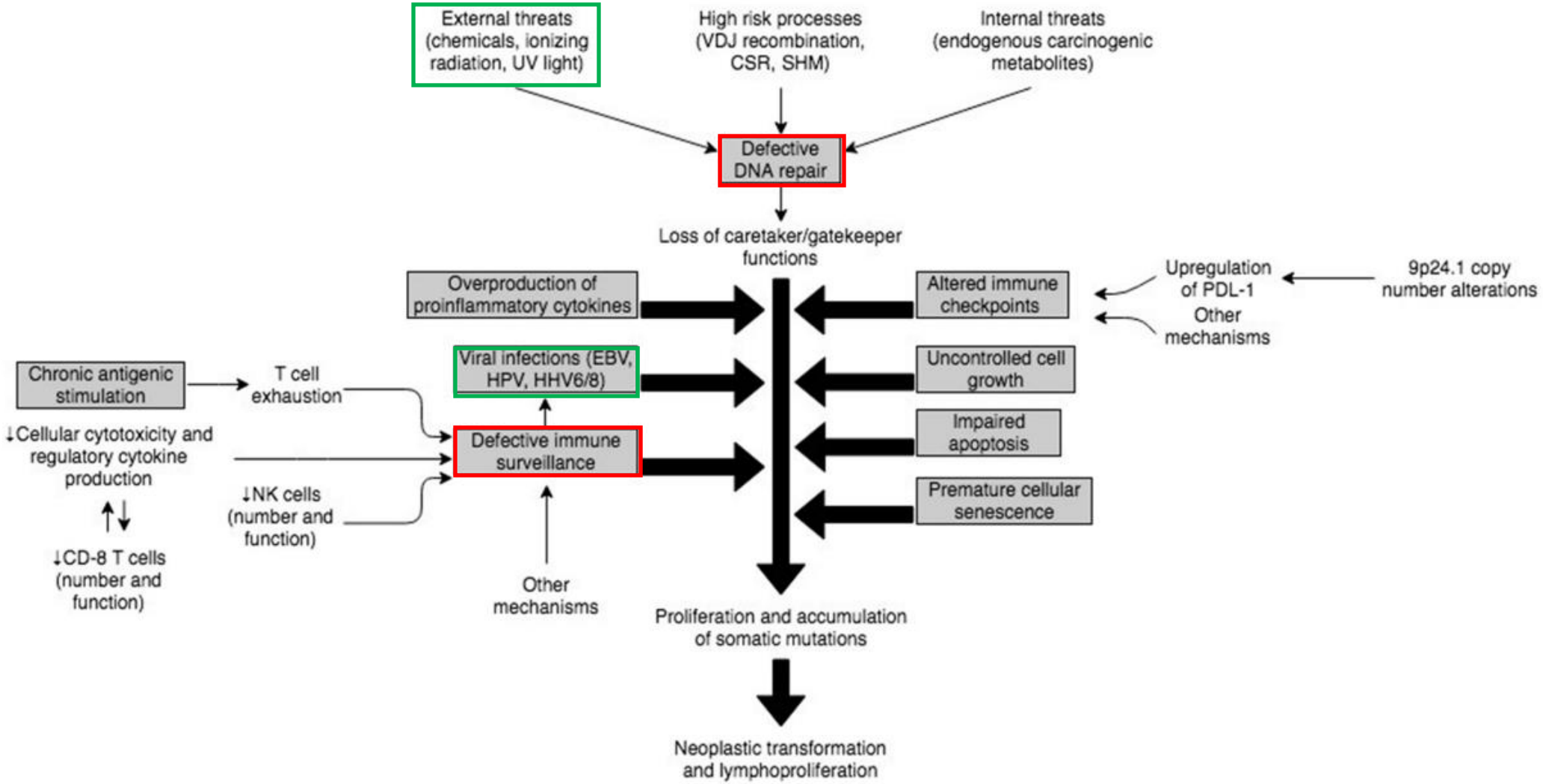
Primary immunodeficiencies and lymphoma: a systematic review of literature

Table 1. Characteristics of patients with lymphoma and PID.

