



# XVIII IPOPI GLOBAL PATIENTS' MEETING

an **IPOPI** event

16-19 OCTOBER 2024  
MARSEILLE, FRANCE

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# Defining PIDs

*Much more than children with infections*

Pere Soler Palacín/Jacques Rivière  
Children's Hospital.

Vall d'Hebron Barcelona Hospital Campus  
Barcelona, Catalonia, Spain

## Disclosures

PSP has received grants from:

- ✓ CSL Behring
- ✓ Takeda
- ✓ Grifols
- ✓ Octapharma
- ✓ Binding Site
- ✓ UCB
- ✓ Pharming

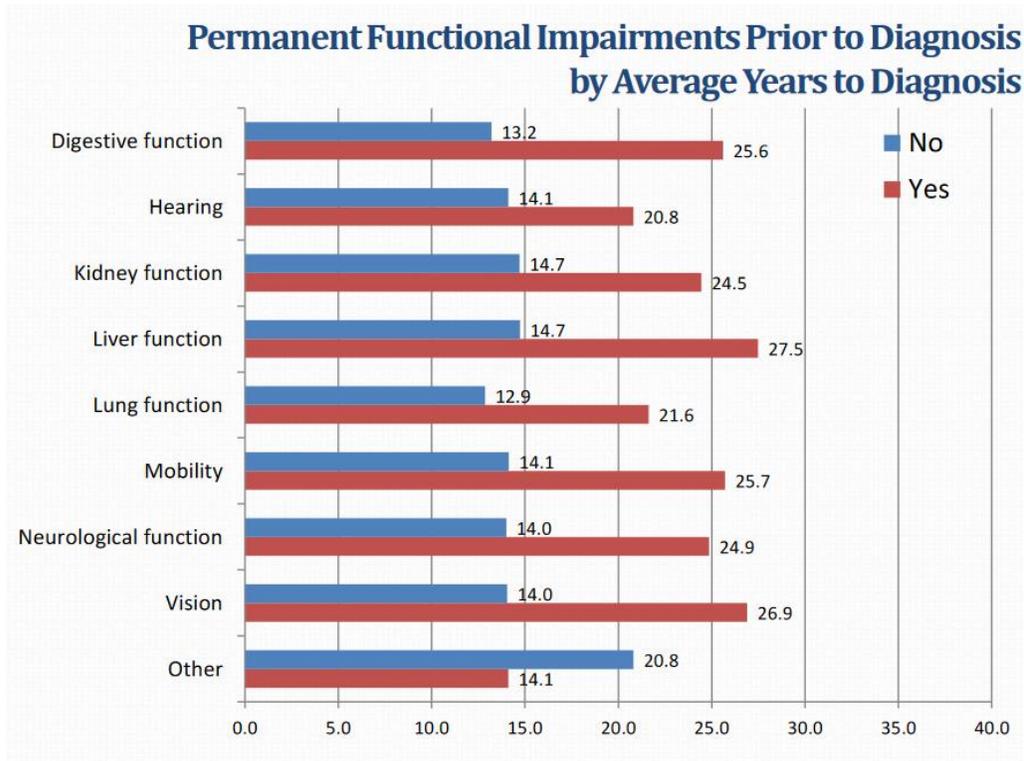
JR from:

- ✓ Grifols
- ✓ CSL Behring
- ✓ Takeda
- ✓ Pharming

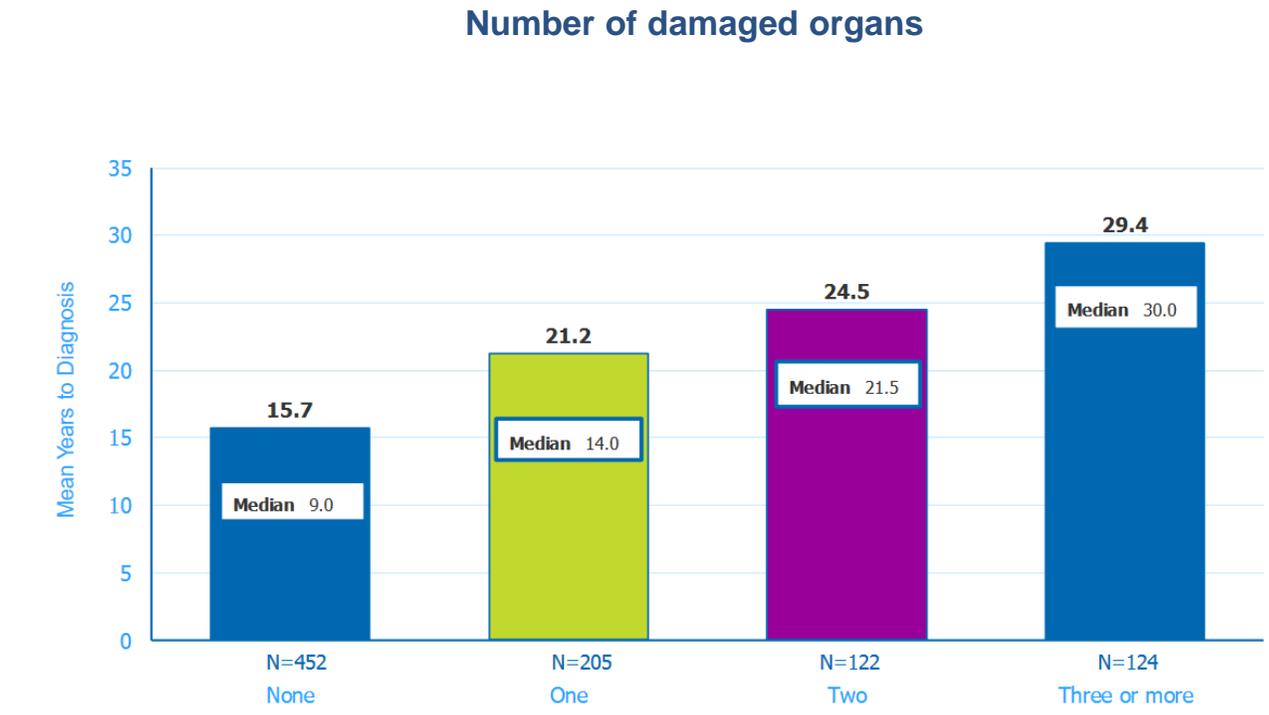
But there are no conflict of interests regarding the content presented in this session

