

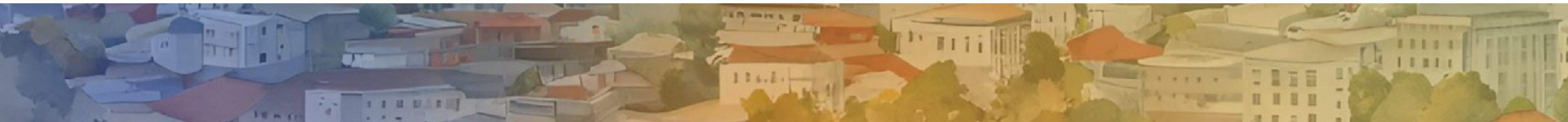


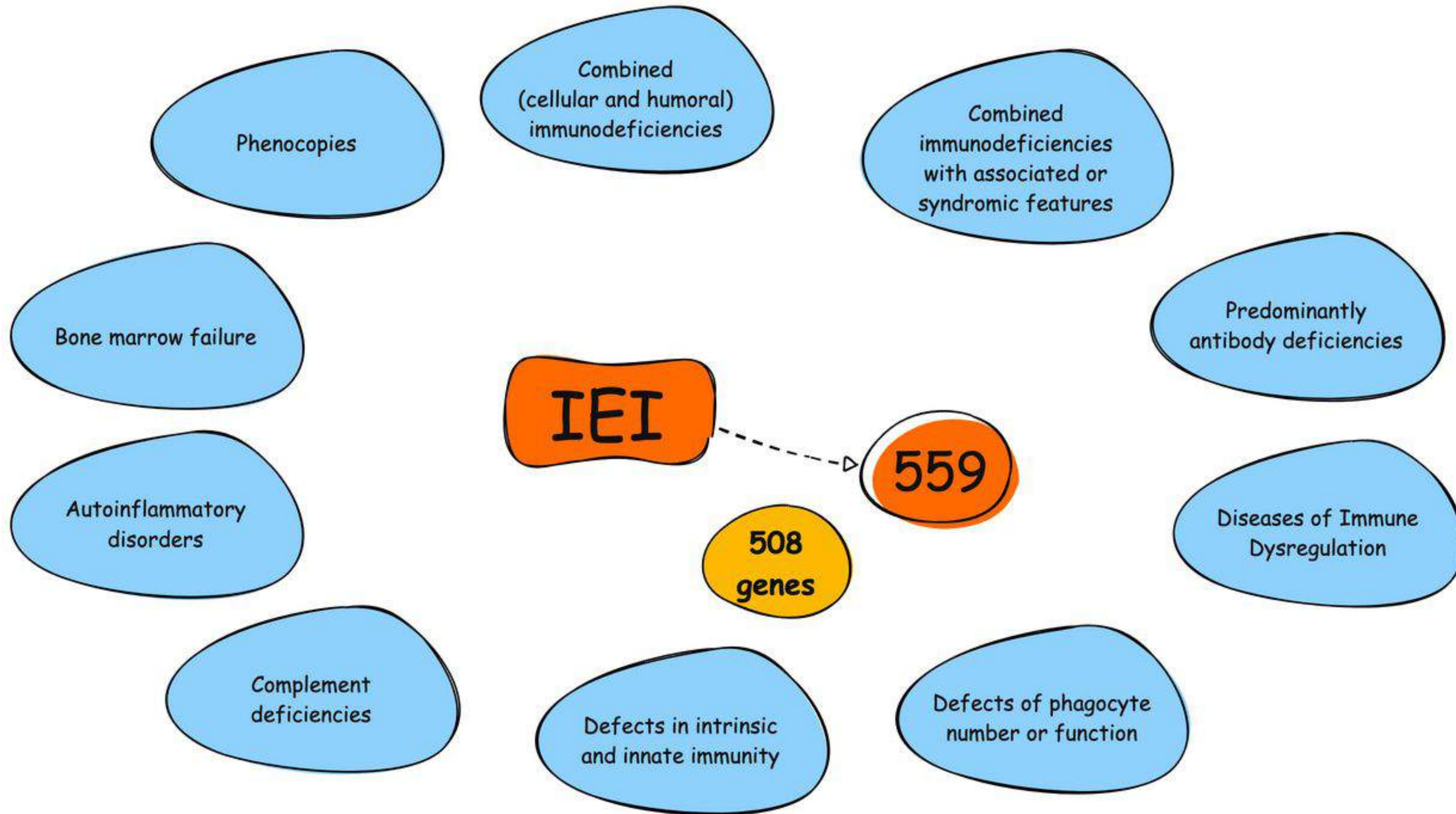
# Non-hematological malignancies in Inborn Errors of Immunity

Ekaterini Goudouris

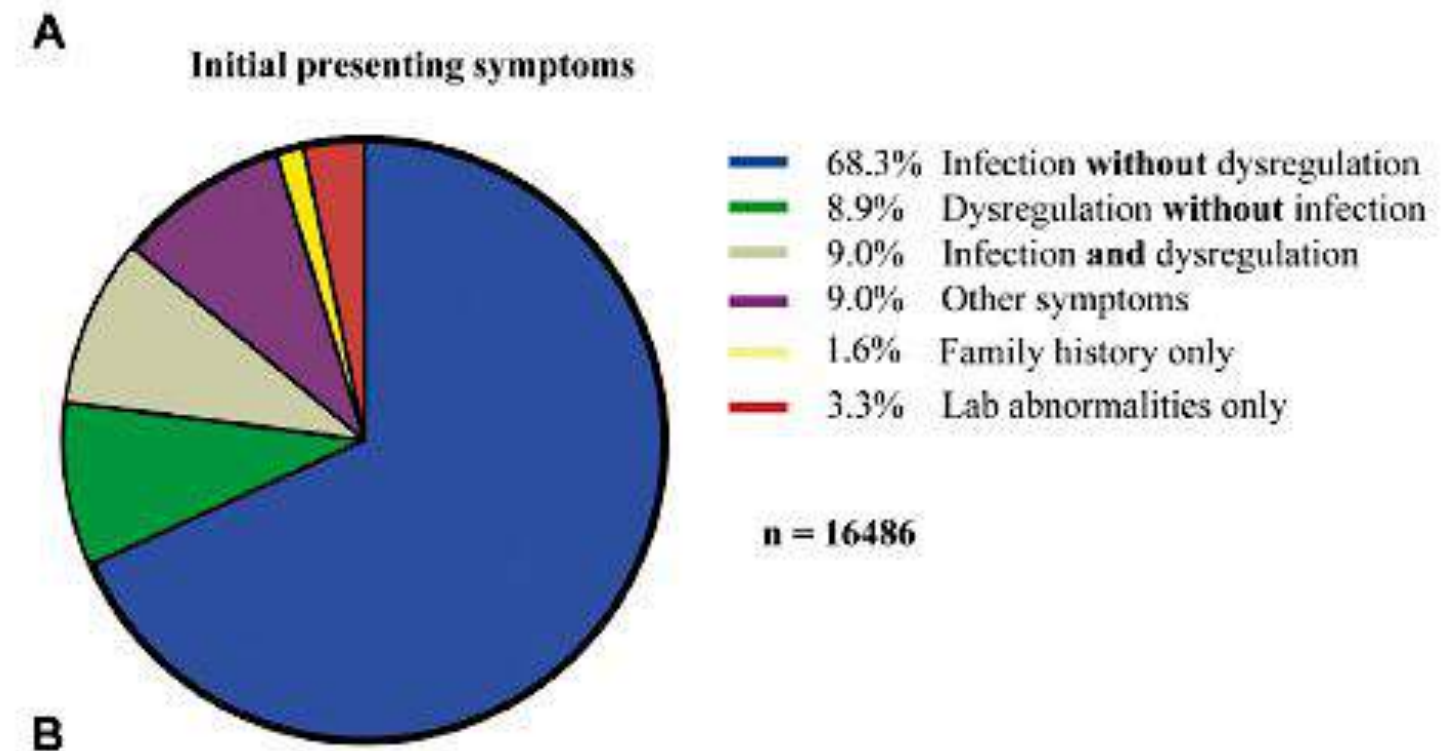
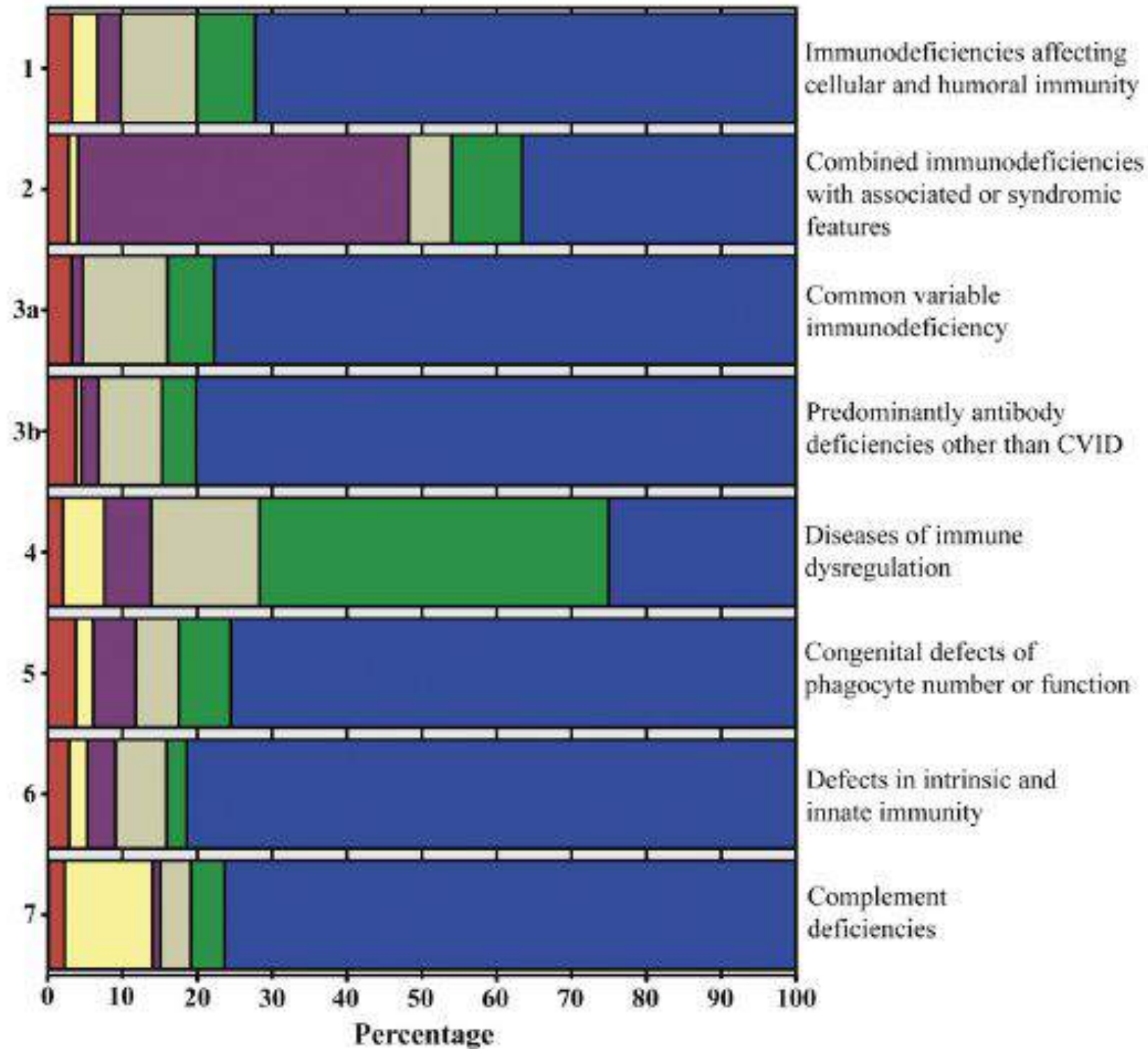
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I declare that I have no conflicts of interest in relation to this presentation.



