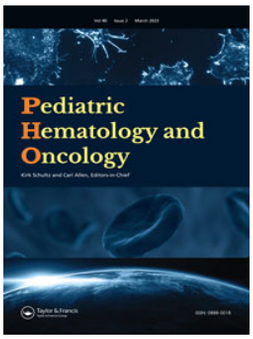

Taylor & Francis
Taylor & Francis Group

Pediatric Hematology and Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipho20

How to recognize inborn errors of immunity in a child presenting with a malignancy: guidelines for the pediatric hemato-oncologist

Jutte van der Werff ten Bosch, Eva Hlaváčková, Charlotte Derpoorter, Ute Fischer, Francesco Saettini, Sujal Ghosh, Roula Farah, Delfien Bogaert, Rabea Wagener, Jan Loeffen, Chris M Bacon & Simon Bomken

To cite this article: Jutte van der Werff ten Bosch, Eva Hlaváčková, Charlotte Derpoorter, Ute Fischer, Francesco Saettini, Sujal Ghosh, Roula Farah, Delfien Bogaert, Rabea Wagener, Jan Loeffen, Chris M Bacon & Simon Bomken (2023) How to recognize inborn errors of immunity in a child presenting with a malignancy: guidelines for the pediatric hemato-oncologist, Pediatric Hematology and Oncology, 40:2, 131-146, DOI: 10.1080/08880018.2022.2085830

To link to this article: https://doi.org/10.1080/08880018.2022.2085830

Published online: 01 Aug 2022.

PEDIATRIC HEMATOLOGY AND ONCOLOGY
2023, VOL. 40, NO. 2, 131–146
https://doi.org/10.1080/08880018.2022.2085830

How to recognize inborn errors of immunity in a child presenting with a malignancy: guidelines for the pediatric hemato-oncologist

Jutte van der Werff ten Bosch[a], Eva Hlaváčková[b,c,d], Charlotte Derpoorter[e,f,g], Ute Fischer[h], Francesco Saettini[i], Sujal Ghosh[h], Roula Farah[j], Delfien Bogaert[k,l], Rabea Wagener[m], Jan Loeffen[m], Chris M Bacon[n,o], and Simon Bomken[n]

[a]Department of paediatrics, UZ Brussel, Brussels, Belgium; [b]Department of Clinical Immunology and Allergology, St. Anne s University Hospital in Brno, Brno, Czech Republic; [c]Faculty of Medicine, Masaryk University, Brno, Czech Republic; [d]Department of Pediatric Oncology, Brno University Hospital, Brno, Czech Republic; [e]Department of Pediatric Hematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium; [f]Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium; [g]Cancer Research Institute Ghent (CRIG), Ghent, Belgium; [h]Department for Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany; [i]Department of Pediatric Hematology, Fondazione MBBM, University of Milano-Bicocca, Monza, Italy; [j]Department of pediatrics, University-Medical-Center-Rizk-Hospital, Beirut, Lebanon; [k]Department of Pediatrics, Division of Pediatric Hemato-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium; [l]Primary Immunodeficiency Research Lab, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, Ghent University Hospital, Ghent, Belgium; [m]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; [m]Translational & Clinical Research Institute, Wolfson Childhood Cancer Research Centre, Newcastle University, Newcastle upon Tyne, UK; [o]Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

ABSTRACT

Inborn errors of immunity (IEI) are a group of disorders caused by genetically determined defects in the immune system, leading to infections, autoimmunity, autoinflammation and an increased risk of malignancy. In some cases, a malignancy might be the first sign of an underlying IEI. As therapeutic strategies might be different in these patients, recognition of the underlying IEI by the pediatric hemato-oncologist is important. This article, written by a group of experts in pediatric immunology, hemato-oncology, pathology and genetics, aims to provide guidelines for pediatric hemato-oncologists on how to recognize a possible underlying IEI and what diagnostic tests can be performed, and gives some consideration to treatment possibilities.

ARTICLE HISTORY
Received 18 February 2022
Revised 16 May 2022
Accepted 27 May 2022

KEYWORDS
Inborn errors of immunity; investigation; malignancy; pediatric; primary immunodeficiency

Introduction

Inborn errors of immunity (IEI), are a group of disorders caused by genetic defects in the immune system, leading to infections, autoimmunity, autoinflammation and an

CONTACT Jutte van der Werff ten Bosch jvdwerff@uzbrussel.be Department of Pediatrics, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.

increased risk of malignancy.[1–10] A majority of those malignancies are of lymphoid origin, but other malignancies occur as well.[1–8] Over 400 different IEI were described, a number likely to increase.[10] The incidence of IEI is estimated to be approximately 1 in 1200,[11] meaning that pediatric hemato-oncologists (PHO) are very likely to be confronted with malignancies in children with IEI. In many cases, the IEI diagnosis has already been established before tumor onset, but in some children, the malignancy can be the presenting feature of their underlying IEI, as important subgroup of patients is un- or misdiagnosed because of the variable phenotype and lack of awareness among physicians.[12–14]

Malignancy is a leading cause of mortality in some groups of patients with IEI, with the relative risk from disease-related and treatment-related mortality varying between subtypes. Consequently, defining uniform management guidelines remains challenging.[15,16] Similar to pediatric patients with other cancer predisposition syndromes, such as trisomy 21, some children with an underlying IEI experience increased toxicity and/or decreased efficacy of standard cancer treatment but this remains difficult to predict, even within a single IEI subtype but some children with co-existent IEI and malignancy might benefit from dose modifications of chemotherapy, avoidance of radiotherapy, increased use of antimicrobial prophylaxis, or immunoglobulin replacement therapy. Conversely, for some patient groups, cancer recurrence poses the greatest threat and dose reductions may not be uniformly desirable.[16] The role of early hematopoietic stem cell transplantation (HSCT) should be considered in some patients, both to achieve malignant disease control and treat the underlying IEI. However, before any of these treatment modifications can be implemented, the diagnosis of IEI has to have been considered (Table 1).

Guidelines have been proposed to improve diagnosis of genetic predisposition syndromes in cancer patients.[17–20] These guidelines do not include specific features of immunodeficiency/immunodysregulation. On the other hand, the warning signs developed by immunologists to help identify patients with a possible IEI do not fully integrate the importance of malignancies.[21] We have brought together pediatric hematologists/oncologists, immunologists, diagnosticians and geneticists to create a shared approach to the identification of IEI in children presenting with malignancy. We aim to inform the pediatric hemato-oncologist about the necessity to think about an underlying IEI, review the differing risks of malignancy according to IEI subtypes and propose warning signs that can be used to identify pediatric cancer patients who

Table 1. Impact of IEI on the malignancy diagnosis, treatment and prognoses.

