VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

SPOTLIGHT ON: LINFOADENOPATIE E DISORDINILINFOPROLIFERATIVI IN IMMUNODEFICIT PRIMARI:

Inquadramento clinico

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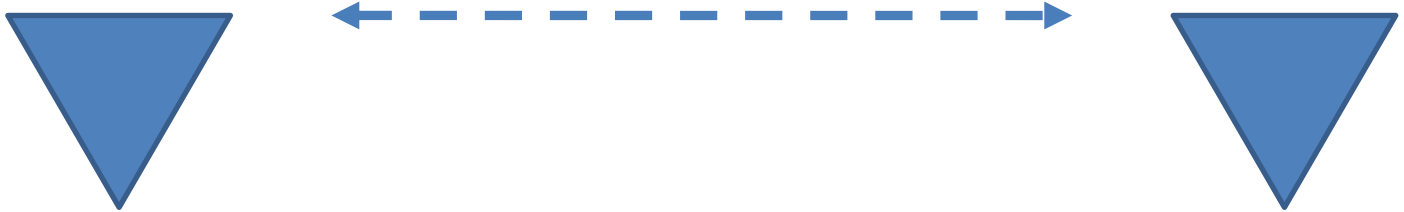
Disclosures of Francesca Conti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pharming Technologies BV	x					x	

Definition

The Inborn Errors of Immunity (IEIs) are clinically heterogeneous and often multisystemic diseases, the majority of which arise from inborn errors in immunologically relevant genes.



Susceptibility to infection with bacteria, viruses and opportunistic organisms

Immune dysregulation phenotypes of IEIs are commonplace:

- multiorgan autoimmunity,
- lymphoproliferation
- malignancy (particularly haematological)
- inflammatory pathology

Incidence: 1:500-1:500.000, but **cumulative prevalence** **1-5:1000 !!!**

Inborn Error of Immunity (IEI) and Primary Immune Regulatory Disorders (PIRD): IUIS Classification, 2024

559 genes causing **IEIs**

IEI are grouped into

10 general categories

I. Combined Immunodeficiencies
II. Combined immunodeficiencies with associated or syndromic features
III. Predominantly antibody deficiencies
IV. Immune dysregulation diseases
V. Congenital defects of phagocyte number &/or function
VI. Defects in innate immunity
VII. Autoinflammatory disorders
VIII. Complement deficiencies
IX. Bone Marrow Failure
X. Phenocopies – Somatic mutations that mimic inherited mutation and PID

129 genes causing **PIRDs**

Autoimmunity, hyperinflammation, lymphoproliferation, malignancy, and severe atopy with less dominant features of immunodeficiency and infection.

- Tregopathies (IPEX, IPEX-like)
- Autoinflammatory syndromes
- hyperinflammatory disorders (predisposition to HLH)
- Debris defects
- **Non malignant lymphoproliferation (ALPS, ALPS-like/ALPS-U)**
- Hematopoietic malignancies
- Congenital atopic hypersensitivity
- IBD
- Rheumatologic diseases

J Hum Immun (2025) 1 (1):
https://doi.org/10.70962/jhi.20250002

Definition of nonmalignant lymphoproliferation (LPDs)

- LPDs are characterized by proliferating (and/or persistent) clonal or polyclonal lymphoid cells that may arise as aberrant responses to immune stimuli or represent intrinsic immune dysregulation
- Clinically and genetically heterogeneous
- Often associated with a wide range of clinical phenotypes
- Clinical presentations: chronic or recurrent lymphadenopathy, splenomegaly, or symptoms resulting from organ infiltration by abnormal lymphoid cells
- Increased predisposition toward developing hematopoietic malignancies, specifically lymphoma

When a lymph node biopsy sample rules out infections and malignancy, the diagnostic and therapeutic paths forward for patients with evidence of lymphoproliferation remain **poorly defined**

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumors: Lymphoid Neoplasms

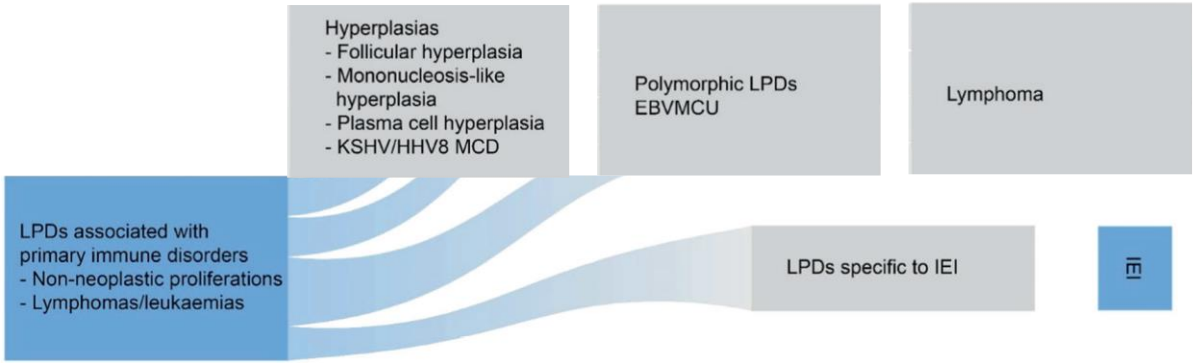


Table 5. Three-part nomenclature for lymphoid proliferations and lymphomas arising in the setting of immune deficiency/dysregulation.

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

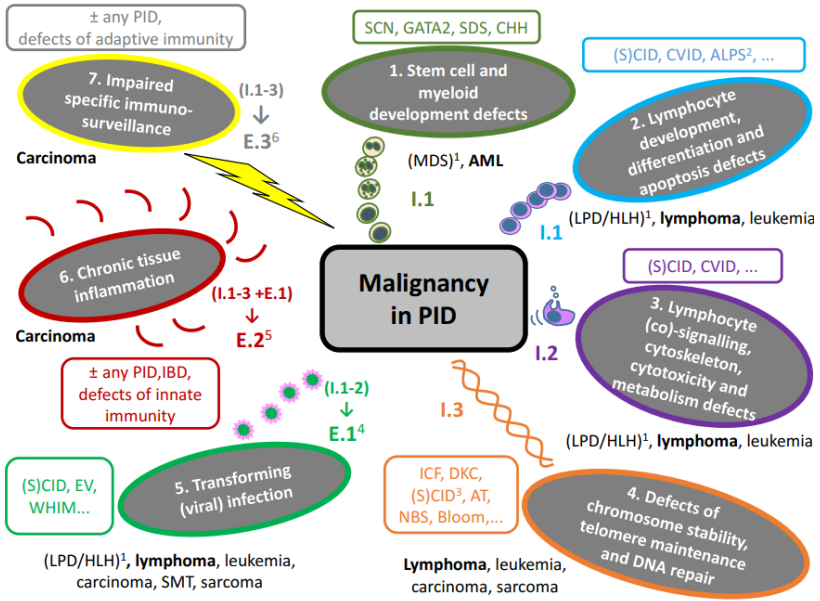
Integrated diagnostic approach

Patients with IEI may develop distinctive types of lymphoid proliferations unique to particular IEI

