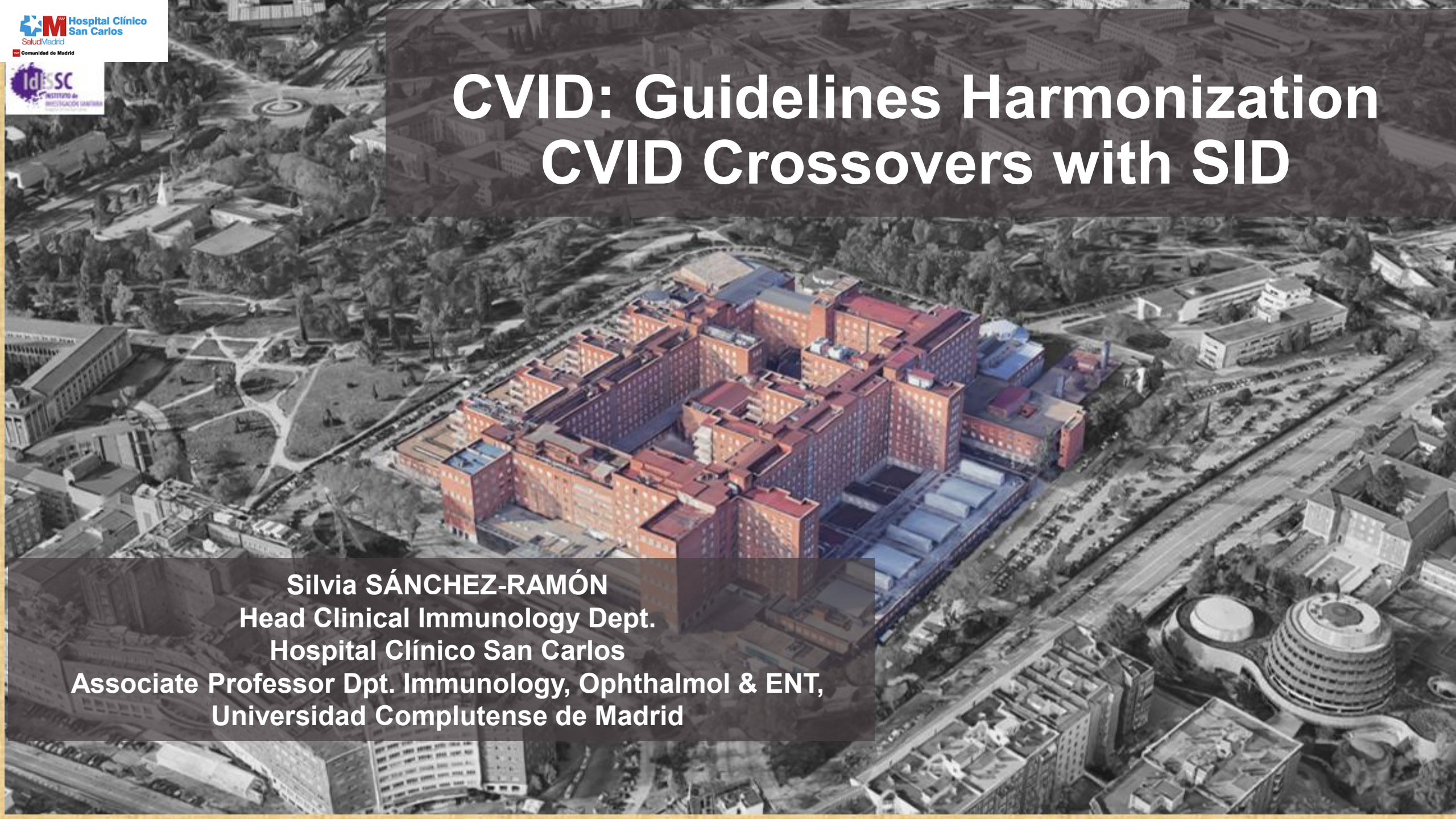
CVID: Guidelines Harmonization
CVID Crossovers with SID



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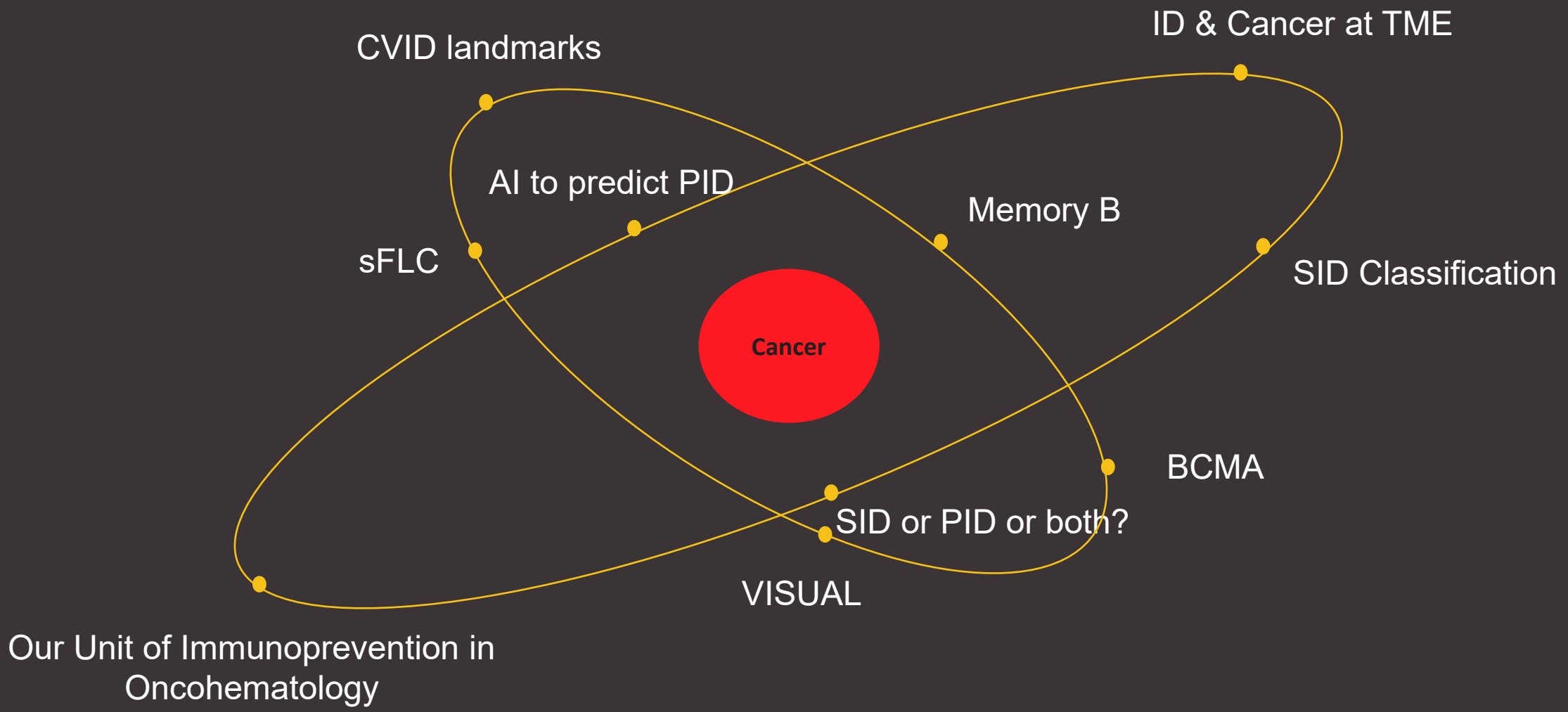
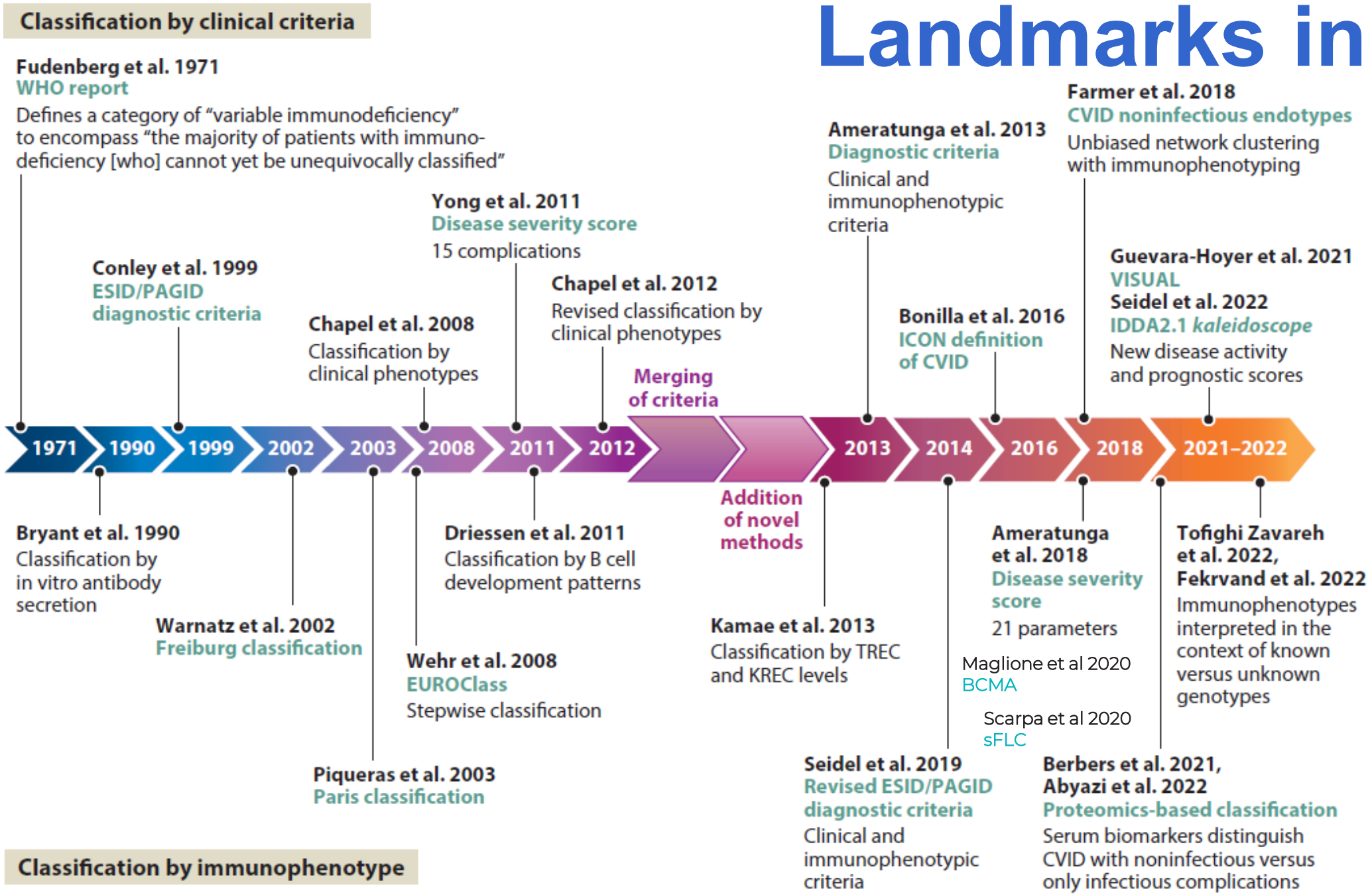
Spouse/partner	N/A

Agenda


CVID landmarks
ID & Cancer at TME
AI to predict PID
Memory B
sFLC
SID Classification
Cancer
BCMA
SID or PID or both?
VISUAL
Our Unit of Immunoprevention in Oncohematology

Landmarks in CVID

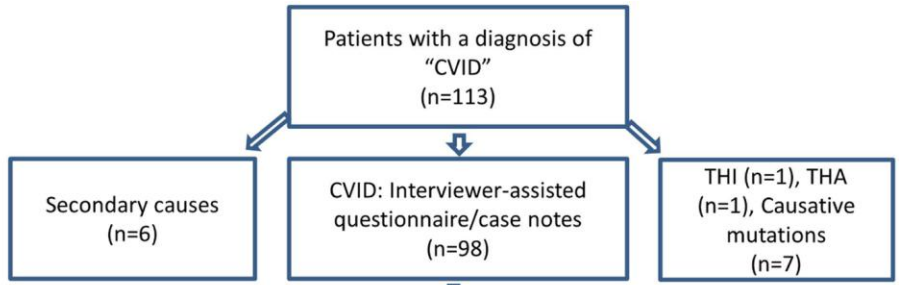


Adapted from Peng XP. Annu Rev Pathol 2023

CVID Diagnostic criteria

Criterion	Description
Serum Immunoglobulins	Marked decrease of IgG and IgA (with or without low IgM)
Age of Onset	Onset of immunodeficiency >2 years of age
Vaccine Response/ Isohemagglutinins	Poor/absent response to vaccines and/or absent isohemagglutinins
Exclusion of Secondary Causes	Exclusion of defined causes of hypogammaglobulinemia (e.g., protein loss, drugs, malignancy)
Exclusion of Monogenic Disorders	Exclusion of known monogenic immunodeficiencies (by genetic testing if indicated)
Clinical Features	Recurrent/severe infections, autoimmunity, lymphoproliferation, granulomatous disease
Immunological Features	Poor antibody production, abnormal B cell subsets (e.g., reduced switched memory B cells)

A.



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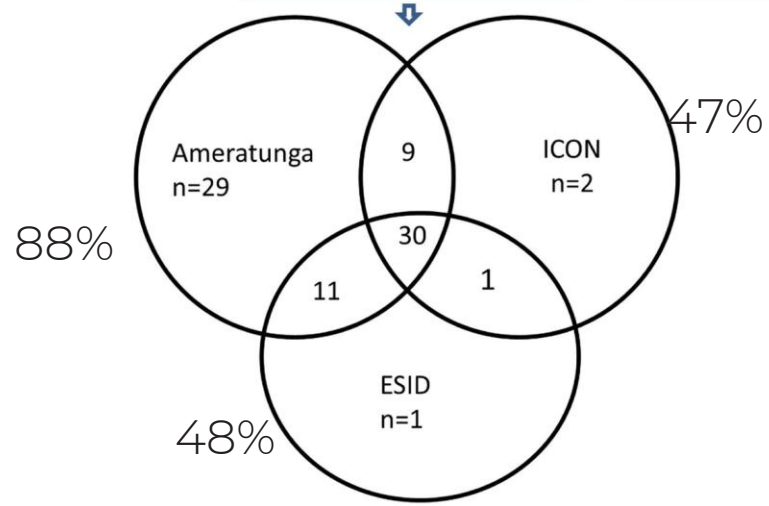


1. Seidel M. JACI Pract 2019. 2. Ameratunga R. Clin Rev Allergy Immunol 2021

How well can we diagnose and predict CVID course?

Wehr et al 2008
Sánchez-Ramón et al 2008
smB phenotype

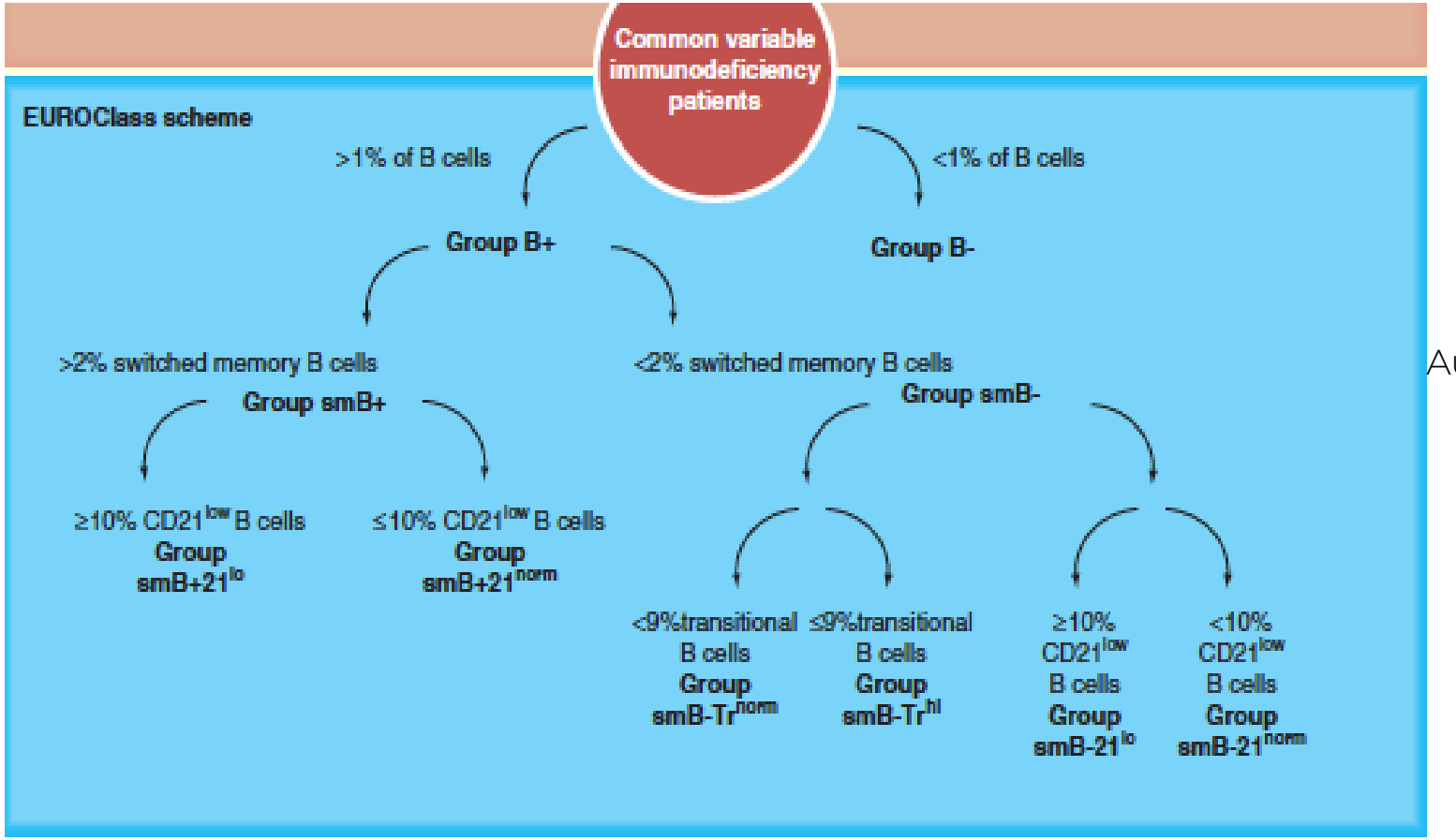
Maglione et al 2020
BCMA

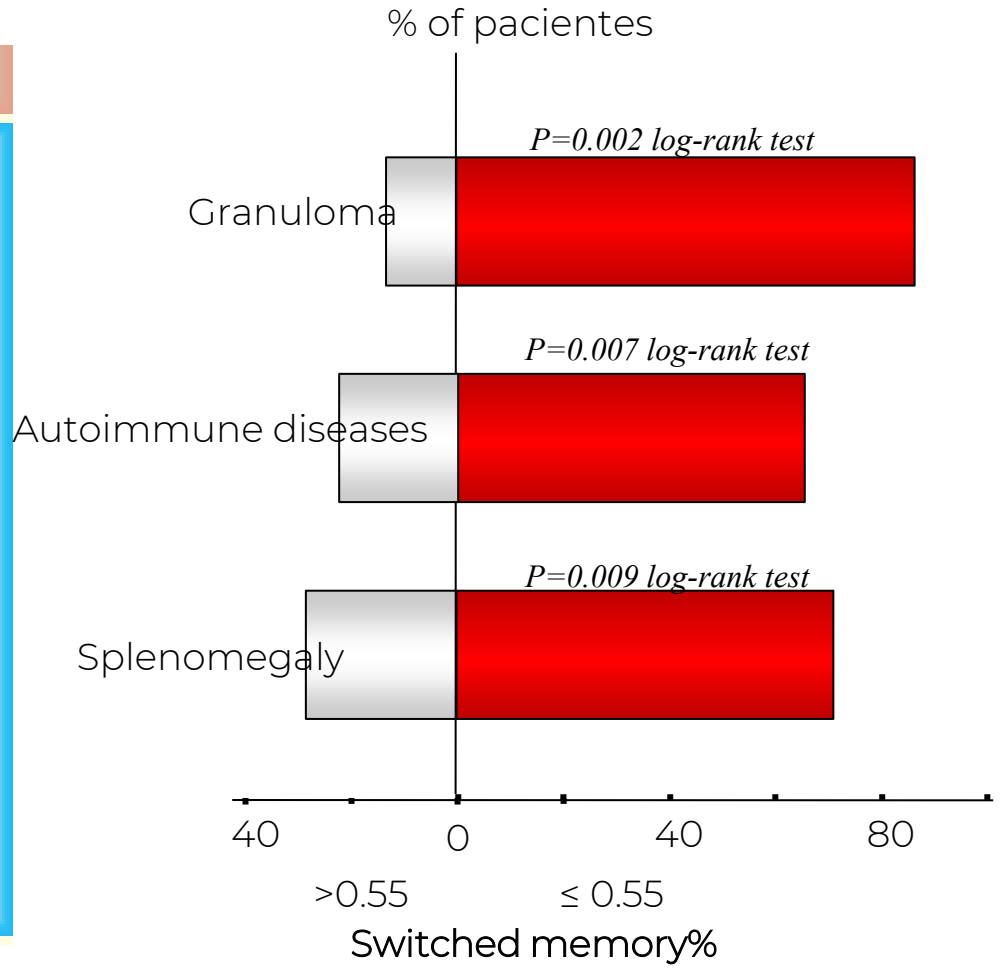
Scarpa et al 2020
sFLC

Guevara-Hoyer et al 2021
VISUAL

Impaired Switched-memory B cells in CVID

Current hallmark of CVID





. Common variable inmunodeficiency in adults: current diagnostic protocol and laboratory measure. Expert Rev. Inmunol. 9 (10). (2013). Sánchez-Ramón Clin Immunol 2008

CVID Severity scale by Ameratunga et al.