- Predisposition to malignancy (impaired cancer immunosurveillance and cancer immunoediting)/increased relapse and second malignancy risk
- Increased incidence of rare and/or more aggressive malignancy in certain age groups
- Increased chemotherapy toxicity
- Increased morbidity and mortality based on underlying IEI
- Indicated avoidance of radiotherapy in certain diagnostic groups (DSB group)
- Risk of severe infection during cancer treatment, based on underlying IEI (CID v predominantly antibody deficiencies)
- Possible prolonged recovery of hematological parameters after chemotherapy
- IEI-based end organ damage (eg, bronchiectasis/granulomatous inflammation)
- IEI-based autoimmunity (eg, cytopenias, inflammatory bowel disease)
- IEI-based immunodysregulation

should be investigated for a possible IEI. We discuss the most common tests used in the work up of an IEI patient and their value in the setting of a newly diagnosed lymphoid malignancy.

Primary immunodeficiencies

The latest classification distinguishes 10 IEI categories: I - combined immunodeficiencies (CID); II - CID with associated or syndromic features; III - predominantly antibody deficiencies (PAD); IV - diseases of immune dysregulation; V - congenital defects of phagocytes; VI - defects in intrinsic and innate immunity; VII - autoinflammatory diseases; VIII - complement deficiencies; IX - bone marrow failure; X - phenocopies of inborn errors of immunity.[10] The incidence of cancer varies between and within these categories of IEI.[21] The prevalence of specific conditions also differs greatly and is influenced by ethnic background and rate of consanguinity but exact epidemiological data of these diseases are not available. There is substantial variation in the risk of malignancy among the various IEI.[22] The majority of IEI-associated malignancies is recognized in children with a diagnosis of a combined immunodeficiency (CID) (groups I and II) or an immune dysregulation disorder particularly those associated with susceptibility to EBV and/or with lymphoproliferation (group IV). Group III is the most common IEI and malignancies in these patients manifest during adult age but also in childhood. Groups V, VI, IX are also related to an increased risk of cancer, in contrast to group VII and VIII.

Severe combined immunodeficiency (SCID), included within groups I and II and characterized by absent or severely diminished T cells, B cells and/or NK cells, is not commonly associated with malignancy as the disease is fatal without early HSCT. In contrast, patients with combined immunodeficiencies (CID), such as CD40L deficiency or cartilage hair hypoplasia, have a less severe immunological phenotype than SCID and have a substantially increased risk of developing malignancy.[23,24] DNA repair disorders (ataxia telangiectasia (AT)) and Nijmegen breakage syndrome carry the greatest risk of malignancy with a cumulative incidence of malignancy of 22.6% by the early 20 s in patients with AT and a crude incidence of 40% by the age of 20 years in patients with NBS.[16,25–28]

Immune dysregulation disorders (Group IV) are well known for their increased incidence of (especially EBV-associated) lymphoma. Examples include immune dysregulation disorders associated with lymphoproliferation such as autoimmune lymphoproliferative syndrome (ALPS) and CTLA4 deficiency, as well as disorders associated with susceptibility to EBV infections and hemophagocytic lymphohistiocytosis (HLH) such as X-linked lymphoproliferative disease (XLP), familial HLH syndromes, CD27 and CD70 deficiencies, and CTPS1 deficiency.[29–31] HLH itself usually manifests in childhood or adolescence. This disease, has many overlapping features with a spectrum of EBV-induced lymphoproliferative disorders and some genetic subtypes are associated with an increased risk of lymphoma.[32]

PAD's (Group III) encompasses disorders with reduced or poorly functioning immunoglobulin as their main feature. Activated phosphoinositide 3-kinase delta syndrome (APDS), caused by mutations in *PIK3CD* (APDS1) or *PIK3R1* (APDS2), is classified

as a PAD but is also associated with features of immune dysregulation, lymphoid hyperplasia and lymphoma.[32] Common variable immunodeficiency (CVID) is the most prevalent IEI. The diagnosis is made based on clinical criteria and the disease affects 0.6 – 3.8:100,000 children and adults.[26,28,29,33] While the risk of malignancy in pediatric CVID patients is probably lower than in some other IEI disorders, there is a particular risk for the development of B-cell lymphomas such as extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas).[34–36]

Congenital defects of phagocyte number or function (group V) such as severe congenital neutropenia (SCN), and GATA2 deficiency, as well as bone marrow failure disorders (group IX) such as those caused by SAMD9(L) mutations, are associated with an increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Severe congenital neutropenia is usually diagnosed at an early age and malignancy will not be the first symptom in these patients.[37–40]

Defects in intrinsic and innate immunity (group VI) are, as a group, less commonly characterized by the occurrence of malignancies. However, certain subtypes of IEI within this group are associated with specific types of cancer, such as HPV-related skin cancer in patients with EVER1 and EVER2 deficiencies.[41]

Spectrum of malignancies in children with IEI

A diverse spectrum of lymphoid malignancies is seen in children with IEI including both precursor and peripheral malignancies of either B- or T-cell origin (Table 2) as recently summarized by Riaz et al.[32] Most common are mature B-cell non-Hodgkin lymphomas.[2,26] Notably, in contrast to sporadically presenting B-NHL, diffuse large B-cell lymphoma represents a substantially greater proportion of cases than Burkitt lymphoma. Another interesting feature is the relative abundance of rare lymphoma subtypes and destructive lymphoproliferative disorders falling short of lymphoma, with a recent study of 36 UK children with IEI referred for HSCT identifying 3 peripheral T cell lymphomas, 2 extranodal marginal zone lymphomas and 6 polymorphic lymphoproliferative disorders.[39] Recent EICNHL/BFM studies identified predisposing disorders in a high proportion of children diagnosed with peripheral T cell lymphomas (25%), extranodal marginal zone lymphomas (27%) and primary central nervous system lymphomas (19–29%%), among which IEI were prevalent.[42–44] Equally, some groups of IEI are associated with a higher prevalence of specific hematological malignancy subtypes including: NBS and T-cell leukemia/NHL, CVID and extranodal marginal zone lymphoma, and IL-2-inducible T cell kinase (ITK) deficiency and classic Hodgkin lymphoma.[45–49] However, low patient numbers hamper the accurate association with specific lymphoid diagnoses in the majority of individual IEI cohorts. EBV-driven lymphoma is, as expected, more prevalent in children with underlying IEI.[50]

As mentioned previously, the incidence of MDS and AML is increased in patients with phagocyte disorders (group V) and bone marrow failure disorders (group IX).[51] Patients with severe congenital neutropenia (SCN) are particularly at risk for MDS and leukemia, mostly AML but also chronic myelomonocytic leukemia (CMML) and acute lymphoblastic leukemia (ALL). Carlsson et al estimated the cumulative incidence of MDS/leukemia in a Swedish cohort of SCN as high as 31%.[36]

Table 2. Types of IEI to consider in a pediatric cancer patient.