Modified by Leukemia; https://doi.org/10.1038/s41375-022-01620-2

LPDs and IEIs

- Nonmalignant lymphoproliferative disorders (**LPDs**) often underly an Inborn Error of Immunity (**IEI**)
- LPDs are associated with an increased predisposition toward developing hematopoietic malignancies, specifically lymphoma



- LPDs diagnosis is challenging
- Difficulties both in the clinical assessment of the patient, histological classification, and in the identification of pathogenic mechanisms to differentiate LPDs

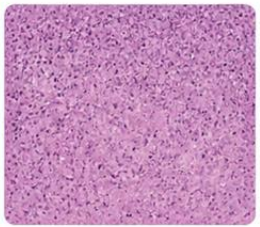
Mechanism based-therapy

2018 Jan;141(1):59-68.e4. doi: 10.1016/j.jaci.2017.06.009

Morphologic features of IEI-associated LPDs

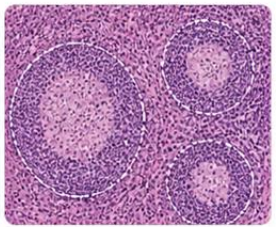
COMMON FINDINGS

Lymphoid depletion



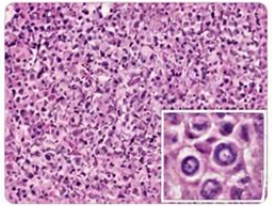
Overall reduction in lymphoid cellularity in lymph node.

Atrophic follicles with progressive depletion of germinal centers



Small, atrophic follicles with reduced or absent germinal centers.

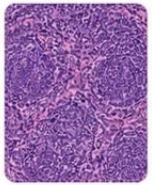
Depletion of small lymphocytes in paracortical area with increase in histiocytes and plasma cells



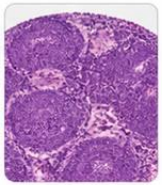
Paracortex shows reduced small lymphocytes and increase in histiocytes and plasma cells.

Similar findings observed in spleen and tonsils at autopsy

Spleen



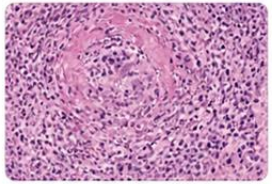
Tonsil



Comparable morphologic changes seen in spleen and tonsils.

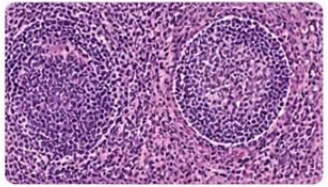
SECONDARY CHANGES

Chronic granulomatous inflammation secondary to infections



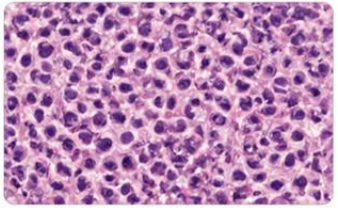
Granuloma formation with epithelioid histiocytes and multinucleated giant cells, often related to persistent infections.

Florid reactive hyperplasia



Prominent lymphoid proliferation with preserved architecture and active germinal centers.

Atypical hyperplasia

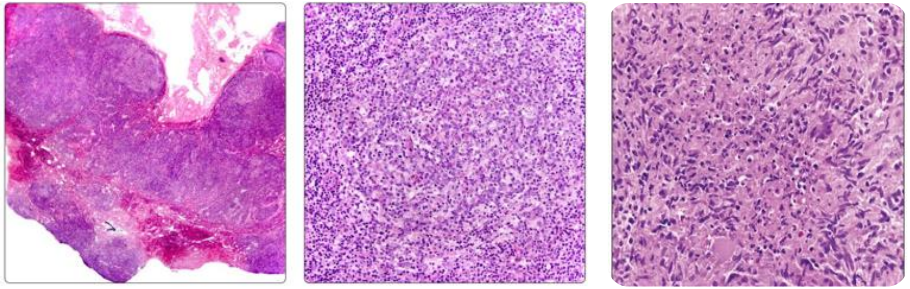


Expansion of atypical lymphoid cells with cytologic atypia and architectural effacement, potentially mimicking lymphoma.

https://basicmedicalkey.com/overview-of-lymphoproliferative-disorders-associated-with-primary-immune-deficiency-disorders/

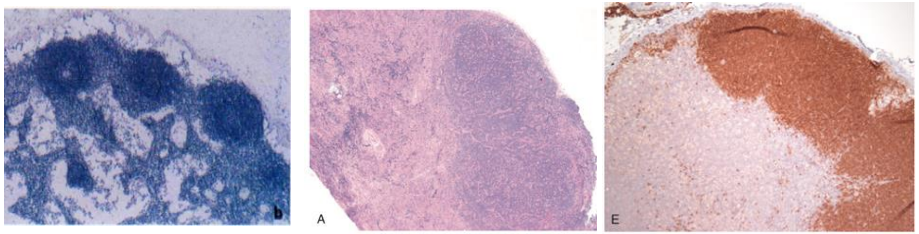
Lymph node morphology and IEIs… a few examples

Common Variable ImmunoDeficiency (CVID)



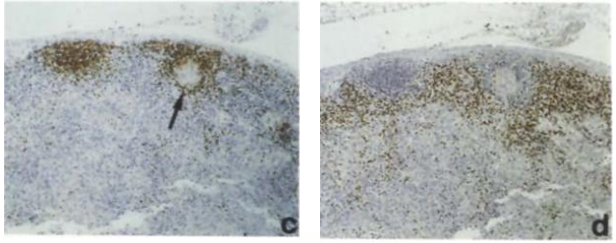
- variable nodal morphology
- follicular hyperplasia
- paracortical expansion

CD40L Deficiency (HIGM-1 syndrome)



- primary follicles with lack of germinal center cell reaction
- paracortex poorly developed

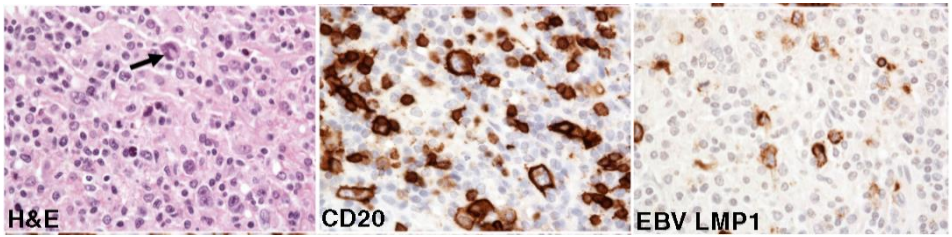
Wiskott-Aldrich Syndrome (WAS)



- reactive changes in the follicles (full-blown to exhausted germinal centers)
- depletion of T cells
- Plasma cells can be prominent, with atypical forms
- eosinophils and extramedullary hematopoiesis can also be observed