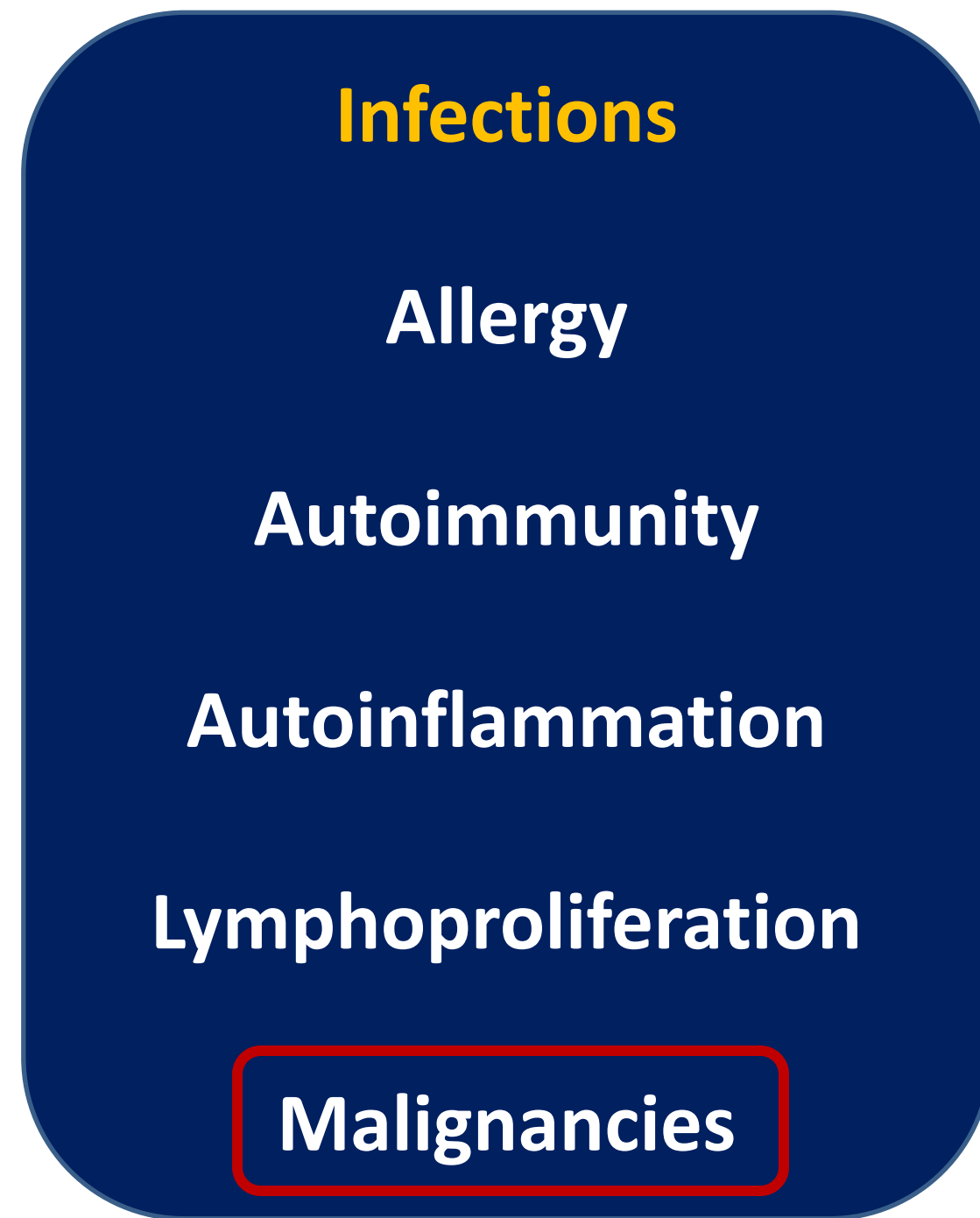
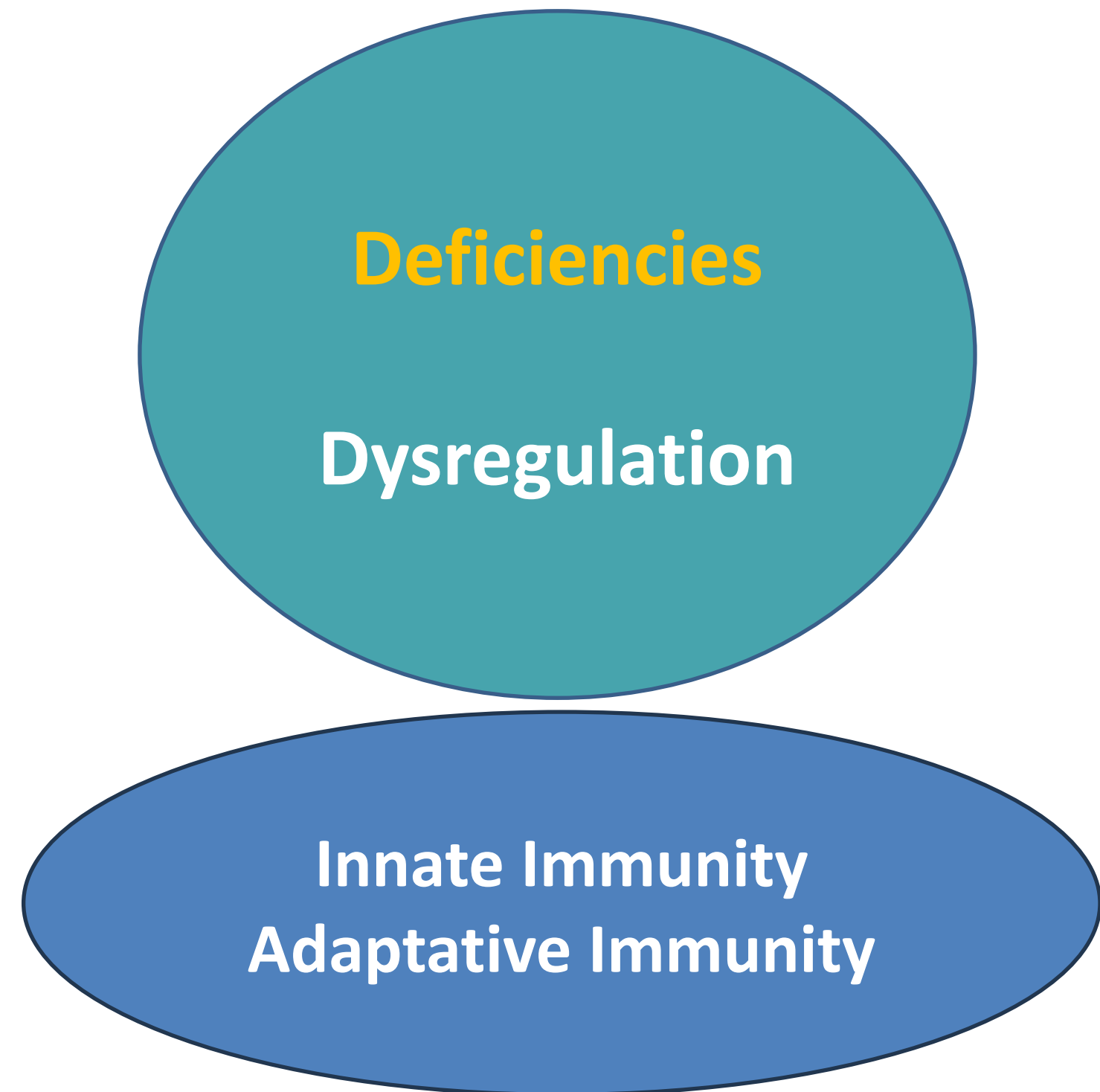


## The importance of recognizing non-infectious manifestations !

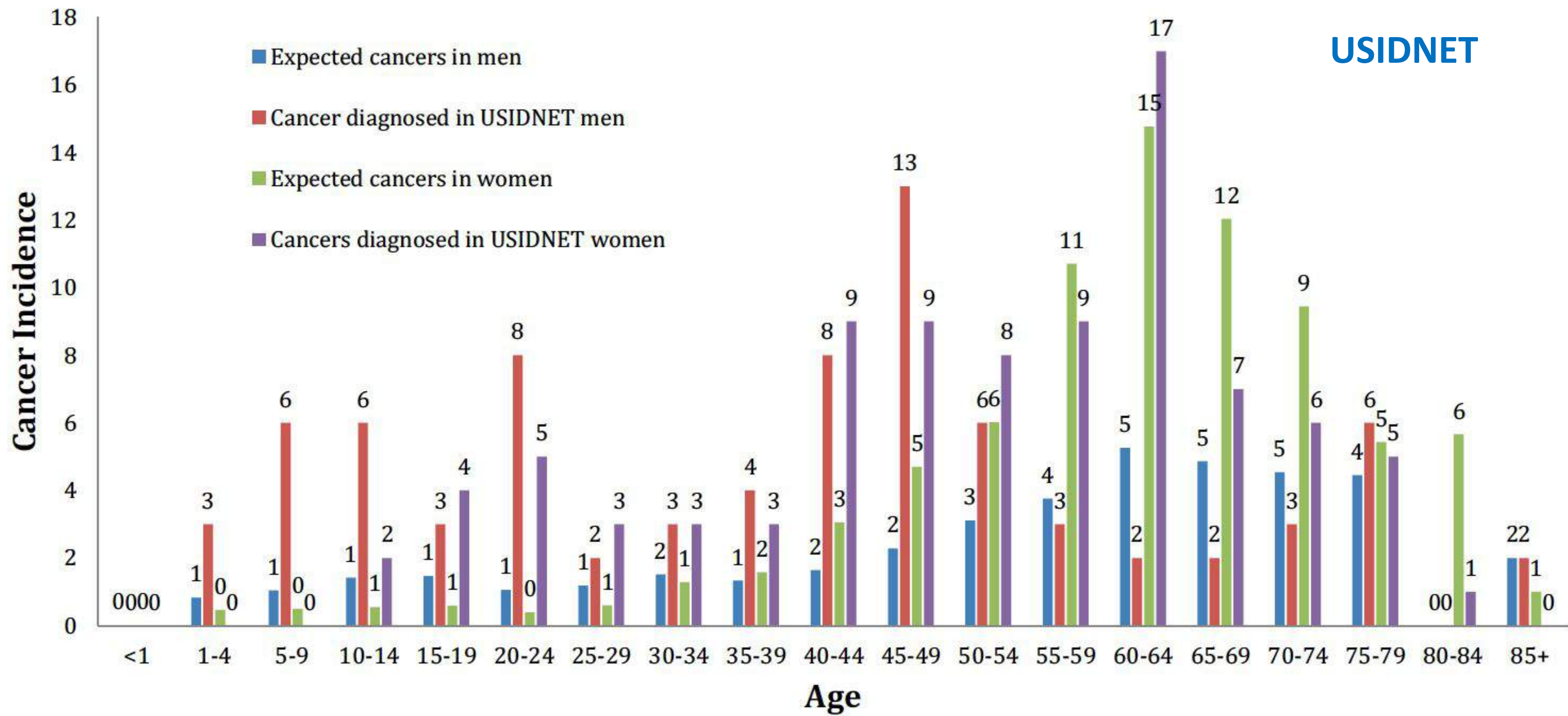


**Conclusions: An exclusive focus on infection-centered warning signs would have missed around 25% of patients with IEI who initially present with other manifestations. (J Allergy Clin Immunol 2021;148:1332-41.)**

Talhammer et al.  
*J Allergy Clin Immunol* 2021;148:1332-41.



- ✓ Panorama of malignancies in IEI
- ✓ Mechanisms by which they occur
- ✓ Thinking about IEI in front of a malignancy X monitoring a malignancy in patients with IEI
- ✓ Management, in general



| Demographic  | No. of Patients | % USIDNET cohort |
|--|-----------------|------------------|
| Average age: 47 y,<br>median age: 29 y,<br>age range: <1 to 89 y |                 |                  |
| Gender   |                 |                  |
| Male   | 2174            | 59.4             |
| Female   | 1484            | 40.6             |

Mayor et al.  
J Allergy Clin Immunol 2018;141:1028-35

**USIDNET**

**TABLE III.** Incidence rates of cancer site-specific diagnoses made in the USIDNET registry

| Cancers type            | Men | Women | Totals |
|-------------------------|-----|-------|--------|
| Lymphoid cancer         | 41  | 41    | 82     |
| Lymphoma                | 32  | 31    | 63     |
| Hematologic tumor NOS   | 3   | 6     | 9      |
| Leukemia                | 5   | 3     | 8      |
| Thymus cancer           | 0   | 1     | 1      |
| Malignant histiocytosis | 1   | 0     | 1      |
| Genitourinary cancer    | 7   | 7     | 14     |
| Bladder cancer          | 3   | 0     | 3      |
| Testicular cancer       | 3   | N/A   | 3      |
| Cervical cancer         | N/A | 2     | 2      |
| Renal cancer            | 1   | 0     | 1      |
| Uterine cancer          | N/A | 2     | 2      |
| Ovarian cancer          | N/A | 3     | 3      |
| Gastrointestinal cancer | 9   | 5     | 14     |
| Stomach/duodenal cancer | 2   | 3     | 5      |
| Colon cancer            | 3   | 1     | 4      |
| Liver cancer            | 3   | 0     | 3      |
| Appendiceal cancer      | 0   | 1     | 1      |
| Pancreatic cancer       | 1   | 0     | 1      |
| Endocrine cancer        | 4   | 5     | 9      |
| Thyroid cancer          | 4   | 3     | 7      |
| Endocrine cancer        | 0   | 2     | 2      |
| ENT cancer              | 5   | 1     | 6      |
| Laryngeal cancer        | 2   | 1     | 3      |
| Mouth cancer            | 1   | 0     | 1      |
| Eye cancer              | 2   | 0     | 2      |
| Skin (NOS)              | 10  | 15    | 25     |
| Lung (NOS)              | 2   | 3     | 5      |
| Bone cancer (NOS)       | 1   | 1     | 2      |
| Breast cancer (NOS)     | 0   | 10    | 10     |
| Unspecified primary     | 1   | 3     | 4      |
| Totals                  | 80  | 91    | 171    |

ENT, Ear-nose-throat; NOS, not otherwise specified.

**TABLE IV.** Incidence rates of the cancer diagnoses by PIDD type and subtype

| PIDD type or subtype  | Cancer in men | Cancer in women | Total no. of cancers |
|---|---------------|-----------------|----------------------|
| CVID  | 48            | 71              | 119                  |
| Severe combined immunodeficiency  |               |                 |                      |
| Common gamma chain deficiency   | 2             | 0               | 2                    |
| SCID unknown type   | 1             | 0               | 1                    |
| Adenosine deaminase deficiency  | 1             | 0               | 1                    |
| Other combined immunodeficiencies   |               |                 |                      |
| WAS   | 8             | 0               | 8                    |
| Ataxia telangiectasia   | 2             | 1               | 3                    |
| Hyper IgE AD STAT3  | 1             | 2               | 3                    |
| Cartilage hair hypoplasia   | 0             | 2               | 2                    |
| DOCK8   | 0             | 1               | 1                    |
| Activated PI3K- $\delta$  | 0             | 1               | 1                    |
| Combined immune deficiency with unknown or unlisted genetic cause                                   | 0             | 1               | 1                    |
| Predominantly antibody deficiencies   |               |                 |                      |
| BTK deficiency  | 4             | 0               | 4                    |
| Hypogammaglobulinemia   | 4             | 5               | 9                    |
| Specific antibody deficiency with normal immunoglobulin concentrations and normal number of B cells | 0             | 3               | 3                    |
| Isolated IgG subclass deficiency  | 0             | 2               | 2                    |
| CD40 deficiency   | 1             | 0               | 1                    |
| CD40L deficiency  | 1             | 0               | 1                    |
| Hyper IgM due to uncertain or unlisted cause  | 4             | 1               | 5                    |
| Selective IgA deficiency  | 0             | 1               | 1                    |
| Immunodeficiency of unknown cause   | 3             | 0               | 3                    |
| Total cancers   | 80            | 91              | 171                  |

| USIDNET registry subjects            | Cancer type       | Fold-change in PIDD cancer incidence from expected |
|--------------------------------------|-------------------|--|
| Men and women combined<br>(n = 3658) | All cancers       | 1.42   |
| Men (n = 2174)                       | All cancers       | 1.91   |
|                                      | Prostate          | N/A  |
|                                      | Lung              | 0.62   |
|                                      | Colon             | 1  |
|                                      | Lymphoma          | 10   |
|                                      | Skin              | 4.55   |
|                                      | Leukemia          | 1.43   |
|                                      | Thyroid           | 4.44   |
|                                      | Stomach           | 3.33   |
|                                      | Bladder           | 2.14   |
|                                      | Testicular        | 1.50   |
|                                      | Remaining cancers |  |
| Women (n = 1484)                     | All cancers       | 1.15   |
|                                      | Breast            | 0.41   |
|                                      | Lung              | 0.48   |
|                                      | Colon             | 0.19   |
|                                      | Lymphoma          | 8.34   |
|                                      | Skin              | 3.33   |
|                                      | Leukemia          | 1  |
|                                      | Thyroid           | 0.49   |
|                                      | Stomach           | 3.75   |
|                                      | Ovarian           | 1.25   |
|                                      | Uterine           | 0.41   |
|                                      | Cervix            | 0.91   |
|                                      | Remaining cancers |  |