Parameter	Mild = 1	Moderate = 5	Severe = 10
CNS		Asymptomatic MRI changes, viral meningitis with no sequelae	Meningitis, CNS granulomatous or lymphocytic vasculitis, Cauda equina syndrome, Other CNS autoimmune disorders incl MS, Peripheral neuropathy including CIDP, Echovirus encephalitis, *Cryptococcal meningitis, etc.
Ocular		Uveitis responding to treatment	Sight threatening disease, e.g., keratitis, retinopathy, or retinal vasculitis
ENT/ORL	Otitis media, acute sinusitis, otitis externa	Chronic rhinosinusitis	Complicated mastoiditis (e.g., hearing loss, intracerebral sepsis) Autoimmune hearing loss
Pulmonary	Mild asthma, uncomplicated pneumonia	Mild GLILD, mild bronchiectasis, moderate-severe asthma, complicated pneumonia	Severe pulmonary dysfunction based on lung function tests, Extensive bronchiectasis, Severe GLILD, lung surgery (not biopsy). Pulmonary hypertension, Lung transplantation, Chest infections due to Pseudomonas*PJP,
Cardiac			
Gut/nutrition	Oral ulceration or glossitis r… treatment, oral candidiasis, … Helicobacter pylori respond… treatment, Uncomplicated Vitamin or mineral deficiency	… complicated vitamin or mineral deficiency.	Severe malnutrition e.g., BMI < 18, or failure to thrive (children)
Liver	Asymptomatic increase in liver enzymes.	Mild NRH, autoimmune hepatitis/granulomatous or viral hepatitis responding to treatment. Portal hypertension on imaging.	NRH with cirrhosis and/or symptomatic portal hypertension, Complicated/ unresponsive viral hepatitis. Liver transplantation. Severe AI hepatitis. Primary biliary cirrhosis,
Spleen	Asymptomatic splenomegaly	Splenectomy-(risk of sepsis) Symptomatic splenomegaly	
Renal	Uncomplicated UTI's	Granulomatous involvement of urinary tract on imaging	Chronic renal failure from e.g., renal vasculitis or granulomatous disease. Renal transplantation.
Hematological	Mild asymptomatic cytopenias,	Requiring treatment	Life threatening/Poorly responsive cytopenias e.g., requiring splenectomy or rituximab, HSCT
Lymph nodes Non-malignant	Mild lymphadenopathy	Extensive incl sarcoid-like granulomatous disorder	
Musculoskeletal	Arthralgia, myalgias, mild osteopenia Mycoplasma/ ureaplasma arthritis responding to treatment	Arthritis, other treatment responsive CTDs, myositis, severe osteoporosis,	Osteomyelitis, Severe CTDs e.g., requiring biologicals,
…		…	Systemic
…		…ency,	Hypophysitis, T1D
…		…	Pyoderma gangrenosum
…		…Alopecia, Vitiligo	
Malignancy			Present (CVID associated)

Mild	Moderate	Severe
1	5	10

Other infections	*Uncomplicated EBV or CMV viremia	Non-life threatening abscesses,	Sepsis, life-threatening abscesses. *CNS EBV/CMV lymphoproliferative disease, *disseminated fungal infection. *Disseminated adenovirus infection
Other autoimmunity	Uncomplicated pernicious anemia,	Sjogren's syndrome, anti-IgA antibodies. Cutaneous lupus	Severe SLE, APLS,
"Allergies" (including non-allergic conditions)	Rhinitis, mild eczema	Severe eczema, food allergies, Multiple antibiotic allergies Reactions to SCIG/IVIG	
Iatrogenic complications		Complications from long term steroids	Life-threatening complications e.g., CSF leak following sinus surgery. Hepatitis C from IVIG, complications from organ transplantation and HSCT, severe complications from immunosuppression
Misc and rare			Amyloidosis, HLH
Sundry			

Diapositiva cedida por K. Guevara

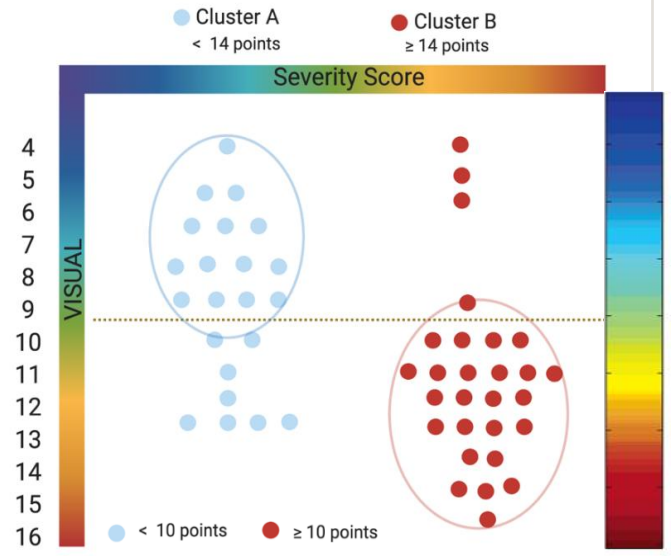
VISUAL score: Variable Immunodeficiency Score Upfront Analytical Link

VISUAL SCORE	1	2	3	4
smB lymphocytes (%)	Normal	< 8%	< 2%	< 1%
IgA (g/L)	Normal-2SD	< 2SD	-	< 0.07
IgM (g/L)	Normal	-	-	> 230
Specific Ab responses	Normal	Alterado ONLY to polysaccharide or protein Ag		Altered to polysaccharide and protein Ag
CD4+ T lymphocytes (µ/mL)	700-1,500	500-700	200-500	<200

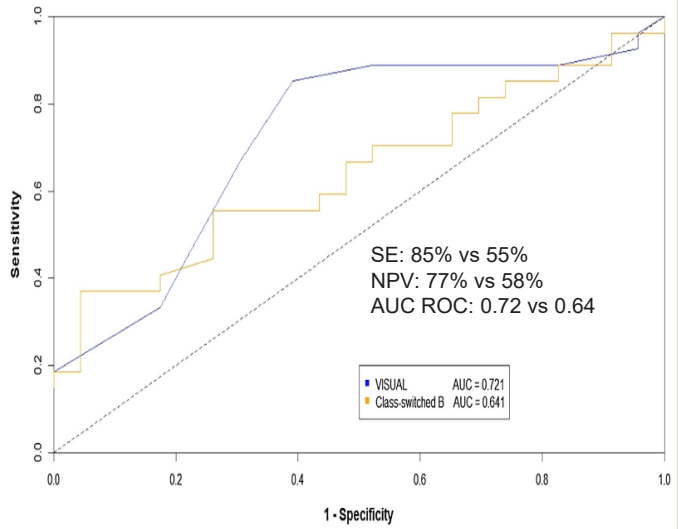
Guevara-Hoyer. Scientific Reports 2021

VISUAL score better predicted a bad CVID prognosis

VISUAL score ≥ 10 showed 8.94-fold higher odds of severe prognosis than below this threshold[1]

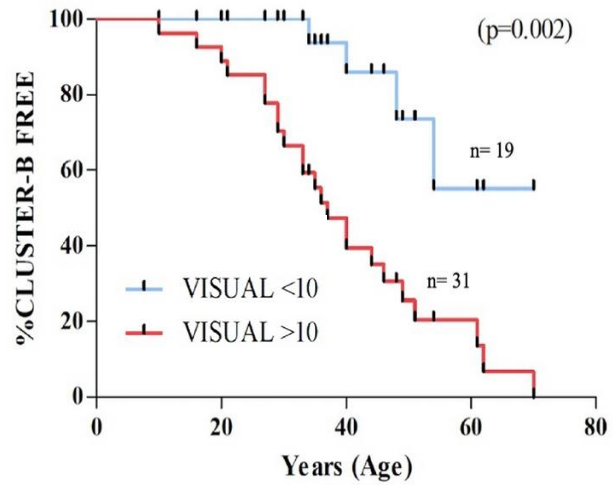


VISUAL provided a more accurate identification of clinically meaningful outcome than smB phenotype alone[2]



Patients with a VISUAL score ≥10 points progressed to cluster B faster than those with a VISUAL score <10[2]

Relationship between patient age and Cluster-B progression:



VISUAL ≥10 superior to smB phenotype (p=0.01)[2]
30% of 50 patients with CVID with bad prognosis would have not been detected by smB[2]

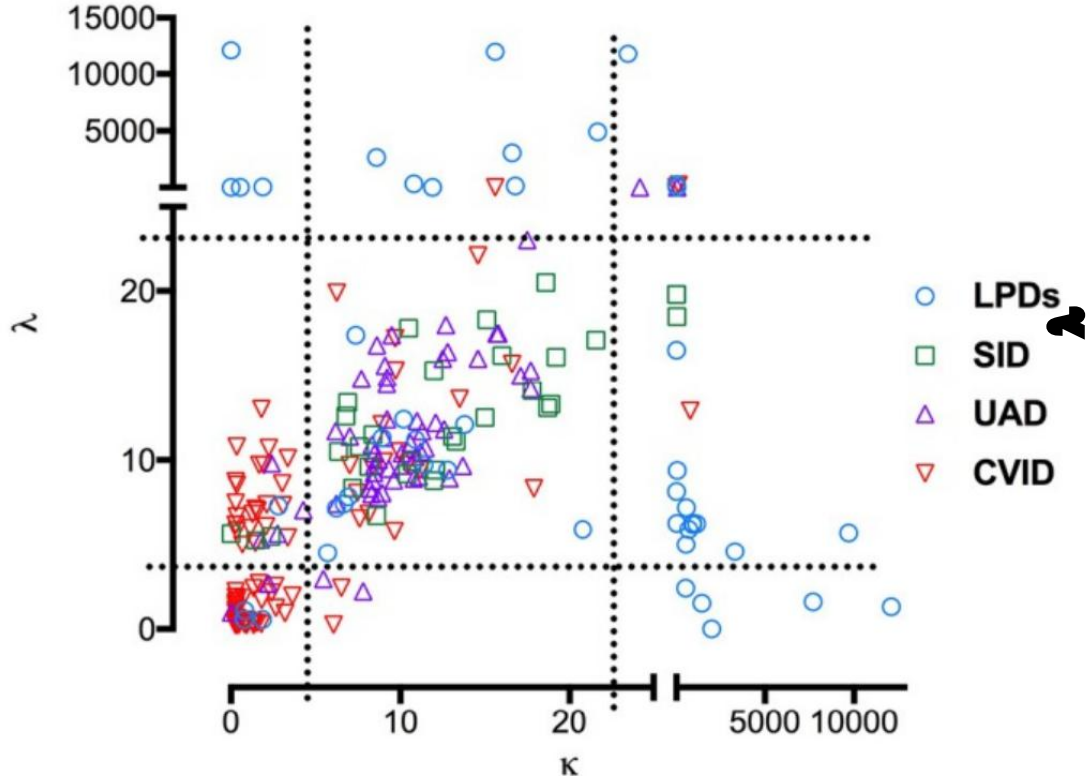
AUC, area under the curve; CVID, common variable immunodeficiency; NPV, negative predictive value; ROC, receiver operating characteristics; SE, sensitivity; smB, switched memory B cells; VISUAL, variable immunodeficiency score upfront analytical link.
1. Sánchez-Ramón S. Unpublished data; 2. Figures reproduced from Guevara-Hoyer K, et al. Sci Rep 2021;11:12211 with permission from Springer Nature (CC BY 4.0).

Serum Free Kappa/Lambda in CVID

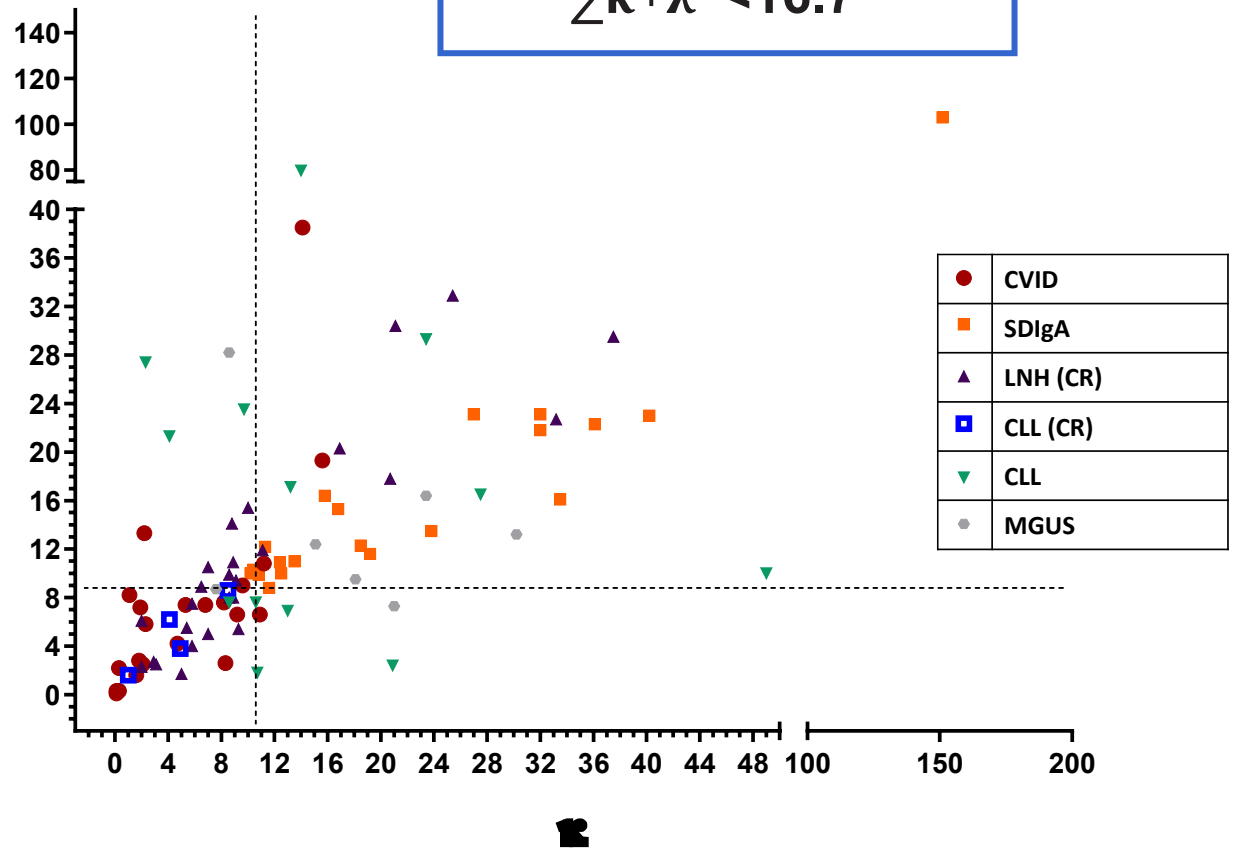
A highly sensitive and specific tool in the diagnostic work-up of CVID

345 adult CVID patients

2 patients with high kappa/Lambda: NHL



$\sum\kappa+\lambda$ <16.7



Compagno N. JACI 2015. Scarpa R. Front Immunol 2020. Hanitsch LG JoCL 2018.

Guevara-Hoyer K. Front Immunol 2020.

sFLC in CVID showed Higher Performance than Vaccine response

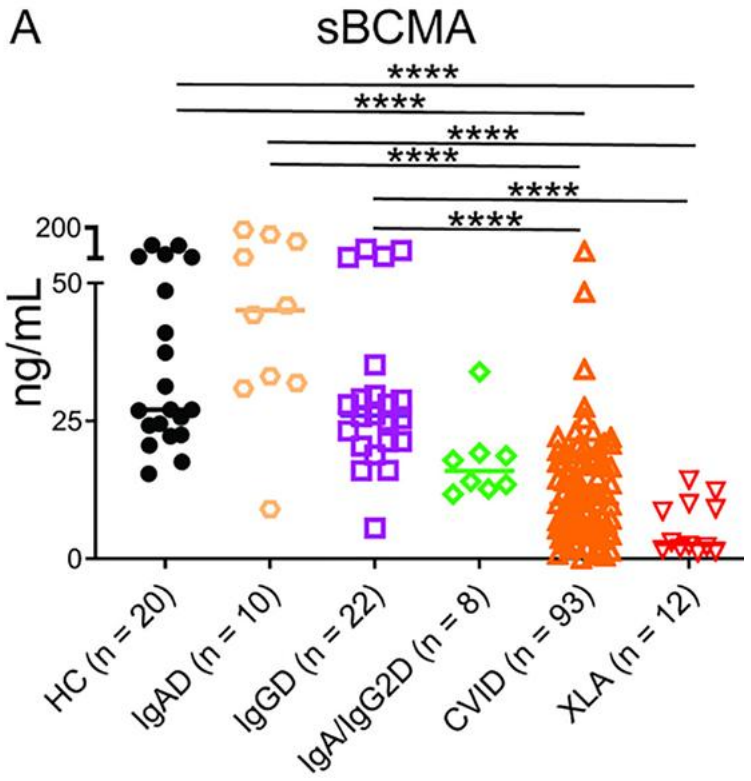
148 CVID patients

Biomarker		%
κλ Phenotype	K-λ+	16,1%
	K+λ-	3,4%
	K-λ+	1,1%
	K-λ-	79,3%
κ/λ ratio	Decreased	2,3%
	Normal	94,3%
	Increased	3,4%
∑κ+λ	**Decreased**	**89,7%**
	Increased	10,3

Biomarker	N	%	95% Inferior limit	95% Superior limit
Altered vaccine responses	69/81	**85,2%**	**0,7745**	**0,9292**
smB	39/92	42,4%	0,3229	0,5249
sFLCs	73/87	83,9%	0,7619	0,9163
∑κ+λ	78/87	**89,7%**	**0,8326**	**0,9605**