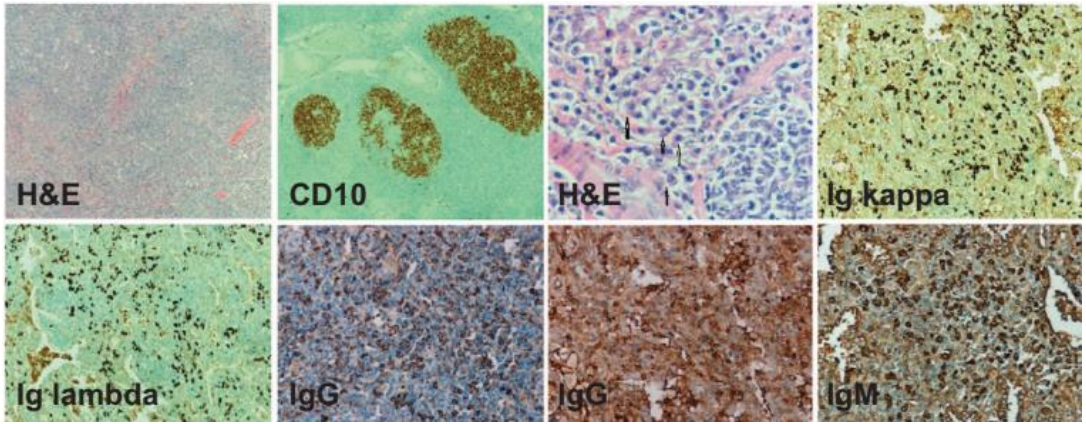
Lymph node morphology and IEIs…a few examples

X-linked immunodeficiency with **M**agnesium defect **EBV** infection and **N**eoplasia **(XMEN)**



- EBV-driven lymphoproliferative disease
- **atypical Reed-Sternberg-like cells**
- staining for **CD20**
- **EBV LMP1**

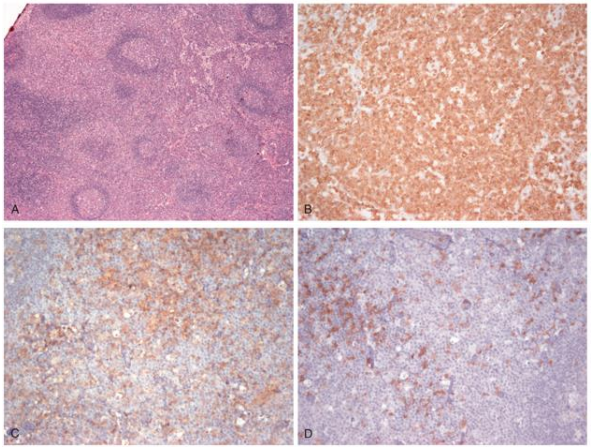
Lipopolysaccharide (LPS)-responsive and beige-like anchor protein deficiency **(LRBA deficiency)**



- nodal architecture can be preserved
- abundant germinal centres
- plasma cells being present despite B cell disruption

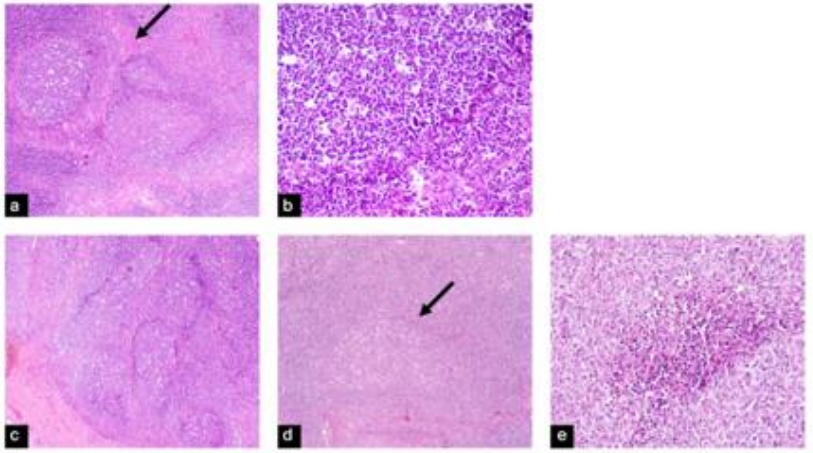
Lymph node morphology and IEIs…a few examples

Autoimmune **Ly**mpho**p**roliferative **S**yndrome **(ALPS)**



- The paracortex of the lymph node is markedly expanded
- Small lymphoid follicles are present
- paracortex is populated by small lymphocytes and many large immunoblasts with prominent nucleoli

Activated **P**I3K-kinase **D**elta **S**yndrome **(APDS)**

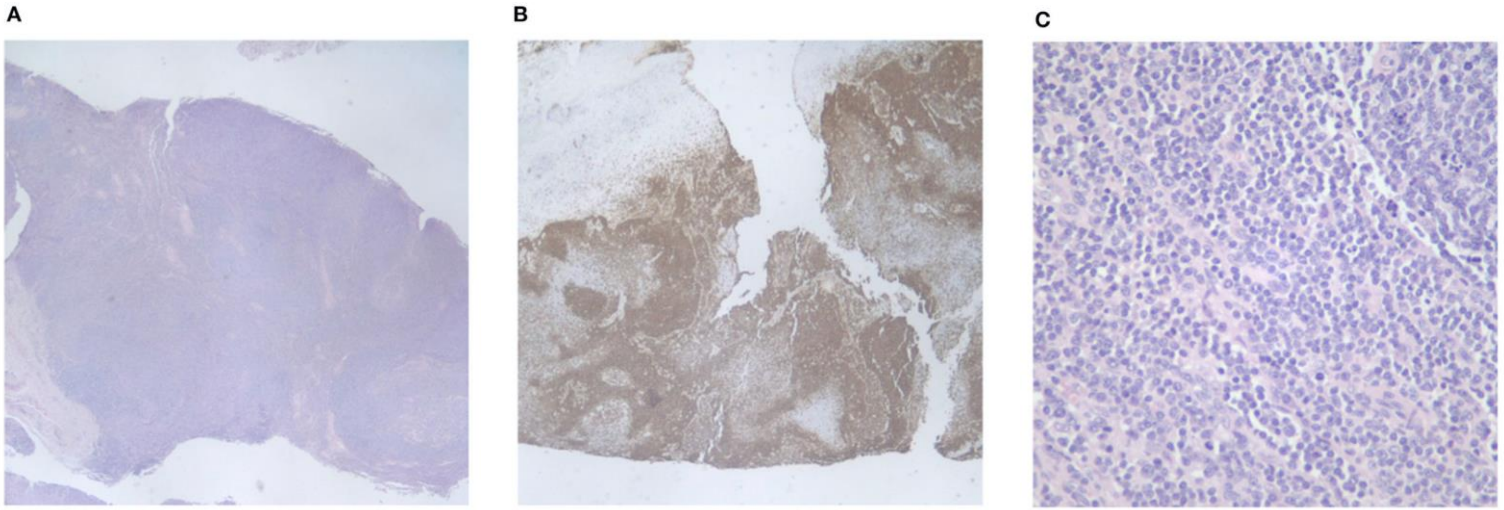


- (A,C,D) large and irregularly expanded "naked" GCs with ill-defined outlines, loss of the mantel zone and polarization, monocytoid B-cell hyperplasia, numerous large histocyte and tingible bodies;
- (A) the arrow shows area of sclerosis around the follicle
- (B) absence of mantel zone surrounding the germinal center
- (E) foci of necrosis

