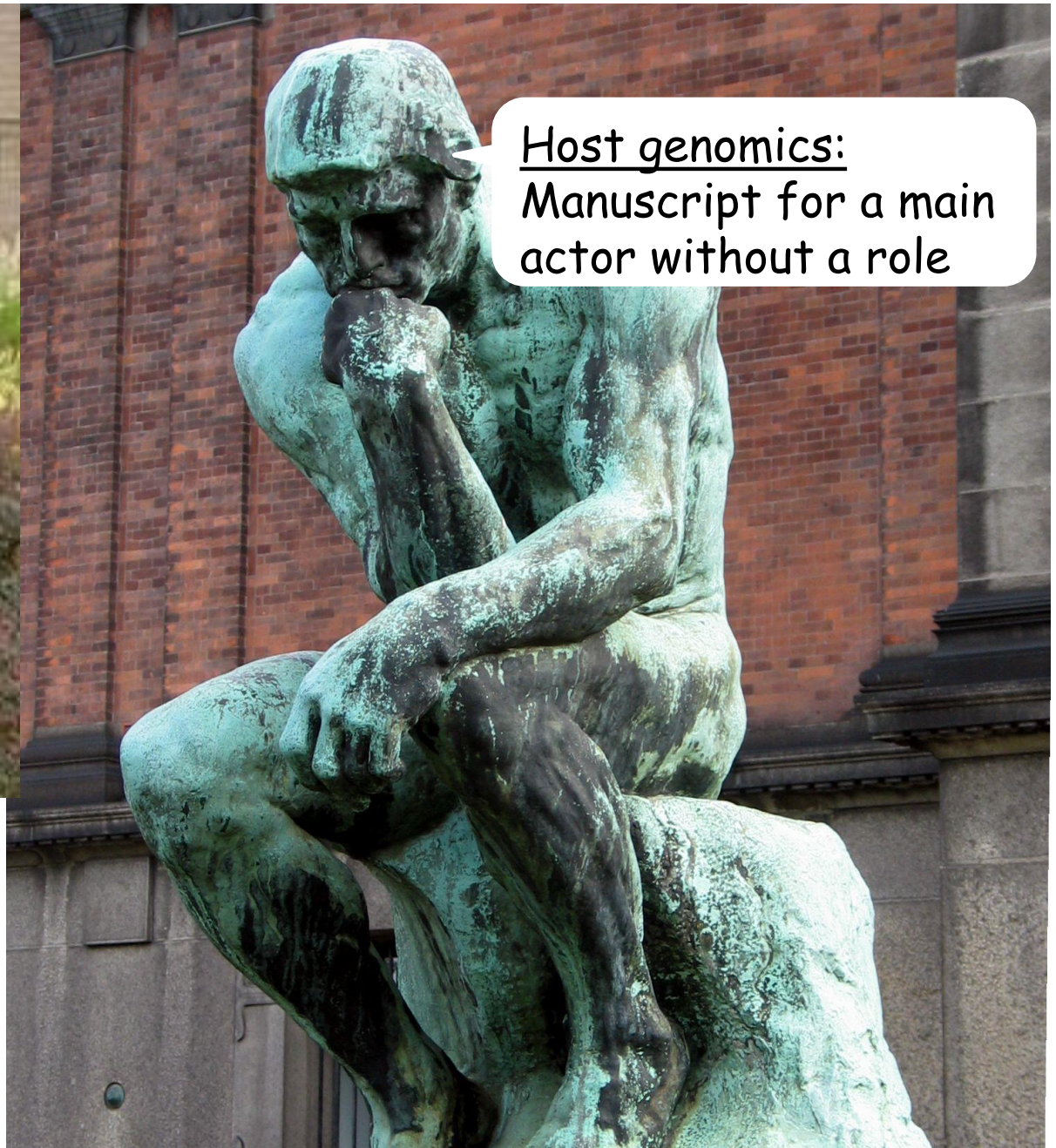
Disclosures Kjeld Schmiegelow

- Medscape (speaker honoraria)
- Amgen (speaker honoraria),
- Servier (consultancy, speaker honoraria, Educational grant)
- Jazz Pharmaceuticals (consultancy, speaker honoraria)

Toxicities in ALL due to host factors - Can we prevent them?

