



# 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*

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Vall d'Hebron Barcelona Hospital Campus

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## Disclosures

PSP has received grants from:

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

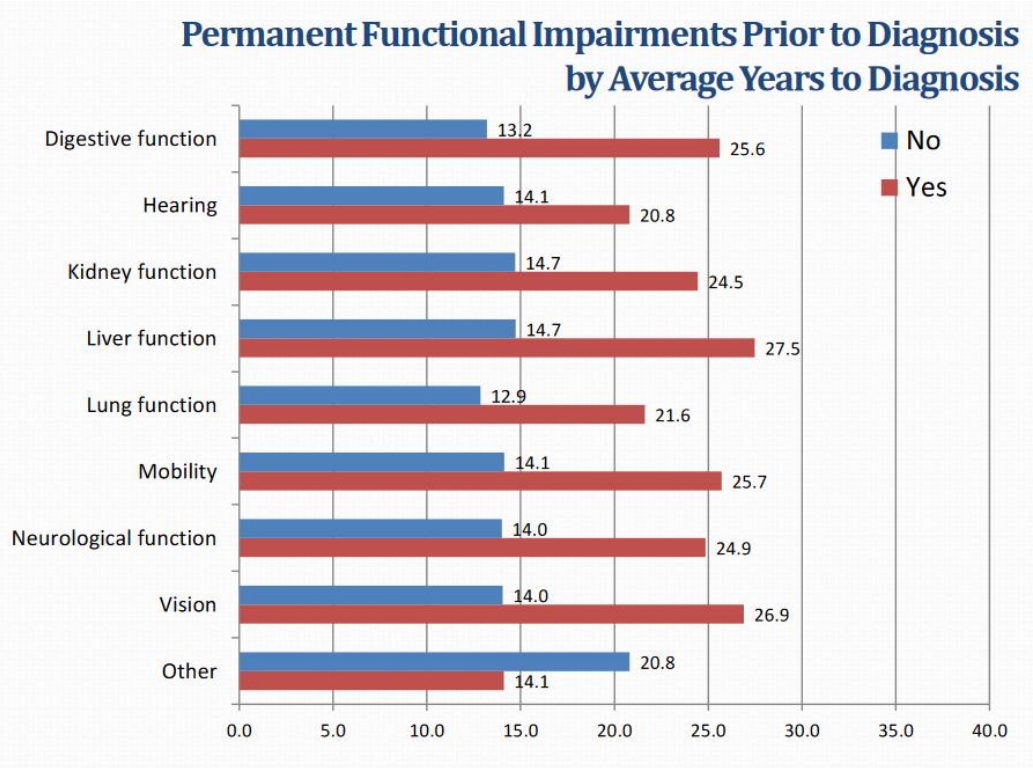
JR from:

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

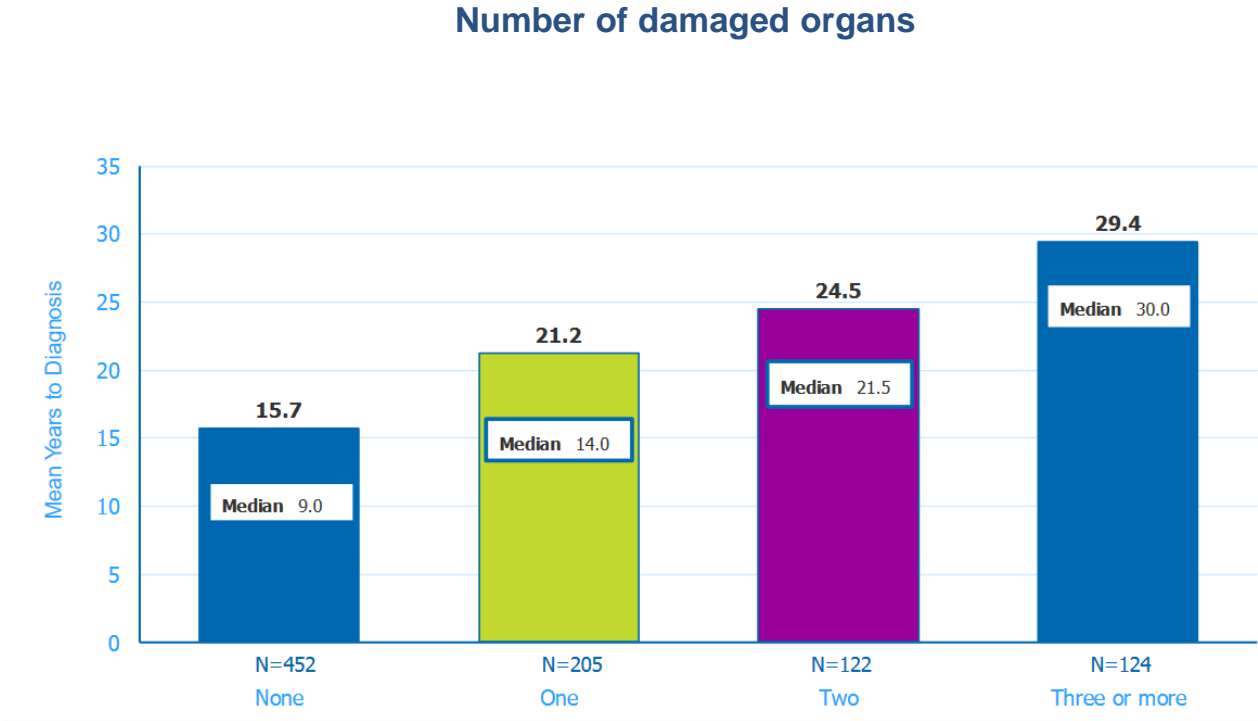
But there are no conflict of interests regarding the content presented in this session