Jaffe, E. *et al* (2016)

Rivalta B *et al* (2021)

Cervical lymph node pathology in a patient with APDS1



(A) Effacement of lymph node architecture, with vague nodular growth pattern
(B)-(C) Increased CD20 tissue staining in the lymph node tissue

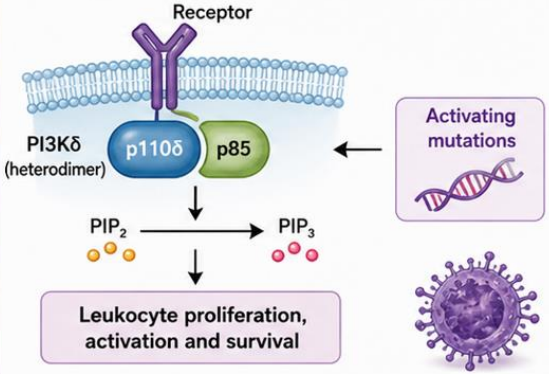
- **Lymphadenopathy** is **common** in APDS patients and the evaluation of this is challenging due to the **broad differential**
- Patients may **have lymphoid hyperplasia** in MALT-associated sites making it **difficult** to **distinguish** between **benign** and **malignant proliferations.**
- **C**lonal lymphocyte populations may also be seen in patients without lymphoma

Front Pediatr. 2018 Dec , doi.org/10.3389/fped.2018.00402

Activated Phosphoionositide-3 kinase Delta Syndrome (APDS)

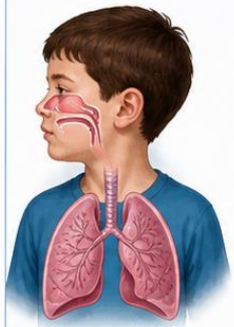
1. MOLECULAR BASIS

APDS is caused by activating mutations in phosphoinositide 3-kinase delta (**PI3Kδ**) which is a heterodimer present predominantly in leukocytes and plays an important role in leukocyte proliferation, activation and survival.



2. CLINICAL PRESENTATION

This syndrome usually presents in childhood with recurrent sinopulmonary infections, immune deficiency and lymphadenopathy but adulthood onset is possible.



- Recurrent sinopulmonary infections
- Immune deficiency
- Lymphadenopathy

Onset in childhood but adulthood onset is possible

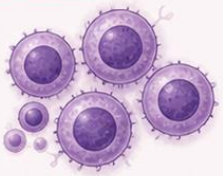
3. ASSOCIATED FEATURES

Patients with APDS also experience:

- Lymphoid hyperplasia
- Autoimmunity
- Increased susceptibility to herpes viruses, especially Epstein–Barr virus (EBV) and cytomegalovirus (CMV)

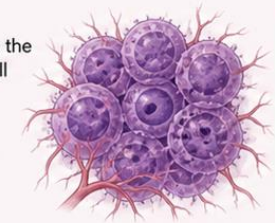
4. RISK OF B-CELL LYMPHOMA

Activating PI3Kδ mutations lead to increased B-cell signaling and proliferation.



→ Combined with immune dysregulation and impaired immune surveillance...

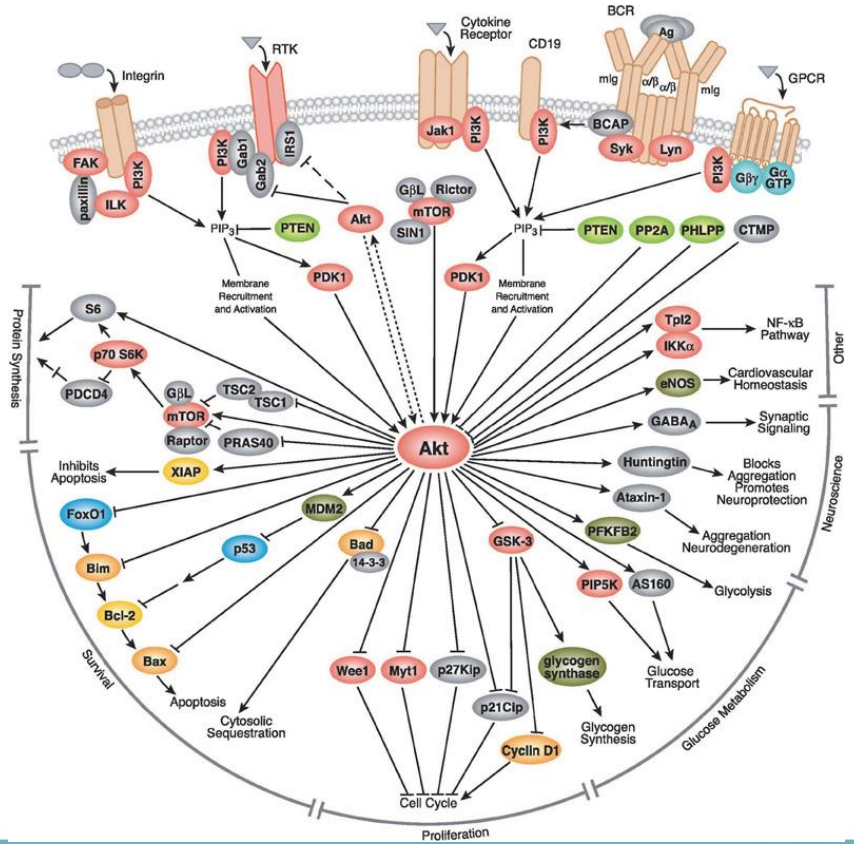
→ ...this may contribute to the development of B-cell lymphoma.



