# An allergist's guide to using genetic testing in the diagnosis and management of immunodeficiency


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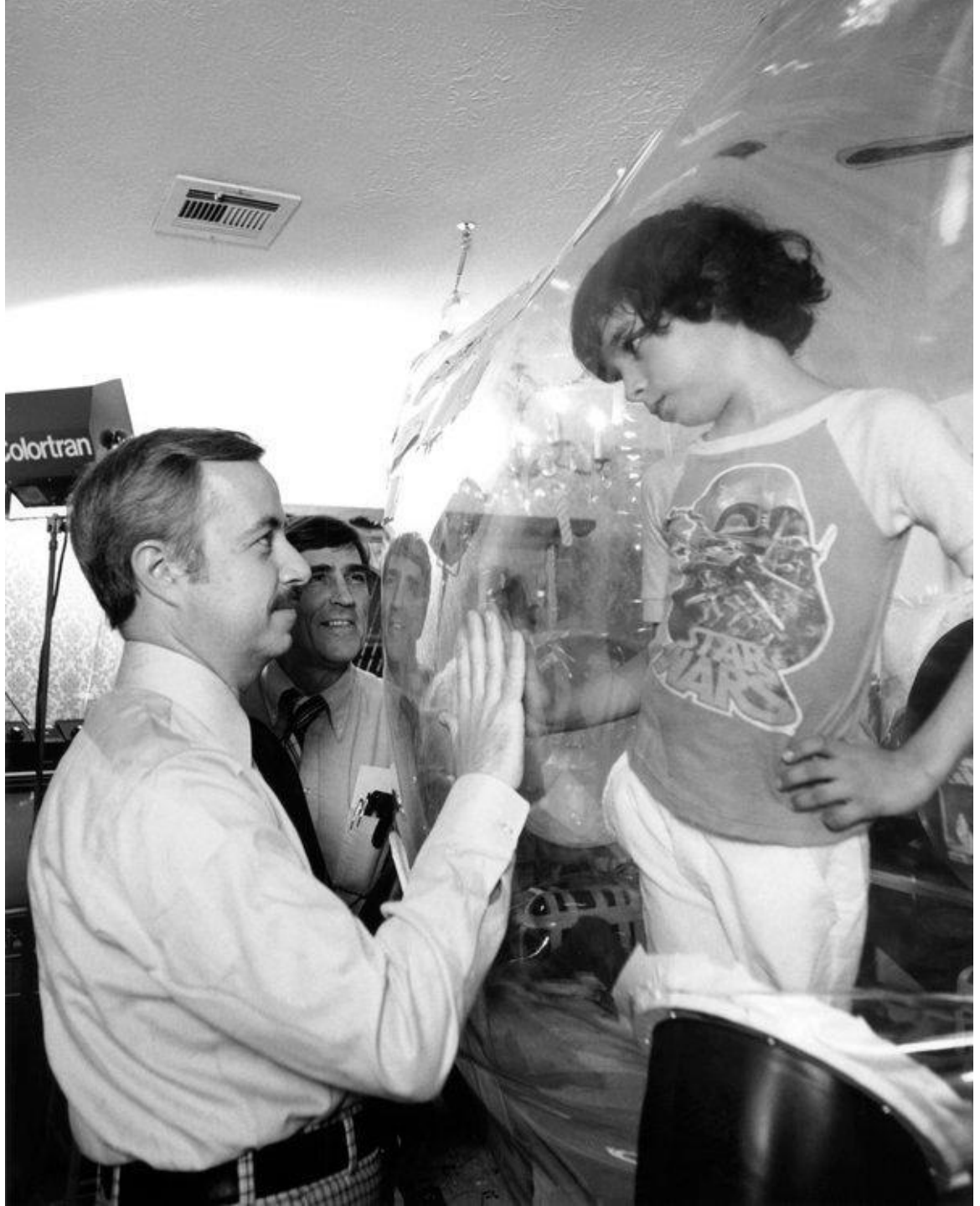
# Objectives

- Identify clinical presentations of deficiencies that would benefit from genetic testing
- Develop a systematic approach to genetic testing in the evaluation of immune mediated disease
- Discuss how to analyze variants of uncertain significance and the limitations of genetic testing

# We have come a long way……

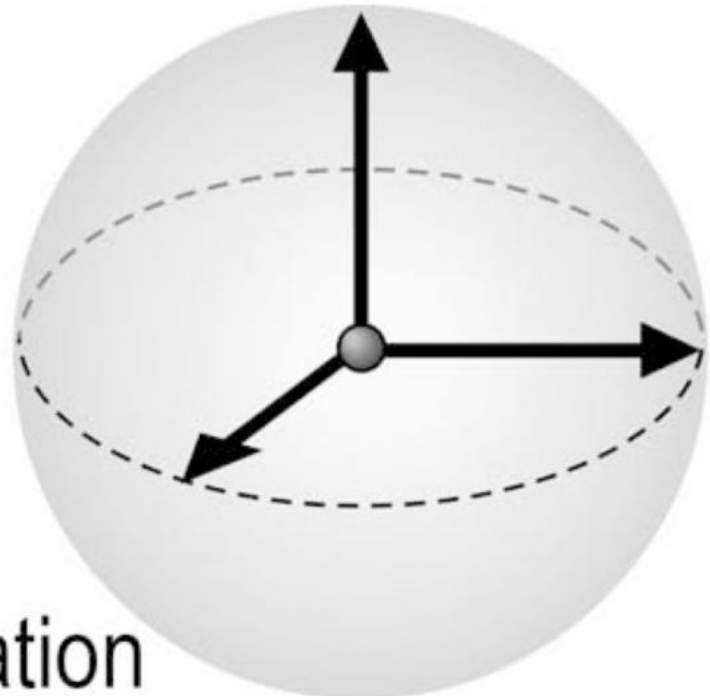
- Witnessed a scientific revolution with memorable breakthroughs in the field of immunology

- “People often ask what’s the measure of someone’s life, but very few people stood as tall as David,” Dr. Shearer said in a 2009 article in the Houston Chronicle “More than any scientist, he taught us by his life.”



Immunodeficiency

Pathogen susceptibility



Autoimmunity/Allergy

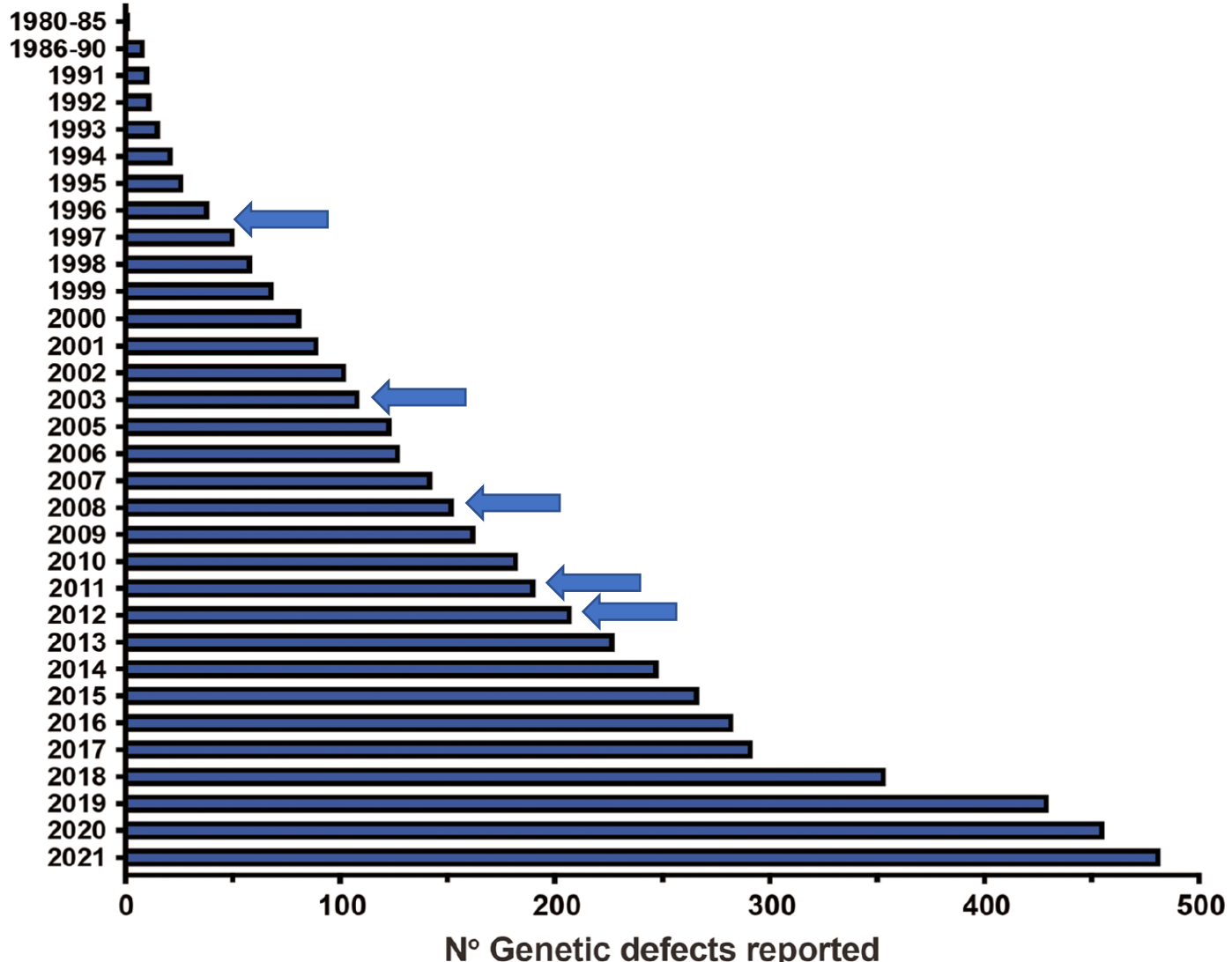
Antigen-dependent inflammation

Autoinflammation

Antigen-independent inflammation

Nigrovic, Lee, Hoffman JACI 2020

# Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies (IUIS) Expert Committee



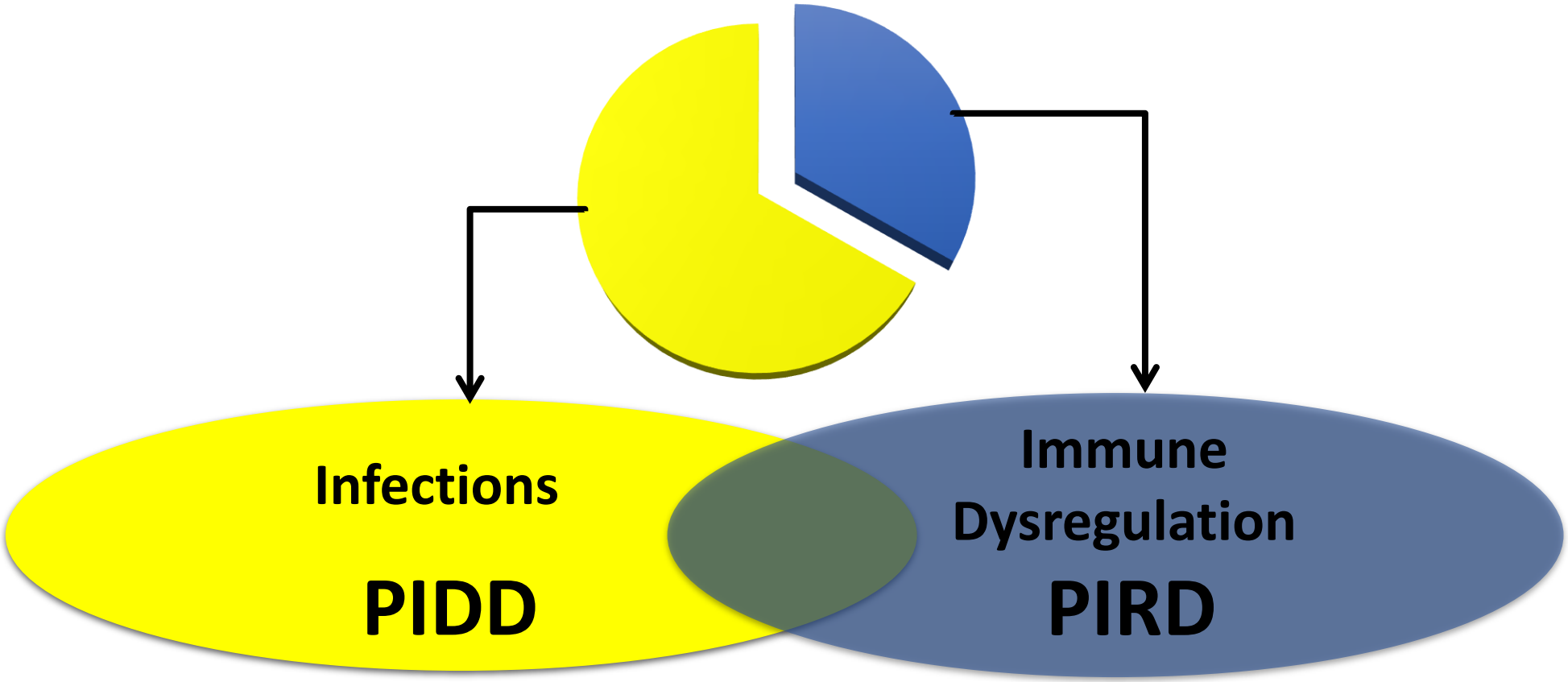

Tangye et al J clin Immunol 2022

# IUIS Phenotypical Classification

| Table | Category |
|---|---|
| Table I | Immunodeficiency Affecting Cellular and Humoral Immunity |
| Table II | CID with syndromic features |
| Table III | Predominately Antibody Deficiencies |
| Table IV | Diseases of Immune Dysregulation |
| Table V | Congenital Defects of Phagocyte Number, Function or Both |
| Table VI | Defects in Intrinsic and Innate Immunity |
| Table VII | Auto-Inflammatory Disorder |
| Table VIII | Complement Deficiencies |
| Table IX | Bone Marrow Failure |
| Table X | Phenocopies of Primary Immunodeficiency (somatic mutations or associated with autoantibodies |

Tangye et al J clin Immunol 2022

# PIDD vs. PIRD




**Primary Immune Deficiency Disorders**

- Infections Dominant
- May have autoimmunity/autoinflammation
  - CVID – Bowel, Lungs, Liver, Skin, etc.
  - CGD – Bowel, etc.
  - WAS – Vasculitis, etc.