Malignancy	IEI (according to IUIS classification, Tangye et al 2020)	Possible test	Possible outcome
ALL, non-Hodgkin lymphoma, classic Hodgkin lymphoma	– Hypomorphic SCID (I) – Combined immune deficiencies (CID) (I) – DNA repair disorders (I) – Primarily antibody disorders (III) – Disorders of immune dysregulation (IV)	– Full blood count – Immunophenotyping	– Low neutrophils and/or lymphocytes – Low CD3, CD4 and or CD8 in CID or presence of double negative T cells (ALPS) and , low switched memory B cells (CVID) – Absent or diminished expression of specific proteins like WAS, CTLA4
		- T cell function -NK cell function (CD107a release)	Diminished (SCID, CID) Diminished (XLP).
		- Immunoglobulin levels and subclasses	Diminished (CVID, CID, DNARD)
		- Radiosensitivity testing	Diminished in DNARD
		Molecular testing example (TREC's/Krec's)	Diminished (SCID, CID)
MDS, AML	– Severe congenital neutropenia disorders – Shwachman-Diamond Syndrome – GATA2 deficiency – - Bone marrow failure disorders	- Full blood count	Low platelets, low red bloodcells (bone marrow failure) and/or neutrophils (SCN). Low monocytes (GATA2).
Brain tumors	– DNA repair disorders	Radiosensitivity	Diminished
Solid tumors	– DNA repair disorders – Dyskeratosis congenita (telomeropathies)	Full Blood counts	Low platelets, red bloodcells, Monocytes or neutrophils (Telomeropathies).
	– PTEN deficiency (APDS-like syndrome) – CVID	Immunoglobulin levels Radiosensitivity	Diminished (CVID, DNARD) Diminished (DNARD)
EBV-associated smooth muscle tumors	– CID – Ataxia telangiectasia – GATA2 deficiency – RLTPR deficiency (*CARMIL2*) – ZAP70 deficiency	Full Blood counts	Low Monocytes (GATA2) Low lymphocytes (CID, AT)
		Immunophenotyping	Low CD3, CD4 or CD8 cells (CID). Low CD8 cells (ZAP70 deficiency)
		NK cell function (CD107 mobilisation)	Diminished
		Immunoglobulin levels	Diminished
Kaposi sarcoma	– Wiskott–Aldrich syndrome (*WAS*) – X-linked magnesium EBV and neoplasia (XMEN) (*MAGT1*) – IFN-γ receptor 1 deficiency (*IFNGR1*) – STIM1 deficiency – OX40 deficiency (*TNFRSF4*)	Full Blood counts Immunophenotyping Immunoglobulin levels	Low Lymphocytes Low subsets (CD3, CD4 and or CD8, low switched memory B cells) Diminished
Non-melanoma skin cancer	– EVER1 (*TMC6*) and EVER2 (*TMC8*) deficiencies – DOCK8 deficiency – Cartilage hair hypoplasia – Xeroderma pigmentosum	Full Blood counts Immunoglobulin levels	Low neutrophils, (CHD), Elevated eosinophils (Dock8) High IgE in DOCK8

Overview of the different malignancies, the different underlying IEI's and possible tests that can be performed by the pediatric hemato-oncologist. It should be stated that the different IEI's given in the table are examples and that the table is not complete. For all groups, genetic testing on germline DNA can be performed.

Data on brain and solid tumors in children with IEI are scarce. DNA repair disorders are the most notorious group of IEI with an increased risk of several childhood cancers including medulloblastoma, glioma, rhabdomyosarcoma, and osteosarcoma.[52] CVID patients have a higher incidence of solid tumors, like gastric cancer especially in adults.[9] Dyskeratosis congenital predisposes to various solid tumors, including EBV driven disorders.[23,53] An increased incidence of non-melanoma skin cancers is seen in DOCK8, EVER1 and EVER2 deficiencies due to chronic cutaneous infections (eg, HPV), cartilage hair hypoplasia, and DNA repair disorders especially xeroderma pigmentosum and Rothmund Thomson syndrome.[23,54–56] EBV-associated smooth muscle tumors are also seen in Ataxia Telangiectasia, and GATA2, CARMIL2 and ZAP70 deficiencies.[8] Childhood Kaposi sarcoma, caused by human herpes virus-8 infection, is also quite unique to the setting of IEI and has been reported in patients with mutations in *WAS*, *IFNGR1*, *STIM1*, *MAGT1*, and *TNFRSF4*.[57]

Clinical warning signs for the pediatric hemato-oncologist

While most IEI-associated lymphoproliferations/lymphoid malignancies affect children with known immunodeficiency, the identification of an underlying IEI in an apparently "sporadic" lymphoid malignancy can present a substantial diagnostic challenge. By definition, these children have not yet been referred for investigation of severe or recurrent infectious/immunological problems. Instead, careful review of the patient´s clinical history and physical examination combined with prudent use of routine laboratory investigations and pathological review can identify a group of patients who warrant additional investigation (Table 3).

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

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

One feature of pediatric cancer patients with IEI is the younger age at presentation compared with sporadic cases. National registry studies have shown a peak in excess childhood cancer diagnoses between 5 and 9 years of age, of which the majority are lymphoid malignancies.[2,3] This younger age is further highlighted by the skew in histopathological diagnoses away from sporadic Burkitt lymphoma toward diffuse large B-cell lymphoma, classic Hodgkin lymphoma and marginal zone lymphomas, all of which pediatric oncologists would usually expect to see in the teenage and young adult population. Irrespective of age at presentation and diagnosis, routine clinical history in a child with known or suspected lymphoid malignancy should actively seek both a personal and family history of recurrent, persistent, severe and/or unusual infections, non-neoplastic lymphoproliferation, malignancy, autoimmunity, autoinflammation, or early childhood death in the family. Consanguinity should be documented as well.

