Understanding Primary & Secondary Immunodeficiencies

Thursday, March 3, 2022

Immune Deficiency Foundation

WELCOME!

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Immune Deficiency Foundation

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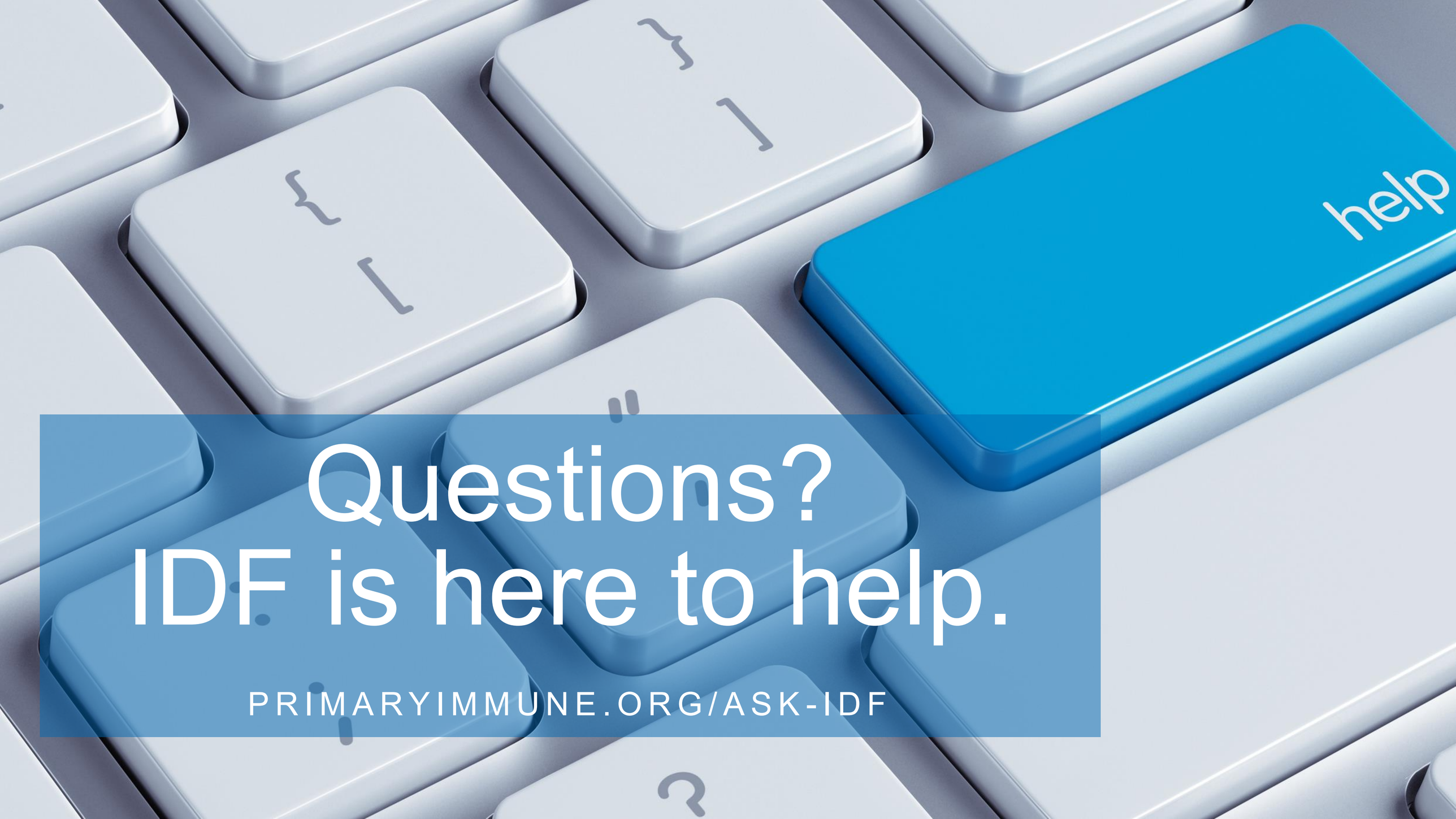
MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.

VISION

IDF seeks to ensure that everyone in the U.S. affected by PI has a fully informed understanding of

1. the PI diagnosis that affects them,
2. all available treatment options,
3. the expected standard of care,
4. all their opportunities for connection and support within the PI community.



Questions?
IDF is here to help.

PRIMARYIMMUNE.ORG/ASK-IDF


Get Connected Groups
JOIN ONE IN YOUR AREA TODAY

Upcoming Forums

- March 9: IDF Lunch & Learn – Hyper IgM Syndrome

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Understanding Primary and Secondary Immune Deficiencies

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Secondary Immune Deficiency (SID)

- Definition ---
  - Secondary hypogammaglobulinemia is characterized by reduced immunoglobulin levels due to a medication or a disease process, leading to decreased antibody production or increased antibody loss.
  - It can be challenging to distinguish between SID and Primary immunodeficiency
    - PI focuses on identifying monogenic causes that affect immune function; over 450 inherited inborn errors of immunity described thus far.
  - Most frequent causes of SID are immunosuppressive medications or loss of immunoglobulins (IgG) in the GI or urinary systems
    - The largest proportion of SID (hypogammaglobulinemia) is due to the increasing use of immunosuppressive drugs, most notably B-cell depleting therapies, and certain cancers

