

2026  
SSAI  
ALLERGOLOGY and  
IMMUNOLOGY  
UPDATE



28<sup>TH</sup> COURSE:  
ALLERGOLOGY AND IMMUNOLOGY UPDATE (AIU)

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## Immunodeficiency Diagnostics beyond Immunoglobulins and Vaccine Tests

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**European Reference Network**  
for rare or low prevalence complex diseases

Network  
Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA)

Sistema Socio Sanitario  
**Regione Lombardia**



Fondazione IRCCS Ca' Granda  
Ospedale Maggiore Policlinico

UNIVERSITÀ DEGLI STUDI DI MILANO



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## Immunodeficiencies in Adults

### Primary

(now named **Inborn Errors of Immunity**)

Results from abnormalities in the development of immune mechanisms

#### Genetically defined

- Germline genetic immune conditions impacting immune system development or function
- Somatic variants in immune-related genes

#### Genetically undefined

- CVID
- Subclasses
- Selective IgA deficiency
- Unclassified Primary Antibody Deficiencies

#### «Acquired» errors of immunity

- Autoantibodies to cytokines

### Secondary

Are consequences of disease, drugs, inadequancies

#### Haematological / Solid Cancer

#### Iatrogenic Immune suppression/dysregulation

- Corticosteroids
- B cell depletion
- Chemotherapy
- Anti-rejection medication
- Checkpoint inhibitors

#### Environmental Exposures

- Malnutrition
- Overcrowding
- Poor air quality

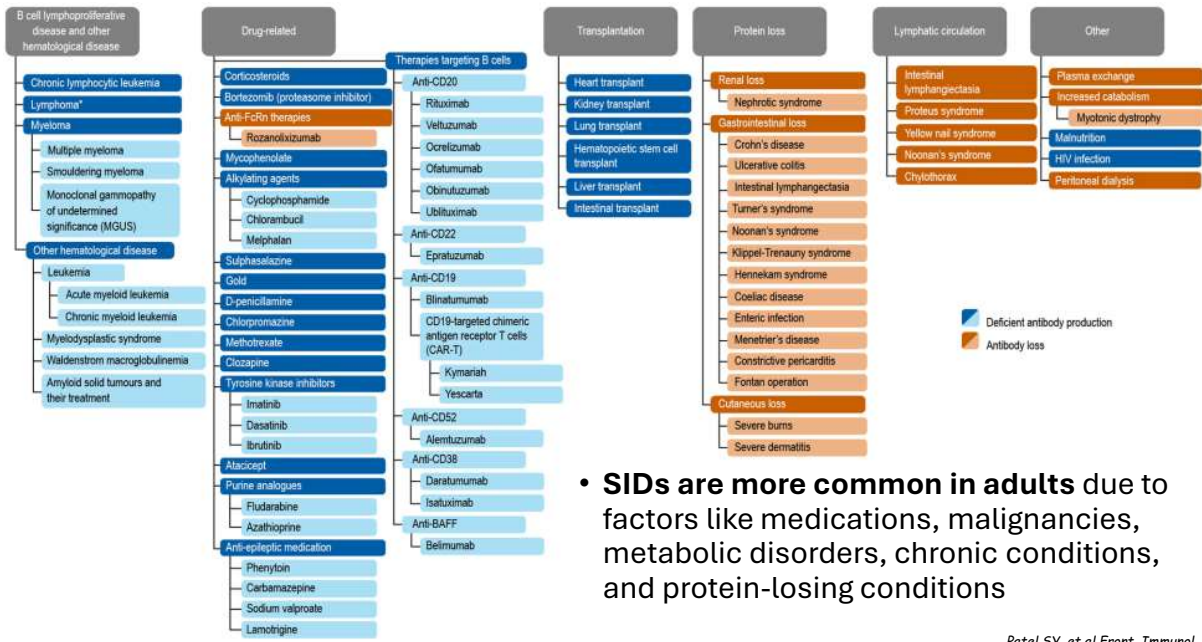
#### Anatomical Defects

- Burns
- Ciliary dysfunction
- Central lines
- Lymphangiectasias

Regina J, et al. *Clinical Reviews in Allergy & Immunology* 2025  
Turvey SE, et al. *J Allergy Clin Immunol* 2024

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## Secondary Immunodeficiencies in Adults



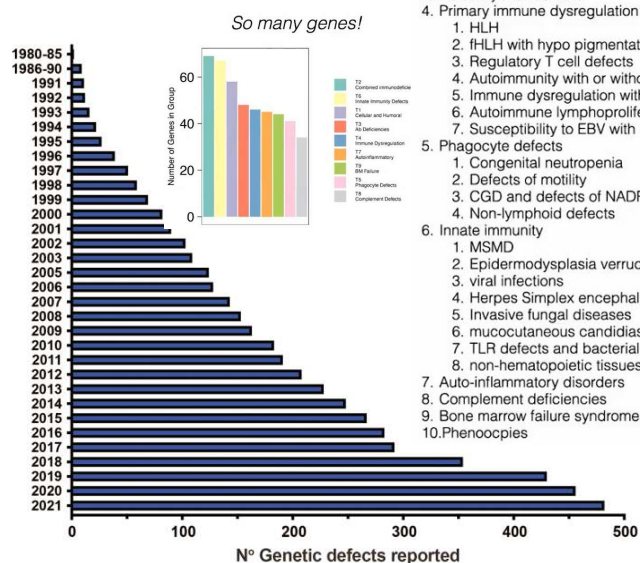
• **SIDs are more common in adults** due to factors like medications, malignancies, metabolic disorders, chronic conditions, and protein-losing conditions

