IDF Lunch & Learn: Primary Immune Regulatory Disorders (PIRD)

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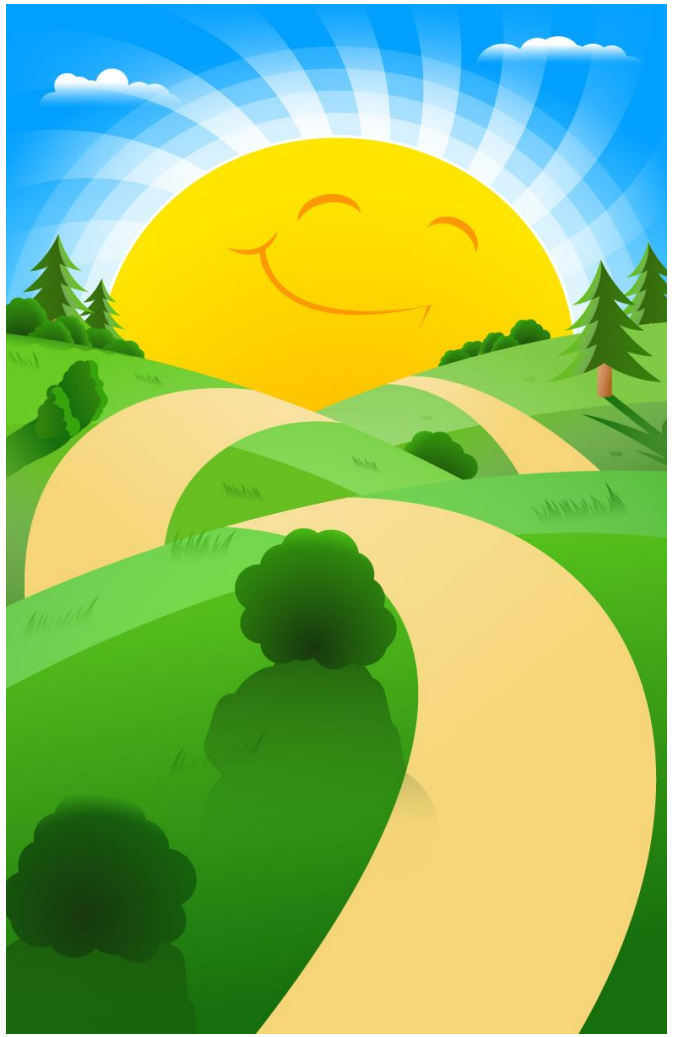
Disclosures

- Grant: Jeffrey Modell Foundation
- Consultant: Sobi

Roadmap for Today

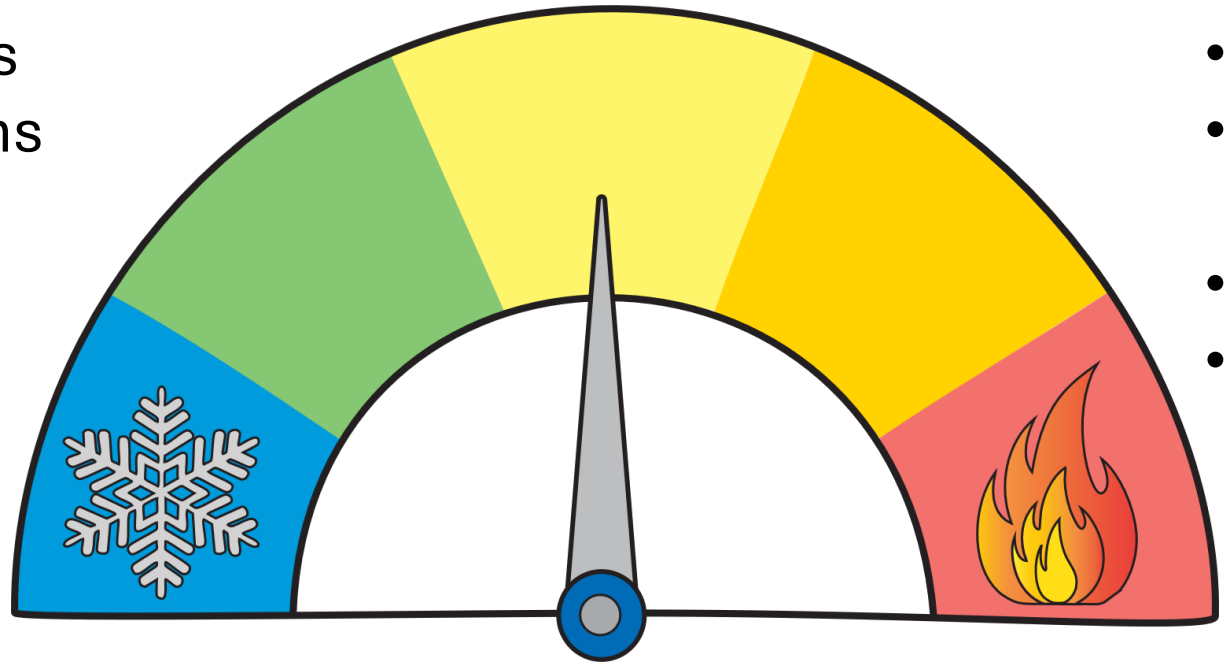
- What is a PIRD?
- When to think about one?
- What symptoms can occur?
- What is the workup for a PIRD?
- How to treat a PIRD?



What is a PIRD?

Disease where symptoms are caused by the immune system not being regulated correctly

- Frequent infections
- Recurrent infections
- Atypical infections
- Chronic infections
- Severe infections

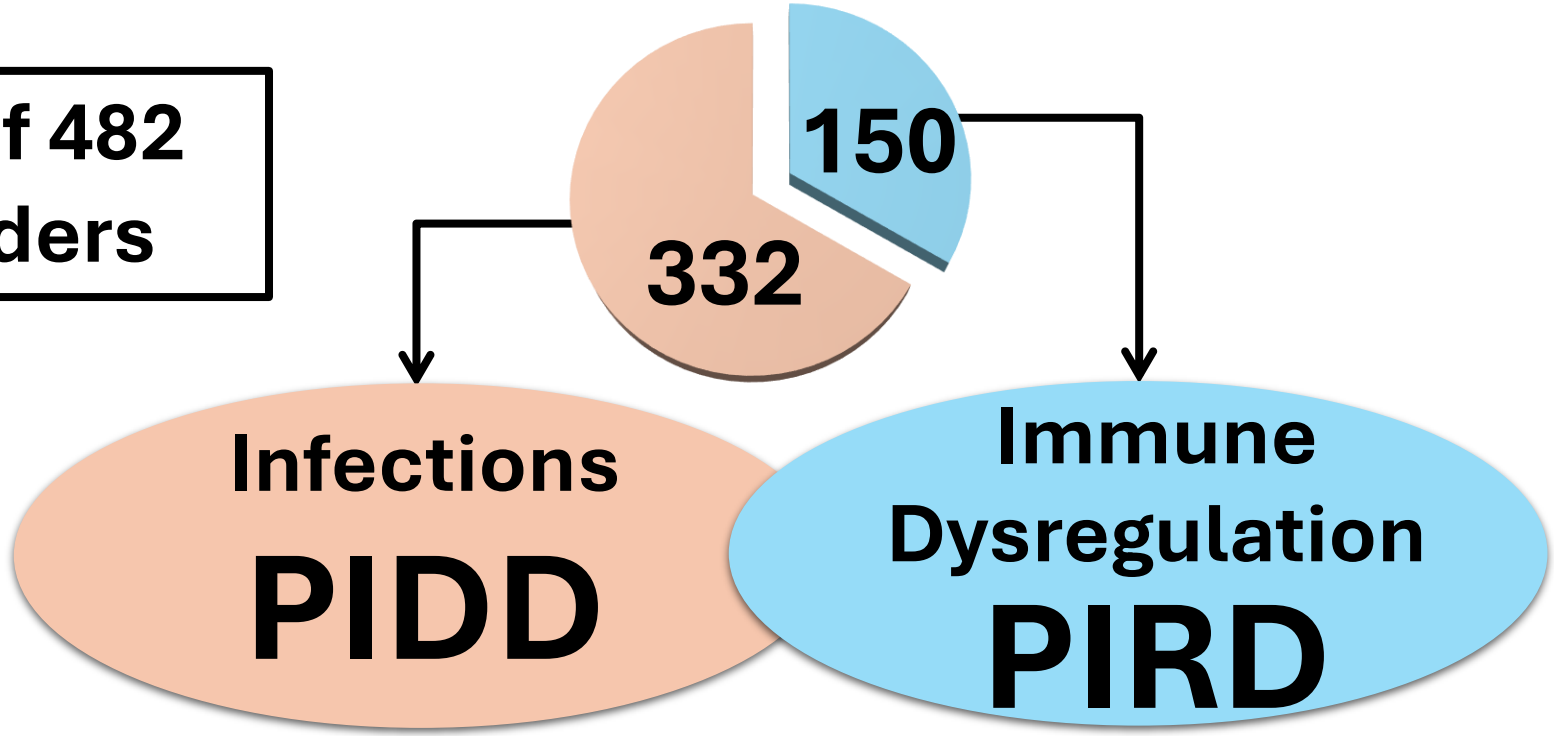


- Autoimmunity
- Hyper or Auto-inflammation
- Lymphoproliferation
- Severe Allergies

Underactivity **Overactivity**

PIRDs Represent 1/3 of Immune Disorders

Total of 482 Disorders



Primary Immune Deficiency Disorders (PIDD)