Type of PID	Numbers of patients % N	Age of diagnosis (PID) % (median; IQR)* N	Age of diagnosis (lymphoma) % (median; IQR) N	Female % N	Familial cases (PIDs) % N	Known mutations % N	Benign LP % N	AI % N	Infections (opportunistic, severe, or recurrent) % N
Overview									
Total	386	8.5 (9; 30)	12 (6; 22.2)	40.2 (129/321)	17 31/182	30.1 (77/255)	18.7 (32/171)	8.8 (34/384)	74.5 (137/184)
B-Cells PIDs									
Total	28.2 109	28 (8.5; 43.5) 71/ 109	31 (12; 46.7) 102/109	50.5 52/106	20.3 14/69	7.5 5/67	25.4 15/59	33.9 20/59	77.8 42/54
B-cell CVIDs	78.3 83	30 (10.5; 44) 60/83	35 (16; 50.3) 81/83	54.9 45/82	17.3 9/52	5.4 3/55	29.8 14/47	36.2 17/47	88.1 37/42
Other B-cell deficiencies	23.8 26	12 (2; 34.75) 12/ 26	14 (6; 21) 21/26	29.1 7/24	29.4 5/17	16.7 2/12	8.3 1/12	25 3/12	41.7 5/12
T-Cells PIDs									
Total	57 220	5.5 (0; 15.5) 88/220	10 (6; 17) 197/220	40.5 64/158	35.3 41/116	30 39/130	7.9 9/114	7 7/100	71.8 74/103
SCID	7.2 17	0 (0; 1) 11/17	1 (0; 3.5) 16/17	53.3 8/15	35.7 5/14	60 9/15	9.1 1/11	16.7 2/12	91.7 11/12
CID	1.4 3	5.5 (5; 6) 2/3	11 (6.5; 11.5) 3/3	100 3/3	100 2/2	100 3/3	50 1/2	50 1/2	100 2/2
Others T-cells PIDs	90.9 200	6 (2 ;15,5) 75/ 200	12 (16; 17) 177/200	37.8 53/140	34 34/100	24.1 27/112	6.9 7/101	4.6 4/86	68.5 61/89
Innate deficiencies	14.2 55	7 (2.75; 15.5) 28/55	6 (3; 14) 53/55	21.8 12/55	51.1 23/45	54.5 30/55	26.7 8/30	30.4 7/23	87.5 21/27
Unclassified deficiencies	0.5 2	4,25 (2.5; 6) 2/2	2.5 (2.5; 2.5) 2/2	50 1/2	100 2/2	100 2/2	0 0/1	0 0/2	100 1/1

Herber M et al. Leukemia & Lymphoma 2020; 61

Potential interplay of mechanisms implicated in pathogenesis of lymphoid malignancies in PIDs



Riaz I et al. Front. Immunol. 2019: 10: 777

EBV induced LPDs

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T-cell proliferation defects

CTPS1
RASGRP1
ITK
CD27
CD70
TNFRSF9

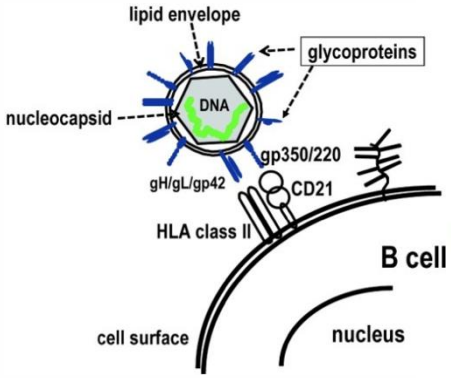
B-LPD

Hyperplasia

Polymorphic | Polyclonal | Polytypic

Monomorphic | Monoclonal | Monotypic

Lymphoma



Expansion phase

T-cell proliferation (clonal expansion)

EBV

T-cell cytotoxicity

Contraction

Memory T Cells

Normal Immune Response

Effector phase

T-cell cytotoxicity/ degranulation defects

UNC13D, STX11
STXBP2, RAB27A
LYST
SH2D1A

-IFN-γ ↑
-macrophage activation

HLH

myeloid function defect(s) (inflammasomme defect)

XLP2 *(XIAP)*

Latour S et al.Immunological Reviews. 2019;291:174–189

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Most prevalent cancer types formation among patients with IEI