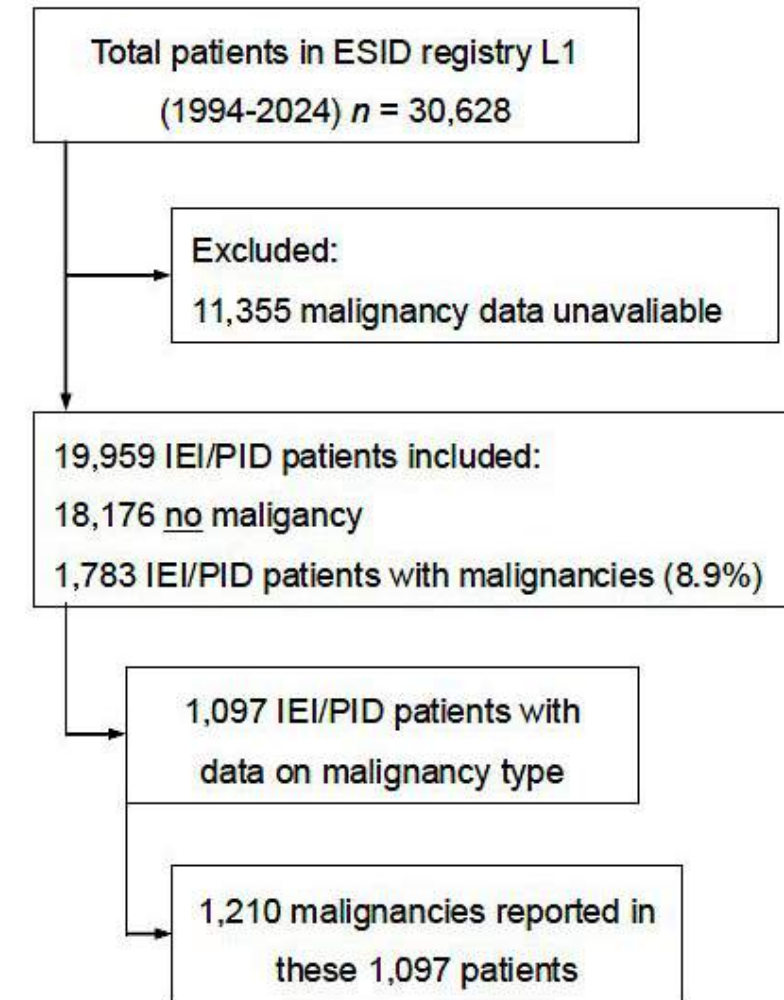
USIDNET

| CVID subjects                        | Cancer type       | Fold-change in PIDD cancer incidence from expected |
|--------------------------------------|-------------------|--|
| Men and women combined<br>(n = 1285) | All cancers       | 1.29   |
| Men (n = 556)                        | All cancers       | 1.75   |
|                                      | Prostate          | 0  |
|                                      | Lung              | 0.80   |
|                                      | Colon             | 0.87   |
|                                      | Lymphoma          | 8.42   |
|                                      | Skin              | 5.63   |
|                                      | Leukemia          | 2  |
|                                      | Thyroid           | 6.67   |
|                                      | Stomach           | 5  |
|                                      | Bladder           | 2.73   |
|                                      | Testicular        | .91  |
|                                      | Remaining cancers |  |
| Women (n = 729)                      | All cancers       | 1.10   |
|                                      | Breast            | 0.38   |
|                                      | Lung              | 0.37   |
|                                      | Colon             | 0.22   |
|                                      | Lymphoma          | 7  |
|                                      | Skin              | 3.68   |
|                                      | Leukemia          | 1.43   |
|                                      | Thyroid           | .2   |
|                                      | Stomach           | 4.29   |
|                                      | Ovarian           | 1  |
|                                      | Uterine           | .476   |
|                                      | Cervix            | 1.11   |
|                                      | Remaining cancers |  |

**Table 2. Demographics of the ESID registry L2 sub-study/survey cohort (n=393).**

| <b>Gender</b>   | <b>Number (percentage)</b>                  |  |
|---|---|--|
| Male  | 210 (53.4%)                                 |  |
| Female  | 183 (46.6%)                                 |  |
| <b>IEI/PID category<sup>o</sup></b>                               | <b>Number (percentage)</b>                  | <b>Percentage in L1 cohort (n=1783 patients)<sup>2</sup></b> |
| Immunodeficiencies affecting cellular and humoral immunity        | 33 (8.4%)                                   | 6.3%   |
| Combined immunodeficiencies with associated or syndromic features | 95 (24.3%)                                  | 17.5%  |
| Predominantly antibody deficiencies                               | 196 (50.1%)                                 | 58%  |
| Diseases of immune dysregulation                                  | 37 (9.5%)                                   | 8.4%   |
| Congenital defects of phagocyte number or function                | 2 (0.5%)                                    | 4.2%   |
| Defects in intrinsic and innate immunity                          | 2 (0.5%)                                    | 1.8%   |
| Autoinflammatory disorders  | 6 (1.5%)                                    | 0.7%   |
| Complement deficiencies   | 6 (1.5%)                                    | 0.84%  |
| Bone marrow failure disorders                                     | 0   | 0.4%   |
| Phenocopies of inborn errors of immunity                          | 6 (1.5%)                                    | 0.3%   |
| Unspecified IEI/PID   | 8 (2.0%)                                    | 1.6%   |
| <b>Genetic IEI/PID diagnosis</b>                                  | <b>Number (percentage)</b>                  |  |
| Yes   | 188 (47.8%)                                 |  |
| No  | 205 (52.2%)                                 |  |
| <b>First malignancy</b>   | <b>Median (range) / Number (percentage)</b> |  |
| Age (in years) at diagnosis of first malignancy                   | 29.0 years (0-86 years)                     |  |
| First malignancy diagnosed in childhood (< 18 years of age)       | 157 (39.9%)                                 |  |
| First malignancy diagnosed in adulthood (≥ 18 years of age)       | 236 (60.1%)                                 |  |
| <b>Second or higher malignancy</b>                                | <b>Median (range)</b>                       |  |
| Age (in years) at diagnosis of second or higher malignancy        | 54.0 years (5-78 years)                     |  |
| <b>Malignancy as presenting feature of IEI/PID</b>                | <b>Number (percentage)</b>                  |  |
| Yes   | 120 (30.8%)                                 |  |
| No  | 269 (69.2%)                                 |  |
| <b>Primary malignancies per patient</b>                           | <b>Number (percentage)</b>                  |  |
| One   | 354 (90.1%)                                 |  |
| Two   | 35 (8.9%)                                   |  |
| Three   | 3 (0.8%)                                    |  |
| More than three   | 1 (0.3%)                                    |  |
| <b>Overall outcome at last follow-up</b>                          | <b>Number (percentage)</b>                  |  |
| Alive   | 285 (72.5%)                                 |  |
| Dead  | 99 (25.2%)                                  |  |
| Unknown   | 9 (2.3%)                                    |  |

## ESID Registry

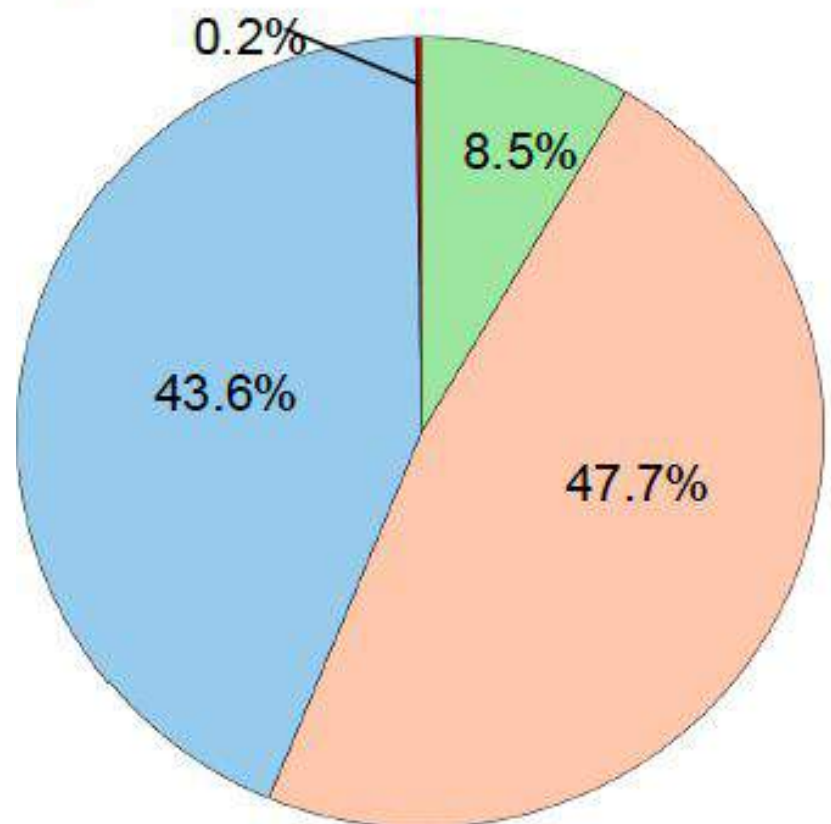


Bogaert et al.

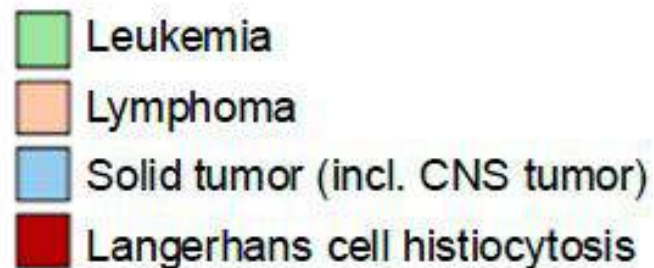
medRxiv preprint doi: <https://doi.org/10.1101/2025.08.26.25334420>