- Mainly infection causing damage
- Treatment focused on infection or prevention

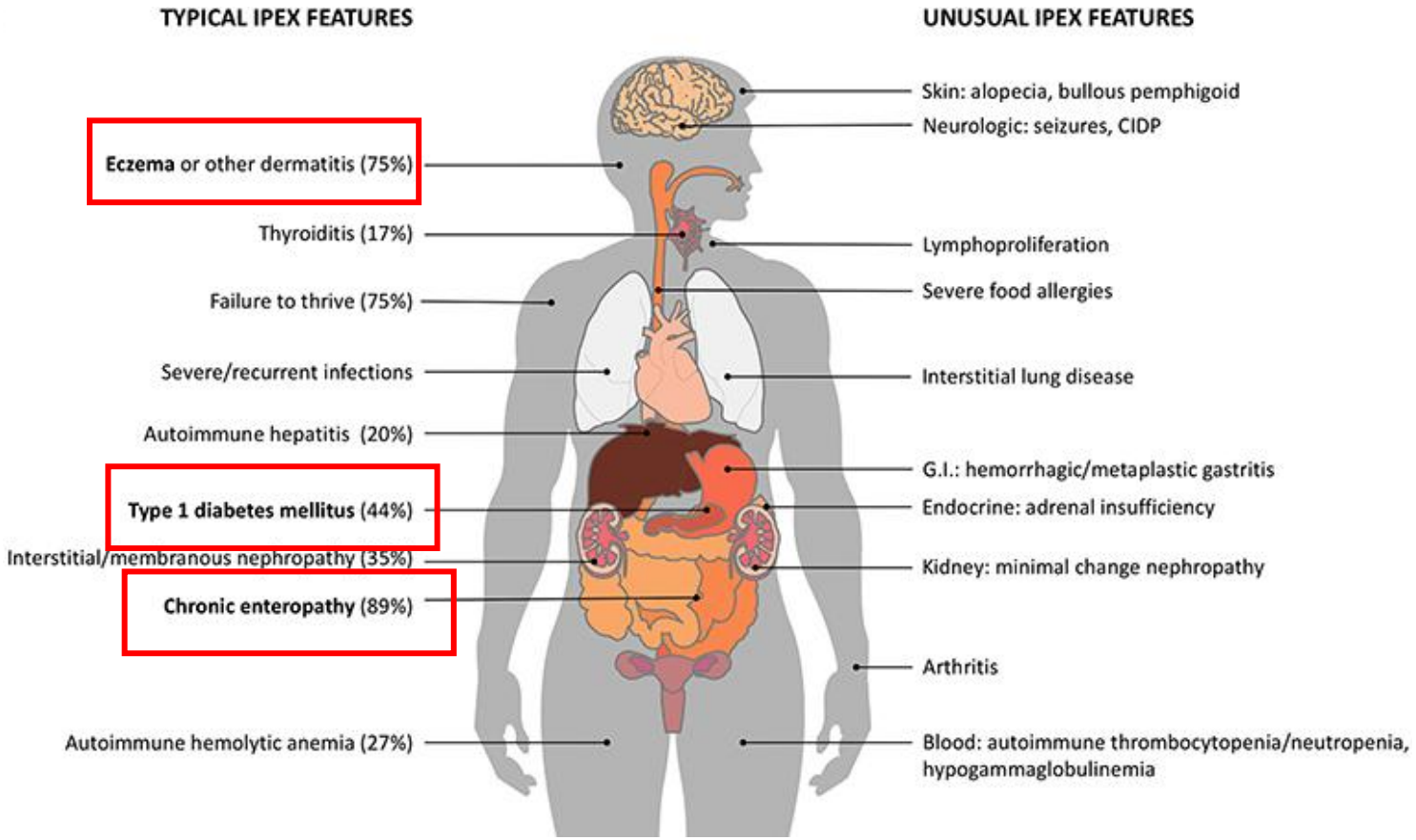
Primary Immune Regulatory Disorders (PIRD)

- Mainly immune system causing damage
- Treatment focused on immune suppression

Modified from Chan AY & Torgerson TR. *Curr Opin Allergy Clin Immunol* (2020)
Tangye SG, et al. J Clin Immunol. (2022)

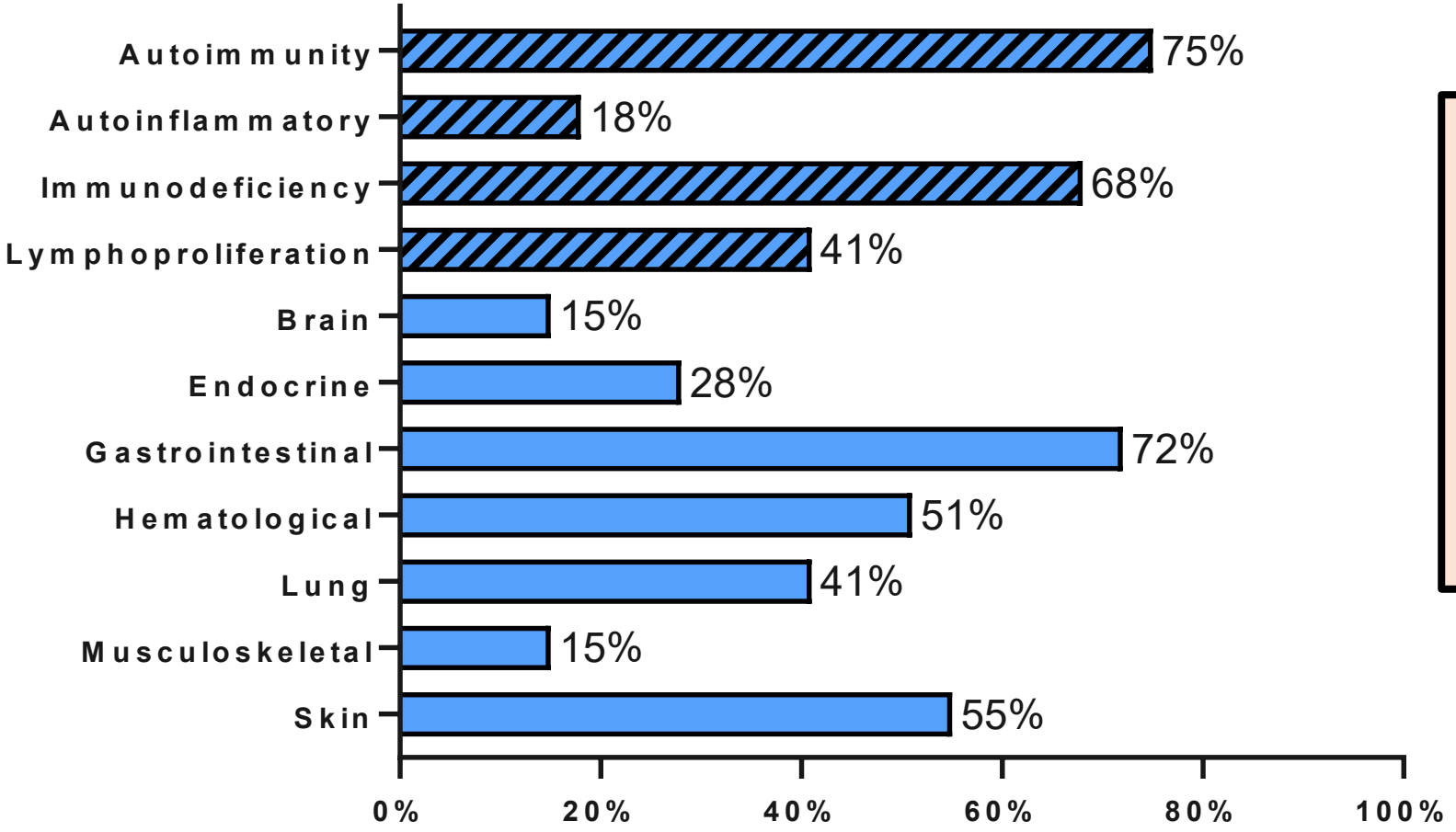
“Classic” PIRD: IPEX

- IPEX = **I**mmunodysregulation, **P**olyendocrinopathy, **E**nteropathy, & **X**-linked disease
- Caused by *FOXP3* gene
- Regulatory T cells (Tregs) are not working correctly



Consonii, F, et al. *Front Pediatr.* (2021)

What Symptoms do PIRD patients have?

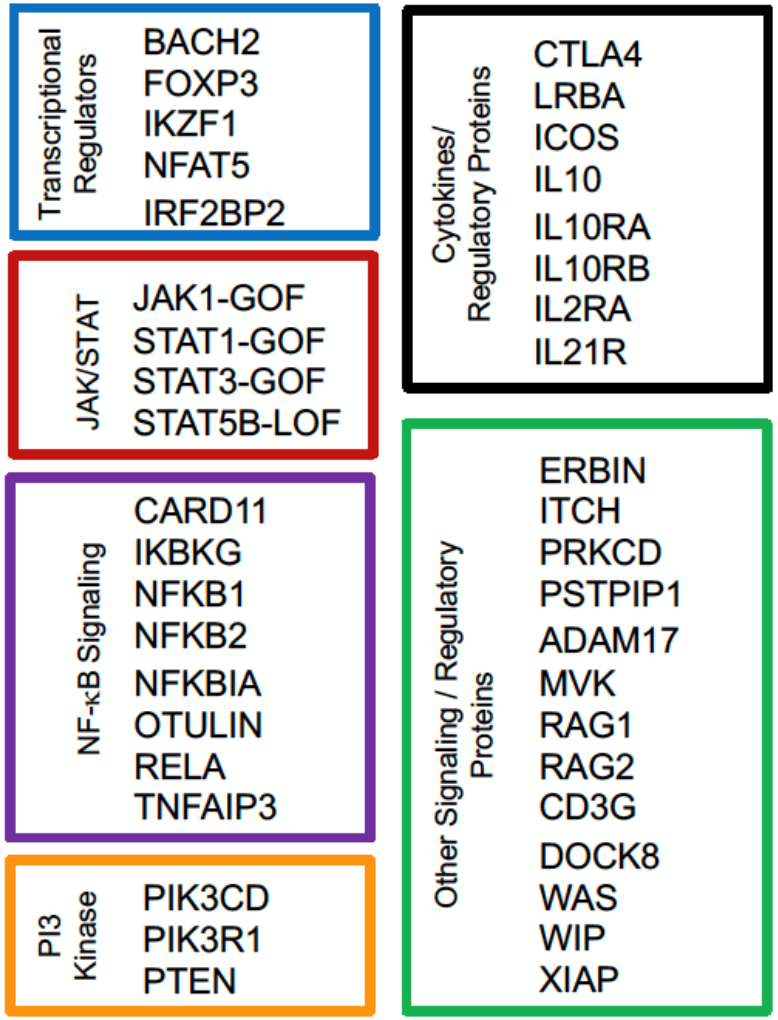


Primary Immune Deficiency Treatment Consortium (PIDTC) Survey

- 44 sites (US & Canada) + 3 European Centers
- 226 patients
- Age range 0-68 years old

Chan AY, Leiding JW, et al. *Front Immunol* (2020)

What causes PIRD?



Genes that regulate how the immune system gets turned on and off

Chan AY, Leiding JW, et al. *Front Immunol* (2020)
From Troy Torgerson

What Diagnoses can be a PIRD?

- IPEX & IPEX-Like
- ALPS & ALPS-Like
- CVID w/ Immune Dysregulation
- Familial HLH
- Autoinflammatory Disorders
- Interferonopathies
- Congenital Hypersensitivity
- Infant-onset/Very-early-onset IBD
- Rheumatologic Disorders

When to think about PIRD?