# Diagnosis delay in IEI: time is life and function

Up to 50% of all patients present some degree of organ damage at diagnosis



2013<sup>1</sup>



2017<sup>2</sup>

IEI: inborn errors of immunity

1. 2013 IDF National Immunoglobulin Treatment Survey. The Immune Deficiency Foundation. PrimaryImmune. Available at: [https://primaryimmune.org/sites/default/files/2013\\_IDF\\_National\\_Immunoglobulin\\_Treatment\\_Survey.pdf](https://primaryimmune.org/sites/default/files/2013_IDF_National_Immunoglobulin_Treatment_Survey.pdf);

2. IDF 2017 National Patient Survey. The Immune Deficiency Foundation. PrimaryImmune. Available at: <https://primaryimmune.org/sites/default/files/national-patient-survey-2017.pdf>

# Classical warning signs need to be updated



## 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 Four or more new ear infections within 1 year.
- 2 Two or more serious sinus infections within 1 year.
- 3 Two or more months on antibiotics with little effect.
- 4 Two or more pneumonias within 1 year.
- 5 Failure of an infant to gain weight or grow normally.
- 6 Recurrent, deep skin or organ abscesses.
- 7 Persistent thrush in mouth or fungal infection on skin.
- 8 Need for intravenous antibiotics to clear infections.
- 9 Two or more deep-seated infections including septicemia.
- 10 A family history of PI.

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## 10 FOR ADULTS 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.

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ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity*

## Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century

Peter D. Arkwright<sup>1</sup> and Andrew R. Gennery<sup>2</sup>



# The 10 warning signs: a time for a change?

Michael D. O'Sullivan<sup>a</sup> and Andrew J. Cant<sup>b</sup>

## Clinical Features That Identify Children With Primary Immunodeficiency Diseases

**WHAT'S KNOWN ON THIS SUBJECT:** Children with severe, recurrent, or unusual infections may have an underlying primary immunodeficiency disease (PID). Ten warning signs have been promoted by patient support groups to help identify children with PID, but the signs have never been tested in a rigorous scientific study.

**WHAT THIS STUDY ADDS:** Family history, intravenous antibiotics for sepsis, and failure to thrive predict at least 89% of children with T-lymphocyte, complement, and neutrophil PID. B-lymphocyte PID are more difficult to diagnose from the clinical features, and a lower threshold is required for assessing antibody levels.

**AUTHORS:** Anbezhil Subbarayan, MBBS,<sup>a</sup> Gloria Colarusso, MB BS,<sup>b</sup> Stephen M. Hughes, MB, PhD,<sup>a</sup> Andrew R. Gennery, MD,<sup>b</sup> Mary Slatter, MBBS,<sup>b</sup> Andrew J. Cant, MD,<sup>b</sup> and Peter D. Arkwright, MB, DPhil<sup>a</sup>

<sup>a</sup>Department of Paediatric Allergy and Immunology, University of Manchester, Royal Manchester Children's Hospital, Manchester, United Kingdom; and <sup>b</sup>Supraregional Paediatric Immunology Center, University of Newcastle, Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom

**KEY WORDS**  
primary immunodeficiency disease, infection, children, diagnosis, family history

**ABBREVIATIONS**  
PID—primary immunodeficiency disease  
SCID—severe combined immunodeficiency disease

J Clin Immunol (2014) 34:10–22  
DOI 10.1007/s10875-013-9954-6

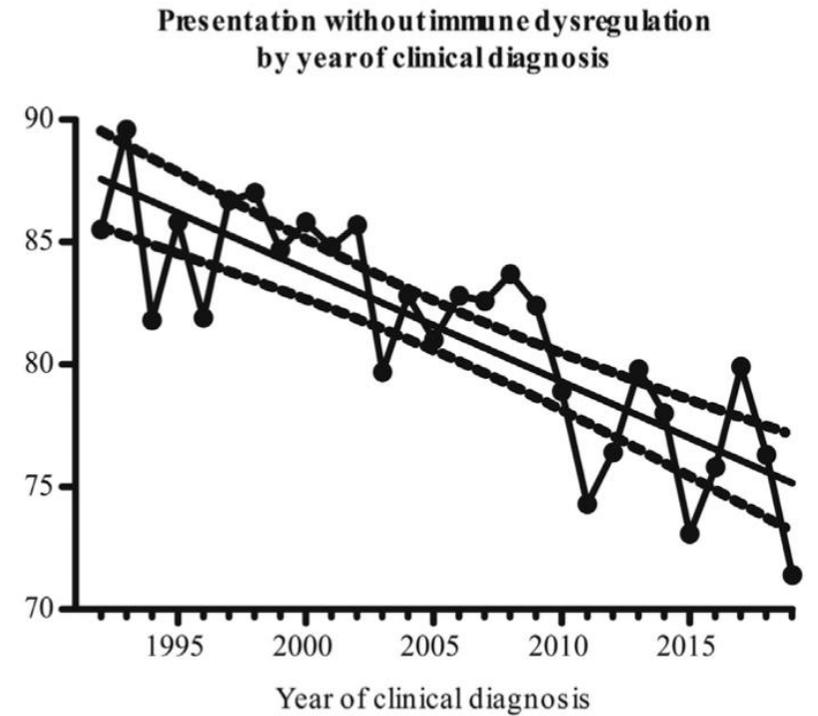
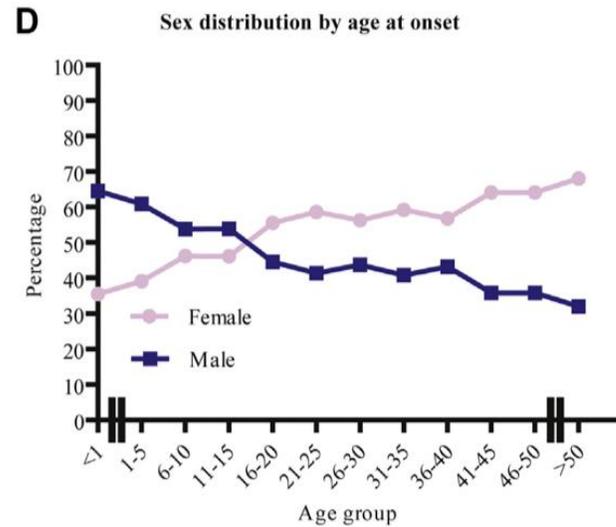
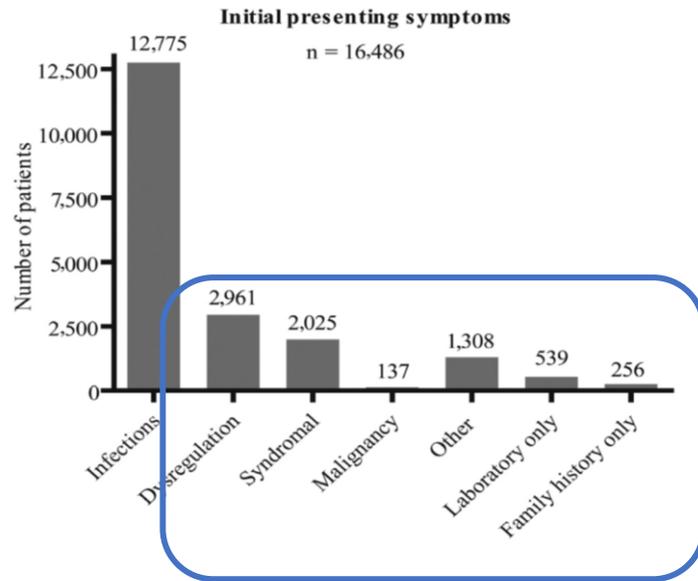
KEY REVIEW ARTICLE