This version posted August 29, 2025

B



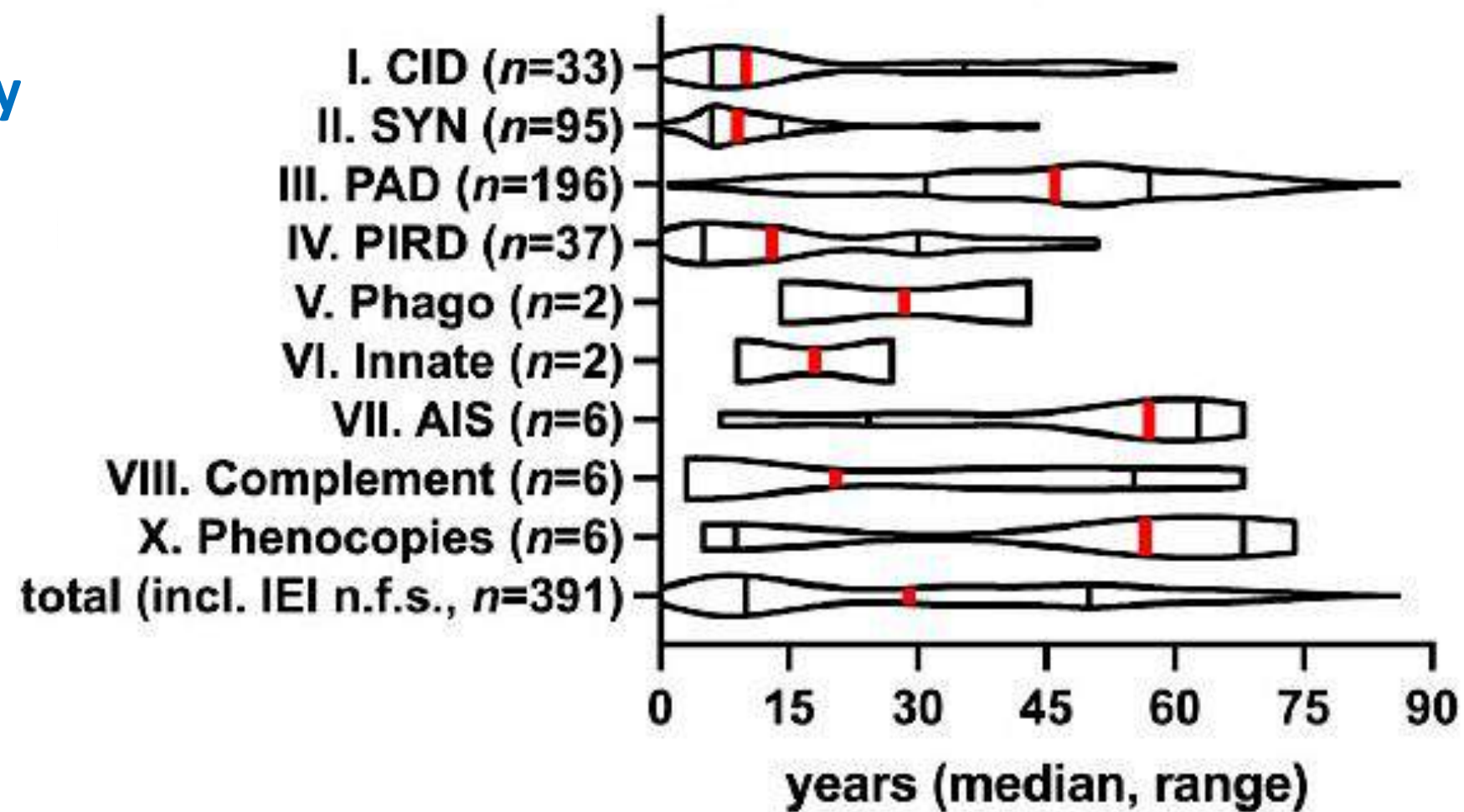
n=436 malignancies



### ESID Registry

D

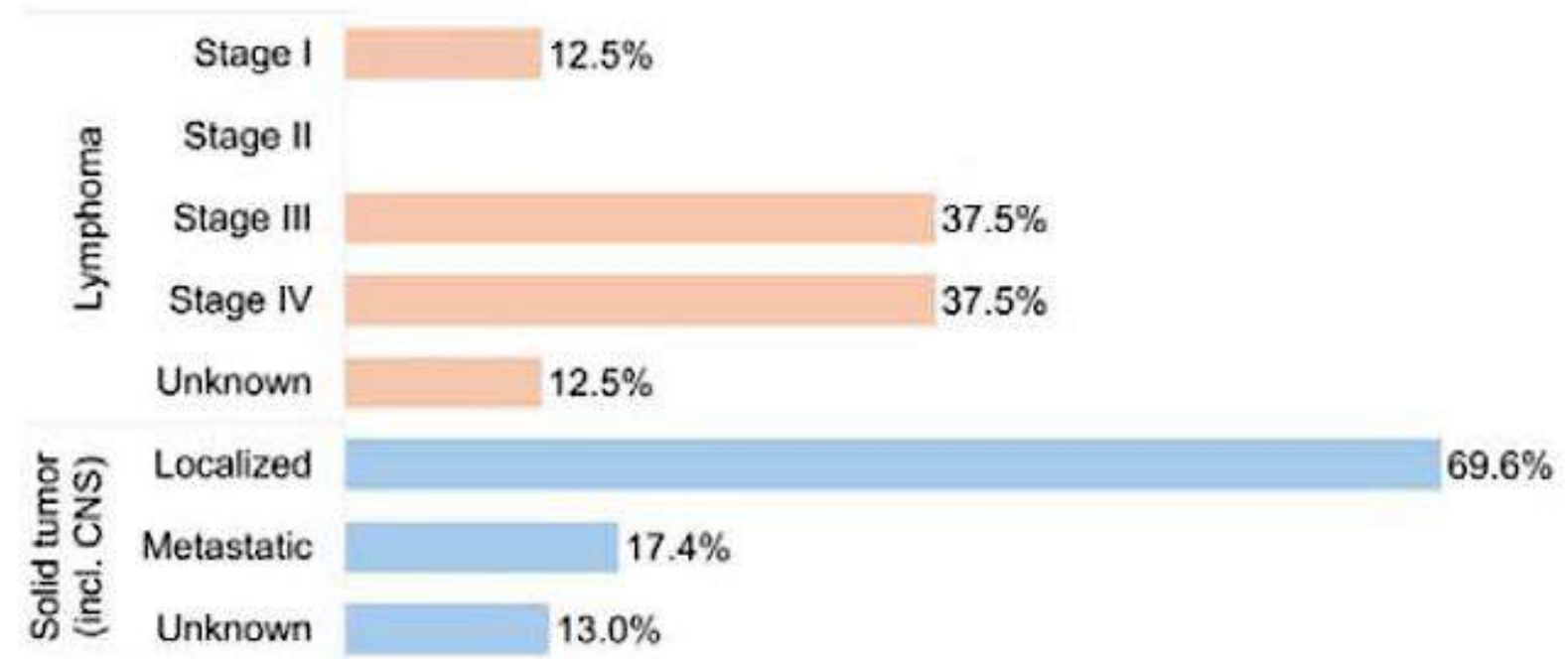
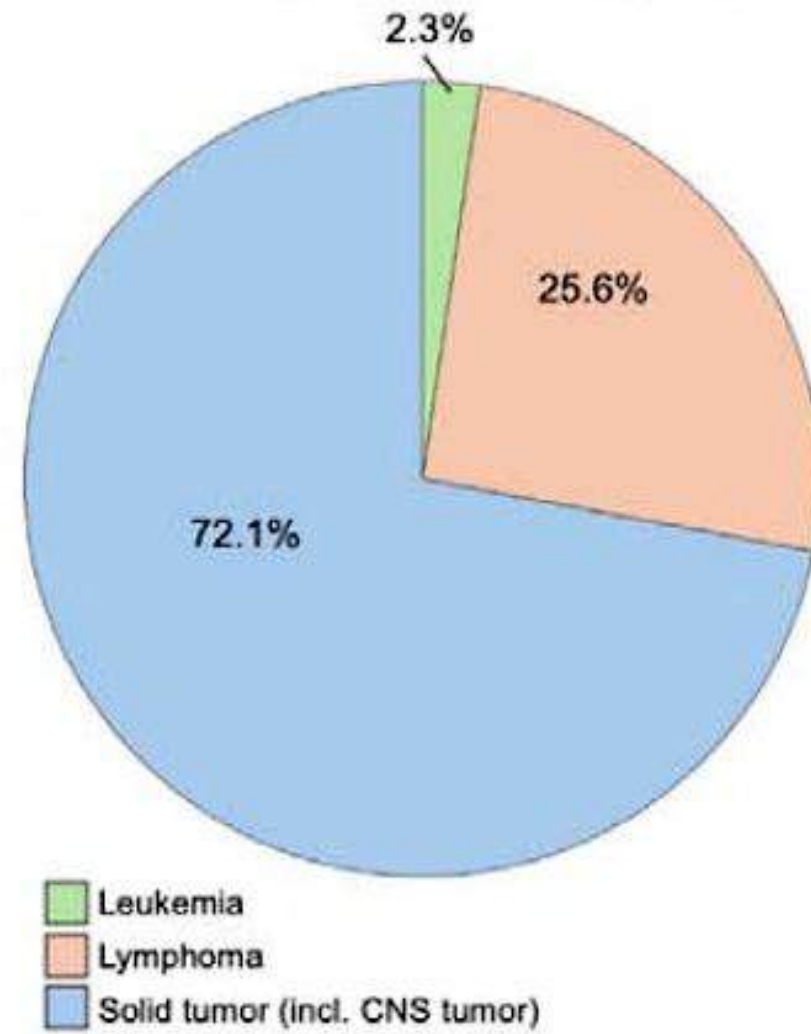
### Age at first malignancy



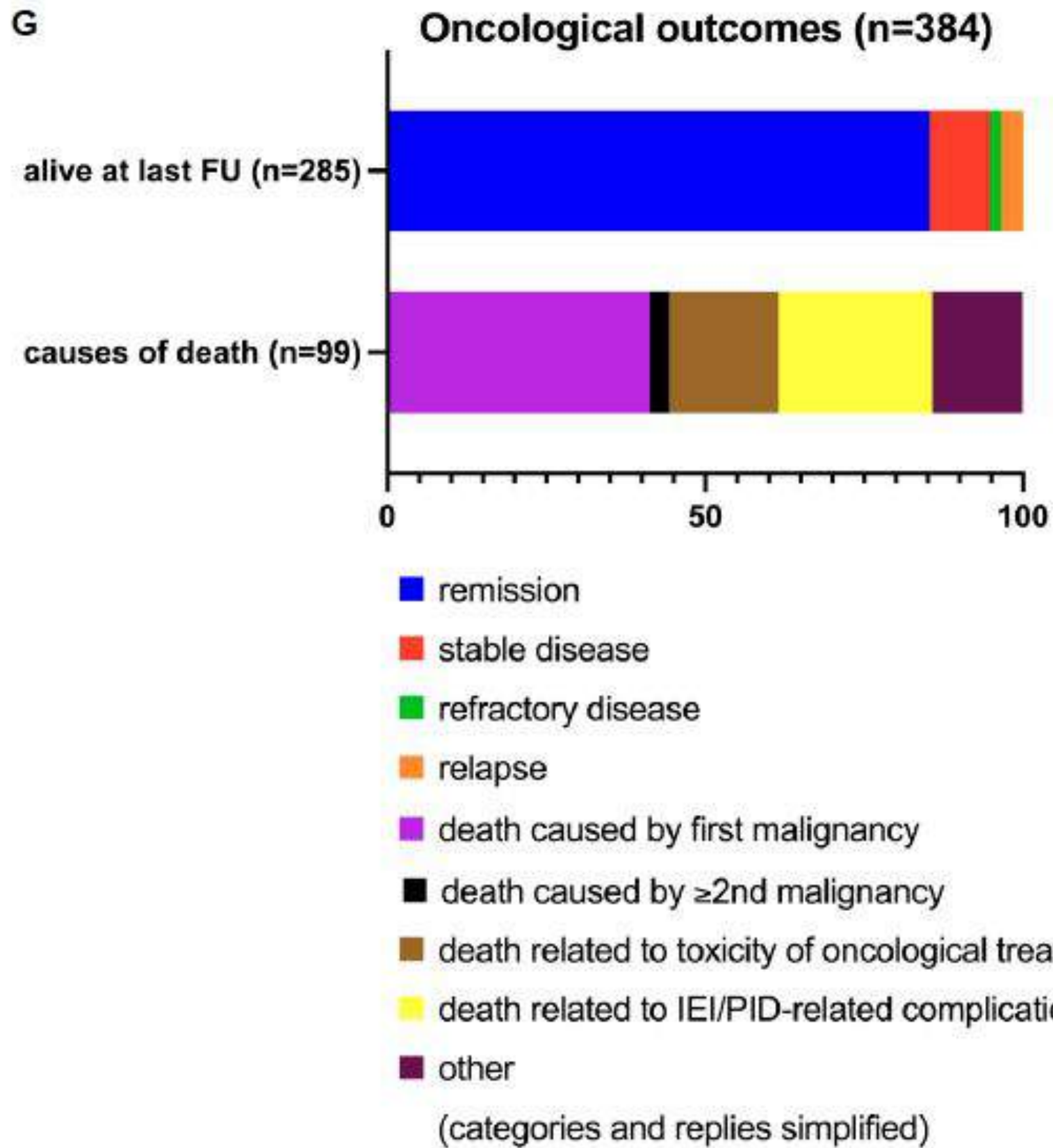
Solid tumor (incl. CNS)