- Early-onset (infants, toddlers, etc.)
- Disease is severe or atypical
- Disease is not responding to standard treatment
- Have multiple diseases
- Seen by multiple subspecialists
- Sometimes have a family history of
  - Multiple immune-mediated diseases
  - Unexplained illnesses or deaths
  - Transplantation

Immune-Mediated GI Diseases

Enteropathy

- Mainly **small** bowel
- Symptoms
  - Watery diarrhea
  - Weight loss
- Examples
  - Celiac disease
  - Protein losing enteropathy

Colitis

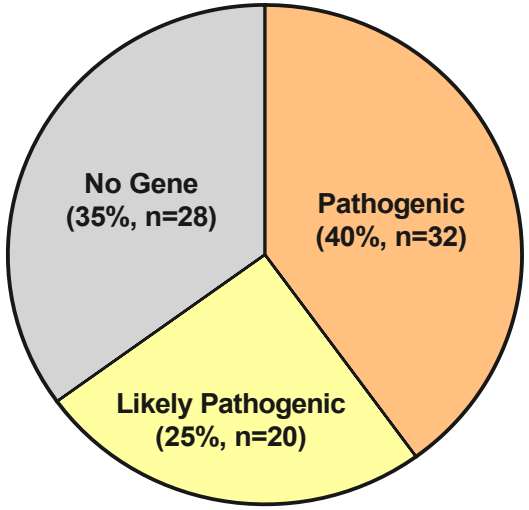
- Mainly **large** bowel
- Symptoms
  - Bloody diarrhea
  - Stomach pain
  - Weight loss
- Examples
  - Ulcerative colitis
  - Crohn’s colitis

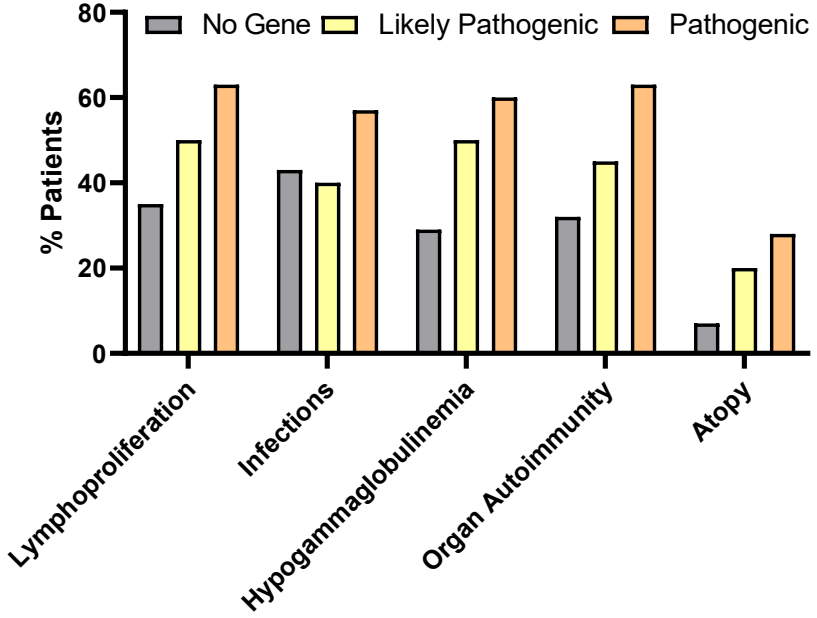
Can be a mixed picture

Autoimmune Cytopenias

- Cell Types Involved
  - Anemia (red blood cells)
  - Thrombocytopenia (platelets)
  - Neutropenia (neutrophils)
  - Lymphopenia (lymphocytes)
- Single vs Multiple Cell Types
  - Evans Syndrome
- Types of Disease Patterns
  - Recurrent
  - Refractory
- Usually positive antibody testing
- Having other symptoms

Pediatric Evans Syndrome

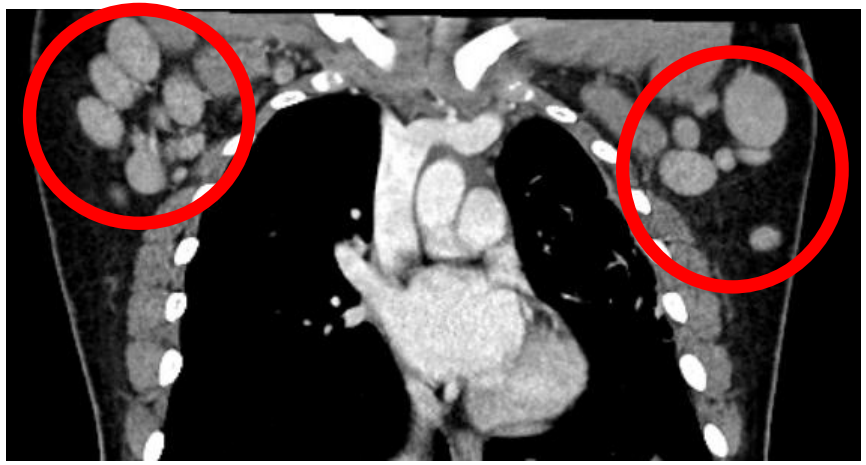


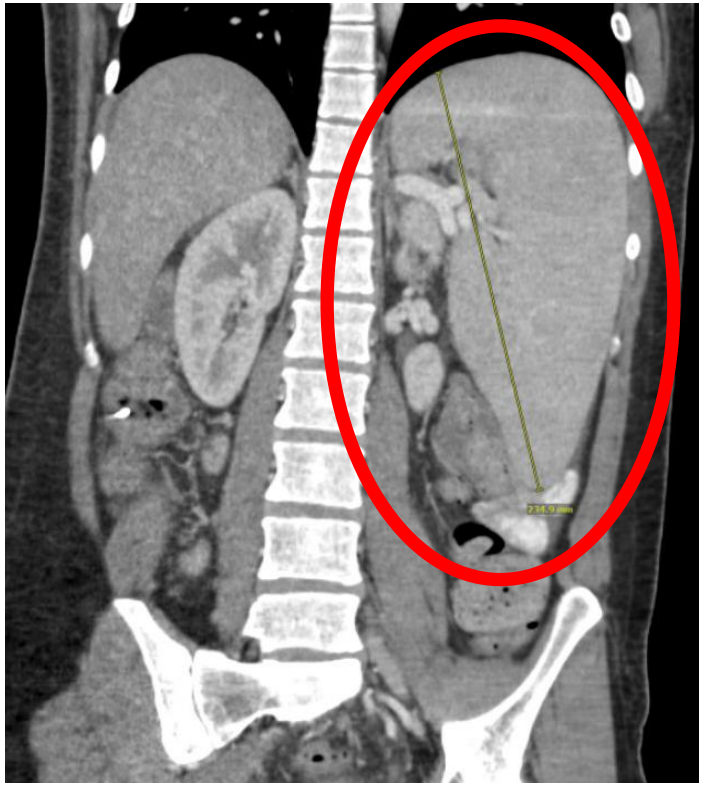


Hadjadj J, et al. Blood (2019)

Lymphoproliferation

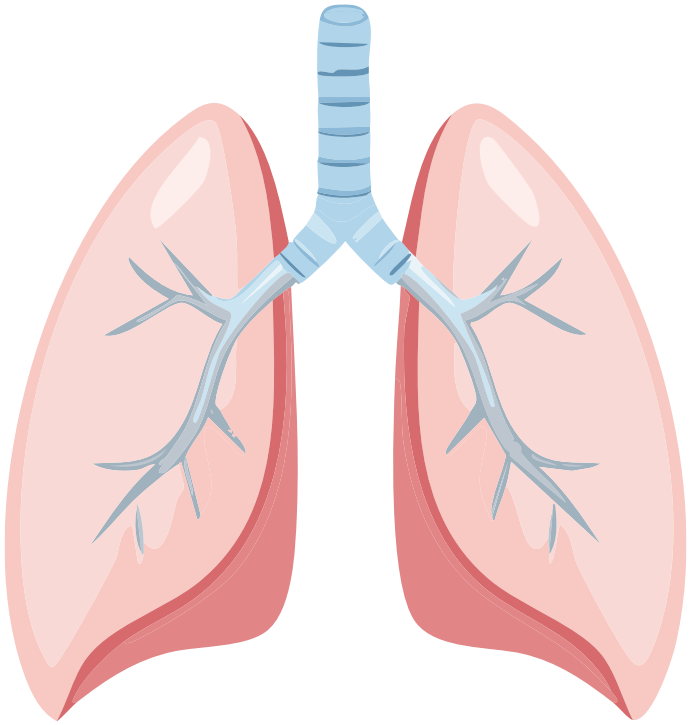
- Areas involved in the body
  - Lymph nodes in neck, armpits, groin (lymphadenopathy)
  - Spleen (splenomegaly)
  - Liver (hepatomegaly)
  - Brain, lungs
- Pattern
  - Chronic, persistent
  - Waxing & waning pattern
- Can be a risk for cancer
- Associated with other symptoms
  - Cytopenia
  - EBV infection
  - Other organ disease





Immune-Mediated Lung Disease

- Caused by mixed picture of infection and overactive immune system
- Types
  - Interstitial Lung Disease
  - Granulomatous and Lymphocytic ILD (GLILD)
  - Bronchiectasis
  - Pneumonitis
- Symptoms
  - Chronic cough
  - Shortness of breath



Other Immune-Mediated Conditions

- Autoimmune endocrine diseases – thyroid, diabetes, adrenal insufficiency
- Inflammatory skin – eczema, psoriasis, panniculitis
- Liver conditions – autoimmune hepatitis
- Rheumatologic conditions – arthritis, myositis, vasculitis
- Kidney conditions – proteinuria, hematuria
- Inflammatory eye disease – uveitis, scleritis, retinitis
- Neurologic conditions – autoimmune encephalitis, CNS HLH

Is there a PIRD Diagnostic Criteria?

