Increased risk of malignancies in inborn errors of immunity

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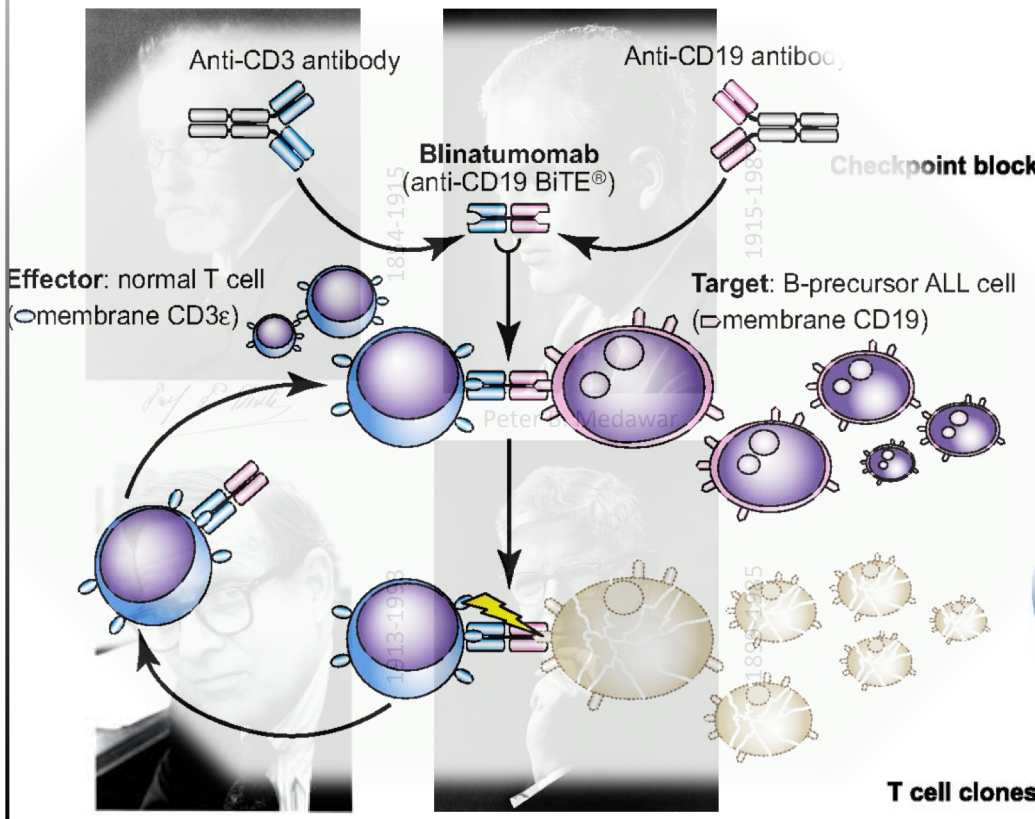
ESID Focus meeting | September 2019

Faculty Disclosure

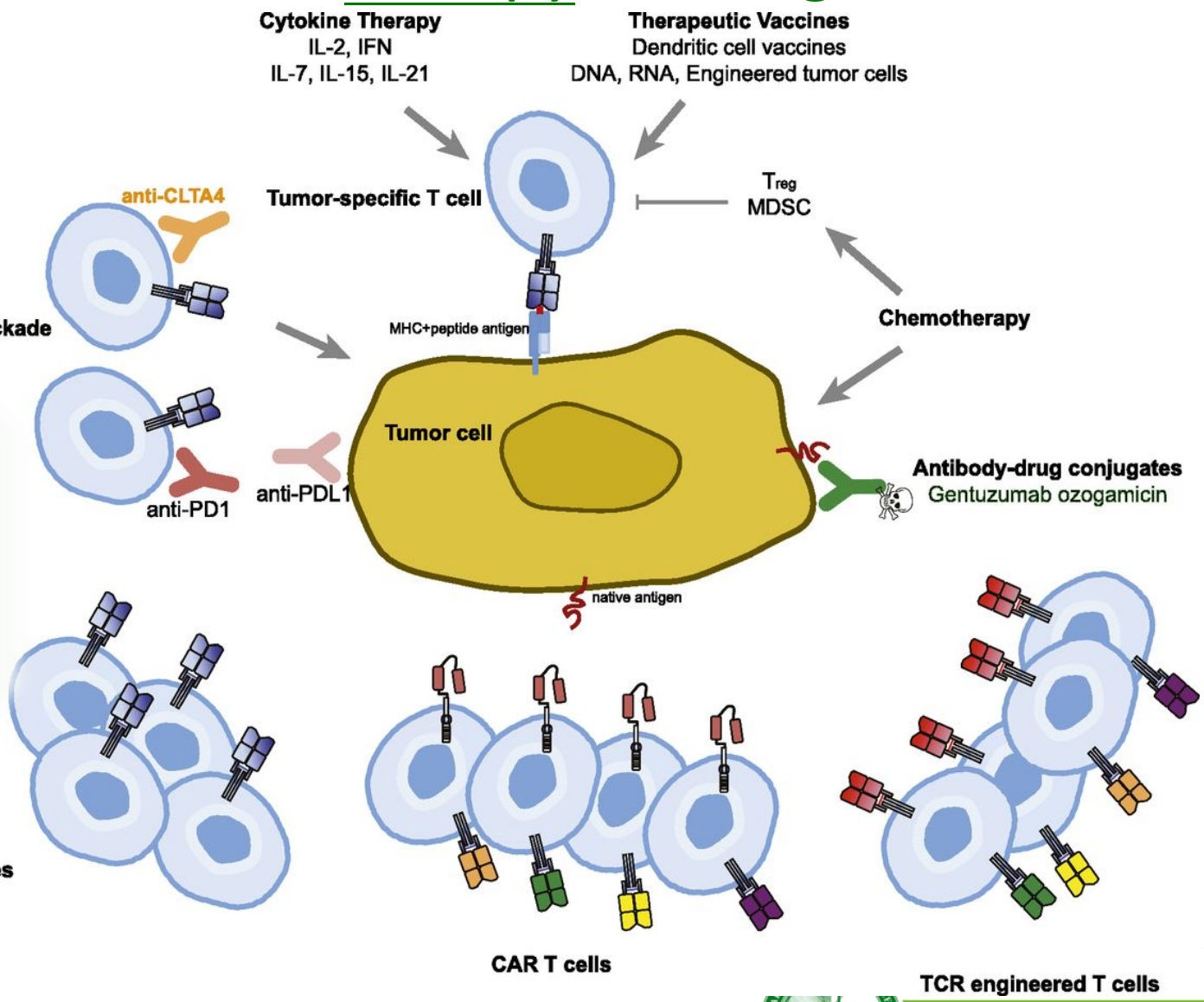
	No, nothing to disclose
X	Yes, please specify (2016-2019): but not related to the content of the presentation

Company Name	*Honoraria/ Expenses Travel grants*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Jazz Pharmaceuticals	6/2016	3/2018						
Novartis	12/2018	7/2016						
Shire/Baxalta	9/2017 10/2018	4/2016						
CSL Behring	6/2016							
Amgen	9/2018							
PharmaMar	2/2017							
Octapharma	9/2017							

From immune surveillance to immune therapy of malignancies



Renato Bassan Blood 2012;120:3094-3095



Marcela V. Maus et al. Blood 2014;123:2625-2635

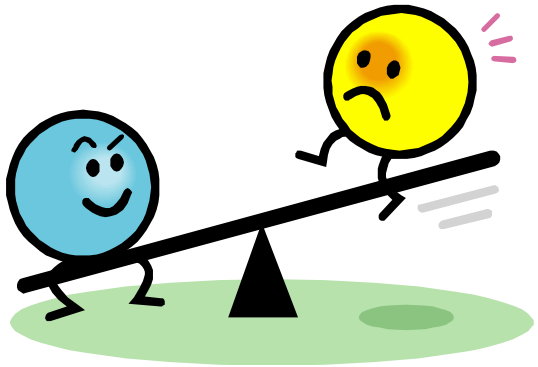
Primary immunodeficiency = Inborn errors of immunity (IEI)