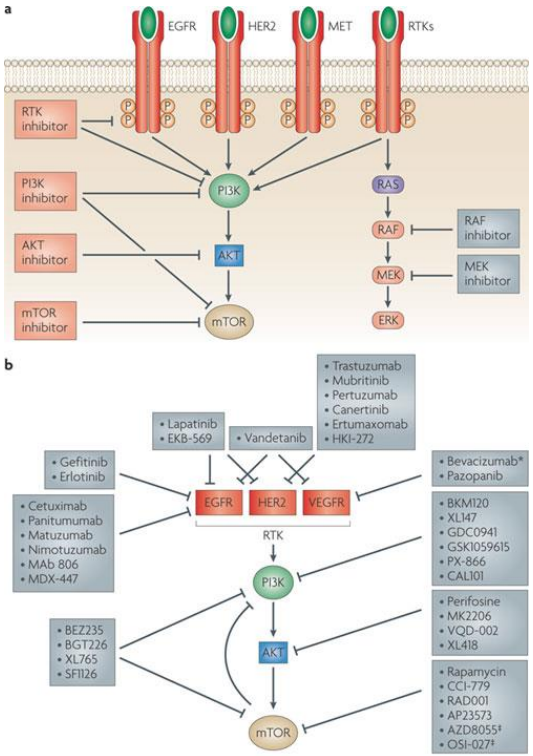
KEY POINT

The combination of immune dysregulation, chronic immune activation and increased B-cell proliferation predisposes patients with APDS to B-cell lymphoma.

The AKT signaling pathway



Targeting the PI3K/AKT/mTOR Pathway



Front. Mol. Neurosci., 15 March 2012

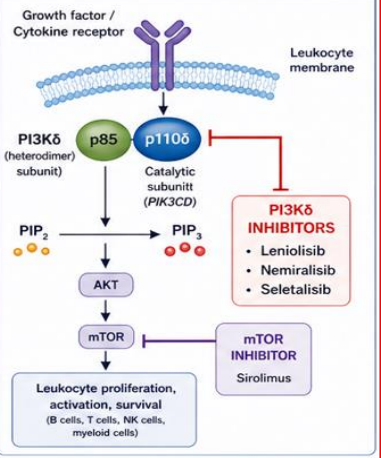
Liu et al. Nature Rev Drug Discovery. 2009;8:627-44

Activated Phosphoinositide-3 Kinase Delta Syndrome (APDS): Targeted Therapies

FROM GENETICS TO THERAPY

Activating germline mutations in *PIK3CD* → Hyperactivation of PI3Kδ pathway → Immune dysregulation, lymphoproliferation, autoimmunity, infections, ↑ risk of B-cel lymphoma

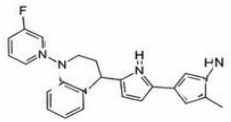
PI3Kδ PATHWAY AND SITE OF ACTION



APDS: CAUSE AND CONSEQUENCES

- Activating germline mutations in *PIK3CD* (gain-of-function)
- Hyperactivation of PI3Kδ pathway
- Clinical manifestations: recurrent infections, lymphoid hyperplasia, autoimmunity, splenomegaly/ lymphadenopathy
- Increased risk of B-cell lymphoma

LENIOLISIB (CDZ173)



Selective PI3Kδ inhibitor (Oral, once-daily)

KEY RESULTS

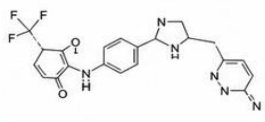
- Significant reduction in severe infections rate by ~70%
- Reduction in lymphadenopathy and splenomegaly
- Improvement in humoral immunity (increased IgM, IgA, IgG)
- Well tolerated: most common AEs diarrhea, URTI, neutropenia

CLINICAL TRIAL REFERENCE

TALENT Study Group
Open-label phase 3 TALENT trial
J Clin Immunol. 2021;41(6):1132–1142.
NCT03462817

Leniolisib is the first-in-class PI3Kδ inhibitor approved by FDA (2023) for APDS in patients ≥ 12 years and weighing ≥ 40 kg.
EMA under evaluation; AIFA under evaluation.

NEMIRALISIB (GS-9820)



Highly selective PI3Kδ inhibitor (Oral, once-daily)

KEY RESULTS

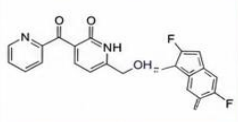
- Marked reduction of serious infections and antibiotic use
- Reduction in lymph node size and spleen volume
- Improvement in immunoglobulin levels and vaccine responses
- Good safety profile; mostly grade 1–2 AEs (diarrhea, headache, URTI)

CLINICAL TRIAL REFERENCE

Lucas CL et al.
Phase 2 NEMO trial
J Clin Invest. 2021;131(20):e150544.
NCT03047848

Nemiralisib showed robust efficacy in reducing infections and immune dysregulation with a favorable safety profile.

SELETALISIB (GS-1059615)



Selective PI3Kδ inhibitor (Oral, once-daily)

KEY RESULTS

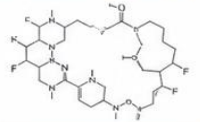
- Significant reduction in infections and hospitalization
- Improvement in lymphoproliferation (spleen and lymph nodes)
- Increase in naive B cells and immunoglobulin levels
- Well tolerated; low discontinuation rate

CLINICAL TRIAL REFERENCE

Holland SM et al.
Phase 2 SPRING trial
Blood. 2022;140(Suppl 1):126–128.
NCT03462654

Seletalisib demonstrated clinical benefit APDS with improvement of immune parameters and low toxicity.

SIROLIMUS (Rapamycin)



mTOR inhibitor (Oral, once or twice daily)

KEY RESULTS

- Reduction in lymphoproliferation (splenomegaly, lymphadenopathy)
- Decrease in B-cell activation and plasmablasts
- Improvement in cytopenias (especially autoimmune)
- Useful in patients intolerant or refractory to PI3Kδ inhibitors

CLINICAL TRIAL REFERENCE

Cortez-Retamozo V et al.
Open-label phase 2 trial of sirolimus in APDS patients
J Allergy Clin Immunol. 2014;134(1):40–48.
NCT01873203

Sirolimus provides clinical benefit, particularly in controlling lymphoproliferation and autoimmune complications.

THERAPEUTIC STRATEGY

Targeting the PI3Kδ pathway (upstream) with selective inhibitors or mTOR (downstream) with sirolimus restores immune homeostasis and improves clinical outcomes in APDS.

COMPARISON OF TARGETED THERAPIES IN APDS

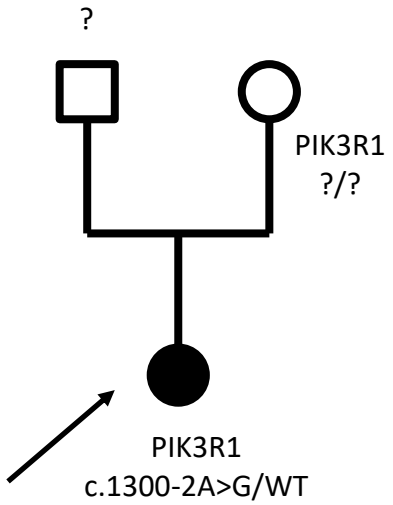
Drug	Target	Selectivity	Administration	Key Indication	Main Benefit
Leniolisib (CDZ173)	PI3Kδ	Selective	Oral, once daily	Infections, lymphoproliferation	↓ infections ~70%, ↑ Ig, ↓ LN/spleen
Nemiralisib (GS-9820)	PI3Kδ	Highly selective	Oral, once daily	Infections, immune dysregulation	↓ infections, ↓ LN/spleen, ↑ Ig
Seletalisib (GS-1059615)	PI3Kδ	Selective	Oral, once daily	Lymphoproliferation, infections	↓ hospitalization, ↑ naive B cells, ↑ Ig
Sirolimus (Rapamycin)	mTOR	— (downstream)	Oral, once/twice daily	Lymphoproliferation, autoimmunity	↓ LN/spleen, ↓ B-cell activation, ↑ cytopenias

Abbreviations: PI3Kδ, phosphoinositide-3 kinase delta; PIP_2, phosphatidylinositol (4,5)-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-trisphosphate; mTOR, mechanistic target of rapamycin; Ig, immunoglobulin; LN, lymph nodes; AEs, adverse events; URTI, upper respiratory tract infection.