Patel SY, et al Front. Immunol. 2019

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## Primary Immunodeficiencies in Adults

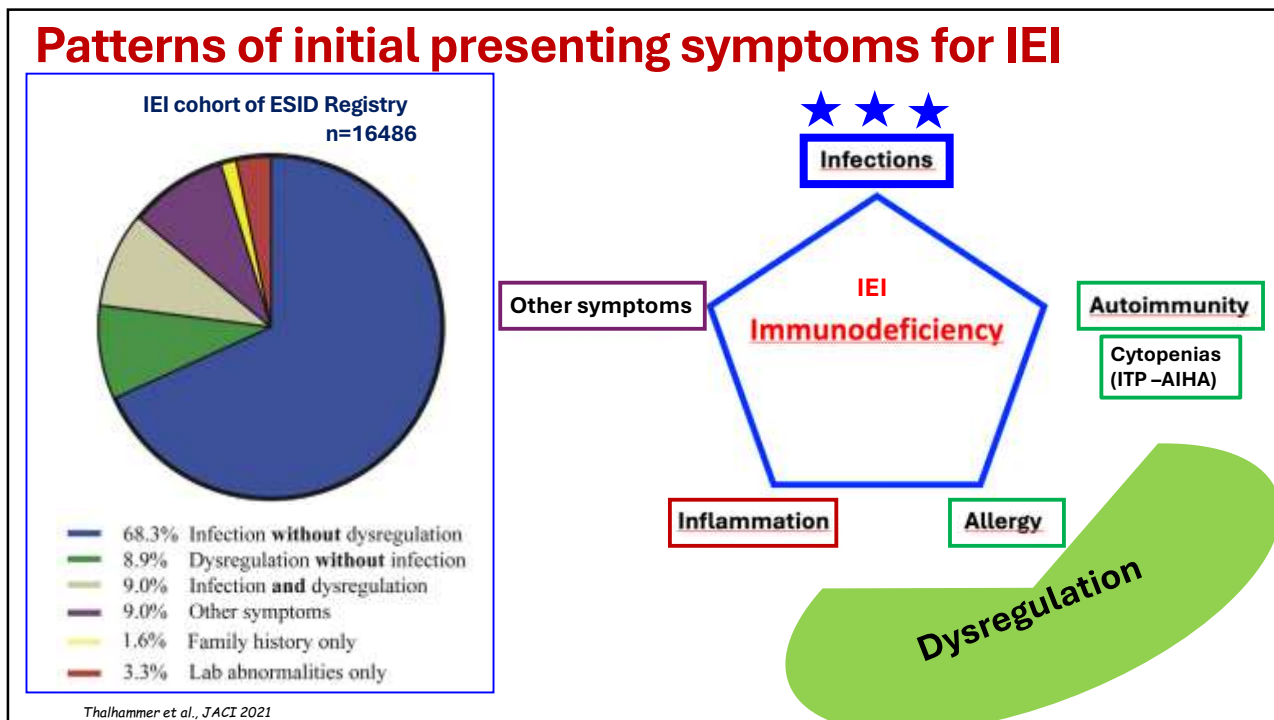
- **Genetic**, not acquired.
- **More than 500** defects are now known, **all immune system components are involved**
- **Impaired maturation or function** of different parts of the immune system
- Individual **IEI** are rare, but **collectively the incidence is probably about 1 in 1200** persons
- Diagnosed in infants, children and adults of all ages