Not Really except for a genetic cause

- Lots of disease variability
- Treat based on symptoms/conditions

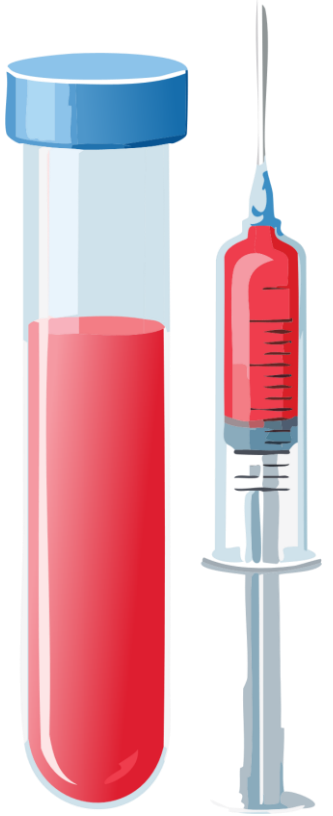
Example Criteria or Scoring Systems

- Autoimmune Lymphoproliferative Syndrome/Immunodeficiencies (ALPS/ALPID) Diagnostic Criteria
  - Lab tests helpful for ALPS caused by known genes and less helpful based on symptoms
  - Genetic testing most helpful
- Immune Deficiency and Dysregulation Activity (IDDA)
  - Being used to assess disease severity
  - Might be helpful to decide on transplant

Magerus A, et al. J Allergy Clin Immunol. 2024
Seidel, MG, et al. JoCI 2022

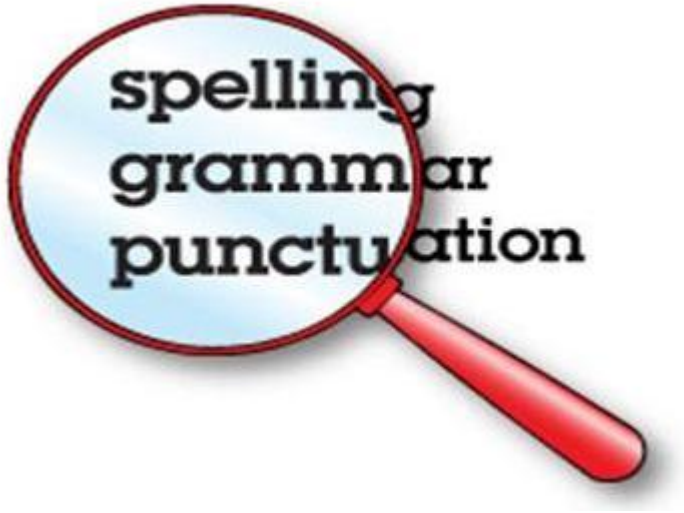
What is the Workup?

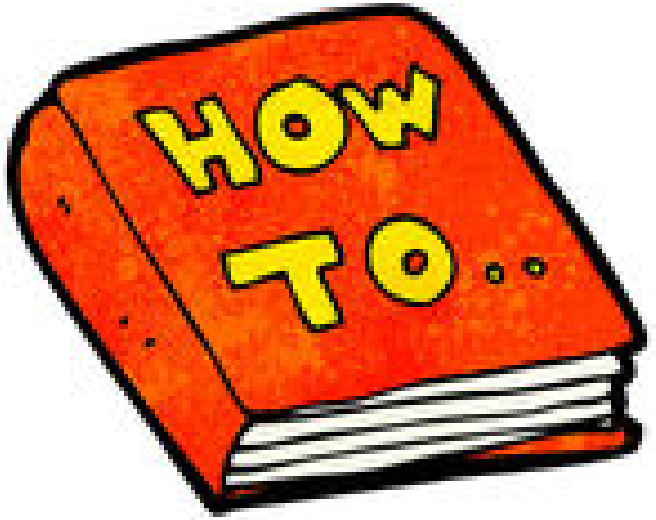
- Check for general inflammation in the body
  - ESR, CRP, albumin
  - Ferritin, sIL2R, CXCL9, IL18
- Check for organ disease if concerned for involvement
  - Kidney function – creatinine, urine tests
  - Liver function – ALT/AST, total bilirubin, PTT, PT/INR
  - Gut – fecal calprotectin, blood in the stool
  - Endocrine organs – TSH/FT4, HgbA1c
- Autoantibodies for organ disease
- Immune Studies
  - Lymphocyte subsets (T, B, NK)
  - Immunoglobulins (IgG, IgA, IgM, IgE)
  - Response to vaccines (tetanus, PCV)
- Genetic Testing



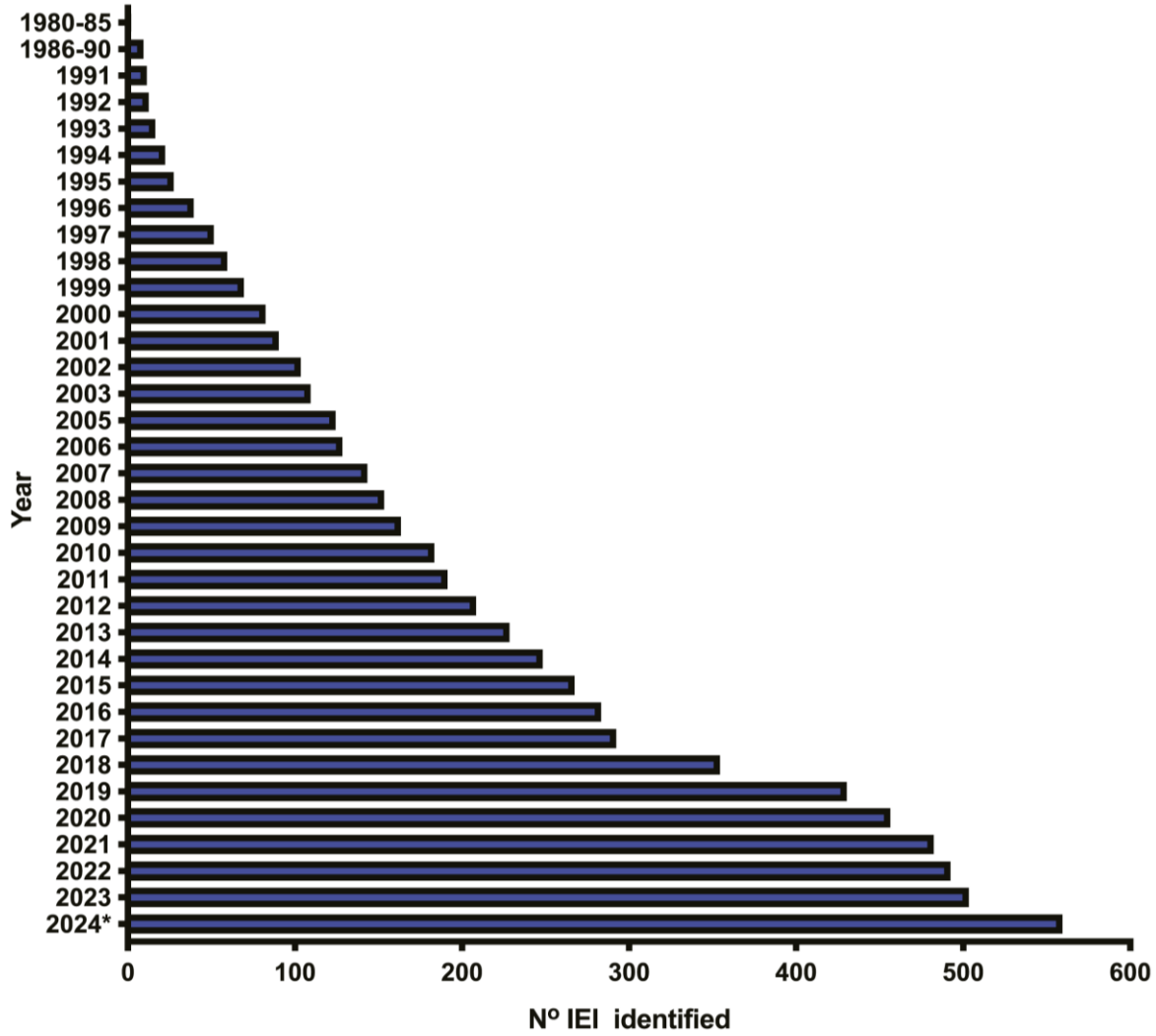
What is Genetic Testing?

- Test to look for spelling, grammar, and punctuation errors in the instruction book for the immune system
- Ways to do testing
  - Large gene panels
  - Whole exome sequencing (WES)
  - Whole genome sequencing (WGS)
- Types of results
  - Positive – pathogenic, likely pathogenic
  - Negative – benign, likely benign
  - Variant of unknown significance (VUS)





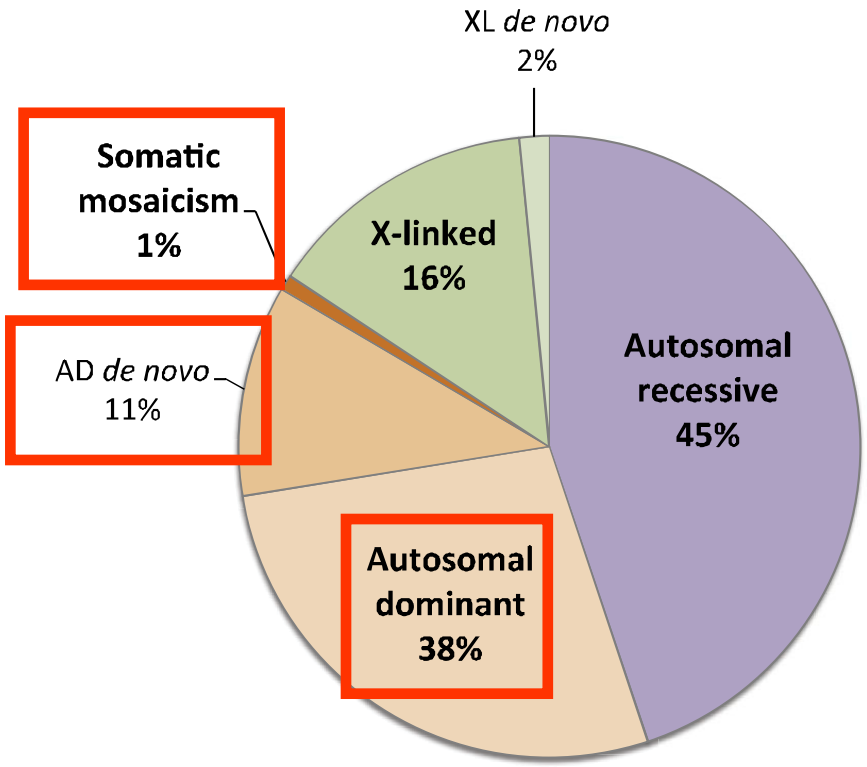
Negative Now may Not be Negative in the Future