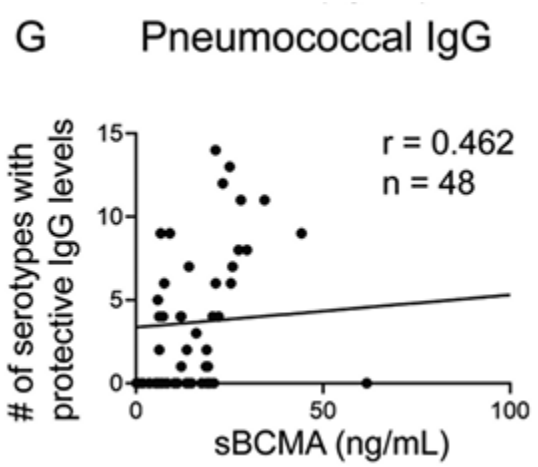
B cell maturation antigen (BCMA) in CVID Diagnosis

sBCMA <15 ng/mL had 97% PPV for CVID or XLA



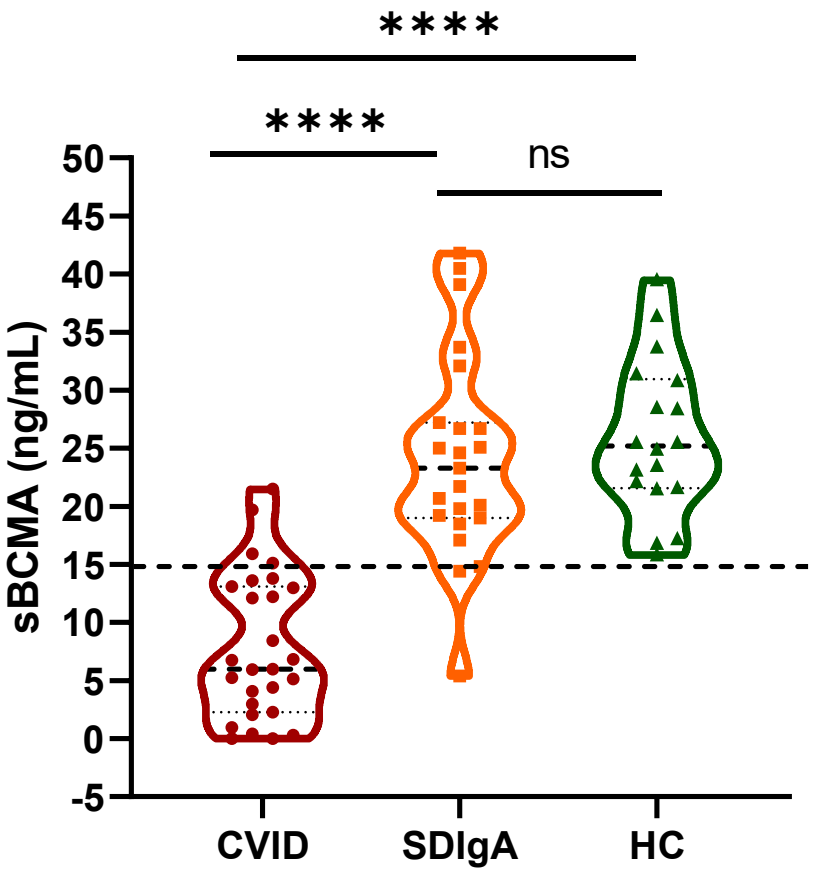
165 patients

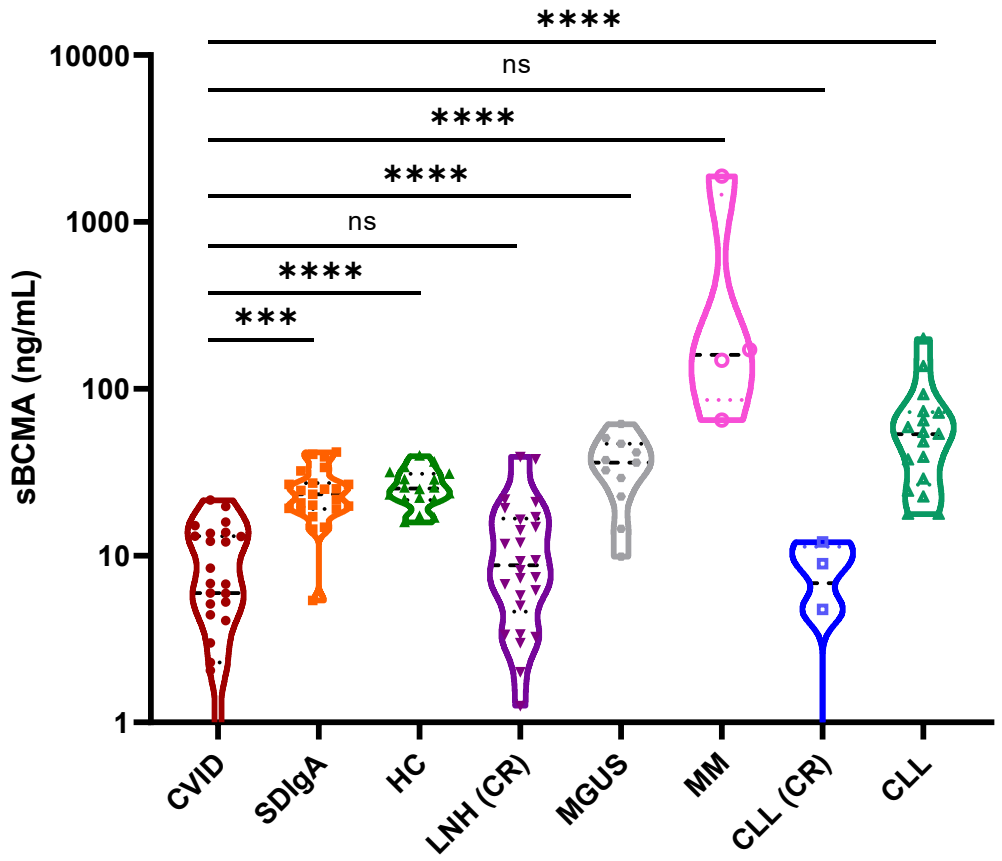
AUC ROC curve	Se	Sp	Optimal Cut-off level
0.9448 for CVID	73% (64 − 81, 95% CI)	96% (87 − 99 CI)	15



Maglione JP. J Allergy Clin Immunol Pract. 2021

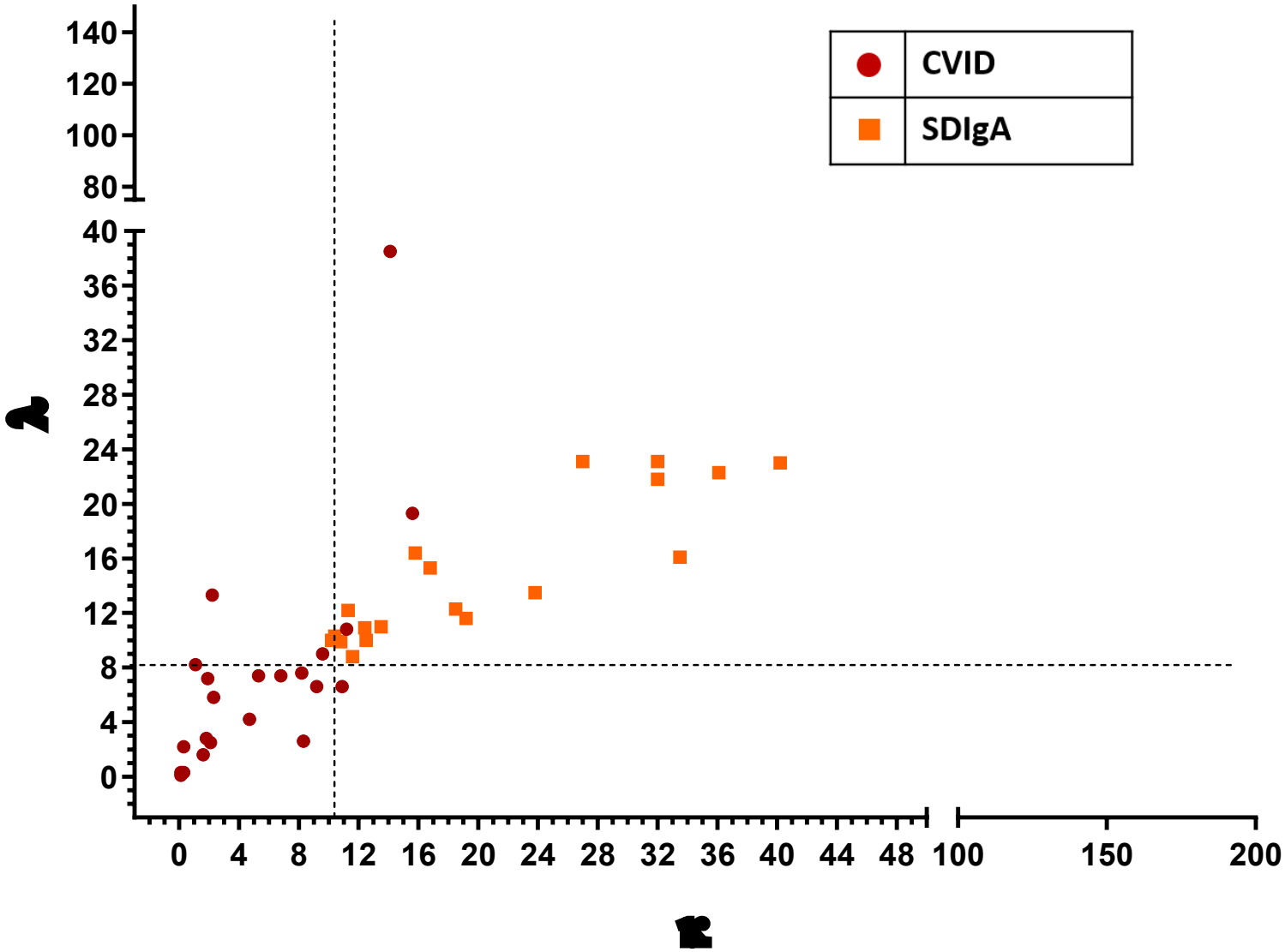
BCMA in CVID versus IgAD and SID Patients

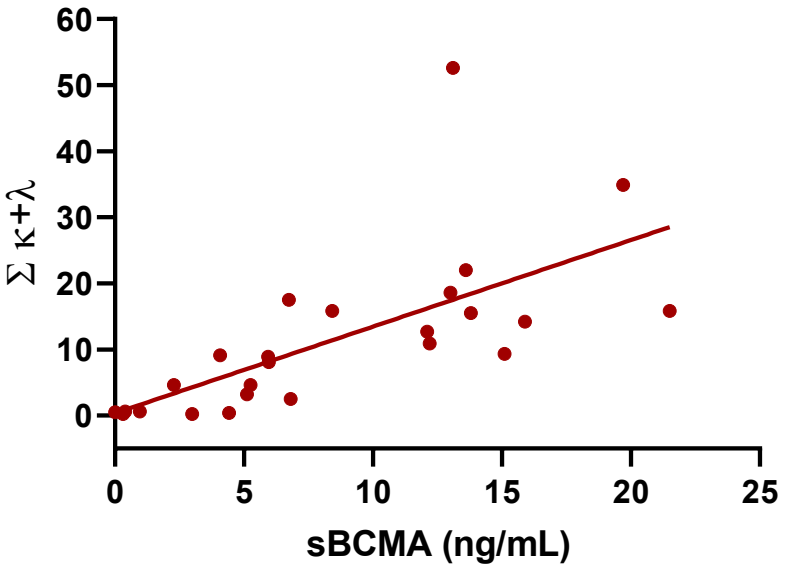




Guerra T. J Clin Immunol 2024

BCMA & in CVID versus IgAD and SID

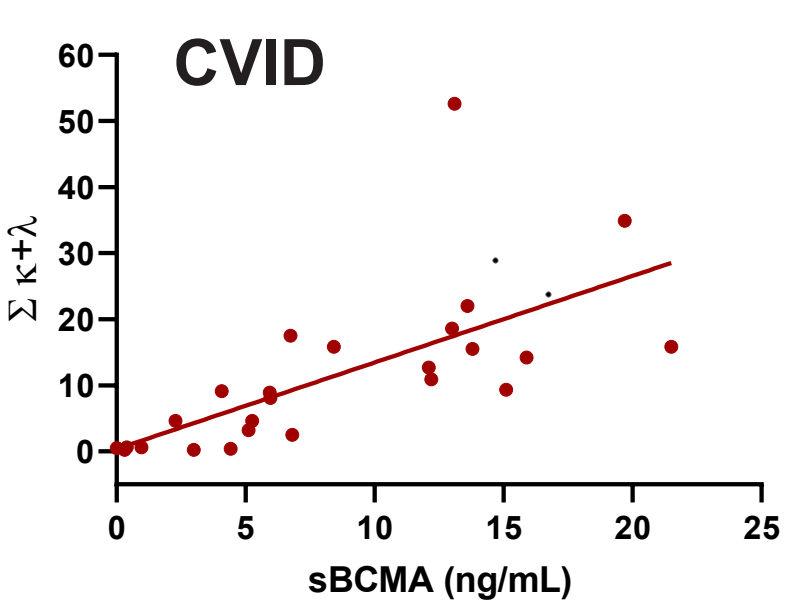


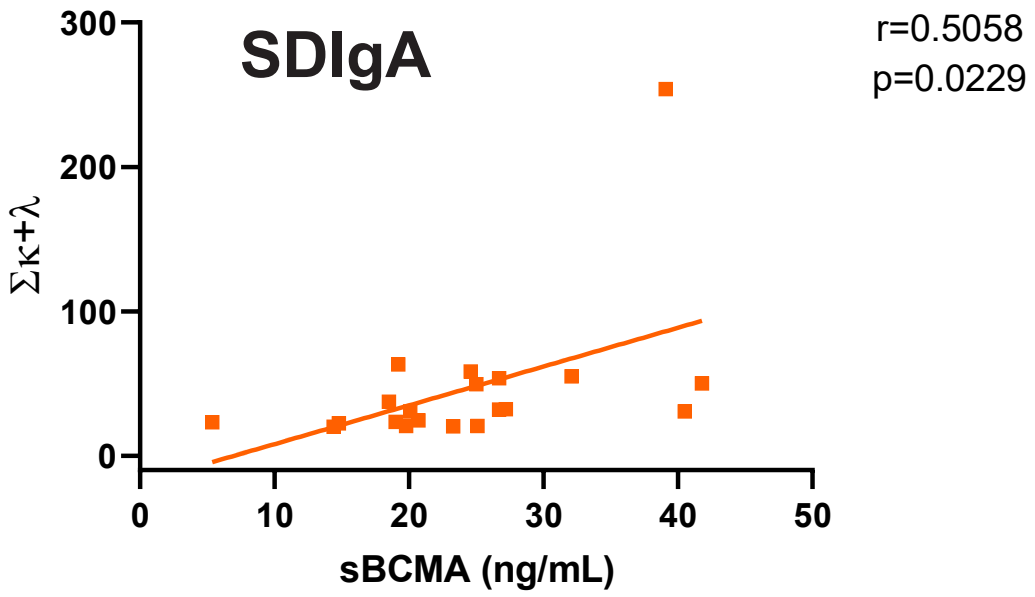


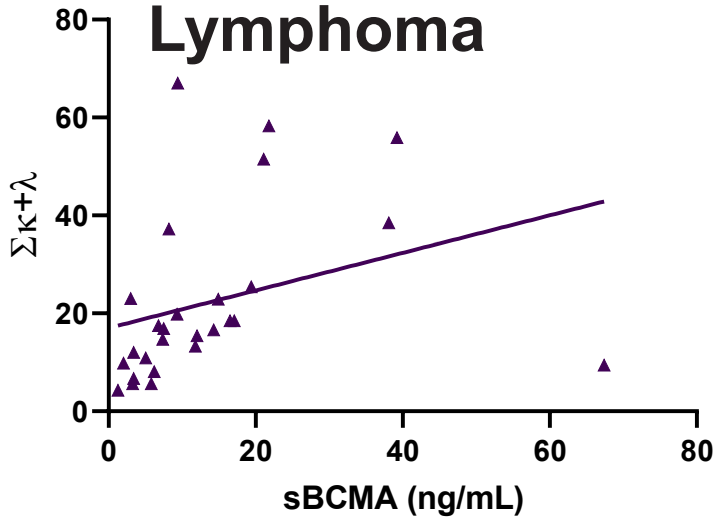
r=0.8229

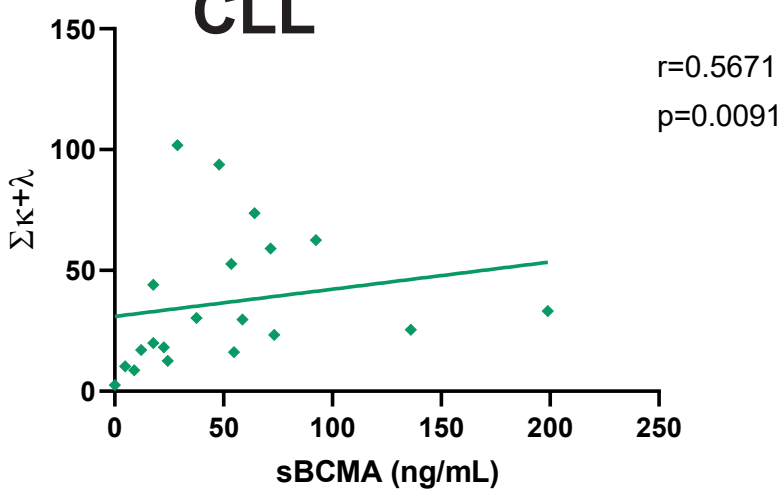
p<0.0001

BCMA directly correlates with sFLC



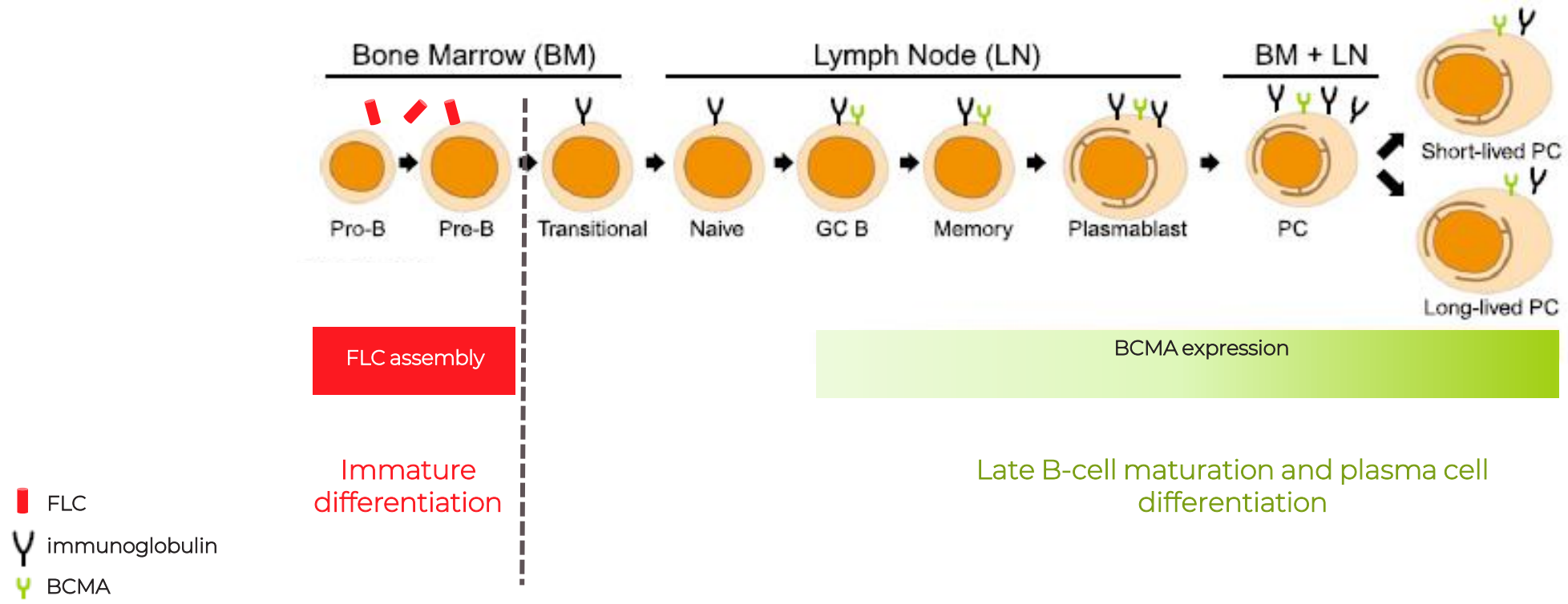






Different markers within different B cell biology events

Normal B cell differentiation



BCMA, B-cell maturation antigen; BM, bone marrow; FLC, free light chain GC, germinal centre; LN, lymph node; PC, plasma cell.
Figure adapted from Dogan A, et al. Blood Cancer J 2020;10(6):73 with permission from Springer Nature (CC BY 4.0).