## Attending to Warning Signs of Primary Immunodeficiency Diseases Across the Range of Clinical Practice

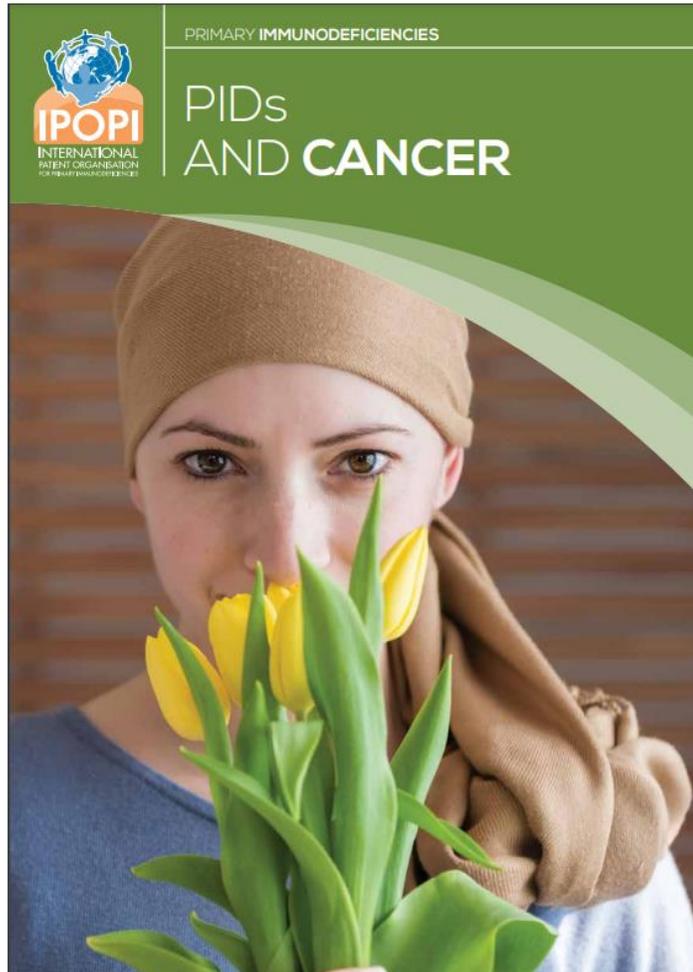
Beatriz Tavares Costa-Carvalho • Anete Sevciovic Grumach • José Luis Franco • Francisco Javier Espinosa-Rosales • Lily E. Leiva • Alejandra King • Oscar Porras • Liliana Bezrodnik • Mathias Oleastro • Ricardo U. Sorensen • Antonio Condino-Neto

# To include non-infectious manifestations

**Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations**



# To include non-infectious manifestations



MALIGNANCY PATTERNS IN VARIOUS PIDS		
PID	Predominant tumour type	Specific reported malignancies
CVID	Lymphoma, GI cancer	NHL, stomach, breast, bladder, cervical cancer
X-linked lymphoproliferative disease	Lymphoma	NHL, Hodgkin's lymphoma
Wiskott-Aldrich syndrome	Lymphoma	Diffuse large B-cell lymphoma, NHL, leukaemia, Kaposi sarcoma
Ataxia-telangiectasia	Lymphoma	Lymphoid leukaemias, T prolymphocytic lymphomas, epithelial tumours

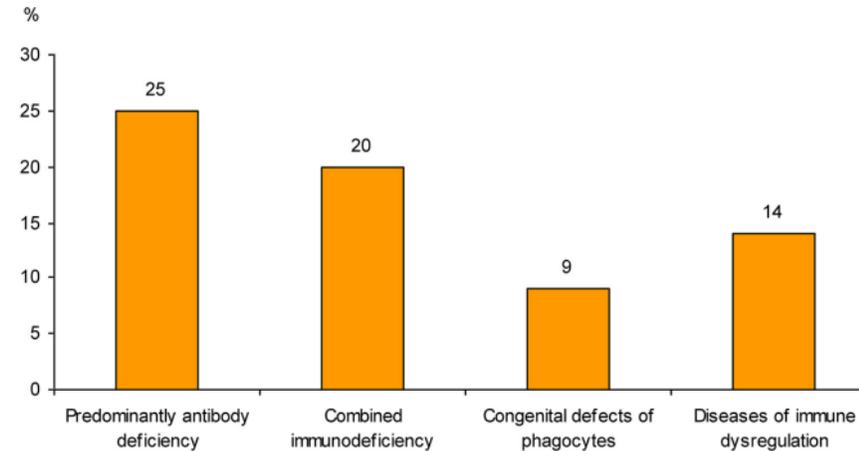
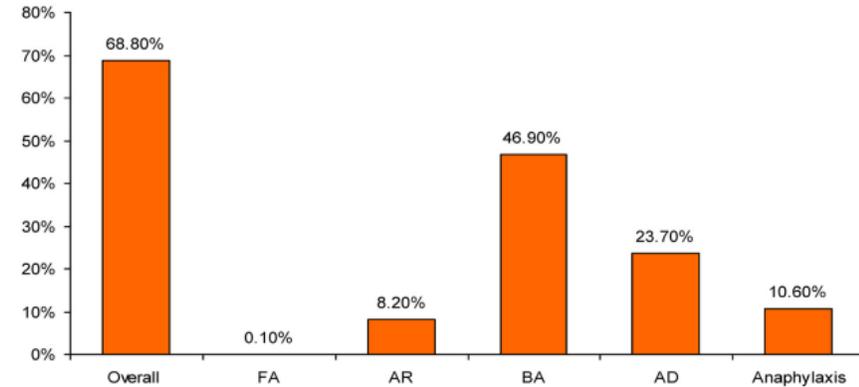
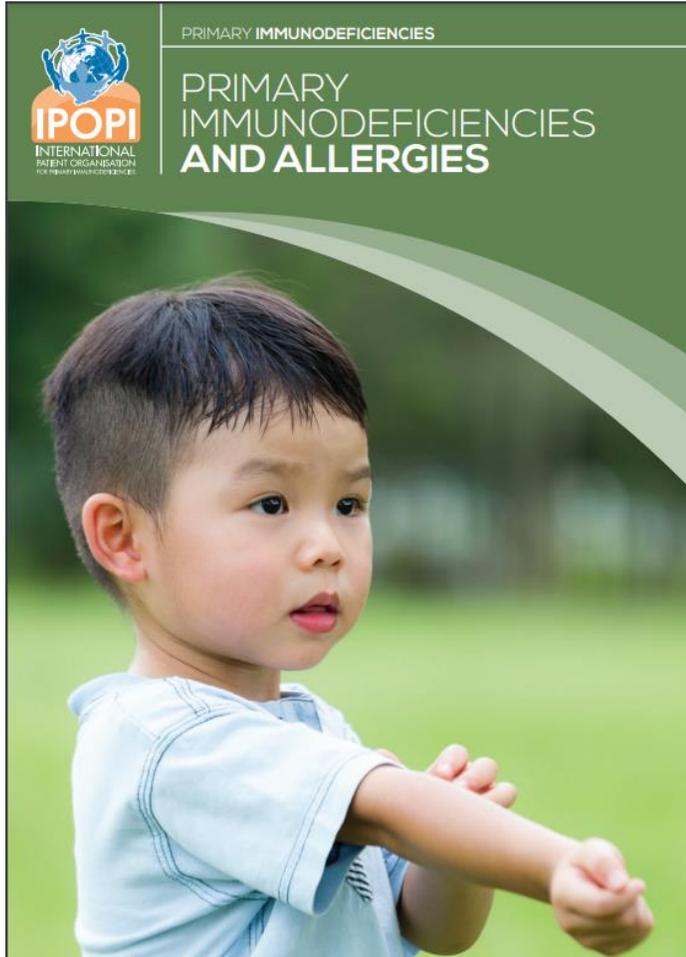
# To include non-infectious manifestations