Medications that Cause Hypogammaglobulinemia

- Anti-rheumatic and anti-inflammatory drugs-
  - Gold, d-penicillamine, sulfasalazine
- Anticonvulsants –
  - Phenytoin, carbamazepine, levetiracetam, valproic acid, oxcarbazepine, chlorpromazine, lamotrigine, and zonisamide
  - Reduction in serum IgA most common
    - Increased incidence of IgA deficiency associated with phenytoin
  - The mechanism for drug-induced hypogammaglobulinemia is unknown

Secondary immunodeficiency (SID) associated with hematological malignancies

- B cell lymphoproliferative diseases (CLL, MM, lymphoma) – a double edge sword for SID
  - B-cells in these diseases are the initiator/origin of an immune deficiency
    - Clonal expansion
  - B-cells are a target for therapy with immunosuppressive or cell deleting drugs
    - Rituximab

- The onset of SID results in serious infections and consequences on quality of life

Arruga, F. et al. "Immune Response Dysfunction in Chronic Lymphocytic Leukemia: Dissecting Molecular Mechanisms and Microenvironmental Conditions." Int J Mol Sci 2020, 21, no. 5

Often the clinician is faced with the dilemma of “which is the cart and which is the horse” –

- does the patients have an underlying primary immune deficiency that was unrecognized prior to using immunosuppressive medications

Prolonged hypogammaglobulinemia and severe B-cell deficiency that required IgG replacement in a patient treated with Rituximab

- Case history –
  - 55 year old female who was treated with 2 courses of Rituximab 7 years ago for idiopathic thrombocytopenia purpura (ITP)
    - Developed 2 episodes of pneumonia
    - Referred to clinical immunology for evaluation with low serum IgG and absent B-cells
  - Immune evaluation-
    - Serum IgG 260 mg/dl, IgA – 24 mg/dl and IgM 40 mg/dl
    - Poor response to vaccines
    - Flow cytometry showed only 1% B-cells
  - Consequences of Rituximab or does she have CVID?
    - Started on Ig replacement therapy
    - Genetic evaluation showed she had LRBA deficiency

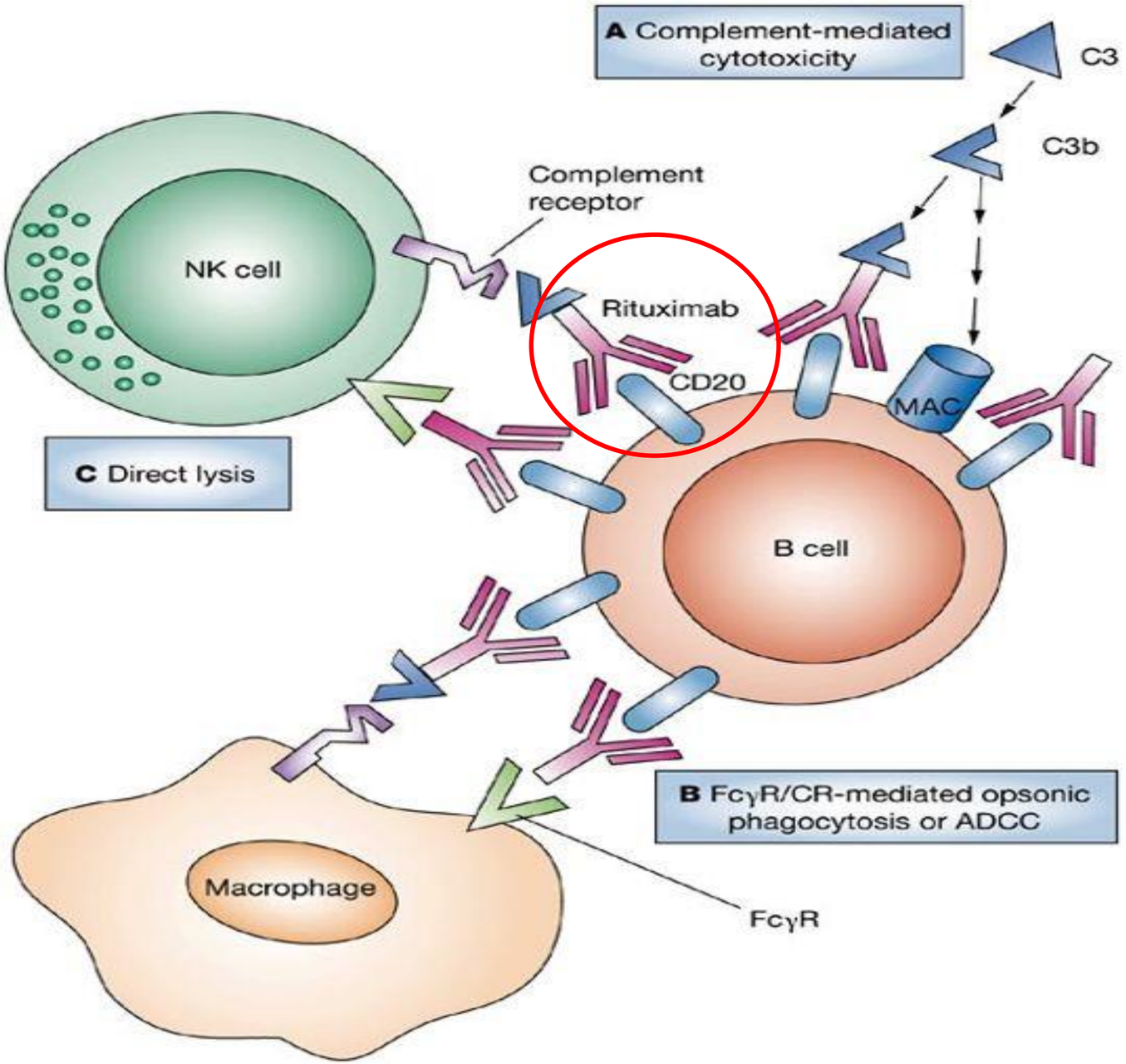
Increased risk for Hematological Malignancies in PIDD patients

Published in final edited form as:
J Allergy Clin Immunol. 2018 March ; 141(3): 1028–1035. doi:10.1016/j.jaci.2017.05.024.

Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry

- 3844 patients (2003-2015)
- 1.42-fold excess relative risk of cancer in PIDD patients vs. general population
  - 10-fold increase in risk of lymphoma in men ($p<0.001$)
  - 8.34-fold increase in risk of lymphoma in women ($p<0.001$)

Mayor, P. C., et al. "Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry." *J Allergy Clin Immunol* 2018 **141**(3): 1028-1035.


A Complement-mediated cytotoxicity
C3
C3b
Complement receptor
NK cell
Rituximab
CD20
MAC
C Direct lysis
B cell
B FcγR/CR-mediated opsonic phagocytosis or ADCC
Macrophage
FcγR

Rituximab -Anti-B-cell therapy - Recommendations

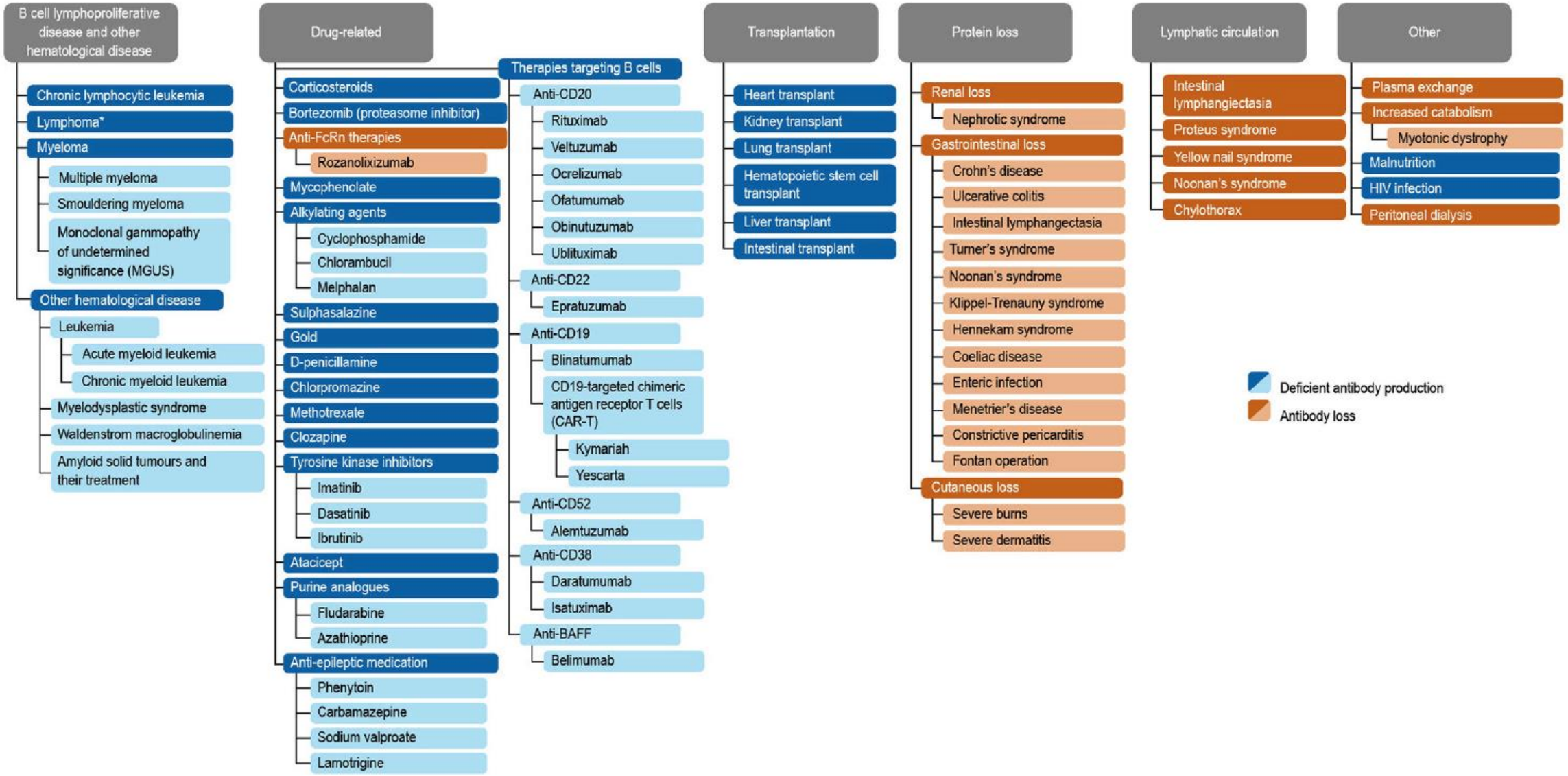
- Prolonged hypogammaglobulinemia and severe B-cell deficiency with infection requiring IgG replacement therapy
  - Concomitant other immunosuppressive therapy may contribute to the secondary immune deficiency
  - Rituximab therapy may impair vaccine responses to some degree, especially polysaccharide vaccines
    - Immunize prior to starting rituximab
  - Patients with autoimmunity treated with rituximab should have *baseline* serum immunoglobulin levels and enumeration of peripheral blood B-cells

Levy R et al Autoimmunity Rev, 2014
Kaplan B et al J Allergy Clin Immunol Pract, 2014
Makatsori M et al QJM, 2014
Pescovitz et al J Allergy Clin Immunol, 2011