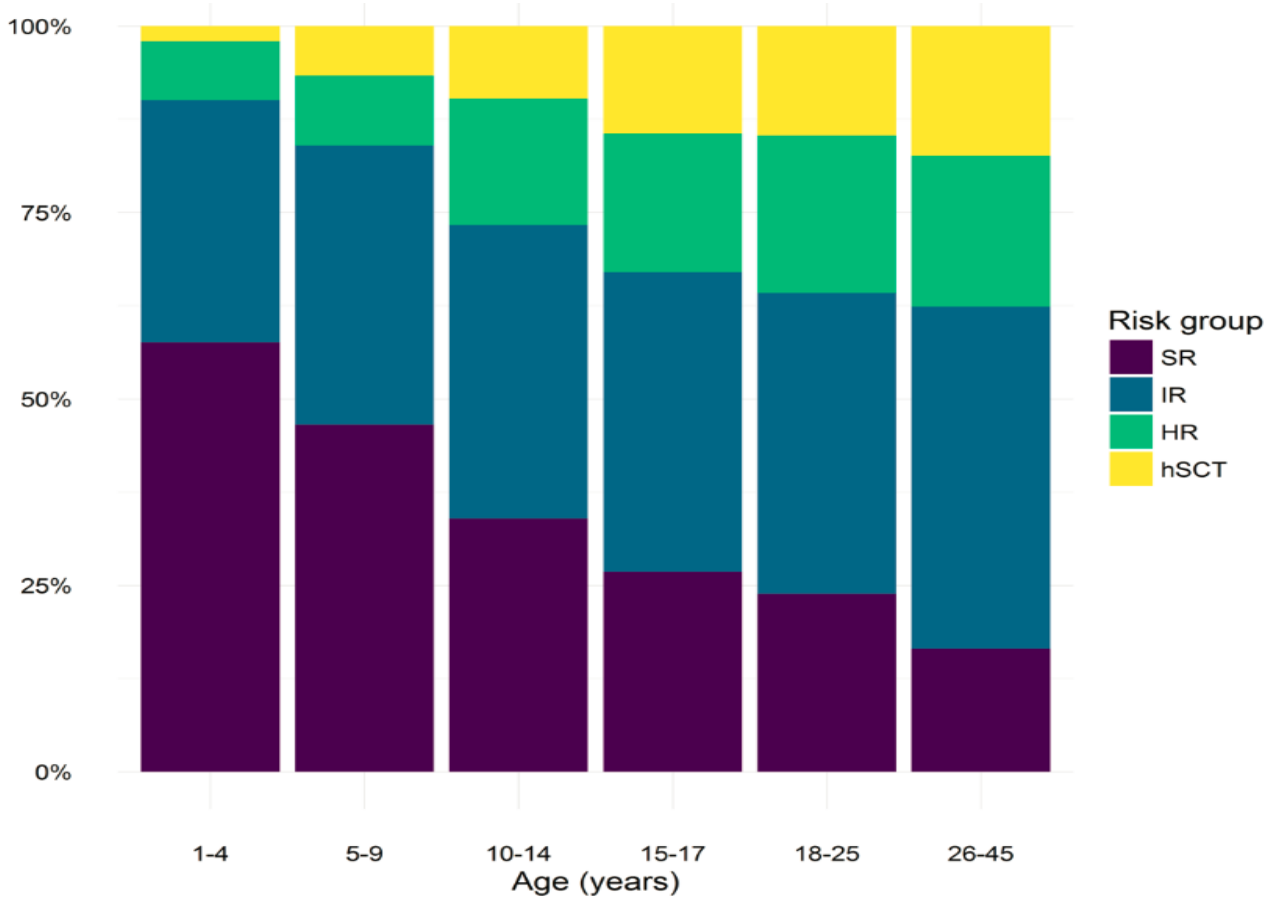


Challenges in hematology
Best of EHA 2022
Under the aegis of
Mumbai Haematology Group

Kjeld Schmiegelow
Pediatric hematology/oncology
Rigshospitalet University Hospital
Copenhagen, Denmark
kschmiegelow@rh.dk

Higher age associates with higher risk group allocation

NOPHO ALL2008 study (1-45 years)



Patients, %	Adults 18-45 y (n = 221)	Adolescents 10-17 y (n = 266)	Children 1-9 y (n = 1022)	*P*
Induction Death	1	1	1	.87
Death in remission	6	6	2	.006
5y CNS relapse	2	3	1	.12
5y Relapse any	**17**	**9**	**6**	**< .001**
SMN	0	1	1	.42

*Very intensive block therapy.†hSCT indications: D29 MRD ≥5.0% (confirmed by FCM), D79 MRD ≥0.1%.

Identical diagnostics/MRD-monitoring/risk grouping across age groups

Higher risk, older groups for AYAs reflect:

- Higher **T-cell** frequency (32%, 25%, 9%), ***rKMT2A*** (6%, 5%, 3%), **higher EOI MRD**

Toft. Eur J Haematol. 2013;90:404. Toft. Leukemia. 2018;32:606.

NOPHO ALL2008; 7/08-12/14

1-9y: 1022; 10-17y: 266; 18-45y: 221

Generally, no difference in treatment delays

13.2%; Henriksen, Ped Blood Cancer 2015
Incidence im = iv; Brigitha, Eur J Cancer 2022