**Primary Immune Regulatory Disorders**

- Immune Pathology Dominant (Autoimmune, Autoinflammatory, etc.)
- May have infections
  - STAT1-GOF – CMC, Mycobacteria
  - PIK3CD – EBV, etc.

Adapted from Chan, Torgerson et al

# Genetic diagnosis of PIDD – does it matter?
## How would it matter for our PBL case, Connor?

- Applies a spectrum of natural history to patients
- Many newly discovered inborn errors of immunity share pathognomonic features
- Age of atypical presentations of known diseases
  - Is the atypical the typical?
- Can help justify/advocate for patient benefits
- Implications for undiagnosed family members
- Genetic counselling
- Prenatal Genetic Diagnosis

**Important implications on prognosis and treatment**

# Genetic diagnosis of PIDD – does it matter?

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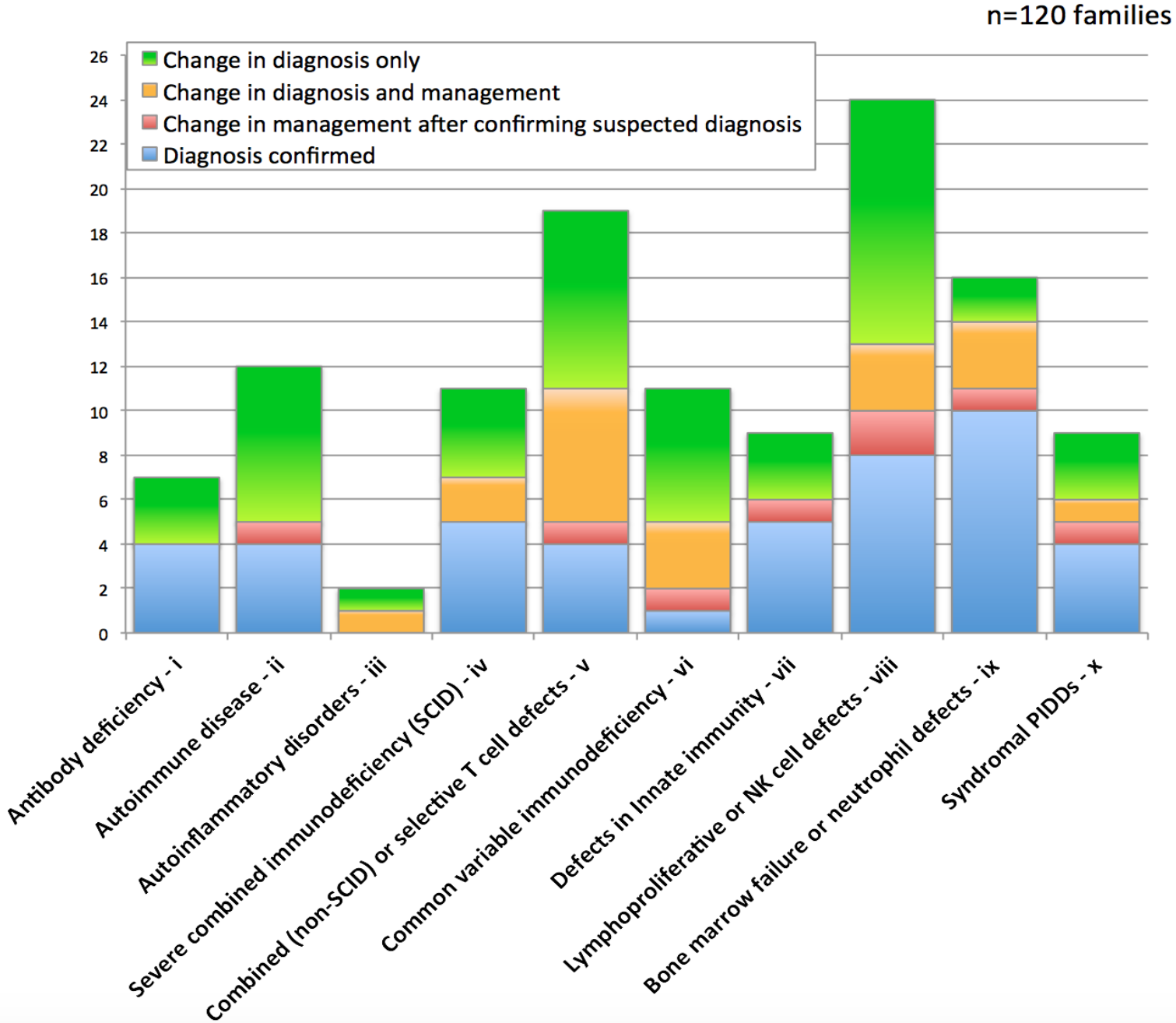
**Important implications on prognosis and treatment**

# Houston Project: Diagnostic Implications

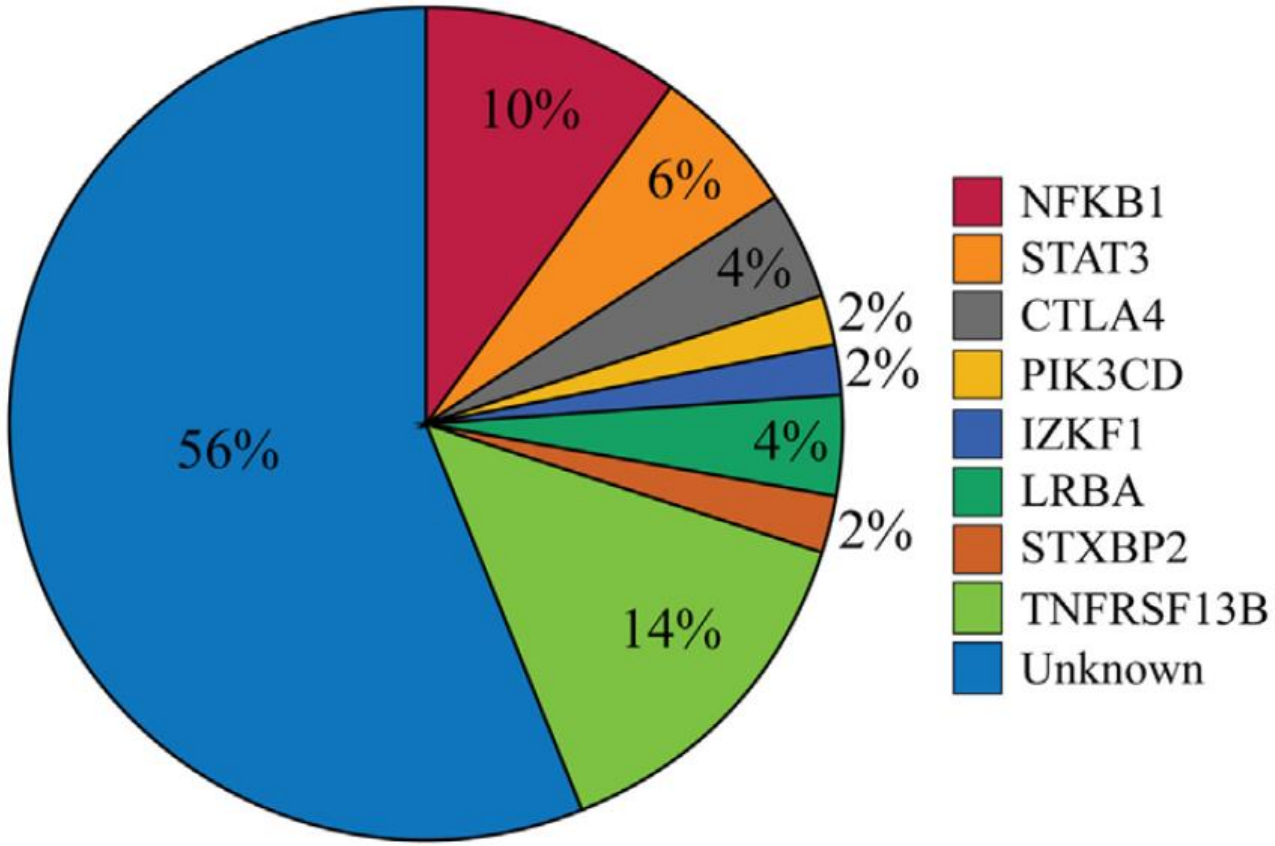



- 25% of cases (26 families, 32 affected individuals) WES directed a change in management
- 10 underwent Bone marrow transplant as a result of WES findings
- 25% of findings were genes reported as disease causing in the 5 years prior to publication

Stray-Petersen et al JACI 2017

# Genetic Diagnosis Using Whole Exome Sequencing in Common Variable Immunodeficiency

*Patrick Maffucci[1,2†], Charles A. Filion[2†], Bertrand Boisson[3,4,5], Yuval Itan[3], Lei Shang[3], Jean-Laurent Casanova[3,4,5,6,7] and Charlotte Cunningham-Rundles[1,2*]*




50 subjects with CVID sequenced if they met the following criteria:

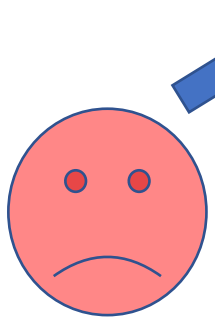
- early onset
- autoimmune/inflammatory manifestations
- low B lymphocytes
- and/or familial history of hypogammaglobulinemia
- 17 mutations found in 15 patients
- 30%

Frontiers 2016

# Types of genetic analyses available

- Sanger “direct” sequencing - individual genes
- “next gen” - massively parallel sequencing panels
- Whole exome sequencing
  - Varying coverage, varying analysis,
- Whole genome sequencing
- Copy number variation (also important)
  - Karyotype, FISH, Chromosomal microarray (CMA, SNPchip)

# Suspected Immune Deficiency or Immune Regulation Disorder



**Recurrent Typical Infections**:
- CBC and diff: Check the ALC and ANC
- IgG, IgA, IgM, IgE
- Diphtheria, tetanus, pneumococcal titers
- DHR
- Infectious studies/Imaging

**Opportunistic infections**:
- Lymphocyte phenotyping
  - T, B and NK cell subsets
- Lymphocyte function studies
- Humoral immunity testing
- DHR
- HIV testing
- Infectious studies/Imaging

**Autoimmunity/Autoinflammation**
- Antibody testing
- Cytokine testing
- Refer to specialist for specific organ system involved

**Genetic Testing**

- VUS
- Known Gene/new phenotype
- Novel gene

Personalize Biologic pipeline

Known gene
Known phenotype

Diagnosis/Targeted therapy

Adapted from:
Heimall et al JACI in practice 2019
Agarwal Ann All Asthma 2019
Stray-Peterson et al JACI 2017

# The Dreaded VUS

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION |
|---|---|---|---|
| C3 | c.763A>G (p.Ile255Val) | heterozygous | Uncertain Significance |
| CIITA | c.2117T>G (p.Leu706Arg) | heterozygous | Uncertain Significance |
| DGAT1 | c.443T>G (p.Phe148Cys) | heterozygous | Uncertain Significance |
| DTNBP1 | c.1019_1020del (p.Glu340Glyfs*7) | heterozygous | Uncertain Significance |
| ERCC6L2 | c.4123A>C (p.Thr1375Pro) | heterozygous | Uncertain Significance |
| IFNGR1 | c.1087C>T (p.Pro363Ser) | heterozygous | Uncertain Significance |
| IL17RA | c.142C>A (p.Leu48Ile) | heterozygous | Uncertain Significance |
| NBAS | c.5724+13A>G (Intronic) | heterozygous | Uncertain Significance |
| TMC8 | c.1435G>A (p.Val479Met) | heterozygous | Uncertain Significance |
| UNC45A | c.250+3delinsCC (Intronic) | heterozygous | Uncertain Significance |

# Variant classification is driven by American College of Medical Genetics and Genomics (ACMG) guidelines

| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | **Strong** | **Supporting** | **Supporting** | **Moderate** | **Strong** | **Very strong** |
| **Population data** | MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2 | | | Absent in population databases PM2 | Prevalence in affecteds statistically increased over controls PS4 | |
| **Computational and predictive data** | | Multiple lines of computational evidence suggest no impact on gene /gene product BP4<br><br>Missense in gene where only truncating cause disease BP1<br><br>Silent variant with non predicted splice impact BP7<br><br>In-frame indels in repeat w/out known function BP3 | Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3 | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5<br><br>Protein length changing variant PM4 | Same amino acid change as an established pathogenic variant PS1 | Predicted null variant in a gene where LOF is a known mechanism of disease PVS1 |
| **Functional data** | Well-established functional studies show no deleterious effect BS3 | | Missense in gene with low rate of benign missense variants and path. missenses common PP2 | Mutational hot spot or well-studied functional domain without benign variation PM1 | Well-established functional studies show a deleterious effect PS3 | |
| **Segregation data** | Nonsegregation with disease BS4 | | Cosegregation with disease in multiple affected family members PP1 | Increased segregation data → | | |
| **De novo data** | | | | De novo (without paternity & maternity confirmed) PM6 | De novo (paternity and maternity confirmed) PS2 | |
| **Allelic data** | | Observed in *trans* with a dominant variant BP2<br><br>Observed in *cis* with a pathogenic variant BP2 | | For recessive disorders, detected in trans with a pathogenic variant PM3 | | |
| **Other database** | | Reputable source w/out shared data = benign BP6 | Reputable source = pathogenic PP5 | | | |
| **Other data** | | Found in case with an alternate cause BP5 | Patient's phenotype or FH highly specific for gene PP4 | | | |