Diagnostics

The suspicion of an underlying IEI in a patient presenting with malignancy warrants further investigation. The presence of an underlying IEI may have an important impact on the standard cancer therapy protocol, to reduce treatment-related toxicity (eg, dose modification of chemotherapy, avoidance of radiotherapy) or reduce the risk of relapse (eg, by performing HSCT after first remission).[58] We advise consulting an immunologist to assist with the diagnostic work-up. There are some pitfalls here. First, there usually is not much time. Especially in hematological malignancies, the oncologist may need to initiate treatment as soon as possible, leaving little time to perform further testing. Some tests, such as the evaluation of immunoglobulin levels or the presence of specific antibodies can be influenced by the chemotherapy as well as the supportive treatments such as blood transfusions. The recent implementation of immunotherapy in the standard of care of an increasing number of cancers will affect the immune system even more, sometimes leading to permanent secondary immunodeficiency. Hence it will be almost impossible to tell apart a primary (inborn) from a secondary (acquired) immunodeficiency.

Immunology

Diagnostic laboratory testing for IEI involves complete blood count (CBC), determination of serum immunoglobulin (Ig) classes and subclasses, evaluation of specific antibody response to polysaccharide and protein vaccine antigen, flow cytometry for extensive quantitation and phenotyping of T-, B- and NK-cell subsets, and various functional tests including lymphocyte proliferation assays, neutrophil function assays (eg, respiratory burst), cytokine secretion and/or intracellular cytokine production upon stimulation, NK cell cytotoxicity assay, assessment of cellular signaling pathways and protein expression analyses (Table 2).[59,60] In patients with solid tumors, lymphocytopenia or neutropenia in the CBC could be an obvious warning sign. In patients with hematological malignancies, sometimes a parental blood sample can give additional information, for example by demonstrating monocytopenia in a relative of a GATA2

deficient proband. Lymphopenia should be further investigated by flow cytometry enabling detection and characterization of T-lymphopenia as seen in (S)CID and DNA repair disorders. Extended B-cell phenotyping is used in classification of CVID.[61] Impaired NK cell function is a feature of HLH and EBV-related lymphoproliferation.[62] Specific protein expression enables confirmation in certain IEI, like CD40L deficiency or IPEX.[63]

To rule out antibody deficiency, measuring immunoglobulin levels including subclasses of IgG, is indispensable.[59,60] The evaluation of specific antibodies such as isohemaglutinin and the titers of common postvaccination serum antibodies is crucial.[64] Specific postvaccination antibody responses to nonconjugated polysaccharide pneumococcal vaccine or Salmonella enterica subsp. Typhi Vi antigen capsular polysaccharide enables *in vivo* evaluation of specific antibody responses.[59] This test might be difficult at diagnosis. Finally, a variety of other tests can be helpful in well-selected cases, like the assessment of telomere length, neutrophil respiratory burst for chronic granulomatous disease (CGD), or *in vitro* evaluation of signaling pathways such as JAK-STAT or Toll like receptor pathways.

Radiosensitivity testing

Radiosensitivity assays have not yet found their way into a routine clinical setting, but can add important information if a DNA repair disorder is suspected. One option is to use the clonogenic cell survival assay which determines the ability of a cell to proliferate to form a large colony.[65] This test has already been used in the identification of several immunodeficiencies which are caused by double stranded DNA breaks such as Artemis deficiency.[66] Another approach is the use of the G2 micronucleus assay, which was used to identify Ataxia Telangiectasia in an atypical patient. This assay uses changes in the micronucleus following low doses of irradiation of peripheral white blood cells as a marker of increased DNA sensitivity.[67]

Role of pathology

Often the first to diagnose a specific malignancy, pathologists have an early opportunity to consider the possibility of an underlying IEI in a child with cancer. This is facilitated by the examination of surgical biopsies. Lymphomas presenting in children with IEI are often histologically identical to those occurring sporadically, even if the age and tissue distribution of specific lymphoma types differs.[68] In contrast, some lymphoid neoplasms such as polymorphic lymphoproliferative disorders and EBV-associated mucocutaneous ulcers are highly associated with immunodeficiency, while the presence of certain morphological features in a common lymphoma type, such as polymorphic or Hodgkin-like features in a frank diffuse large B-cell lymphoma, may also suggest immunodeficiency.[69–72] These lesions are typically EBV-positive, as are some immunodeficiency-associated marginal zone lymphomas and T/NK-cell lymphomas, and all pediatric lymphomas should be tested for EBV-association by *in situ* hybridization with positive findings correlated with peripheral blood EBV levels and serology.[73,74] However, EBV-positivity alone is not sufficient to indicate an underlying IEI.

Any non-neoplastic lymphoid tissue sampled should be carefully examined for the abnormal constituent cell populations or altered lymphoid architecture described in several IEIs.[75–78]

In contrast to the lymphoid neoplasms, histopathological features of carcinomas and other solid tumors that might suggest underlying IEI in children are poorly recognized.[79] Histopathologists must nevertheless be cognizant that cancer types rarely seen in children may be associated with IEI, especially when a specific link has been identified such as between squamous cell carcinoma and Fanconi anemia, or cholangiocarcinoma secondary to Cryptosporidium-induced sclerosing cholangitis in CD40L-deficient patients.[80,81] Hematopathologists should be aware of morphological and immunophenotypic features that might suggest an atypical presentation of a bone marrow failure syndromes/phagocyte defect during diagnosis of AML/MDS, such as the bone marrow hypocellularity, prominent megakaryocytic dysplasia, and reduction in B-cells, NK cells, monocytes and hematogones characteristic of GATA2-deficient patients.[82] If an IEI is suspected in a patient with a malignancy, the presence of EBV can be evaluated in the tumor and other relevant tissues and samples, especially peripheral blood. If underlying chronic EBV infection is suspected, immune phenotyping of B- and T-cells and NK-cell function should be performed before starting a therapy.