Personalized Care: A Real-Life Example of Tailored Medicine

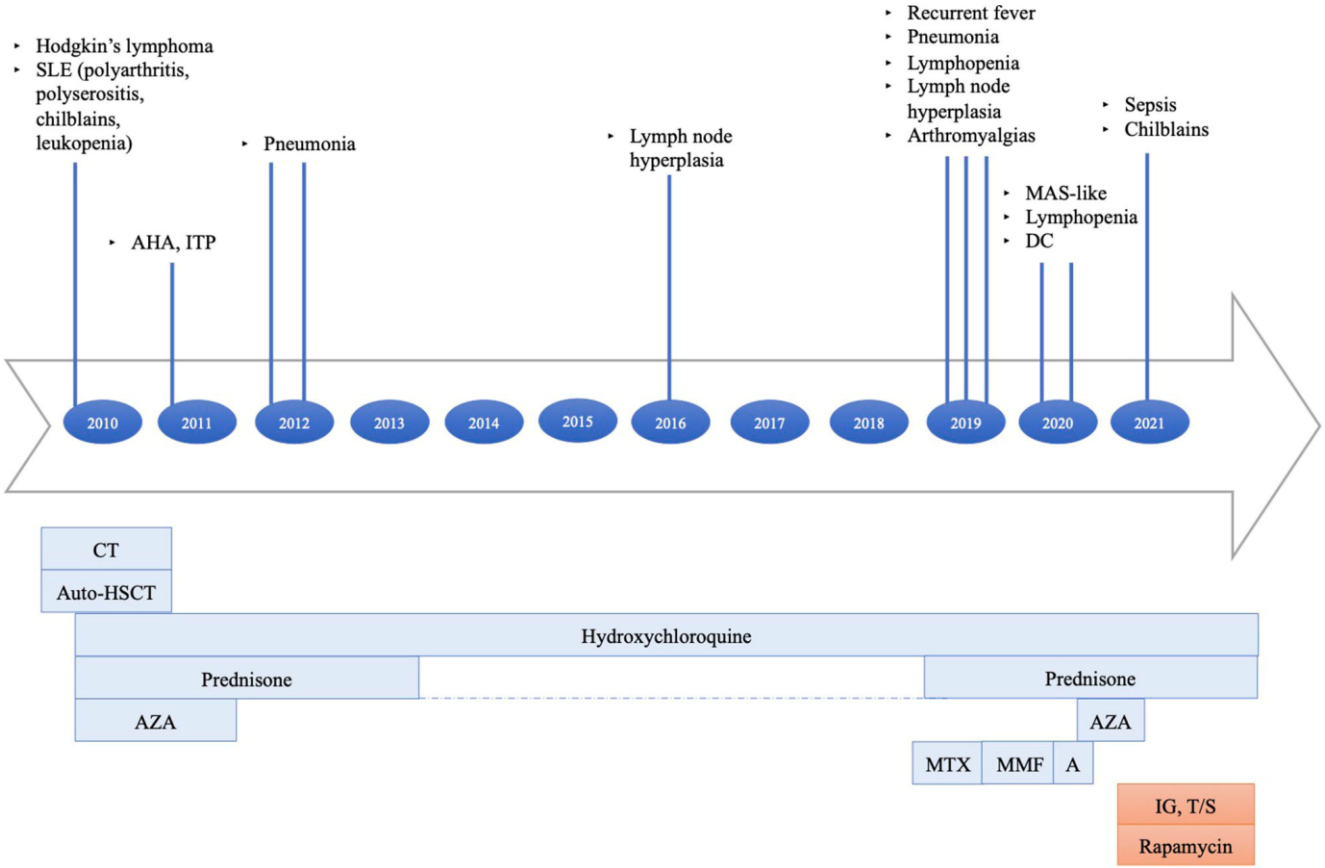
I. E. A., F, 34-year-old

- Adenotonsillectomy during infancy
- Poor growth
- 19-year-old: diagnosis of Hodgkin's lymphoma (CT + autologous bone marrow transplant)
- 20 year-old: diagnosis of Systemic Lupus Erythematosus (poorly controlled by multidrug treatment)
- 21-year-old: autoimmune haemolytic anemia, pleuropericarditis
- Reccurrent respiratory infections
- Severe lymphopenia
- Partial IgA deficiency
- Hepatosplenomegaly
- Bronchiectasis, mediastinal adenopathy, lung nodules