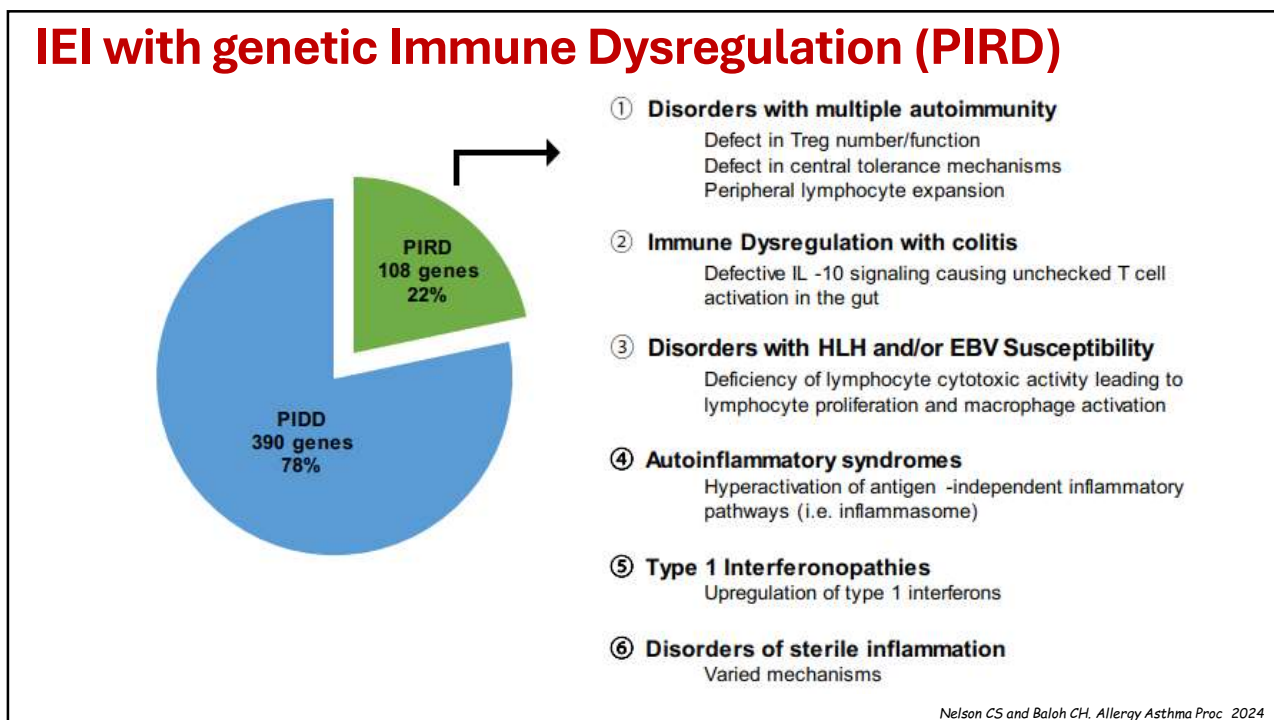
1. Combined immunodeficiencies (includes SCID)
2. Syndromic immunodeficiencies
3. Antibody deficiencies
4. Primary immune dysregulation
  1. HLH
  2. fHLH with hypo pigmentation
  3. Regulatory T cell defects
  4. Autoimmunity with or without lymphoproliferation
  5. Immune dysregulation with colitis
  6. Autoimmune lymphoproliferation
  7. Susceptibility to EBV with lymphoproliferation
5. Phagocyte defects
  1. Congenital neutropenia
  2. Defects of motility
  3. CGD and defects of NADPH oxidase
  4. Non-lymphoid defects
6. Innate immunity
  1. MSMD
  2. Epidermodysplasia verruciformis
  3. viral infections
  4. Herpes Simplex encephalitis
  5. Invasive fungal diseases
  6. mucocutaneous candidiasis
  7. TLR defects and bacterial susceptibility
  8. non-hematopoietic tissues
7. Auto-inflammatory disorders
8. Complement deficiencies
9. Bone marrow failure syndromes
10. Phenoocopies

Tangye S, et al. J Clin Immunol 2022

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# IEI warning signs and red flags in adults




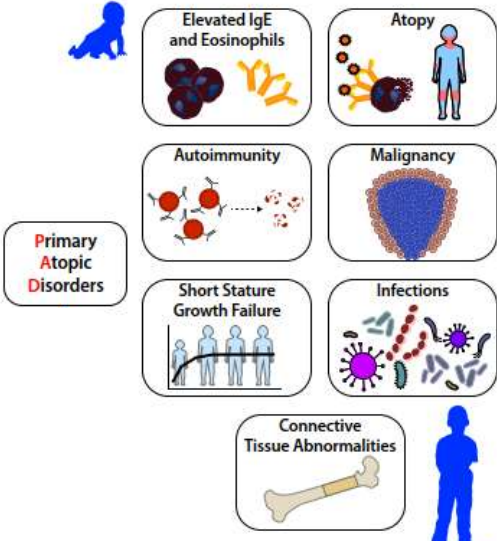
**10** Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

- 1** Two or more new ear infections within 1 year.
- 2** Two or more new sinus infections within 1 year, in the absence of allergy.
- 3** One pneumonia per year for more than 1 year.
- 4** Chronic diarrhea with weight loss.
- 5** Recurrent viral infections (colds, herpes, warts, condyloma).
- 6** Recurrent need for intravenous antibiotics to clear infections.
- 7** Recurrent, deep abscesses of the skin or internal organs.
- 8** Persistent thrush or fungal infection on skin or elsewhere.
- 9** Infection with normally harmless tuberculosis-like bacteria.
- 10** A family history of PI.

Presented as a public service by:





**Primary Atopic Disorders**

**Clinical Red Flags**  
for monogenic allergic diseases

vusegn-uruyun m, et al. v Allergy Clin Immunol 2021

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# IEI Diagnostic Algorithm

Diagnostics:

**STEP 1**

**History:**

- \*Clinical history
- \*Type and frequency of **infection**
  - **CLIPP** (ELVIS)
  - \*Course
  - \*Location
  - \*Intensity
  - \*Pathogen
  - \*Pattern
- \***Clinical signs**
  - **GARFIELD**
  - \*Granulomas
  - \*Autoimmunity
  - \*Recurrent Fever
  - \*Inexplainable Eczema
  - \*Lymphoproliferation
  - \*Inflammatory bowel Disease
- \*Family history

**Exclude:**

- \*Secondary causes of immune and of antibody deficiency
- \*Consider all the IEI

**STEP 2**

**Basic laboratory tests:**

- \*Complete blood count
- \*Serum immunoglobulin levels: IgG, IgA, IgM and IgE
- \*IgG subclasses\* (IgG1-IgG4)
- \*Total complement levels (CH50, C3, C4)
- \*Lymphocytes subsets
- \*Vaccines titres (Pneumococcus, Tetan toxin)

➢ Up to 25% of IEI cases have been reported to be diagnosed in adulthood

➢ More than 50% of adults with IEI have a Primary Antibodies Deficiency

Cunningham-Rundle C. Ann Allergy Asthma Immunol 2025  
Soomann M, et al. Ped Infect Dis J 2025

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**Diagnosics:**

**STEP 3**

**Advanced laboratory tests:**

- B cell subset analysis
- T cell subset analysis
- Response to mitogens and antigens in vitro
- Response to vaccination in vivo
- Flow cytometry for proteins expression