Molecular genetics

There have been very few studies on the genetic identification of preexisting IEI in pediatric cancer patients.[26,37,83–86] Several studies have shown that about 10% of all childhood cancers are linked to an underlying germline mutation in a known cancer predisposition gene, but the contribution of germline mutations in IEI genes remains to be elucidated.[83–85] Standard genetic testing is of very little added value here. Routine molecular diagnostic algorithms will only identify a small proportion of IEIs in cancer (Table 4). Chromothripsis might be a molecular indicator for an underlying Ataxia Telangiectasia but no other routine molecular diagnostic have been proposed as indicators for IEI in the current work-up for cancer.[87]

High-throughput genetic sequencing technologies, like standardized next-generation sequencing (NGS) seem to be the future to screen germline DNA for a preexisting condition including IEI.[15] Different NGS approaches are conceivable (Table 4). One common obstacle is the interpretation of variants with regard to their functional impact but understanding of this challenge is growing and will likely lead to improved computational approaches in due course. A cost-effective approach is the application of panel-sequencing to a defined set of targeted IEI genes. However, it needs to be taken into account that the number of newly identified IEI genes is still increasing, which makes it a challenge to keep a gene panel up to date and patient samples would need to be regularly re-sequenced if additional genes need to be analyzed. Applying WES and WGS overcomes these drawbacks since the analysis can be focused on a targeted set of IEI genes by applying *in silico* gene panels which can be easily adapted for new IEI genes. In combination with clinical data, additional analysis of the parents (trio-sequencing) can be beneficial for the interpretation of the inheritance and the functional impact of the variants.[88]

Table 4. Variant detection methods.

Genetic method	Detects	Resolution	Pro	Con
Array CGH	DUP, DEL	≈0,07 Mbp	Routine diagnostic, cost efficient, available in many centers	Limited to copy number variation detection, does not detect most common IEI variants
SNP-array	DUP, DEL, CNN-LOH	≈0,05–0,1 Mbp	Routine diagnostic, cost efficient, available in many centers	Limited to copy number variation and LOH detection, does not detect most common IEI variants
Panel sequencing	SNV, indels	≈1 bp (SNV) ≈<20 bp indel	High throughput, cost-efficient, targeted panel	Limited set of genes that needs to be regularly updated and added to, no retrospective analyses of novel genes
Whole exome sequencing	SNV, indels	≈1 bp (SNV) ≈<20 bp indel	High throughput, covers most coding genes, in silico panels, retrospective analyses of newly identified genes possible	Limited to the coding genome, requires bioinformatics support
Whole genome sequencing	TRA (un/balanced), INV, DUP, DEL, SNV	≈1 bp (SNV) ≈0,01 Mbp SV	High throughput, covers most of the genome, in silico panels, retrospective analyses of newly identified genes possible	Requires bioinformatics support, available in few centers, large data storage capacities necessary
Sanger sequencing	SNV, indel	≈1 bp (SNV) ≈<40 bp (indel)	Routine diagnostic, cost efficient (if done for few specific variants), available in many centers	Low throughput

(bp, base pairs; CGH, comparative genomic hybridization; CNN-LOH, copy number neutral loss of heterozygosity; DEL, deletion; DUP, duplication; indel, insertion and deletion; INS, insertion; INV, inversion; SNV, single nucleotide variants; SV, structural variants; TRA, translocation.

Discussion

This article aims to support the PHO to recognize a possible underlying IEI in a child presenting with cancer. Along with a personal history of severe infections, a suggestive syndromic phenotype, or a family history of IEI, the type of cancer and age of the patient should be considered as warning signs. IEI patients have a high incidence of specific malignancies, especially leukemia and specific types of lymphoma at a relatively younger age. Another warning sign is an unexpected toxicity, such as prolonged bone marrow aplasia or lymphopenia which could be a sign of an underlying DNA repair disorder. Some baseline immunological tests are readily available to the PHO and can help. Measurement of immunoglobulin levels before the start of therapy is easy and

cheap and will identify all patients with antibody deficiencies and sometimes other IEIs. Lymphocyte subset analysis will give an idea of basic cellular immunological make-up and specific antibody testing an indication of immunological response. However results can be affected once therapy has started and it may be more difficult to tell the difference between an underlying primary immunodeficiency and a secondary immunodeficiency. In these cases, patients need to be monitored closely after cessation of therapy to see if immunological tests recover. Although there are not many data on that recovery after treatment for malignancy, stem cell transplantation excluded, this is believed to take up to 6 months or longer.[89] Ongoing studies will help to clarify the normal kinetics. Vaccination responses could be performed after the treatment is completed and the lymphocyte counts has normalized and routine re-vaccination is performed.[90] It should be noted that not all available functional immunological tests are discussed in this article and further more specialized testing may be recommended by an immunologist. Genetic testing of the child's germline DNA is becoming increasingly available and offers the ability to detect IEIs even during treatment.

It should be stressed that very often the diagnosis of an underlying IEI may be suspected, but not always be confirmed in time to allow treatment adaptation accordingly. Especially in these cases, the treatment and supportive care options should be considered, and careful balancing of treatment decisions is warranted.

Conclusion

The risk of malignancy is increased in many IEI patients. The presence of an underlying IEI in a child with cancer can have a significant impact on the treatment, including the need for dose reduction because of increased toxicity, or early use of HSCT. This article stresses the importance of recognizing these patients at an early stage. There are clinical warning signs, including the type of cancer and the age of onset, that could be used by the PHO to identify pediatric cancer patients with an underlying IEI. The analysis of immunoglobulins and lymphocyte subsets can give information but more specialized immunological testing may be required. Molecular genetic diagnostics, like NGS will play an increasing role in screening or confirming a diagnosis.

Acknowledgement

This article is based upon work from COST Action 16223 LEukaemia GENe Discovery by data sharing, mining and collaboration (Legend), supported by COST (European Cooperation in Science and Technology).

Disclosure statement

The authors have no conflicts of interest to disclose.