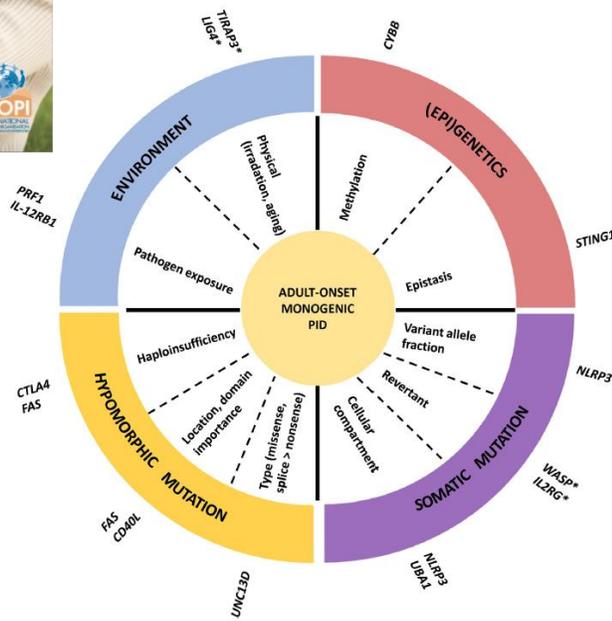
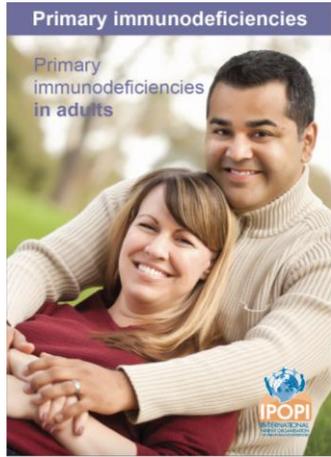
## Possible autoimmune symptoms in people with PIDs

PID	Possible autoimmune disorders
Common variable immunodeficiency (CVID)	<ul style="list-style-type: none"> <li>• Thrombocytopenia</li> <li>• Evans syndrome</li> <li>• Haemolytic anaemia</li> <li>• IBD</li> <li>• Neutropenia</li> <li>• Rheumatoid arthritis</li> <li>• Haemolytic or pernicious anaemia</li> <li>• Systemic lupus erythmatosus</li> <li>• Psoriasis</li> </ul>
Severe combined immunodeficiency (SCID) (especially in Omenn syndrome)	<ul style="list-style-type: none"> <li>• Alopecia</li> <li>• Dermatitis</li> <li>• Thrombocytopenia</li> </ul>
X-linked chronic granulomatous disease (CGD)	<ul style="list-style-type: none"> <li>• IBD</li> </ul>
X-linked (or Bruton's) agammaglobulinaemia (XLA)	<ul style="list-style-type: none"> <li>• Juvenile rheumatoid arthritis</li> <li>• Rheumatoid arthritis/dermatomyositis</li> </ul>
Wiskott-Aldrich syndrome (WAS)	<ul style="list-style-type: none"> <li>• Haemolytic anaemia</li> <li>• Dermatitis</li> <li>• IBD</li> <li>• Vasculitis</li> </ul>
Hyper IgM syndrome (hyper IgM)	<ul style="list-style-type: none"> <li>• Autoimmune neutropenia</li> <li>• IBD</li> <li>• Rheumatoid arthritis</li> <li>• Uveitis</li> </ul>