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Disease	Genetic defect or probable pathogenesis	Inheritance	Mechanism of malignancy formation	Type of malignancy
Combined immunodeficiencies				
Severe combined immunodeficiency	Mutations in *IL2RG*, *JAK3*, *IL7RA*, *RAG1*, *RAG2*, *DCLRE1C*, *CORO1A*, *CD3D*, *CD3E*, *CD3Z*, *PTPRC*, *PRKDC*, *ADA*, and *AK2*	AR in most cases, also XL	Probably impaired function of immune system and decreased viral clearance (EBV)	NHL, Hodgkin lymphoma, leukemia Multiple renal and pulmonary leiomyomata EBV-associated lymphoma (Artemis) Burkitt lymphoma (ADA deficiency treated with PEG-ADA)
ITK deficiency (an EBV-associated lymphoproliferative disease)	Mutations in *ITK* (IL-2-inducible T cell kinase)	AR	Impaired function of immune system, decreased viral clearance (EBV)	Lymphoma
MAGT1 deficiency (ie, XMEN)	Mutations in *MAGT1* (magnesium transporter 1)	XL		Lymphoma
Well-defined syndromes with immunodeficiency				
Wiskott-Aldrich syndrome	Mutations in *WAS*	XL	Impaired function of immune system, decreased viral clearance (EBV), probably impaired genetic stability	Diffuse large B cell lymphomas, NHL of larynx, leukemia, cerebellar astrocytoma, Kaposi sarcoma, smooth muscle tumors
Ataxia-telangiectasia	Mutations in *ATM*	AR	Impaired genetic stability	Lymphoid leukemias, lymphomas (both B and T cell, NHL), epithelial tumors
Nijmegen breakage syndrome	Mutations in *NBS1*	AR	Impaired genetic stability	Brain tumors, lymphomas (both B and T, NHL, DLBCL and T-LBL), leukemia
Cartilage-hair hypoplasia	Mutations in *RMRP*	AR		NHL basal cell carcinoma
Autosomal dominant hyperimmunoglobulin E syndrome (AD-HIES)	Mutations in *STAT3*	AD		NHL, squamous cell carcinoma of the vulva, pulmonary adenocarcinoma with liver, bone, and spinal cord metastases
AR-HIES (DOCK8 deficiency)	Mutations in *DOCK8*	AR	Probably defective tumor suppression genes in DOCK8 deficiency	Squamous cell carcinoma, cutaneous T cell lymphoma/leukemia, Burkitt lymphoma
Predominantly antibody deficiencies				
X-linked agammaglobulinemia	Mutations in *BTK*	XL		Lymphoproliferative disorders, gastric adenocarcinoma, colorectal cancer
Common variable immunodeficiency	Unknown in most cases, mutations in *TNFRSF13B* (encodes TACI), *TNFRSF13C* (encodes BAFF-R), CD19, CD20, CD81, and ICOS	Variable	Probably defective tumor suppression genes	NHL, epithelial tumors (carcinomas of stomach, breast, bladder, cervix), carcinoma of the vulva (ICOS deficiency), tonsillar carcinoma of epithelial origin (TNFRSF13B)
X-linked hyperimmunoglobulin M syndrome	Mutations in *CD40L*	XL	Probably defective clearance of Cryptosporidium	Carcinomas of the liver, pancreas, biliary tract and associated neuroectodermal endocrine cells
IgG subclass deficiency	Unknown	Variable		Lymphoma
Selective IgA deficiency	Unknown	Variable		Lymphoma, gastrointestinal carcinoma

Less severe defect of Immune system can be undiagnosed in younger age

CVID epidemiological evidence suggests there may be two peaks of diagnosis, one during childhood prior to age 10, and the second during adulthood peaking at the third to fourth decade of life

Lymphoma as an Exclusion Criteria for CVID Diagnosis Revisited

Authors hypothesized that lymphoma could
be the revealing symptom of an underlying primary immunodeficiency (PID)

Within a French cohort of adult patients with **hypogammaglobulinemia** (**225 pts**), **47** patients who developed a **lymphoma** either during follow-up or before the diagnosis of hypogammaglobulinemia were identified

	Hypogamma first	Lymphoma first	*p*-value
Number	22	25	
Sex: male/female	13/9	13/12	0.77
Age at hypogammaglobulinemia diagnosis (median, years)	34	33	0.97
Age at lymphoma diagnosis (median, years)	44	31	0.007
Consanguinity (nb, %)	3 (14%)	5 (20%)	0.71
Familial history of immune deficiency	5 (23%)	6 (24%)	1
CVID-like phenotype	7 (32%)	12 (48%)	0.37
HGUS	3 (14%)	1 (4%)	0.33
LOCID	12 (55%)	12 (48%)	0.77
Disease-related complications (nb, %)	17 (77%)	17 (68%)	0.53
Serum IgG (median, g/L)	2.4	3.1	0.60
Serum IgA (median, g/L)	0.10	0.30	0.43
Serum IgM (median, g/L)	0.30	0.26	0.19
EUROclass (nb, %)			0.58
$CD19^+$ B cells $< 1\%$	7 (32%)	6 (24%)	
$CD19^+$ B cells $> 1\%$ and smB + cells $\leq 2\%$	10 (46%)	15 (60%)	
$CD19^+$ B cells $> 1\%$ and smB + cells $> 2\%$	5 (23%)	4 (16%)	
$naCD4^+$ T cells $< 20 \times 10^6$/L	9 (41%)	7 (28%)	0.38
Genetic diagnosis	3 (14%)	7 (28%)	0.30
1st lymphoma pathology			0.003
DLBCL	7 (32%)	8 (32%)	
MALT	7 (32%)	0 (0%)	
Other B-cell NHL	4 (18%)	3 (12%)	
T-cell lymphoma	2 (9%)	2 (8%)	
Hodgkin lymphoma	2 (9%)	12 (48%)	
Lymphoma EBV status (positive/tested, %)	5/13 (38%)	8/16 (50%)	0.71
> 1 distinct lymphoma during follow up	1 (5%)	5 (20%)	0.19

genetic analyses identified a molecular diagnosis in 10/47 (21%)