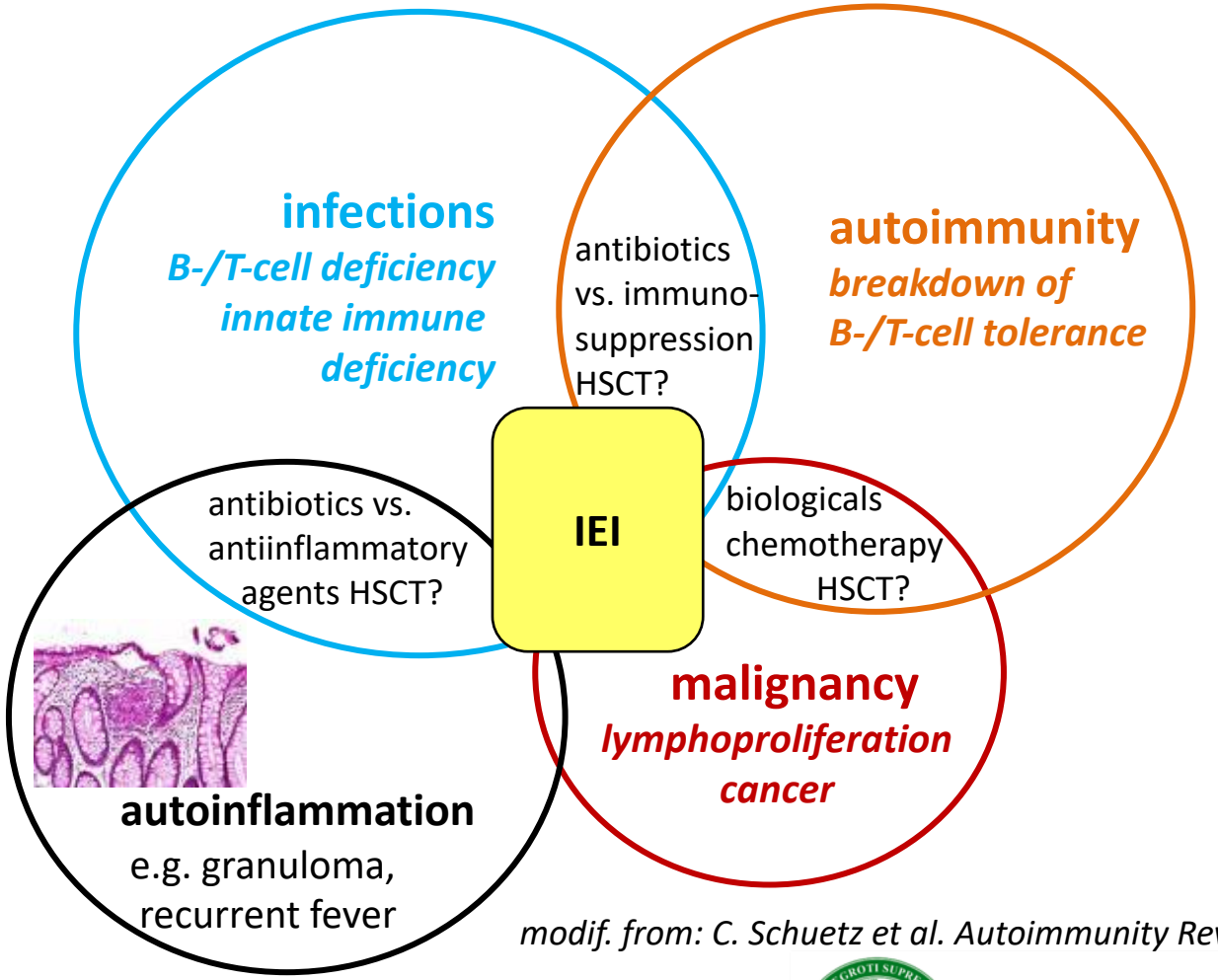
→ infections, autoimmunity, autoinflammation, cancer

ability to fight infections (danger)

versus

tolerance of self (no danger)



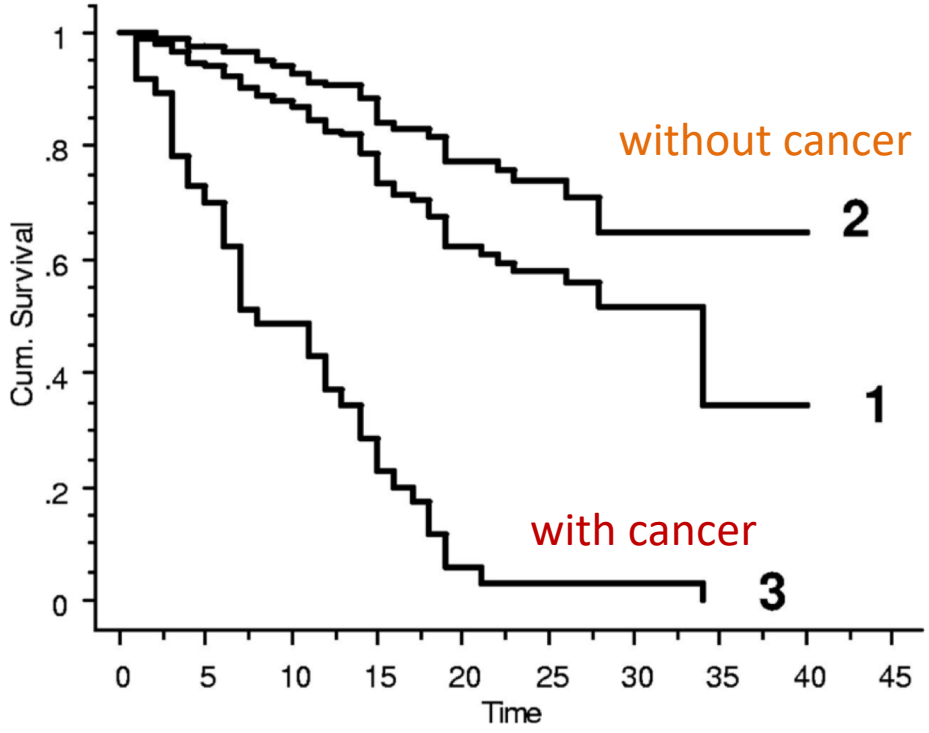


modif. from: C. Schuetz et al. Autoimmunity Revs. 2010

Inborn errors of immunity and cancer – relevance?

- 4-25% of patients with IEI[1,2]
  1.4-fold risk[3]
- Second most common cause of death of patients with IEI
- >70% of malignancies are lymphoproliferative disorders (10-fold risk!)
- Greatest risk in DNA repair disorders
- Outcome of malignancies in IEI is worse than in general population

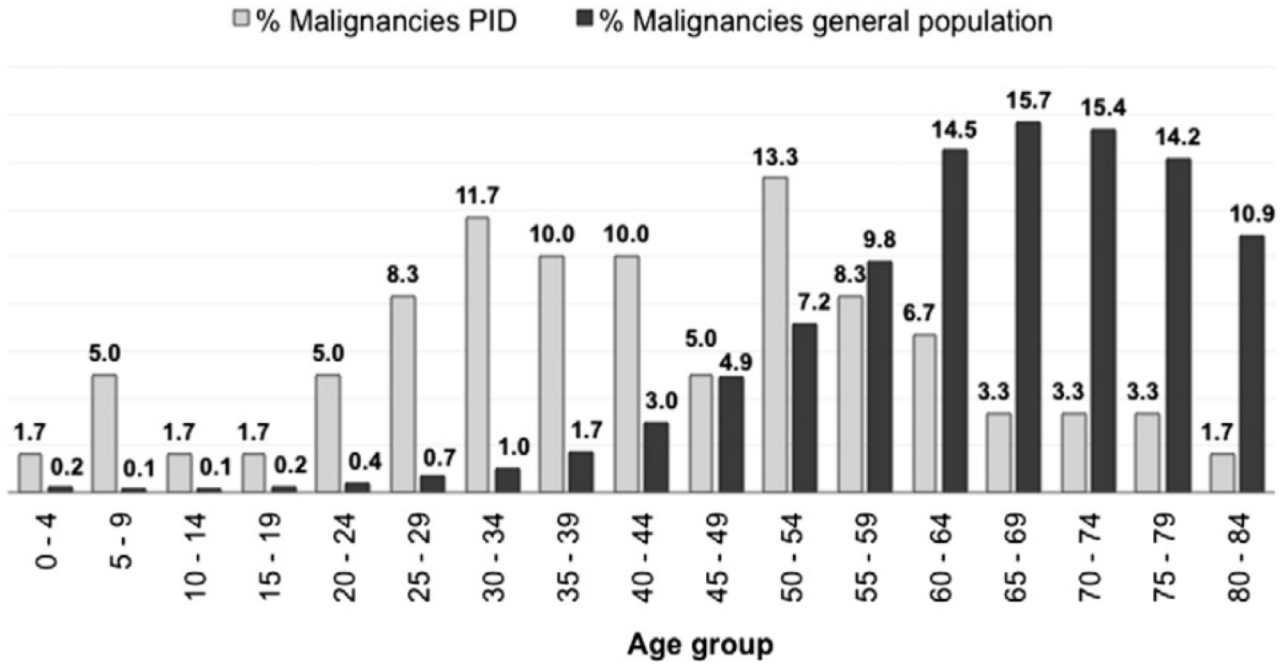
- Example: survival in CVID[5]

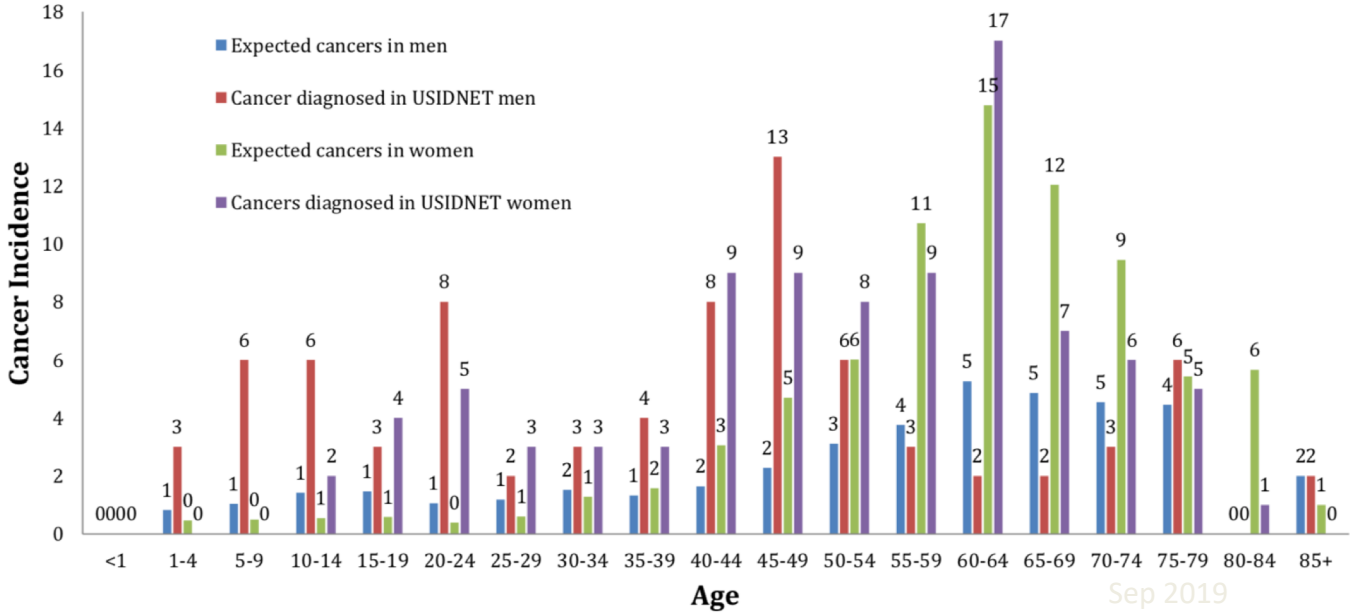


1. *Mueller BU, Pizzo PA. J Pediatr 1996;126:1–10*
2. *Salavoura et al., Anticancer Res 2008;28:1263–9*
3. *Mayor et al., JACI 2018; 141(3): 1028-1035*
4. *Hauck et al. JACI 2018; 141(1):59-68.*
5. *Quinti I. et al., BLOOD 2012;120:1953-1954.*
6. *Pulvirenti et al., Front Immunol. 2018; 9:2546. doi: 10.3389/fimmu.2018.02546*