1 host
1 disease
Many organs

8.3%; Rank, JCO 2020

Not systematically monitored

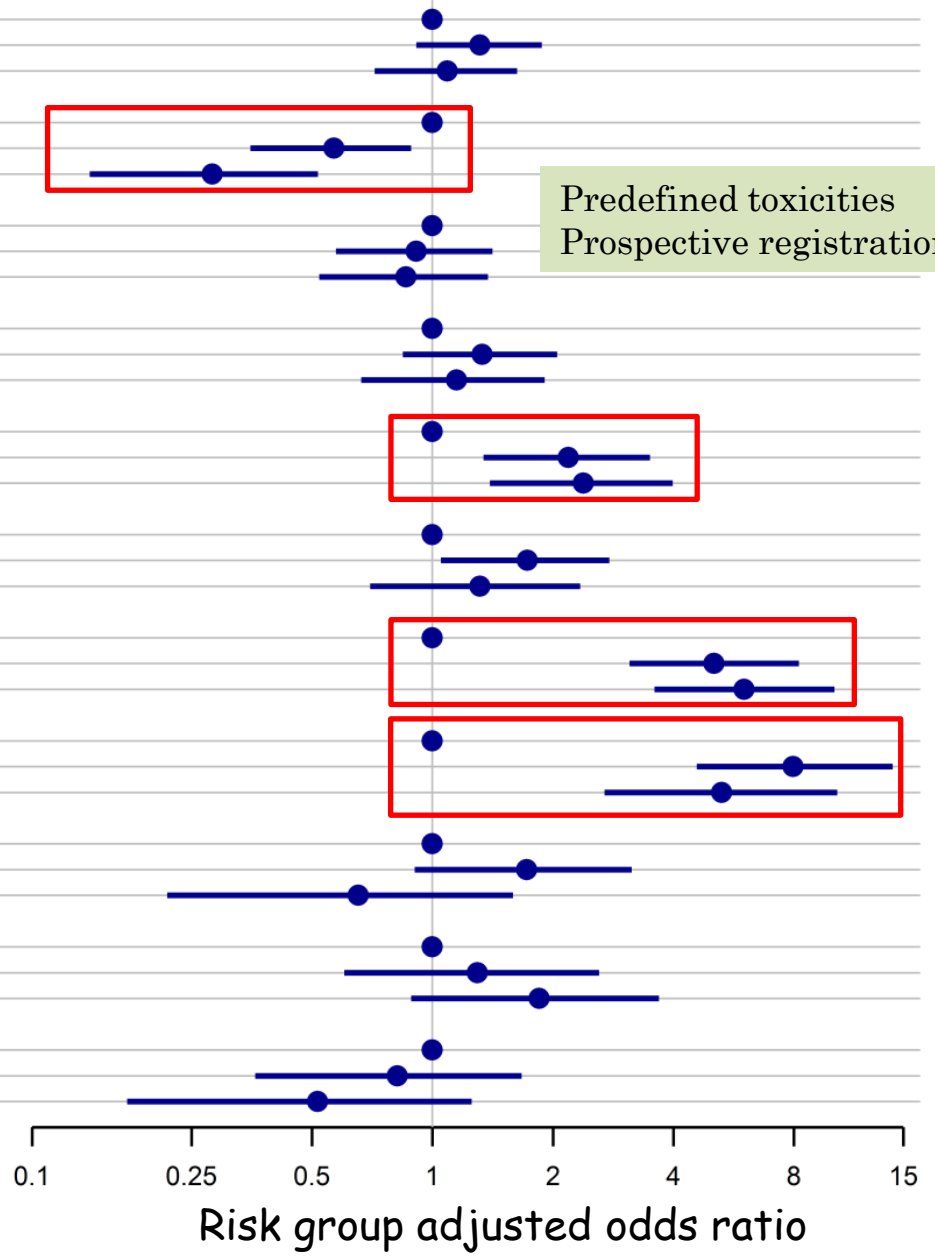
7.9%; Rank, Blood 2018

6.3%; Mogensen, Ped Blood Cancer 2018

5.5%; Anastosopoulou, Eur J Paed Neurol 2020
53% due to PRES; 11% due to SVT

3.7%; Anastasopoulou, Ped Blood Cancer 2019

	Y/N (%)	OR (95% CI)	P	P trend
Intensive care w/wo assisted ventilation				
1-9	145 / 864 (14.4%)	1.0 (1.0- 1.0)		0.50
10-17	54 / 208 (20.6%)	1.3 (0.9- 1.9)	0.14	
18-45	40 / 172 (18.9%)	1.1 (0.7- 1.6)	0.68	
Anaphylatic reaction to asparaginase				
1-9	146 / 863 (14.5%)	1.0 (1.0- 1.0)		<0.001
10-17	25 / 237 (9.5%)	0.6 (0.4- 0.9)	0.016	
18-45	11 / 201 (5.2%)	0.3 (0.1- 0.5)	<0.001	
Invasive Fungal infection				
1-9	98 / 911 (9.7%)	1.0 (1.0- 1.0)		0.92
10-17	32 / 230 (12.2%)	0.9 (0.6- 1.4)	0.68	
18-45	28 / 184 (13.2%)	0.9 (0.5- 1.4)	0.54	
Peripheral paralysis				
1-9	100 / 909 (9.9%)	1.0 (1.0- 1.0)		0.45
10-17	30 / 232 (11.5%)	1.3 (0.8- 2.1)	0.21	
18-45	20 / 192 (9.4%)	1.1 (0.7- 1.9)	0.61	
Pancreatitis				
1-9	60 / 949 (5.9%)	1.0 (1.0- 1.0)		<0.001
10-17	29 / 233 (11.1%)	2.2 (1.3- 3.5)	0.001	
18-45	24 / 188 (11.3%)	2.4 (1.4- 4.0)	0.001	
Hyperlipidemia				
1-9	72 / 937 (7.1%)	1.0 (1.0- 1.0)		0.12
10-17	26 / 236 (9.9%)	1.7 (1.0- 2.8)	0.027	
18-45	15 / 197 (7.1%)	1.3 (0.7- 2.3)	0.37	
Thrombosis				
1-9	36 / 973 (3.6%)	1.0 (1.0- 1.0)		<0.001
10-17	40 / 222 (15.3%)	5.0 (3.1- 8.2)	<0.001	
18-45	37 / 175 (17.5%)	6.0 (3.6-10.1)	<0.001	
Osteonecrosis				
1-9	23 / 986 (2.3%)	1.0 (1.0- 1.0)		<0.001
10-17	35 / 227 (13.4%)	8.0 (4.6-14.1)	<0.001	
18-45	18 / 194 (8.5%)	5.3 (2.7-10.3)	<0.001	
Seizures				
1-9	38 / 971 (3.8%)	1.0 (1.0- 1.0)		0.88
10-17	16 / 246 (6.1%)	1.7 (0.9- 3.1)	0.086	
18-45	5 / 207 (2.4%)	0.7 (0.2- 1.6)	0.39	
PCP				
1-9	29 / 980 (2.9%)	1.0 (1.0- 1.0)		0.37
10-17	11 / 251 (4.2%)	1.3 (0.6- 2.6)	0.48	
18-45	13 / 199 (6.1%)	1.8 (0.9- 3.7)	0.089	
PRES				
1-9	37 / 972 (3.7%)	1.0 (1.0- 1.0)		0.37
10-17	9 / 253 (3.4%)	0.8 (0.4- 1.7)	0.60	
18-45	5 / 207 (2.4%)	0.5 (0.2- 1.3)	0.18	