Allain V et al. Journal of Clinical Immunology (2023) 43:181–191

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Case History

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SID Masking PID in a Patient With Lymphoma

2003 : 67-year-old female

History of recurrent respiratory infections from childhood, one episode of pneum

Present: multiple lymphadenopathies in several regions, including the lung and b
Inguinal node biopsy found **stage IV-B follicular lymphoma**

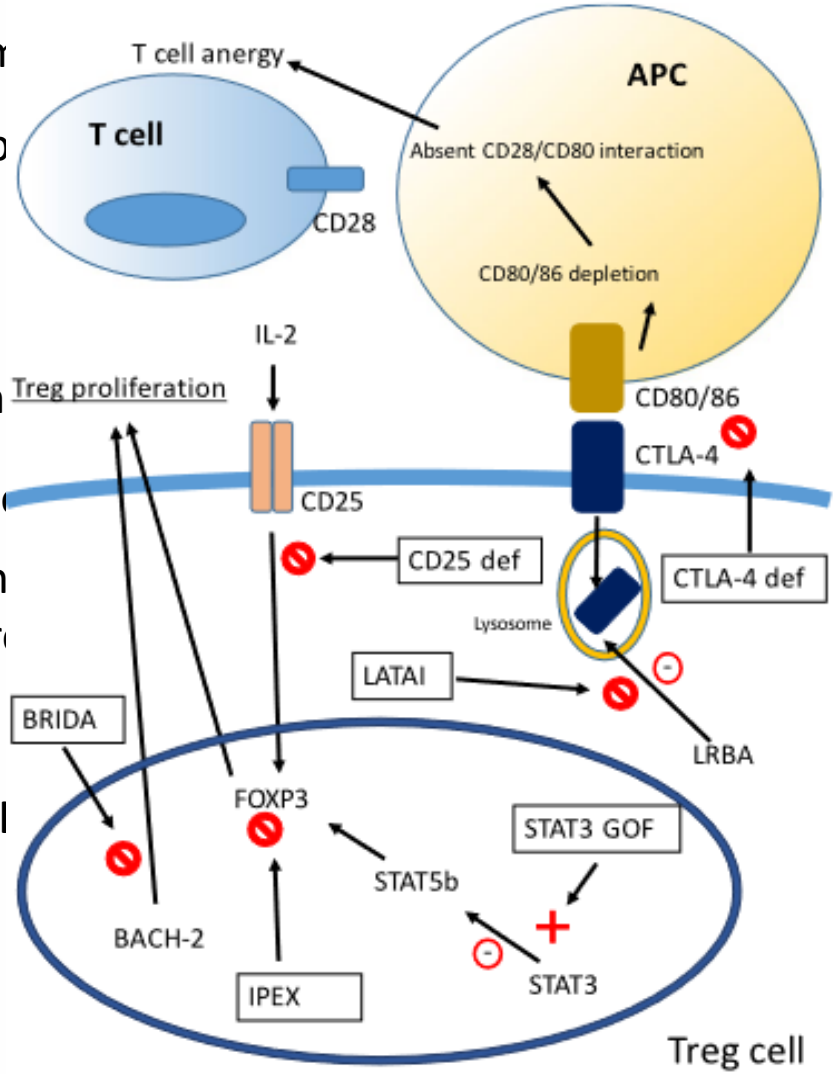
Treatment: fludarabine, cyclophosphamide and rituximab (FCR) → CR

2006: recurrence of lymphoma (POD24) and received 4 rituximab followed by m

2016: Referred to the Immunology department due to severe panhypogammagl

- Functional (specific) antibody response was normal after immunization (Pneumo-23) and anti-tetanus toxoid antibodies….. but she was on Ig-r
  In contrast, the response to anti-Salmonella typhi was low
- Due to **chronic diarrhea**, severe malnutrition and low bodyweight, she which revealed marked villous atrophy → severe **celiac-like entero**
- In the meantime **recurrent herpes zoster** infections were diagnosed
  → Immune dysfunction and dysregulation of T cells

Exome analysis revealed a homozygous LRBA variant (LRBA): c.3076C>T (p.Gln



Lymphoma appears to be the first manifestation of IEI in about 10% of the cases

Ballow M et al. Front. Immunol. 2022; 13:928062

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When should you screening for IEI in new lymphoma cases?

- a personal previous history of recurrent unusual infections, in terms of severity, or frequency or of severe or unusual therapy associated toxicity
- a family history of known inherited conditions, strong infectious or cancer history or a consanguineous parental relationship
- unusual presentations of malignancy, unusual sites of disease or unusual characteristic cyto-/molecular genetics

Why should you make a screening for IEI in new lymphoma cases?