Cancer Incidence in IEI

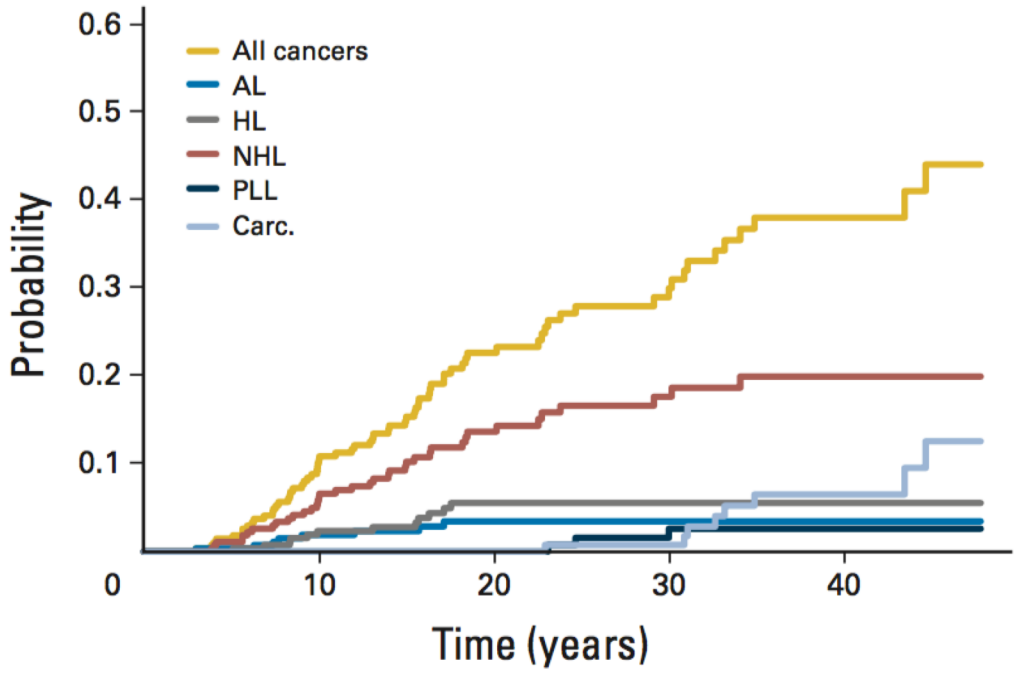
- Jonkman-Berk et al., NL-(ESID)
  Clin Immunol 2015, 156:154-162
- n_{cancer}=**70 in 745 patients (10%)**
- typically lymphoma and skin tumors in patients with hypogamma/CVID and AT at younger age than „normal“
- Mayor et al., USIDNET,
  J Allergy Clin Immunology 2018; 141(3): 1028-1035
- n_{cancer} =**171 in 3658 patients (4,7%)**
- vast majority lymphoma and „lymphoid“ cancers, skin, hematologic, (thyroid in CVID)

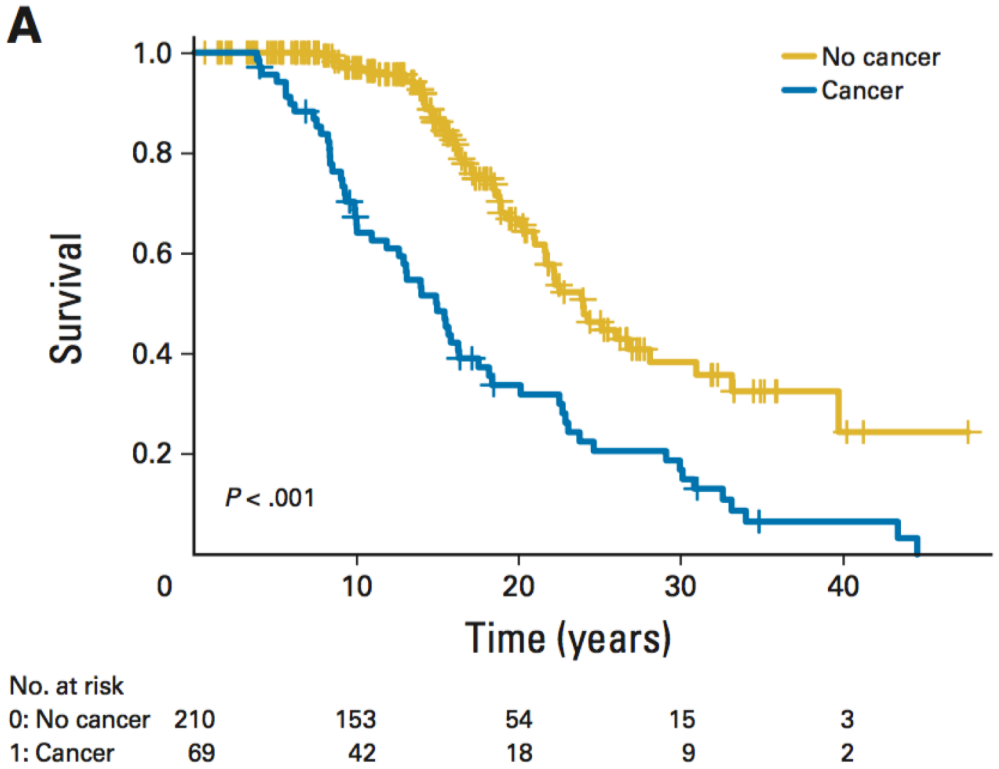




Cancer in Ataxia teleangiectasia

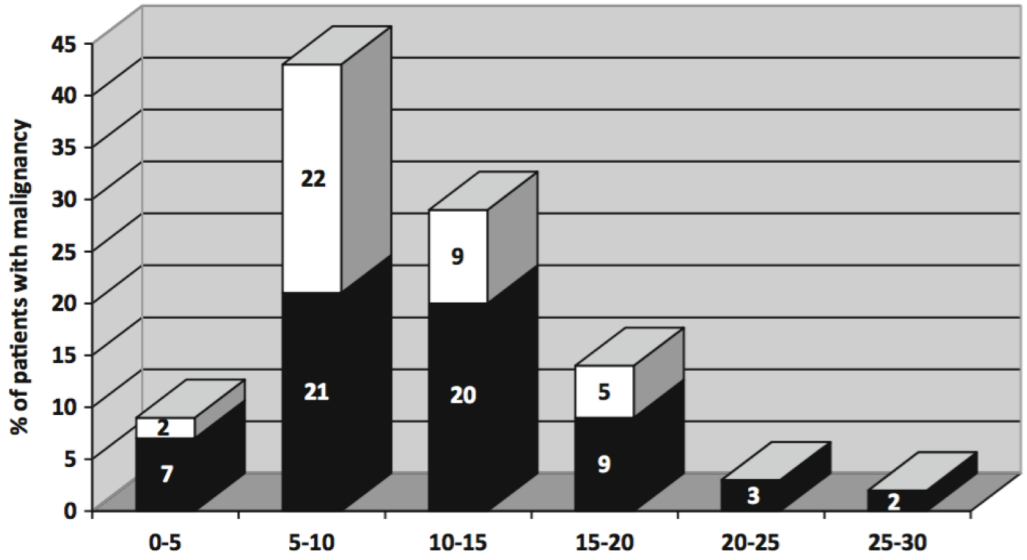
- Suarez et al., *JCO 2015; 33:202-208*
- 70 malignancies in **69 of 279 pts (25%)**
- NHL, HD, Ca, ALL, T-PLL, AML