Predefined toxicities
Prospective registration q 3 months

Schmiegelow, Lancet Oncol 2016
Toft, Eur J Haematol 2016
Toft, Leukemia 2018

Options for prevention of toxicity

Primary intervention / prophylaxis (anticipated toxicity risk)

- Infections: pre-emptive antibiotics
- Asp-hypersensitivity reactions: Pre-medication (antihistamine, steroid, H1/H2 antagonists)
- Asparaginase-associated hepatotoxicity: Lower Asp dose, change in schedule
- Tromboembolism: LMWH +/- antithrombin
- Osteonecrosis: Lipid-lowerin medication
- Vincristine-induced peripheral neuropathy: Individualized reduction in VCR dose

Changes in choice and dosage of the anticancer therapy

Secondary prevention

– Truncation of treatment with ”guilty” drug

– Prophylactic interventions (as above) & re-exposure

Toxicities that may lead to truncation of Asparaginase therapy

ASP-associated acute toxicities often leads to *changes in ASP therapy*, incl truncation:

- **Hypersensitivity** / inactivation (**5-10%** / 5-10% with Peg-ASP) — Less in AYA
- **Pancreatitis** (1-10 % dependent on N of doses) — More in AYA
- **Thromboembolism** (up to 20% in AYA) — More in AYA
- Hyperammonemia and encephalopathy (?)
- Hepatotoxicity and hyperbilirubinemia (<10% in younger, non-obese children)
- Hyperglycemia (not least with steroids) (4-20%; *non-ketotic*)
- **Hyperlipidemia** (very common; clinical significance?)
  - **Osteonecrosis** — More in AYA

im vs iv: Does not influence risk of hypersensitivity reactions*

Obesity (BMI >30 kg/m^2) is a general risk factor**

≥ 10 yrs more toxicity & risk of Asp truncation*** (IRR 3.5) and of relapse** (IRR 4.3)

Schmiegelow, Lancet Oncol, 2016
*Brigitha, Eur J Cancer 2022
**Egnell, Eur J Haematol 2020
***Egnell, Br J Haematol 2022

Common Asparaginase Toxicities in Adult Patients

Toxicity	Presentation	Incidence of Grade 3/4 AEs, %
Hypersensitivity	Allergic reaction Silent inactivation	4-10
Hepatotoxicity	Hyperbilirubinemia Transaminitis	24-39 34-54
Thrombosis	DVT/PE Cavernous sinus thrombosis	11-27
Pancreatitis	Laboratory finding Clinical	5-13
Hypertriglyceridemia	Laboratory finding	7-51
CNS toxicity	Fatigue Encephalopathy	2-14

Stock. Blood. 2019;133:1548. Toft. Leukemia. 2018;32:606. Aldoss. Blood. 2020;135:987.

Obesity and Asparaginase-Associated Toxicities

Grade 3/4 toxicities in CALGB 10403 (pediatric regimens) in AYA pts (≤40 yr) (N = 289)

Grade 3/4 AEs, n (%)	BMI <30 kg/m^2 n = 197 (%)	BMI 30-40 kg/m^2 n = 71 (%)	BMI ≥40 kg/m^2 n = 21 (%)	*P* Value
Nonhematologic	152 (77.2)	57 (80.3)	18 (85.7)	.685
Infection	43 (21.8)	19 (26.8)	9 (42.9)	.092
Hepatic toxicity	61 (31.0)	37 (52.1)	13 (61.9)	.001
ALT increase	47 (23.9)	25 (35.2)	11 (52.4)	.009
AST increase	14 (7.1)	17 (23.9)	6 (28.6)	<.0001
Hyperbilirubinemia	23 (11.7)	22 (31.0)	10 (47.6)	<.0001
Pancreatitis	4 (2.0)	2 (2.8)	2 (9.5)	.123
Hyperglycemia	52 (26.4)	28 (39.4)	10 (47.6)	.030

- Mostly after first dose, and often no recurrence (enhanced by myelosuppression; leukemia)
- Risks factors: older age, high BMI, *higher asparaginase dose (dose reduction feasible)*
- Prophylaxis /intervention:
  - Delay Asp (until after myelosuppressive phase)
  - L-carnitine may ameliorate (at least in some preclinical models)

Advani. Blood Adv. 2021;5:504.

Reasons for Discontinuation of ASNase in Children (1-17 yrs) on NOPHO ALL2008

Reason for Discontinuation	Main Cohort, n (%) (Total n = 1401)	Subcohort,* n (%) (Total n = 1115)	No ASNase Activity,† n
Clinical hypersensitivity	**208 (14.8)**	**157 (14.1)**	**139**
Pancreatitis	88 (6.3)	53 (4.8)	1
Thrombosis	24 (1.7)	14 (1.3)	--
Hyperlipidemia	10 (0.7)	8 (0.7)	--
Liver toxicity	7 (0.5)	7 (0.6)	--
Other (sepsis, seizure, study refusal, abdominal pain)	21 (1.5)	16 (1.4)	--
ASNase inactivation	--	(46 SI only) (4.1)	186
Total number of patients w/o exposure	**358 (25.5)**	**255 (22.9)**	**140**

*Patients with ASNase enzyme activity measurements.
†Only applies to patients in the subcohort.