**B Second and higher malignancies (n=43)**



**ESID Registry**

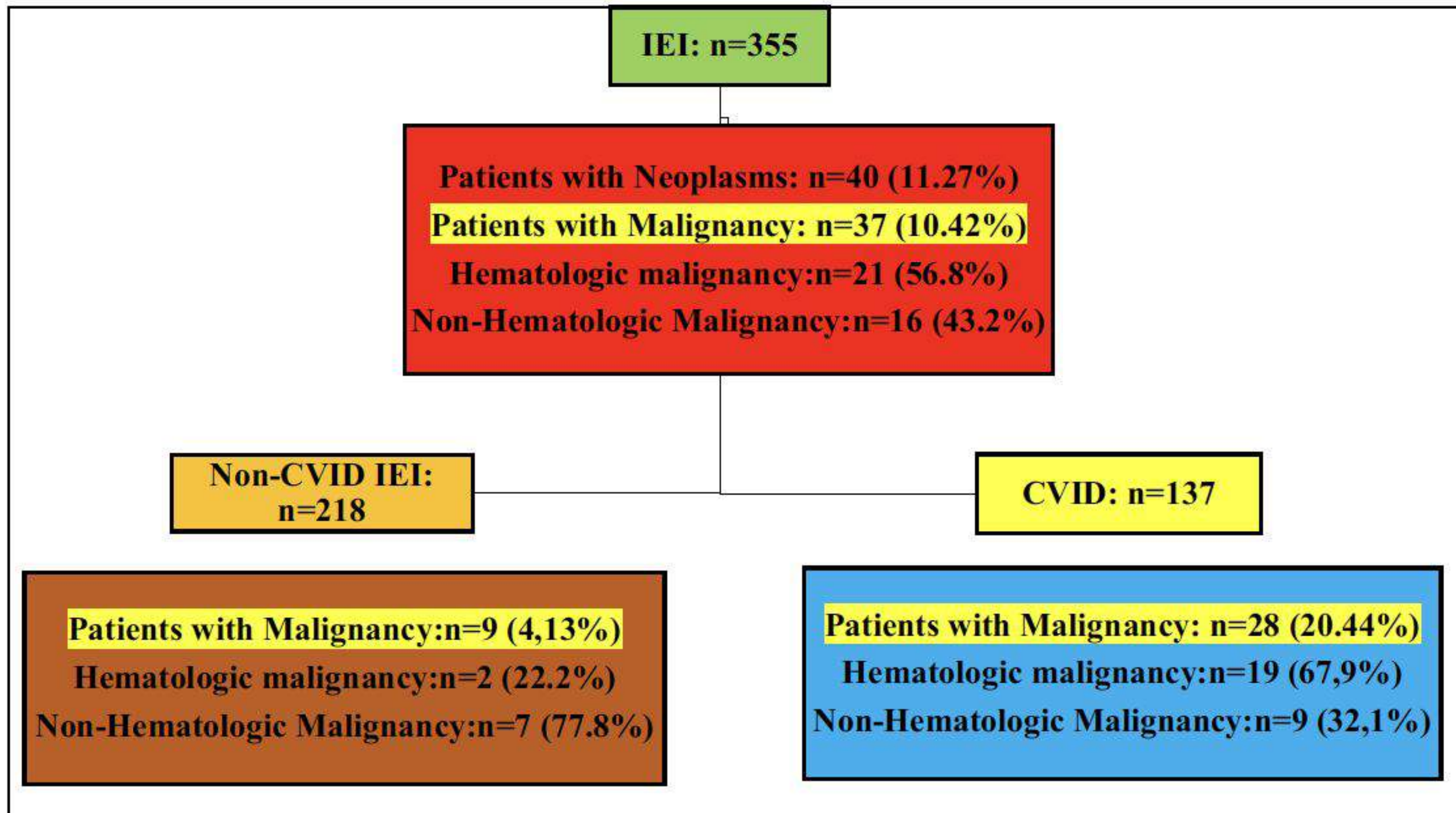


ESID Registry

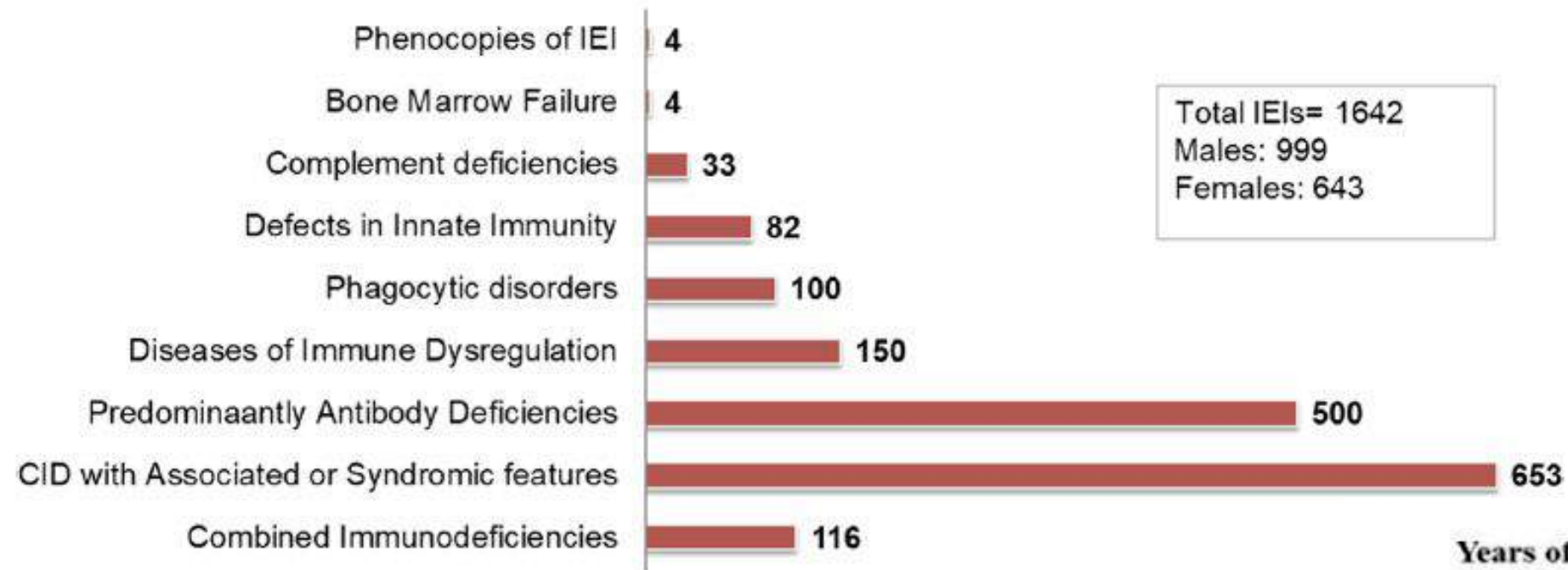
**Table 1** Clinical and demographic characteristics of patients with IEI and associated neoplasms

| Characteristic                                      | Neoplasia (n=40)     | Characteristic                               | Neoplasia (n=40) |
|---|----------------------|--|------------------|
| <b>Age Median (Range)</b>                           | 51.50 (19, 91)       | <b>Neoplasm n(%)</b>                         |                  |
|   |                      | Benign                                       | 3 (7.5%)         |
|   |                      | Malignant                                    | 37 (92.5%)       |
| <b>Gender n(%)</b>                                  |                      | <b>Type of Malignancy n(%)</b>               |                  |
| Female  | 18 (45.0%)           | Hematologic Malignancy                       | 21 (52.5%)       |
| Male  | 22 (55.0%)           | Non-hematologic malignancy                   | 16 (40 %)        |
| <b>History of consanguineous marriage n(%)</b>      | 10 (25.0%)           | <b>Bronchiectasis n(%)</b>                   | 9 (22.5%)        |
| <b>Family History of Malignancy n(%)</b>            | 9 (22.5%)            | <b>Lymphadenopathy n(%)</b>                  | 24 (60.0%)       |
| <b>Complications n(%)</b>                           | 34 (85.0%)           | <b>Hepatomegaly n(%)</b>                     | 12 (30.0%)       |
| <b>Death n(%)</b>                                   | 5 (12.5 %)           | <b>Splenomegaly n(%)</b>                     | 11 (27.5%)       |
| <b>Age at onset of IEI symptoms Median (Range)</b>  | 16.50 (1.00, 67.00)  | <b>Enteropathy n(%)</b>                      | 4 (10.0%)        |
| <b>Age at Diagnosis of IEI Median (Range)</b>       | 45.00 (13.00, 71.00) | <b>Nodular Regenerative Hyperplasia n(%)</b> | 4 (10.0%)        |
| <b>Age at Diagnosis of Neoplasia Median (Range)</b> | 39.50 (12.00, 78.00) | <b>Primary Biliary Cirrhosis n(%)</b>        | 2 (5.0%)         |
| <b>Malignancy History Before IEI Diagnosis n(%)</b> | 22 (60.0%)           | <b>Autoimmunity n(%)</b>                     | 3 (7.5%)         |
| <b>Main Category IUIS n(%)</b>                      |                      | <b>Genetic Results n(%)</b>                  |                  |
| CID   | 4 (10.0%)            | N-Miss                                       | 9                |
| CID-SF  | 2 (5.0%)             | Negative                                     | 12 (38.7 %)      |
| PAD   | 32 (80.0%)           | Positive                                     | 19 (61.3%)       |
| Phenocopies   | 2 (5.0%)             |  |                  |
| <b>Phenotype IUIS n(%)</b>                          |                      | <b>Histological Type n(%)</b>                |                  |
| CVID  | 30 (75.0%)           | Leukemia                                     | 3 (8.1%)         |
| GS  | 2 (5.0%)             | Myeloma                                      | 1 (2.7%)         |
| HIES  | 1 (2.5%)             | Carcinoma                                    | 13 (35.1%)       |
| SIgA  | 1 (2.5%)             | Sarcoma                                      | 2 (5.4%)         |
| CID   | 1 (2.5%)             | Mixed-type                                   | 1 (2.7%)         |
| MHC1D   | 1 (2.5%)             | Hodgkin lymphoma                             | 2 (5.4%)         |
| NBS   | 1 (2.5%)             | Non-Hodgkin lymphoma                         | 15 (40.5%)       |
| SIgM  | 3 (7.5%)             |  |                  |

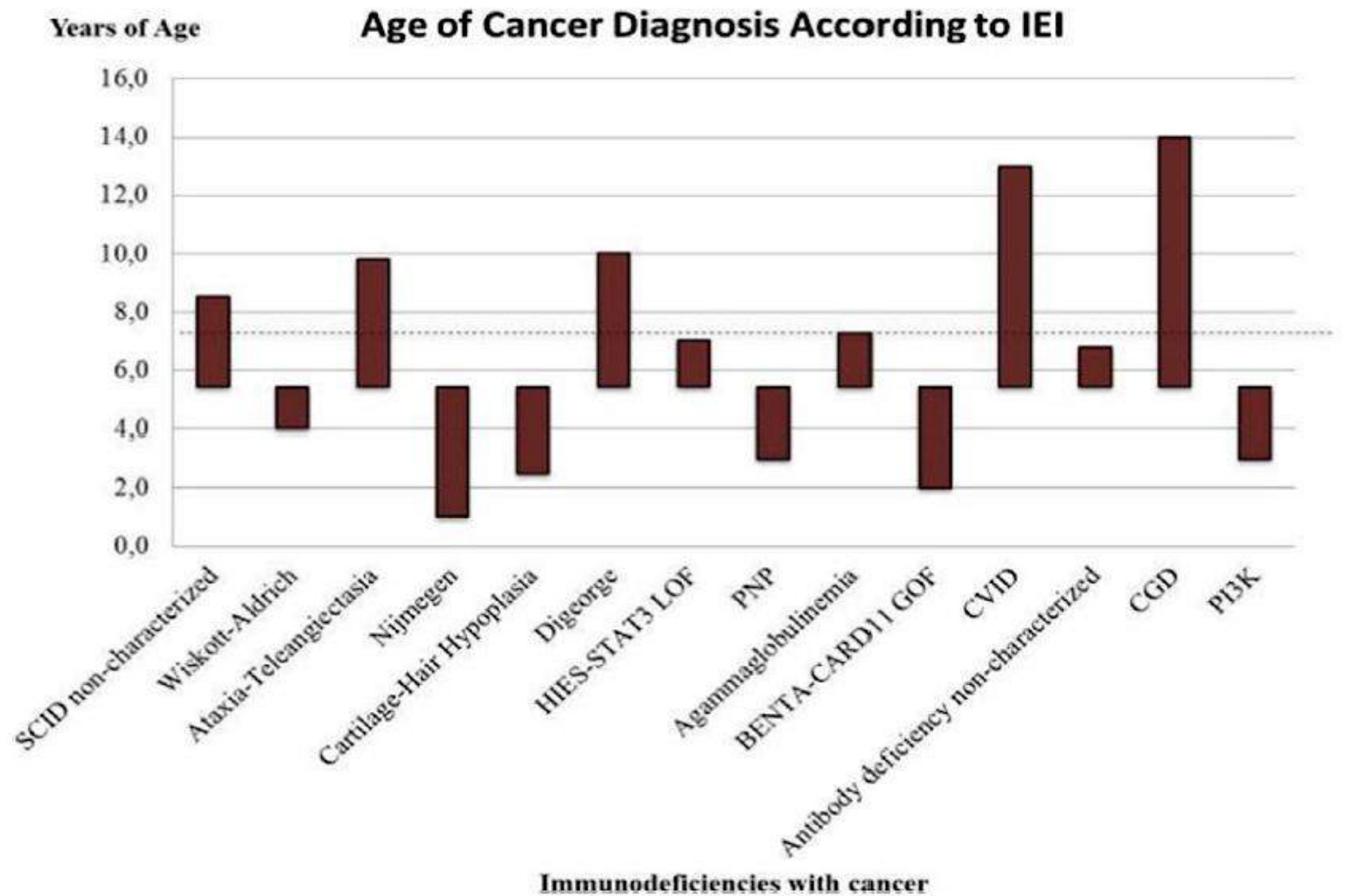
Note: Overall patient distribution by IUIS main categories– CID (n=21), Syndromic CID (n=22), PAD (n=238), Phenocopies (n=2); by phenotypes– CVID (n=137), SIgMD (n=38), SIgAD (n=20), HIES (n=8), MHC1 def. (n=6), NBS (n=2), GS (n=2)



**Distribution of IELs from 1989-2022 in Hospital de Pediatría Garrahan based in 9 main categories (excluding Autoinflammatory syndromes) of IUIS Classification**



Mitchell et al.  
*Journal of Clinical Immunology. 2024;44:138*

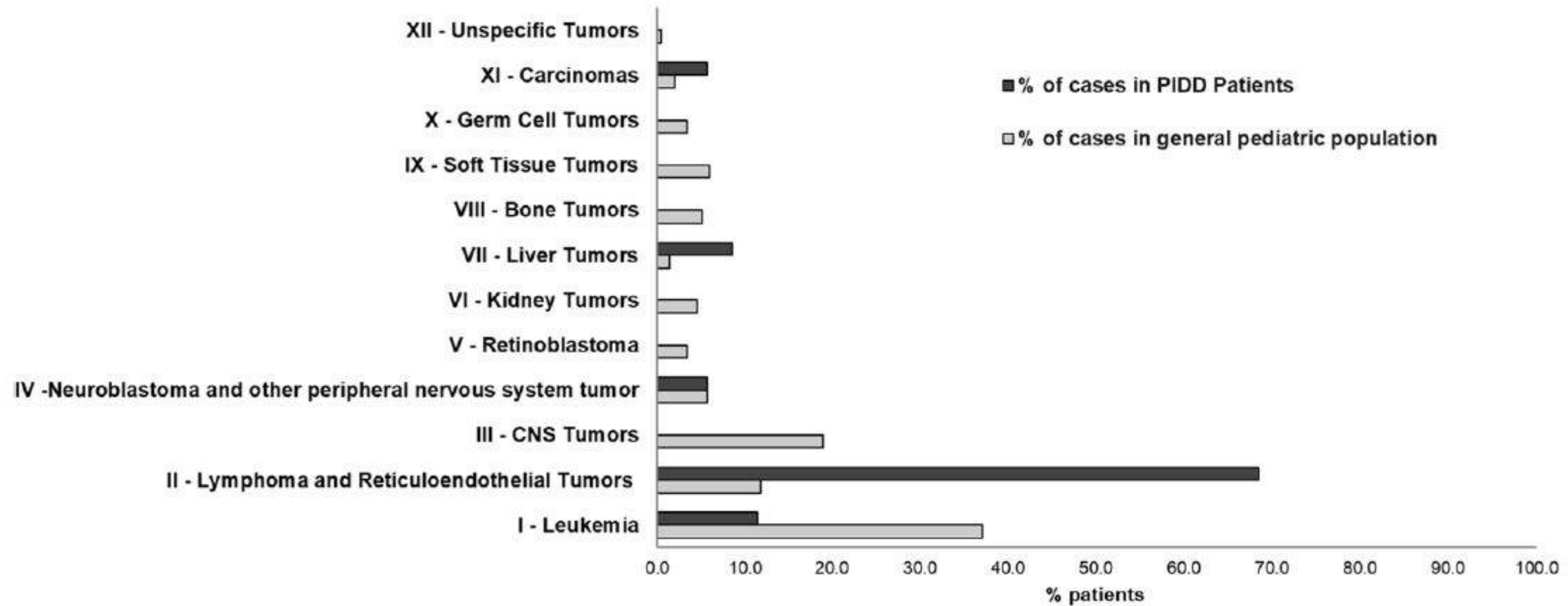


Mitchell et al.  
*JoCI. 2024;44:138*

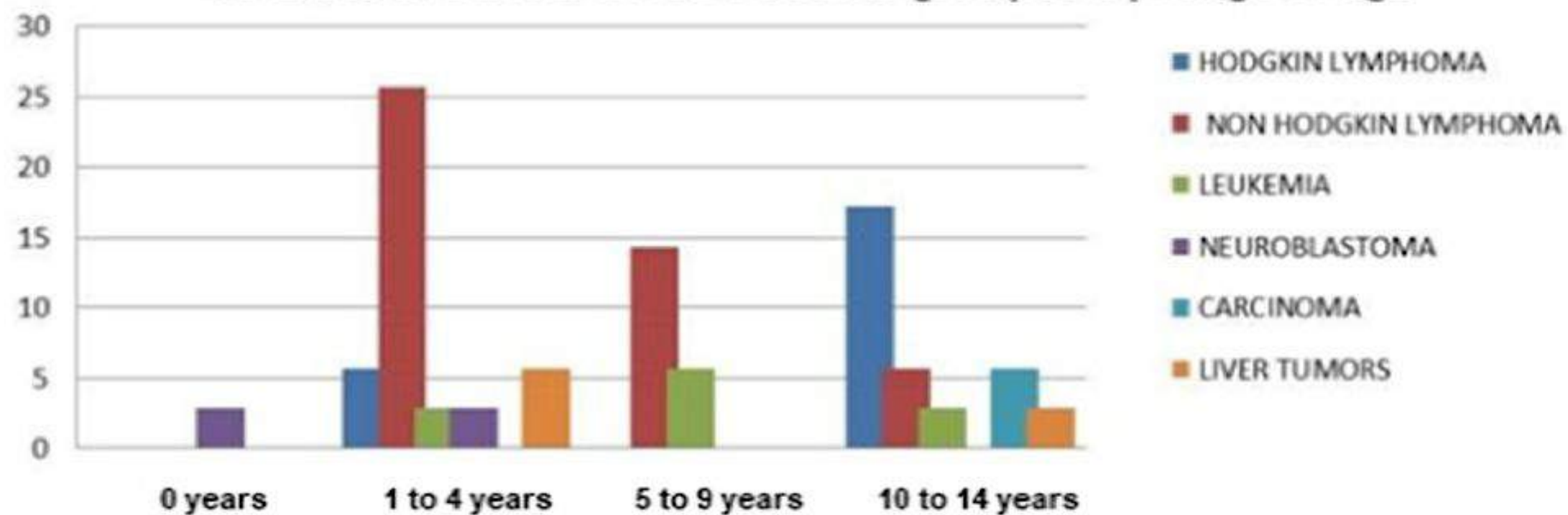
**Table 2** Number of cases and types of cancer in our cohort