Richards et al. *Genet Med* 2015;17:405-24

# NOW YOU HAVE GENETIC DATA: WHAT NEXT?

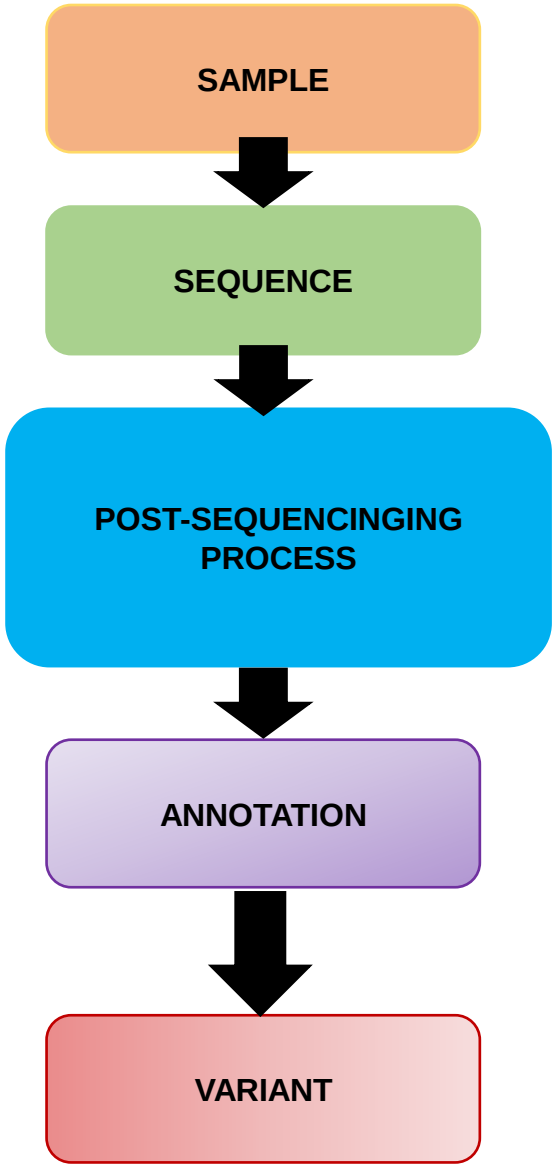
**A few things to keep in mind:**

● Just because you have done genetic testing does not mean you will get a conclusive answer right away

● You may need to move from a targeted panel to exome or genome sequencing
- Consider the pros and cons of each
- Need for confirmatory testing such as sanger candidate genes

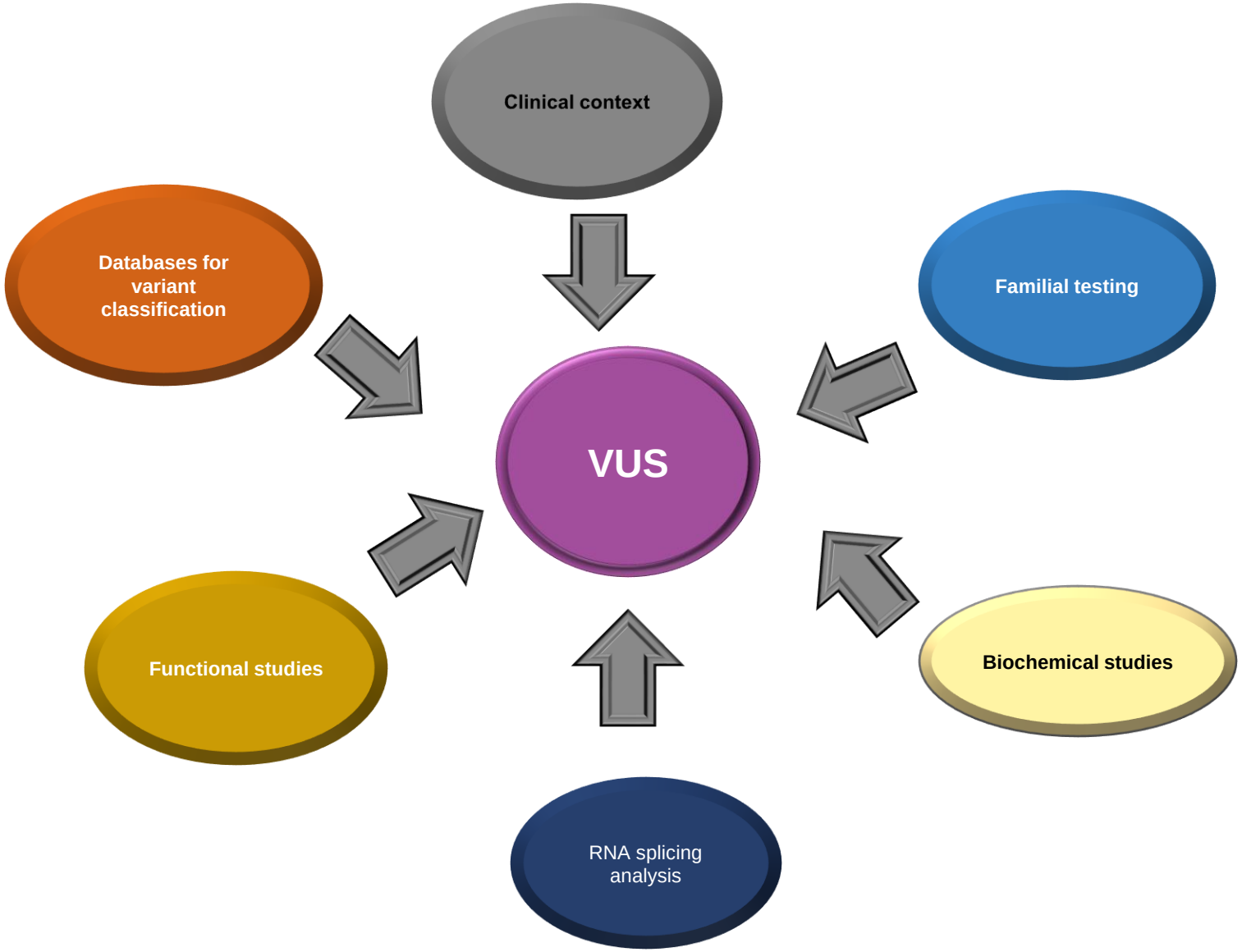
● You may need to do a SNP array to assess for copy number variations

● Disease may not be monogenic
- complex trait or a syndromic diagnosis
- a variation missed by the current methods of NGS and may require other molecular approaches




Forbes, Abraham, Butte AAAAI 2022

# TEASING OUT THE SIGNIFICANCE OF VUSs

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# ACMG codes amenable to practical review and modification

- PM2:  penetrance
- PP4:  phenotype/expressivity
- PS3:  functional modeling
- PM1:  hotspot/domain
- PP1:  familial segregation
- PS2/PM6:  *de novo*/AD proband counting
- PM3:  *trans*/AR proband counting

# Case Example

- 4 month-old term girl
- Difficulty with thrush at 1 month – no other infections
- Initially presented with encephalopathy:  positive influenza test
- Developed seizures followed by cardiac arrest
- Placed on ECMO and weaned off
- In PICU:  pseudomonal sepsis and HLH
- Candidal esophagitis
- Ecthyma gangrenosum (*Pseudomonas*-positive) and bilateral necrosis of nasal and basilar skull bones with erosion extending through middle ear to tympanic membranes:  *E. coli*, *E. faecalis*, and enteric organisms
- Found to be neutropenic and placed on G-CSF

# Genetic Results

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION |
|---|---|---|---|
| C5 | c.1680G>A (p.Trp560*) | heterozygous | PATHOGENIC |
| ELANE | c.639del (p.His213Glnfs*27) | heterozygous | Uncertain Significance ??? |
| G6PD | c.376A>G (p.Asn126Asp) | heterozygous | Uncertain Significance |
| GUCY2C | c.1024A>C (p.Asn342His) | heterozygous | Uncertain Significance |
| HYOU1 | c.1647C>T (Silent) | heterozygous | Uncertain Significance |
| RTEL1 | c.2600C>T (p.Pro867Leu) | heterozygous | Uncertain Significance |
| TOP2B | c.113A>T (p.Asn38Ile) | heterozygous | Uncertain Significance |

Courtesy: Howard Rosenblatt, M.D, Ph.D.

# Variant Summary

ELANE, Exon 5, c.639del (p.His213Glnfs*27), heterozygous, Uncertain Significance

- This sequence change creates a premature translational stop signal (p.His213Glnfs*27) in the ELANE gene. While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 55 amino acid(s) of the ELANE protein.
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with ELANE-related conditions.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Courtesy: Howard Rosenblatt, M.D, Ph.D.

# Parental Results

- Father

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION | RESULT |
|---|---|---|---|---|
| TOP2B | c.113A>T (p.Asn38Ile) | heterozygous | Uncertain Significance | Detected |
| C5 | c.1680G>A (p.Trp560*) | N/A | PATHOGENIC | Not detected |
| ELANE | c.639del (p.His213Glnfs*27) | N/A | Uncertain Significance | Not detected |
| GUCY2C | c.1024A>C (p.Asn342His) | N/A | Uncertain Significance | Not detected |

- Mother

20%

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION | RESULT |
|---|---|---|---|---|
| C5 | c.1680G>A (p.Trp560*) | heterozygous | PATHOGENIC | Detected |
| ELANE | c.639del (p.His213Glnfs*27) | possibly mosaic | Uncertain Significance | Detected |
| GUCY2C | c.1024A>C (p.Asn342His) | heterozygous | Uncertain Significance | Detected |
| TOP2B | c.113A>T (p.Asn38Ile) | N/A | Uncertain Significance | Not detected |

Courtesy: Howard Rosenblatt, M.D, Ph.D.

# Parental mosaicism is well-known in this disease

Two paternal mosaicism of mutation in *ELANE* causing severe congenital neutropenia exhibit normal neutrophil morphology and ROS production

Qiao Liu[a], Liang Zhang[a], Zhou Shu[b], Yuan Ding[b], Xue-Mei Tang[b], Xiao-Dong Zhao[a,b,c,*]

[a] Chong Qing Key Laboratory of Child Infection and Immunity, Children's Hospital of Chongqing Medical University, Chongqing 400014, China
[b] Division of Immunology, Children's Hospital of Chongqing Medical University, Chongqing 400014, China
[c] Ministry of Education Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Children's Hospital of Chongqing Medical University, Chongqing 400014, China

Clinical Immunology 203 (2019) 53–58

**Mosaicism of an *ELANE* Mutation in an Asymptomatic Mother**

Tomonari Shigemura[1] · Norimoto Kobayashi[1] · Kazunaga Agematsu[2] · Osamu Ohara[3] · Yozo Nakazawa[1]

Journal of Clinical Immunology (2019) 39:106–111

**Paternal Somatic Mosaicism of a Novel Frameshift Mutation in *ELANE* Causing Severe Congenital Neutropenia**

Hee-Jung Kim, MD, PhD,[1]* Min-Jung Song,[1] Ki-O Lee,[2] Sun-Hee Kim,[1] and Hee-Jin Kim[1]

**Pediatr Blood Cancer 2015;62:2229–2231**

**Mosaicism of an *ELANE* Mutation in an Asymptomatic Mother in a Familial Case of Cyclic Neutropenia**

Osamu Hirata[1] · Satoshi Okada[1] · Miyuki Tsumura[1] · Shuhei Karakawa[1] · Itaru Matsumura[2] · Yujiro Kimura[3] · Toshiro Maihara[4] · Shin'ichiro Yasunaga[5] · Yoshihiro Takihara[5] · Osamu Ohara[6] · Masao Kobayashi[1]

J Clin Immunol (2015) 35:512–516

Paternal mosaicism proves the pathogenic nature of mutations in neutrophil elastase in severe congenital neutropenia

Phil J. Ancliff, Rosemary E. Gale, Michael J. Watts, Ri Liesner, Ian M. Hann, Stephan Strobel, and David C. Linch

BLOOD, 15 JULY 2002 • VOLUME 100, NUMBER 2

Mechanism:

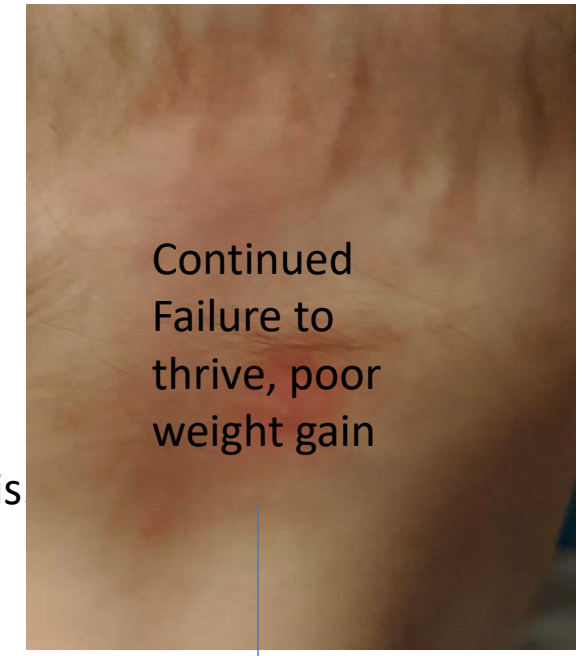
- De novo event in the parent very early in embryogenesis
- Negative selection pressure during myelopoiesis

# Case 2

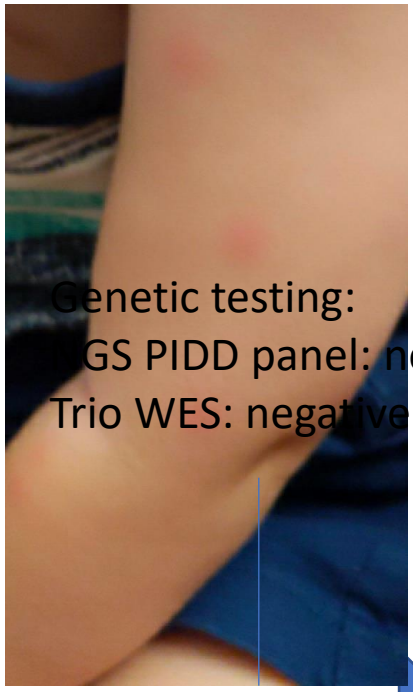
1 week of age
Hospitalized: severe fungal diaper infection and oral thrush