CAR-T-cell Therapy

- **Chimeric antigen receptor**, or **CAR T-cell therapy**, is a novel treatment option for ALL and adult B cell lymphoma.
  - The patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient’s blood. Then the gene for a special receptor that binds to a certain protein on the patient’s cancer cells is added to the T cells in the laboratory.
    - The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion.
- CAR T-cell therapy is a cause of SID due to its CD19+ B cell depleting effect.
  - has significant immune adverse effects including B cell depletion and hypogammaglobulinemia.
  - It has been recommended that screening quantitative immunoglobulins and specific antibody titers in response to vaccines be sent prior to and 3 months after initiation of CAR-T cell therapy to risk stratify the need for prophylactic IgG-RT

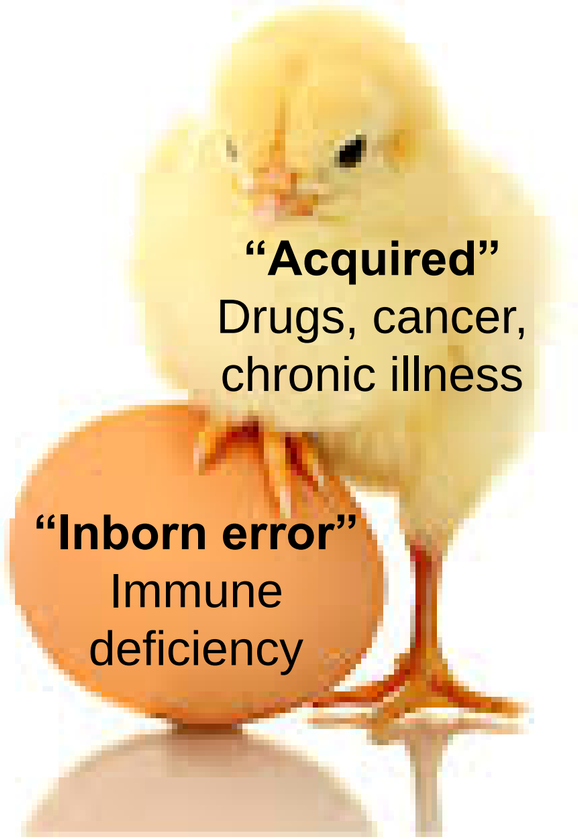
Common causes of secondary antibody deficiency



Patel, S. Y., J. Carbone, and S. Jolles. "Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management." *Front Immunol* 10 (2019): 33

Primary or secondary antibody deficiency?