|  |  |                             |   |
|--|--|-----------------------------|---|
| 35 Neoplasms (34 patients)   |  |                             |   |
| 24 Lymphomas   |  | 4 leukemias                 | 7 Solid Tumors  |
| 8 Hodgkin:<br>4 Mediastinal (2 EBER +)<br>2 Scleronodular (1 EBER)<br>1 Periorbital<br>1 Hepatic | 16 Non-Hodgkin:<br>9 DLBCL (5 EBER +)<br>4 Burkitt<br>1 Anaplastic Large Cell Lymphoma (ALCL)<br>1 T Cutaneous<br>1 Primary Leptomeningeal Lymphoma (PLML) | 2 B-ALL<br>1 T-ALL<br>1 AML | 2 Hepatocarcinoma<br>2 Cutaneous Squamous Cell Carcinoma<br>2 Neuroblastoma<br>1 Hepatoblastoma |

### Distribution of cases following the International Clasification of Childhood cancer (ICCC)

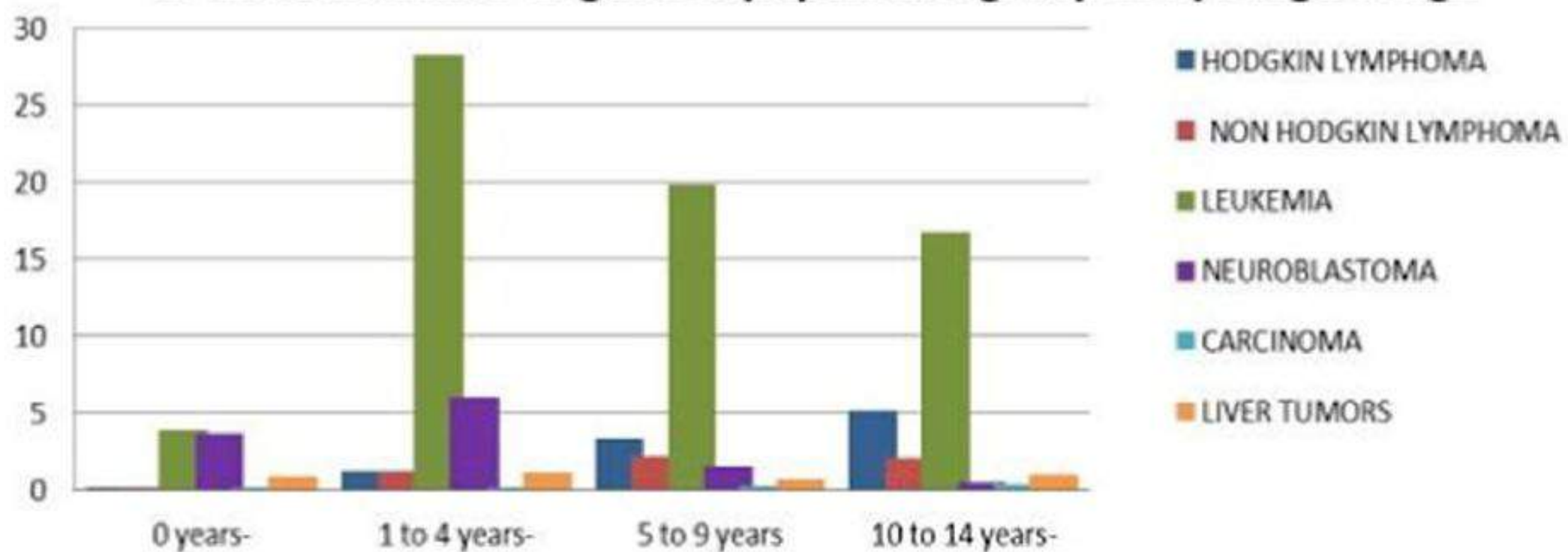


**% Cases in Cancer in PID Patients grouped by range of age**



a

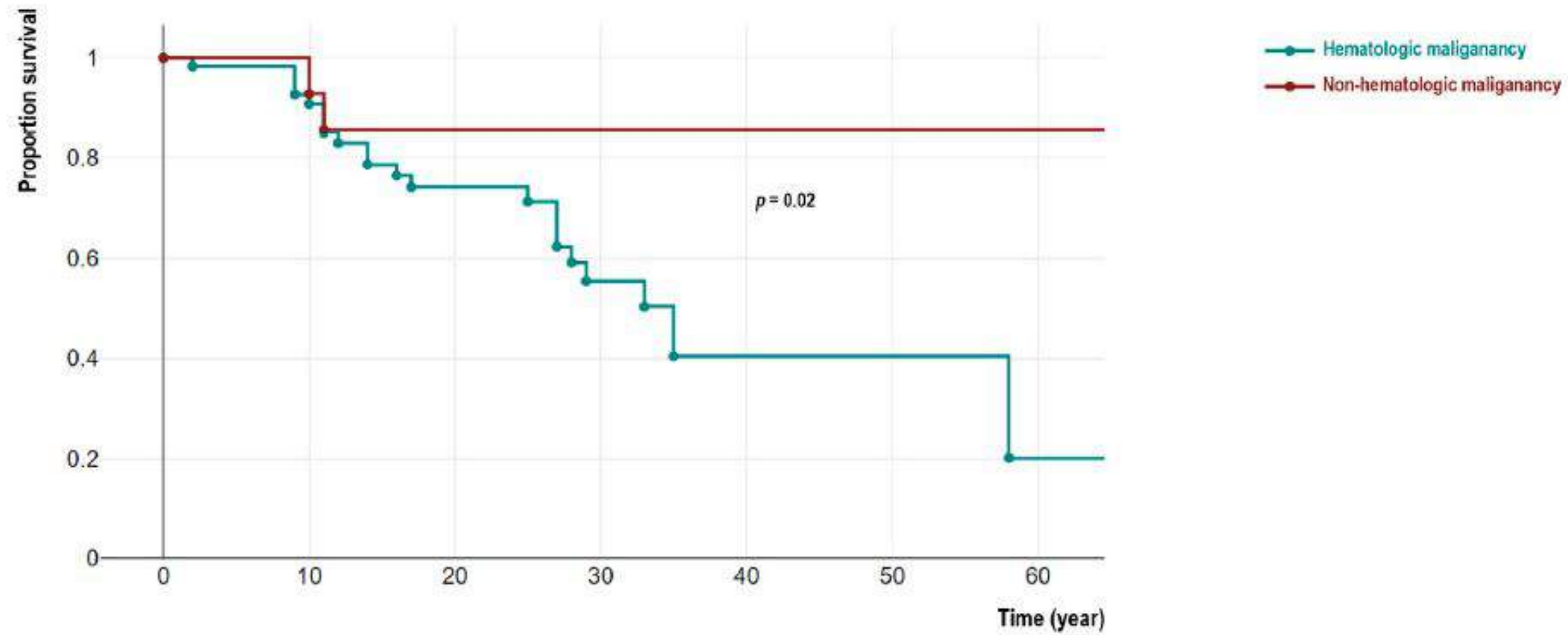
**% Cases in Cancer in general population grouped by range of age**



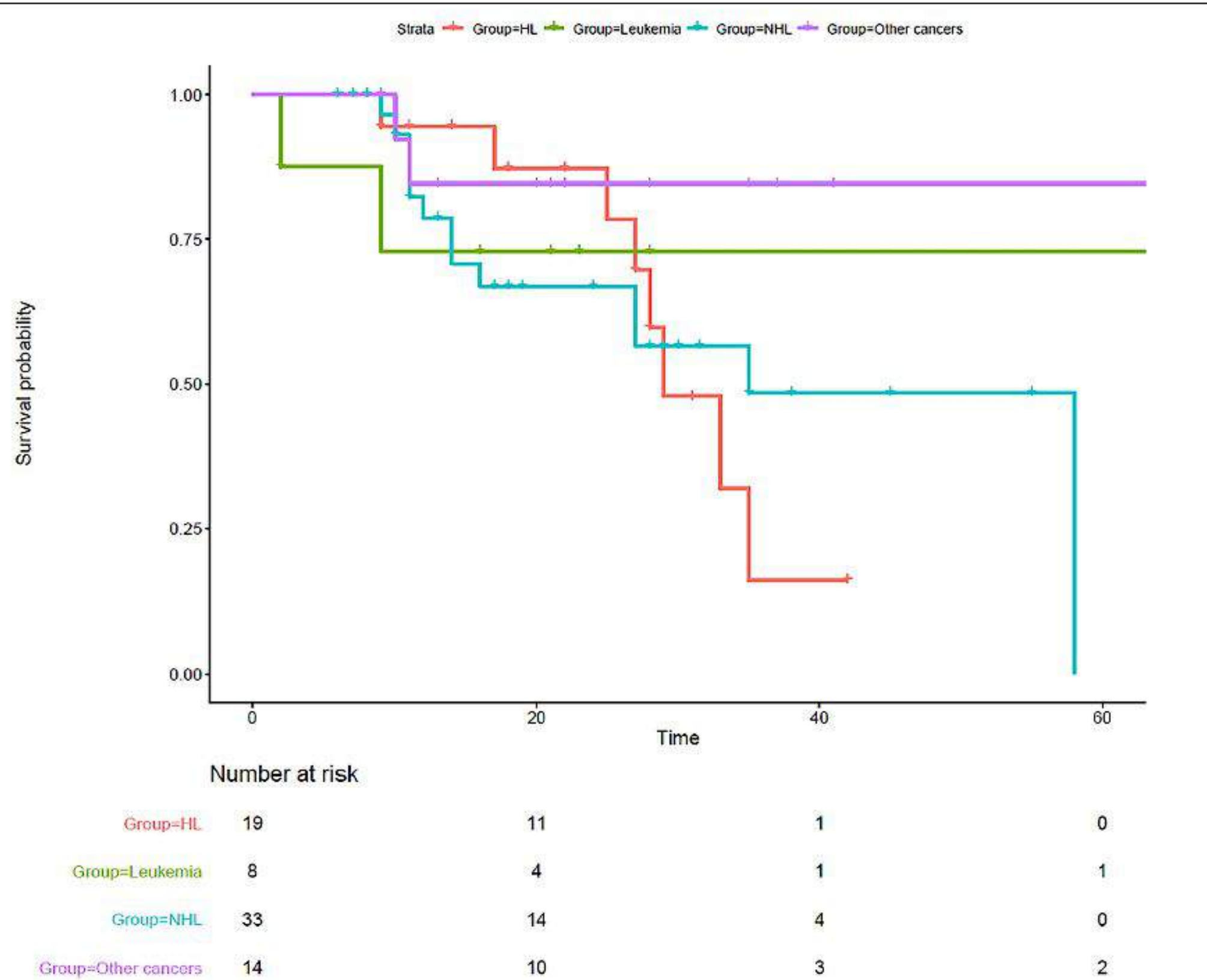
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**Table 1.** Comparison of clinical and immunologic data of IEI patients with non-hematologic and hematologic tumors.