- ✓ Improve understanding of toxicities following conventional chemotherapy or radiotherapy, prevent infectious comorbidities that can be severe, even lifethreatening, avoid unnecessary irradiation
- ✓ Define specific prophylaxis, supportive care, punctual cancer screening and promote a correct lifestyle, psycological support…
- ✓ Define initial therapy and dose modification and possible early evaluation of timing and delivery of HSCT

Treatment and prognosis

Lymphoma in immunodeficient and immunocompetent patients

Are they the same disease, with the same characteristics and behaviour ?

Lymphoma subtypes in ID patients

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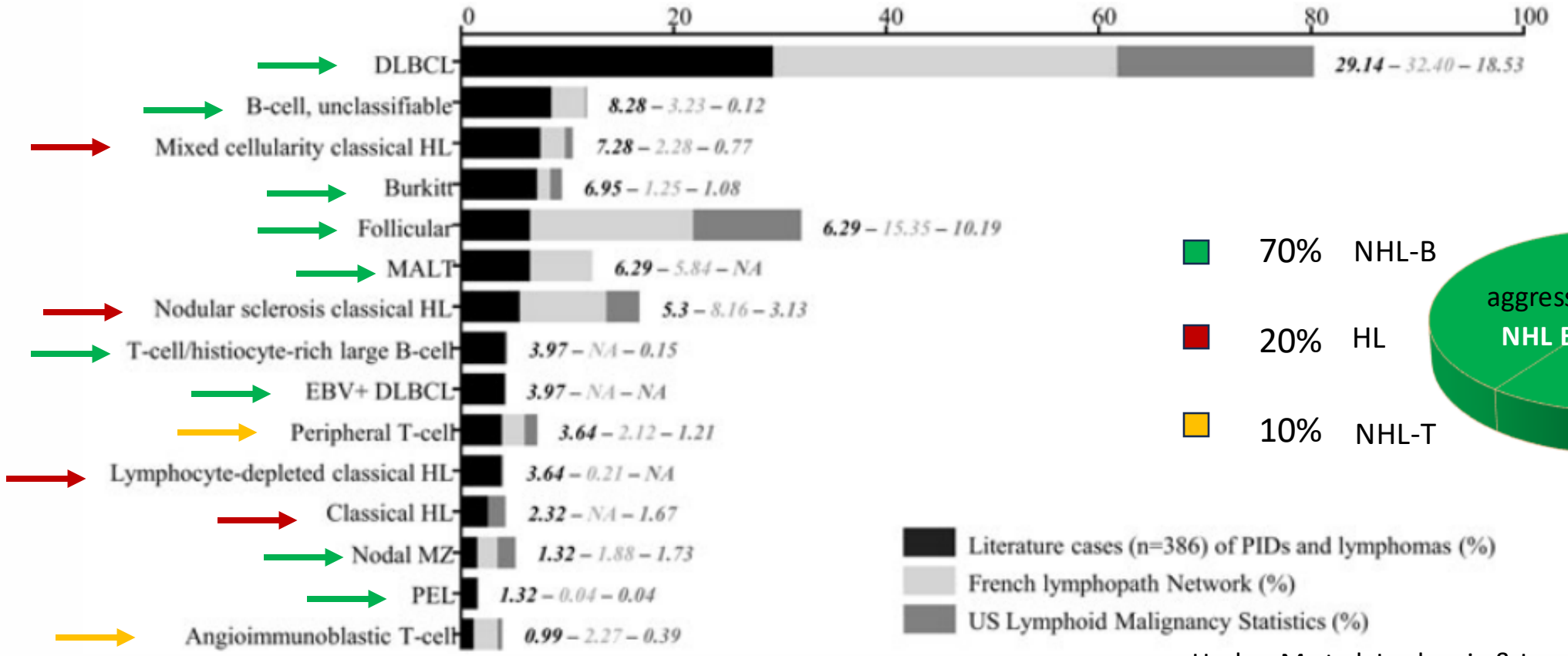
Lymphomas account for two-thirds of all malignancies reported in PIDD patients, which include **non-Hodgkin's lymphoma** (NHL) in about 80% and **Hodgkin's lymphoma** in 20%.

The vast majority of lymphomas reported in the context of PIDDs are **B cell lymphomas**



Herber M et al. Leukemia & Lymphoma 2020; 61

Clinical common features of Immunodeficiency-associated lymphoproliferative disorders

- ✓ A tendency to present in extranodal sites, especially the central nervous system and gastrointestinal tract
- ✓ A rapid clinical progression when untreated
- ✓ B-cell origin with frequent diffuse large cell histology
- ✓ A polymorphic cell population
- ✓ Common association with Epstein Barr virus (EBV) in 30–60%

Prognosis

The prognosis for patients with IEI and cancer is **generally worse** than the prognosis of patients with the same malignancies in the general population.