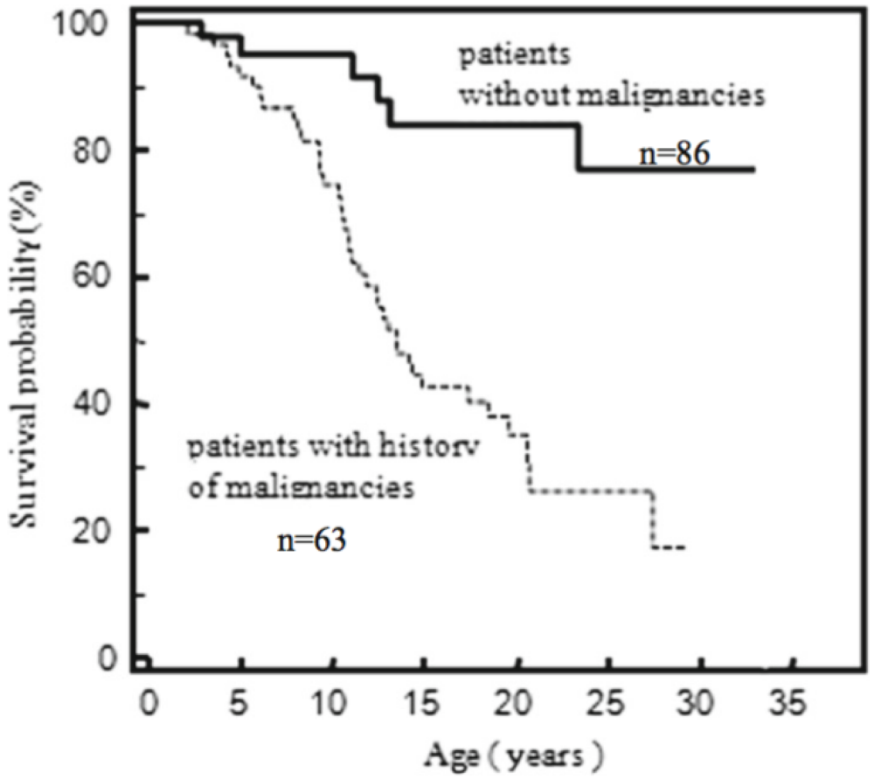




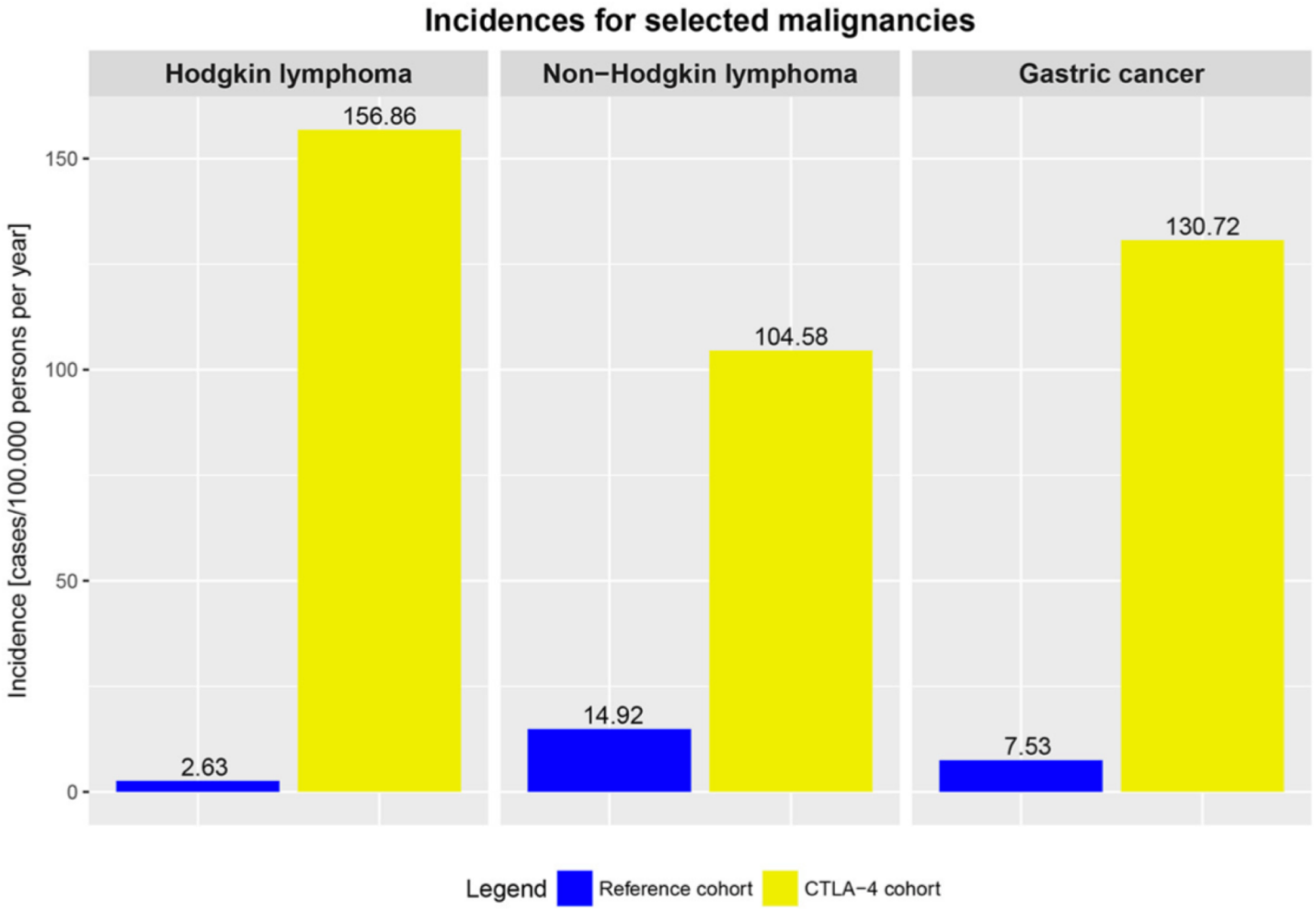
Cancer in Nijmegen Breakage Syndrome

- Wolska-Kusnierz et al,
  J Clin Immunol 2015, 35:538-549
- 80 malignancies in **60 of 149 patients (42%)**
- mostly B-NHL, T-NHL, HD, T-ALL...





Cancer in CTLA4 Haploinsufficiency



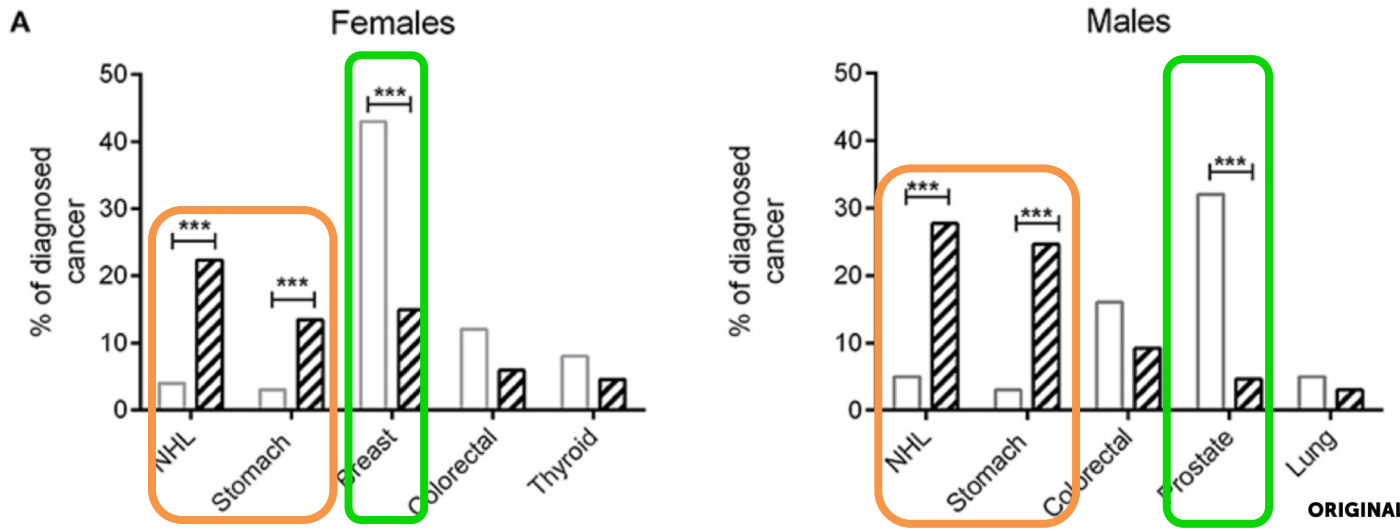
ORIGINAL RESEARCH
published: 10 September 2018
doi: 10.3389/fimmu.2018.02012

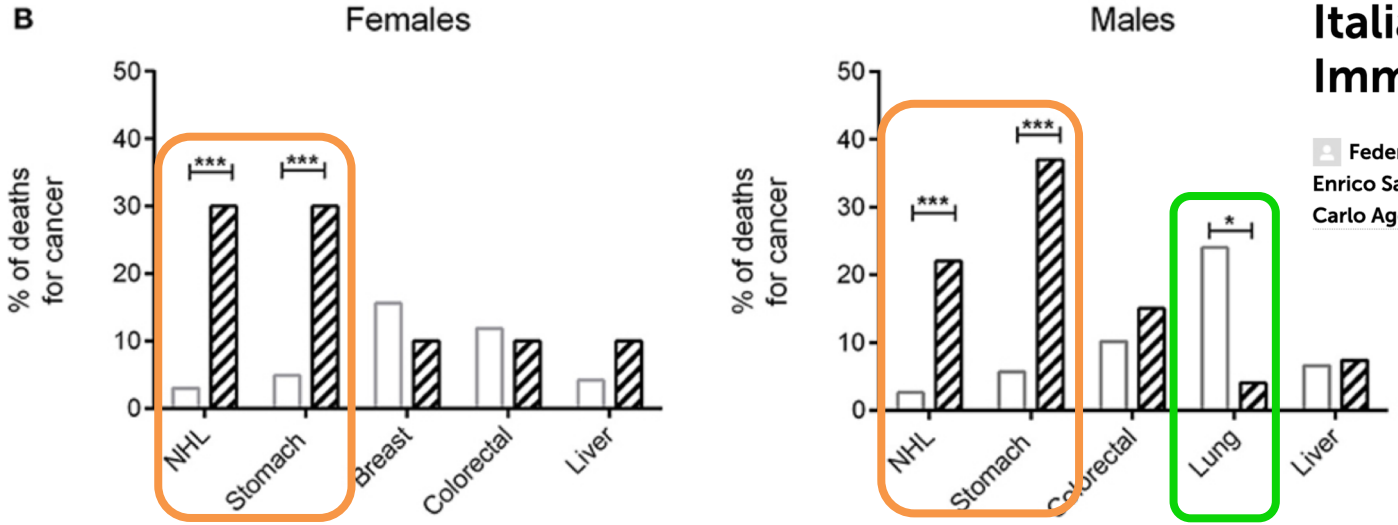
frontiers in Immunology

Increased Risk for Malignancies in 131 Affected *CTLA4* Mutation Carriers

David Egg[1], Charlotte Schwab[1], Annemarie Gabrysch[1], Peter D. Arkwright[2], Edmund Cheesman[2], Lisa Giulino-Roth[3], Olaf Neth[4], Scott Snapper[5], Satoshi Okada[6], Michel Moutschen[7], Philippe Delvenne[7], Ann-Christin Pecher[8], Daniel Wolff[9], Yae-Jean Kim[10], Suranjith Seneviratne[11], Kyoung-Mee Kim[12], Ji-Man Kang[13], Samar Ojaimi[14], Catriona McLean[15], Klaus Warnatz[1], Maximilian Seidl[1] and Bodo Grimbacher[1]*