Højfeldt. Blood. 2021;137:2373.

ASNase Truncation Increases Relapse Rates in ALL (Observational Studies)

Update on Pieters 2011[1]	Efficacy (EFS / DFS / relapse rate)		*P* < .05
	Less-Intensive ASNase, %	More-Intensive ASNase, %	
Extra 20 wk ASNase in T-ALL POG 8704[2] (EFS)	55	68	Yes
Extra 20 wk ASNase in T-NHL POG 8704[2] (4-Yr CCR)	64	78	Yes
≤ or >25 wk ASNase DFCI 91-01[3] (5-Yr EFS)	73	90	Yes
Extra 20 wk ASNase in IRG AIEOP ALL-91[4] (DFS)	72	76	No
Erwinase vs E coli ASNase EORTC-CLG 58881[5] (EFS)	60	73	Yes
Extra 20 wk ASNase I-BFM-SG/IDH-ALL-91[6] (DFS)	79	88	Yes
Erwinase vs *E coli* ASNase DFCI 95-01[7] (5-Yr EFS)	78	89	Yes
Truncated vs cont ASNase (*Erwinia*) (COG AALL0331/AALL0232)[8] (DFS)	Event HR: 1.5	Event HR: 1.1	Yes
Truncated (including no activity) vs cont Asp (NOPHO ALL2008)[9]	Relapse risk 11.1	Relapse risk 6.7	Yes

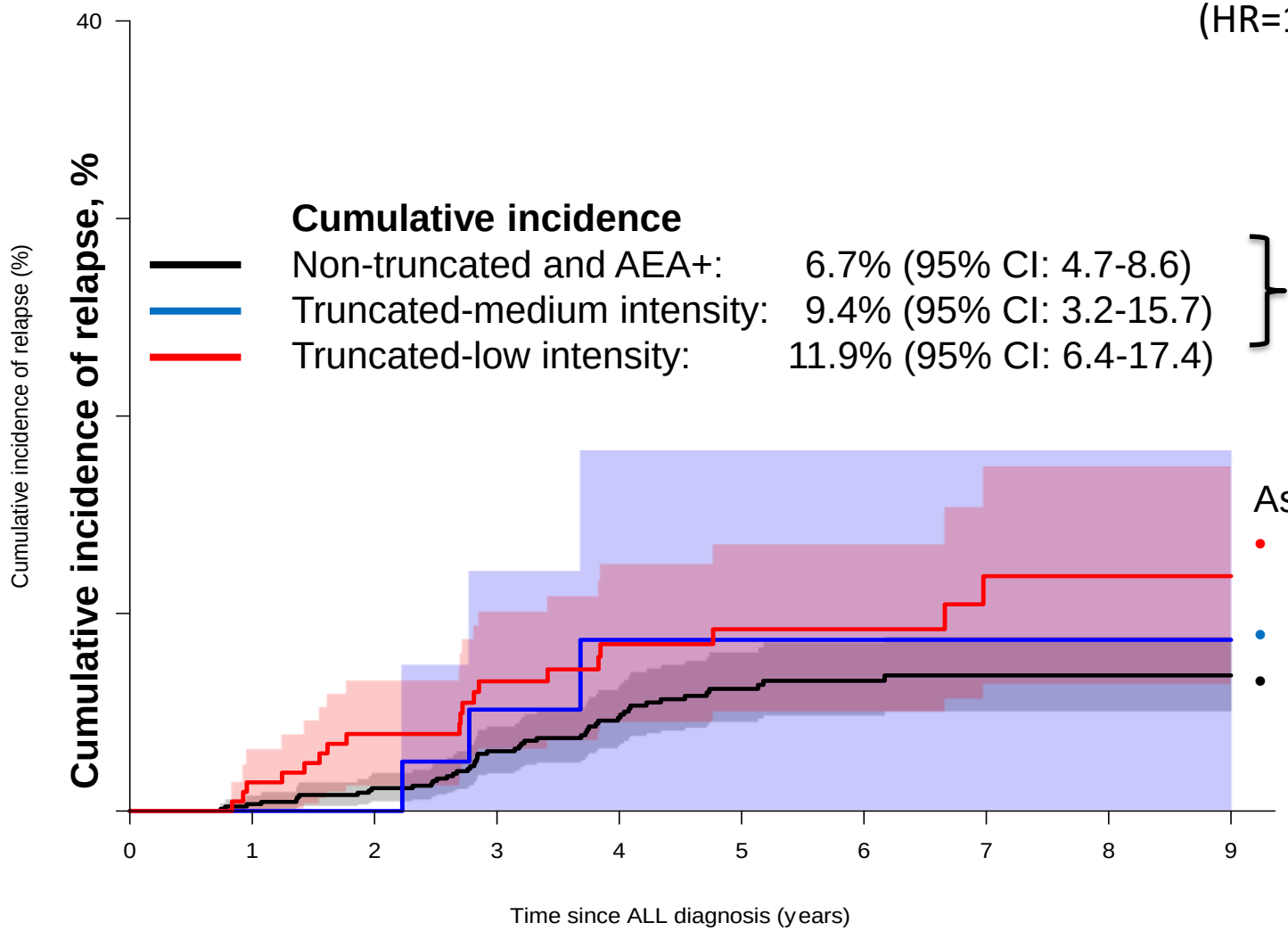
1. Pieters. Cancer. 2011;117:238. 2. Amylon. Leukemia. 1999;13:335. 3. Silverman. Blood. 2001;97:1211. 4. Rizzari. J Clin Oncol. 2001;19:1297. 5. Duval. Blood. 2002;99:2734. 6. Pession. J Clin Oncol. 2005;23:7161. 7. Moghrabi. Blood. 2007;109:896. 8. Gupta. J Clin Oncol. 2020;38:1897. 9. Gottschalk. Blood. 2021;137:2373.