Measurement of antibody titers against vaccine-specific antigens

- Protein antigens (T cell-dependent): tetanus, diphtheria, hepatitis B, measles, rabies, etc.
- Polysaccharide antigens (T cell-independent): pneumococcal polysaccharide, typhoid

T cell functional assays

- Proliferation and cytokine production in response to mitogens, specific antigens, or allogeneic lymphocytes

Flow cytometry with Primary Immuno-Deficiency-specific markers

Cytotoxicity assays

- T cell and NK cell cytotoxicity (granzyme B and perforin expression/function)

Cytokine analysis

- Inflammatory cytokines: IL-1, TNF- $\alpha$ , IL-6, IL-8, interferons
- Autoantibodies:
  - Anti-IFN- $\alpha$  (severe COVID-19)
  - Anti-IFN- $\gamma$  (mycobacterial disease)
  - Anti-IL-6 (staphylococcal infections)
  - Anti-IL-17/IL-22 (chronic mucocutaneous candidiasis, CMC)

HLA typing

Genetic studies

- Targeted gene panels or whole exome/genome sequencing

Phagocytic function tests

- Dihydrorhodamine (DHR) oxidation test

Complement studies

- AH50, properdin, factor D, factor H

Innate immunity functional assays

- IL-12/23-IFN- $\gamma$  pathway (mycobacterial disease)
- IL-17 pathway (CMC)
- TLR signaling pathway

Soomann M, et al. Ped Infect Dis J 2025  
Muñoz-Echeverría L, et al. Rev Esp Quimioter 2025

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**III. Predominantly antibody deficiencies**  
 Recurrent bacterial infections eg : Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays : IgG, IgA, IgM

**IgG, IgA and/or IgM ↓↓**

Exclude 2° causes: drugs [Hx], myeloma [bone marrow], Lymphoma . Ig loss (not hypo-IgM) in urine, GI or skin

**B Lymphocyte (CD19+) enumeration (CMF)**

**B absent or ≤2%**      **B >1%**

Agammaglobulinemia → Hyper IgM → Ab defects → CVID → IgG defects → IgA deficiency

**STEP 3**

**Advanced laboratory tests:**

- B cell subset analysis
- T cell subset analysis
- Response to mitogens and antigens in vitro
- Response to vaccination in vivo
- Flow cytometry for proteins expression

Flow cytometric analysis of lymphocyte subsets

- T cells (CD3<sup>+</sup>)
- Helper T cells (CD3<sup>+</sup>CD4<sup>+</sup>)
- Cytotoxic T cells (CD3<sup>+</sup>CD8<sup>+</sup>)
- Naïve T cells (CD45RA<sup>+</sup> with CD62L<sup>+</sup> or CCR7<sup>+</sup>)
- Memory T cells (CD45RO<sup>+</sup>)
- B cells (CD19<sup>+</sup>/CD20<sup>+</sup>)
- Memory B cells (CD19<sup>+</sup>CD27<sup>+</sup>)
- Natural killer (NK) cells (CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup>)

Bousfiha A, et al. J Clin Immunol 2022  
Salzer U, et al. EJI FCC. 2019. PMID:31814814

Muñoz-Echeverría L, et al. Rev Esp Quimioter 2025  
Cunningham-Rundle C. Ann Allergy Asthma Immunol 2025

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**IgG, IgA and/or IgM ↓↓**

Exclude 2° causes: drugs [1st], myeloma [bone marrow], Lymphoma - Ig loss (not hypo-IgM) in urine, GI or skin

**B Lymphocyte (CD19+) enumeration (CMF)**

B absent      **B >1%**

### Antigen - independent      Antigen - dipendente

• CD27 has been identified as a marker for memory B cells  
• After in vitro stimulation, B cells expressing CD27 (but not CD27(-) cells) secrete large amounts of both IgM and IgG.

• CD27(+)|IgM(-)|IgD(-) B cells produce IgG (<2% indicate a defective germinal center development)

**Common Variable Immunodeficiency (CVID) Diagnostic Criteria (2016)**

**At least one of the following:**

- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency

**AND marked decrease of IgG and marked decrease of IgA,** with or without low IgM levels (measured at least twice; < 2SD of the normal levels for their age);

**AND at least one of the following:**

- poor antibody response to vaccines (and/or absent iso-haemagglutinins); i.e. absence of protective levels despite vaccination where defined
- **low switched memory B cells (<70% of age-related normal value)**

AND secondary causes of hypogammaglobulinaemia have been excluded  
 AND diagnosis is established after the 4th year of life (but symptoms may be present before)  
 AND no evidence of profound T-cell deficiency

<http://esid.org/Working-Parties/Registry/Diagnosis-criteria>

**Send to reference center**

Bousfiha A, et al. J Clin Immunol 2022

Cunningham-Rundle C. Ann Allergy Asthma Immunol 2025

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### Common Variable Immunodeficiency (CVID)

**Clinical presentation**

**Leading symptoms**  
 Hypogammaglobulinemia  
 Recurrent bacterial RTIs

**In addition**

• Lymphoproliferation, Splenomegaly	35%
• Lymphoma	4%
• Autoimmunity	29%
• Autoimmune cytopenia	15%
• Granulomatous disease	10%
• Interstitial lung disease	20%
• Enteropathy	10%
• Hepatopathy	7%

### Comorbidities change across age

Comorbidity	Younger Cohort (%)	Older Cohort (%)
Branchitis	11	8
GILD	2	3
Granuloma	4	5
GI involvement	14	9
Autoimmunity	20	9
Lymphoproliferopathy	6	5
Lymphoma	0	4
Splenomegaly	19	6