ORCID

Charlotte Derpoorter http://orcid.org/0000-0002-6947-0989

References

1. Jonkman-Berk BM, van den Berg JM, Ten Berge IJM, et al. Primary immunodeficiencies in the Netherlands: national patient data demonstrate the increased risk of malignancy. *Clin Immunol*. 2015;156(2):154–162. doi:10.1016/j.clim.2014.10.003.
2. Mayor PC, Eng KH, Singel KL, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States immune deficiency network registry. *Allergy Clin Immunol*. 2018;141(3):1028–1035. doi:10.1016/j.jaci.2017.05.024.
3. Kralickova P, Milota T, Litzman J, et al. CVID-associated tumors: Czech nationwide study focused on epidemiology, immunology, and genetic background in a cohort of patients with CVID. *Front Immunol*. 2019;9:3135.
4. Gangemi S, Allegra A, Musolino C. Lymphoproliferative disease and cancer among patients with common variable immunodeficiency. *Leuk Res*. 2015;39(4):389–396. doi:10.1016/j.leukres.2015.02.002.
5. Piquer GM, Alsina L, Giner Muñoz MT, et al. Non-Hodgkin lymphoma in pediatric patients with common variable immunodeficiency. *Eur J Pediatr*. 2015;174(8):1069–1076. doi:10.1007/s00431-015-2508-6.
6. Olsen JH, Hahnemann JM, Børresen-Dale AL, et al. Cancer in patients with ataxia-telangiectasia and in their relatives in the Nordic countries. *J Natl Cancer Inst*. 2001;93(2):121–127. doi:10.1093/jnci/93.2.121.
7. Kiykim A, Eker N, Surekli O, et al. Malignancy and lymphoid proliferation in primary immune deficiencies; hard to define, hard to treat. *Pediatr Blood Cancer*. 2020;67(2):e28091. doi:10.1002/pbc.28091.
8. Magg T, Schober T, Walz C, et al. Smooth muscle tumors as manifestation of primary immunodeficiency disorders Epstein-Barr virus(+). *Front Immunol*. 2018;9:368.
9. Pulvirenti F, Pecoraro A, Cinetto F, et al. Gastric cancer is the leading cause of death in Italian adult patients with common variable immunodeficiency. *Front Immunol*. 2018;9:2546.
10. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. *J Clin Immunol*. 2020;40(1):24–64. doi:10.1007/s10875-019-00737-x.
11. Bousfiha A, Jeddane L, Picard C, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J Clin Immunol*. 2020;40(1):66–81. doi:10.1007/s10875-020-00758-x.
12. Modell V, Knaus M, Modell F, et al . Global overview of primary immunodeficiencies: a report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery. *Immunol Res*. 2014;60(1):132–144. doi:10.1007/s12026-014-8498-z.
13. Derpoorter C, Bordon V, Laureys G, et al. Genes at the crossroad of primary immunodeficiencies and cancer. *Front Immunol*. 2018;9:2544.
14. Haas OA. Primary immunodeficiency and cancer predisposition revisited: embedding two closely related concepts into an integrative conceptual framework. *Front Immunol*. 2018;9:3136.
15. Bogaert DJ, Laureys G, Naesens L, et al. GATA2 deficiency and haematopoietic stem cell transplantation: challenges for the clinical practitioner. *Br J Haematol*. 2020;188(5):768–773. doi:10.1111/bjh.16247.
16. Bomken S, van der Werff Ten Bosch J, Attarbaschi A, et al. Current understanding and future research priorities in malignancy associated with inborn errors of immunity and DNA repair disorders: the perspective of an interdisciplinary working group. *Front Immunol*. 2018;9:2912.
17. Wolska-Kuśnierz B, Gregorek H, Chrzanowska K, Inborn Errors Working Party of the Society for European Blood and Marrow Transplantation and the European Society for Immune Deficiencies, et al. Nijmegen breakage syndrome: clinical and immunological features, long-term outcome and treatment options - a retrospective analysis. *J Clin Immunol*. 2015;35(6):538–549. doi:10.1007/s10875-015-0186-9.
18. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: an easy-to-use selection tool. *Eur J Med Genet*. 2016;59(3):116–125. doi:10.1016/j.ejmg.2016.01.008.

19. Ripperger T, Bielack SS, Borkhardt A, et al . Childhood cancer predisposition syndromes-A concise review and recommendations by the cancer predisposition working group of the society for pediatric oncology and hematology. *Am J Med Genet A*. 2017;173(4):1017–1037. doi:10.1002/ajmg.a.38142.
20. Druker H, Zelley K, McGee RB, et al. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. *Clin Cancer Res*. 2017;23(13):e91–e97. doi:10.1158/1078-0432.CCR-17-0834.
21. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. *Ann N Y Acad Sci*. 2011;1238:7–14. doi:10.1111/j.1749-6632.2011.06206.x.
22. Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. *J Allergy Clin Immunol*. 2018;141(1):59–68.e4. doi:10.1016/j.jaci.2017.06.009.
23. Vakkilainen S, Taskinen M, Mäkitie O. Immunodeficiency in cartilage-hair hypoplasia: pathogenesis, clinical course and management. *Scand J Immunol*. 2020;92(4):e12913. doi:10.1111/sji.12913.
24. Schuetz C, Niehues T, Friedrich W, et al. Autoimmunity, autoinflammation and lymphoma in combined immunodeficiency (CID). *Autoimmun Rev*. 2010; 9(7):477–482. doi:10.1016/j.autrev.2010.02.005.
25. Kwan A, Abraham RS, Currier R, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA*. 2014;312(7):729–738. doi:10.1001/jama.2014.9132.
26. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, et al. Ataxia telangiectasia: a review. *Orphanet J Rare Dis*. 2016;11(1):159. doi:10.1186/s13023-016-0543-7.
27. Attarbaschi A, Carraro E, Abla O, European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the International Berlin-Frankfur t-Münster (i-BFM) Study Group, et al. Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents. *Haematologica*. 2016;101(12):1581–1591. doi:10.3324/haematol.2016.147116.
28. Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. *JCO*. 2015;33(2):202–208. doi:10.1200/JCO.2014.56.5101.
29. Straus SE, Jaffe ES, Puck JM, et al. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. *Blood*. 2001;98(1):194–200. doi:10.1182/blood.V98.1.194.
30. Ghosh S, Köstel Bal S, Edwards ESJ, et al. Extended clinical and immunological phenotype and transplant outcome in CD27 and CD70 deficiency. *Blood*. 2020;136(23):2638–2655.
31. Janka G. Hemophagocytic syndromes. *Blood Rev*. 2007;21(5):245–253. doi:10.1016/j.blre.2007.05.001.
32. Riaz IB, Faridi W, Patnaik MM, et al. A systematic review on predisposition to lymphoid (B and T cell) neoplasias in patients with primary immunodeficiencies and immune dysregulatory disorders (inborn errors of immunity). *Front Immunol*. 2019;10:777.
33. Tangye SG, Latour S. Primary immunodeficiencies reveal the molecular requirements for effective host defense against EBV infection. *Blood*. 2020;135(9):644–655.
34. Gathmann B, Mahlaoui N, Gérard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014;134(1):116–126. doi:10.1016/j.jaci.2013.12.1077.
35. Aghamohammad A, Parvaneh N, Tirgari F, et al. Lymphoma of mucosa-associated lymphoid tissue in common variable immunodeficiency. *Leuk Lymphoma*. 2006;47(2):343–346. doi:10.1080/10428190500285285.
36. Ho H, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: updated clinical spectrum, sequelae, and insights to pathogenesis. *Front Immunol*. 2020;11:149.