Management of cancer can be challenging in these individuals compared with immunocompetent patients, since they are more likely to develop widespread cancer requiring **more aggressive** cytotoxic therapies, and they are more likely to develop **life-threatening infections** and end-organ damage

The increased risk of infection leads to individual modulation of the chemotherapeutic dosage due to the inability of patients with IEI to tolerate standard dose

Salavoura K et al. Anticancer research 2008; 28: 1263-1270

Treatment

Patients with lymphoma and IEI can receive the same chemotherapy protocols used in immunocompetent individuals with a similar malignancy

Supportive care and Particular warnings:

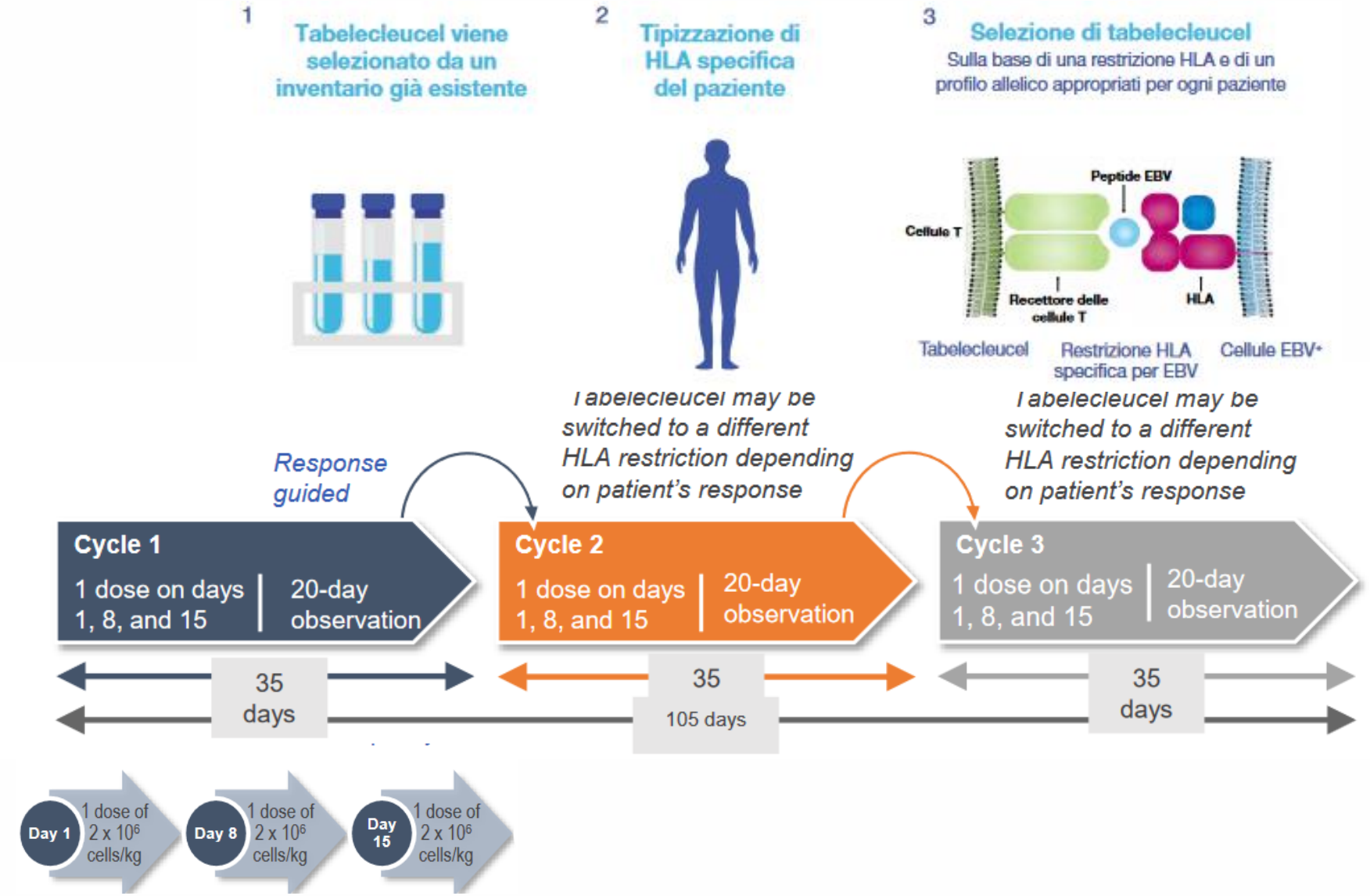
- Prophylaxis with immunoglobulin replacement and careful antimicrobial drugs
- Prompt treatment of active infections with broad-spectrum antibiotics and long treatment durations
- Evaluate the opportunity to modulate dose treatment
- Dose modification or omission altogether of alkylating agents and radiation in patients with particular disorders
- Allogeneic hematopoietic stem cell transplantation (HSCT) as a potentially curative therapeutic option