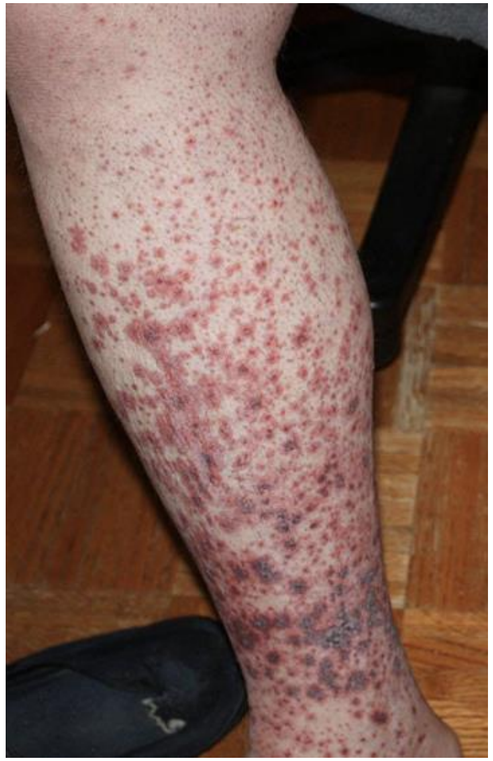
Primary



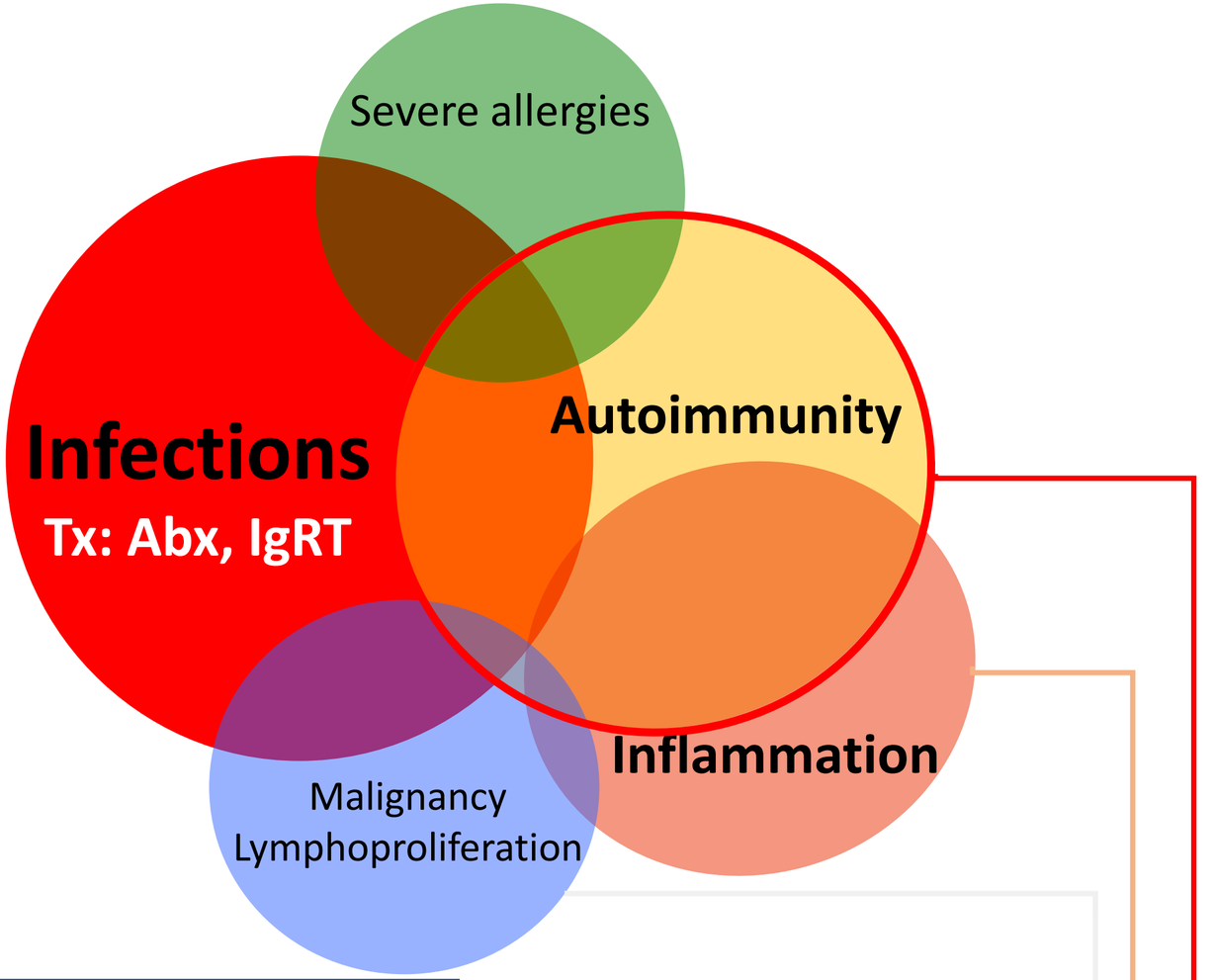
Secondary

	Primary (PID, PAD)	**Secondary (SAD)**
Classical Onset	Pediatric > Adult	Adult > Pediatric
Diagnostic workup	immune profiling + genetics	trigger profiling > immune
Treatment	IgRT, “targeted” biologics, HSCT	treatment of triggers **+ ?**
Incidence	**1:2,000 in children** **1:1,200 in patients of any age**	**<30x higher (iatrogenic)**

Warning signs for PID



Example of ITP:
Purpura and petechiae



- Often hard to treat
- May precede infections
- Multi-autoimmune diseases

Non-infectious complications in PID

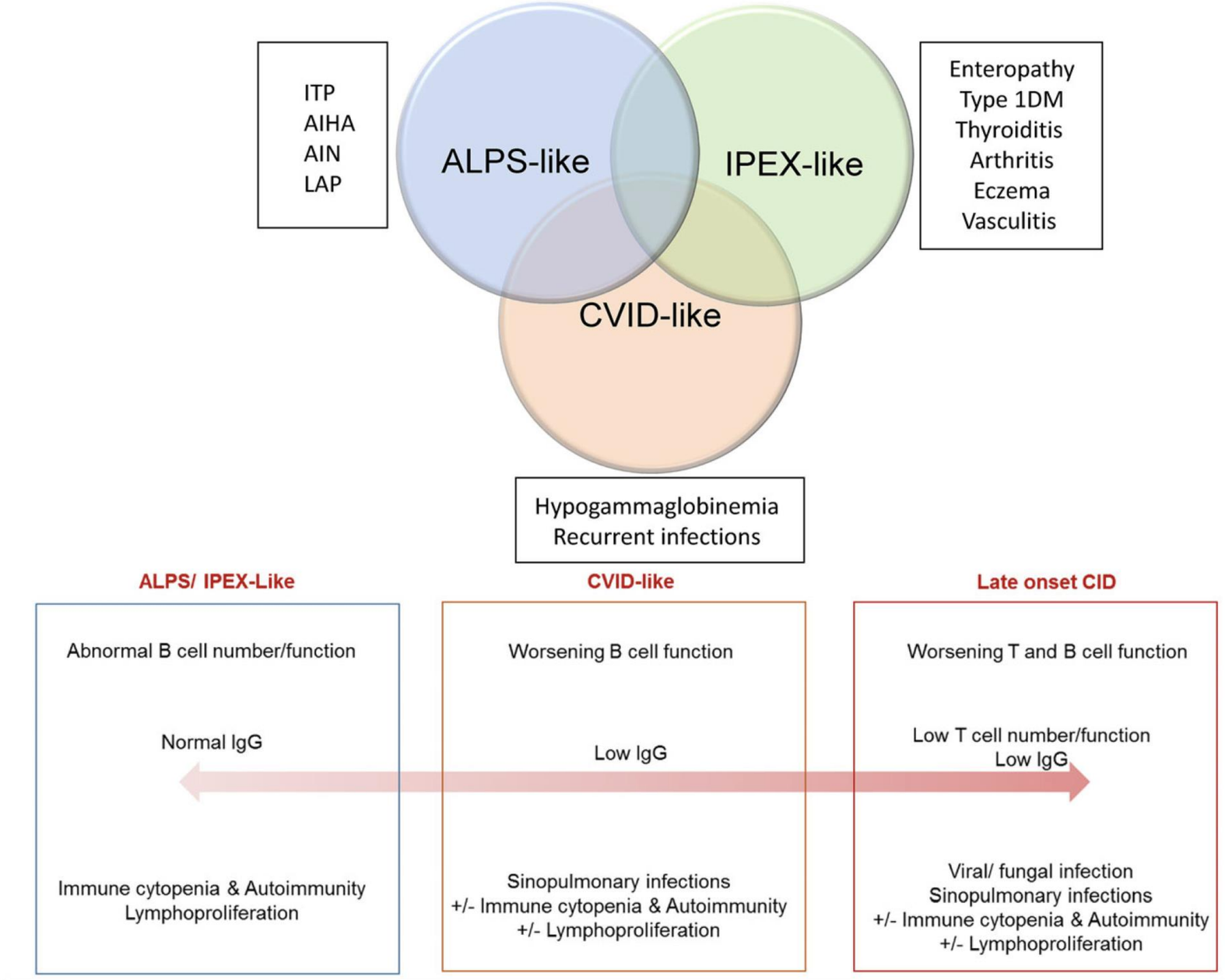
Autoimmunity is very common in PID, especially in (PIRD)