At 9 months of age hospitalized Osteomyelitis and treated with IV antibiotics for 2 weeks

12-14 months of age: fevers and papular erythematous rash
Biopsy revealed neutrophilic dermatosis



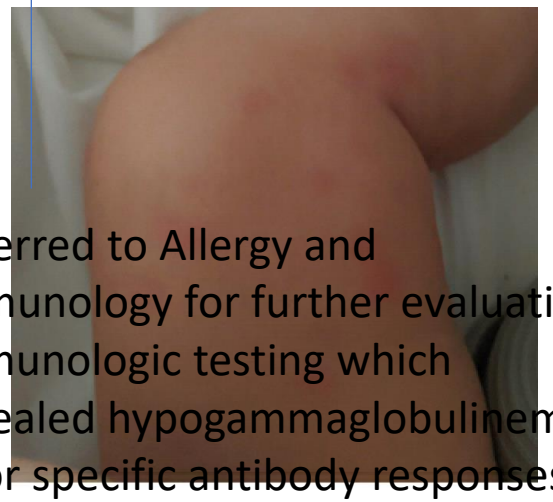
Continued Failure to thrive, poor weight gain



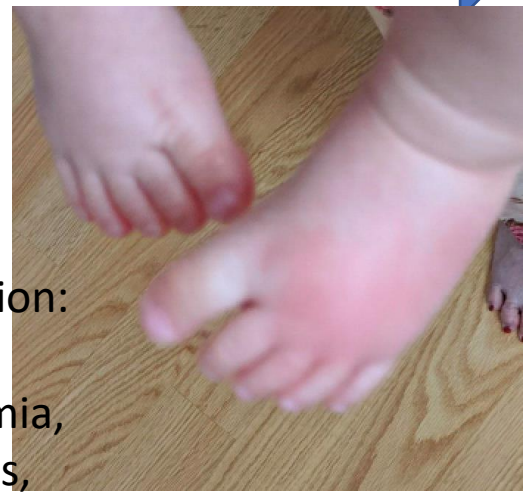
Genetic testing:
GS PIDD panel: negative
Trio WES: negative

6 months of age: diagnosed with influenza and treated with Tamiflu

10 months of age: antibiotics were discontinued then he developed cellulitis :treated with cephalexin for three more months then put on amoxicillin for prophylaxis



Referred to Allergy and Immunology for further evaluation: immunologic testing which revealed hypogammaglobulinemia, poor specific antibody responses, lymphopenia, anemia.



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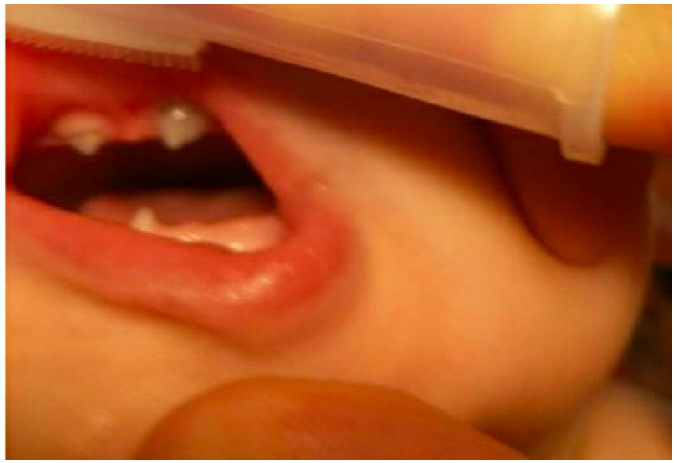
# Case 2: The story evolves…..

Around the time of genetic testing: lost his hair and it it was thin/wiry. Teeth started to erupt - conical shape



Concern for Immunodeficiency and ectodermal dysplasia: the team sent a specific panel to sequence IKBKG

His mutation is a VUS predicted to be deleterious in the IKBKG gene c.836_838delAGG (p.E279del).
Diagnosed with Immunodeficiency with Ectodermal Dysplasia caused by NEMO deficiency

Why did the team have to send a specific panel to look at IKBKG?
NEMO has a pseudogene and is will not be identified with conventional sequencing techniques

# CONSIDER GENE-SPECIFIC ISSUES

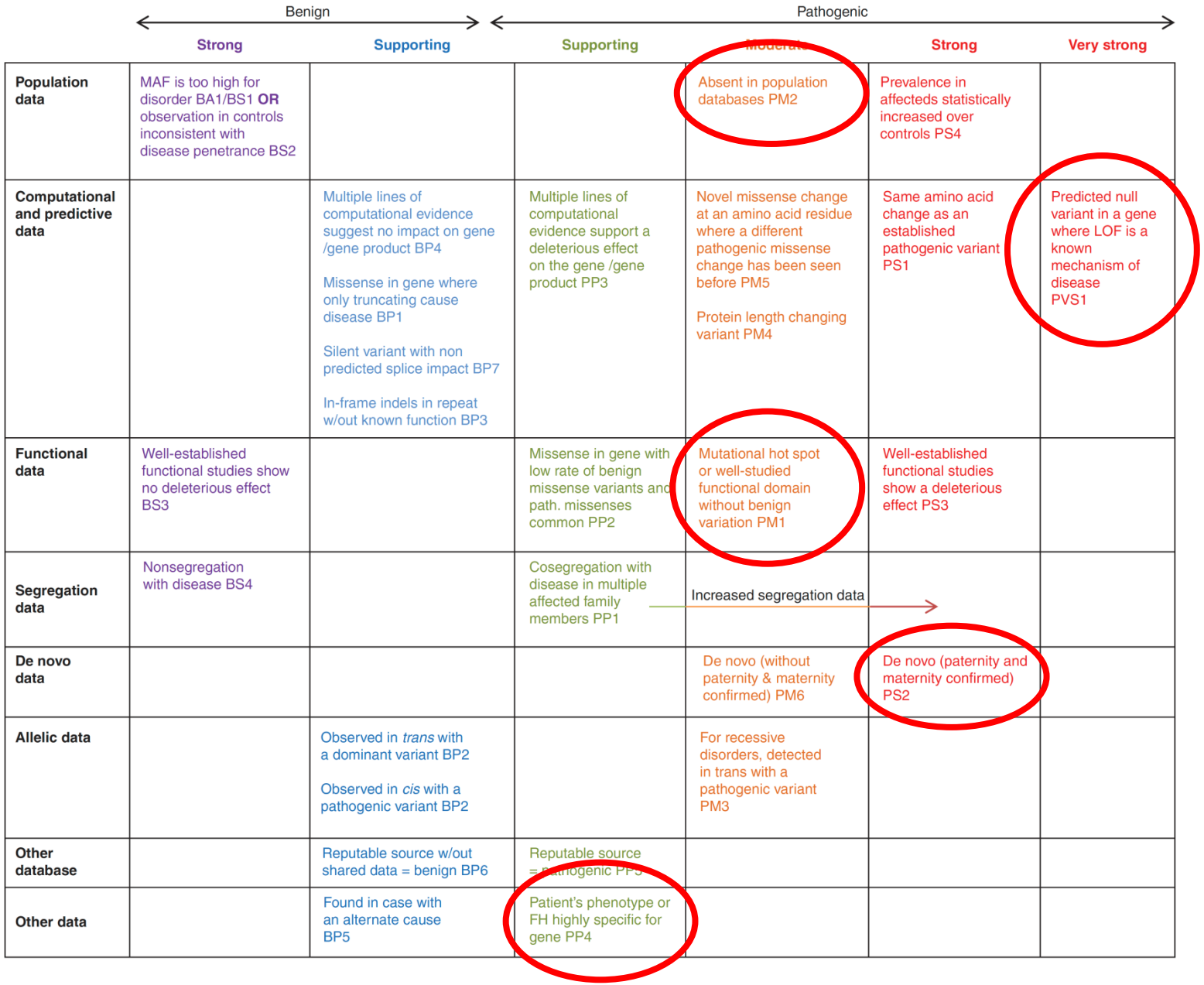
| DISORDER | GENE | ISSUE |
|---|---|---|
| SCID | *CORO1A, DCLRE1C* | Del/dups prevalent |
| Fanconi anemia | *FANCA* | Deletions prevalent |
| Cartilage Hair Hypoplasia | *RMRP* | Promoter insertions |
| NEMO deficiency | *IKBKG* | Pseudogene |
| AR-CGD | *NCF1* | Pseudogene |
| Shwachman Diamond syndrome | *SBDS* | Pseudogene |

# Our classification:

- PM2
- PVS1_Strong
- PM1
- PS2
- PP4

2 Strong + 2 Moderate + 1 Supporting =

*Pathogenic*



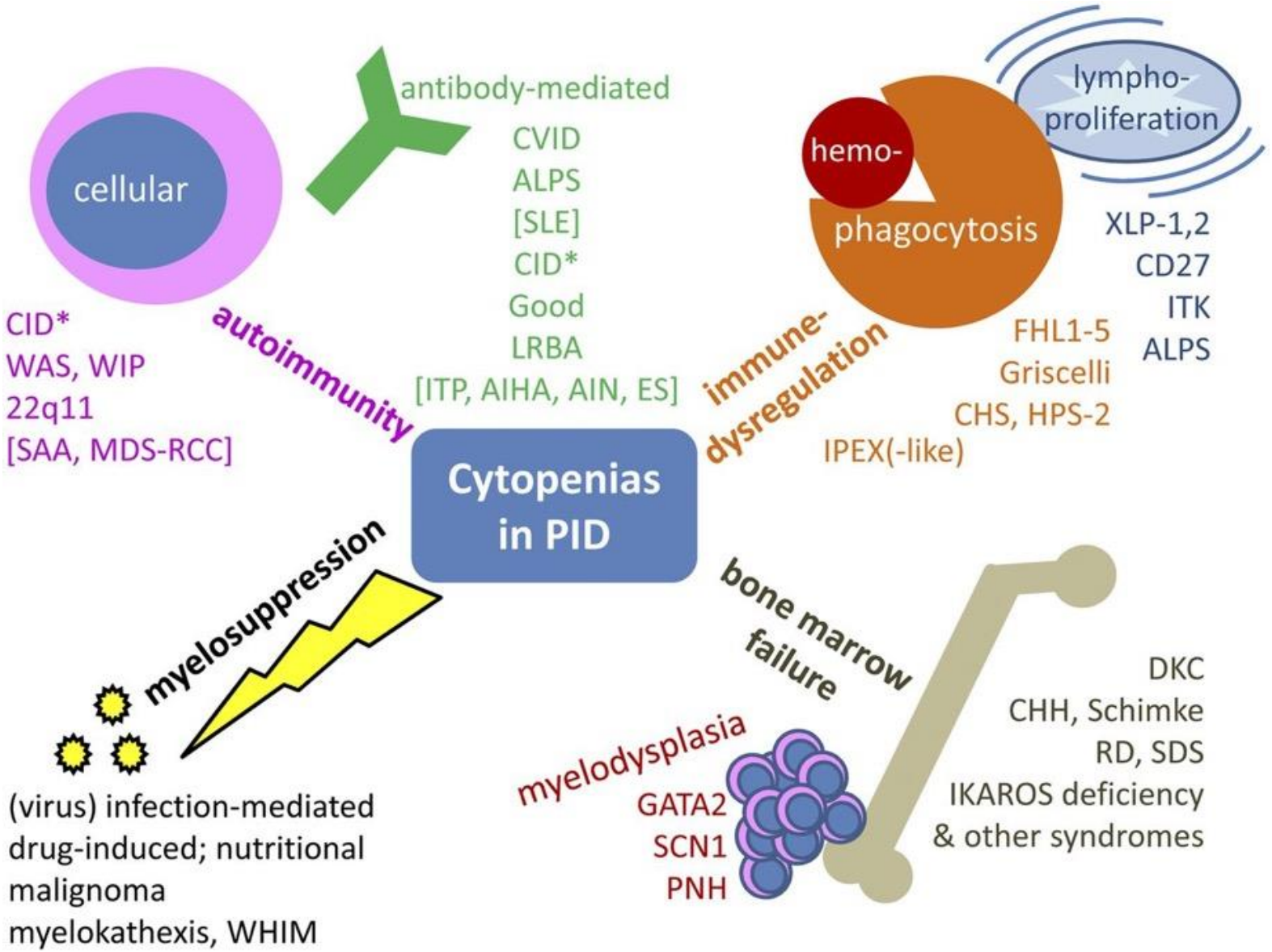
| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | Strong | Supporting | Supporting | Moderate | Strong | Very strong |
| **Population data** | MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2 | | | Absent in population databases PM2 | Prevalence in affecteds statistically increased over controls PS4 | |
| **Computational and predictive data** | | Multiple lines of computational evidence suggest no impact on gene /gene product BP4<br><br>Missense in gene where only truncating cause disease BP1<br><br>Silent variant with non predicted splice impact BP7<br><br>In-frame indels in repeat w/out known function BP3 | Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3 | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5<br><br>Protein length changing variant PM4 | Same amino acid change as an established pathogenic variant PS1 | Predicted null variant in a gene where LOF is a known mechanism of disease PVS1 |
| **Functional data** | Well-established functional studies show no deleterious effect BS3 | | Missense in gene with low rate of benign missense variants and path. missenses common PP2 | Mutational hot spot or well-studied functional domain without benign variation PM1 | Well-established functional studies show a deleterious effect PS3 | |
| **Segregation data** | Nonsegregation with disease BS4 | | Cosegregation with disease in multiple affected family members PP1 | Increased segregation data → | | |
| **De novo data** | | | | De novo (without paternity & maternity confirmed) PM6 | De novo (paternity and maternity confirmed) PS2 | |
| **Allelic data** | | Observed in *trans* with a dominant variant BP2<br><br>Observed in *cis* with a pathogenic variant BP2 | | For recessive disorders, detected in trans with a pathogenic variant PM3 | | |
| **Other database** | | Reputable source w/out shared data = benign BP6 | Reputable source = Pathogenic PP5 | | | |
| **Other data** | | Found in case with an alternate cause BP5 | Patient's phenotype or FH highly specific for gene PP4 | | | |