Inhibitors of EBV replication and mechanism of action

Strategies to inhibit EBV replication	Common therapies	Mechanism of action
Reduction of immunosuppressants	Calcineurin inhibitors, anti-metabolite agents	Restores T-cell function and enhances the EBV-specific T-cell response
Nucleoside analogs	Acyclovir, valacyclovir, ganciclovir, valganciclovir	Inhibits herpesvirus DNA polymerase[3]
HDAC inhibitors	Valproic acid, nanatinostat	Induces EBV lytic reactivation and triggers apoptotic cell death
EBV-specific cytotoxic T-lymphocyte therapy	Tabelecleucel	Travels through microvascular wall, expands upon contacting tumor cell target antigens, and destroys tumors via cytotoxic effectors[1]
Monoclonal antibodies	Rituximab	Destroys cells bearing CD20 antigen, which host the virus

Ford M et al. Current Hematologic Malignancy Reports 2023; 18 226–23

Tabelecleucel, an off-the-shelf EBV-specific T cell Immunotherapy in EBV-associated diseases (NCT04554914)



Errori congeniti dell'immunità e linfomi nell'adulto

Unmet need and future directions

1. Careful evaluation of the warning signs and development of screening tools suitable for identification of IEI at diagnosis of lymphoproliferative disease

2. Develop consensus guidelines for initial therapy, dose modification and supportive care, dependent on underlying IEI

3. Prospective studies addressing the timing and delivery of HSCT dependent on underlying IEI

4. Understand the role of Immunetherapies

5. Develop multidisciplinary expert team to improve management of adult patients with IEI

Bomken S et al. Front. Immunol. 2018; 9:2912

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Chi *ricerca* *ama*

Insieme contro i linfomi

Thank you For the attention!

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Proposed unifying nomenclature of Immunodeficiency-Associated LPDs

Society for Hematopathology and the European Association for Haematopathology

3-Part unifying nomenclature		
Name of lesion	**Viral status**	**Specific immunodeficiency setting**
B-cell hyperplasia (eg, plasmacytic hyperplasia)	eg, EBV$^{+/-}$, HHV8$^{+/-}$	eg, Posttransplant (solid organ), iatrogenic (methotrexate), immune senescence Inborn errors of immunity (…)
Polymorphic B-cell lymphoproliferations (eg, mucocutaneous ulcer)		
Lymphoma (WHO terminology) (eg, diffuse large B-cell lymphoma, Anaplastic large cell lymphoma, ALK^{-})		

Natkunam Y et al.Blood. 2018;132(18):1871-1878

The 5th edition of the WHO Classification of lymphoid Tumours

Histological diagnosis	Viral association	Immune deficiency/dysregulation setting
∘ Hyperplasia (specify type) ∘ Polymorphic lymphoproliferative disorder ∘ Mucocutaneous ulcer ∘ Lymphoma (classify as for immunocompetent patients)	∘ EBV +/− ∘ KSHV/HHV8 +/−	∘ Inborn error of immunity (specify type) ∘ HIV infection ∘ Posttransplant (specify: solid organ/bone marrow) ∘ Autoimmune disease ∘ Iatrogenic/therapy-related (specify) ∘ Immune senescence

This nomenclature underlines the concept that similar lesions are present in different immunodeficiency settings

Patients with IEI may develop distinctive types of lymphoid proliferations unique largely dependent on the immune dysregulation conferred by the germline aberration underlying a respective IEI.

Therefore, they have been incorporated into the overarching framework and nomenclature of “lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation.”