Cancer in CVID





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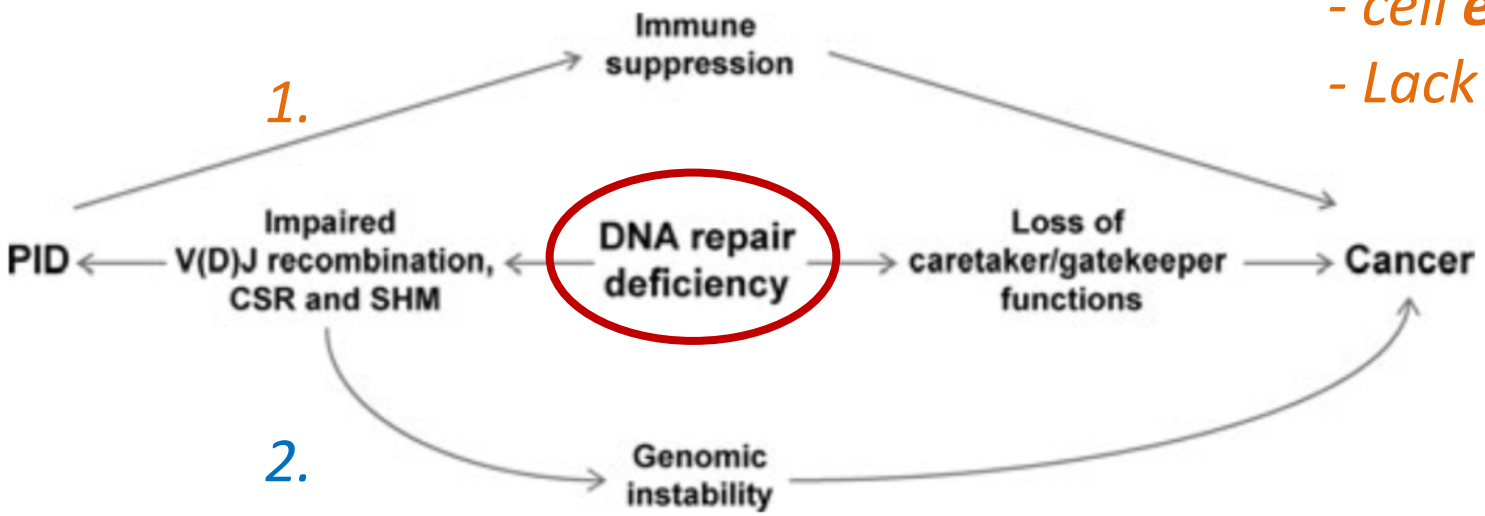
ORIGINAL RESEARCH ARTICLE

Front. Immunol., 05 November 2018 | https://doi.org/10.3389/fimmu.2018.02546

Gastric Cancer Is the Leading Cause of Death in Italian Adult Patients With Common Variable Immunodeficiency

Federica Pulvirenti[1], Antonio Pecoraro[2], Francesco Cinetto[3], Cinzia Milito[1], Michele Valente[4], Enrico Santangeli[1], Ludovica Crescenzi[2], Francesca Rizzo[3], Stefano Tabolli[5], Giuseppe Spadaro[2], Carlo Agostini[3] and Isabella Quinti[1*]

Which mechanisms cause malignancies in IEI?
→ example DNA repair: it's not always lack of immunosurveillance



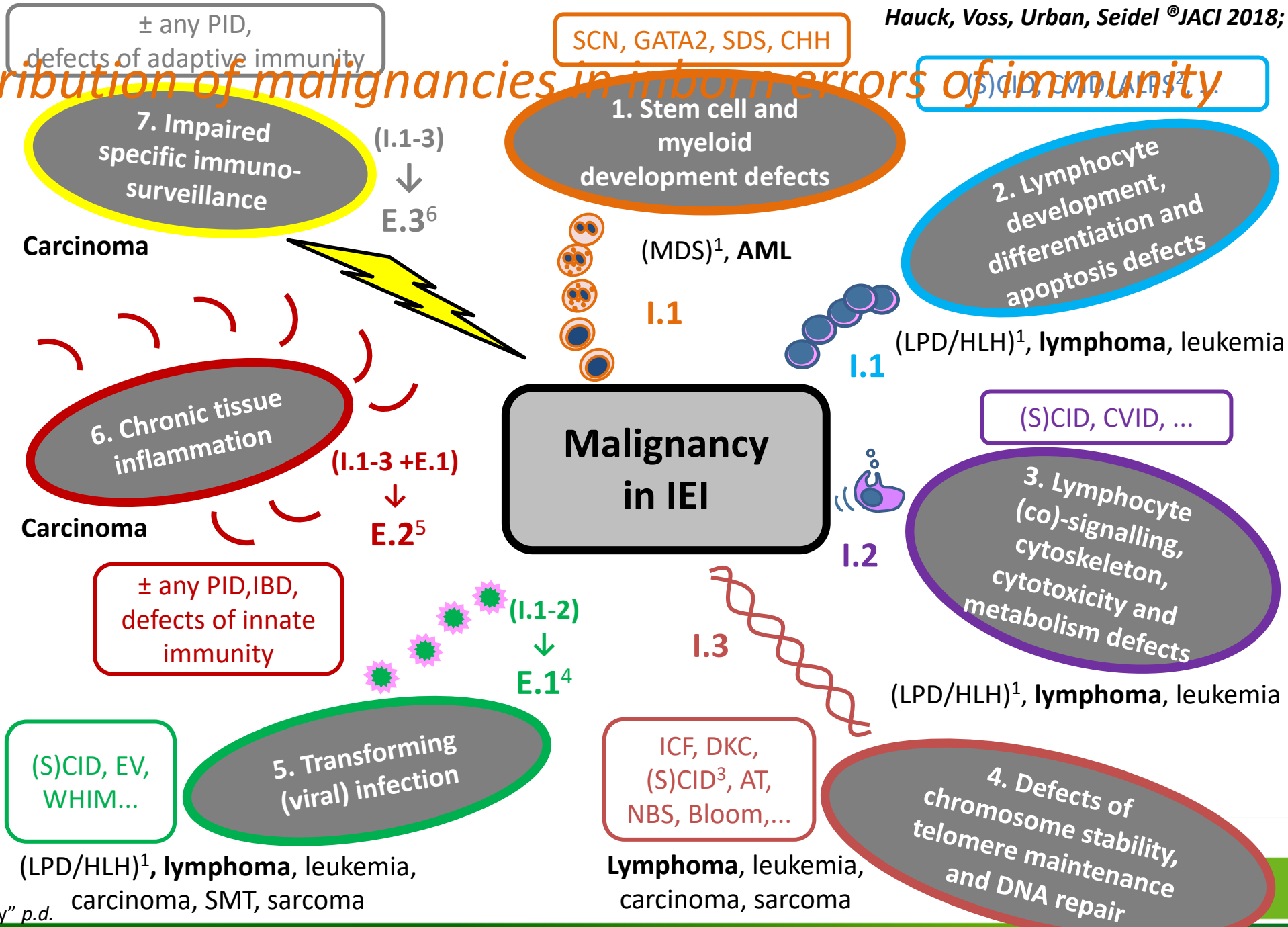
1. Tumorigenesis "in series" to IEI
*- cell **extrinsic** tumor predisposition;*
*- Lack of **immune surveillance***

2. Tumorigenesis "in parallel" to IEI
*- cell **intrinsic** tumor predisposition*
Hauck et al. 2018

De Miranda, Björkman, and Pan-Hammarström
Ann. N.Y. Acad. Sci. 1246 (2011) 50–63

Distribution of malignancies in inborn errors of immunity

Hauck, Voss, Urban, Seidel ®JACI 2018; 141(1):59-68



[1], no "malignancy" *p.d.*

Examples NHL and ALL: linked to which IEI ?

NHL → 160 patients with genetic + 53 chromos./other conditions
EICNHL, i-BFM
Attarbaschi et al., Haematologica 2016