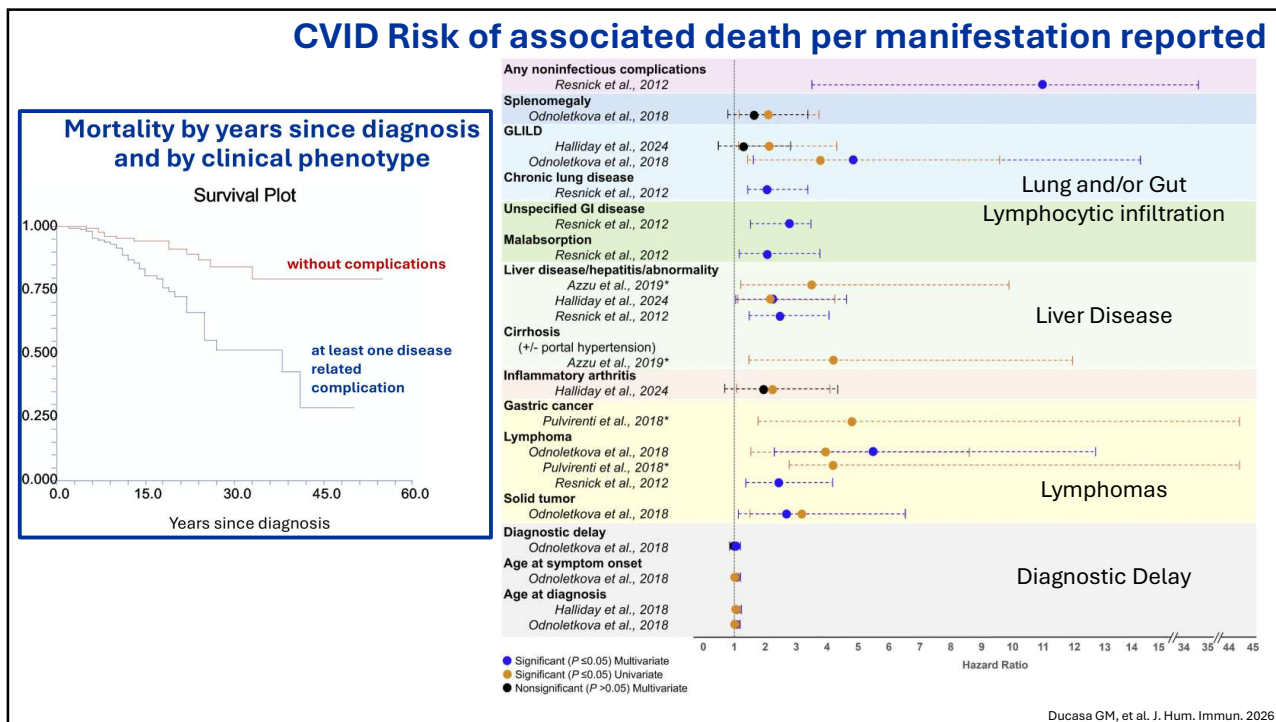
Cohort: Younger (orange), Older (blue). \* p<0.05

**HD**

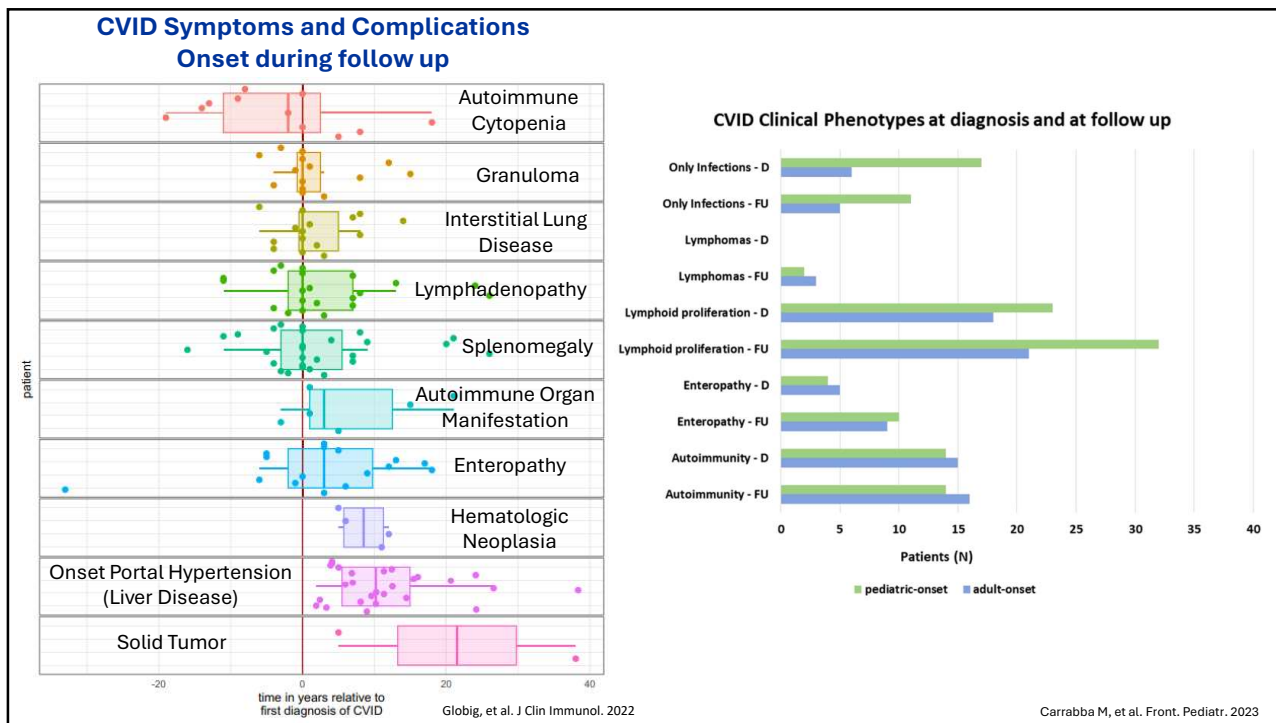
**CVID**

Ho HE, Cunningham-Rundles C. Front Immunol. 2022  
 Carrabba M, et al. Front. Pediatr. 2023