Alaggio R et al. Leukemia (2022) 36:1720–1748

ESID

10 Warning Signs of PID - General

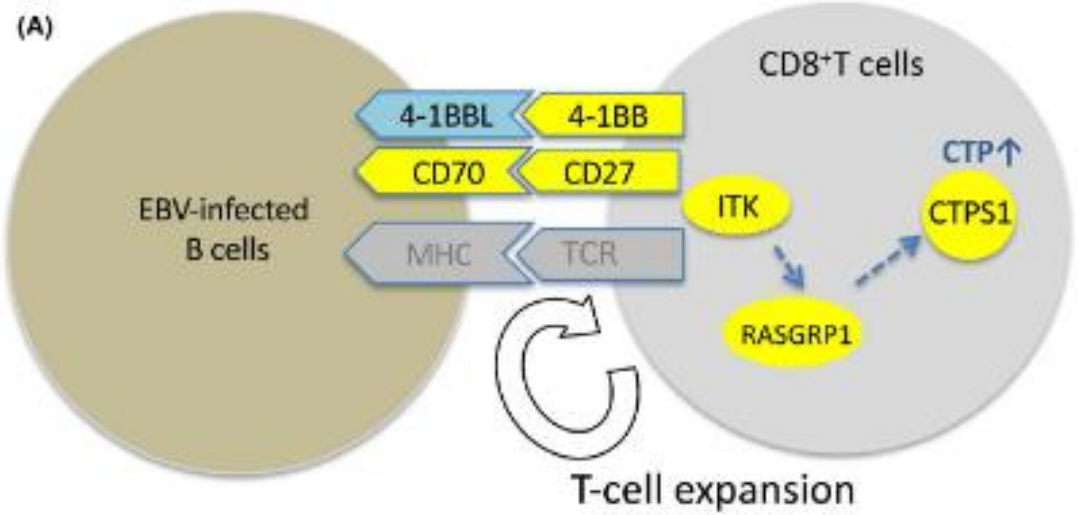
1) Four or more new ear infections within 1 year
2) Two or more serious sinus infections within 1 year
3) Two or more months on antibiotics with little effect
4) Two or more pneumonias within 1 year.
5) Failure of an infant to gain weight or grow normally
6) Recurrent, deep skin or organ abscesses
7) Persistent thrush in mouth or fungal infection on skin
8) Need for intravenous antibiotics to clear infections
9) Two or more deep-seated infections including septicemia
10) A family history of PI

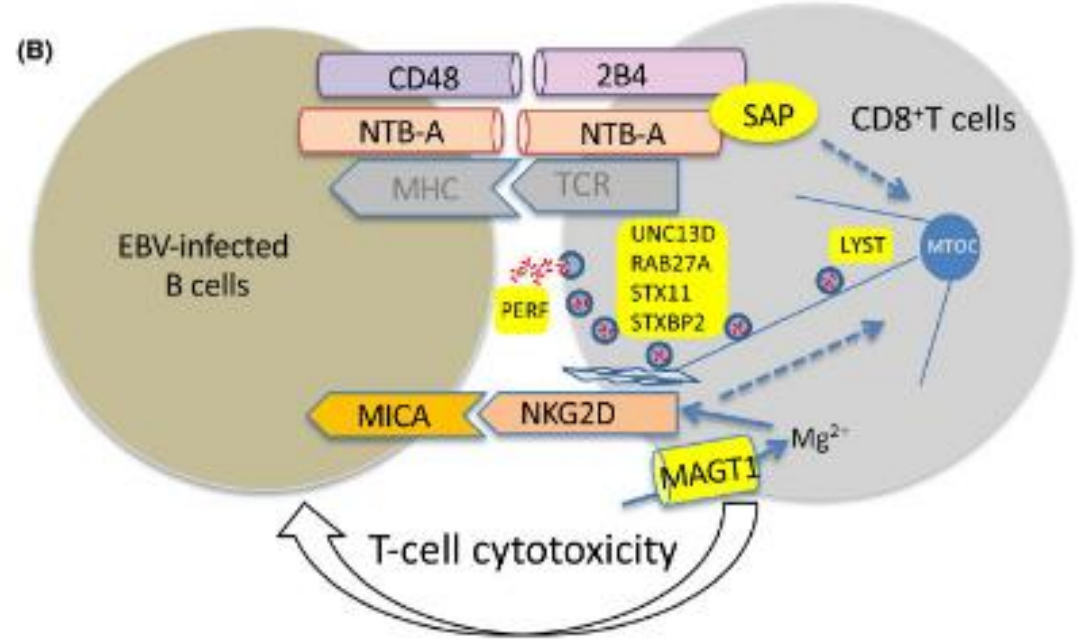
The Jeffrey Modell Foundations' 10 warning signs in adult of primary immune deficiency

1. ≥ 2 new ear infections within 1 year
2. ≥ 2 new sinus infections within 1 year, in the absence of allergy
3. 1 pneumonia per year for > 1 year
4. Chronic diarrhea with weight loss
5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. Recurrent need for IV antibiotics to clear infections
7. Recurrent, deep abscesses of the skin or internal organs
8. Persistent thrush or fungal infection on skin or elsewhere
9. Infection with normally harmless tuberculosis-like bacteria
10. A family history of PID

* The **Jeffrey Modell Foundation** (JMF) is an international, non-profit, organization dedicated to helping individuals and family members affected by primary immunodeficiency disorders

Defective signaling pathways in immunodeficiencies associated with high vulnerability to EBV infection





There are still **a number of patients with a high susceptibility to EB**V, in whom the molecular/genetic basis of their disease is **not known** and remains to be determined

We can speculate that these uncharacterized forms are caused by **defects in molecules/components involved in** T–B cell interactions and required for **T-cell cytolytic responses and/or T-cell expansion**

Latour S et al.Immunological Reviews. 2019;291:174–189