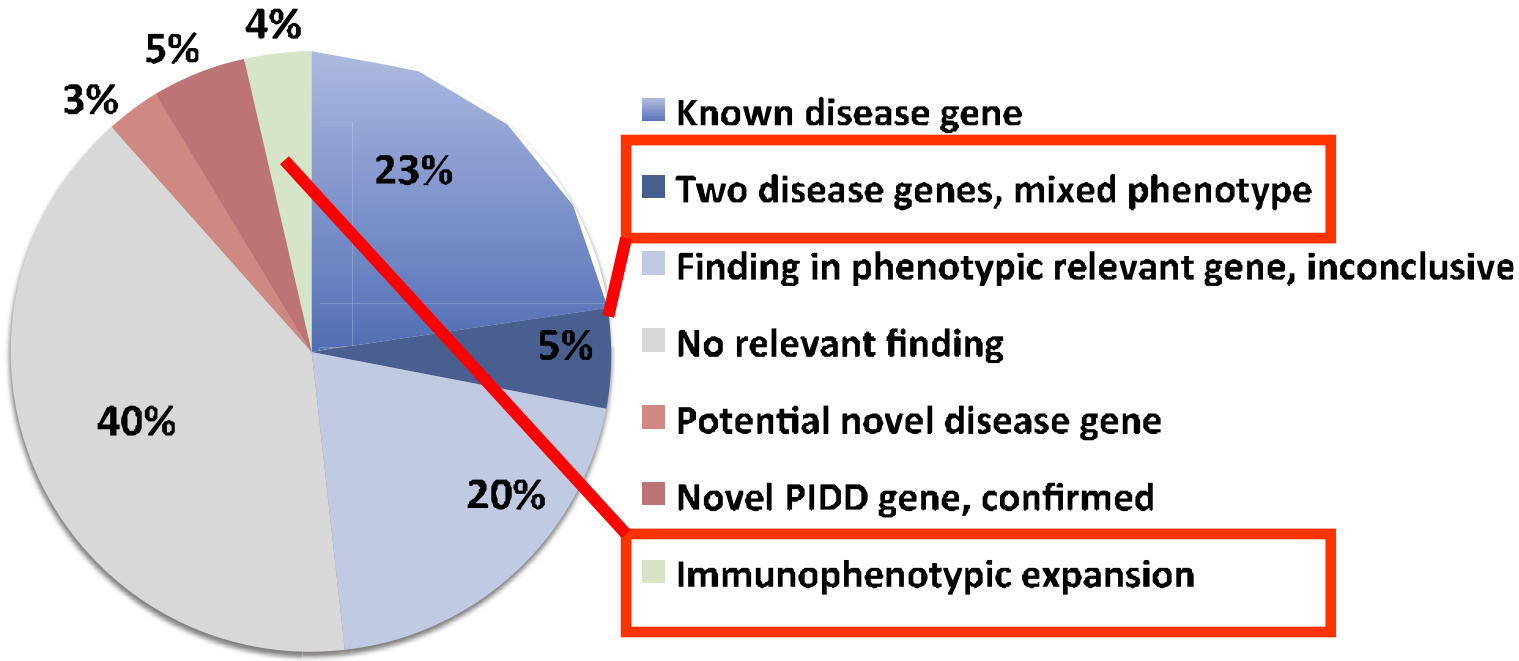


- Increasing number of new genes and phenotypes being discovered each year
- Rapidly evolving technology to improve genetic testing
- Decreasing costs for genetic testing allowing more insurances to cover the costs

Poli, CE et al. *J Hum Immun*. (2025)

Changing Genetic Landscape in Patients with Immune Disorders

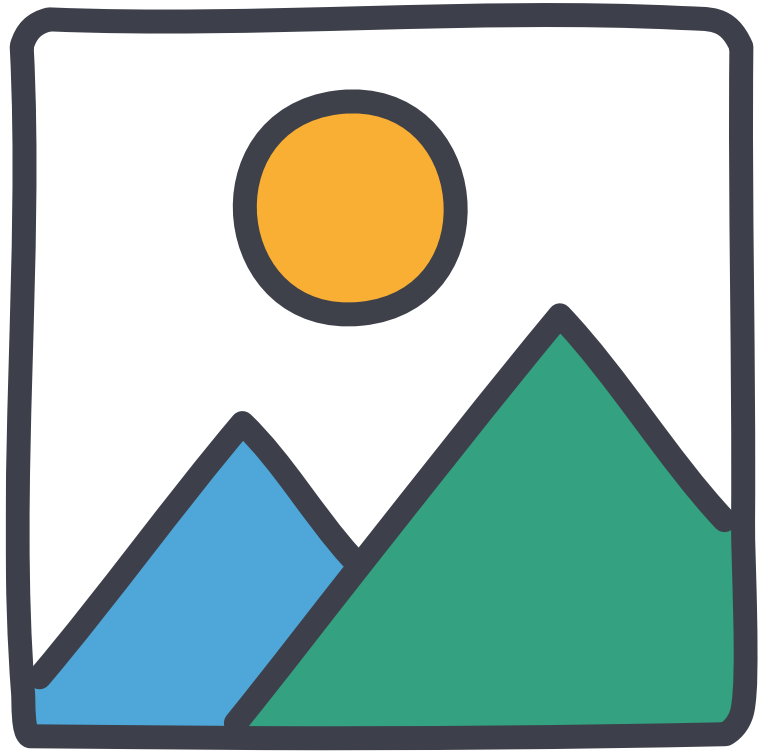




Stray-Pederson, A et al. *J Allergy Clin Immunol*. 2017

Challenges in Genetic Testing

- Panel testing
  - Companies have different genes in panels
- WES/WGS
  - Analysis can be improved when different clinical disease and symptoms are used
  - Consider reanalysis if new symptoms
- Holes in the genetic testing
  - Some genes are difficult to detect
  - Some deletion and duplication regions can be missed
  - Sometimes the genetic change is not in every cell of the body

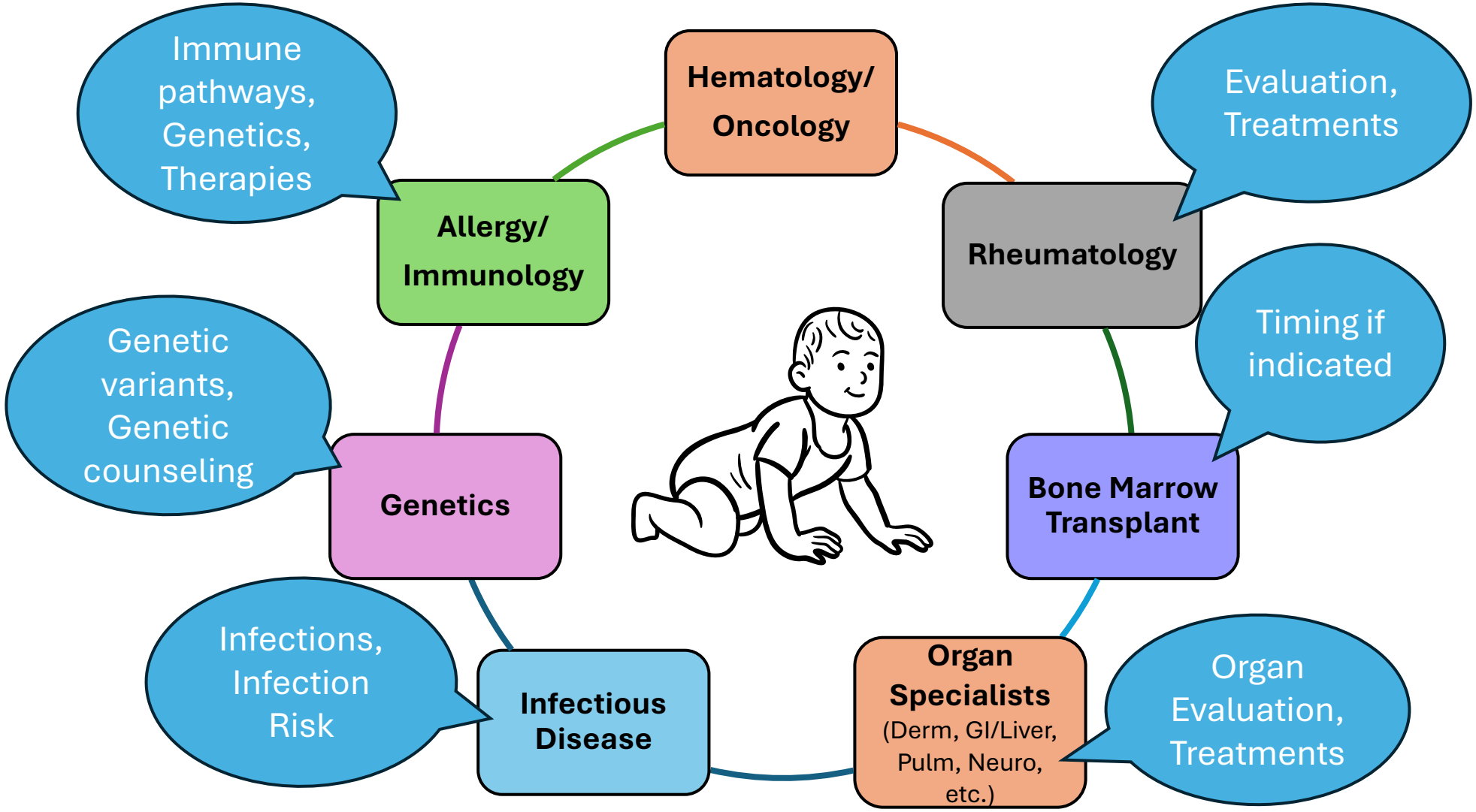


How to treat PIRD?