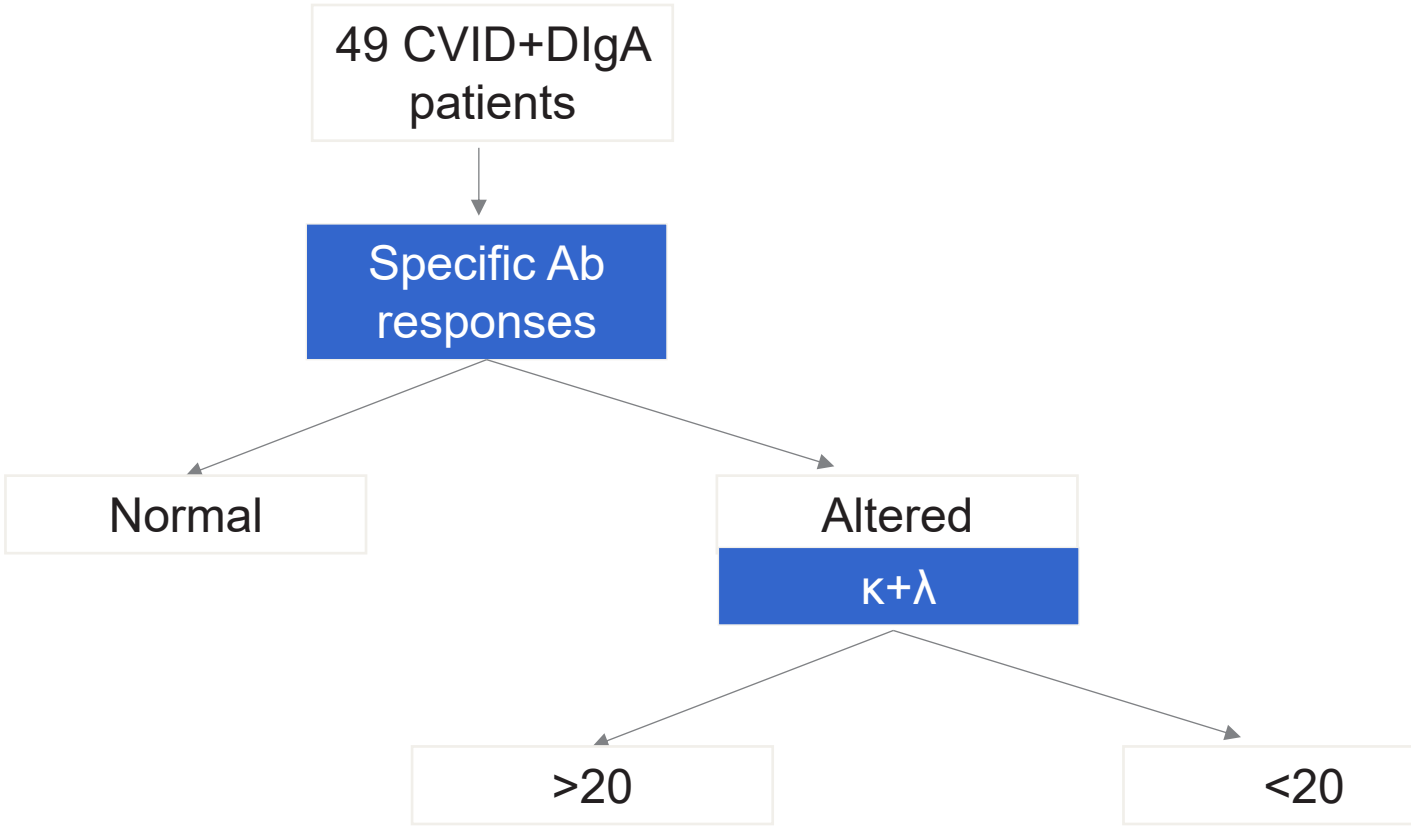
Comparison of Diagnostic Performance Among Biomarkers: Multivariate analysis

Compared to Healthy Controls and IgA Deficiency patients

Biomarker	AUC ROC curve	Sensitivity	Specificity	Optimal cut-off level
smB phenotype	0.923 (CI 95% 0.841–1.005)	69%	94%	**2.0**
Specific Ab response		**100%**	**82%**	**-**
VISUAL score	0.8971 (CI 95% 0.79–0.99)	72.73%	94.74%	**10.0**
sBCMA	0.9625 (CI 95% 0.92–1.00)	92.68%	85.00%	**15.0**
∑κ+λ	0.9380 (CI 95% 0.86–1.00)	**100.00%**	**88.00%**	**20.2**

Multivariant analysis for Diagnostic performance in CVID

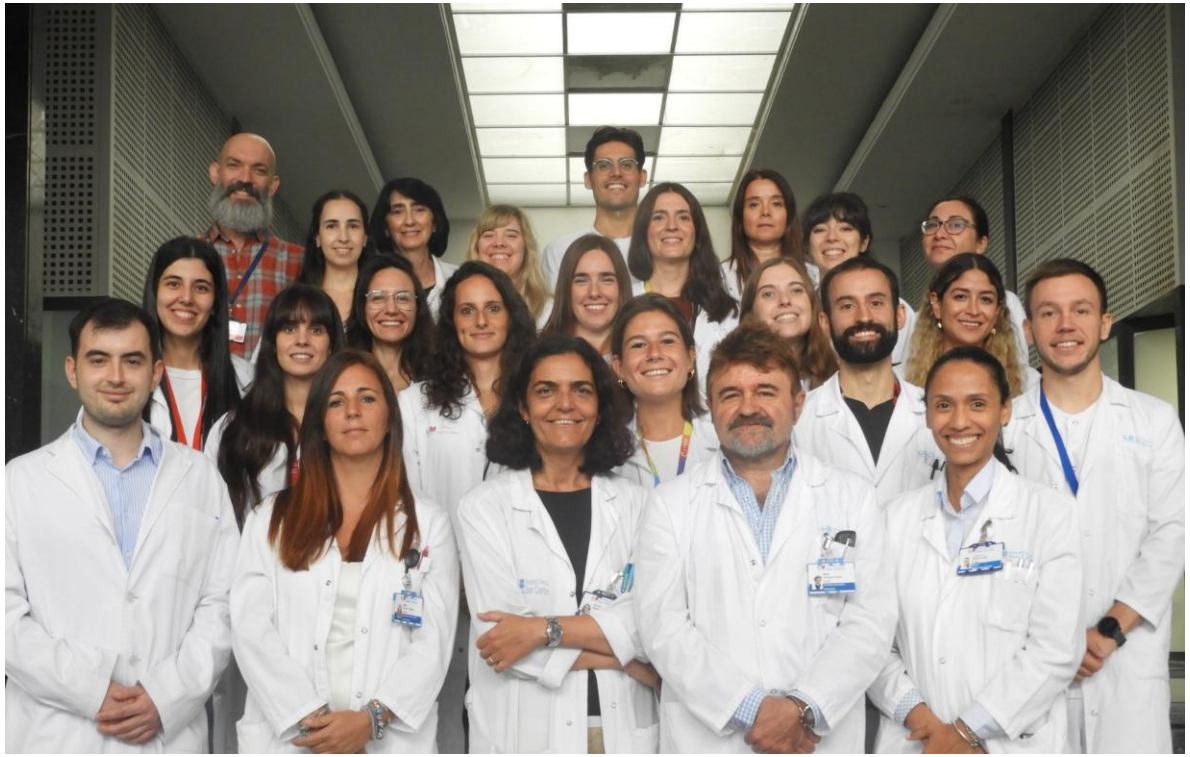
		sBCMA	κ+λ	smB
κ+λ	ρ	0.631		
	p value (bilateral)	<0.0001		
	n	49		
smB	ρ	0.407	0.145	
	p value (bilateral)	0.001	0.18	
	n	49	49	
VISUAL	ρ	-0.587	-0.295	-0.605
	p value (bilateral)	<0.0001	0.06	<0.0001
	n	49	49	49



Sensitivity and specificity 100%.

Conclusions

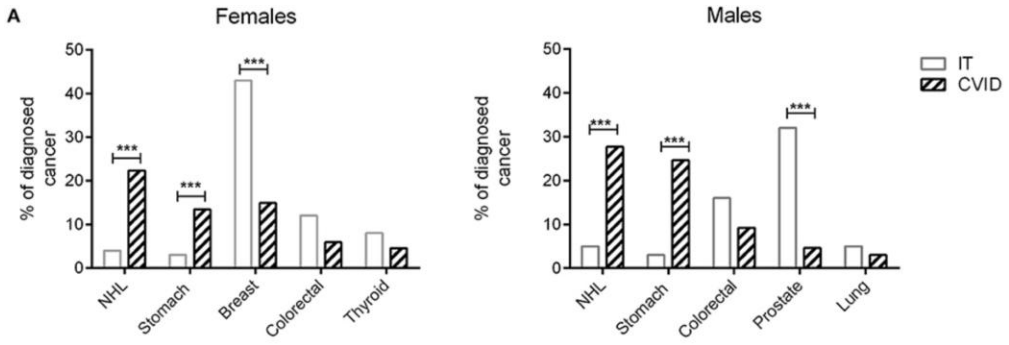
- ❑ BCMA and sum of kappa/lambda FLCs discriminate CVID from other PID and SID.
- ❑ sBCMA and ∑κ+λ can complement vaccine responses in CVID diagnosis to take immunoglobulin-replacement therapy decisions without delay.
- ❑ Cut-offs of sBCMA of 15 and ∑κ+λ of 20 have an excellent CVID diagnostic performance.
- ❑ VISUAL may add predictive information over switched memory B cells
- ❑ High sBCMA and ∑κ+λ titles may indicate risk of B-cell lymphoproliferation



Thank You / Questions

Cancer in Common Variable Immunodeficiency

- 473 CVID patients (Resnick ES): 21%
  - Lymphoma 8.2%. Most common NHL
  - Other cancers 7%
- 295 CVID patients (Kralickova P): x6
  - Lymphoma 6.1% (NHL=HL) & Gastric cancer 2%
  - ITP as a risk factor of lymphoma
  - CTLA4 and PIK3CD mutation (n=8)
- 455 CVID patients (Pulvirenti F): cancer 25.5%; 4% >1 cancer
  - Lymphoma 8.4% (NHL>HL) & Gastric cancer 5.5%
  - Policlonal lymphadenopathy: premalignant
  - Other cancers: 17.1%

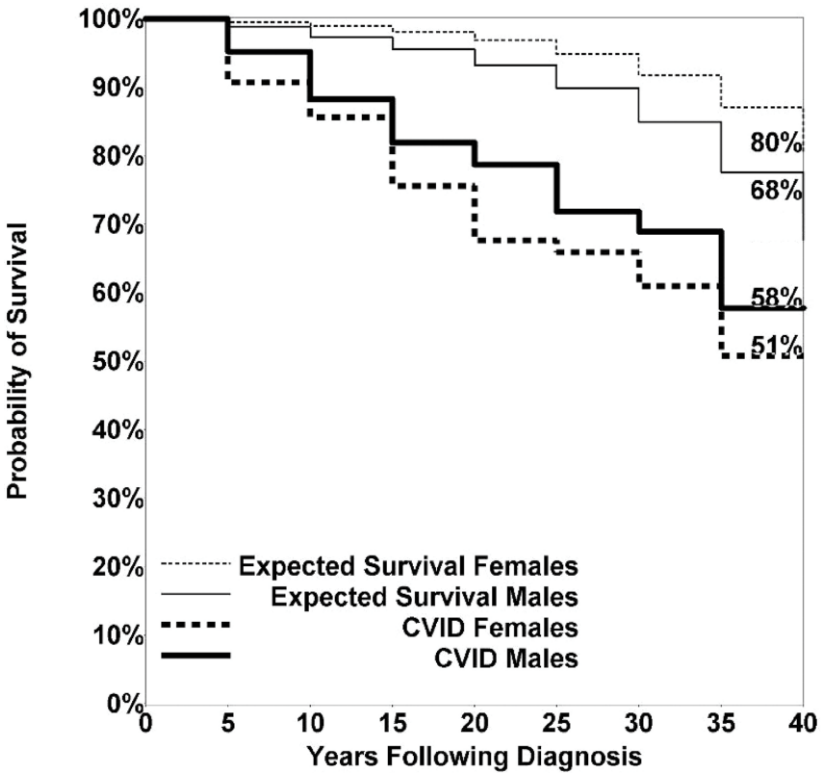


Vajdic CM Blood 2010. Resnick ESBlood 2012. Kralickova P Front Immunol 2019. Pulvirenti F Front Immunol 2018. Chapel H Blood 2008

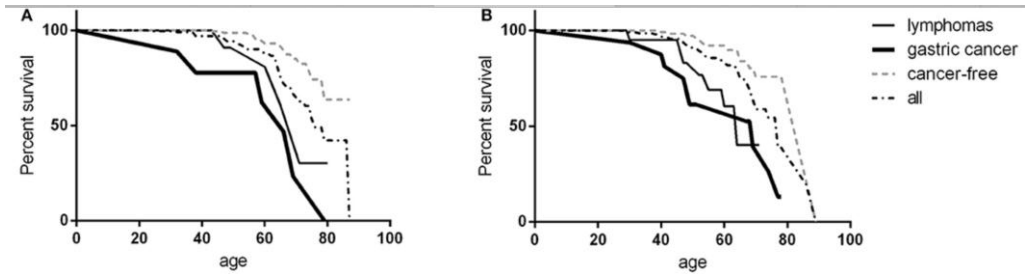
Cancer as a leading cause of Mortality in CVID

- 473 CVID patients (Resnick ES):
  - **Risk of death x11** in non-infectious complications: lymphoma
  - **2nd cause of death** after lung failure (lymphoma)

- 455 CVID patients (Pulvirenti F):
  - **Cancer 1st cause of death: 60.3%**
  - **Gastric Ca: leading cause mortality x10-fold excess** mortality



Female Male



1. *Resnick ESBlood 2012*

2. *Pulvirenti F Front Immunol 2018*

Secondary Immunodeficiency

- SID is an **acquired impairment of the immune system**[1,2]
- SID may occur due to **external factors**, such as an **underlying condition** or a **side effect of medication**[1,2]
- SID is **30x more common** than PID[3]

- A patient with cancer not only confronts with the disease, but also with immune **vulnerability**.

PID, primary immunodeficiency; SID, secondary immunodeficiency.
1. Ballow M, et al. Front Immunol. 2022;13:928062; 2. Sánchez-Ramón S, et al. Front Immunol. 2019;10:586;
3. Patel SY, et al. Front Immunol. 2019;10:33.

Edges between SID & PID

SID and PID show similar infection profiles

CVID

	Number of patients	%
Recurrent bronchitis, sinusitis, otitis	243	98
Pneumonia	190	76.6
Viral hepatitis	16	6.5
History of severe *Herpes zoster*	9	3.6
Giardia enteritis	8	3.2
Pneumocystis carinii infections	7	2.8
Mycoplasma pneumonia	6	2.4
Chronic mucocutaneous candidiasis	3	1.2
Salmonella diarrhea	3	1.2
Sepsis (Pseudomonas, pneumococcus, *H. influenzae*, Listeria	3	1.2
Campylobacter enteritis	3	1.2
Meningitis (*H. influenzae*, pneumococcus, and pseudomonas)	2	<1
Osteomyelitis	2	<1
Septic arthritis	2	<1
Recurrent parotitis	1	<1
Pyoderma gangrenosum	1	<1
Nocardia brain abscess	1	<1
Anaerobic leg infection leading to amputation	1	<1
HIV infection	1	<1
Cryptococcal lung abscess	1	<1
Viral myocarditis	1	<1
Cytomegalovirus, intestinal infection	1	<1
Microbacterium avium, lung	1	<1
Fatal measles encephalitis	1	<1
Mycoplasma joint infection	1	<1
Psoas abscess (*Escherichia coli* and Bacteriodes)	1	<1
Pelvic abscess after appendectomy, unknown organism	1	<1

Cunningham-Rundles C J Clin Immunol 1989

SID

	No. of patients n=77	%
Recurrent bronchitis, sinusitis, pneumonia	66	78
Pneumonia	32	42
History of Herpes Zoster	17	22
***H. Pyiori* infection**	15	19
Sepsis (*Pseudomona sp, pneumococcus, H. influenzae, Listeria*)	13	17
Recurrent urinary tract infections	12	16
Recurrent oral herpes	7	9
Mycoplasma pneumonia		
VEB	5	6
Pulmonary TB	5	6
Oropharyngeal candidiasis	4	5
Viral hepatitis	4	5
Campylobacter enteritis	3	4
***Aspergillus* sp.**	3	4
Cellulitis	3	4
Cytomegalovirus infection	2	3
Meningitis (*Pseudomona* sp, pneumococcus, *H. influenzae*)	1	1
Human Papillomavirus	1	1
Cryptogenic Organizing Pneumonia	1	1
Recurrent parotitis	1	1
***Pneumocystis jirovecii* infection**	1	1
Osteomyelitis	1	1
Pyoderma gangrenosum	1	1

Ochoa J 2020 Clin Immunol

Changing paradigm from oncogene-targeting to immune checkpoint-modulating

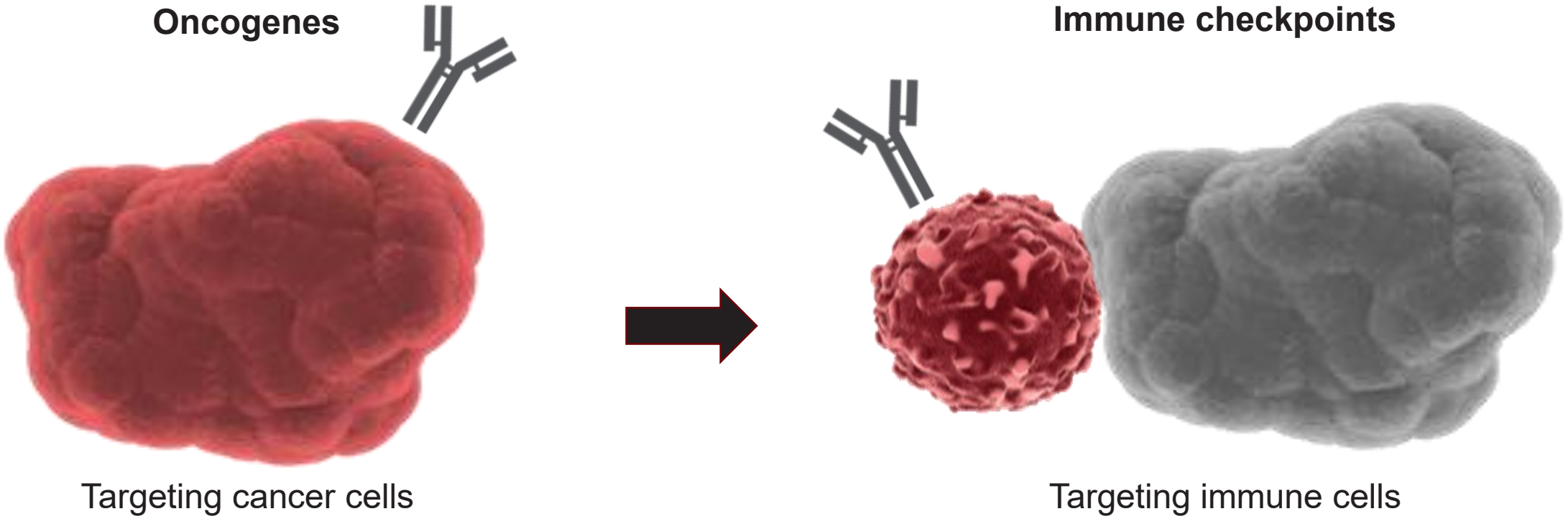


Figure provided courtesy of the speaker.[3]

Cancer immunotherapy has emerged as one of the main pillars of cancer treatment because it is personalised, long-lasting, targeted and as safe as other methods, such as surgery, radiotherapy and chemotherapy[1,2]

The Cancer & Immunity Nexus: 3E Theory

Elimination:[1,2]

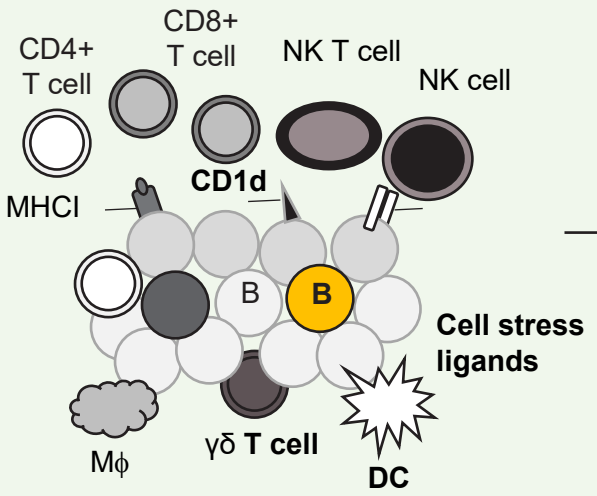
Immune cells recruited to try to mount an efficient anti-tumour immune response

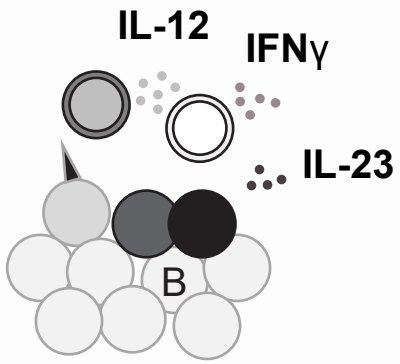
Equilibrium:[1,2]

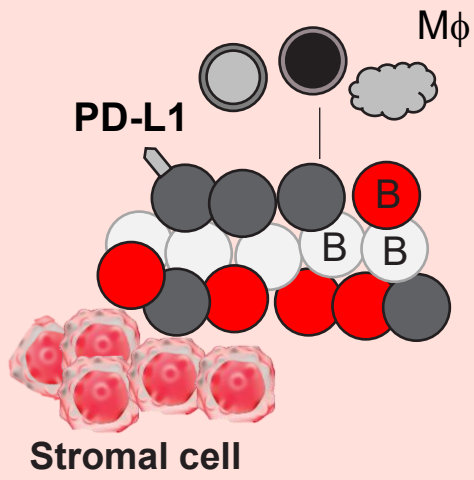
Balance between tumour containment and selective immune pressure

Escape:[1,2]

Selected tumour clones can elude the immune response and successfully progress







Immunosuppressive cell types

- TAM
- MDSC
- T_{reg} cell

Upregulation of surface molecules

- HLA-G and/or HLA-E
- CD155 and/or CD112
- CD47
- PD-L1 and/or PD-L2
- CD39 and/or CD73

Dysregulation of secreted signalling molecules

- CCL4 ↓
- IL-2 ↓
- IL-15 ↓
- IL-12 ↓
- CCL2 ↑
- IL-10 ↑
- TG β ↑

Tumour survival
Tumour proliferation
Defective cytotoxicity

Figure adapted from O'Donnell JS, *et al.* 2019.[1]

If Immunodeficiency is First: Can we Advance its Complications?