	SCID LS/OS	XLA	sIgAD	pDGS	CGD	HLH-like	COMP	WAS	HIGM	PIRD: CVID, P-CID Lo-CID, IPEX(-like), ALPS(-like)			APECED
Common genes associated with AI	*RAG IL2RG*	*BTK*	*n.a.*	*del22q11 TBX FOXN1*	*CYBB NCF1 NCF2*	*IKBKG ITK XLP1 XLP2*	*C1QRS,3,5 C6,8 C2,4A,7*	*WAS*	*AICDA*	*CTLA4, LRBA, PIK3CD ADA1/2, RAG, IKZF1 NFKB1, STAT1-GOF NFKB2, STAT3-GOF*		*FOXP3 CD25 STAT5B*	*FAS, FASLG CASP10 GATA2*	*AIRE*
Common types of AI													
AIC (AIHA, ITP, AN)	+++	+++	++	++	+	++	-	+	++	+++		++	+++	-
Thyroid disease (AIT)	++	++	++	++	+	-	-	-	-	+		+	+	+
Other endocrinopathies*	-	-	-	-	-	-	-	-	-	+		+++	-	+++
Enteropathy	+	+	-	-	+		-	+	+	+		+++	-	+
Arthritis	-	-	-	+	+	-	+	+	-	+ (*S3GOF, LRBA, CTLA4*)		+	-	-
Alopecia / Vitiligo	-	+	-	-	-	-	-	-	-	+ (*RAG, NFKB2*)		+	-	+
Autoimmune lung dz	-	-	-	-	+	-	-	-	-	+		-	-	+
Vasculitis	-	-	-	-	-	-	+ (*C2,4,7*)	+	-	+ (*RAG, ADA2*)		-	-	-
GN	-	-	-	-	+	-	-	+	-	-		-	+	-
APLA	-	-	-	-	+	-	-	-	-	-		-	-	-
SLE	-	-	+	-	+	-	+	-	-	+ (*CTLA4*)		-	-	-
CNS infiltration	-	-	-	-	-	-	-	-	-	+ (*CTLA4, LRBA*)		-	-	-
Hepatitis	-	-	-	-	-	-	-	-	-	+ (*NFKB1, S3GOF*)		+	-	+

Primary Immune Regulatory Disorder (PIRD) group:

Modified from
Walter JE et al. Current Opinion in Pediatrics 2019
PMID: 11981286

Primary immune regulatory diseases (PIRD): clinical phenotypes



Chandrakasan 2019 Pediatric Blood & Cancer PMID: 30697957

HOW TO DIAGNOSE AND TRACK PIRD PATIENTS?