# 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.



These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. © 2016 Jeffrey Modell Foundation. For information or referrals, contact the Jeffrey Modell Foundation: [info4pi.org](mailto:info4pi.org)

## 10 Warning Signs of Primary Immunodeficiency FOR ADULTS

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. Gennerly<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.

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

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

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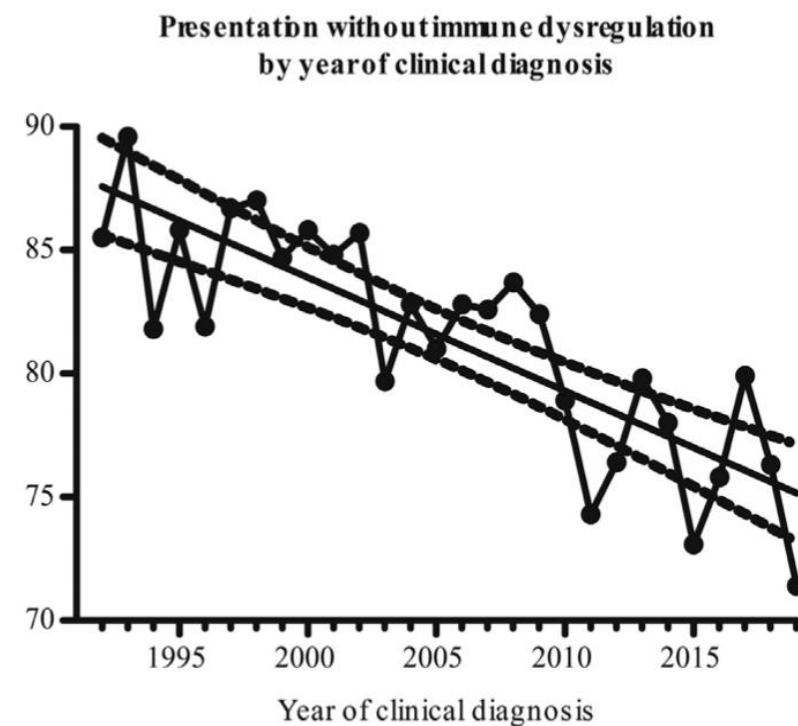
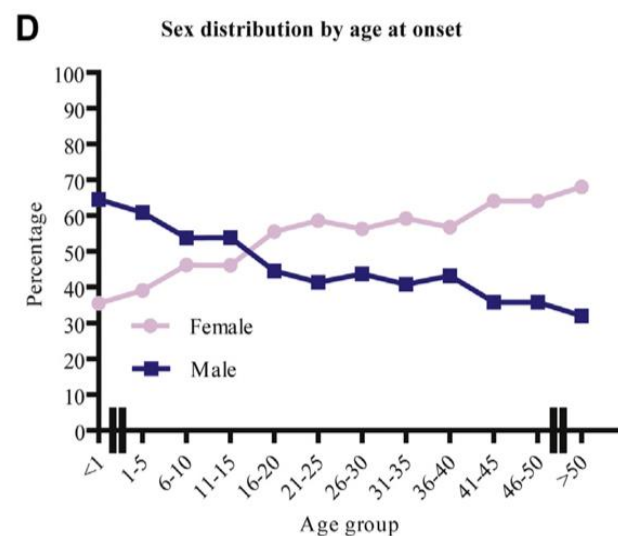
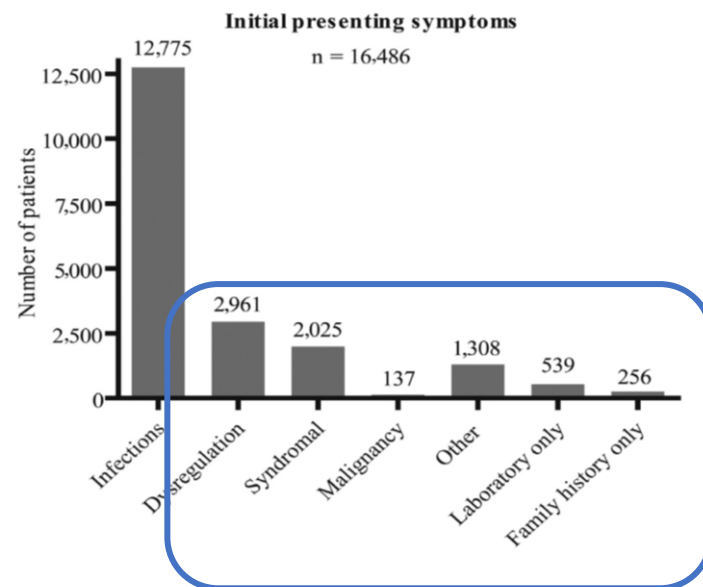
KEY REVIEW ARTICLE