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# Diagnostic Algorithm

## STEP 4

Diagnostics:

### Genetics:

•Mutation analysis (tNGS, WES, WGS)

### Special laboratory test:

•E.g., flow cytometry staining for ICOS, TACI, BAFF-R, etc  
 •Functional testing

## Monogenetic Antibody Deficiencies

B ↓↓

### ➤ Agammaglobulinemia

with defects in precursor B cell differentiation  
 • BTK,  $\mu$ ,  $\lambda 5$ , Ig $\alpha$ , Ig $\beta$ , BLNK, ...

B =

### ➤ Ig class switch recombination deficit (IgCSR), previously called HyperIgM

• CD40L, CD40, AID, UNG, ...

B =/↓

### ➤ Subgroup of CVID and CVID-like

• ICOS, CD19, BAFF-R, ...

Notarangelo L, et al. Sci Immunol. 2020

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## CVID presents

### Many defects on the way of B cells maturation

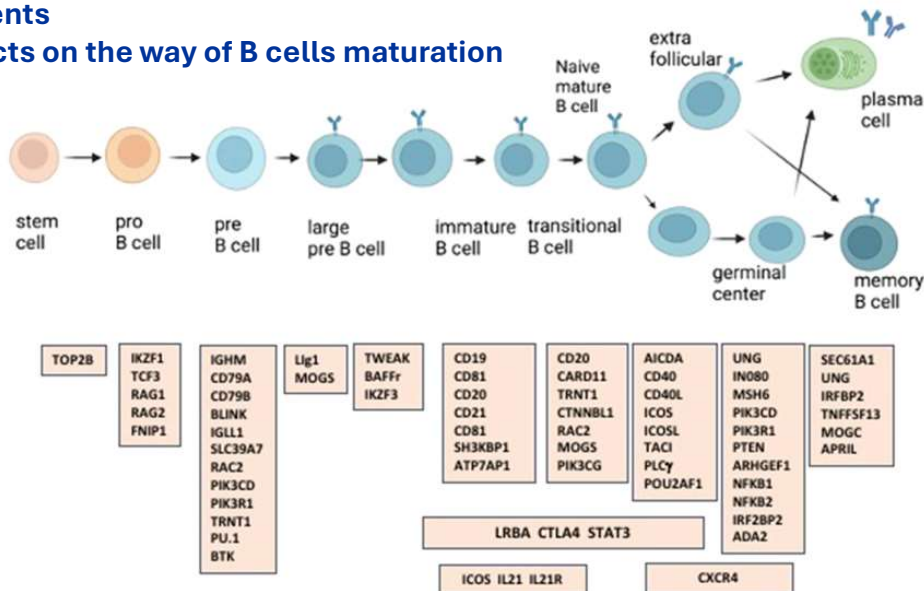
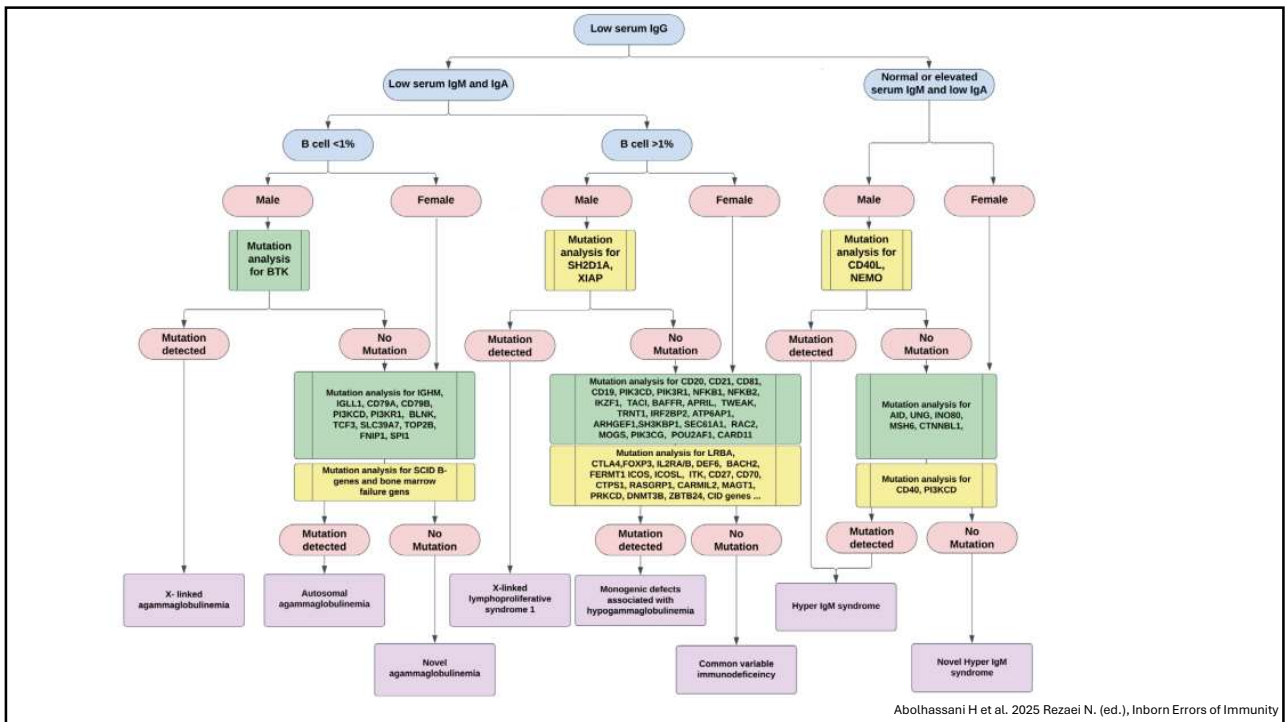