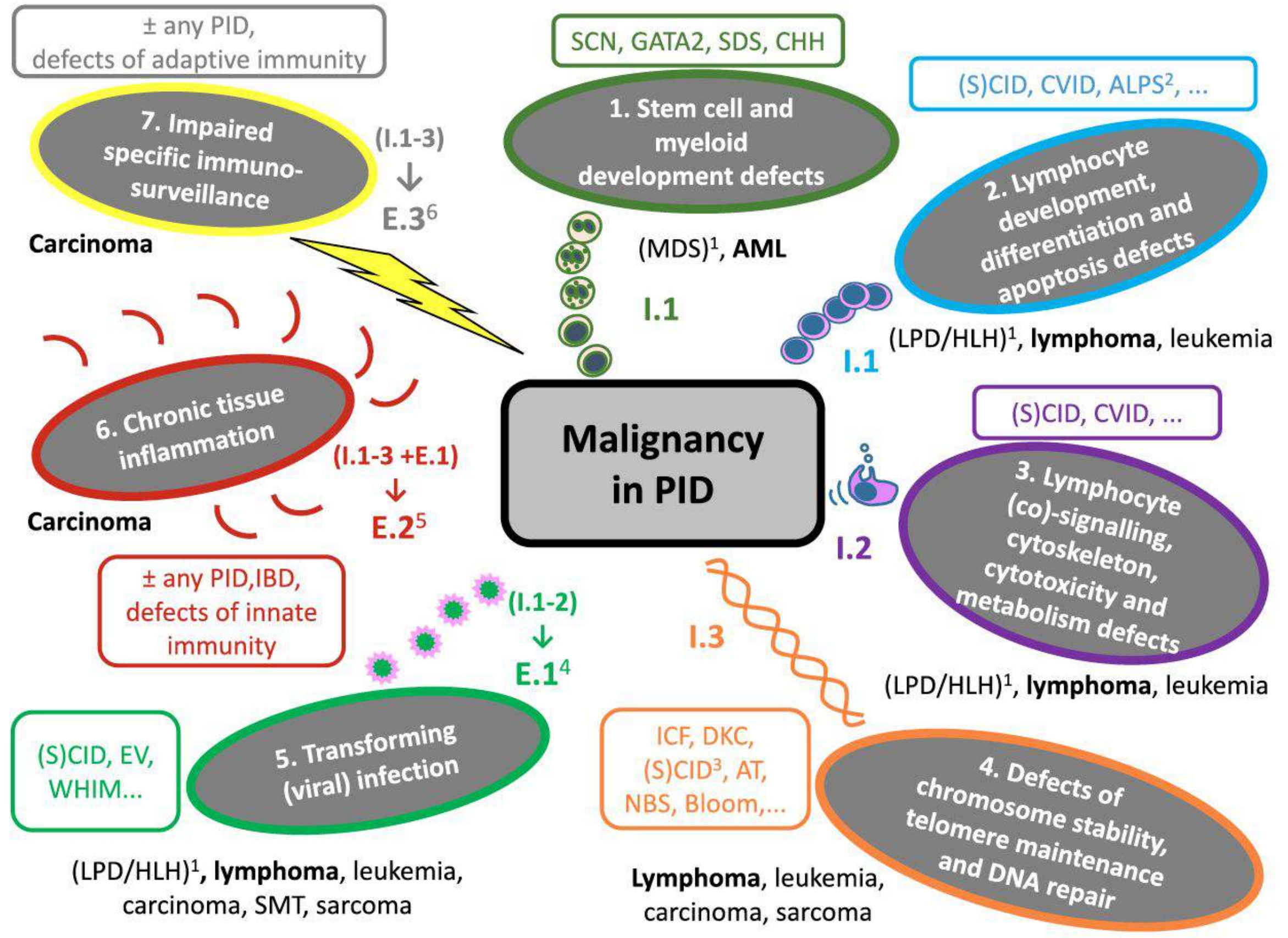
| Parameters  | Hematologic Cancers<br>( <i>n</i> = 117) | Non-Hematologic Cancers<br>( <i>n</i> = 27) | <i>p</i> -Value |
|---|--|---|-----------------|
| Sex ratio (M/F)                                       | 66/51                                    | 18/9  | 0.32            |
| Parental consanguinity (%)                            | 77 (65.8)                                | 20 (74.0)                                   | 0.40            |
| Mortality (%)   | 43 (36.7)                                | 5(18.5)                                     | 0.07            |
| Median age at IEI onset, year (IQR)                   | 3.5 (1.5–8.0)                            | 5.0(2.5–12.2)                               | 0.22            |
| Median age at the diagnosis of malignancy, year (IQR) | 13.0 (6.0–20.5)                          | 19.2 (12.0–28.0)                            | 0.08            |
| Median age at the time of study *, year (IQR)         | 17.0 (10.9–24.2)                         | 27.4 (22.7–36.4)                            | 0.01 *          |
| Otitis media (%)                                      | 39 (33.3)                                | 7 (25.9)                                    | 0.27            |
| Sinusitis (%)   | 43 (36.7)                                | 12 (44.4)                                   | 0.28            |
| Pneumonia (%)   | 60 (51.3)                                | 13 (48.1)                                   | 0.76            |
| Bronchiectasis (%)                                    | 23 (19.6)                                | 11 (40.7)                                   | 0.02 *          |
| Severe infections (%)                                 | 4 (3.4)                                  | 0   | 0.98            |
| Chronic enteropathy (%)                               | 14 (11.9)                                | 11 (40.7)                                   | <0.001 *        |
| Failure to thrive (%)                                 | 27 (23.0)                                | 7 (25.9)                                    | 0.75            |
| Autoimmunity (%)                                      | 18 (15.3)                                | 4 (14.8)                                    | 1.00            |
| Allergy and atopic diseases (%)                       | 26 (22.2)                                | 4 (14.8)                                    | 0.39            |
| Lymphoproliferation (%)                               | 37(31.6)                                 | 6 (22.2)                                    | 0.33            |



**Figure 2.** Comparison of survival analysis of cohort of IEI patients with hematologic and non-hematologic malignancies.



**Fig. 4** Survival analysis of cohort of 82 IEI patients with malignancies based on the type of cancers



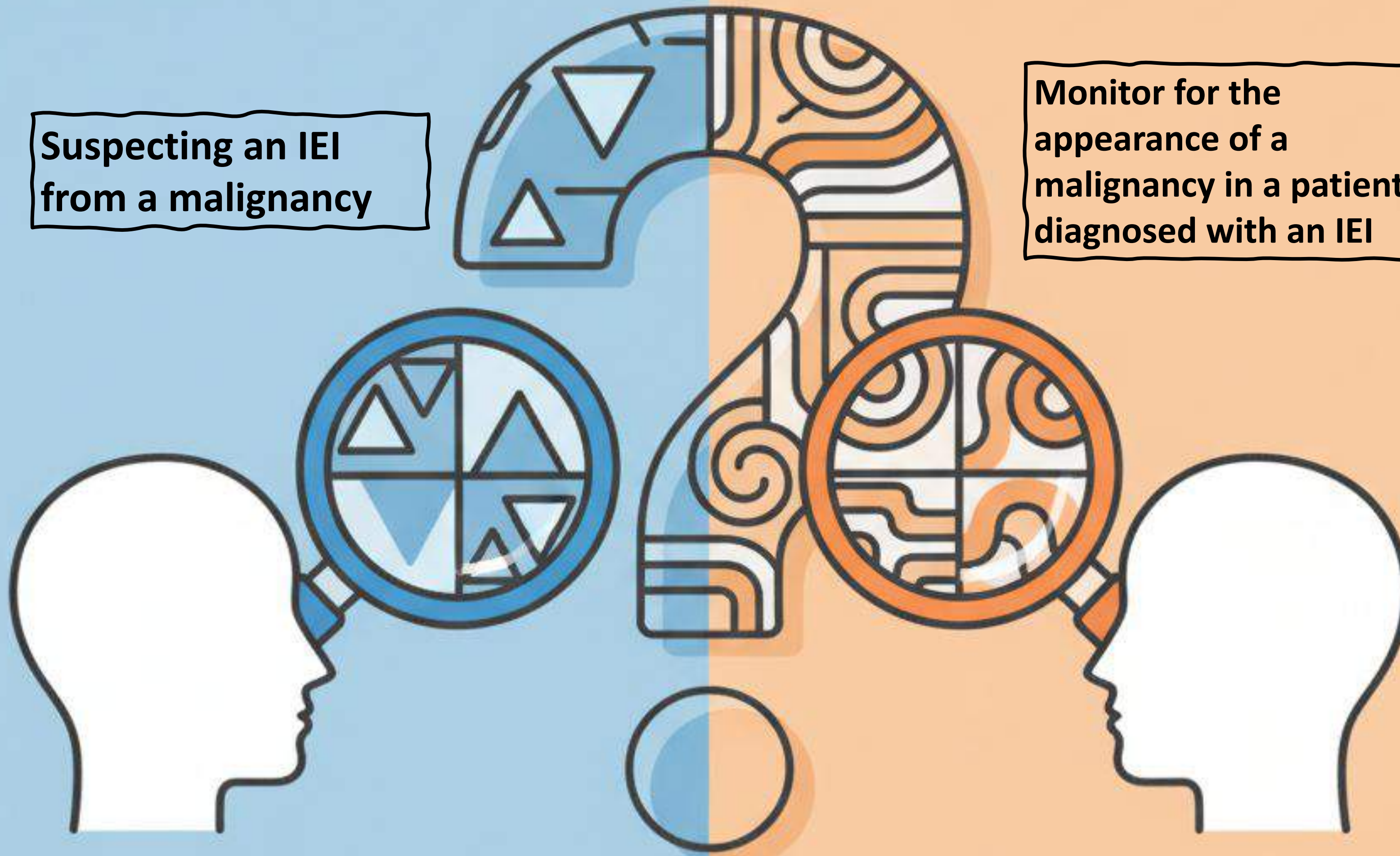
**Table 1.** Examples of malignant diseases and inborn errors of immunity associated with oncogenesis mechanisms.

| Type of malignancies   | Inborn errors of immunity   | Main mechanisms of oncogenesis  |
|--|---|---|
| MDS, AML   | Congenital neutropenias<br>Chédiak-Higashi syndrome   | Defects in the development of stem and myeloid cells                          |
| Lymphomas, leukemias, HLH  | CVID, ALPS  | Defects in lymphocyte development, differentiation, and apoptosis             |
|  | CVID, combined deficiencies of T and B cells  | Defects in co-signaling, cytoskeleton, cytotoxicity, or lymphocyte metabolism |
| Lymphomas, leukemias, carcinomas, sarcomas                           | Ataxia telangiectasia, nijmegen syndrome, combined deficiencies of T and B cells, congenital dyskeratosis | Defects in DNA repair, telomere maintenance, and chromosomal stability        |
| Lymphomas, leukemias, carcinomas, sarcomas, HLH, smooth muscle tumor | WHIM, epidermodysplasia verruciformis, combined deficiencies of T and B cells                             | Viral infections  |
| Carcinomas   | Innate immunity defects, IBD, virtually any IEI   | Chronic tissue inflammation   |
|  | Adaptive immunity defects, virtually any IEI  | Impaired immune surveillance  |

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CVID: common variable immunodeficiency; ALPS: autoimmune lymphoproliferative syndrome; HLH: hemophagocytic lymphohistiocytosis; WHIM: warts, hypogammaglobulinemia, infections, and myelocathexis; IBD: inflammatory bowel disease; IEI: inborn errors of immunity. Adapted from Hauck et al.<sup>6</sup>.

**Suspecting an IEI  
from a malignancy**

**Monitor for the  
appearance of a  
malignancy in a patient  
diagnosed with an IEI**



# Critical Oncological Warning

## Signs

### Suspicious Tumor

#### Manifestations

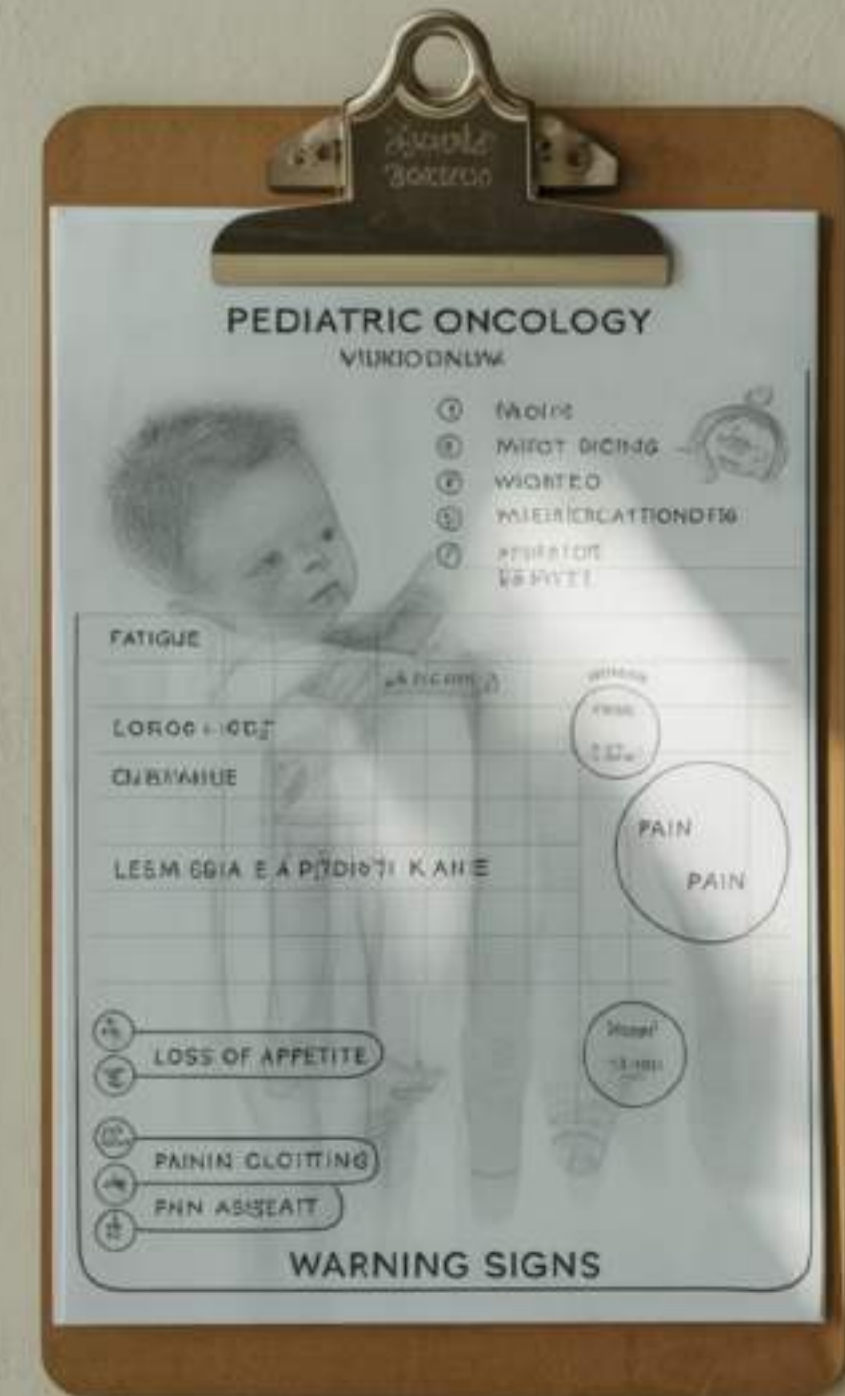
- Solid tumor in pediatric or young adult age (<30-40 years)
- Multiple synchronous or metachronous primary tumors
- Exaggerated toxicity to chemotherapy or radiotherapy
- Aggressive histology or atypical location

### Associated Infectious

#### Manifestations

- Persistent and refractory HPV infections
- Chronic mucocutaneous candidiasis
- Recurrent cutaneous viral infections
- Multiple and resistant genital warts

The presence of a family history of IEI, consanguinity, or other immunodeficiency manifestations reinforces diagnostic suspicion and warrants comprehensive immunological investigation.