# To include non-infectious manifestations



# To be adapted to aging



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## Patients by age classes

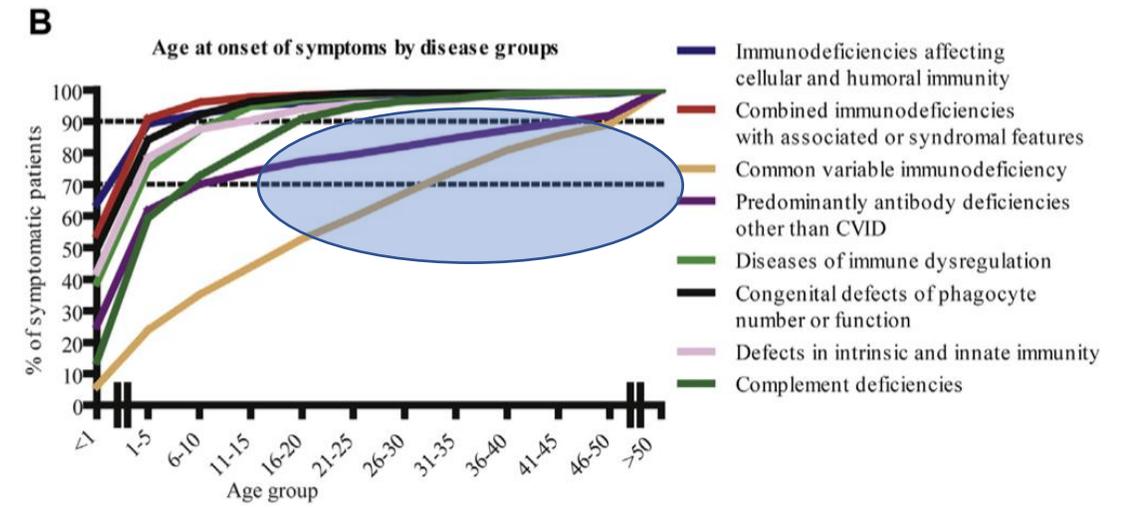
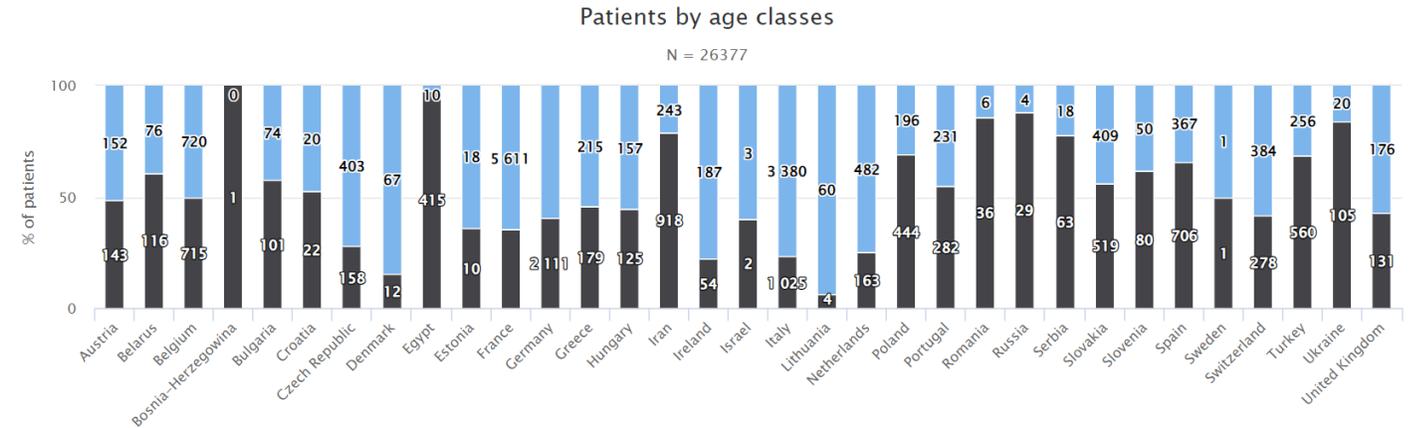
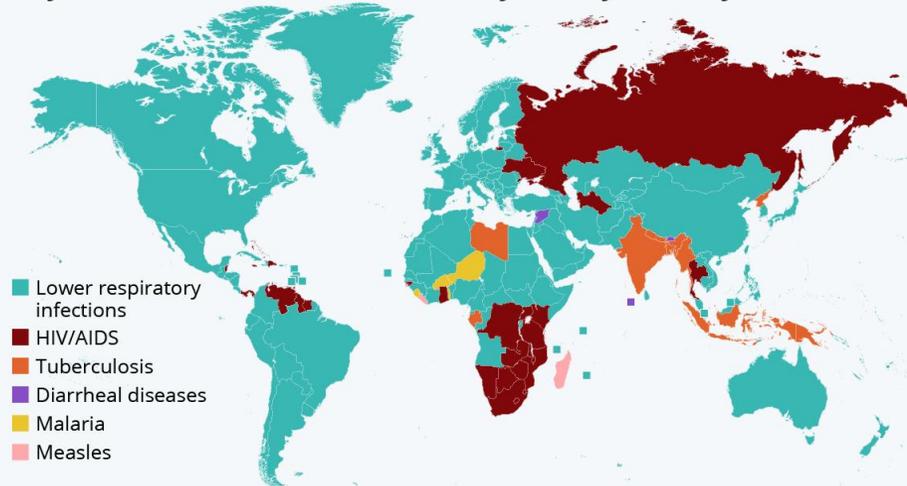