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

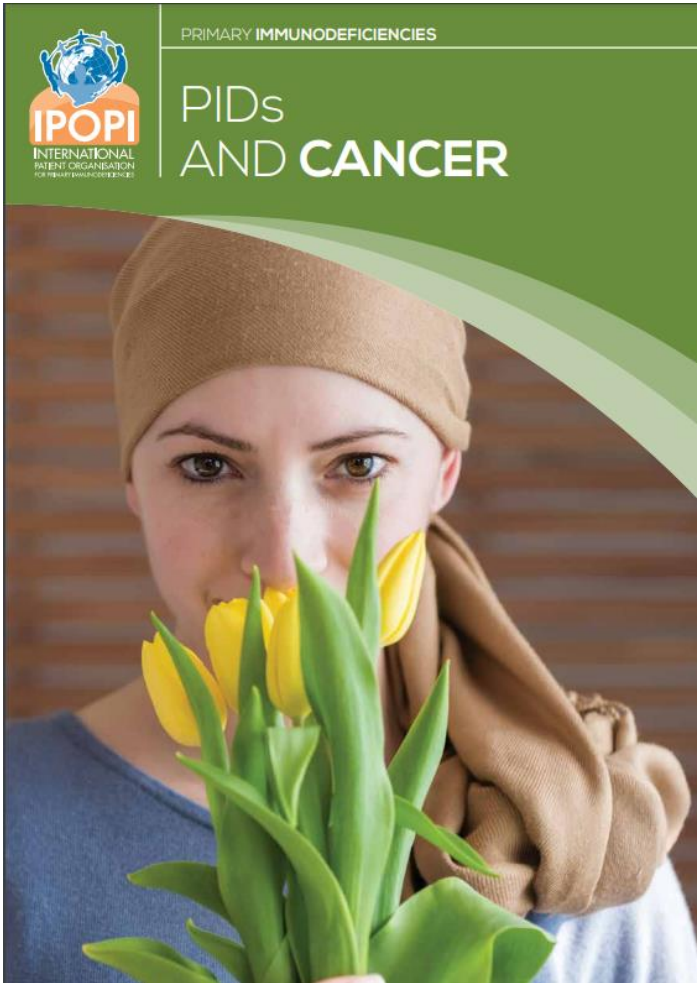
Beatriz Tavares Costa-Carvalho • Anete Sevciovic Grumach • José Luis Franco • Francisco Javier Espinosa-Rosales • Lily E. Leiva • Alejandra King • Oscar Porras • Liliana Bezrodnik • Mathias Oleastro • Ricardo U. Sorensen • Antonio Condino-Neto