# A negative genetic test does not mean the end of the diagnostic journey

- Reanalysis by the commercial genetics laboratory can sometimes increase diagnostic yield
- It may or may not be offered free of charge
- What the laboratory prioritizes may not be what you prioritize
- Reanalysis yields diagnosis as new genes are discovered
- Functional testing to understand immune pathway disruptions can still inform targeted therapies

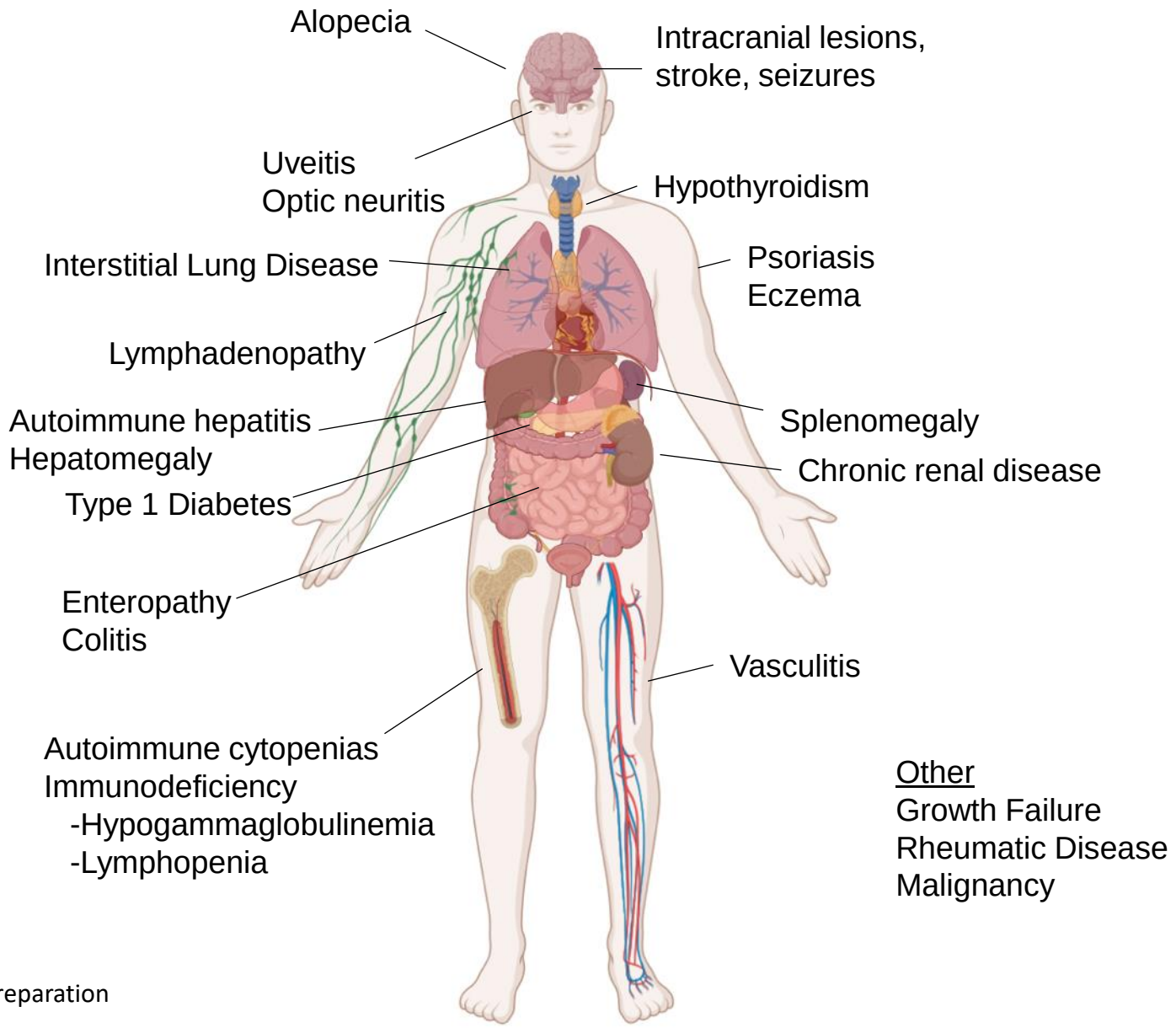
# What do you do?….When

- When the diagnosis won’t occur fast enough to treat the patient?
- What if you never have a diagnosis?
- What if the diagnosis doesn’t help you treat the patient?




Seidel Blood 2014

# Clinical Manifestations of Immune Dysregulation




Leiding, Vogel, Cooper, Forbes-Satter in preparation

# PIRD Disorders

**Debris Defects**
- Complement deficiency
- Phagocyte Defects
- Interferonopathies
  - DNAse I
  - TREX1 Complex
  - IFIH1/MDA5
  - STING

**Autoinflammatory**
- TRAPS (TNFRSF1A, TNFRSF11A)
- CAPS (NLRP3)
- FMF (MEFV)
- CANDLE – Proteosome-opathies
- DADA2
- DIRA – IL-1 opathies

**Congenital Hypersensitivity Syndromes**
- PGM3
- STAT5-GOF
- JAK1-GOF

**HLH**
- SH2D1A, XIAP
- PRF1
- Degranulation Defects
  - MUNC13-4
  - RAB27A
  - LYST
- Signaling
  - ITK
  - MAGT1
  - STAT1-GOF

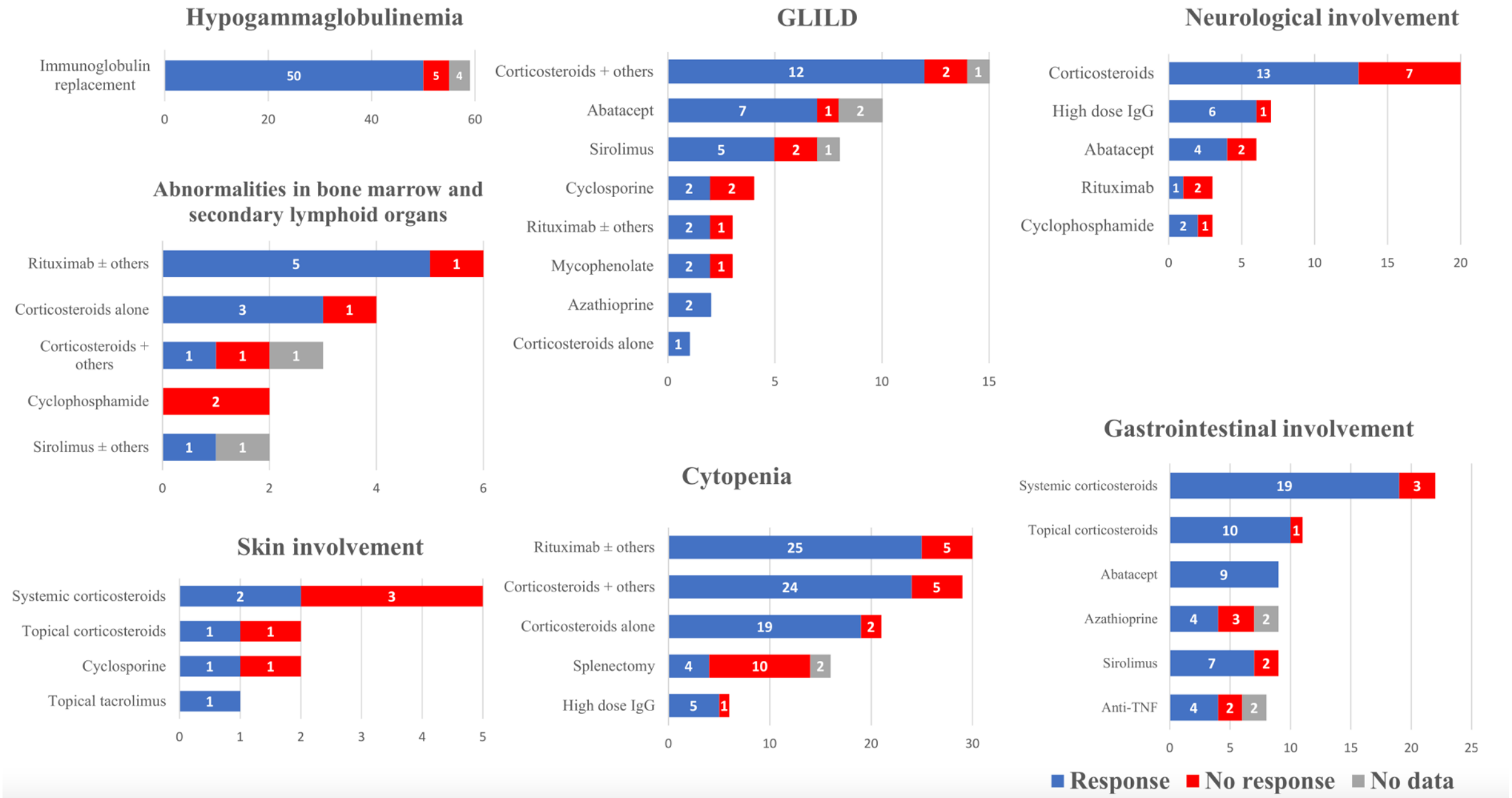
**Non-Malignant Lymphoproliferation**
- ALPS (FAS, FASL, etc.)
- ALPS-Like/ALPS-U
  - STAT3-GOF
  - hCTLA4
  - PIK3CD/PIK3R1, etc.
  - RALD

**Treg-Opathies**
- IPEX (FOXP3)
- IPEX-Like
  - CD25
  - STAT5B
  - hCTLA4
  - LRBA
  - STAT1-GOF
  - STAT3-GOF
  - IL10R1/2
  - Etc.