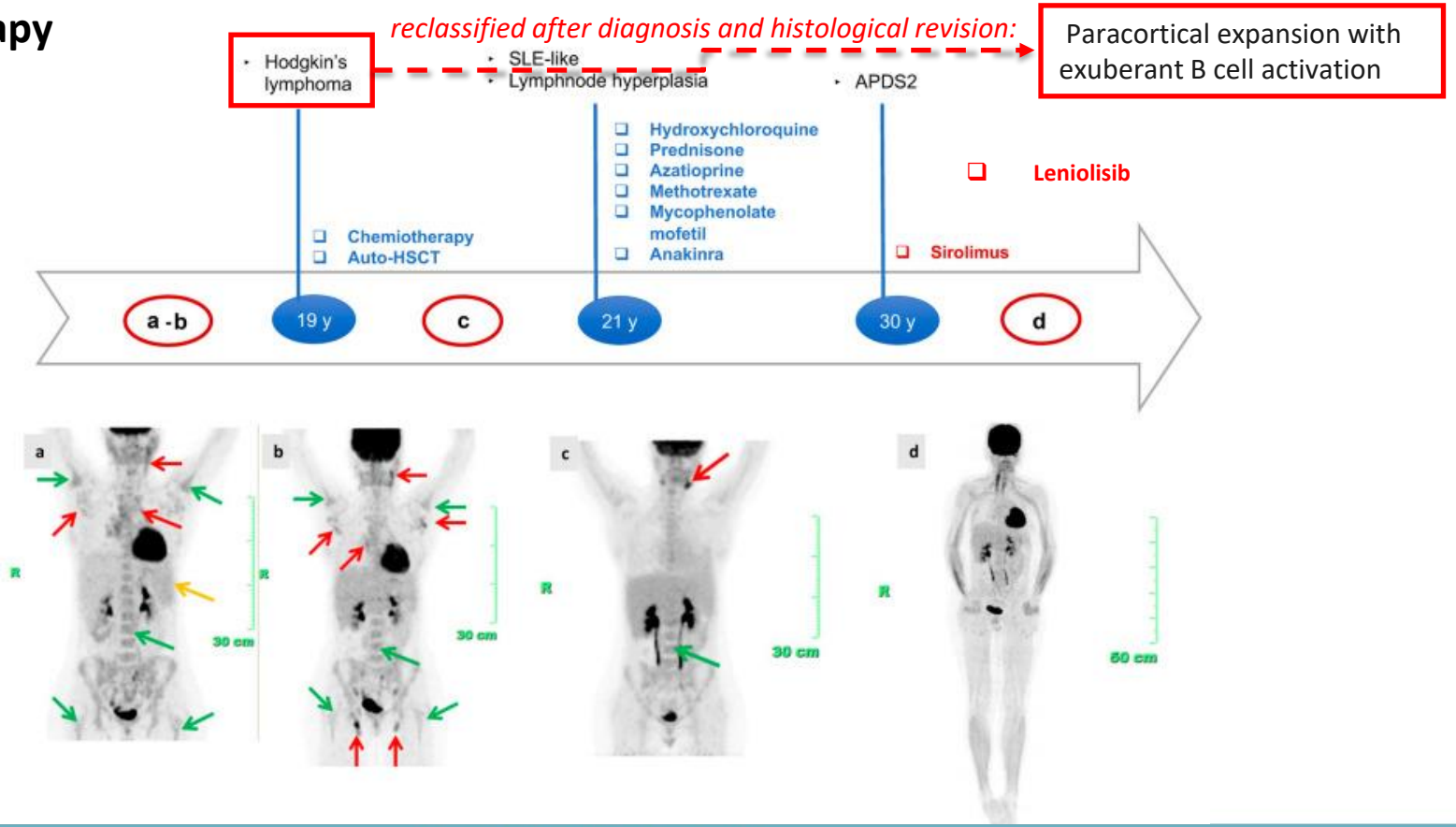
No relevant family history data reported

A Therapeutic Odyssey Before Diagnosis



2021 | https://doi.org/10.3389/fped.2021.702546

A Case of Lymphoproliferative Disorder Achieving Complete Response with Sequential Targeted Therapy



Lymphoproliferation in inborn errors of immunity: From challenging diagnosis to histologic revision

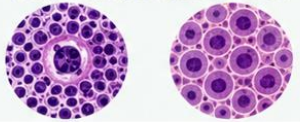
METHODS

- Retrospective study of **38** patients
- Patients with **IEI** confirmed by genetic or clinical testing
- Centralized review of histological specimens
- Multiparametric immunophenotypic and statistical analysis

RESULTS

26% of patients developed lymphoma.

Most common lymphomas: Hodgkin lymphoma and DLBCL.

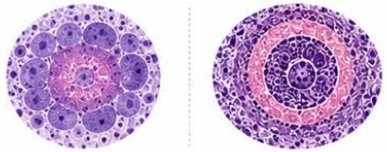


Several cases initially classified as lymphoma were reclassified as reactive hyperplasia.

Initially diagnosed as lymphoma

Reclassified as reactive hyperplasia

Identification of Castleman-like patterns and germinal center transformations.



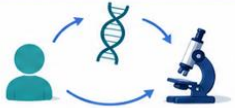
Castleman-like patterns

Germinal center transformations

CLINICAL IMPLICATIONS

A multidisciplinary approach involving immunologists, hematologists, pathologists, and clinical geneticists is essential.

Thorough histological review is crucial to avoid misdiagnosis.



Integration of clinical, genetic, and pathological data is key.

Potential reduction of inappropriate use of aggressive therapies.

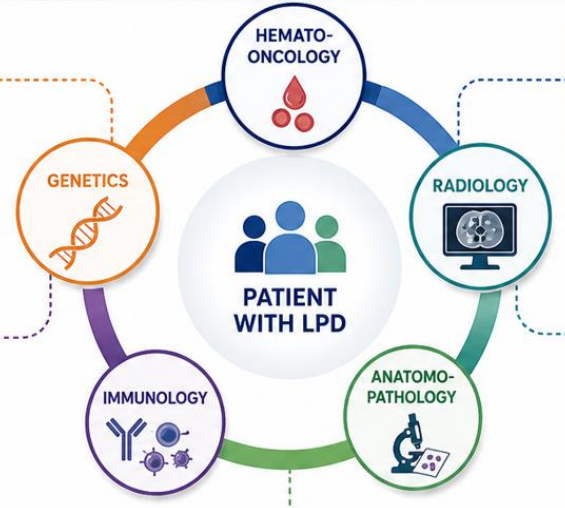
Integration of clinical, genetic, and pathological data enables more accurate diagnosis, prevents inappropriate treatment, and improves the management of patients with IEI.

J Hum Immun. 2026;2(2). doi:10.70962/jhi.20250174

INTEGRATED CARE AND OPTIMAL MANAGEMENT OF LPDs

MULTIDISCIPLINARY APPROACH: THE LPDs TASK FORCE

COLLABORATION • COMMUNICATION • COORDINATION
for accurate diagnosis, personalized therapy and improved outcomes



GENETICS

- Identification of germline variants (e.g., *PIK3CD, PRF1, CTPS1, ATM, NBN*, others)
- Risk stratification and prognosis
- Family counseling and cascade testing
- Support for targeted therapy and clinical trial eligibility

HEMATO-ONCOLOGY

- Clinical assessment and staging
- Treatment planning (targeted therapy, immunotherapy, chemotherapy)
- Monitoring of response and toxicity
- Management of complications (infections, cytopenias, autoimmunity)
- Long-term follow-up and survivorship

IMMUNOLOGY

- Immune evaluation (humoral and cellular)
- Infection risk assessment and prevention
- Management of immunodeficiency (IVIG, prophylaxis, vaccines)
- Autoimmunity monitoring and treatment

RADIOLOGY

- Imaging for diagnosis and staging (CT, MRI, PET/CT)
- Assessment of disease extent and organ involvement
- Response evaluation according to standardized criteria
- Guidance for biopsies and interventional procedures

ANATOMO-PATHOLOGY

- Histopathological diagnosis and classification
- Immunophenotyping (IHC, flow cytometry)
- Detection of EBV and other pathogens
- Correlation with clinical, immunologic and genetic data

KEY BENEFITS

- Accurate and early diagnosis
- Personalized and targeted therapy
- Optimal management of complications
- Reduced morbidity and mortality
- Improved quality of life

INTEGRATED MANAGEMENT PATHWAY

1. REFERRAL & INITIAL EVALUATION
2. MULTIDISCIPLINARY DISCUSSION
3. INTEGRATED DIAGNOSIS & RISK STRATIFICATION
4. PERSONALIZED TREATMENT PLAN
5. MONITORING & ADAPTATION
6. LONG-TERM SUPPORT & QUALITY OF LIFE

OUR GOAL

The right diagnosis, the right treatment, for the right patient, at the right time.