Impact of Truncation of ASP Therapy *NOPHO ALL2008 (1.0-17.9 y)*

Cox regression (incl. < or > 10y; d29 MRD; WBC & CNS3 @Dx):

Relapse HR = 1.69 (95% CI: 1.05–2.74, *P*=0.03)

(HR=1.33; P=0.20 if not incl. asp activity)



Cumulative incidence

Non-truncated and AEA+: 6.7% (95% CI: 4.7-8.6)

Truncated-medium intensity: 9.4% (95% CI: 3.2-15.7)

Truncated-low intensity: 11.9% (95% CI: 6.4-17.4)

HR = 1.49; *P* = .3

HR = 1.80; *P* = .03
Non-truncated vs truncated

Asparaginase therapy intensity

- Low intensity: <10 weeks of asp treatment OR no ASP enzyme activity (AEA; 5-15% off target)
- Intermediate: ≥10 weeks of asp treatment
- High intensity: No ASP truncation *AND* positive AEA

Højfeldt, Blood 2021

“Hypersensitivity” reactions related to asparaginase

- **Clinical hypersensitivity** (mild to anaphylaxis)*:

  ~10%[4]; closely associated with Asparaginase inactivation[1,4]

  Anti-histamines/steroids do not mitigate inactivation

  !! Switch to alternative asparaginase (5-10% also react towards Erwinia chrysanthemi)

- **Silent inactivation** due to antibodies (5-10%)
  - Day 7 < 100 IU/L and/or day 14 < LLQ for PEG-asp[2]

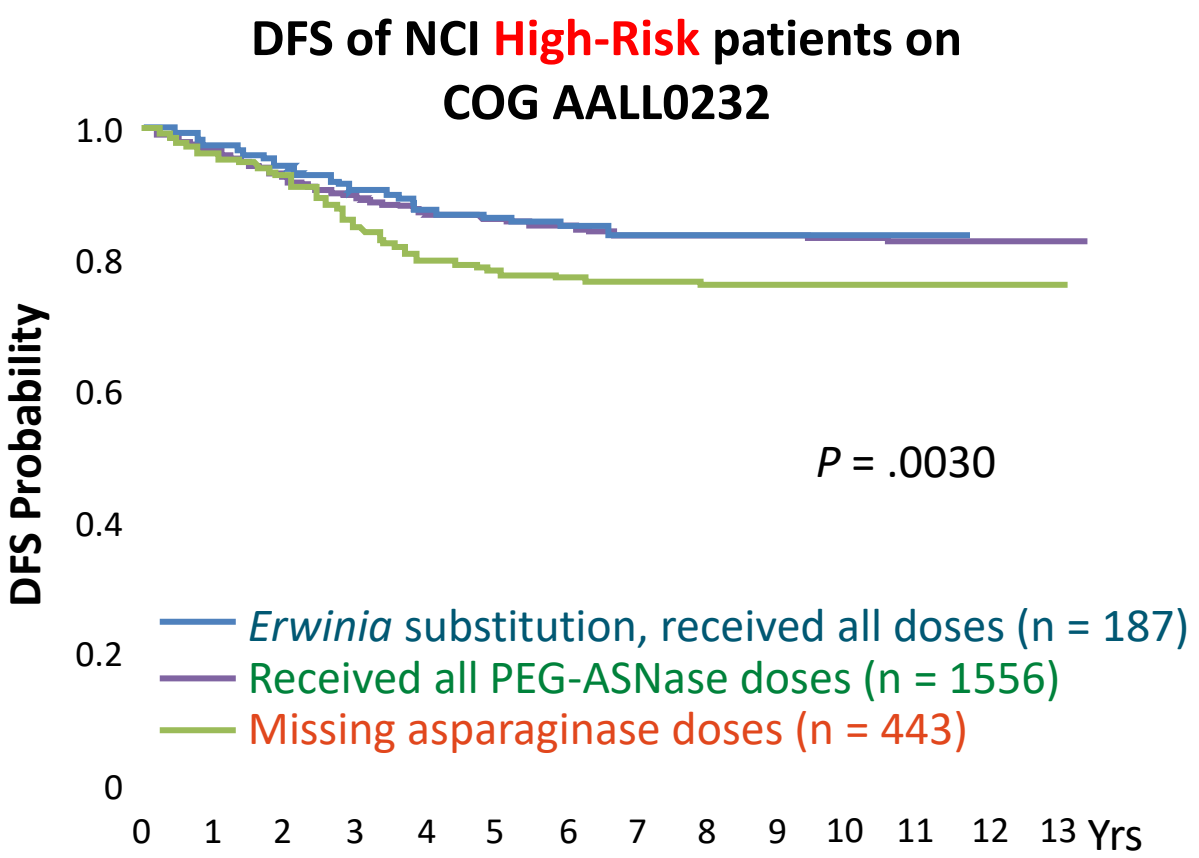
- **Intolerance** (1-5%; vomiting, stomach ache, rash)
  - not antibody but often ammonia associated;
  - usually *occurs later in infusion* than Asparaginase allergy, that often is at first drops)[1]