FIGURE 2 | Mechanism of adult-onset IEL. An example of one or two genes is given for every mechanism. \*late onset phenotype, but not adult-onset.

# To be adapted geographically

## Transmittable Diseases Causing the Biggest Health Burdens

Transmittable diseases/disease types that cause the most years of lost life and lost healthy life, by country\*



\* Early death or lost healthy life due to being in a state of poor health or disability due to the disease

Source: NYRequirements



statista

## New available tools to screen PIDs



Newborn screening

++



10 JMF warning signs

+



PIDCAP

++

SPIRIT

++

HPOs

+/-



AI and ML models

+



Massive genome initiatives

+/-

Albumin protein gap

+/-

# Pediatric warning signs (Europe and North America)



≥ 10 acute otitis media	Systemic autoimmune diseases, not including autoimmune cytopenia (celiac disease, arthritis, etc)
≥ 3 sinusitis or orbital cellulitis	Endocrinopathology: Hypothyroidism, hyperparathyroidism, diabetes, etc. (Not described as autoimmune)
≥ 3 pneumonia	Hematological malignancy
Failure to thrive	Solid organ neoplasia (only those that have been associated with inborn errors of immunity in pediatrics: thyroid)
Deep abscesses (in organs)	Oral (dental/palatal) anomalies
≥ 3 recurrent skin abscess	Chronic diarrhea; or ≥ 10 episodes of acute diarrhea)
Mucocutaneous candidiasis (oropharynx, cutaneous, excluded vaginal) in patients ≥ 12 months of age: ≥ 2 episodes	Chronic viral skin infection; or ≥ 20 acute episodes
≥ 2 systemic infections (including sepsis)	Chronic eczema or other dermatological manifestations related to inborn errors of immunity
≥ 1 serious infections that alone indicate IEI study (meningitis caused by HSV, etc.)	Recurrent fever
Family history of inborn errors of immunity	Inflammatory bowel disease in patients ≥ 2 years of age
Consanguinity or other family history compatible with manifestations of inborn errors of immunity (lymphomas, etc)	Inflammatory bowel disease in patients < 2 years of age
Cytopenia (not specified as autoimmune)	Bronchiectasis without cystic fibrosis
Autoimmune cytopenia <sup>a</sup>	Vaccine reaction
Presence of 2 or more warning signs	