**Table 3.** Warning signs for the pediatric hemato-oncologist.

| <b>Presenting history</b> | <b>Signs</b>   |
|---------------------------|--|
| Family history            | 1. IEI case in the family<br>2. Multiple miscarriages<br>3. Unexplained infant death<br>4. Consanguinity   |
| Past medical history      | 5. Failure to thrive or unexplained diarrhea<br>6. Recurrent sinopulmonary infection (eg, pneumonia, sinusitis, otitis media)<br>7. Severe bacterial, viral or fungal infection (eg, septicemia, encephalitis, meningitis, osteomyelitis, mastoiditis)<br>8. Deep skin or inner organ abscesses<br>9. Persistent mucocutaneous fungal infection or deep mycotic infection<br>10. Multiple warts or mollusca of the skin<br>11. Severe eczema or dermatitis<br>12. Autoimmunity or multiple autoimmunity (eg, inflammatory bowel disease, type 1 diabetes mellitus, cytopenias, vasculitis)<br>13. Hepato/splenomegaly and/or benign lymphadenopathy<br>14. Recurrent parenteral antibiotic courses |
| Clinical features         | 15. Microcephaly<br>16. Developmental delay<br>17. Cerebellar ataxia<br>18. Ocular or cutaneous telangiectasia<br>19. Short stature/osseous dysplasia<br>20. Facial dysmorphisms<br>21. Tonsil/lymph nodes atrophy<br>22. Bronchiectasis/granulomatous inflammation  |

**Table 3.** Main inborn errors of immunity to be considered according to the malignancy found.

| Malignancies                             | Inborn errors of immunity                         |
|--|---|
| Non-Hodgkin and Hodgkin lymphomas, ALL   | Combined deficiencies of T and B cells not severe |
|  | Defects of DNA repair                             |
|  | Predominantly antibody deficiencies               |
|  | Diseases of immune dysregulation                  |
| MDS, AML                                 | Congenital neutropenia,                           |
|  | Shwachman-Diamond syndrome,                       |
|  | GATA2 deficiency,                                 |
|  | Diseases with bone marrow failure                 |
| CNS tumors                               | Defects of DNA repair                             |
| Solid tumors                             | Defects of DNA repair                             |
|  | Congenital dyskeratosis (telomeropathies)         |
|  | PTEN deficiency (APDS-like)                       |
|  | CVID  |
| Smooth muscle tumors associated with EBV | Combined deficiencies T and B not severe          |
|  | Ataxia telangiectasia                             |
|  | Deficiency of GATA2                               |
|  | Deficiency of CARMIL2                             |
|  | Deficiency of ZAP70                               |
| Kaposi's sarcoma                         | Wiskott-Aldrich syndrome                          |
|  | XMEN syndrome                                     |
|  | Deficiency of IFN $\gamma$ receptor 1             |
|  | Deficiency of STIM                                |
|  | Deficiency of OX40                                |
| Skin cancer, not melanoma                | Epidermodisplasia verruciformis                   |
|  | Deficiency of DOCK8                               |
|  | Cartilage hair hypoplasia                         |
|  | Xeroderma pigmentosum                             |
|  | Chronic mucocutaneous candidiasis                 |

ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CNS: central nervous system; EBV: Epstein-Barr virus; IFN $\gamma$ : interferon gamma. Adapted from Bosh et al.<sup>16</sup>.

Goudouris et al.

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**Table 1.** Types of IEI and reported malignancies.

| Type of IEI   | Genes  | Frequency | Types of Malignancy   |
|---|--|-----------|---|
| CVID  | <i>CD19, CD20, CD21, CD81, NFKB1/2, IKZF1, TNFRSF13B, TNFRSF13C</i>  | 8.2–21%   | Lymphoma (NHL and MALT mostly), leukemia, gastric carcinoma   |
| IgA deficiency  | Unknown  | Rare      | Lymphoma, gastric carcinoma   |
| X-linked agammaglobulinemia                                 | <i>BTK</i>   | 4.1–6%    | Gastric adenocarcinoma, intestinal carcinoma  |
| SCID  | <i>ADA, AK2, JAK3, IL2RG</i>   | 1.5%      | Lymphoma, leukemia, EBV-related SMTs  |
| SCID with defective DNA repair                              | <i>RAG1/2, NHEJ1, PRKCD, DCLRE1C, LIG4</i>   | Unknown   | Lymphoma, leukemia  |
| CID   | <i>STAT3-GOF, ZAP70, RHOH, ITK, CARD11, MALT1, ORAI1, STIM1, STK4, PIK3CD, PIK3R1, OX40, W1PF1, CTLA4, LRBA, CTPS1, ADA, PNP</i> | Unknown   | Lymphoma, leukemia  |
| AT  | <i>ATM</i>   | 25–40%    | Lymphoma (NHL, HL), leukemia  |
| NBS   | <i>NBN</i>   | 40%       | Lymphoma (NHL, HL), medulloblastoma, neuroblastoma, dysgerminoma, thyroid cancer                    |
| Bloom syndrome  | <i>BLM</i>   | 33%       | Lymphoma, Leukemia, colorectal carcinoma, breast cancer, skin cancers (BCC, SCC), Wilms' tumor      |
| Wiskott-Aldrich syndrome                                    | <i>WAS</i>   | 13–23%    | Lymphoma, leukemia, myelodysplastic syndrome  |
| DOCK8 deficiency  | <i>DOCK8</i>   | 16.3%     | Squamous cell carcinomas (skin, mucosa), NHL  |
| ALPS  | <i>TNFRSF6, TNFSF6</i>   | 25%       | Lymphoma (NHL, HL), myelodysplastic syndrome, ALL   |
| CD40L deficiency (X-linked Hyper IgM syndrome)              | <i>CD40LG</i>  | Unknown   | Liver, biliary tract, pancreatic carcinomas   |
| DiGeorge Syndrome   | 22q11.2 deletion, <i>TBX1</i>  | 0.9%      | Thyroid cancer, hepatoblastoma, neuroblastoma, ALL, lymphoma, Wilms' tumor, teratoid/rhabdoid tumor |
| Myeloid development defects (Severe Congenital Neutropenia) | <i>ELANE, HAX1, GF11, G6PC3</i>  | 21–31%    | Myelodysplastic syndrome, AML   |
| Stem cell development defects                               | <i>GATA2, RMRP, SBDS</i>   | Unknown   | HPV-related carcinoma, EBV-related SMTs, leukemia (AML), myelodysplastic syndrome                   |
| Diseases of Immune Dysregulation-EBV susceptibility         | <i>SH2DIA, XIAP, CD27, CD70, CD137, CARMIL2, GATA2, MAGT1, PRKCD, RASGRP1, CTPS1</i>   | Unknown   | Lymphoma (NHL, HL), EBV-related SMTs  |
| Diseases of Immune dysregulation with colitis               | <i>IL10RA, IL10RB</i>  | Unknown   | Lymphoma  |
| Chronic mucocutaneous candidiasis                           | <i>AIRE, IL17RA, IL17RC, IL17F, STAT1-GOF, TRAF3IP2</i>  | Unknown   | Oral and esophageal SCC   |
| WHIM  | <i>CXCR4</i>   | 30%       | B-cell lymphoma, AML, genital and squamous cell carcinoma   |

**Table 2.** Main types of cancer reported in some inborn immunity errors.

| Inborn errors of immunity   | Reported malignancies                       |
|-----------------------------|---|
| Selective IgA deficiency    | Gastric                                     |
|                             | Lymphomas                                   |
| CVID                        | Lymphomas (more frequently non-Hodgkin)     |
|                             | Gastric                                     |
|                             | Thymus                                      |
|                             | Breast                                      |
|                             | Bladder                                     |
| X-linked agammaglobulinemia | Cervical                                    |
|                             | Gastric                                     |
| Wiskott-Aldrich syndrome    | Colorectal                                  |
|                             | Lymphoma                                    |
| 22q11.2 deletion syndrome   | Lymphoblastic leukemia                      |
|                             | Myelodysplasia-myeloproliferative disorders |
| Ataxia telangiectasia       | Lymphoma                                    |
|                             | Acute leukemia                              |
|                             | Lymphoma                                    |
|                             | Lymphoblastic leukemia                      |
|                             | Breast                                      |
| WHIM syndrome               | Liver                                       |
|                             | Gastric                                     |
|                             | Esophagus                                   |
| WHIM syndrome               | Glioma                                      |
|                             | Lymphoma                                    |
|                             | Genital and squamous carcinoma              |
| WHIM syndrome               | Acute myeloid leukemia                      |

IgA: immunoglobulin A; CVID: common variable immunodeficiency; WHIM: warts, hypogammaglobulinemia, infections and myelocathexis. Adapted from Tiri et al.<sup>13</sup>.

# Attempting to prevent ...





**TABLE 1** | Therapeutic and preventive approaches successfully used or potentially can be implemented to prevent primary immunodeficiency-associated cancer hallmarks.

| Hallmark or Process                       | Agent or Cause  | Drug or Modality   |
|---|---|--|
| <b>Avoiding immune destruction</b>        | EBV infection**                                       | EBV-specific cytotoxic T lymphocytes   |
|   | Costimulatory agonist<br>Regulatory T cells**         | Anti-GITR, anti-ICOS, anti-OX40, and anti-CD27<br>Anti-CD25  |
| <b>Deregulating cellular energetics</b>   | Immunometabolism                                      | IDO1 inhibitors, A2AR antagonists, Arginase inhibitors, and Glutaminase inhibitors   |
| <b>Evading growth suppressors</b>         | Dual checkpoint blockade*                             | Anti-CTLA-4 (Ipilimumab), anti-PD1 (Nivolumab), anti-PDL1 (Atezolizumab), anti-TIM3, anti-LAG3, anti-TIGIT, and anti-VISTA |
| <b>Genome instability and mutation</b>    | DNA repair defect*                                    | Decrease radiation exposure  |
|   | Epigenetic changes*                                   | DNMT inhibitors and HDAC inhibitors  |
| <b>Inducing angiogenesis</b>              | RAS-associated autoimmune leuko-proliferative disease | Cetuximab, Pantitumumab, and Bevacizumab   |
| <b>Sustaining proliferative signaling</b> | EBV infection**                                       | Butyrate and Ganciclovir   |
|   | HPV infection*  | L1 virus-like particles vaccine  |
|   | BTK activation*                                       | Ibrutinib and Acalabrutinib  |
|   | PI3K activation**                                     | Rifampicin, Buparlisib, Alpelisib, Nemiralisib, and Idelalisib   |
|   | PI3K or NFkB activation**                             | Rituximab, Ibritumomab Tiuxetan, and Tositumomab   |
|   | mTOR activation**                                     | Everolimus   |
|   | MAPK/ERK activation**                                 | Trametinib   |
|   | Stem cell and myeloid development defects             | Bone marrow transplantation, CSF1R inhibitor, and HDAC inhibitors class IIa  |
| <b>Tumor-promoting inflammation</b>       | Cytokines   | JAK inhibitors, TGF inhibitors, and MET inhibitors   |
|   | <i>H. pylori</i> infection*                           | Standard triple therapy consisting of proton pump inhibitor, clarithromycin, and amoxicillin                               |
|   | Chronic inflammation*                                 | Nonsteroidal anti-inflammatory drugs   |

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**Table 5** Suggested malignancy screening for adult patients with IEI

| Component                        | Recommendation   |
|----------------------------------|--|
| Clinical Symptom Assessment      | At each visit (or at least annually), evaluate for new-onset, persistent, or progressive constitutional or organ-specific symptoms suggestive of malignancy, including unexplained weight loss, fever, night sweats, fatigue, altered bowel habits, hematochezia, palpable masses, bone pain, or menstrual irregularity.   |
| Physical Examination             | A central element of malignancy surveillance, physical examination should be performed at every visit—or at least annually—with focused attention on identifying newly emerging, or progressive findings. This includes any abnormal changes in palpable lymph nodes, organomegaly, mucosal or skin lesions, or unexplained physical signs that may warrant further diagnostic evaluation.   |
| Laboratory Investigations        | Annually: complete blood count, peripheral blood smear, biochemical panel, $\beta$ 2-microglobulin, LDH, serum free light chains ( $\kappa/\lambda$ ), and lymphocyte subset analysis. Bone marrow biopsy should be considered in cases of unexplained cytopenias or abnormal smear findings.  |
| Oncogenic Pathogen Screening     | Employ PCR-based testing for oncogenic viruses—such as EBV, HPV, HHV-8, HBV, and HCV—when clinically indicated, regardless of IVIG treatment status. For <i>H. pylori</i> , prioritize non-serologic diagnostic methods (e.g., stool antigen or urea breath test) due to potential serologic interference. Patients eligible for vaccination should be referred for age- and risk-appropriate immunization against oncogenic viruses (e.g., HBV, HPV). |
| Imaging and Endoscopy            | At least annually or as clinically indicated: perform abdominal and superficial ultrasonography (including lymph node stations) and chest radiography or CT. Baseline upper and lower GI endoscopies are recommended for all patients; repeat every 2 years if asymptomatic. Perform promptly in symptomatic cases, regardless of timing   |
| Age-Appropriate Cancer Screening | Include routine screenings (e.g., cervical, breast, colorectal cancer) per national or international guidelines, unless contraindicated due to immunodeficiency or comorbidities.  |
| Risk-Based Stratification        | Patients belonging to IUIS group IX (Bone Marrow Failure), II (Combined immunodeficiencies with associated or syndromic features), and IV (Diseases of Immune Dysregulation), and those with monogenic defects (e.g., NBS, XLP, Fanconi anemia, DOCK8 deficiency, AT, WAS, CVID, CHH, congenital neutropenia, SIgAD, agammaglobulinemia) should be prioritized for intensive malignancy surveillance due to higher cancer susceptibility (1,8).        |

In terms of treatment, chemotherapy regimens generally do not differ from those used for immunocompetent patients, except for individual modulation of dosing chemotherapy mainly in the defect of DNA repair, and for the execution of a aggressive anti-infective prophylaxis

## Take Home Messages ...

Early identification of malignancies as an initial manifestation of IEI (or at any time) is relevant and can save lives.

Hematologic malignancies are more common; however, the risk of solid tumors significantly exceeds that of the general population, with a higher risk in men.

Defective immunosurveillance, chronic inflammation, oncovirus, and genomic instability constitute the pathophysiological pillars that explain the increased oncological risk in this vulnerable population.

Absolute contraindication to radiotherapy and rigorous monitoring for chemotherapy toxicity in A-T, Fanconi, Bloom, and NBS (DNA repair defects).

Need for evidence in IEI: oncological surveillance strategies, systematic screenings, specific protocols per mutation.



**¡Muchas gracias por la  
invitación y atención!**

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