**IBD**
- Infant Onset-IBD
- VEO-IBD
- EO-IBD

**Rheumatologic Dz**
- JIA, SoJIA, Etc.
- Lupus
- Scleroderma

# Therapeutic options for CTLA-4 Insufficiency

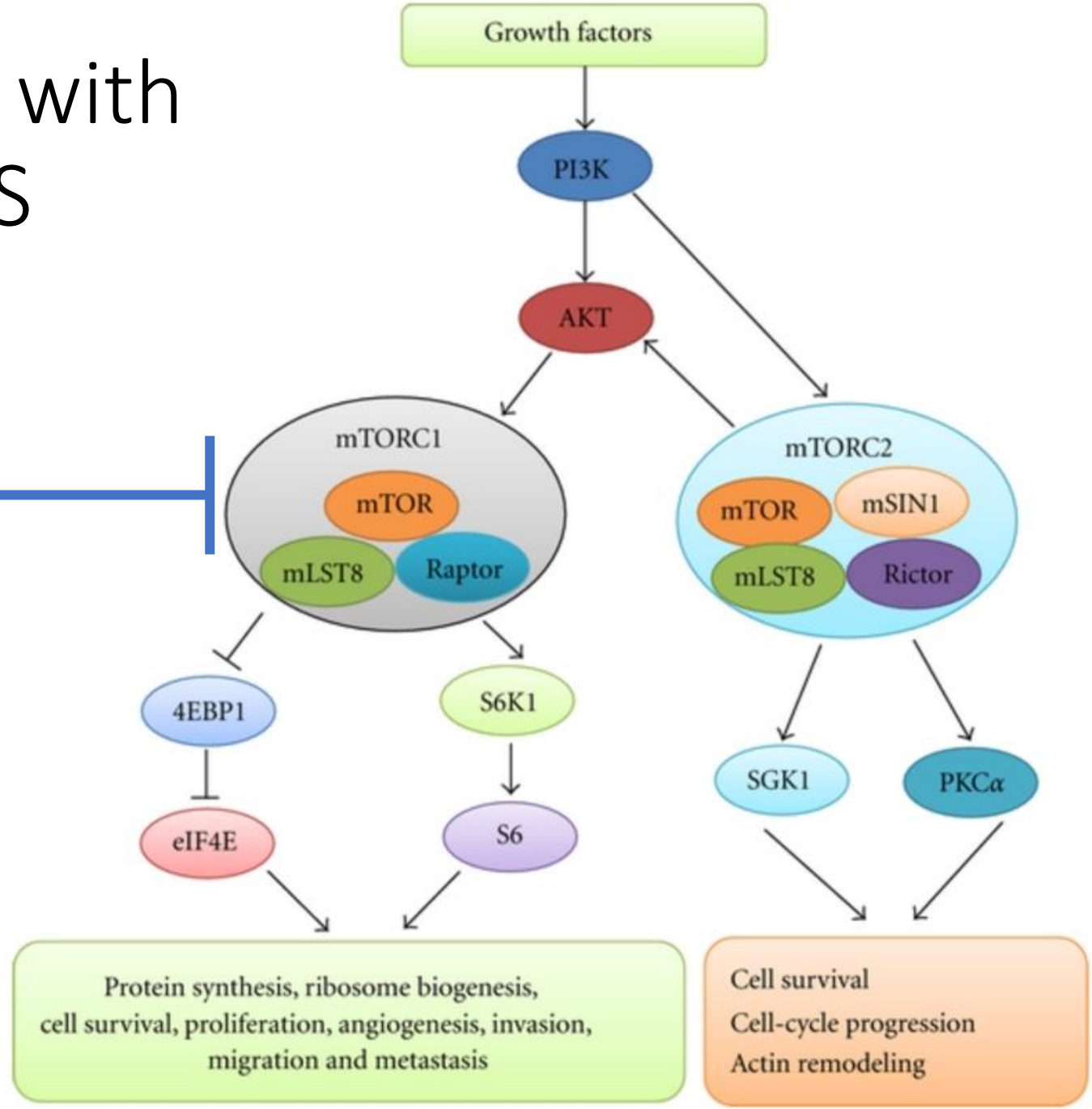



Egg….Grimbacher epub June 7, 2021 JACI

# Downstream inhibition with mTOR blockade in APDS

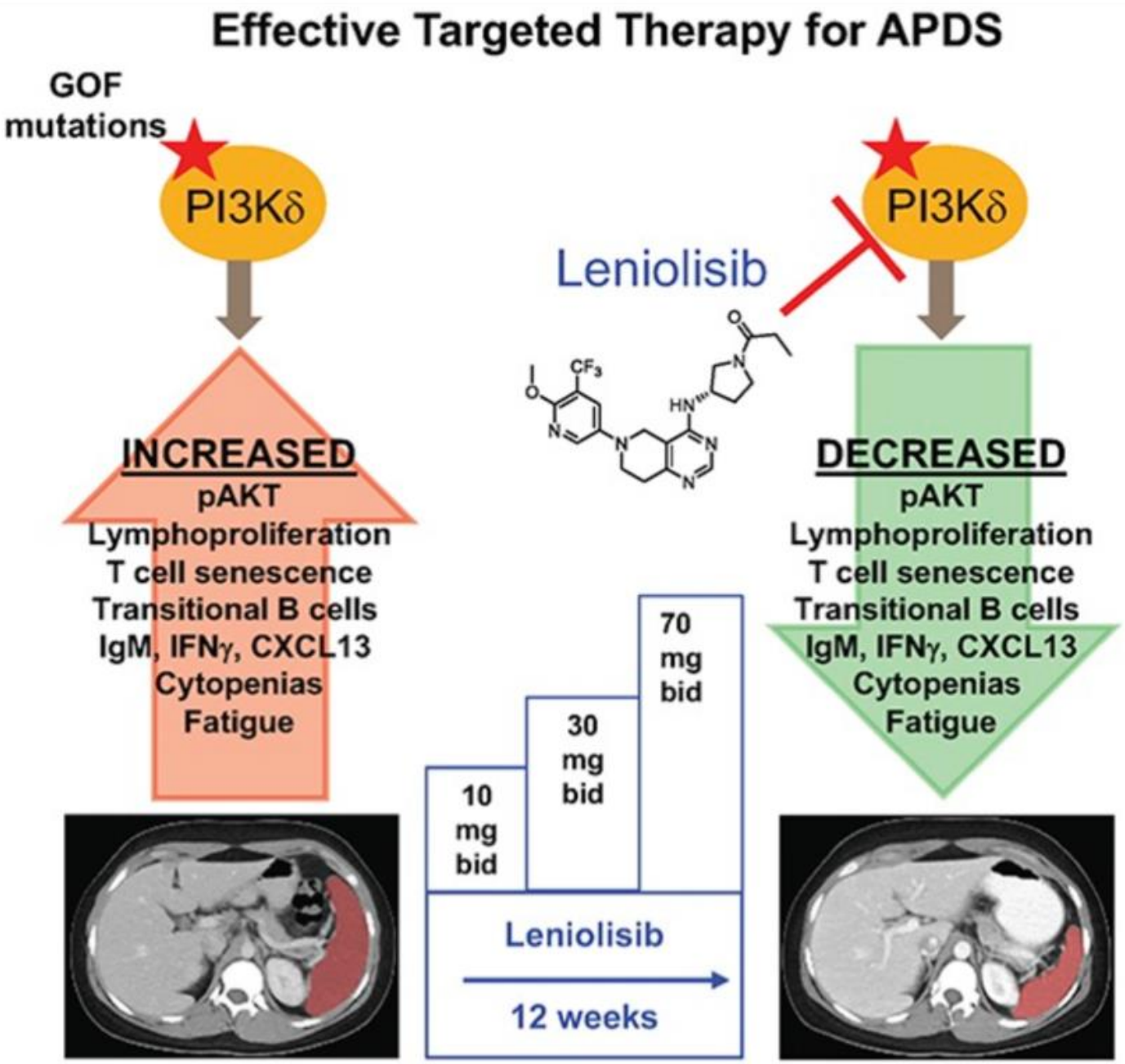
Rapamycin (sirolimus)

- Significant benefit in the treatment of non-neoplastic lymphoproliferative disease
- Less benefit in treating APDS related-cytopenias and gastrointestinal disease




Maccari et al *Front Immunol 2018*

adapted from research gate.net

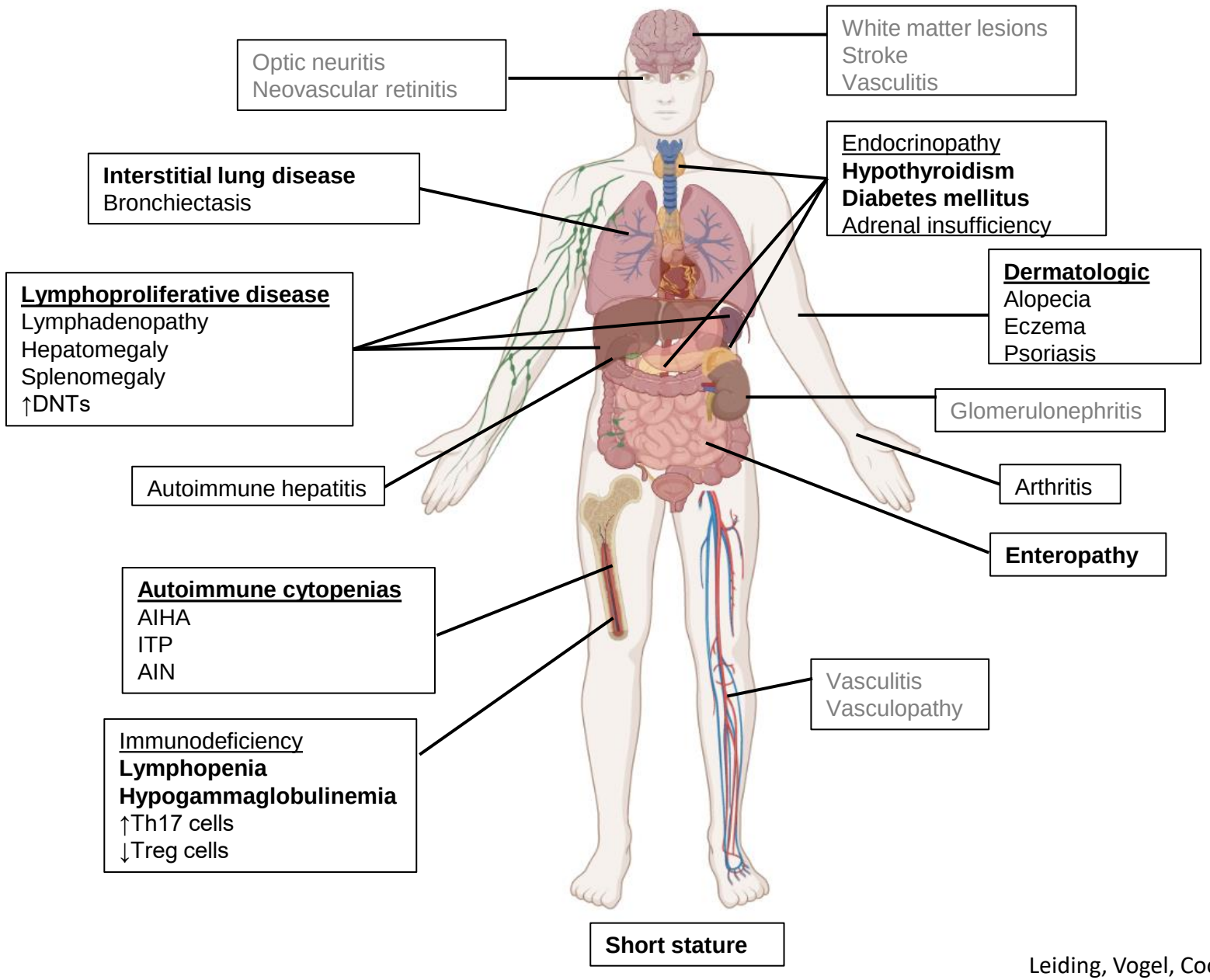



# Treatment with Leniolisib

- reduction in the frequency of elevated transitional B cells
- normalization of naive B-cell frequencies.
- CD27+CD38+ plasmablasts was also drastically reduced in 4 of 6 patients
- PD-1+CD4+ (reflecting either chronic activation/exhaustion or increased circulating follicular helper T cells) were reduced
- CD57+CD4- T cells (usually associated with senescence) were markedly reduced
- Normalization of IgM
- Discontinuation of IgG replacement
- Lymphoproliferation and cytopenias improved

Rao Blood 2017

# Clinical Manifestations of STAT3 GOF disease

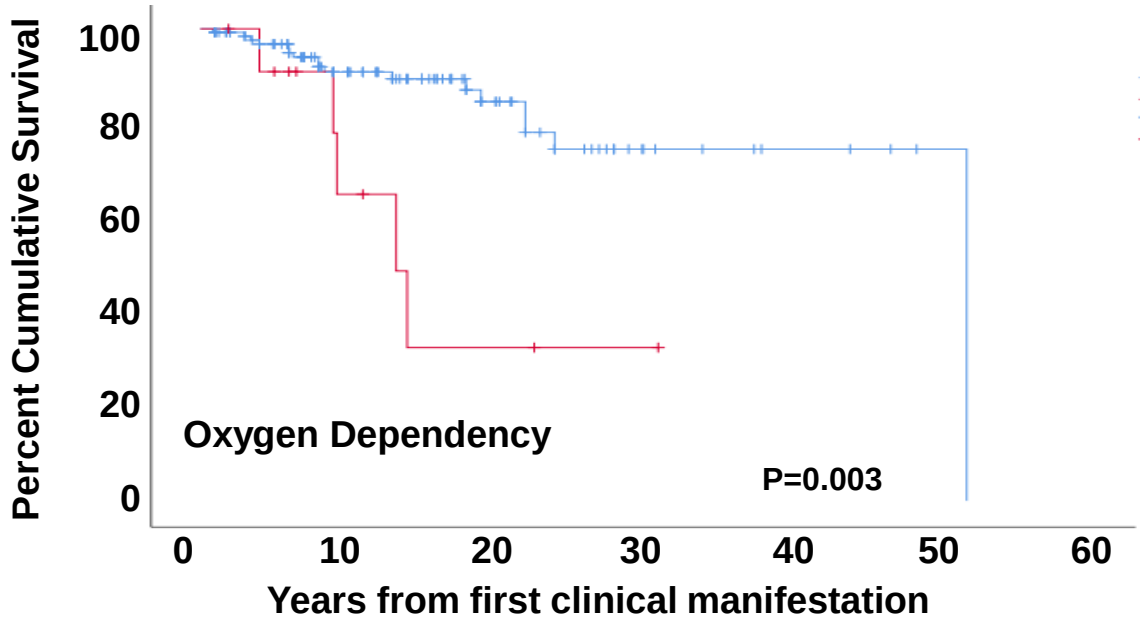


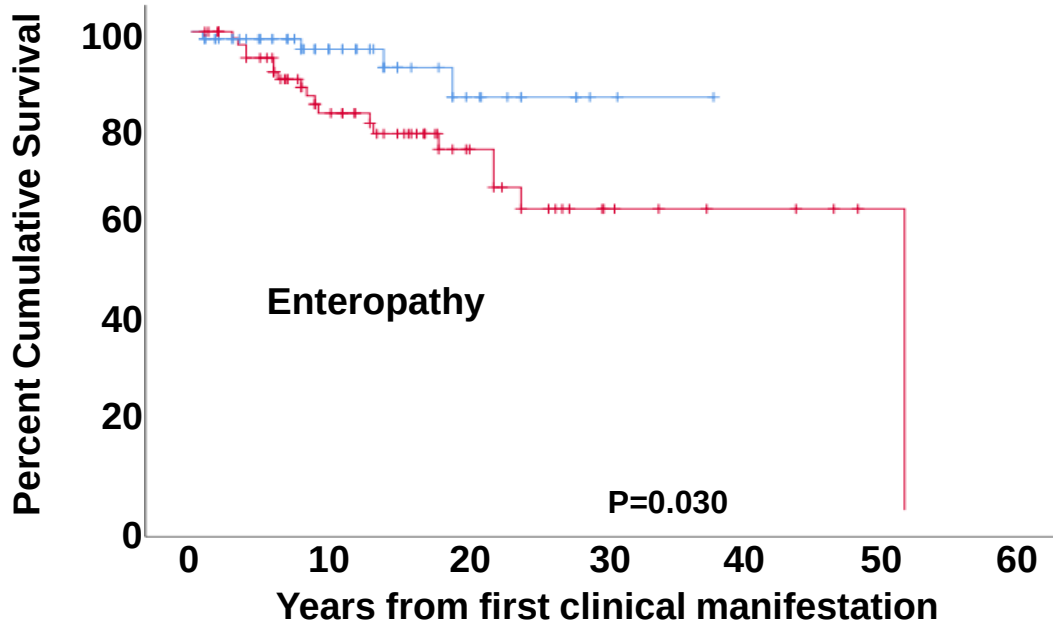

| | |
|---|---|
| **Age at Diagnosis** | Median 12 years (3 months – 73 years) |
| **Age at onset of symptoms** | Median 2.3 years (4 months-73 years) |
| **Sex** | Male:Female 1.25 |