ALL → 4.45%
AIEOP-BFM2000+9
Schütte et al., EJMG 2016

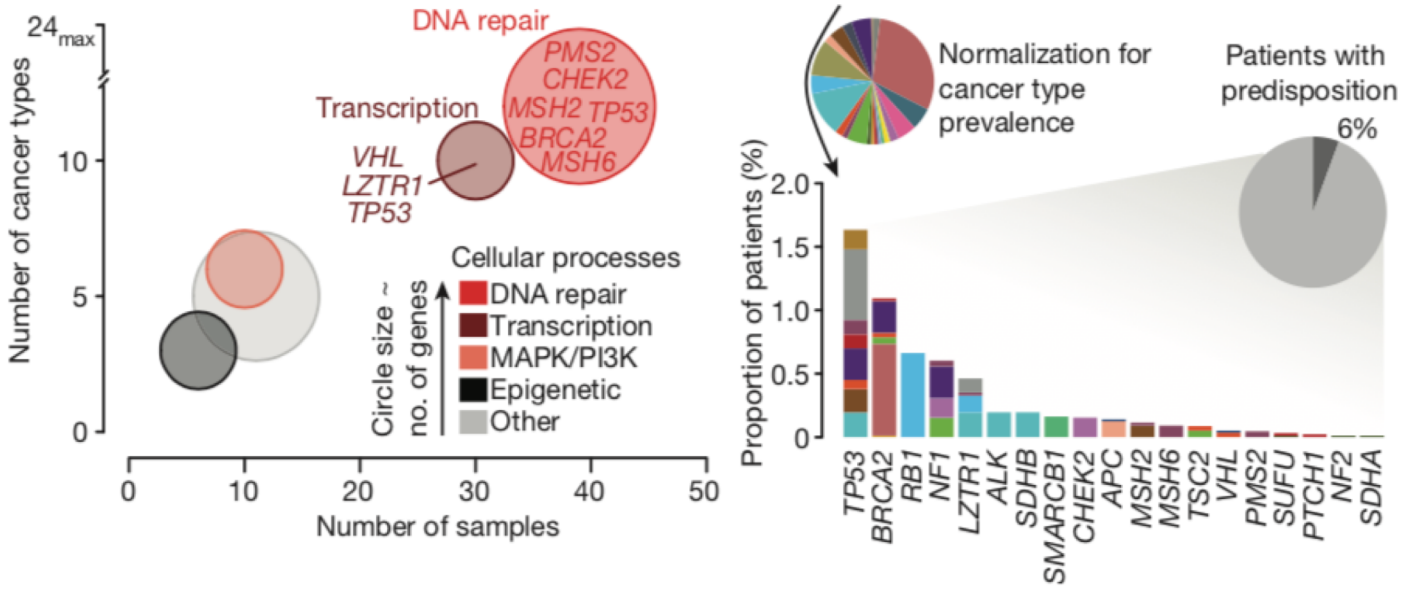
Table 1. Four categories of pre-existing conditions in 213 patients with non-Hodgkin lymphoma.

Type of pre-existing condition	Condition (mode of transmission, incidence *per* live birth)	N. patients
All patients		213
Cancer predisposition syndrome (n>1 patient)		124
	Ataxia telangiectasia (AR, 1:4000)	32 (26%)
	Nijmegen breakage syndrome (AR, 1:100,000)	26 (21%)
	Constitutional mismatch repair disease (AR and AD*, n.a.)	21 (17%)
	X-linked lymphoproliferative syndrome (recessive, 1:1,000,000)	11 (9%)
	Wiskott-Aldrich syndrome (X-linked recessive, 1:100,000-250,000)	7 (6%)
Immunodeficienc		
Genetic disease (n>1 patient)		
	Others (each in 1 patient)	26 (65%)

Type of condition	Condition	n (N = 242)	Frequency (BFM 2000)
Cancer predisposition syndromes		**29**	**21/4939 (0.43%)**
	Neurofibromatosis type I	8	6/4939 (0.12%)
	Ataxia telangiectasia	8	7/4939 (0.14%)
	Nijmegen breakage syndrome	6	4/4939 (0.08%)
	Noonan syndrome	2	2/4939 (0.04%)
	Fanconi anemia	1	0/4939
	Li Fraumeni syndrome	1	0/4939
	Lynch syndrome	1	0/4939
	LEOPARD syndrome	1	1/4939
	Rothmund Thomson syndrome	1	1/4939
Genetic conditions with no known cancer predisposition		**44**	**44/4939 (0.89%)**
	Gilbert's disease	13	13/4939 (0.26%)
	Thalassemia minor	7	7/4939 (0.14%)
	Cystic fibrosis	4	4/4939 (0.08%)
	Glucose-6-P-DH deficiency	4	4/4939 (0.08%)
	alpha-1-AT deficiency	2	
	Primary ciliary dyskinesia	2	
	Di George syndrome	1	

The unbiased approach: "The landscape of genomic alterations in childhood cancers" – Gröbner et al. Nature 2018

- *n*=961 (tumor samples, not naturally distributed)
- TP53 the most frequent germline predisposition across many tumor entities
- DNA repair pathways the largest group
- IEI not frequently detected, but leukemia and lymphoma under-represented !



Gröbner et al., Nature 2018; 555(7696):321-327

The educational approach: The "Iceberg Map" of germline predisposition to childhood cancer – a kind of metareview

we collected published data:

- *n*=2016 (tumor samples, not naturally distributed) from 4 studies:
  - 348 germline mutations
  - In 47 genes

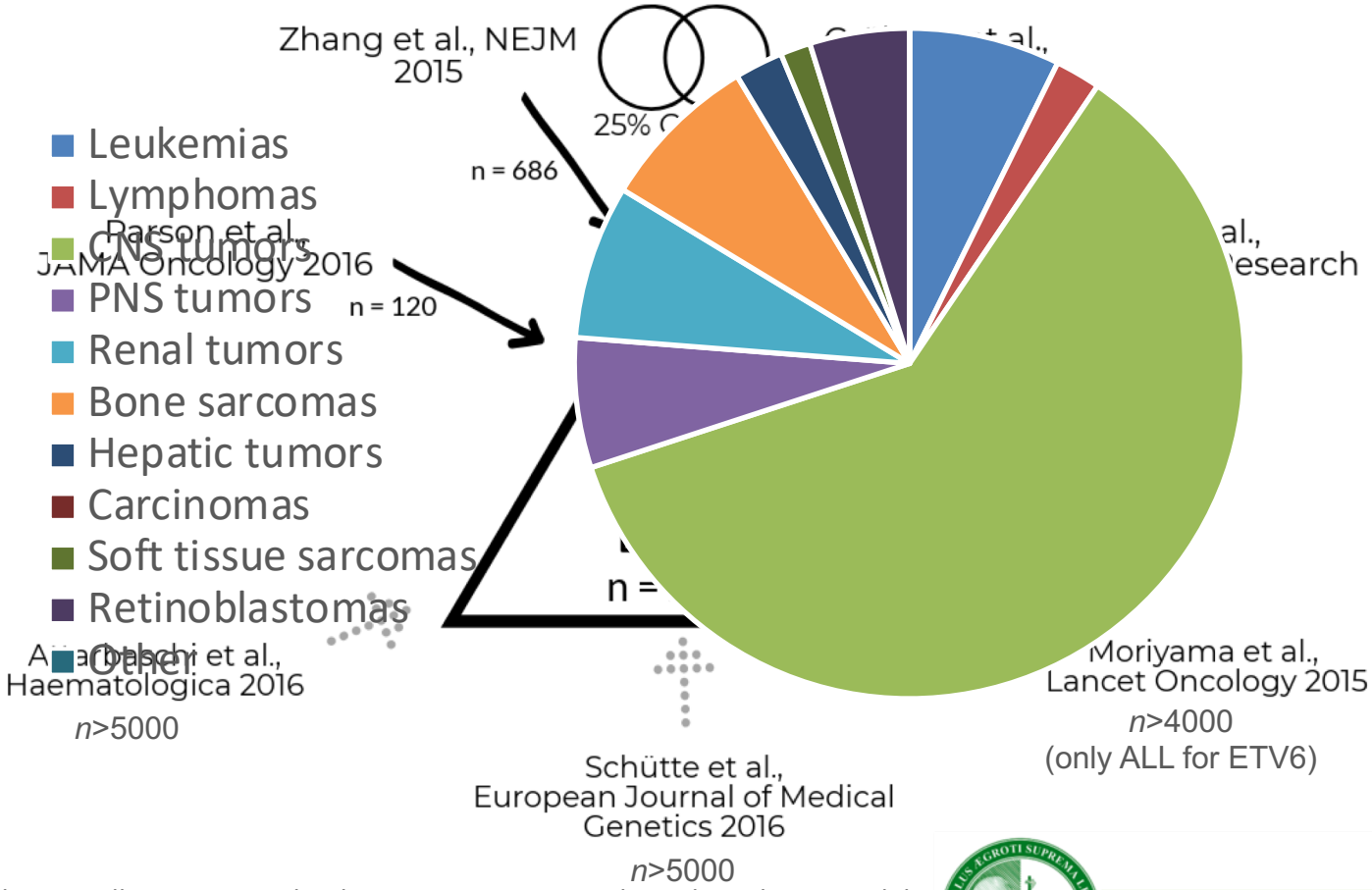
plus…

- retrospective or history data from 3 studies comprising >10.000 patients (ALL; NHL)

… in 12 childhood cancer types (more natural distribution, but still lacking data on HD, and AML)

… thus, strictly, no meta-analysis

Composition of 'tumor sample cohort'



Oliver Kindler, Franz Quehenberger, Martin Benesch, and Markus G Seidel
Curr Opin Pediatr. 2018; 30:855 – 863; PMID: 30124581