FIGURE 1

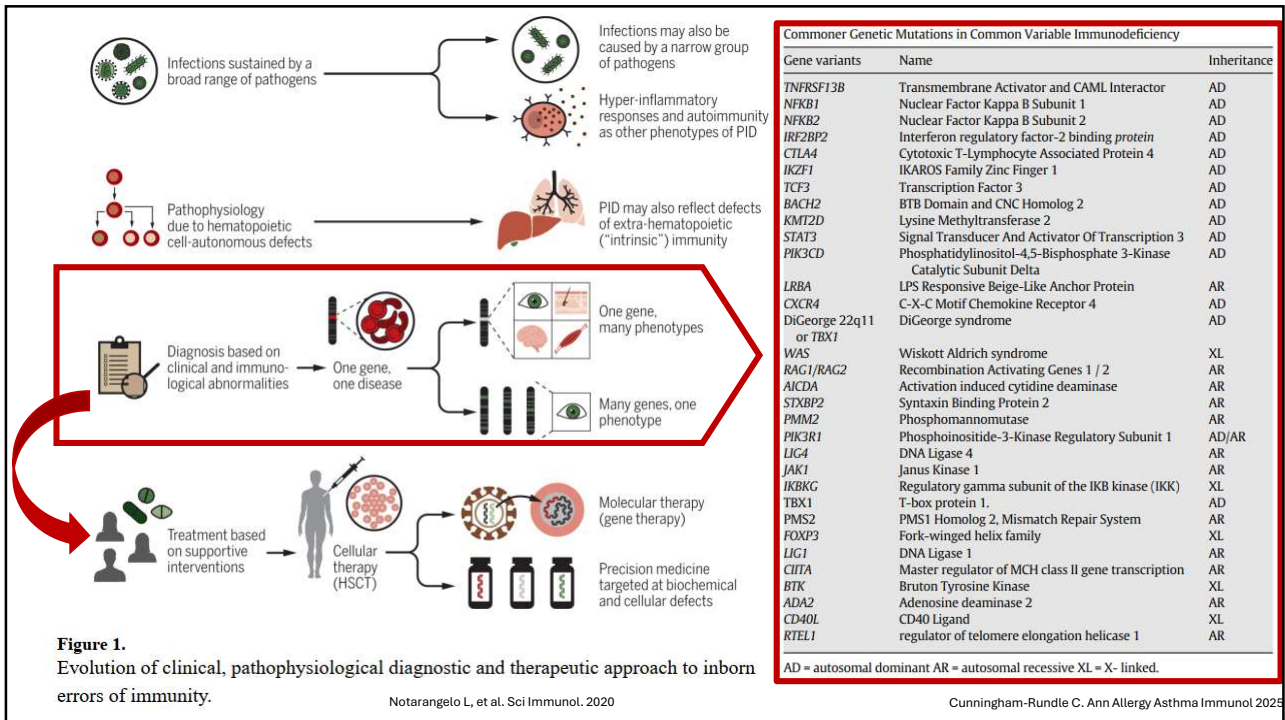
A number of the immune defects found in patients with CVID, are in genes involved in the generation and maturation of human B cells.