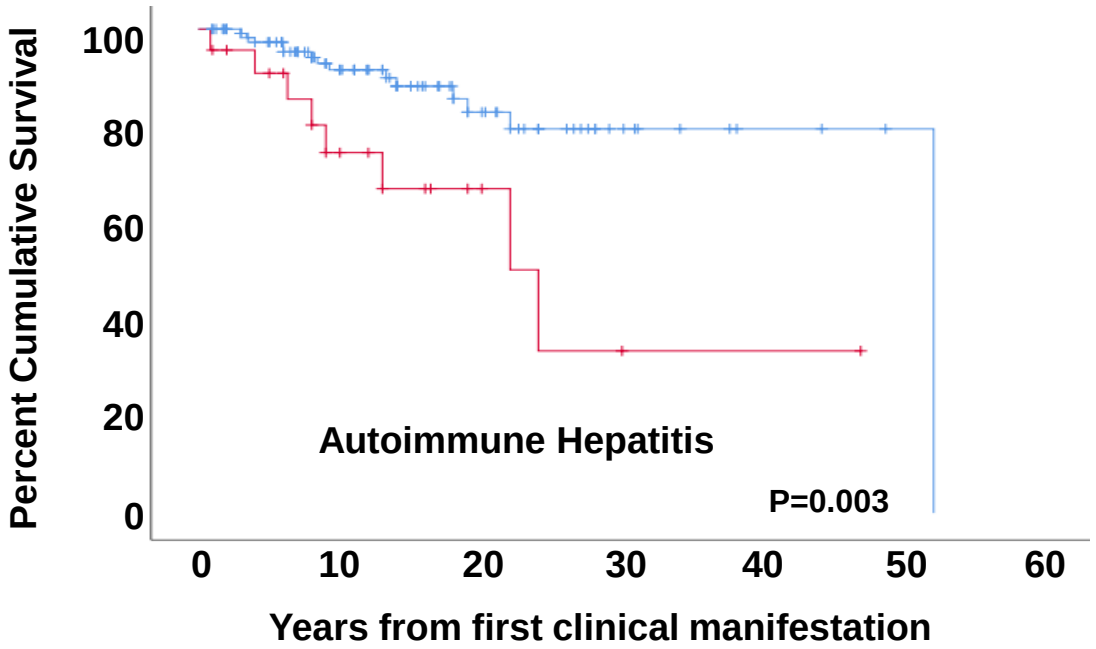
Leiding, Vogel, Forbes-Satter JACI 2022

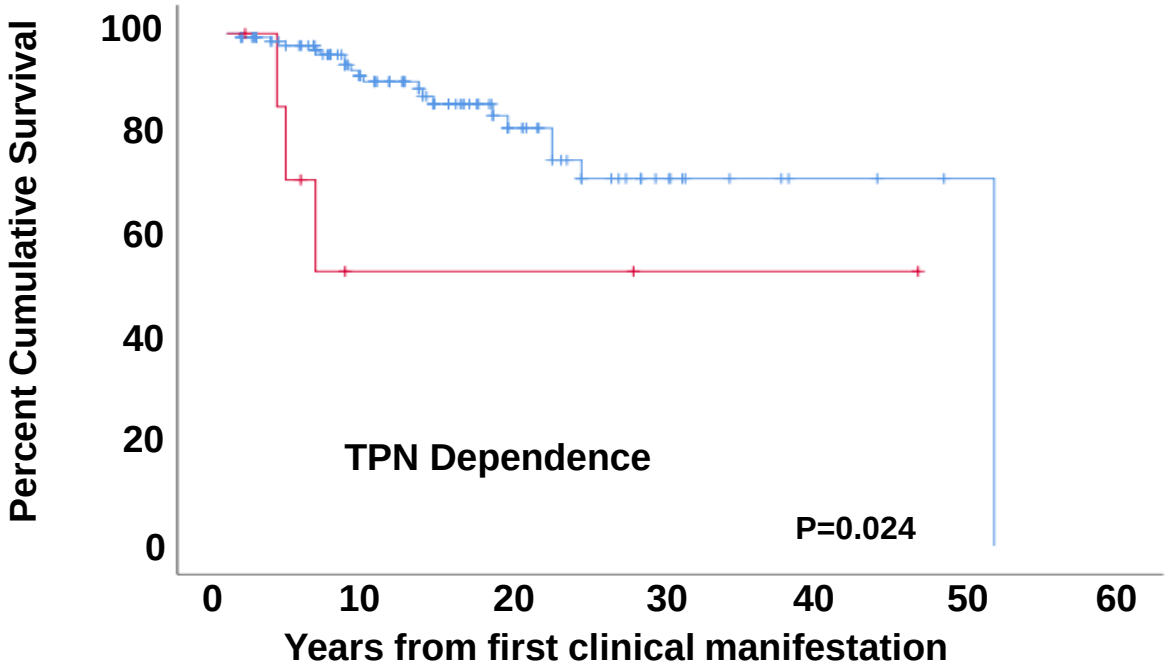
Leiding, Vogel, Cooper, Forbes-Satter Frontiers in Pediatrics Accepted December 2022

# Survival based on Clinical Manifestations

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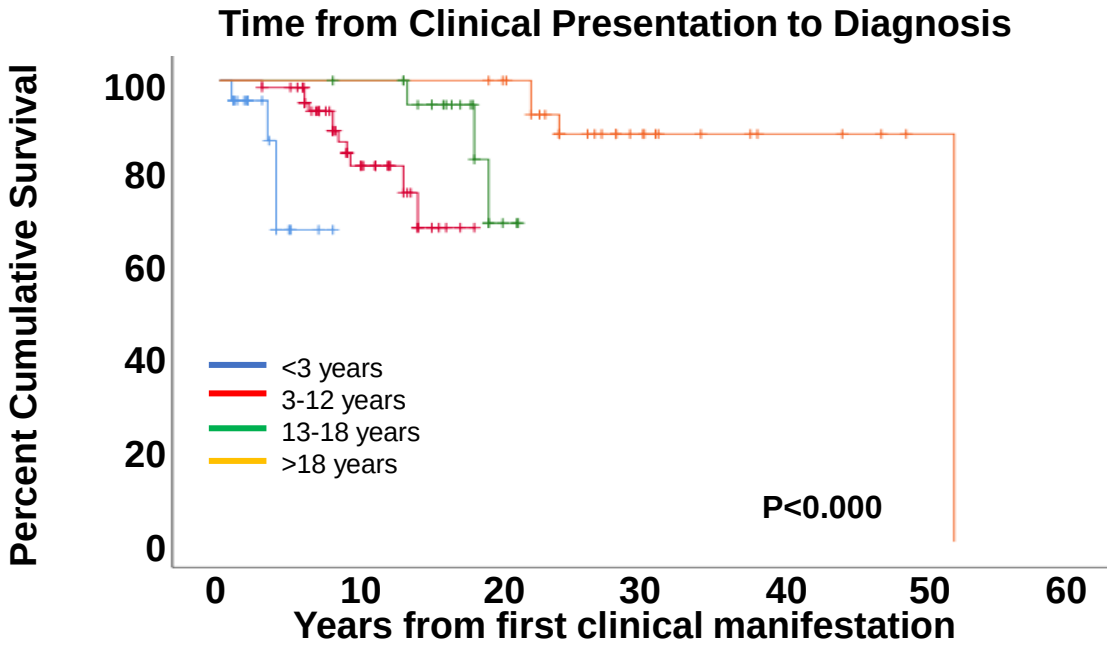
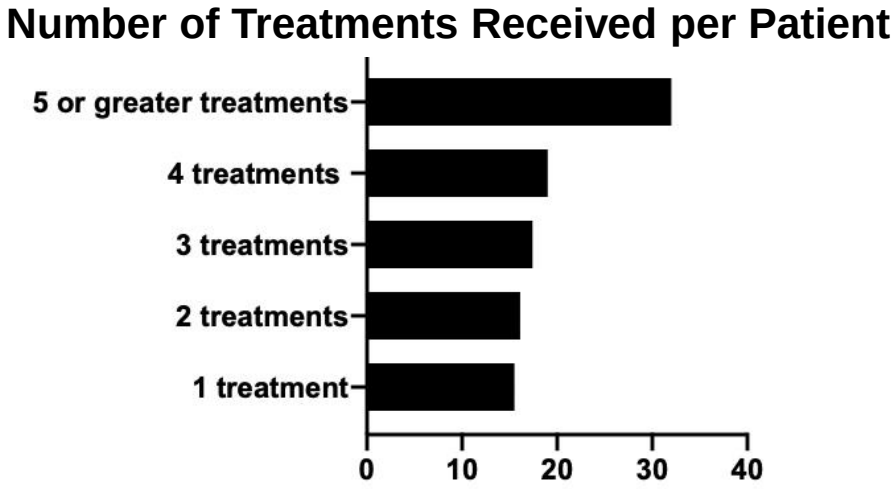
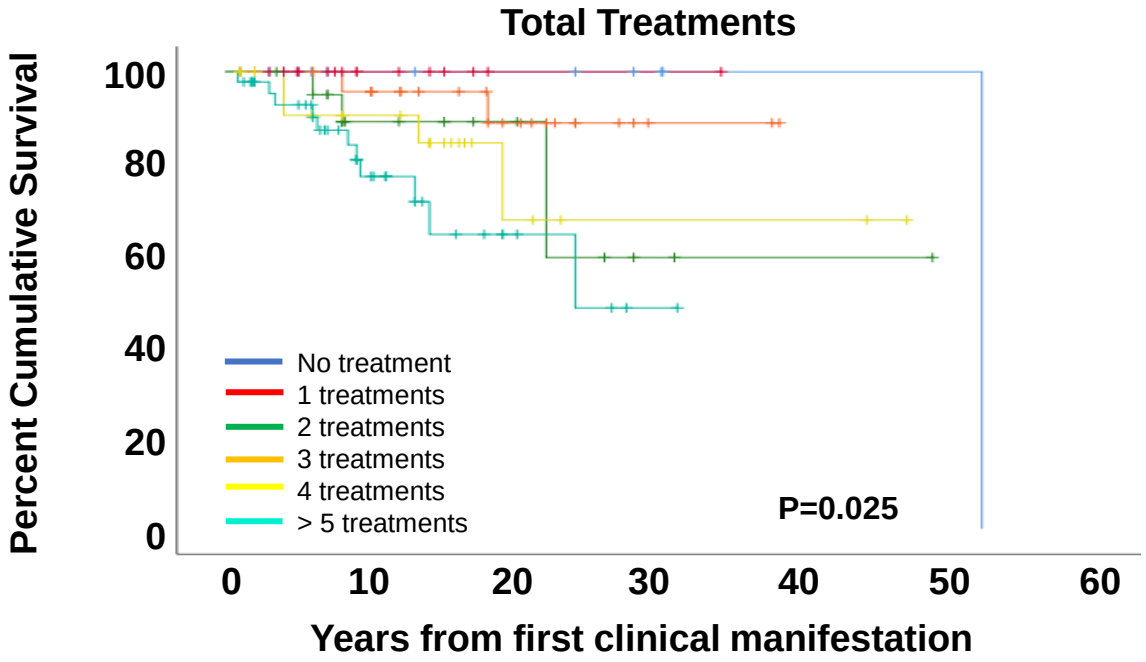
# Case for Early Diagnosis and Targeted therapy