perspectives **icebergs** IEI & oncogenes clinical relevance

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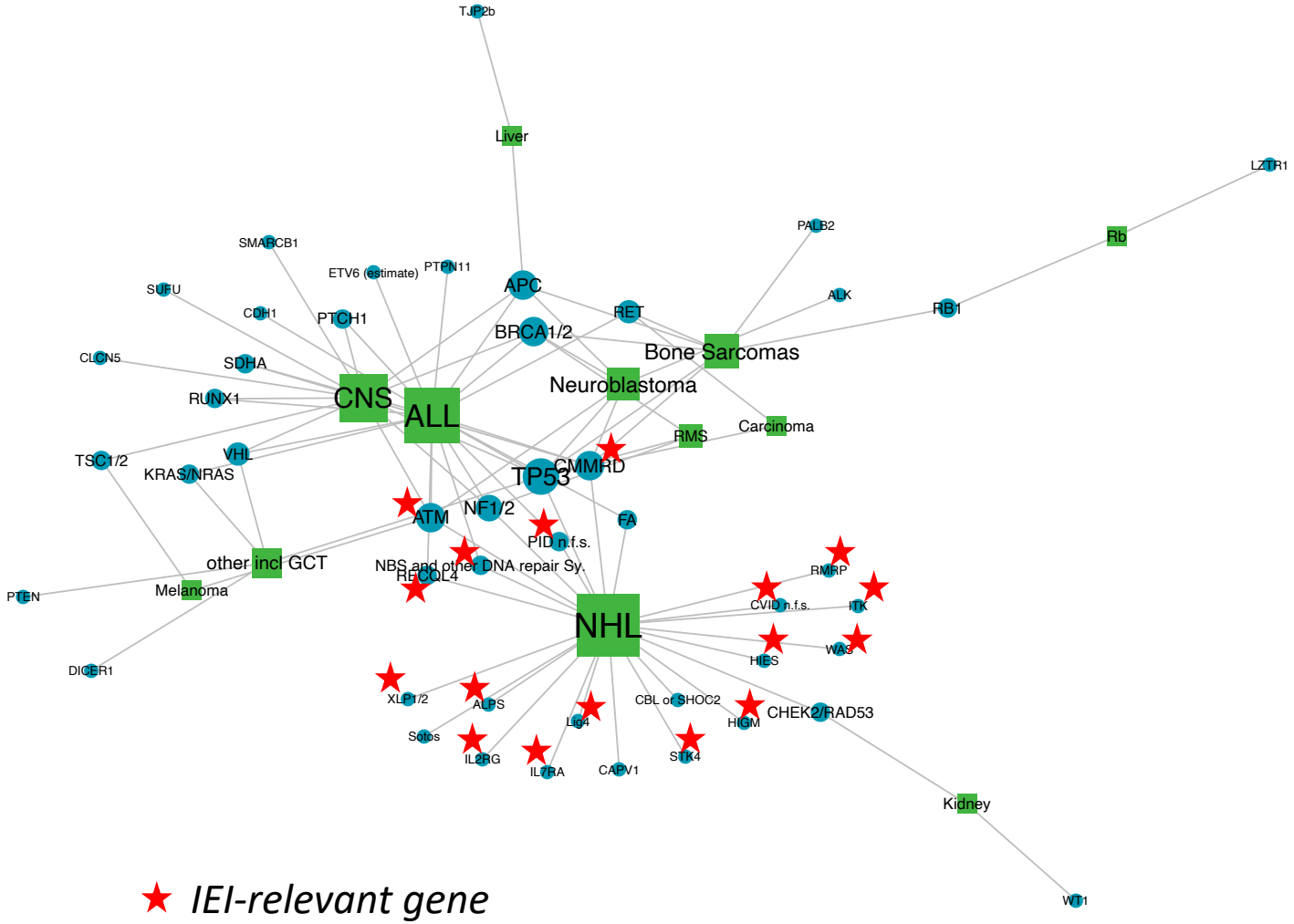

★ *IEI-relevant gene*

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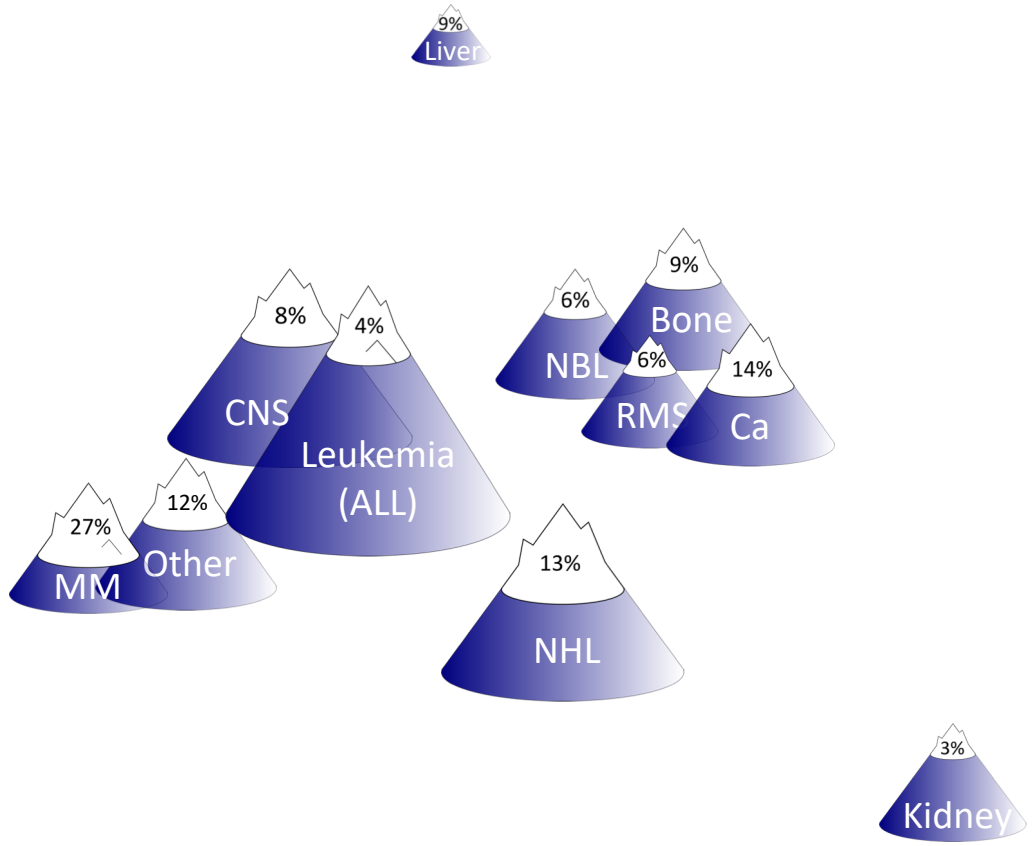

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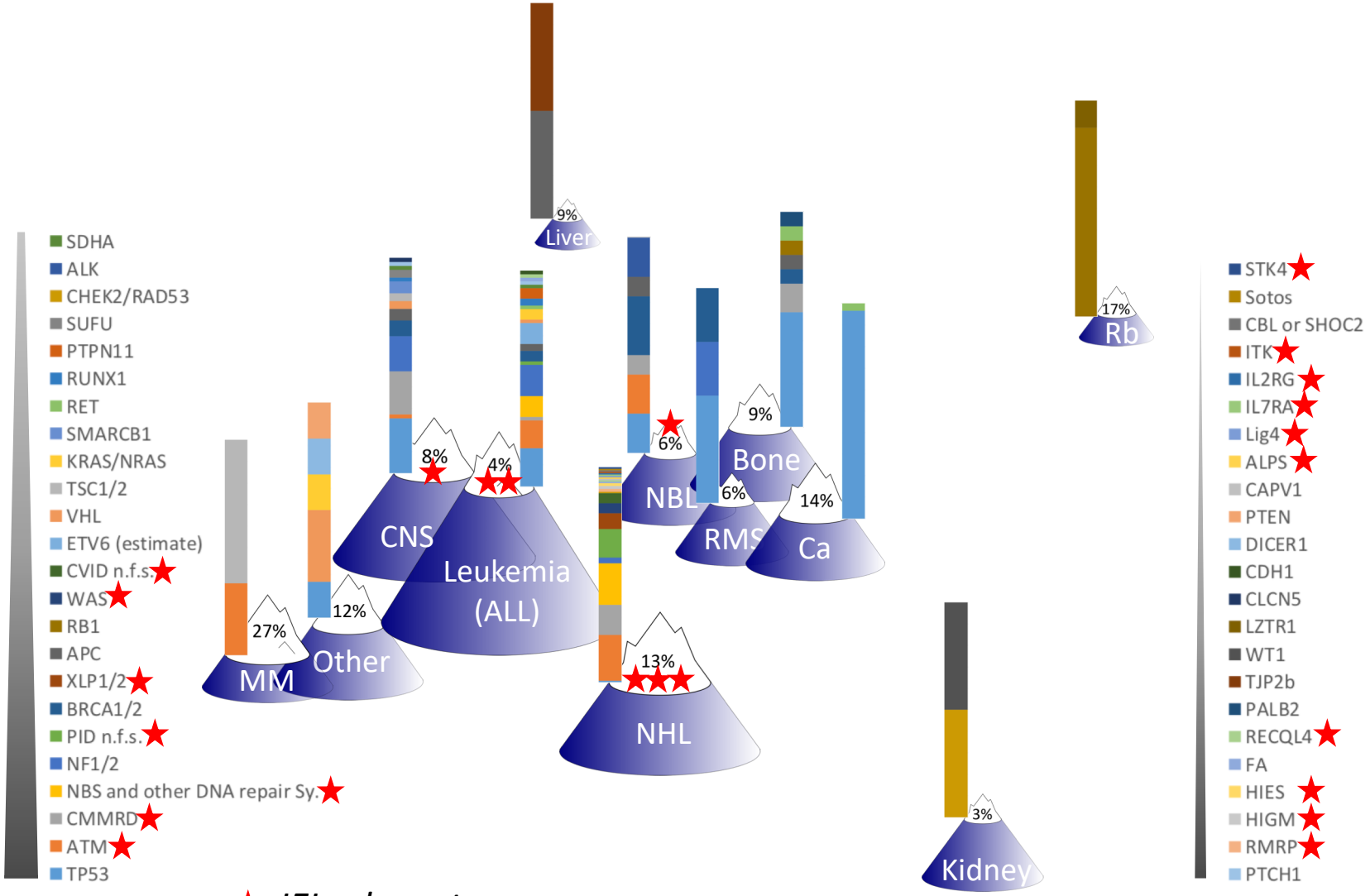


★ *IEI-relevant gene*

Malignancies in inborn errors of immunity (IEI) – Conclusions

1. There are **intrinsic and extrinsic mechanisms** of tumorigenesis in IEI
2. Today we only see the **tips of the icebergs (4-13%) considered to be caused by germline predisposition** in pediatric oncology,
3. The pattern of germline mutations differs between tumor entities and can give **clues about tissue factors and tumor propagating events**
4. **IEI represent a relevant proportion of CPS in leukemia and lymphoma**
5. The **relative prevalence of tumor types, and the age and sex distribution, differ** between IEI patients and the general population
6. The **outcome of malignancies in PID patients is worse** than in the general population

Malignancies in IEI – Needs and perspectives

For immunologists

Diagnose malignancy early

- **screening / surveillance**? Imaging, biomarkers?
- pitfalls?