37. Carlsson G, Fasth A, Berglöf E, et al. Incidence of severe congenital neutropenia in Sweden and risk of evolution to myelodysplastic syndrome/leukaemia. *Br J Haematol*. 2012;158(3):363–369. doi:10.1111/j.1365-2141.2012.09171.x.
38. Satgé DA. A tumor profile in primary immune deficiencies challenges the cancer immune surveillance concept. *Front Immunol*. 2018; 9:1149. doi:10.3389/fimmu.2018.01149.
39. Shiba N, Funato M, Ohki K, et al. Mutations of the GATA2 and CEBPA genes in paediatric acute myeloid leukaemia. *Br J Haematol*. 2014;164(1):142–145. doi:10.1111/bjh.12559.
40. Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood*. 2014; 123(6):809–821. doi:10.1182/blood-2013-07-515528.
41. de Jong SJ, Créquer A, Matos I, et al. The human CIB1-EVER1-EVER2 complex governs keratinocyte-intrinsic immunity to β-papillomaviruses. *J Exp Med*. 2018;215(9):2289–2310. doi:10.1084/jem.20170308.
42. Prunotto G, Offor UT, Samarasinghe S, et al. HSCT provides effective treatment for lymphoproliferative disorders in children with primary immunodeficiency. *J Allergy Clin Immunol*. 2020;146(2):447–450. doi:10.1016/j.jaci.2020.03.043.
43. Mellgren K, Attarbaschi A, Abla O, On behalf of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Group, et al. European intergroup for childhood non-hodgkin lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) group. *Ann Hematol*. 2016;95(8):1295–1305. doi:10.1007/s00277-016-2722-y.
44. Ronceray L, Abla O, Barzilai-Birenboim S, European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the International Berlin-Frankfurt-Münster (i-BFM) Study Group, et al. Children and adolescents with marginal zone lymphoma have an excellent prognosis with limited chemotherapy or a watch-and-wait strategy after complete resection. *Pediatr Blood Cancer*. 2018;65(4):e26932. doi:10.1002/pbc.26932.
45. Thorer H, Zimmermann M, Makarova O, et al. Primary central nervous system lymphoma in children and adolescents: low relapse rate after treatment according to Non-Hodgkin-Lymphoma Berlin-Frankfurt-Münster protocols for systemic lymphoma. *Haematologica*. 2014;99(11):e238–e241. doi:10.3324/haematol.2014.109553.
46. Attarbaschi A, Abla O, Ronceray L, et al. Primary central nervous system lymphoma: initial features, outcome, and late effects in 75 children and adolescents. *Blood Adv*. 2019;3(24):4291–4297. doi:10.1182/bloodadvances.2019001062.
47. Moshier EL, Godbold JH, Cunningham-Rundles C, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012;119(7):1650–1657. doi:10.1182/blood-2011-09-377945.
48. Quinti I, Agostini C, Tabolli S, et al. Malignancies are the major cause of death in patients with adult onset common variable immunodeficiency. *Blood*. 2012;120(9):1953–1954. doi:10.1182/blood-2012-05-431064.
49. Huck K, Feyen O, Niehues T, et al . Girls homozygous for an IL-2-inducible T cell kinase mutation that leads to protein deficiency develop fatal EBV-associated lymphoproliferation. *J Clin Invest*. 2009;119(5):1350–1358. doi:10.1172/jci37901.
50. Bienemann K, Borkhardt A, Klapper W, et al. High incidence of Epstein-Barr virus (EBV)-positive Hodgkin lymphoma and Hodgkin lymphoma-like B-cell lymphoproliferations with EBV latency profile 2 in children with interleukin-2-inducible T-cell kinase deficiency. *Histopathology*. 2015;67(5):607–616. doi:10.1111/his.12677.
51. Tesi B, Davidsson J, Voss M, Rahikkala E, et al. Gain-of-function *SAMD9L* mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. *Blood*. 2017;129(16):2266–2279. doi:10.1182/blood-2016-10-743302.
52. de Miranda NF, Björkman A. Pan-Hammarström. DNA repair: the link between primary immunodeficiency and cancer. *Q.Ann N Y Acad Sci*. 2011;1246(1):50–63.
53. Alter BP, Giri N, Savage SA, et al. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. *Blood*. 2009;113(26):6549–6557. doi:10.1182/blood-2008-12-192880.