# 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 |



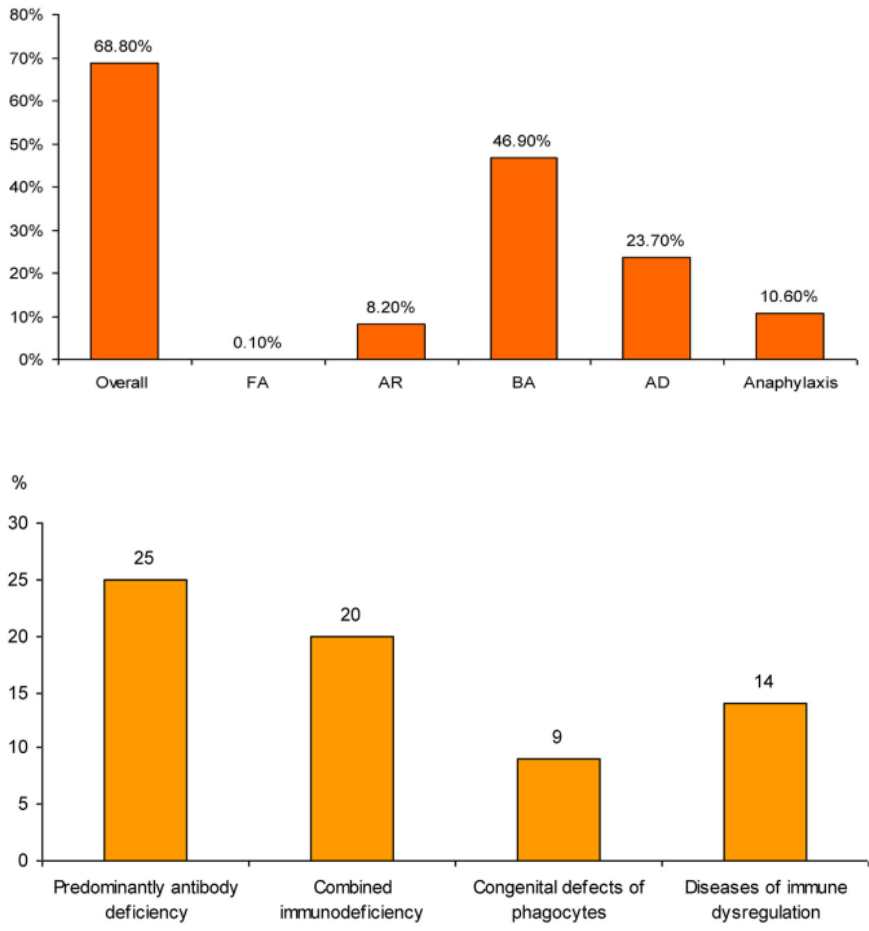
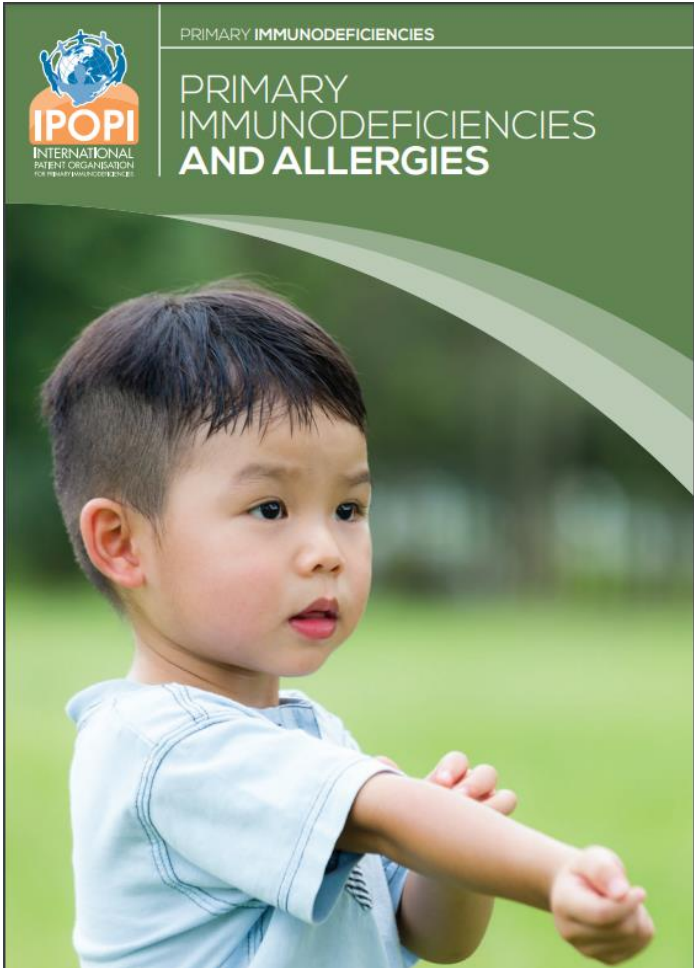
# To include non-infectious manifestations