CVID-like

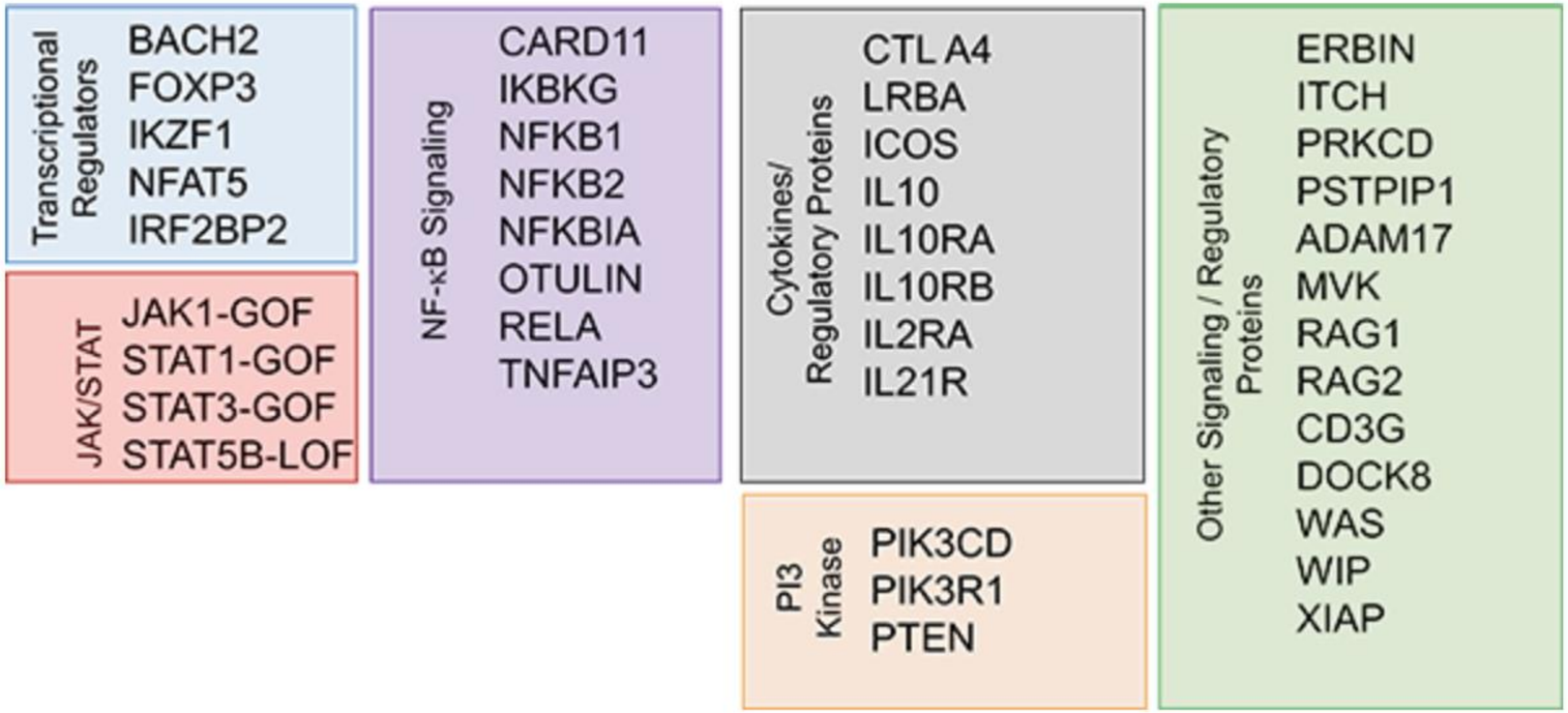
ALPS-like

IPEX-like

Too complicated
Too hard to access immune testing

Genetic evaluation for PIRD

Genetic defects associated with PIRD



www.rarediseasesnetwork.org

Biallelic defect: *LRBA, RAG1*, RAG2*, DOCK8 , STAT5B, WIP, CASP8, FADD, TPP2.* ***Gain of Function**:*** *JAK1, STAT1, STAT3, PIK3CD, PI3KR1.*
Haploinsufficiency**: *CTLA4, NFKB1, NFKB2, NFAT5, BACH2, PTEN.* ***Dominant Negative**:*** *FAS, FASLG, CARD11.*
X-linked**: *FOXP3, IKBKG, WAS, MAGT1.* ***Somatic mutations:*** *FAS, KRAS, NRAS*

Chandrakasan 2019 Pediatric Blood & Cancer PMID: 30697957

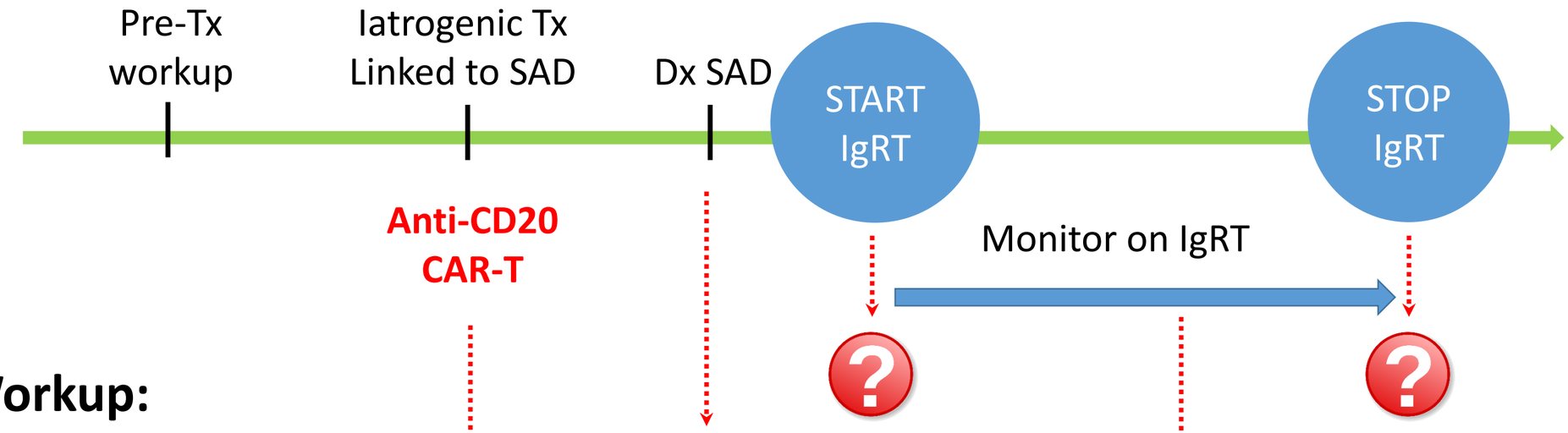
Who is at risk and need of IgRT?

If you discover…

..PID:
High likelihood for need for IgRT

How about SID?
… not everyone needs IgRT:
We lack consensus between specialties

When to start IgRT, how long to treat, when to stop?