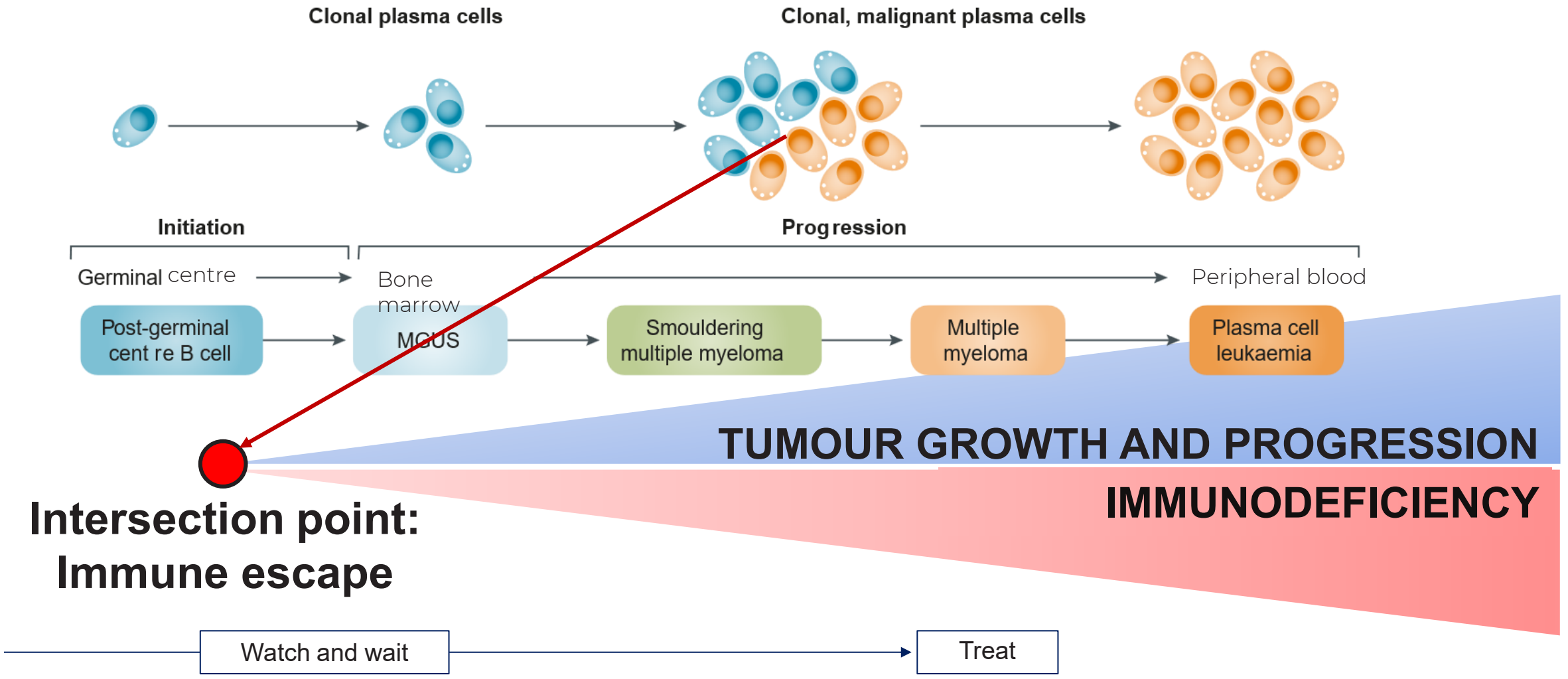
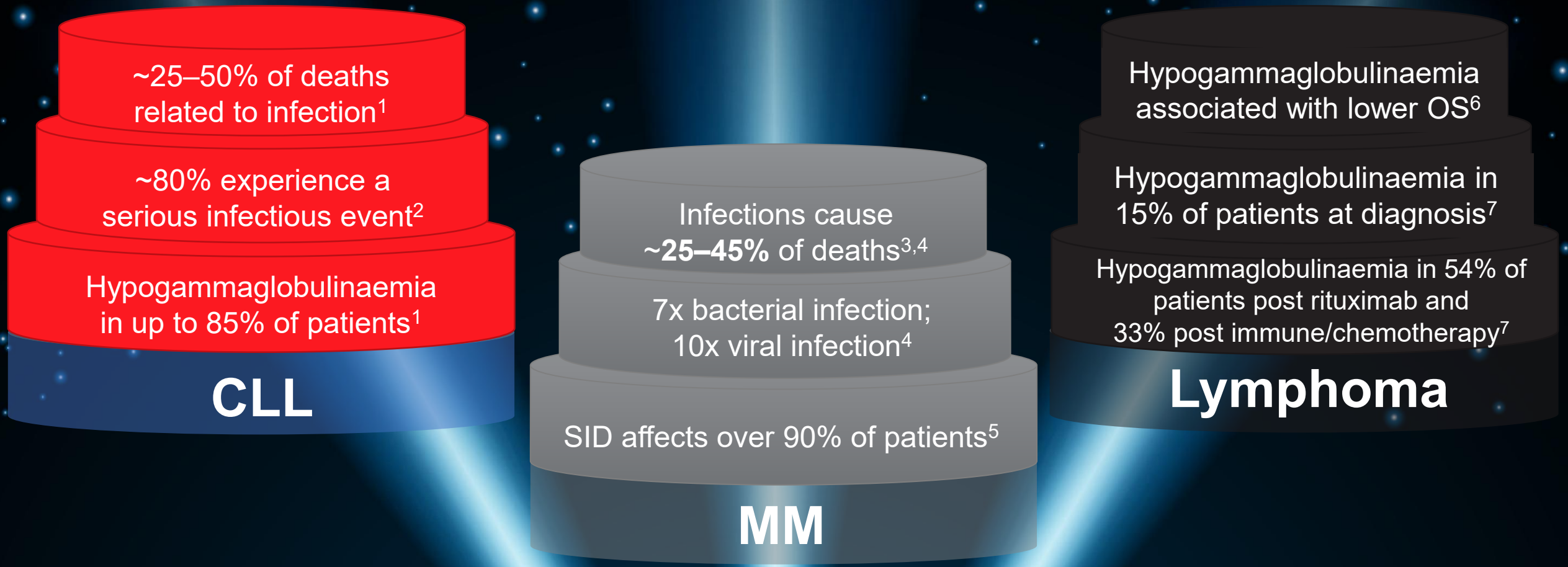


Figure adapted from Kumar S, *et al.* 2017.

A focus on SID incidence and the consequences



Beyond Infections…

Cardiovascular disease
Second malignancy
Bone disease
Frailty
Dental problems
Psychological and emotional problems
Social and financial problems

Domain	Recommendations	Strength of recommendation[a]	Level of evidence[a]
Cardiovascular disease	Modifiable risk factors		
	Regular physical activity and advice regarding nutrition and diet as per international cardiovascular primary prevention guidelines [17].	2	C-LD
	Optimal control of modifiable cardiac risk factors such as hypertension, dyslipidemia and diabetes mellitus.	2	C-LD
	BTK inhibitors [18]		
	Cardiovascular assessment (including BP measurement and pulse-taking (or ECG rhythm strip) should be conducted at every visit.	2	C-LD
	Weekly home BP monitoring for three months, followed by monthly monitoring should be considered.	2	C-EO
	Transthoracic echocardiogram recommended in all high-risk patients at baseline and in all patients that develop AF.	2	C-EO
	Anthracycline induced cardiomyopathy	1	See reference
	We refer readers to the recently updated, comprehensive ESC guidelines on cardio-oncology [18]		
	Early referral to a cardiologist/cardio-oncology service.	2b	C-EO
Immunity and infections	Vaccinations as per consensus guidelines (e.g. [19,20]), preferably before treatment or during maintenance (although poor vaccine responses are well described in CLL and iNHL).		
	Annual inactivated influenza vaccine	1	B-NR
	Pneumococcal vaccine (pneumococcal conjugate vaccine, followed by pneumococcal polysaccharide 23-valent vaccine ≥2 months later).	1	B-NR
	COVID-19 vaccination as per local guidelines.	1	B-NR
	Recombinant varicella zoster virus vaccine [21]	1	B-NR
	Consider other inactive vaccines (including respiratory syncytial virus, hemophilus influenzae B, human papilloma virus, and hepatitis B vaccine) as per age, comorbidities and local recommendations, 3–6 months following treatment.	1	B-NR
	Avoidance of live vaccines.	1	C-LD
	Consideration of IVig/SCIg in patients with hypogammaglobulinemia and severe/recurrent bacterial infection.	2	B-R
Secondary malignancy	Preventative measures:		
	Cessation of smoking [22], avoidance of excessive alcohol consumption, adherence to sun protection guidelines.	1	A
	Age based screening programs guided by personal and family history, radiation exposure and other risk factors		
	Skin cancer surveillance [23]	1	C-LD
	Fecal occult blood testing (colonoscopy in high risk).	1	A
	Breast cancer screening program (mammography).	1	A
	Cervical screening (Pap-smears).	1	A
	Prostate cancer screening (PSA) as per local guidelines (not universally recommended in asymptomatic men).	2	C-EO
Bone disease	Optimization of vitamin D and calcium status.	2	C-LD
	Weight bearing exercise.	2	C-LD
	Bone densitometry screening in patients with high corticosteroid exposure or other risk factors.	2	C-LD
	Early referral to metabolic bone clinic/commencement of antiresorptive therapy.	2	C-LD
Frailty	Treatment of underlying CLL/iNHL [24]	1	B-R
	A geriatric assessment (e.g. PGA) should be performed on all patients >65 yo and updated at key milestones [25].	1	B-R
	Motivate patients to maintain regular exercise, including aerobic exercise and resistance exercise for all major muscle groups.	2	C-LD
	Consider exercise physiology referral.	2	C-EO
	Occupational therapy and physiotherapy referral as required.	2	C-EO
Psychological and emotional	Screening (PGA, or other tools including HADS, PHQ-9, GAD-7, distress thermometer, and targeted history) at diagnosis and at regular intervals, particularly at times of change of disease status and management.	2	C-EO
	Early psychology referral (preferably with cancer/chronic disease expertise).	2	C-EO
	Involvement with patient's primary care physician.	2	C-EO
	Provide information on local disease peer support groups.	2	C-EO
	Carer support	2	C-EO
	Screen for impaired sexual health and impact on relationships.	2	C-EO
Social and financial	Early social work referral.	2	C-EO
Education and information	Provision of (linguistically appropriate) disease-specific patient information.	2	C-EO
	Care-coordination.	2	C-EO
	Involvement of family in consults (with patient consent), particularly when change of disease status or management plan.	2	C-EO
	Provide information on local cancer support services.	2	C-EO
Dentition	At least annual dental review.	2	C-EO
	Education regarding optimal dental hygiene.	2	C-EO

Pasquale L. Fedele & Stephen Opat . Leukemia & Lymphoma 2025

SID scope

- Need classification
- Infectious risk stratification

Antibody deficiency

B cell memory defect

T cell deficiency

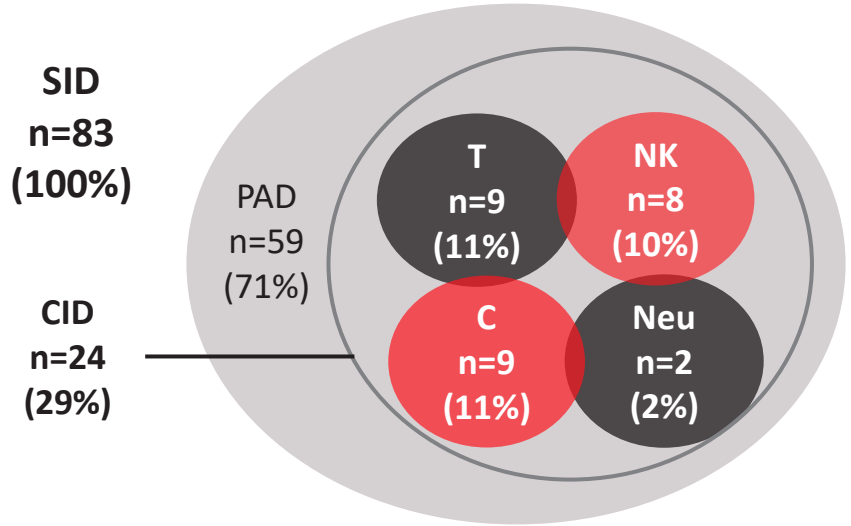
Neutropenia

Hypocomplementemia

Defects on Mo/MDSCs

Defects on NK cells

Immunophenotyping: Classification of SID to B-CLPD by analogy with PID



- Severe infection: **3.69-fold higher** risk with CID compared with PAD **(P=0.001)***
- Progression of cancer observed earlier in CID compared with PAD: **HR=3.21 (P=0.005)†**

Progression-free survival according to immune defect phenotype

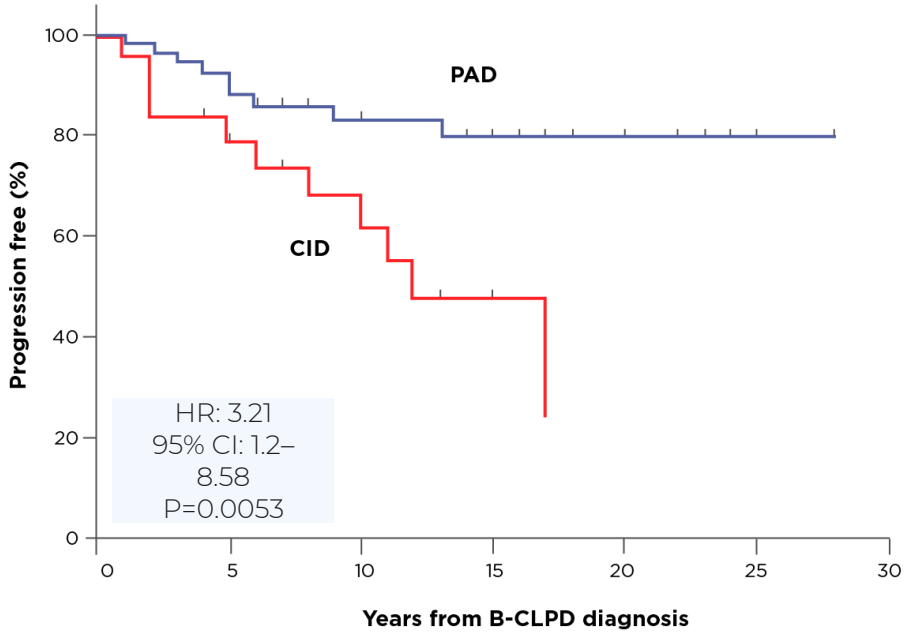


Figure adapted from Ochoa-Grullón J, et al. 2022.

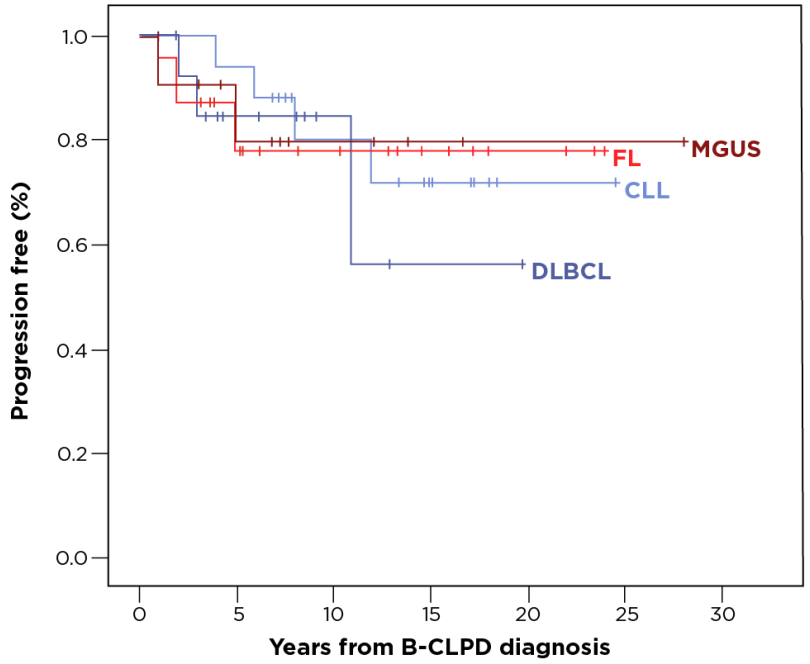
*95% CI: 1.30–10.40. †95% CI: 1.20–8.58.

B-CLPD, B-cell chronic lymphoproliferative disease; C, complement factor; CI, confidence interval; CID, combined immunodeficiency; HR, hazard ratio; PAD, primary antibody deficiency; PID, primary immunodeficiency; Neu, neutrophils; NK, natural killer cells; SID, secondary immunodeficiency; T, T lymphocyte.

Ochoa-Grullón J, et al. Biomed. 2022;10(8):2020.

Can we study SID across different B-CLPDs?

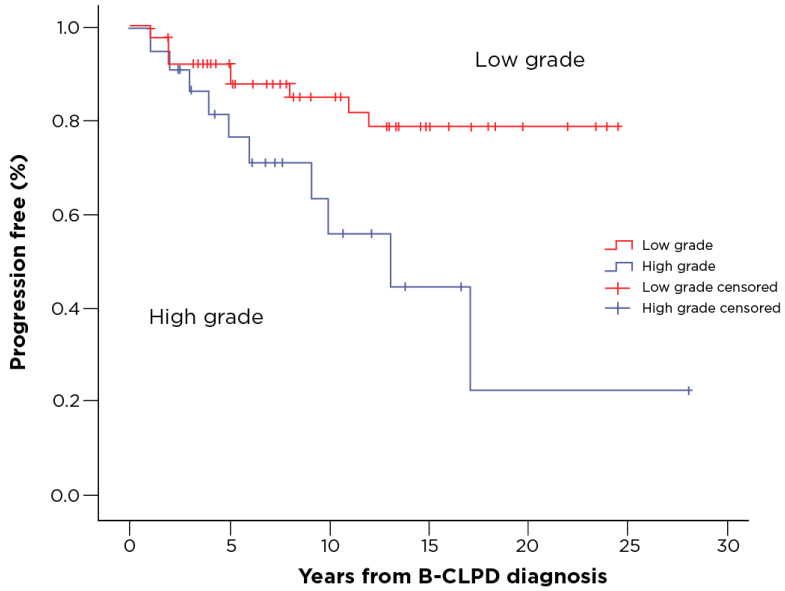
Cancer progression across different B-CLPDs



Cancer progression: No difference by disease

Figure adapted from Ochoa-Grullón J, *et al.* 2022, Ochoa-Grullón J, *et al.* 2021 and speaker experience.[1–3]

Cancer progression adjusted by clinical stage



High grade/low grade adjusted by B-CLPD diagnosis
HR: 3.285; 95% CI: 1.324–8.147; P=0.010

B-CLPD, B-cell chronic lymphoproliferative disorder; CI, confidence interval; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; MGUS, monoclonal gammopathy of unknown significance; SID, secondary immunodeficiency.