<u>Goal for precision therapies based on genetics and symptoms</u>

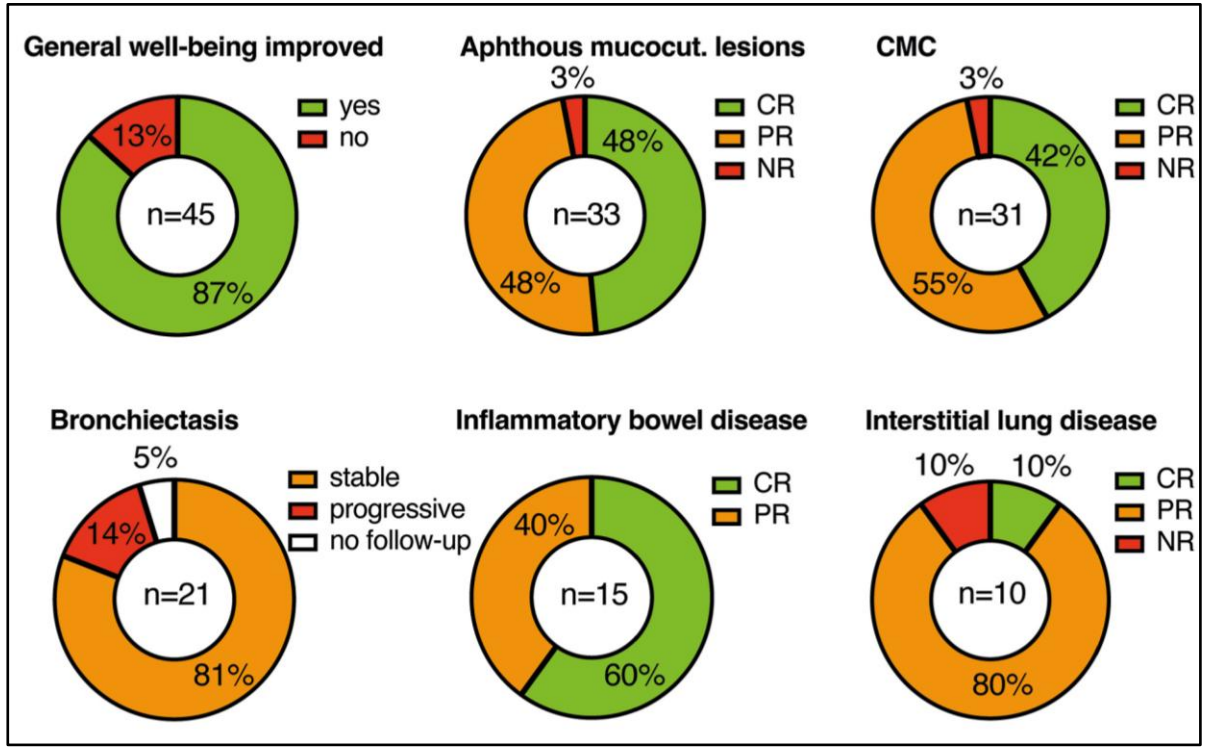
- Immune Suppressive Medicines
  - Steroids
  - Steroid-Sparing Agents (Monoclonal Antibodies (Cytokines, Anti-CD20), Small Molecules (Jakinibs, mTOR inhibitors))
- Immune Protective Medicines
  - Antibody Replacement (IVIG or SCIG)
  - Antimicrobial Prophylaxis
- Immune System Replacement
  - Hematopoietic Stem Cell Transplant (HSCT)
  - Gene Therapy

Collaborative Care is Key for PIRD Patients

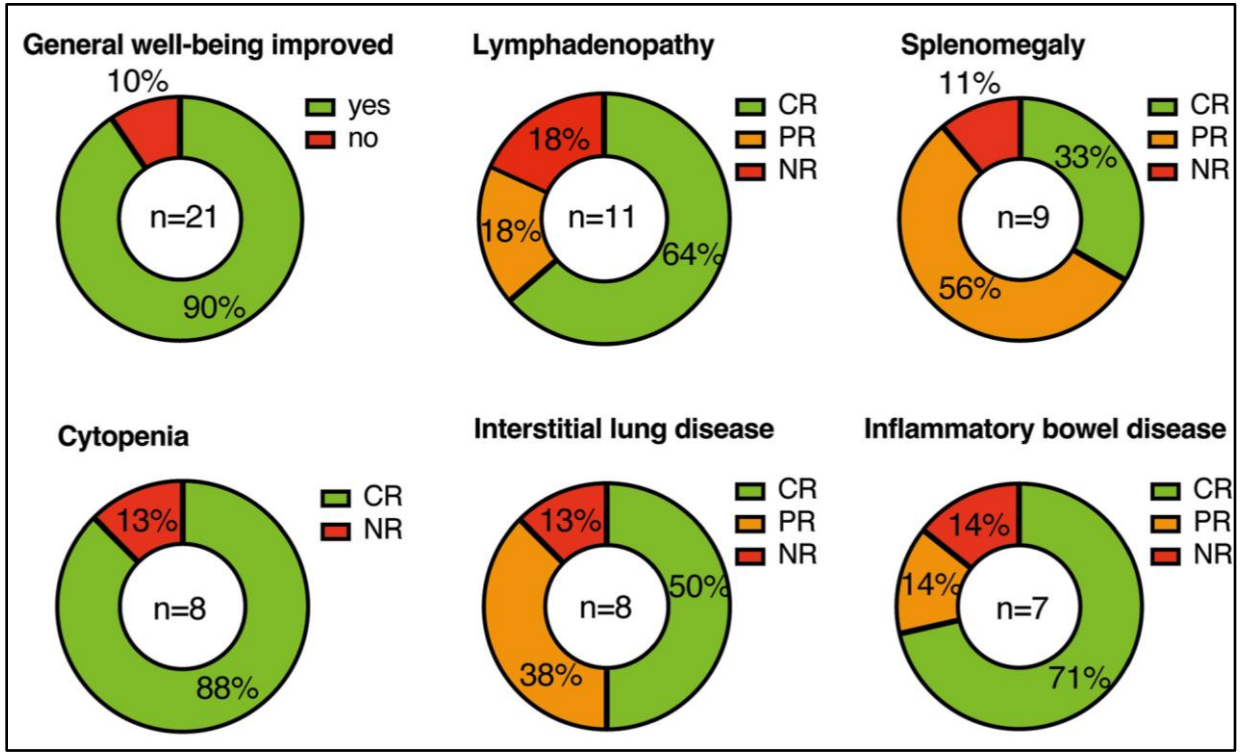


Jak Inhibitors in Diseases with JAK/STAT Gain-of-Function (GOF)

STAT1-GOF



STAT3-GOF



CR: Complete Response

PR: Partial Response

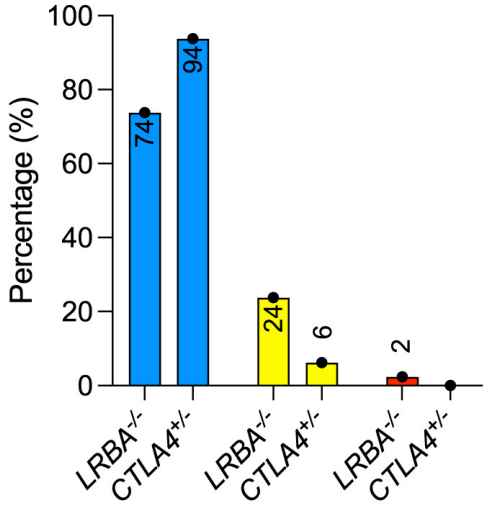
NR: No Response

Not FDA approved for this indication

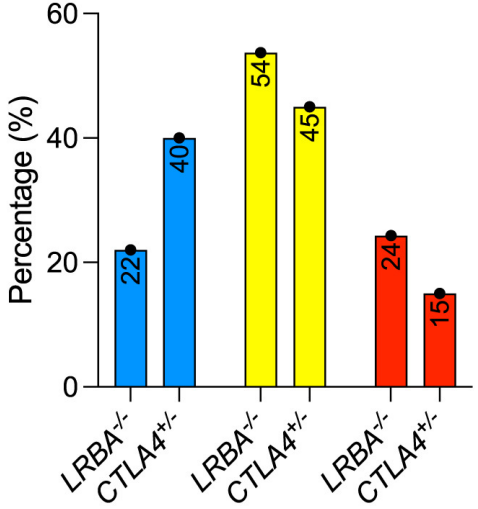
Fischer M, et al. J Allergy Clin Immunol. 2024