Treat malignancy better (also for oncologists)

- individualize therapy, based on pathways and **expectable toxicities**
- Infection risks, preexisting organ damage

Follow-up

- …transplanted SCID patients, because part of their intrinsic **tumor predisposition may persist**

Prevention?

- Infectious triggers?
- long-term immunomodulatory treatment?
- reduce selection pressure (e.g. GCSF in SCN)

<u>Guidelines and prospective studies needed</u>

For oncologists

Biology

- Which pathways of tumorigenesis are shared, which differ between IEI and "normal" cancers
- what are the *second hits* in IEI
- Are there **different evolutionary events** and selection in IEI patients that are **druggable**

Therapy

- Will **immunotherapy** work against cancer in IEI patients – functional immune system as prerequisite?
- higher mutational burden as benefit (more neoantigens)?

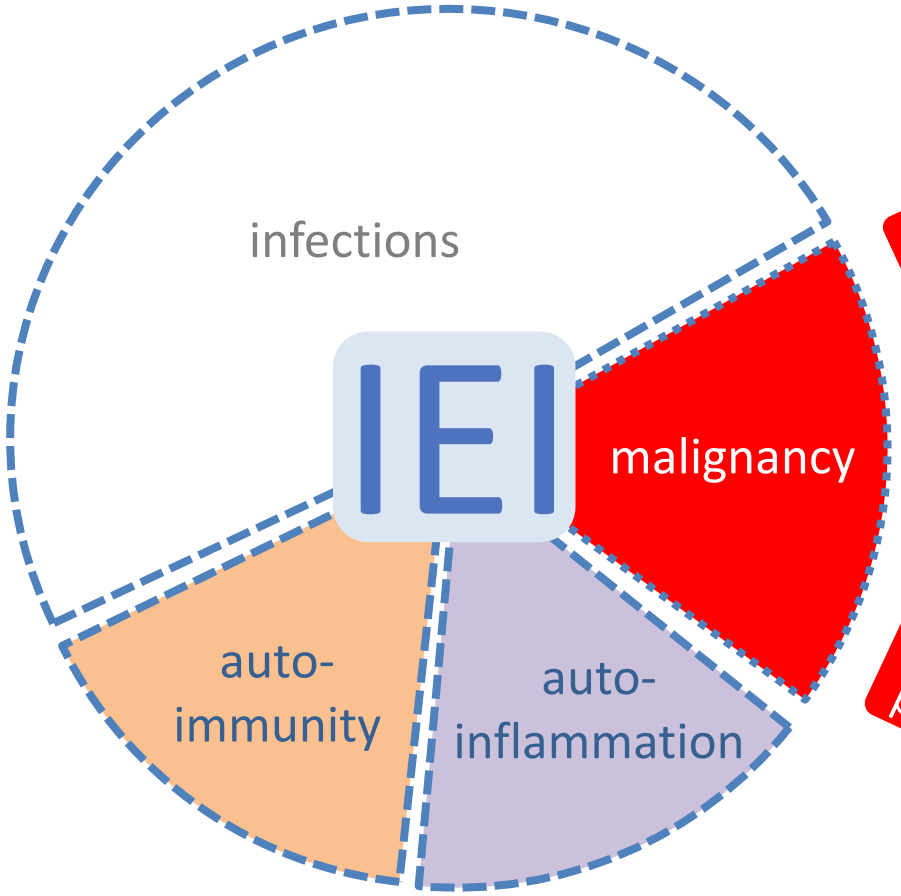
In practice

- Patients should be **screened for "preexisting conditions"** including underlying IEI

<u>Guidelines and prospective studies needed</u>

clinical relevance
IEI & oncogenes
icebergs
perspectives

Malignancies in IEI – Needs and perspectives



I. Improve clinical diagnosis → awareness, screening, guidelines

II. Improve histopathological diagnosis → IEI-specificity? targets?

III. Improve treatment incl. HSCT → adapt toxicity, include IEI in HSCT evaluation (pro/con!), residual CPS in DNARD!

IV. Understand tumor pathogenesis

V. Assess novel targeted therapies → Specific second hits, identify (preventable) progression steps?

VI. Identify IEI/DNARD following primary malignancy diagnosis

ESID CWP | IEWP

EBMT IEWP

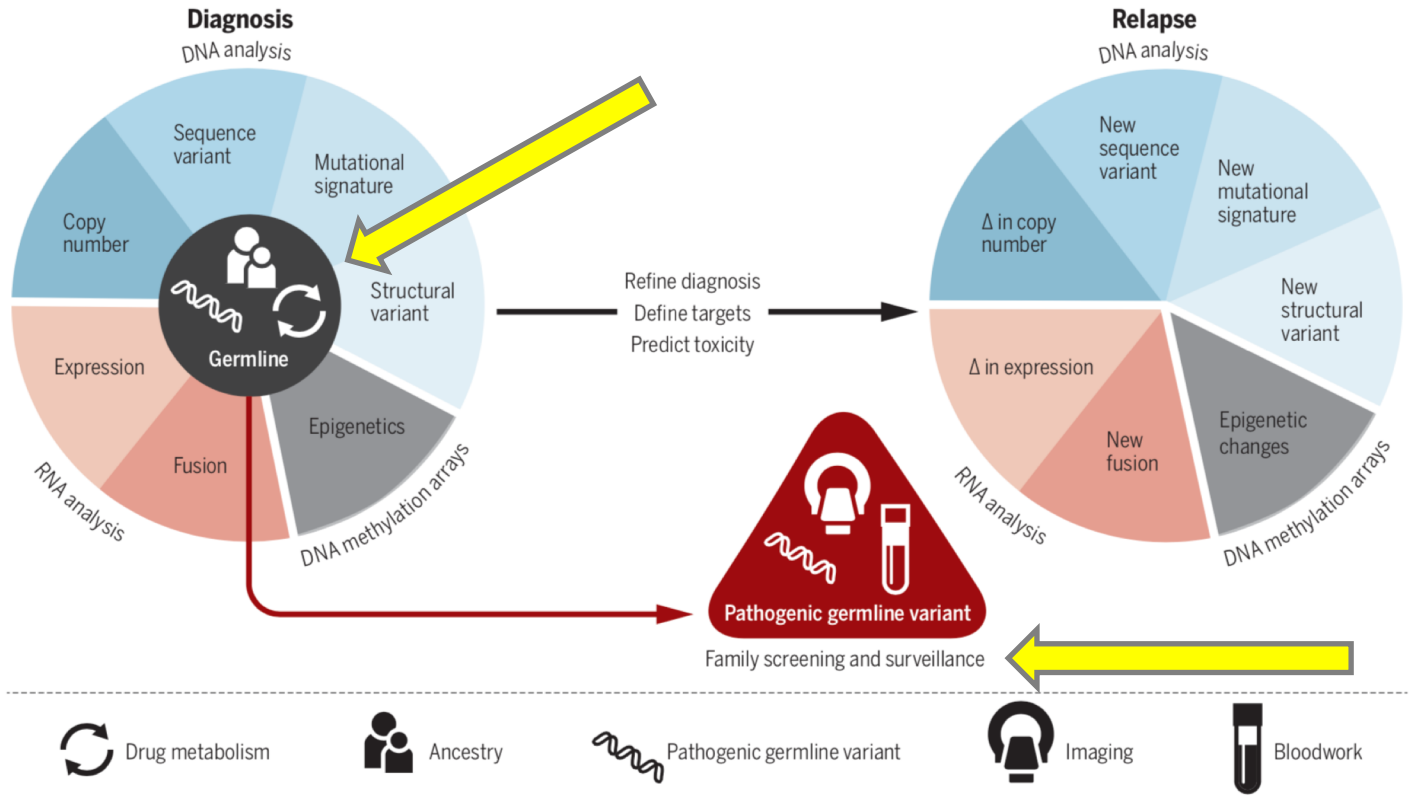
ERN RITA

iBFM Host Var. TF

EICNHL

Bomken et al., 2018, Front Immunol 9: 2912. doi: 10.3389/fimmu.2018.02912

Malignancies in IEI – Ethical concerns and biological opportunities



- AN increasing proportion of IEI patients will be identified through oncology
- Incorporate cancer predisposition in genetic counseling for IEI
- Awareness for (often unsatisfactory) screening options
  - Regular ultrasound? Blood tests?
  - MRI instead of CT (even lung)?
  - Few realistic surveillance options for leukemia and lymphoma predisposition…
- Handle expectable and unexpected toxicities
  - Develop recommendations
- Different psychological approach to cancer of patients with chronic disease

Sweet-Cordero and Biegel, Science 2019; 363, 1170–1175.

- there are more targets (many not functionally evaluated) than targeted drugs

- urgent need for better screening and prevention

- limited understanding of the genomics of relapse, metastasis, and of toxicity or poor response to tx

Acknowledgements

Pediatric
Hematology-Oncology

THANK YOU for your attention

Research Unit
Pediatric Hematology & Immunology

www.sic-reg.org

- Oliver Kindler, Graz (icebergs, sic-reg.org)
  Victoria Tesch, Graz (CMMRD, LRBA)
  Rebecca Voss, Graz/Freiburg (Fanconi A. and IEI as CPS)
- *Collaborators*
  Kaan Boztug, Vienna (Inborn Errors of Immunity)
  Fabian Hauck, Munich (IEI and malignancies)
  Andrew Gennery, Newcastle (IEI and malignancies)
  Katharina Wimmer, Innsbruck (CMMRD)
- *Team and Head of Pediatric Hematology Oncology, Graz*
  Martin Benesch, Graz | until 2017: Christian Urban
  Styrian Children's Cancer Aid Fund, Austria
- *Previous Mentors and Collaborators*
  Helmut Gadner, Vienna | Oskar Haas, Vienna
  Michael Freissmuth, Vienna | Tom Look, Boston
  Elisabeth Förster-Waldl, Andreas Heitger, Vienna