1. Ochoa-Grullón J, et al. Biomed. 2022;10:2020; 2. Ochoa-Grullón J, et al. 2021. Protocolisation of the treatment with gammaglobulins in patients with haemtological malignancy.

The Need for Change: Optimizing Diagnosis Flux in Patients with BCLPD

Reactive strategy

- Oncohematological patients with recurrent and severe infections.
- High risk hospitalizations.

Proactive strategy

- Multidisciplinary team: Hematology, Immunology, Preventive Medicine, Pharmacy
- AI for early PID diagnosis.
- Optimized protocols for vaccines and IgRt administration.

Patients

✓ Early detection and prophylaxis = less infections, better QoL.
✓ Personalized medicine.

Hospital

✓ Reduction of hospitalizations and costs.
✓ Optimization of resources with AI (89,5% of diagnostic sensitivity).

Optimising diagnostic flow for patients with B-cell targeted therapies or BCLPD

HEMATOLOGY DEPT.
Unit of Oncohematology
Dr. Celina Benavente Cuesta
Coordination of patients' flow: Dr. Ascensión Peña

Patients at diagnosis of:

- NHL ("Preferent" CODE for high-grade)
- CLL
- MGUS with infections
- MM

IMMUNOLOGY DEPT.
Consultation of Immunoprevention in OncoHematology
Dra. Silvia Sánchez-Ramón
Immune evaluation & Immunoprevention

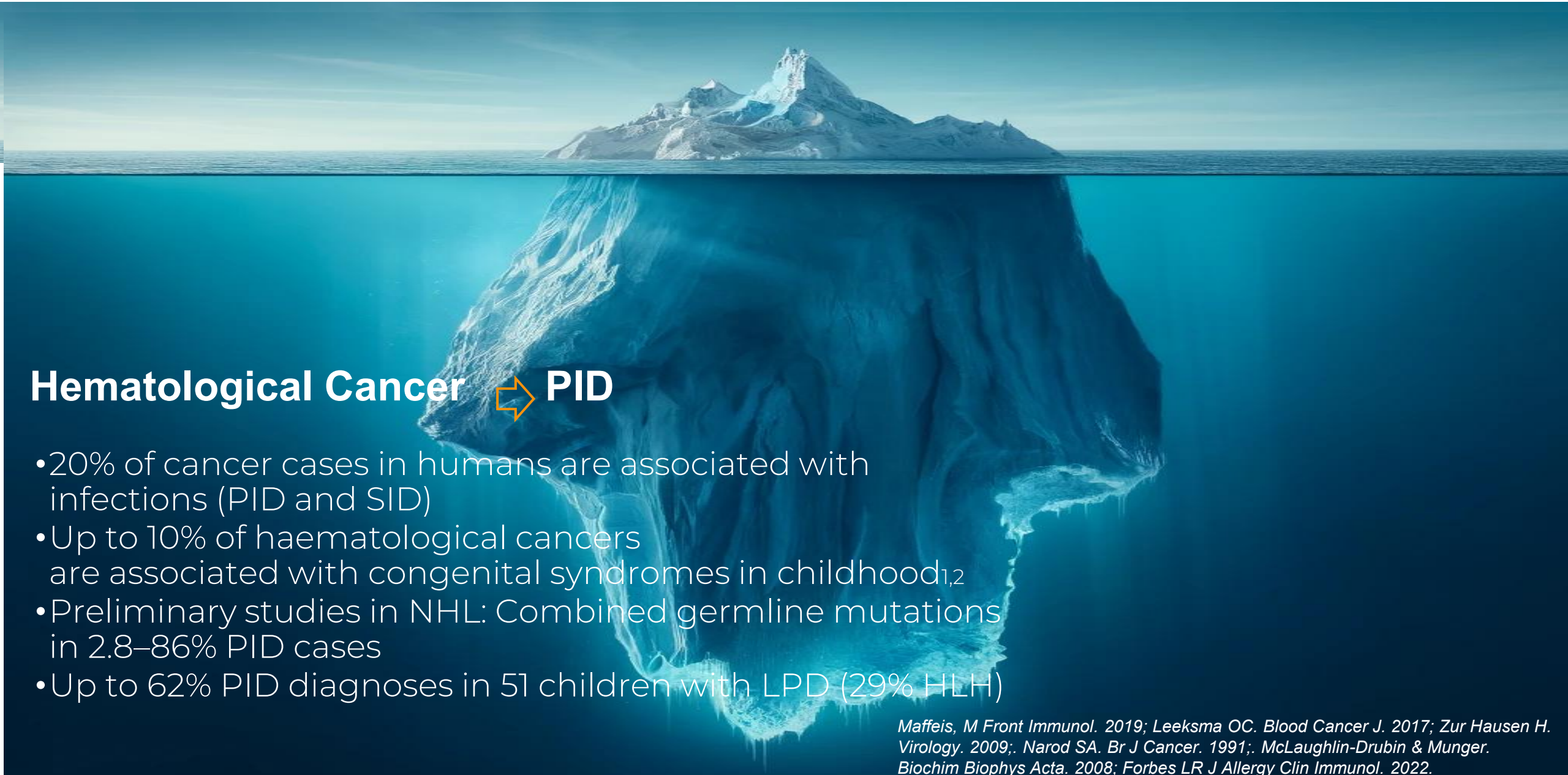
SPECIALIZED NURSE: education and training of the patient

PREVENTIVE MEDICINE DEPT.
Dr. Alberto Mariano Lázaro
Dr. Gloria Mato Chain
Complete vaccination

PHARMACY DEPT.
Dra. Teresa Benítez Giménez
Protocol of Treatment: IgIV & IgSC

PHARMACOLOGY DEPT.
Dr. Leonor Laredo Velasco
Pharmacoeconomic studies

PID: The Cancer Paradox

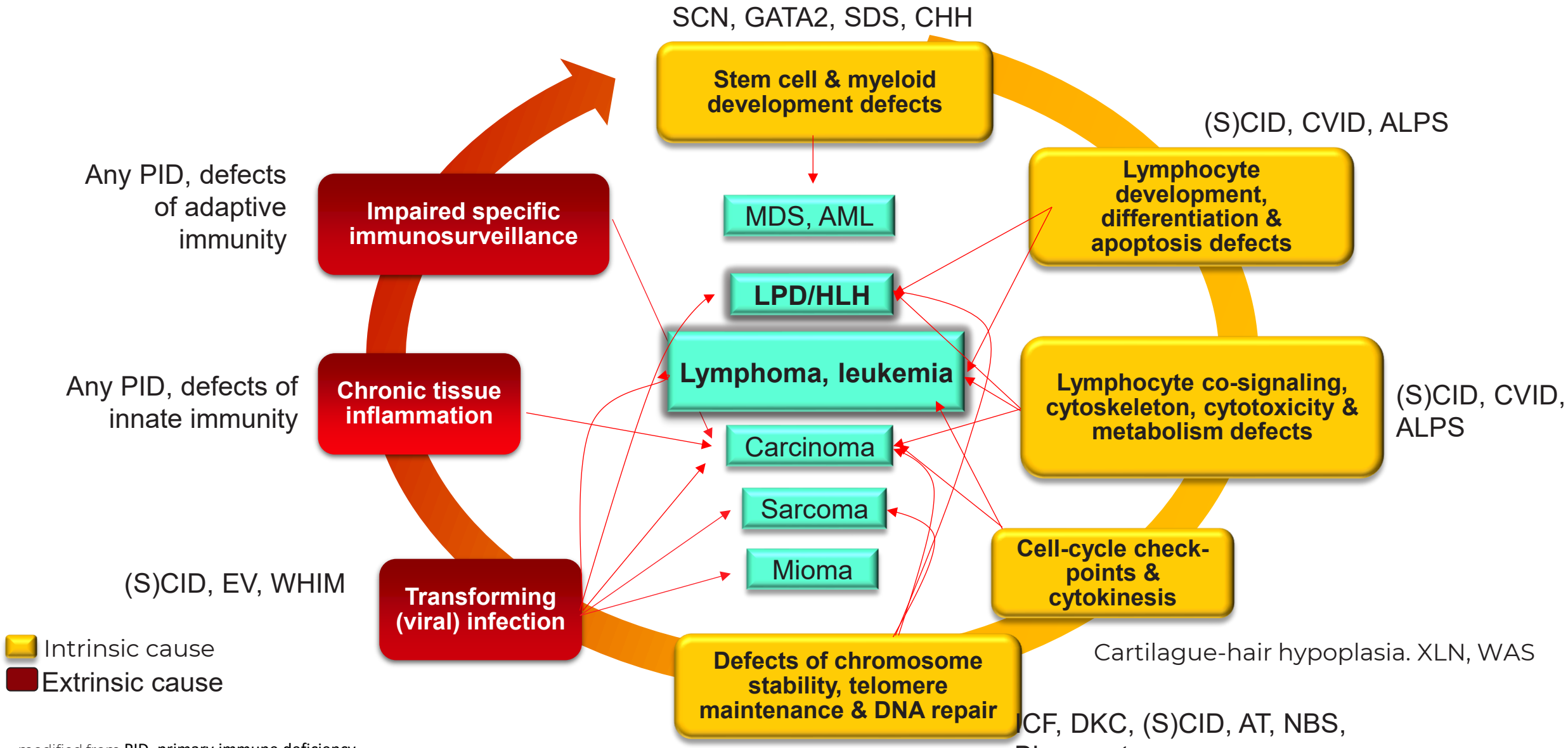


Hematological Cancer ⇨ PID

- 20% of cancer cases in humans are associated with infections (PID and SID)
- Up to 10% of haematological cancers are associated with congenital syndromes in childhood[1,2]
- Preliminary studies in NHL: Combined germline mutations in 2.8–86% PID cases
- Up to 62% PID diagnoses in 51 children with LPD (29% HLH)

Maffeis, M Front Immunol. 2019; Leeksma OC. Blood Cancer J. 2017; Zur Hausen H. Virology. 2009;. Narod SA. Br J Cancer. 1991;. McLaughlin-Drubin & Munger. Biochim Biophys Acta. 2008; Forbes LR J Allergy Clin Immunol. 2022.

Mechanisms of malignancy in PID



modified from PID, primary immune deficiency.

Adapted from Hauck F, *et al. J Allergy Clin Immunol* 2018;141(1):59−68.e4. Ballow M, et al. Front Immunol 2022;13:928062.

Navigating the labyrinth: How to distinguish PID from SID

Variables	PID	SID
Recurrent/severe infections, autoimmune disease, enteropathy	• **PAST** medical history[1] • Family history[1]	• **AFTER** cancer and/or cancer therapy, other causes[1]
Immunological variables at B-CLPD diagnosis	• Low IgG/IgA (<2 SD)[1] • Low levels of natural Ab[1] • Low Ab responses at cancer diagnosis (primary and secondary)[1] • Very low serum-free kappa/lambda (CVID)[1] • Defect in memory B-cell phenotype[1] • Specific PID signatures of T-cell subsets[2]	• Normal/low secondary responses[1]
B-cell reconstitution after therapy	• Not applicable[1]	• Rare but **possible**[1]
Response to cancer therapy	• Toxicity, infections, secondary cancer, recurrence[1]	-
Genetic studies	• Germline mutations associated with PID/B-CLPD[1]	-
Preventive strategies	• Active surveillance of other complications (endoscopy), choose cancer immunotherapy, PCR/IH oncogenic viruses[1] • Family evaluation[3,4] • Genetic counselling[3,4] • Specific targeted therapies[4,5]	-

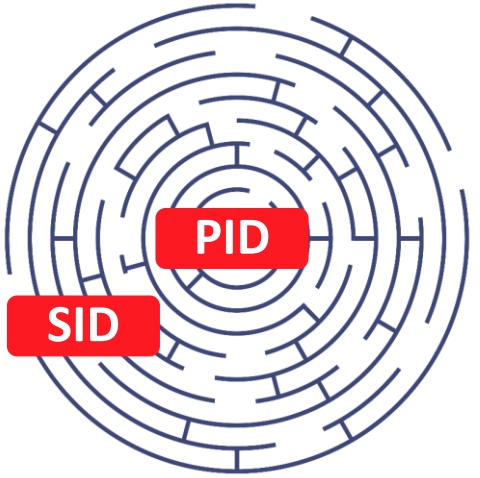


Image developed courtesy of speaker.[4]

Ab, antibody; B-CLPD, B-cell chronic lymphoproliferative disorder; CVID, common variable immunodeficiency; Ig, immunoglobulin; IH, immunohistochemistry; PCR, polymerase chain reaction; PID, primary immunodeficiency; SD, standard deviation; SID, secondary immunodeficiency.

1. Ballow M, *et al*. *Front Immunol.* 2022;13:928062; 2. Yi S, *et al. Clin Transl Immunol.* 2020;e1105; 3. Lehman H, *et al. Curr Med Res Opin.* 2015;31(4):697–706; 4. Content based on the knowledge and experience of the speaker; 5. Ochoa-Grullón J, *et al*. *Biomed*. 2022;10:2020.

AI Model to Identify IEI in Patients with SID

151 B-CLPD patients with SID

CVID ESID Criteria

1. Increased susceptibility to infection (prior B-CLPD)

2. Marked decrease of IgG & IgA

110 “Suspected-PID”

41 “SID”

37 variables
(19 clinical and 18 analytical)

Bivariate analysis → Statistically significant variables

Logistic regression model and unsupervised machine learning algorithm (*Rpart)*

Diagnostic Tree Decision Model

AI Model to Identify IEI in Patients with SID

151 B-CLPD patients with SID

110 "Suspected-PID"

41 "SID"

19 clinical variables

18 immunological variables

Bivariant analysis

	"SUSPECTED PID GROUP" N= 110	"SID GROUP" N=41	p
Age at B-CLPD diagnosis (median(SD))	53.57 (15.35)	59.54 (11.91)	**0.037**
Rituximab treatment	63 (61.76)	13 (38.24)	**0.028**
Childhood recurrent/severe infections	57 (53.77)	0 (0)	**<0.001**
Recurrent/severe infections pre-BCLPD	53 (51.46)	1 (2.56)	**<0.001**
Family history of B-CLPD	41 (37.96)	5 (12.82)	**0.006**
IgRT	72 (67.29)	15 (39.47)	**0.004**
IgG at B-CLPD diagnosis	574.00 (387.50 - 928.00)	712.00 (494.00 - 1325.00)	**0.027**
sFLC kappa	10.40 (6.50 - 17.40)	16.90 (10.80 - 23.40)	**0.002**
sFLC lambda	9.10 (5.70 - 16.40)	17.00 (11.10 - 24.10)	**<0.001**
Sum kappa+lambda	19.10 (11.90 - 36.80)	36.00 (26.70 - 73.20)	**<0.001**
smB memory B	0.00 (0.00 - 6.50)	7.80 (0.00 - 23.65)	**0.010**
Leukocytes	6000.00 (4600.00 - 9200.00)	8000.00 (5800.00 - 14900.00)	**0.0275**

Palacios-Ortega et al. Journal of Clinical Immunology 2024.

Clues for clinical assessment at B-CLPD diagnosis:

Clues for analytical assessment at B-CLPD diagnosis:

IMPORTANCE OF FOCUSED CLINICAL HISTORY!!

IMPORTANCE OF FOCUSED ANALYTICAL ASSESMENT!!

Early age at diagnosis

Childh… …ere

…y history of B-CLPD

Higher needs of IgRT

More vulnerable to immunodepletion and infection-related complications??

Higher needs of Rituximab

More aggressive B-CLPD??

sFLC

…(κ +

Switched m… cells (smB)

Leukocytes

Palacios-Ortega et al. Journal of Clinical Immunology. October 2024

AI Model to Identify IEI in Patients with SID

65 NHL patients with SID

19 clinical variables

18 immunological variables

52 NHL “Suspected-PID”

13 NHL “SID”

Variable	"PID-suspected NHL group" No. = 52	"SID NHL Group" No. = 13	P-value
Childhood recurrent&severe infections	21 (40.4%)	0 (0%)	0.005
Infections prior to NHL diagnosis	23 (44.2%)	1 (7.7%)	0.01
Infections after NHL diagnosis	30 (57.7%)	4 (30.8%)	0.08
Malabsorptive syndrome	17 (32.7%)	2 (15.4%)	0.22
Second primary neoplasia	15 (28.8%)	2 (15.4%)	0.32
Family history of B cell neoplasms	8 (15.4%)	0 (0%)	0.13
Serum IgM at NHL diagnosis (mg/dL)	56.12±44.54 40	225.23±19.79 56	<0.0001
Sum kappa+lambda (mg/dL)	23.48±15.06 15	33.00±12.00 23	0.03
Class-switched memory B cells (%)	2.06±5.29 0	6.33±2.12 9	0.006

AI Model to Identify IEI in Patients with SID

151 B-CLPD patients with SID

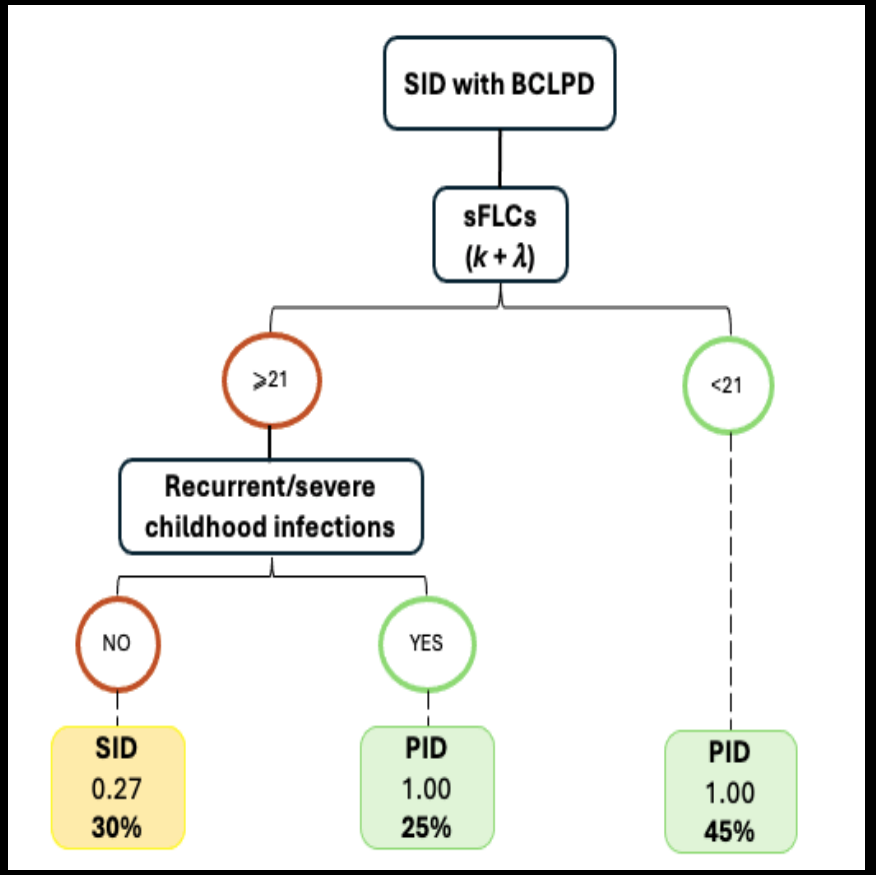
110 "Suspected-PID"

41 "SID"