CTLA4-Ig in CTLA4 & LRBA Diseases

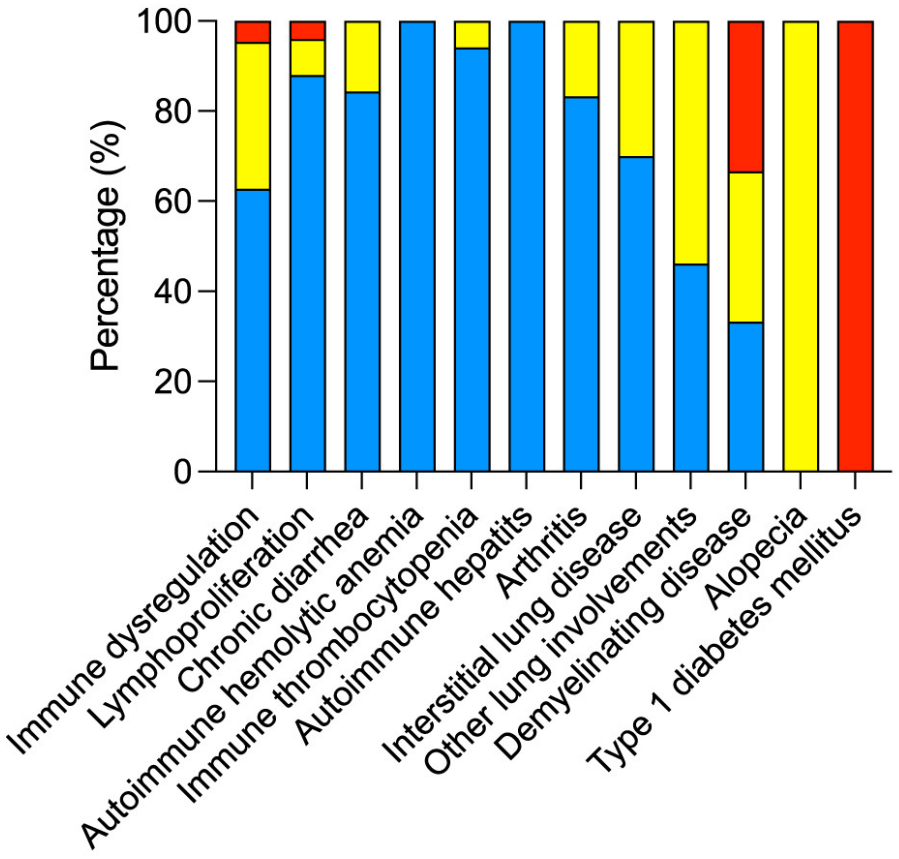
Abatacept



Other Immunosuppressive Therapies



Symptom Improvement on Abatacept Therapy



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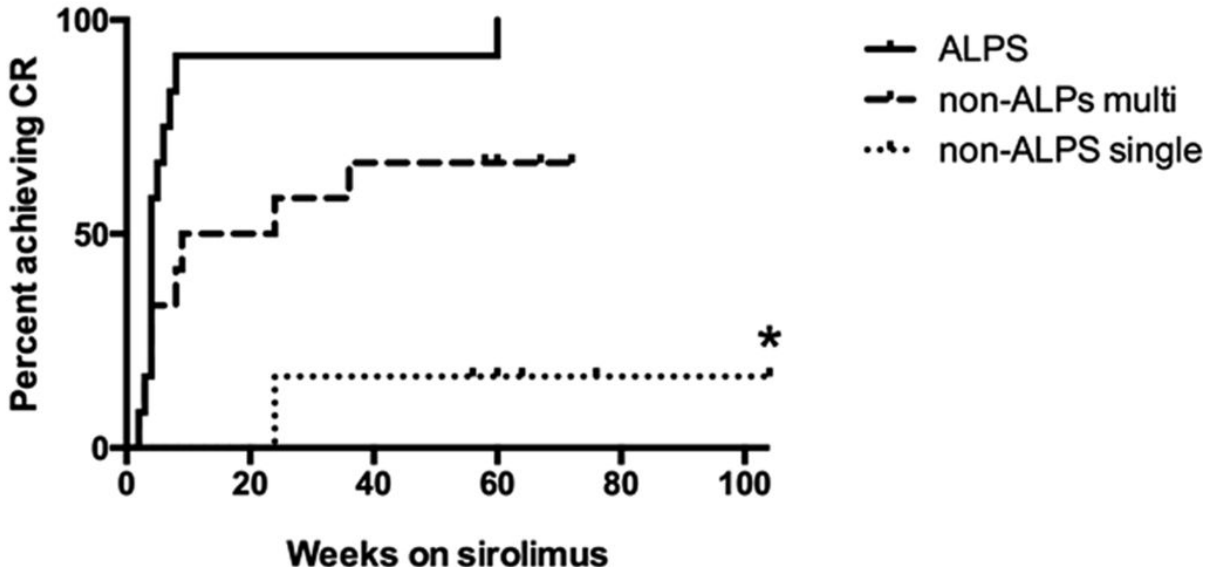
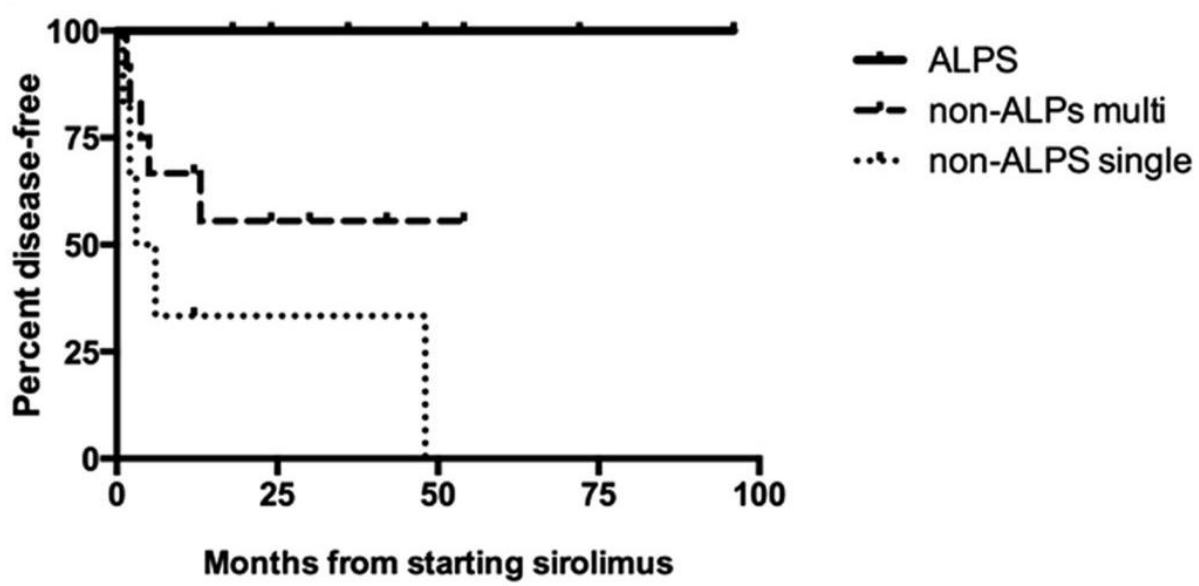
Taghizade N, et al. J Allergy Clin Immunol. 2023

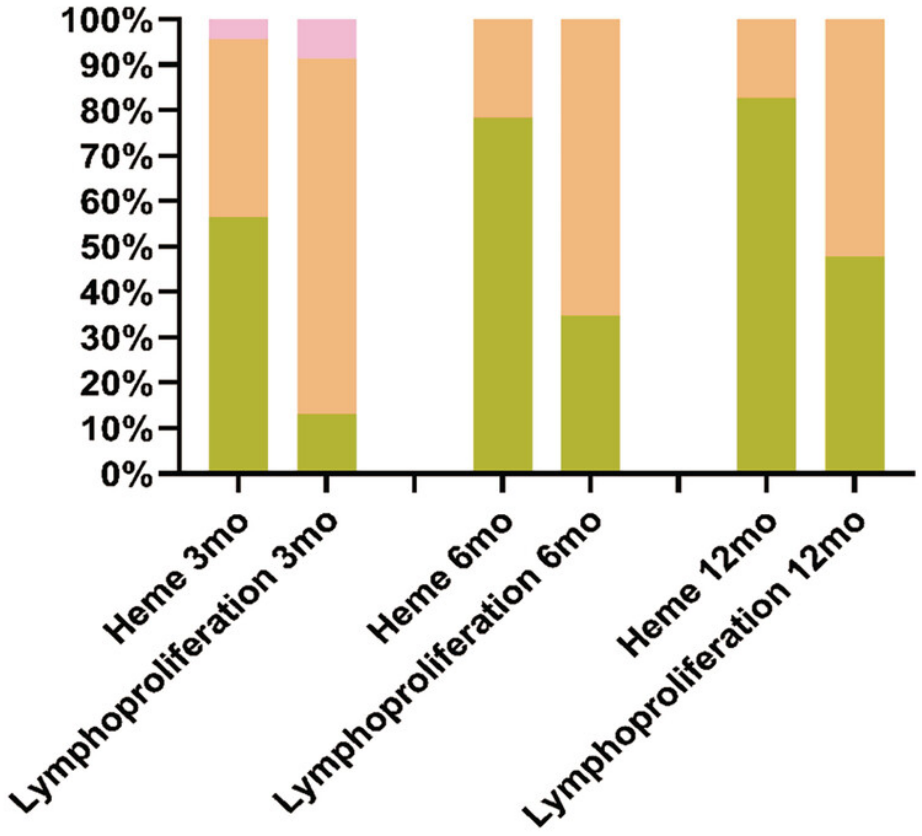
Sirolimus in ALPS & ALPS-like Diseases





Bride KL, et al. Blood. 2016

Sirolimus in ALPS & ALPS-like Diseases



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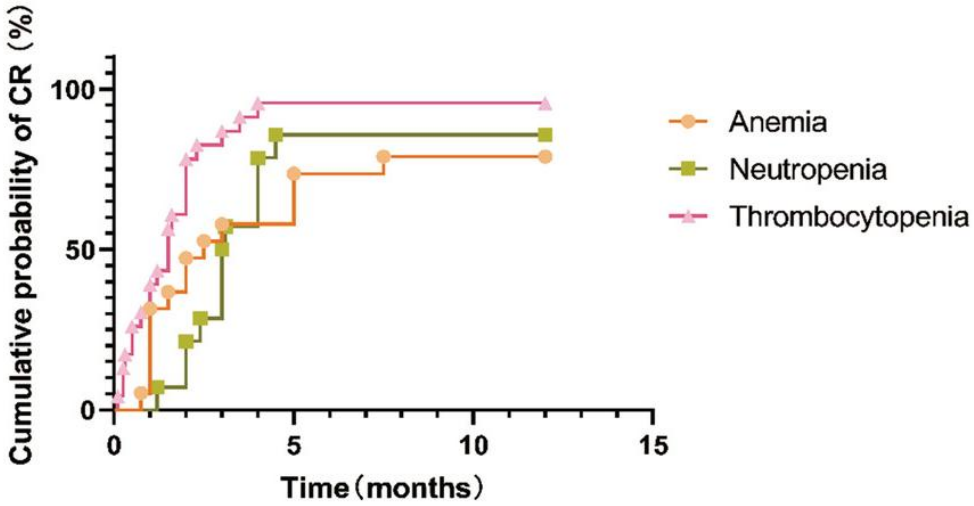
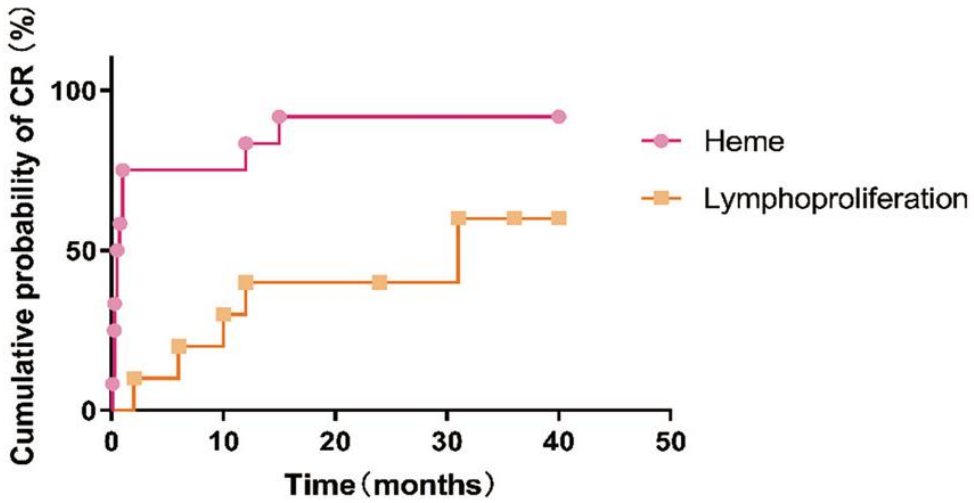
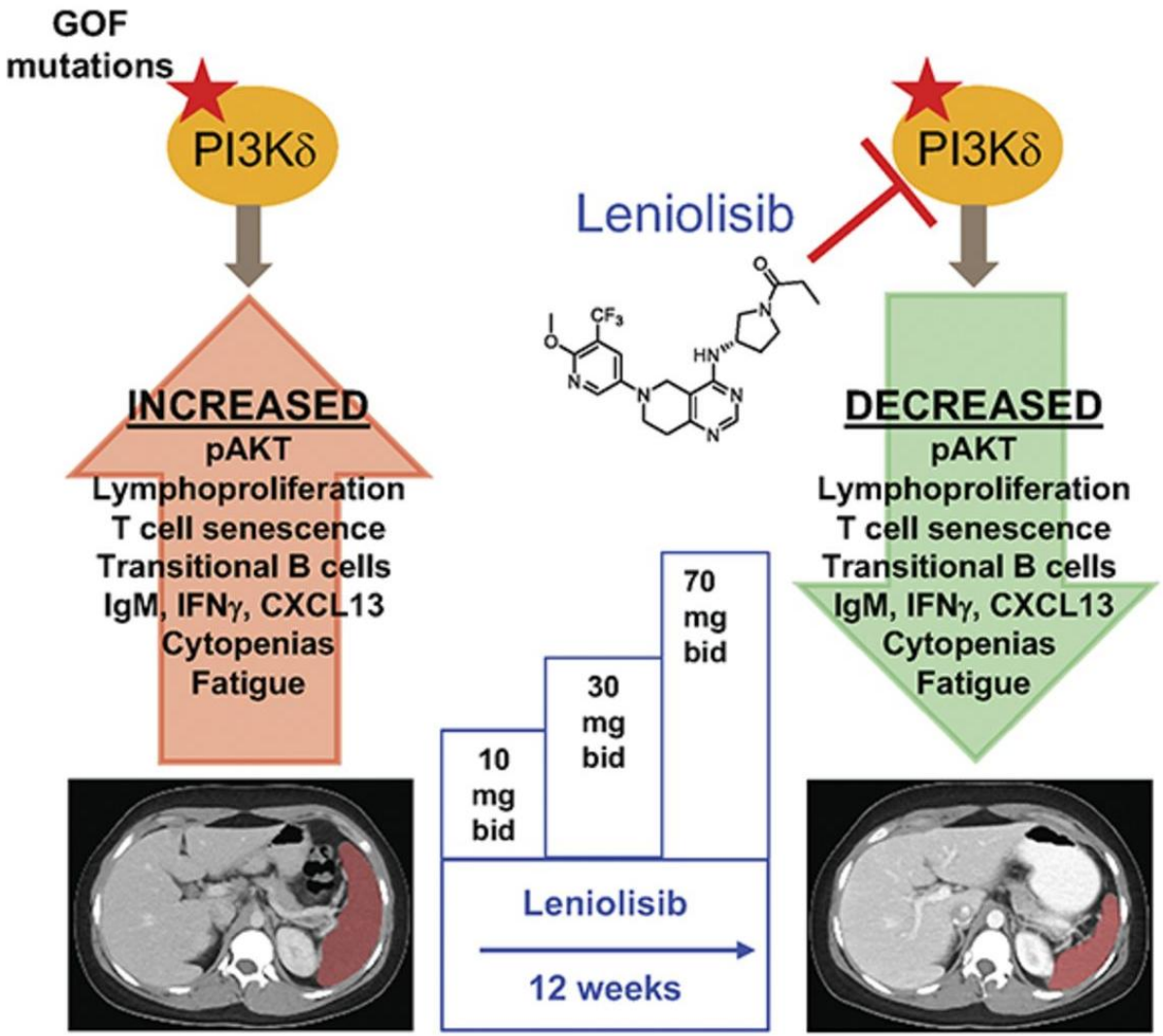