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

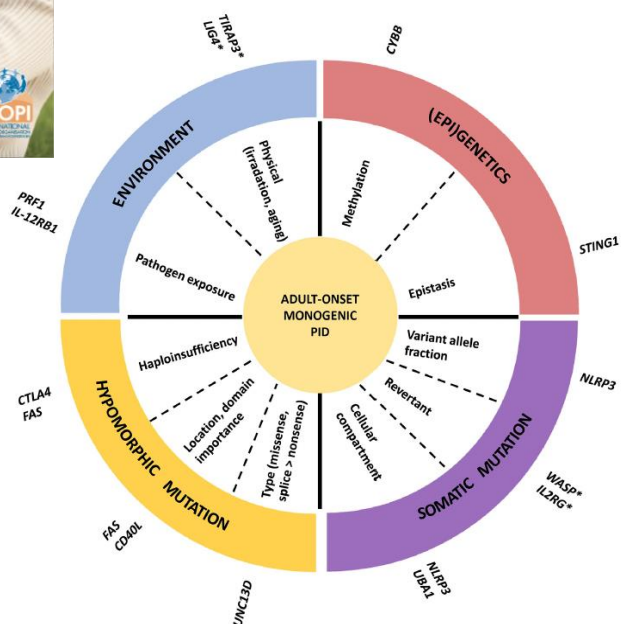
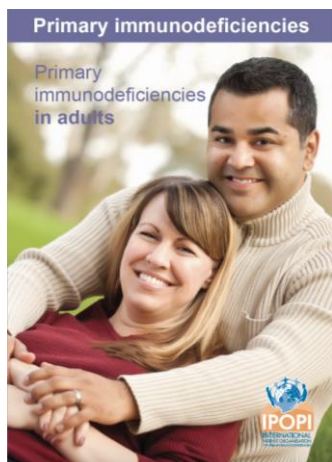
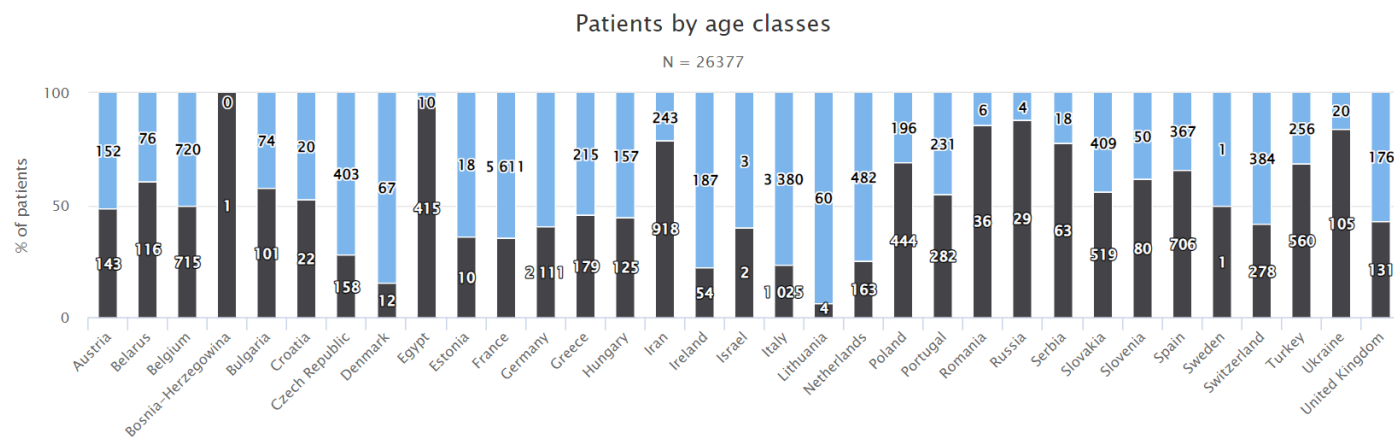
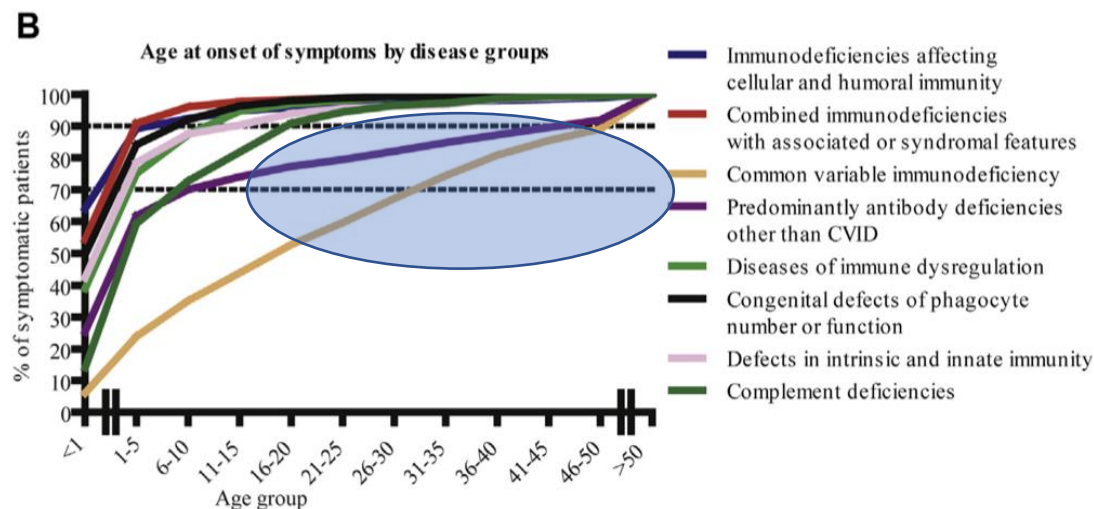