TOGETHER WE MAKE THE DIFFERENCE

FUTURE PERSPECTIVES

Toward better outcomes for patients with IEI-associated LPDs

1 IDENTIFY IEI FOLLOWING PRIMARY LPDs DIAGNOSIS

- Systematic evaluation for underlying IEI in all patients with primary LPDs
- Use of genetic testing and immune profiling
- Early recognition of IEI to guide management and family counseling

2 IMPROVE CLINICAL DIAGNOSIS

- Increase awareness of IEI-associated LPDs among clinicians
- Develop clinical algorithms and decision-support tools
- Promote multidisciplinary evaluation and data sharing

3 IMPROVE HISTOPATHOLOGICAL DIAGNOSIS

- Standardize pathological criteria for IEI-LPDs
- Incorporate ancillary studies (IHC, flow cytometry, molecular tests)
- Enhance training and expert review networks

BETTER OUTCOMES FOR PATIENTS WITH IEI-LPDs

4 IMPROVE TREATMENT PROTOCOL

- Develop evidence-based, risk-adapted treatment strategies
- Define optimal sequencing and combination of therapies
- Establish international registries and real-world data platforms

5 IMPLEMENT THE USE OF TARGETED THERAPY

- Expand access to targeted agents (e.g., PI3Kδ inhibitors, mTOR inhibitors)
- Personalize therapy based on molecular alterations and patient characteristics
- Monitor response and resistance to optimize long-term outcomes

COLLABORATION IS KEY

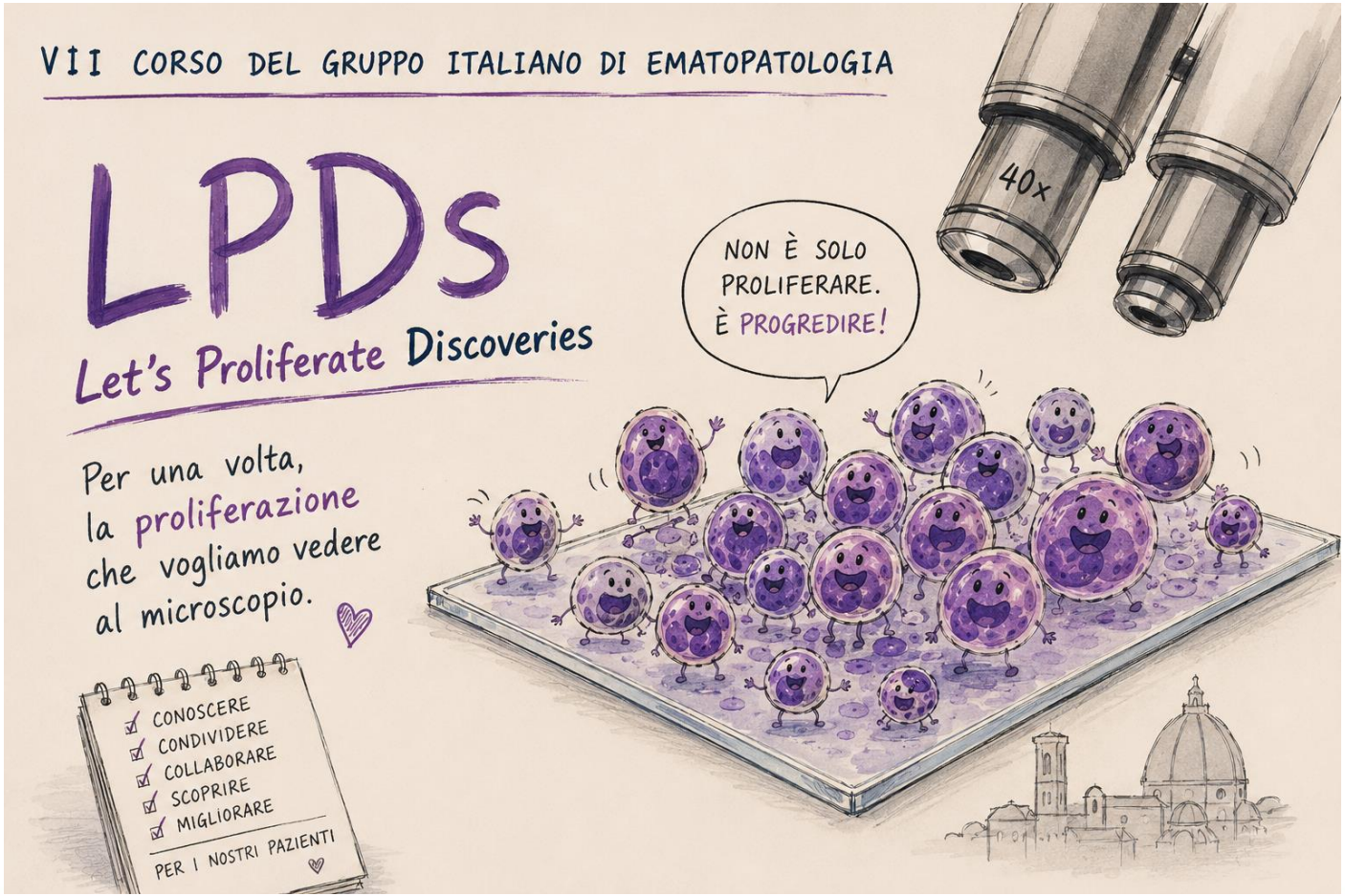
MULTIDISCIPLINARY TEAMS | DATA SHARING & NETWORKS | INTERNATIONAL COLLABORATION | RESEARCH & INNOVATION

Advancing knowledge, improving care, transforming lives.

TAKE HOME MESSAGES

- Patients with IEI may develop **distinctive and heterogeneous types** of lymphoid proliferations, unique to the particular IEI → **diagnosis is often challenging!**
- The types and frequency of these proliferations are largely dependent on the immune dysregulation conferred by the **germline aberration** underlying a respective IEI
- Given the overlap with other IDD settings, IEI-associated lymphoid proliferations and lymphomas have been incorporated into the overarching framework and nomenclature of **"lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation."** (WHO-HAEM5)
- **Clinical history, immunological, and histological** characterization are critical for establishing a prompt diagnosis of an underlying IEI
- LPDs in the context of IEI may take advantage of **mechanism-based therapies** → , with an urgent need for a **specific diagnostic and treatment strategy path** to prevent delayed diagnosis

IDD: ImmunoDeficiency/Dysregulation


VII CORSO DEL GRUPPO ITALIANO DI EMATOPATOLOGIA
LPDs
Let's Proliferate Discoveries
Per una volta, la proliferazione che vogliamo vedere al microscopio.
NON È SOLO PROLIFERARE. È PROGREDIRE!
40x
CONOSCERE
CONDIVIDERE
COLLABORARE
SCOPRIRE
MIGLIORARE
PER I NOSTRI PAZIENTI