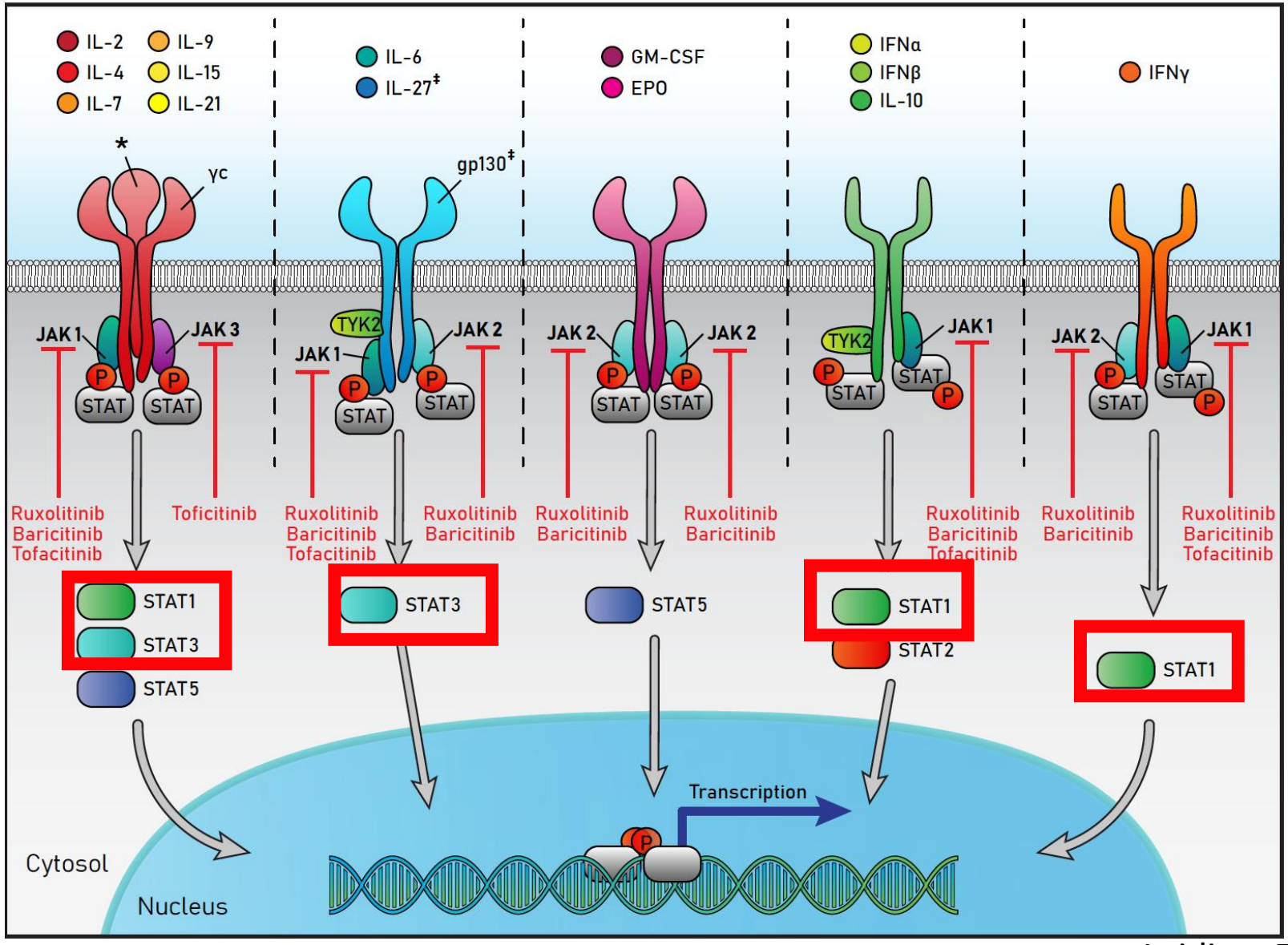




Leiding, Vogel, Forbes-Satter JACI 2022

# Back to Conner…..

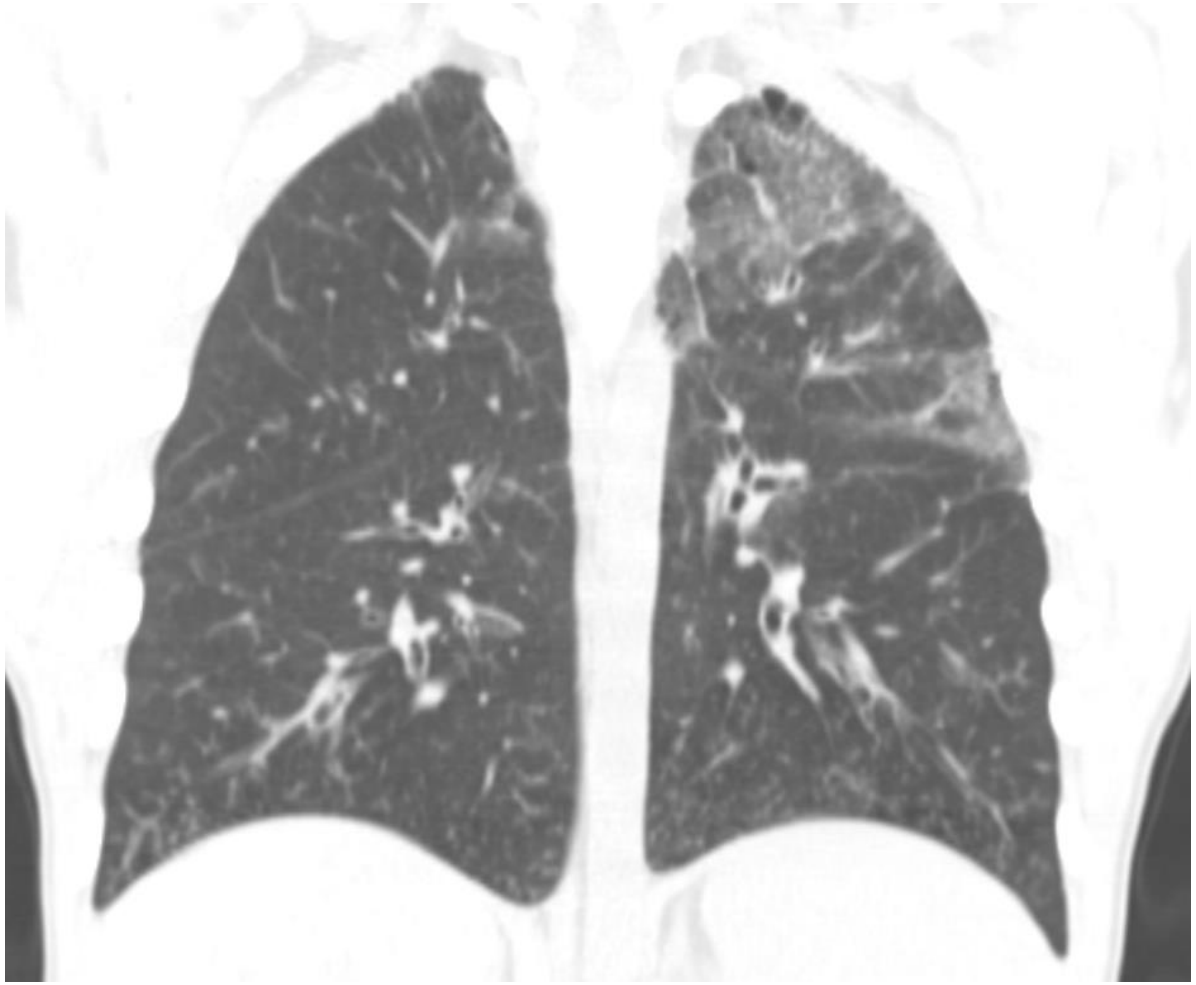
- Let’s say Conner gets better on immunoglobulin replacement for 4-5 years..
- Then he develops signs of inflammatory bowel disease later confirmed by endoscopy/colonoscopy
- Non-infectious complications and multi-organ disease should prompt genetic testing
- You send a targeted >500 gene clinically available panel and he has a pathogenic variant in *CTLA4*:c.410C>T, p.Pro137Leu
- You may consider targeted therapy: abatacept rather than infliximab.

# Janus Kinase Inhibition

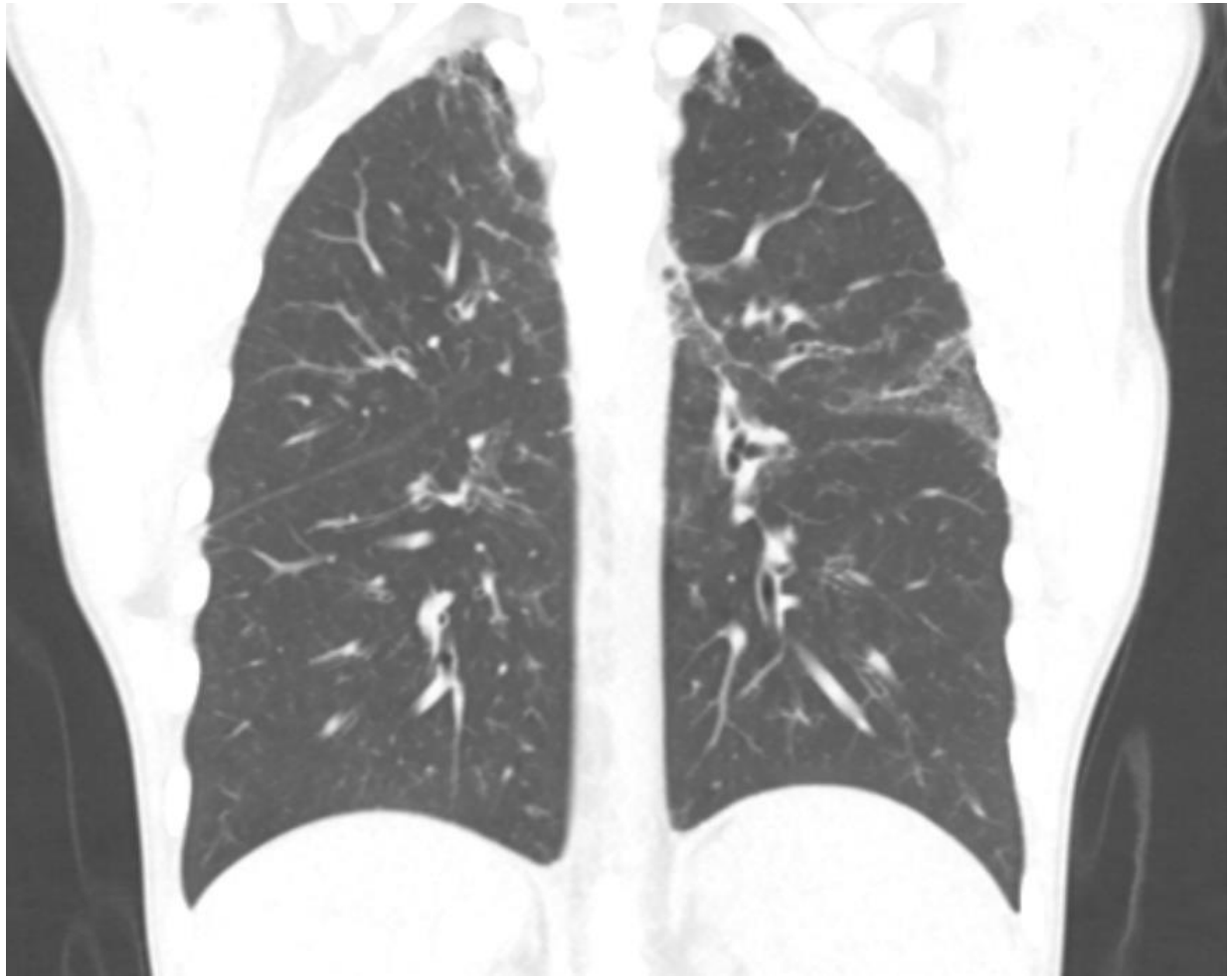



Leiding, Forbes, JACI *in Practice* 2019

# Clinical Images of STAT3 GOF Patient



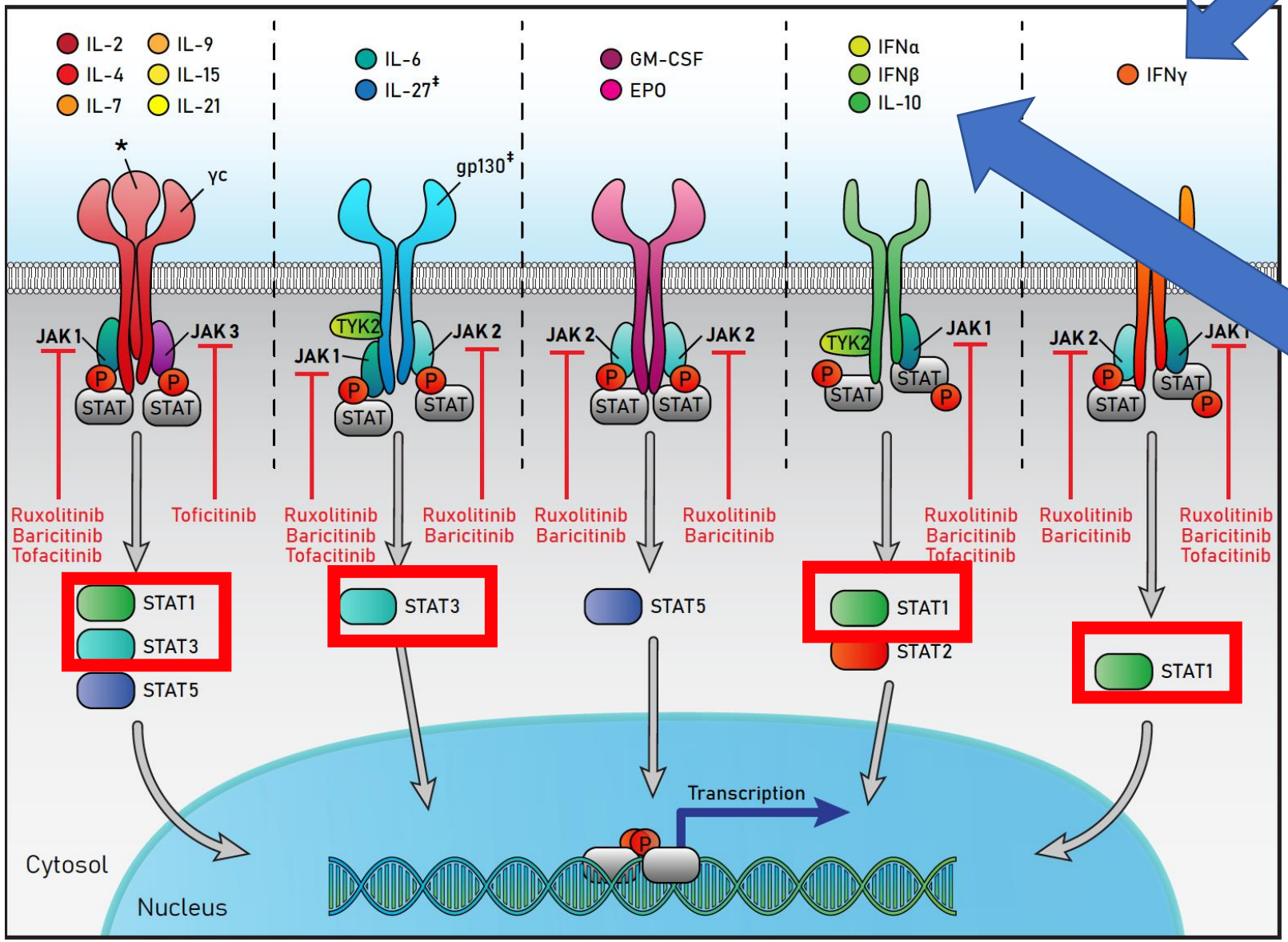
Before Jakinib



6 months after Jakinib

# Broader use of Janus Kinase Inhibition

- Hemophagocytic lymphohistiocytosis
- Macrophage Activation Syndrome




Interferonopathies

- SAVI
- CANDLE
- POMP
- Acardi Gourtieres

Leiding, Forbes, JACI *in Practice* 2019

# Targeted therapy beyond HLH-1994/2004 protocols

- Monoclonal antibody against IFN- g in primary and MAS-HLH
  - Emapalumab - treatment of pediatric and adult patients with primary haemophagocytic lymphohistiocytosis (HLH)
  - refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy
- A phase I trial evaluating ruxolitinib for patients with HLH - NCT02400463
- Phase 1b ELA026 IgG1 SIRP-directed mAB (NCT05416307) – treat secondary HLH by targeting an activation marker on activated macrophages and lymphocytes

Texas Children's Hospital®

# Thank You!

Baylor College of Medicine

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## Immunology Allergy Retrovirology Section
## Forbes-Satter Lab

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