FIGURE 2 | Mechanism of adult-onset IPI. An example of one or two genes is given for every mechanism. \*late onset phenotype, but not adult-onset.

## Patients by age classes



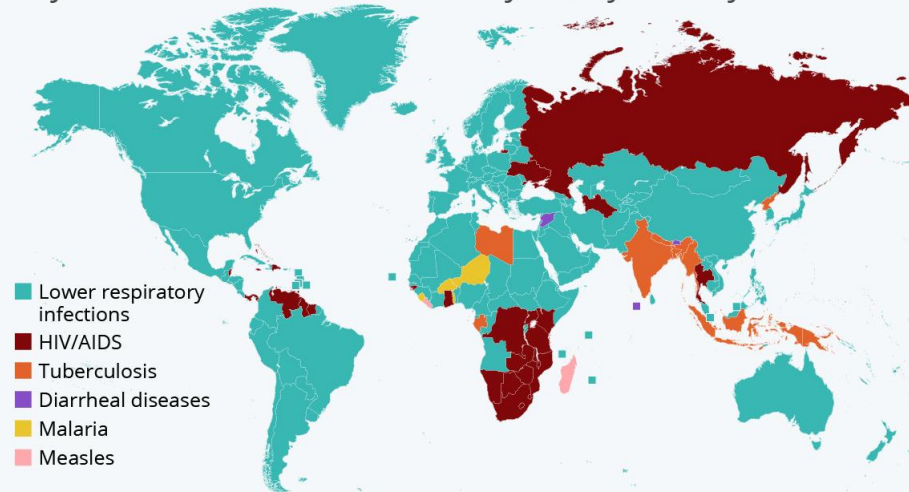
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# To be adapted geographically

## 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

|   |                            | IEI |
|---|----------------------------|-----|
|    | 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)

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|  |  |
|--|--|
| ≥ 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