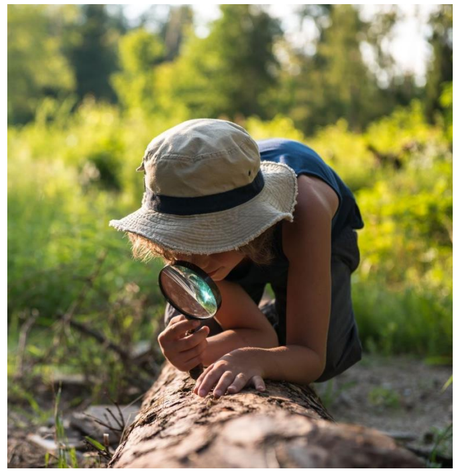
Workup:

Infectious history	✓	Yes pre/post tx
IgG	✓	↓ pre/post tx
IgA, IgM	✓	↓ pre/post tx
Vaccine titers	✓	↓ pre
Immune subsets	✓	↓ B cells
PAD Genetics?	✓	

IgA, IgM
Neoantigen challenge
(salmonella, SARS-CoV2)
B cell immune reconstitution
(counts, subsets [switched memory])

Jolles, S. AJH 2021 Treating Secondary Antibody Deficiency in Patients with Haematological Malignancy: European Expert Consensus. PMID: 33453130
Barmettler JAMA 2018 Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia PMID: 30646343

How to distinguish and treat primary among those presumed to have secondary immunodeficiency?



1. **Clinical history**
   - multiple autoimmune manifestations
   - progression with age
   - complicated treatment refractory course (**RTX**)
2. **Family history**

   variable penetrance of disease (infectious and non-infectious)
3. **Basic immune phenotyping (Ig)** can be falsely reassuring:

   CVID/CID < ALPS < IPEX-like PIRDs
4. **Genetic screen** is of high importance
5. **Biomarkers** are needed for diagnosis and treatment response
6. **Bridge therapy** to control immune dysregulation

Multi-center multidisciplinary approach for pediatric and adult patients

Hematology team
BMT team
Pulmonary team
Rheumatology team
GI team

Pediatric and Adult Hematology team
Adult Pulmonary team

Pediatric Hematology group
Pediatric Pulmonary group

Adult BMT group
Adult Malignant Heme group

THANK YOU!

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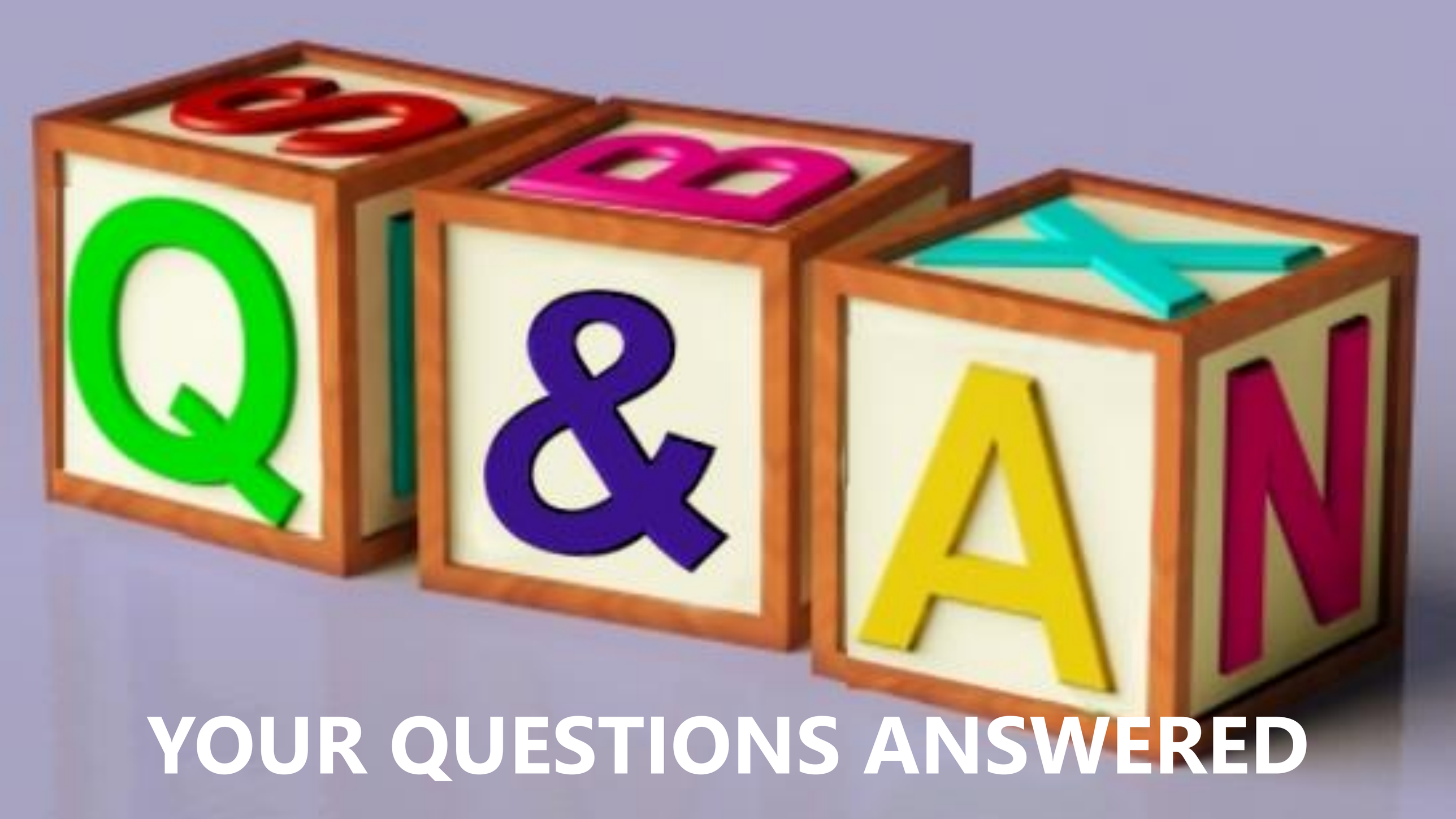

YOUR QUESTIONS ANSWERED

THANK YOU!

Mark Ballow, MD
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