Cunningham-Rundles C, et al. Front. Genet. 2024

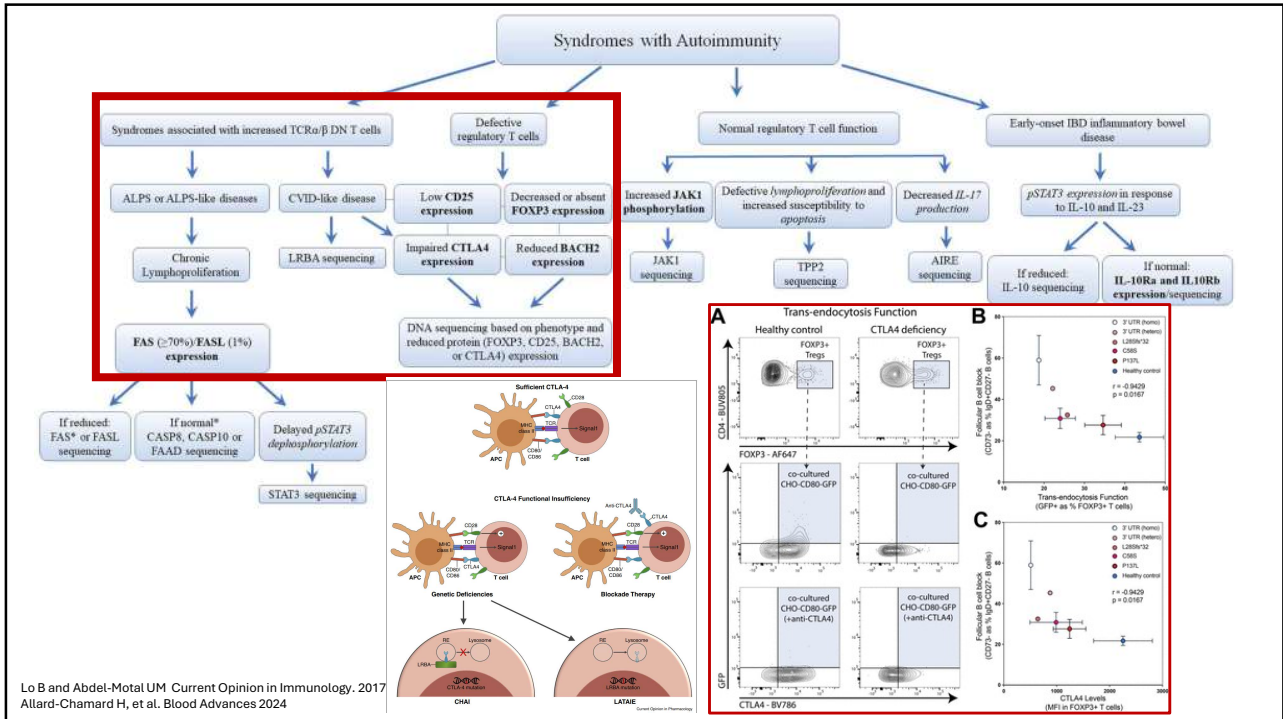
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**B-cell dysregulation**

- Rituximab
- Belimumab

**Lymphoproliferation**

- Corticosteroids
- Rituximab

**Nodular regenerative hyperplasia**

- Corticosteroids

**Granulomas**

- Rituximab
- Corticosteroids
- Anti-TNF
- IVIG

**Cytopenias**

- Corticosteroids
- IVIG
- Rituximab
- Splenectomy
- Sirolimus
- Eltrombopag
- Bortezomib

**T-cell dysregulation/exhaustion**

- Sirolimus
- IL-2
- JAK-inhibitors
- PI-3K-inhibitors
- Emapalumab
- Ustekinumab
- Abatacept
- PD-1 inhibitor
- cAMP inhibitor

**GI/LD**

- Corticosteroids
- Rituximab
- Azathioprine
- Mycophenolate
- Abatacept

**Enteropathy**

- Corticosteroids
- 5-ASA
- Anti-TNF
- Vedolizumab
- Ustekinumab
- Tofacitinib
- Guselkumab

**Gastrointestinal dysbiosis/endotoxemia**

- Rifaximin
- Larazotide

**Immune dysregulation**

Condition	Features
ALPS	Elevated CD3 <sup>+</sup> TCRαβ <sup>+</sup> CD4 <sup>+</sup> CD8 <sup>-</sup> T cells
XLP1	Reduced INKT cells, decreased intracellular SAP in NK and CD8 + T cells <sup>b</sup>
XLP2	Decreased intracellular XIAP in lymphocytes <sup>b</sup>
IPEX Syndrome	Decreased Foxp3 <sup>+</sup> regulatory T cells <sup>b</sup>
CTLA-4 haploinsufficiency	Decreased CTLA-4 expression in Tregs <sup>b</sup>
LRBA deficiency	Decreased intracellular LRBA in stimulated PBMC <sup>c,c</sup> and decreased CTLA-4 in Tregs <sup>b</sup>
STAT3-GOF	Delayed dephosphorylation of STAT3 following stimulation with IL-6 <sup>c</sup>
Familial HLH3, 4 and 5, Chediak-Higashi, Griscelli or Hermansky-Pudlak Syndromes	Decreased CD107a expression on NK cells following incubation with target cells <sup>d</sup>
Familial HLH2 (PRF1 mutations)	Decreased intracellular perforin in CD8 and NK cells <sup>b</sup>

**Cytokine analysis**

- Inflammatory cytokines: IL-1, TNF-α, IL-6, IL-8, interferons
- Autoantibodies:
  - Anti-IFN-α (severe COVID-19)
  - Anti-IFN-γ (mycobacterial disease)
  - Anti-IL-6 (staphylococcal infections)
  - Anti-IL-17/IL-22 (chronic mucocutaneous candidiasis, CMC)

**Intrinsic and innate immune defects**

Condition	Defect
MMSD	Decreased expression of IFNγR1, IL12Rβ1 <sup>a</sup> , reduced phosphorylation of STAT1, or STAT4 <sup>b,c</sup>
STAT1 GOF	Delayed dephosphorylation of STAT1 following stimulation with IFNγ or IFNα <sup>b,c</sup>
IL17RA deficiency	Decreased expression of IL17RA on lymphocytes and monocytes <sup>a</sup>
IRAK-4 and MyD88 deficiency	Decreased LPS-induced intracellular TNF-α in monocytes <sup>b,c</sup>

**Pathway Diagram:** STING inh., DNA/RNA sensing, STING, ER stress, PKR inh?, TLR7, I Type I interferon response, JAK inh.

Fevang B. Expert Rev Clin Immunol. 2023  
Created with BioRender.com  
Knight V. Int J Lab Hematol. 2019  
Muñoz-Echeverría L, et al. Rev Esp Quimioter 2025

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