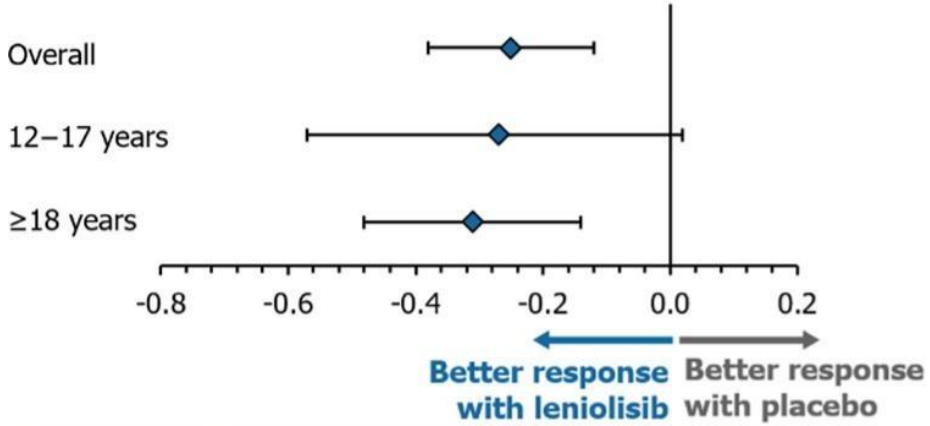


Gu H, et. al Pediatr Allergy Immunol. 2025

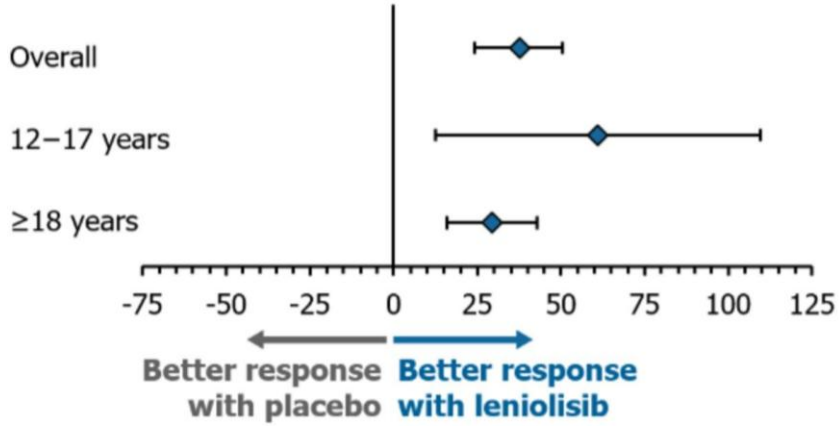
PI3K inhibitors in Activated PI3K Diseases (APDS)



Decreased Lymph Node Size



Increased B Cells

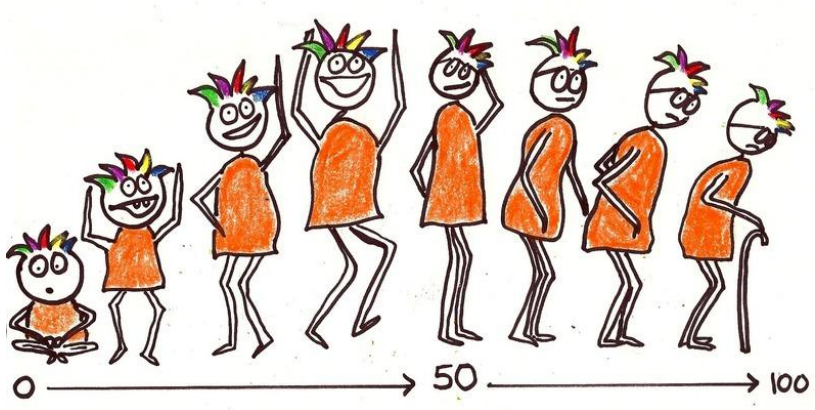


Rao VK, et al. Blood 2017
Rao VK, et al. Clin Immunol. 2025

Natural History Study on PIRD

Primary Immune Deficiency Treatment Consortium (PIDTC): 6906 PIRD Protocol

- Patients on best available therapy or had a BMT
- Family members without symptoms



Clinical Criteria +/- PIRD Gene

MAJOR

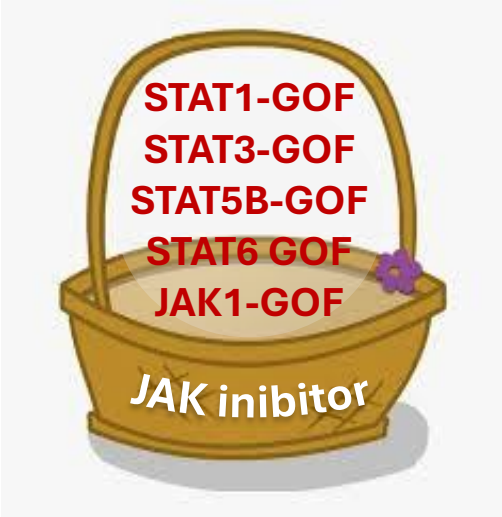
- Immune-mediated **Gastrointestinal** disease
- Immune-mediated **Lung** disease
- Immune-mediated **Cytopenias**
- Non-malignant **Lymphoproliferation**

MINOR

- Autoimmune **Endocrinopathy**
- Immune-mediated **Liver** disease
- Immune-mediated **Skin** disease
- **Rheumatologic** disease
- **Hypogammaglobulinemia**
- **Onset** of immune dysregulation at **< 5 y/o**

Basket Clinical Trial: JAK inhibitor to Treat JAK/STAT Pathway Disorders
NIH UG3/UH3 Grant - NCATS

Basket Clinical Trial



Many Diseases
One Treatment

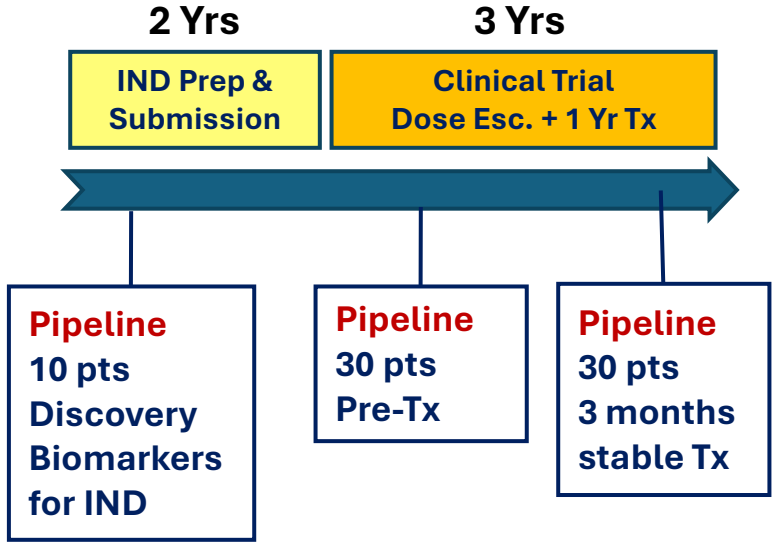
Study Team:

PI – Lisa Forbes, Baylor
Co-PI – Troy Torgerson, Allen Institute Immunology

Co-I – Josh Milner, Columbia
Co-I – Megan Cooper, Wash. U.
Co-I – Alice Chan, UCSF

Clinical Trial Sites

★ **Confirmed Clinical Trial Sites**
☆ Additional Potential Clinical Trial Sites



Modified slide from Lisa Forbes-Satter

Take Home Points

- PIRD = **P**rimary **I**mmune **R**egulatory **D**isorders
- Disease where symptoms are caused by the immune system not being regulated correctly
- Clinical Features - Autoimmunity, Inflammation, Infections, Lymphoproliferation, Severe Allergies
- Evaluation
  - General inflammation and organ function
  - Immune labs
  - Autoantibody testing based on organ disease
  - Genetic testing
- Multidisciplinary care team helpful
- Precision therapies based on genetics & symptoms
  - Immunosuppression
  - Immune protective (IVIG, prophylaxis)
  - Immune replacement (HSCT, gene therapy)