19 clinical variables

18 immunological variables

AI Model

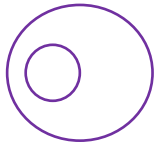


Accuracy 92%

Genetic questions

HETEROZYGOUS MUTATIONS

AR heritage



SOMATIC MUTATIONS

MOSAICISM

POLYGENY / OLIGOGENY

Late-onset PID

Genetic Variations around Hematologic Cancer

66% of 59 "Suspected-PID" → genetic variants related with IEI
30% redundant variants

	LIKELY/PATHOGENIC	VUS
1. Immunodeficiencies affecting cellular and humoral immunity **2. Combined immunodeficiencies with associated or syndromic features**	PMS2 (2), SKIV2L (1), PRKDC (1), DNMT3B (1), ATM (1)	ERCC6L2 (3), STAT3* (2), POLE (2), FOXN1*(1), PRKDC (1), JAK3 (1), DOCK8 (1), IL7R (1)
3. Predominantly antibody deficiencies	TNFRSF13B*(2), TRNT1 (1),	TNFRSF13B*(2), MSH6(1), CD19 (1), PIK3CD (1)
4. Diseases of immune dysregulation	PRF1 (2), STXBP2* (2), TET2 (1)	LYST (2), PDCD1 (1), LRBA (1), BACH2* (1)
5. Congenital defects of phagocyte number or function	CLPB (1), NCF1 (1), SBDS (1)	SBDS (2), GATA2* (1), NCF1 (1)
6. Defects in intrinsic and innate immunity	-	MYD88 (1)
7. Autoinflammatory disorders	-	PLCG2*(1), MEFV* (1)
8. Complement deficiencies	-	-
9. Bone Marrow failure	CTC1 (2)	CTC1 (1)
10. Phenocopies of IEI	-	NRAS (1)

Genetic screening revealed the presence of IEI in 66% of 59 “Suspected-PID”

59 “Suspected-PID”

	LIKELY PATHOGENIC	40%	60%
1. Immunodeficiencies affecting cellular and humoral immunity 2. Combined immunodeficiencies with associated or syndromic features	PMS2 (2), SKIV2L (1), PRKDC (1), DNMT3B (1), ATM (1)	35.3%	ERCC6L2 (3), STAT3* (2), POLE (2), FOXN1*(1), PRKDC (1), JAK3 (1), DOCK8 (1), IL7R (1)
3. Predominantly antibody deficiencies	TNFRSF13B*(2), TRNT1 (1),	15.7%	TNFRSF13B*(2), MSH6(1), CD19 (1), PIK3CD (1)
4. Diseases of immune dysregulation	PRF1 (2), STXBP2* (2), TET2 (1)	21.6%	LYST (2), PDCD1 (1), LRBA (1), BACH2* (1)
5. Congenital defects of phagocyte number or function	CLPB (1), NCF1 (1), SBDS (1)	13.7%	SBDS (2), GATA2* (1), NCF1 (1)
6. Defects in intrinsic and innate immunity	-		MYD88 (1)
7. Autoinflammatory disorders	-	4%	PLCG2*(1), MEFV* (1)
8. Complement deficiencies	-		-
9. Bone Marrow failure	CTC1 (2)		CTC1 (1)
10. Phenocopies of IEI	-		NRAS (1)

25 PID

	LIKELY PATHOGENIC	36%	64%
1. Immunodeficiencies affecting cellular and humoral immunity 2. Combined immunodeficiencies with associated or syndromic features	PRKDC (1)	25%	PRKDC (1), DOCK 8 (1), CARD 11 (1), WIPF1 (1), DNMT3B (1)
3. Predominantly antibody deficiencies	TNFRSF13B*(3), NFKB1* (1)	30%	IGLL1 (1), PIK3R1 (1), NFKB1* (1), TCF3* (1), BLNK (1)
4. Diseases of immune dysregulation	RASGRP1 (1)	10%	LRBA (1)
5. Congenital defects of phagocyte number or function	NCF1 (2)	15%	GFI1* (1), NCF1 (1), SBDS (1)
6. Defects in intrinsic and innate immunity	-		-
7. Autoinflammatory disorders	MEFV* (1)	20%	PLCG2* (2), NOD2* (1), ADAR1 (1), MEFV* (1)
8. Complement deficiencies	-		-
9. Bone Marrow failure	-		-
10. Phenocopies of IEI	-		-

Maria Palacios-Ortega et al. “Dissecting Secondary Immunodeficiency: Identification of Primary Immunodeficiency within B-Cell Lymphoproliferative Disorders”. Journal of

Genetic screening revealed the presence of IEI in 66% of 59 “Suspected-PID”

59 “Suspected-PID”

25 PID

40%

60%

36%

64%

	LIKELY PATHOGENIC	
1. Immunodeficiencies affecting cellular and humoral immunity 2. Combined immunodeficiencies with associated or syndromic features (35.3%)	PMS2 (2), SKIV2L (1), PRKDC (1), (1), ATM (1	ERCC6L2 (3), STAT3* (2), POLE
3. Predominantly antibody deficiencies (15.7%)	TNFRSF13B*(2), TRNT	TNFRSF13B*(2),
4. Diseases of immune dysregulation (21.6%)	PRF1 (TET2 (	
5. Congenital defects of phagocyte number or function (13.7%)	CLPB (1), SBDS (1)	(1), NCF1 (1)
6. Defects in intrinsic and innate immunity	-	MYD88 (1)
7. Autoinflammatory disorders (4%)	-	PLCG2*(1), MEFV* (1)
8. Complement deficiencies	-	-
9. Bone Marrow failure	CTC1 (2)	CTC1 (1)
10. Phenocopies of IEI	-	NRAS (1)

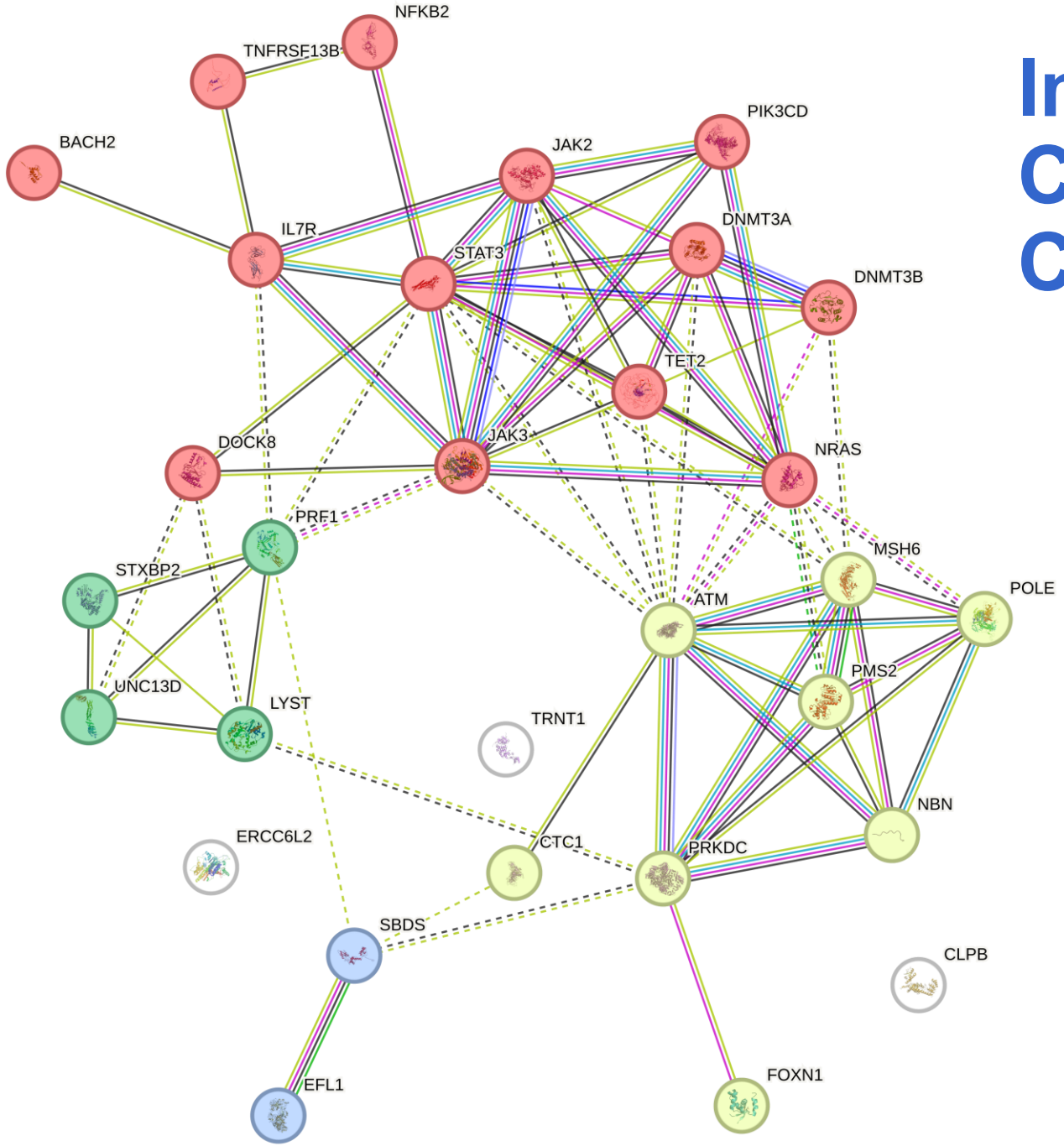
	LIKELY PATHOGENIC	
1. Immunodeficiencies affecting cellular and ith associated (25%)	PRKDC (1)	PRKDC (1), DOCK 8 (1), CARD 11 (1), WIPF1 (1), DNMT3B (1)
3. Predominantly antibody deficiencies (30%)	TNFRSF13B*(3), NFKB1* (1)	IGLL1 (1), PIK3R1 (1), NFKB1* (1), TCF3* (1), BLNK (1)
(10%)	RASGRP1 (1)	LRBA (1)
cyte number or (15%)	NCF1 (2)	GFI1* (1), NCF1 (1), SBDS (1)
6. Defects in intrinsic and innate immunity	-	-
7. Autoinflammatory disorders (20%)	MEFV* (1)	PLCG2* (2), NOD2* (1), ADAR1 (1), MEFV* (1)
8. Complement deficiencies	-	-
9. Bone Marrow failure	-	-
10. Phenocopies of IEI	-	-

Altered immunosurveillance

Defects in DNA repair processes

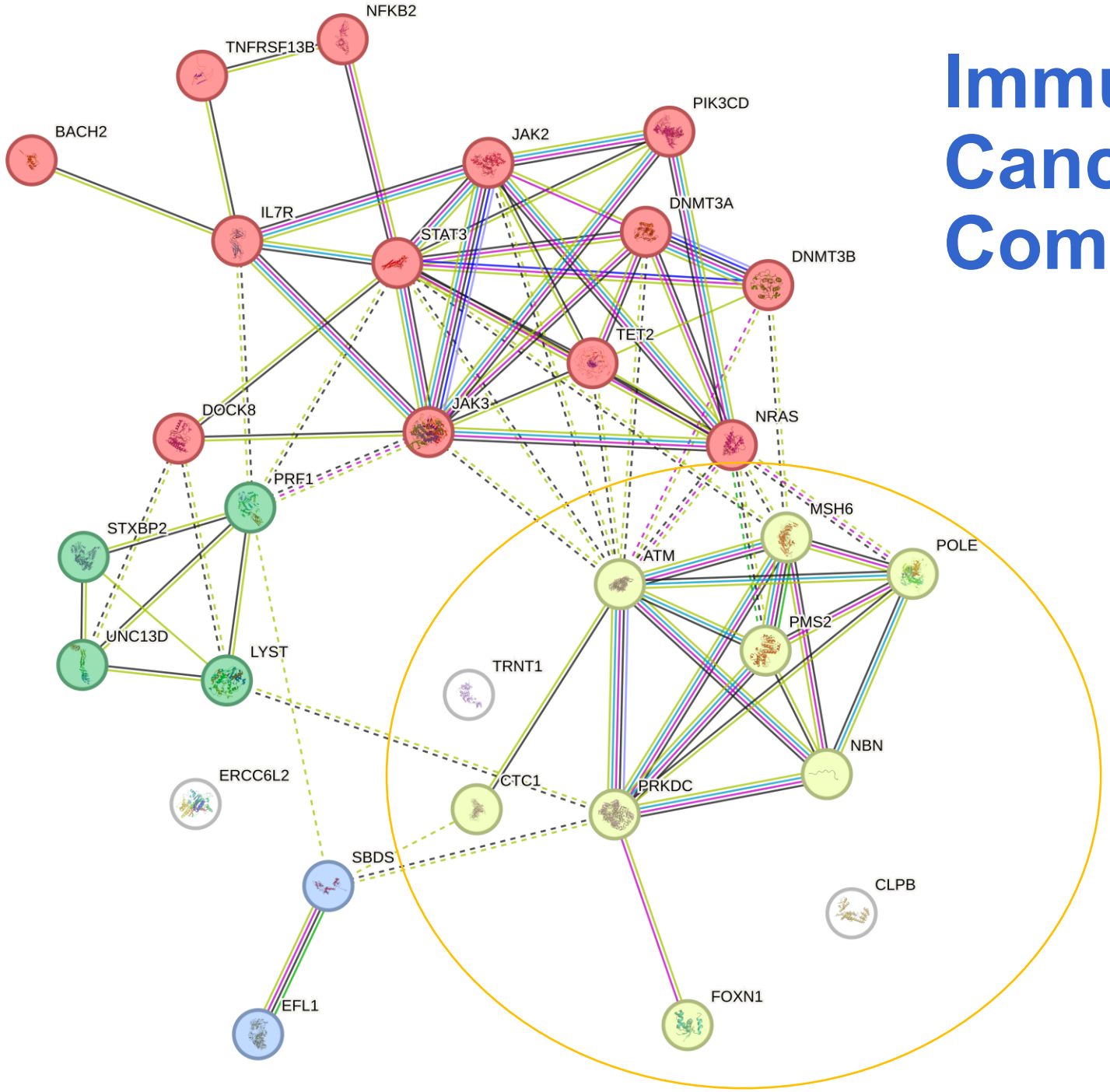
Impaired B-cell biology

Maria Palacios-Ortega et al. “Dissecting Secondary Immunodeficiency: Identification of Primary Immunodeficiency within B-Cell Lymphoproliferative Disorders”. Journal of



Immunodeficiency & Cancer Development: Common Pathways

Genetic Network
VUS + Pathogenic
Variants

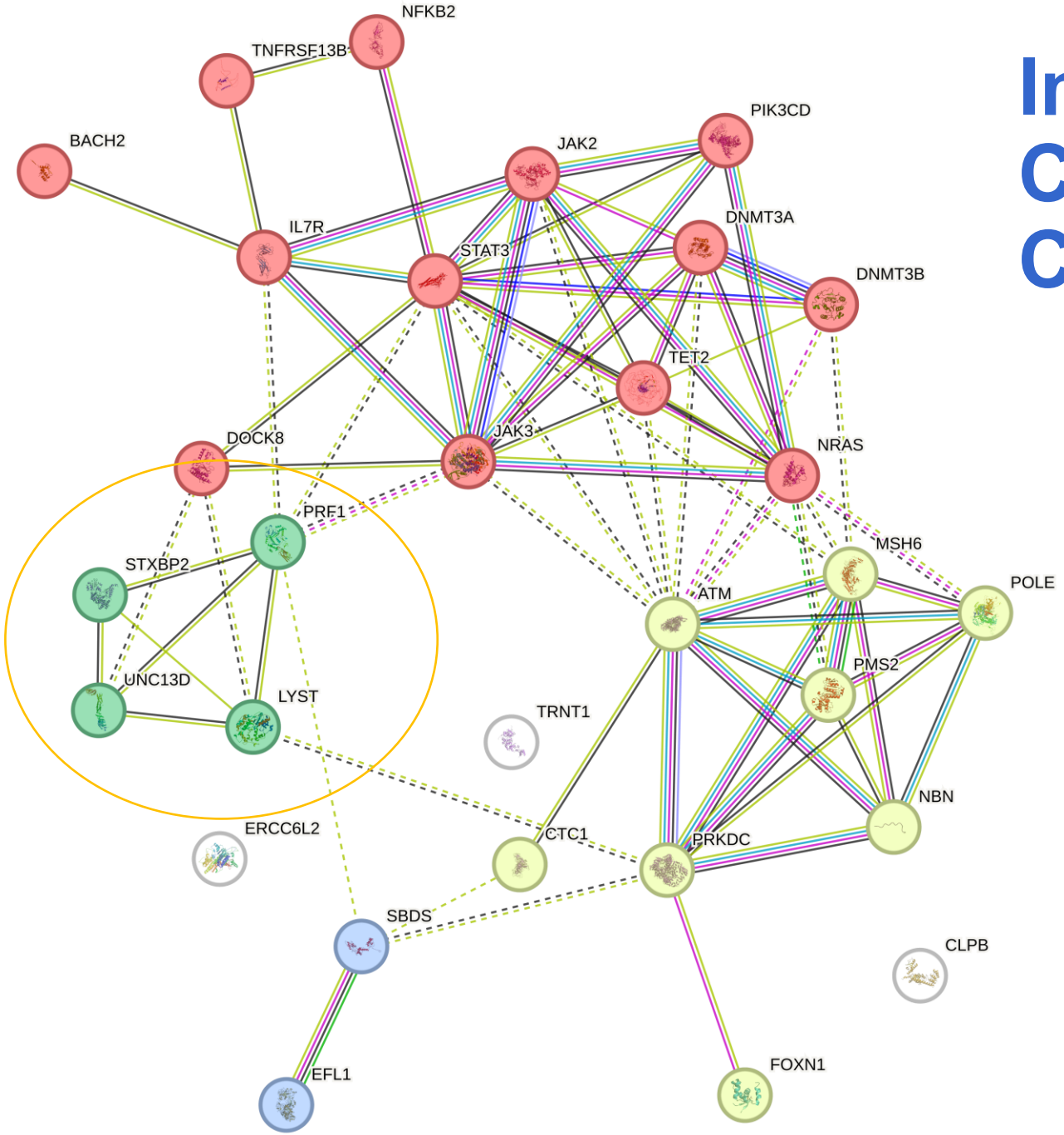


Immunodeficiency & Cancer Development: Common Pathways

DNA repair genes

PRKDC

Oncogenic cell development
AND
B cell maturation impairment



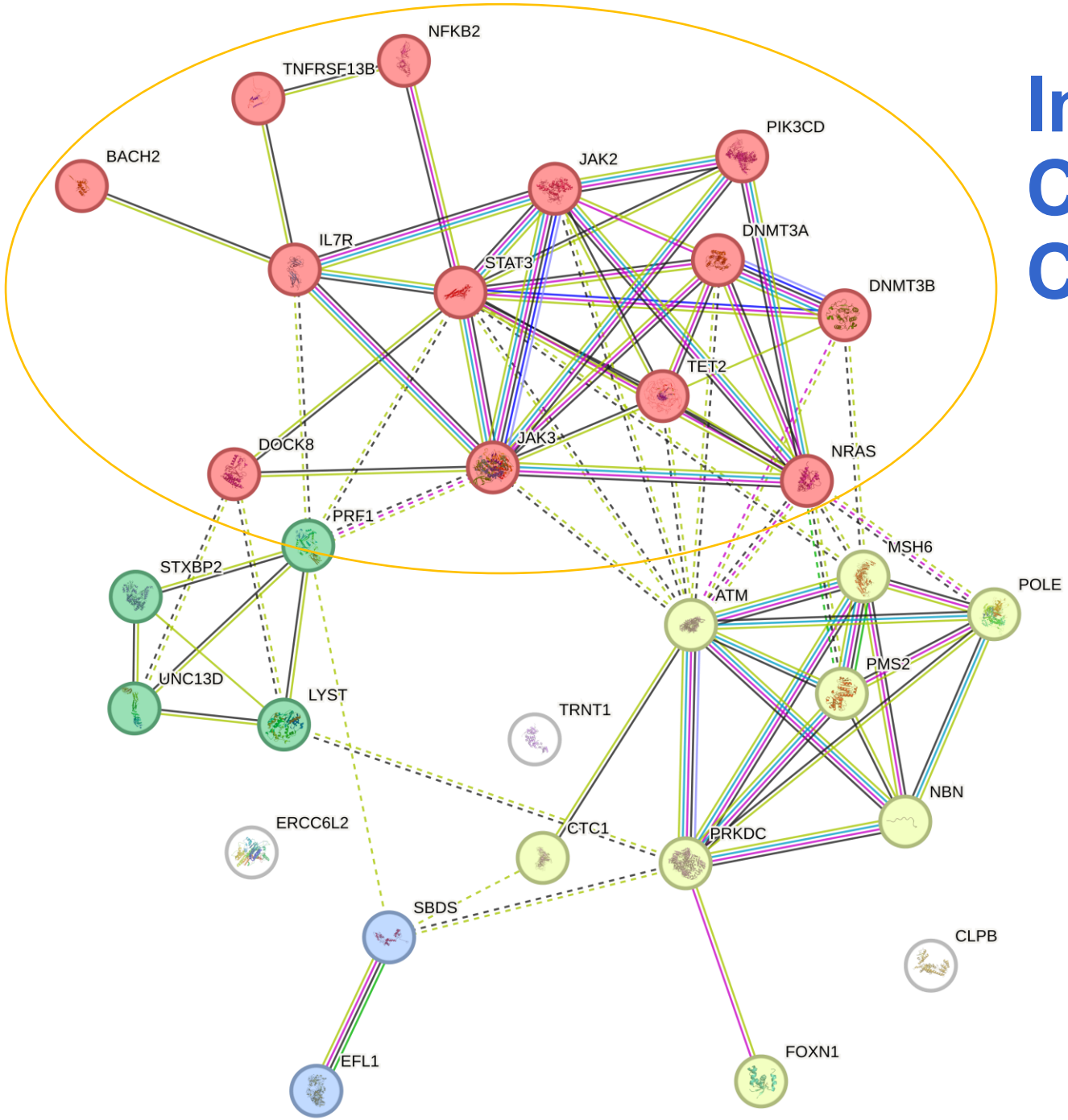
Immunodeficiency & Cancer Development: Common Pathways