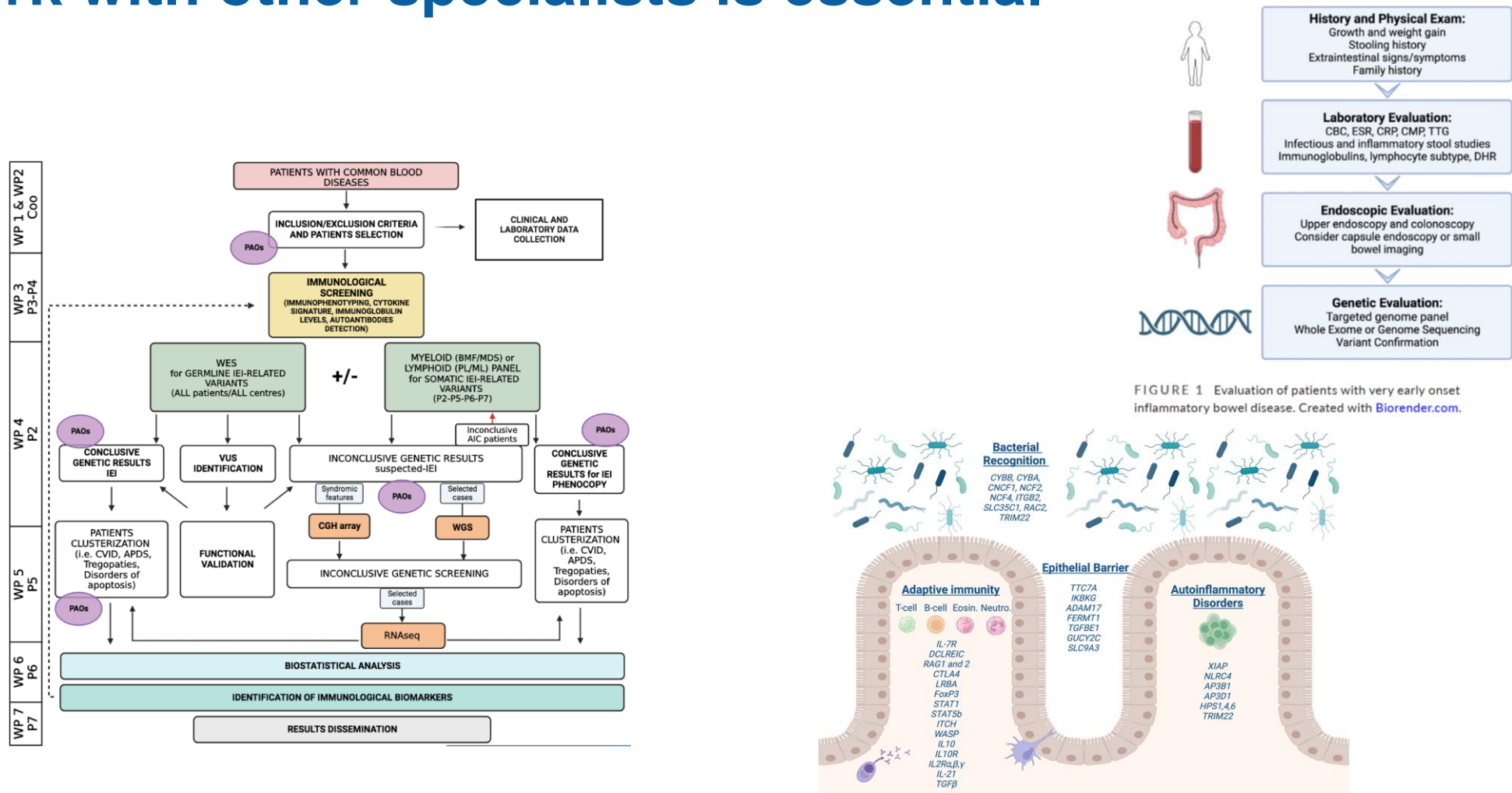
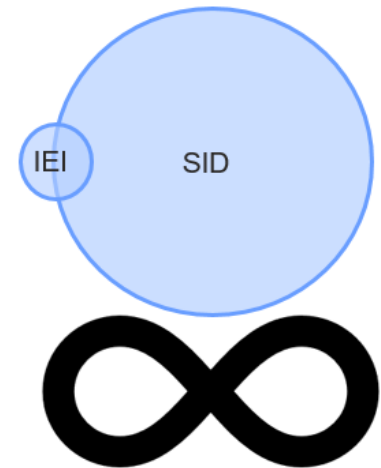


FIGURE 1 Evaluation of patients with very early onset inflammatory bowel disease. Created with Biorender.com.



- **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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