54. Aydin SE, Kilic SS, Aytekin C, inborn errors working party of EBMT, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. *J Clin Immunol*. 2015;35(2):189–198. doi:10.1007/s10875-014-0126-0.
55. Sharma R, Lewis S, Wlodarski MW. DNA repair syndromes and cancer: insights into genetics and phenotype patterns. *Front Pediatr*. 2020;8:570084. doi:10.3389/fped.2020.570084.
56. Brigida I, Chiriaco M, Di Cesare S, et al. Large deletion of MAGT1 gene in a patient with classic Kaposi sarcoma, CD4 lymphopenia, and EBV infection. *J Clin Immunol*. 2017;37(1):32–35. doi:10.1007/s10875-016-0341-y.
57. Jackson CC, Dickson MA, Sadjadi M, et al. Kaposi sarcoma of childhood: inborn or acquired immunodeficiency to oncogenic HHV-8. *Pediatr Blood Cancer*. 2016;63(3):392–397. doi:10.1002/pbc.25779.
58. Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. *Am J Hematol*. 2011;86(1):48–55. doi:10.1002/ajh.21903.
59. Locke BA, Dasu T, Verbsky JW. Laboratory diagnosis of primary immunodeficiencies. *Clin Rev Allergy Immunol*. 2014;46(2):154–168. doi:10.1007/s12016-014-8412-4.
60. McCusker C, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol*. 2011;7 Suppl 1. doi:10.1186/1710-1492-7-S1-S11.
61. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood*. 2008;111(1):77–85. doi:10.1182/blood-2007-06-091744.
62. Bryceson YT, Pende D, Maul-Pavicic A, et al . A prospective evaluation of degranulation assays in the rapid diagnosis of familial hemophagocytic syndromes. *Blood*. 2012;119(12):2754–2763. doi:10.1182/blood-2011-08-374199.
63. Kalina T, Bakardjieva M, Blom M, et al. EuroFlow standardized approach to diagnostic immunopheneotyping of severe IEI in newborns and young children. *Front Immunol*. 2020;11:371
64. Oliveira JB, Fleisher TA. Laboratory evaluation of primary immunodeficiencies. *J Allergy Clin Immunol*. 2010;125(2):S297– S 305. doi:10.1016/j.jaci.2009.08.043.
65. Franken NA, Rodermond HM, Stap J, et al. Clonogenic assay of cells in vitro. *Nat Protoc*. 2006;1(5):2315–2319. doi:10.1038/nprot.2006.339.
66. Ijspeert H, Lankester AC, van den Berg JM, et al. Artemis splice defects cause atypical SCID and can be restored in vitro by an antisense oligonucleotide. *Genes Immun*. 2011;12(6):434–444. doi:10.1038/gene.2011.16.
67. Claes K, Depuydt J, Taylor AM, et al. Variant ataxia telangiectasia: clinical and molecular findings and evaluation of radiosensitive phenotypes in a patient and relatives. *Neuromolecular Med*. 2013;15(3):447–457. doi:10.1007/s12017-013-8231-4.
68. Swerdlow SH, Campo E, Harris NL, et al., Eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. IARC: Lyon 2017.
69. Natkunam Y, Goodlad JR, Chadburn A, et al. EBV-positive B-cell proliferations of varied malignant potential: 2015 SH/EAHP workshop report-Part 1. *Am J Clin Pathol*. 2017;147(2):129–152. doi:10.1093/ajcp/aqw214.
70. de Jong D, Roemer MGM, Chan JKC, et al. B-cell and classical Hodgkin lymphomas associated with immunodeficiency: 2015 SH/EAHP workshop report-Part 2. *Am J Clin Pathol*. 2017;147(2):153–170. doi:10.1093/ajcp/aqw216.
71. Natkunam Y, Gratzinger D, Chadburn A, et al. Immunodeficiency-associated lymphoproliferative disorders: time for reappraisal? *Blood*. 2018;132(18):1871–1878. doi:10.1182/blood-2018-04-842559.
72. Dojcinov SD, Venkataraman G, Raffeld M, et al . EBV positive mucocutaneous ulcer-a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol*. 2010;34(3):405–417. doi:10.1097/PAS.0b013e3181cf8622.
73. Gong S, Crane GM, McCall CM, et al. Expanding the spectrum of EBV-positive marginal zone lymphomas: a lesion associated with diverse immunodeficiency settings. *Am J Surg Pathol*. 2018;42(10):1306–1316. doi:10.1097/PAS.0000000000001113.

74. Gratzinger D, de Jong D, Jaffe ES, et al. T- and NK-cell lymphomas and systemic lymphoproliferative disorders and the immunodeficiency setting: 2015 SH/EAHP workshop report-Part 4. *Am J Clin Pathol*. 2017;147(2):188–203. doi:10.1093/ajcp/aqw213.
75. Coulter TI, Chandra A, Bacon CM, et al . Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study. *J Allergy Clin Immunol*. 2017;139(2):597–606.e4. doi:10.1016/j.jaci.2016.06.021.
76. Unger S, Seidl M, Schmitt-Graeff A, et al. Ill-defined germinal centers and severely reduced plasma cells are histological hallmarks of lymphadenopathy in patients with common variable immunodeficiency. *J Clin Immunol*. 2014;34(6):615–626. doi:10.1007/s10875-014-0052-1.
77. Lim MS, Straus SE, Dale JK, et al. Pathological findings in human autoimmune lymphoproliferative syndrome. *Am J Pathol*. 1998;153(5):1541–1550. doi:10.1016/S0002-9440(10)65742-2.
78. Facchetti F, Blanzuoli L, Ungari M, et al. Lymph node pathology in primary combined immunodeficiency diseases. *Springer Semin Immunopathol*. 1998;19(4):459–478. doi:10.1007/BF00792602.
79. Furquim CP, Pivovar A, Amenábar JM, et al. Oral cancer in Fanconi anemia: review of 121 cases. *Crit Rev Oncol Hematol*. 2018;125:35–40. doi:10.1016/j.critrevonc.2018.02.013.
80. Ganapathi KA, Townsley DM, Hsu AP, et al. GATA2 deficiency-associated bone marrow disorder differs from idiopathic aplastic anemia. *Blood*. 2015;125(1):56–70. doi:10.1182/blood-2014-06-580340.
81. Nuovo GJ, Ishag M. The histologic spectrum of epidermodysplasia verruciformis. *Am J Surg Pathol*. 2000;24(10):1400–1406.
82. Hayward AR, Levy J, Facchetti F, et al. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. *J Immunol*. 1997;158(2):977–983.
83. Zhang J, Walsh MF, Wu G, et al. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med*. 2015;373(24):2336–2346. doi:10.1056/NEJMoa1508054.
84. Schutte P, Moricke A, Zimmermann M, et al. Preexisting conditions in pediatric ALL patients: spectrum, frequency and clinical impact. *Eur J Med Genet*. 2016;59(3):143–151. doi:10.1016/j.ejmg.2015.12.008.
85. Grobner SN, Worst BC, Weischenfeldt J, ICGC MMML-Seq Project, et al. The landscape of genomic alterations across childhood cancers. *Nature*. 2018;555(7696):321–327. doi:10.1038/nature25480.
86. Kindler O, Quehenberger F, Benesch M, et al. The iceberg map of germline mutations in childhood cancer: focus on primary immunodeficiencies. *Curr Opin Pediatr*. 2018;30(6):855–863. doi:10.1097/MOP.0000000000000680.
87. Ratnaparkhe M, Hlevnjak M, Kolb T, et al. Genomic profiling of acute lymphoblastic leukemia in ataxia telangiectasia patients reveals tight link between ATM mutations and chromothripsis. *Leukemia*. 2017;31(10):2048–2056. doi:10.1038/leu.2017.55.
88. Kuhlen M, Taeubner J, Brozou T, et al. A family-based germline sequencing in children with cancer. *Oncogene*. 2019;38(9):1367–1380. doi:10.1038/s41388-018-0520-9.
89. Perkins JL, Harris A, Pozos TC. Immune dysfunction after completion of childhood leukemia therapy. *J Pediatr Hematol Oncol*. 2017;39(1):1–5. doi:10.1097/MPH.0000000000000697.
90. Rendo M, Sgrignoli R, Dela Cruz W. EPR20-073: the effects of chemotherapy on the efficacy of pneumococcal vaccination using pneumococcal vaccine antibody titers as correlate. *JNCCN*. 2020;18(3.5):EPR20-073. doi:10.6004/jnccn.2019.7490.