# Adults' warning signs (Europe and North America)

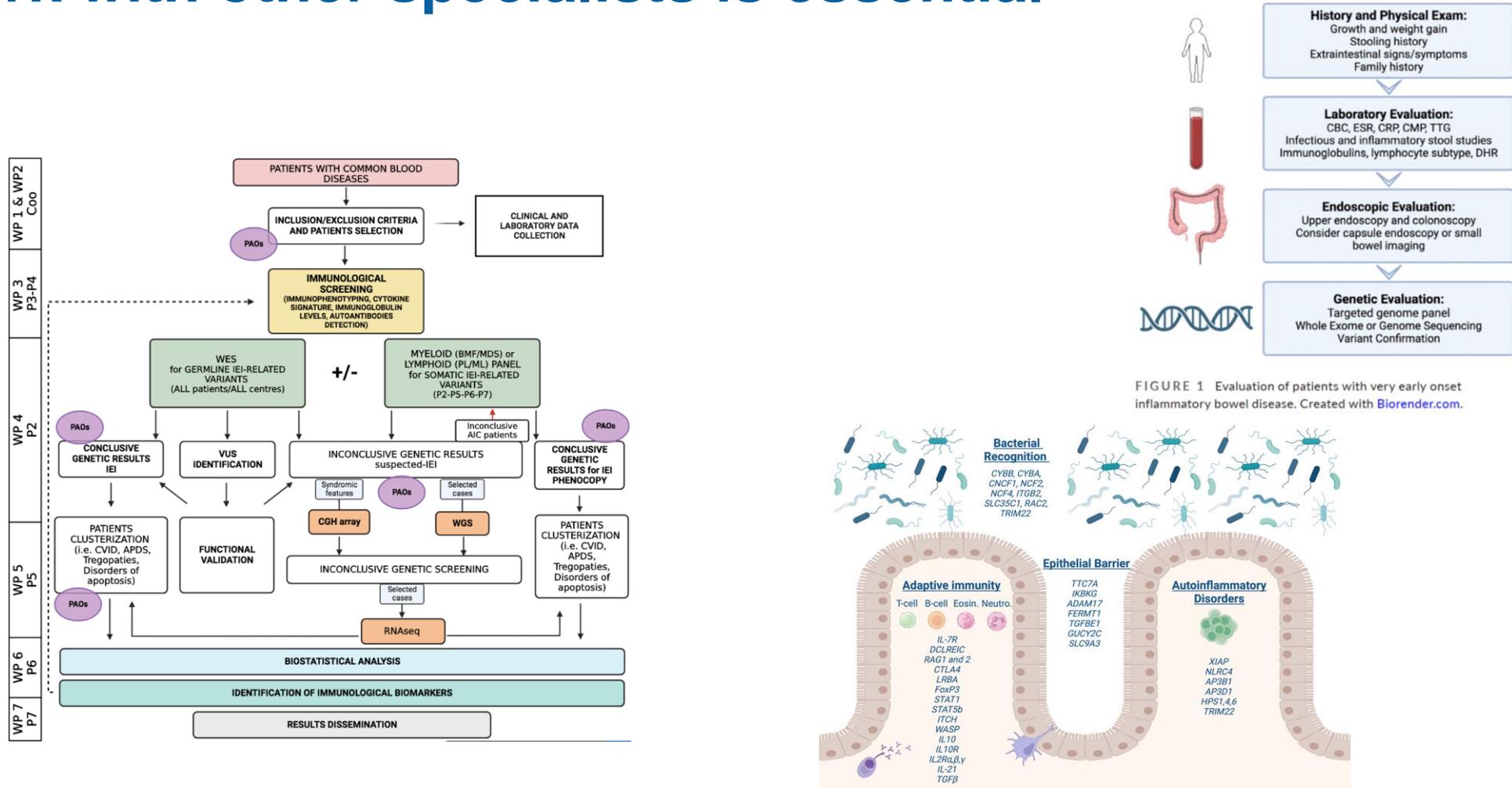
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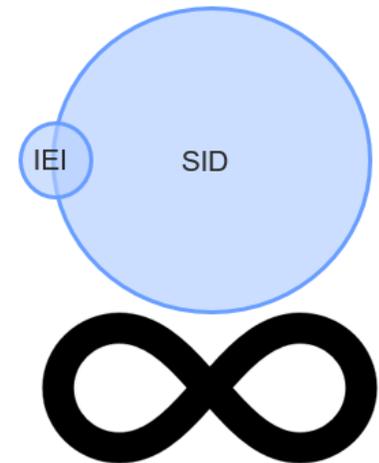


≥ 8 acute otitis media	Consanguinity or other family history compatible with manifestations of inborn errors of immunity (haematological neoplasms)
≥ 8 sinusitis or chronic sinusitis	Presence of cytopenia (without specifying if autoimmune)
≥ 3 pneumonia	Autoimmune cytopenia
Chronic diarrhea	Presence of bronchiectasis without cystic fibrosis
Deep abscesses (in organs and/or ganglia)	Systemic and endocrine autoimmune diseases (celiac disease, arthritis, systemic lupus, thyroiditis, etc.)
Recurrent skin abscesses of repetition (3 or more)	Haematological neoplasia (excluding multiple myeloma, chronic myeloid leukemia, Waldenström's disease, etc)
Oropharyngeal or cutaneous candidiasis (excluding vaginal candidiasis)	Solid organ neoplasia (only those related with inborn errors of immunity: skin, stomach, thyroid)
Recurrent viral infections (colds, herpes, warts, condylomas, etc.) 25 or more episodes	Inflammatory bowel disease
2 or more systemic infections including sepsis	Recurrent fever
Unique severe condition that alone require study for inborn errors of immunity	Oral (dental/palatal) anomalies
Atypical mycobacteria infection	Chronic eczema or other dermatological manifestations related to inborn errors of immunity <sup>b</sup>
Family history of inborn errors of immunity	Presence of 2 or more warning signs

# Teamwork with other specialists is essential



- **Early diagnosis** is key for the outcome
- There are multiple “missed” opportunities along **patients’ journey**
- Beware of **non-infectious clinical phenotypes** → teamwork with non-immunologists increases awareness
- **Data science and IA** may help in allowing an earlier diagnosis and multidisciplinary work. But Is it all primary or secondary?



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# Thank you for your attention!

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