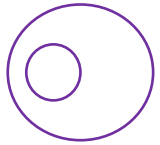
Degranulation

PRF1

Immune dysregulation AND anti-tumor immunosurveillance disruption

Immunodeficiency & Cancer Development: Common Pathways



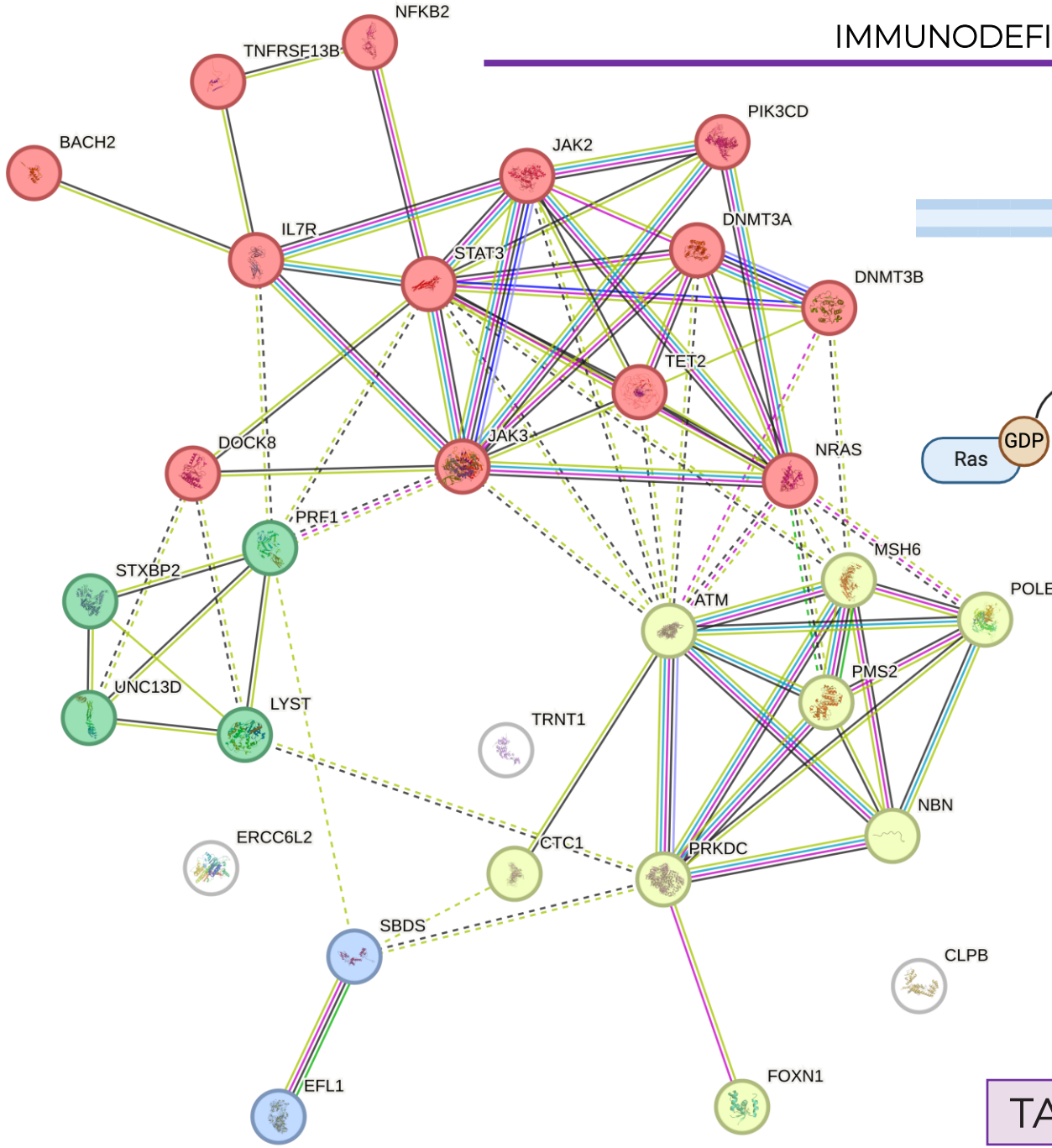


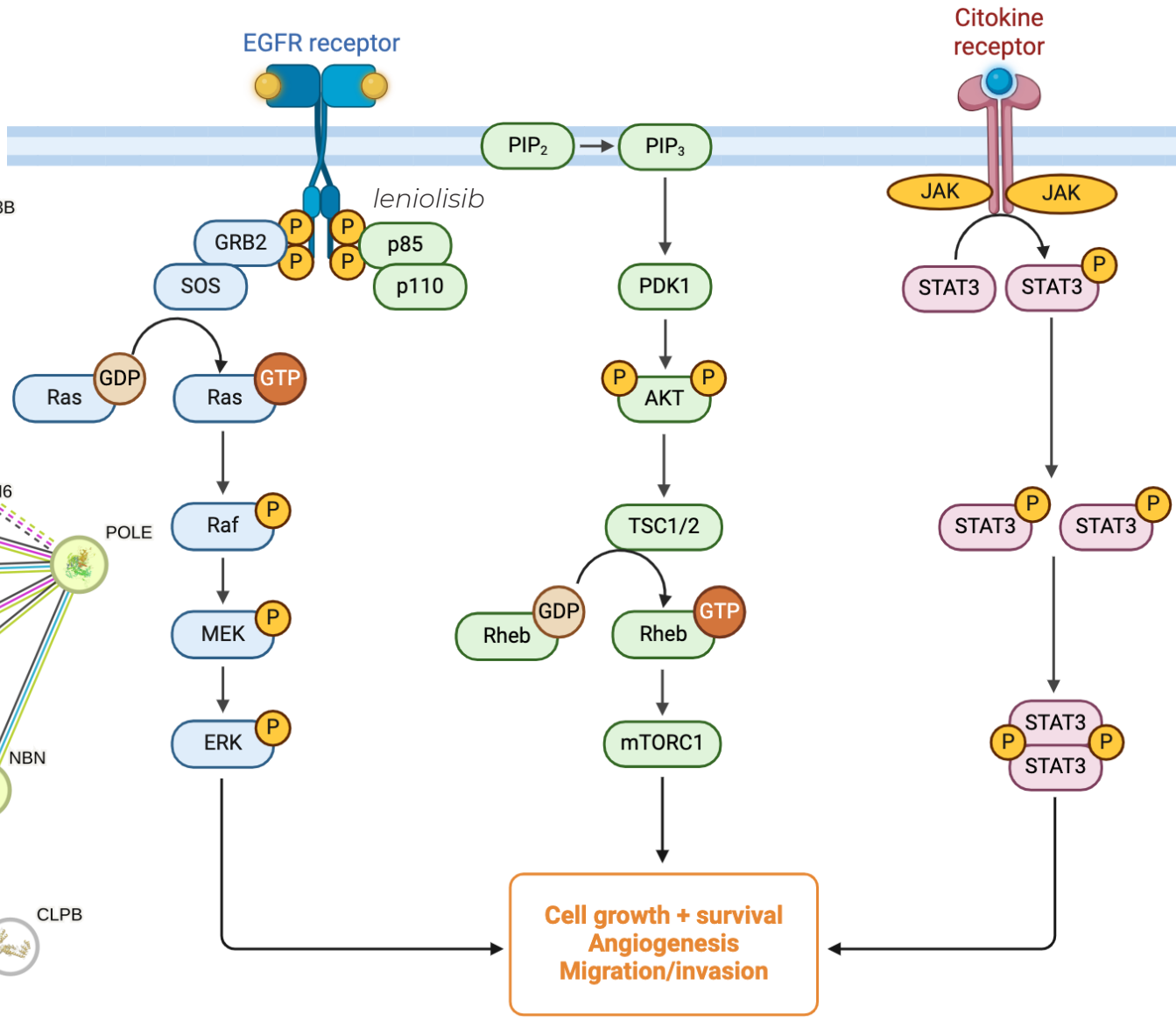
Phosphoinositide-3-kinase δ (PI3Kδ)

PI3KCD and PIK3R1

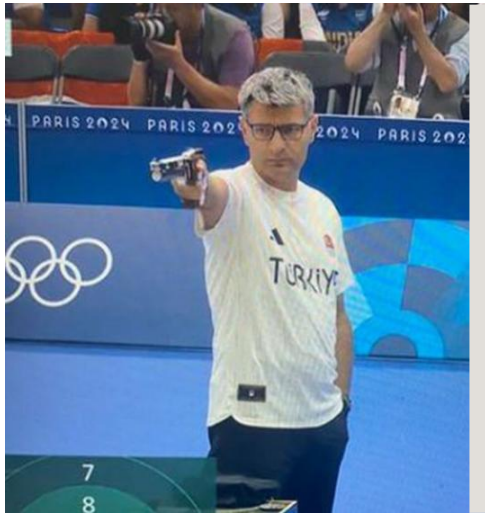
Activated PI3 Kinase Delta Syndrome (APDS) AND Malignancies (Lymphomas and solid tumors)

IMMUNODEFICIENCY AND CANCER DEVELOPMENT: COMMON PATHWAYS





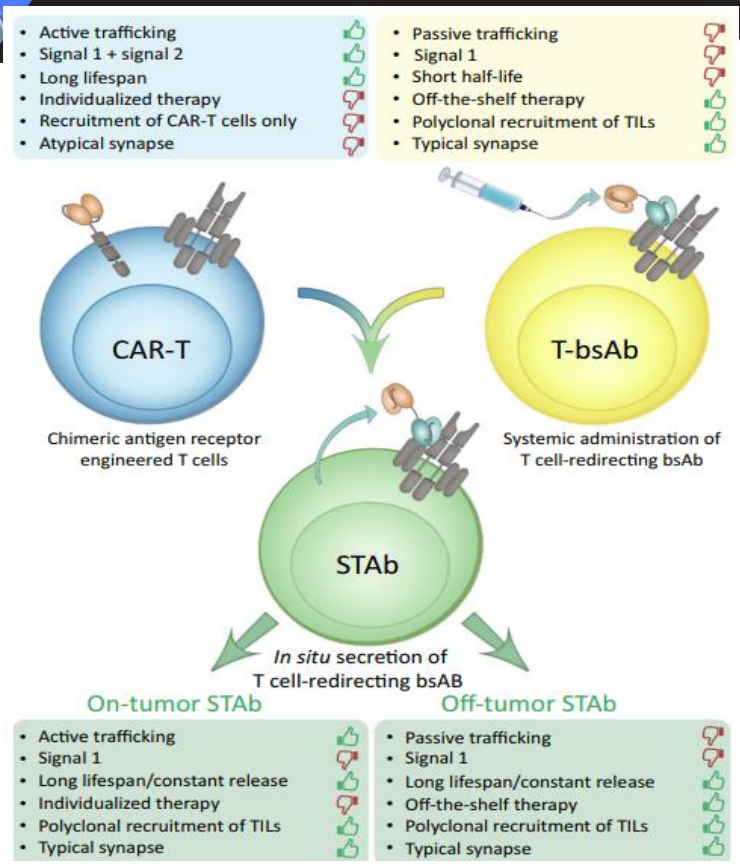
TARGETED THERAPIES → Personalized medicine



Targeted therapies based on pathophysiology

Condition	Targeted therapy
IPEX	Tacrolimus, cyclosporin, sirolimus
STAT1 GOF	Ruxolitinib (JAK1/2 inhibitor)
STAT3 GOF	Tocilizumab, siltuximab, ruxolitinib
LRBA deficiency	Abatacept
CTLA4 haploinsufficiency	Abatacept
APDS	Sirolimus, leniolisib
XIAP and *NLRC4*	IL-18 binding protein
Primary HLH	Emapalumab, ruxolitinib

Advanced therapies in refractory cases



Multicentric Study: B-LINK

Hematology & Immunology Departments

400 SID B-CLPD patients

sFLC levels: κ+λ ≤21
+
Severe / Recurrent Infections (Childhood)

"Suspected PID"

"SID"

Variables and Data Collection

Genetic Studies

WES (all patients)
Genomic DNA (genomic variants) + Tumor level if possible (somatic variants)

Variants Selection and Analysis ("PID associated genes")
+
Functional Variant Validation

Genetic counseling

Aim:

- To verify the results obtained in the pilot study.
- To define distinct clinical and immunological patterns in patients with underlying PIDs underlying the B-CLPD cohort.
- To set a new standard for early, precise diagnosis and intervention, ultimately enhancing patient outcomes and quality of life on a global scale.
- To bring us closer to personalized medicine.

The third perspective in PID-SID genetic crossovers: the tumour microenvironment

PID evolving into BCLPD

Meta-analysis of 48 studies worldwide (8123 patients with CVID):

- 790 cases with malignancy[1]
- NHL was the most prevalent malignancy (41%) in patients with CVID[1]

PID mimicking SID

- Onset as BCLPD[2]
- Germinal variants of IEI: Undiagnosed[2]

Somatic PID variants in B-cell clones

Induction of an immunosuppressive microenvironment?[3]

BCLPD, B-cell lymphoproliferative disorder; CVID, common variable immunodeficiency; IEI, inborn errors of immunity; NHL, non-Hodgkin lymphoma; PID, primary immunodeficiency;
SID. secondary immunodeficiency.

1. Kiaee F, *et al. Expert Rev Clin Immunol*. 2019;15:1105–1113; 2. Ballow M, *et al. Front Immunol.* 2022;13:928062; 3. Guevara-Hoyer K, *et al. Front Immunol.* 2022;13:937872.

Exploring gene networks associating CVID and NH lymphoma

1309 NHL samples[1]

50 CVID-associated genes and their variants[1]

323 (**25%** at least one variant)[1]
~**50%** co-occurrence of variants[2]

Gene	Prevalence (%) in samples studied (somatic mutation)	No. samples altered
PIK3CD	6	72
KMT2C	5	64
STAT3	4	57
MSH2	3	40
NFKB2	2.4	31
PTEN	1.8	24
PIK3R1	1.3	17
LRBA	0.9	12

Table adapted from Guevara-Hoyer K, *et al.* 2022.[1]

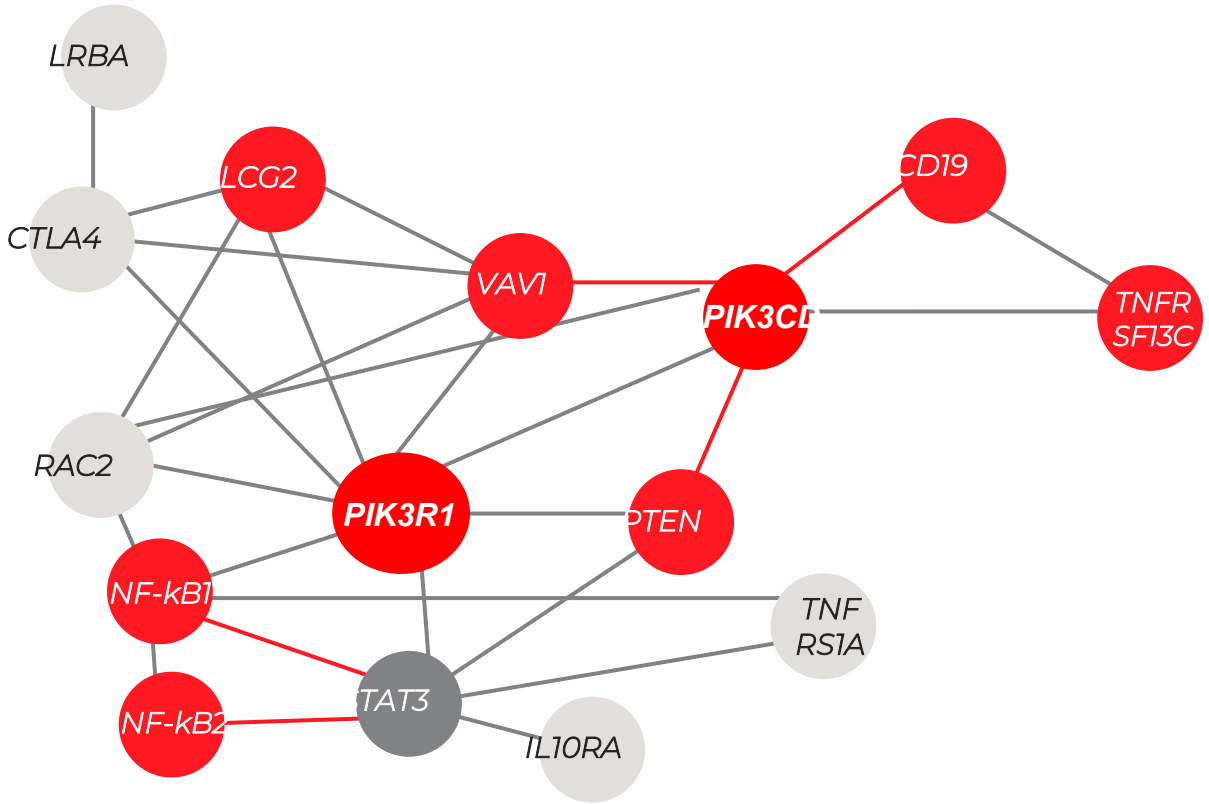
BCLPD, B-cell lymphoproliferative disorder; CVID, common variable immunodeficiency; NHL, non-Hodgkin lymphoma.

1. Guevara-Hoyer K, et al. Front Immunol. 2022;13:937872

Exploring gene networks associating CVID and lymphoma

CVID phenotype ➡ BCLPD (NHL)

BCLPD ➡ CVID-like somatic variants?



BCLPD, B-cell lymphoproliferative disorder; CD, cluster of differentiation; CVID, common variable immunodeficiency; NHL, non-Hodgkin lymphoma.
Guevara-Hoyer K, et al. Front Immunol. 2022;13:937872.


Driver variant
Passenger variant

Early Diagnosis, Management, and Humanization in the Care of Immunodeficiency in Oncohematology

- Importance of a **Multidisciplinary Unit**
- The clinical relevance of an adequate assessment and classification of the immunodeficiency in B-CLPD by serum biomarkers and immune phenotyping in predicting disease progression and guiding treatment decisions.
- The challenges in diagnosing primary versus secondary immunodeficiency and the importance of early recognition.
- Our preliminary results in molecular diagnostics not only represent an improvement in protocols but could also lead to a revolution in cancer management.
- Personalized treatment must go hand in hand with **education and support**, so that the patient understands their process and actively participates in their own health.
- The role of **specialized nursing** is key in this transformation, ensuring accessibility and continuous follow-up.

¡Thank you!
Tusen tack!!

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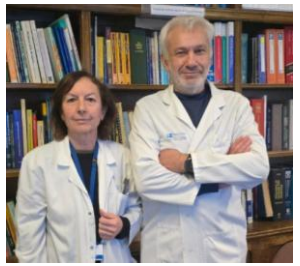

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