    Asparaginase activity monitoring (TDM) distinguish hypersensitivity vs intolerance

1. Kloos, *Br J Haematol* 2020
2. Schmiegelow, *Lancet Oncology* 2016
3. Pieters, *Cancer* 2011
4. Tong, *Blood* 2014
5. Vrooman, *J Clin Oncol* 201
6. Gupta, *J Clin Oncol* 2020

Asparaginase discontinuation & *Erwinia* replacement on Outcome in Childhood ALL: Report From the Children's Oncology Group

N=5,195 (AALL0331) & 3,001 (AALL0232)
Cumulative incidence of PEG-Asp discontinuation:
12.2% ± 4.6% in AALL0331
25.4% ± 0.8% in AALL0232
NCI HR* not receiving all Asp doses: **DFS HR 1.5** (1.2-1.9; *P* = .002)
w/ *Erwinia,* then HR 1.1 (0.7-1.6; *P* = .69)
NCI SR not receiving all Asp doses: **DFS HR 1.2** (0.9 -1.6; *P* = .23)
With slow early response: DFS HR 1.7 (1.1- 2.7; *P* = .03)



*Age ≥10yrs a/o WBC ≥50 x10^9/L

Gupta, J Clin Oncol 2020

Premedication

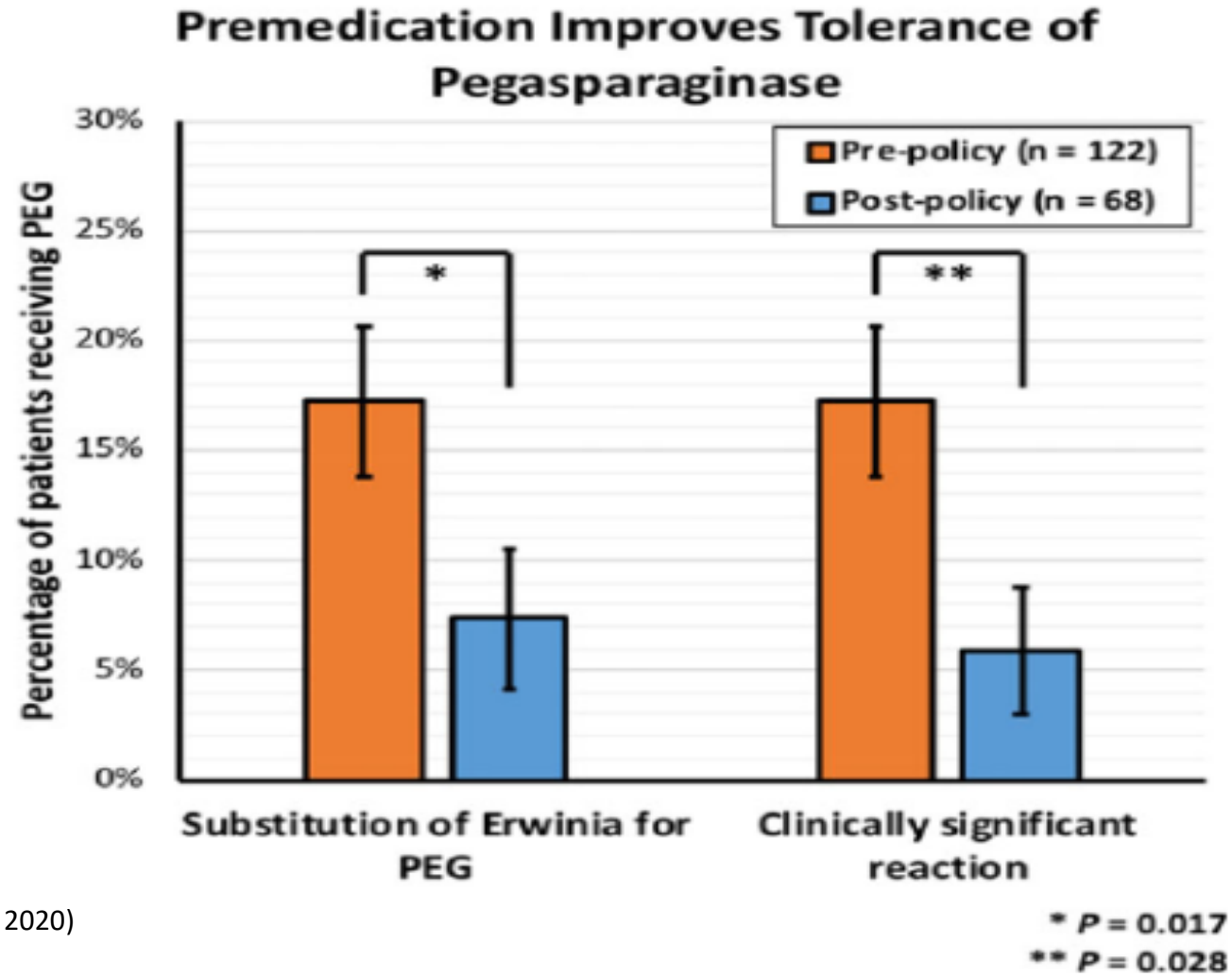
Premedicate 20-30 minutes prior to Asp:

- Antihistamine
- H2-receptor antagonist (GI symptoms)
- Glucocorticosteroids

Reduces *hypersensitivity reactions*

Therapeutic drug monitoring MANDATORY

- PEG-Asp: 7 (14) days later (every dose)
- *Erwinia*: 2 days later
- Also allows lower dosage (450 vs 1,500 IU/m^2; Kloos, J Clin Oncol 2020)



Interpret SAA trough levels

- ≤ 0.1 units/mL despite adequate dose, change to *Erwinia* asparaginase
- ≥ 0.1 units/mL and reaction not severe, re-challenge with PEG

Cost-effective*

Cooper, Ped Blood Cancer 2019
*McCormick, Ped Blood Cancer 2021

THROMBOSIS IN NOPHO ALL2008

NOPHO ALL2008 cohort:

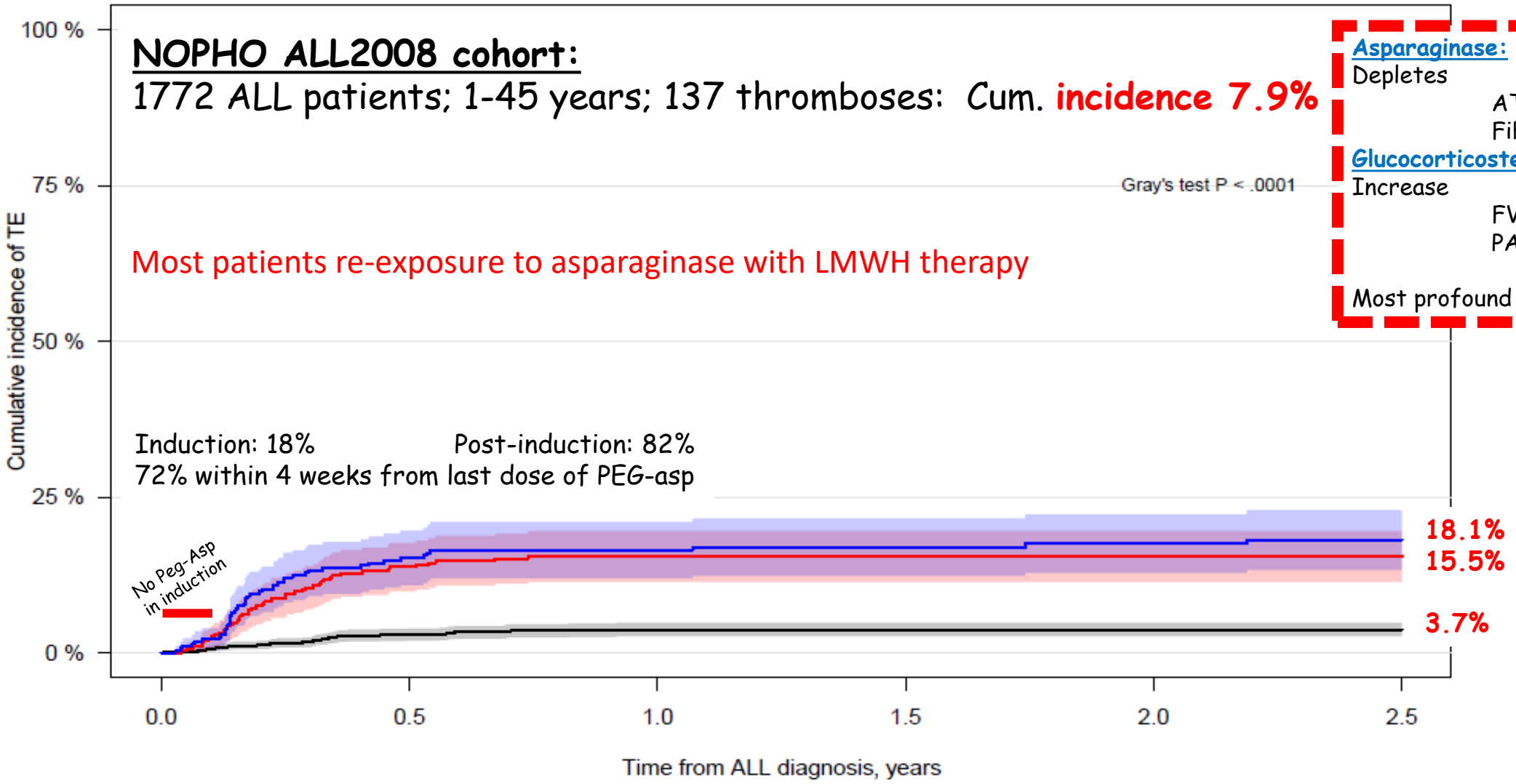
1772 ALL patients; 1-45 years; 137 thromboses: Cum. **incidence 7.9%**

Most patients re-exposure to asparaginase with LMWH therapy

Asparaginase:
Depletes
AT, protein S + C
Fibrinogen

Glucocorticosteroids:
Increase
FVIII/vWF
PAI-1 (hypofibrinolysis)

Most profound in pts >10yrs



At risk:											
1.0−9.9 years :	1192	1158	1110	1074	1057	1024	991	953	913	874	832
10.0−17.9 years :	306	272	246	230	219	210	202	195	184	175	169
18.0−45.9 years :	274	226	192	165	147	138	130	120	111	107	100

Rank, Blood 2018

CSV thromboembolism in NOPHO ALL2008

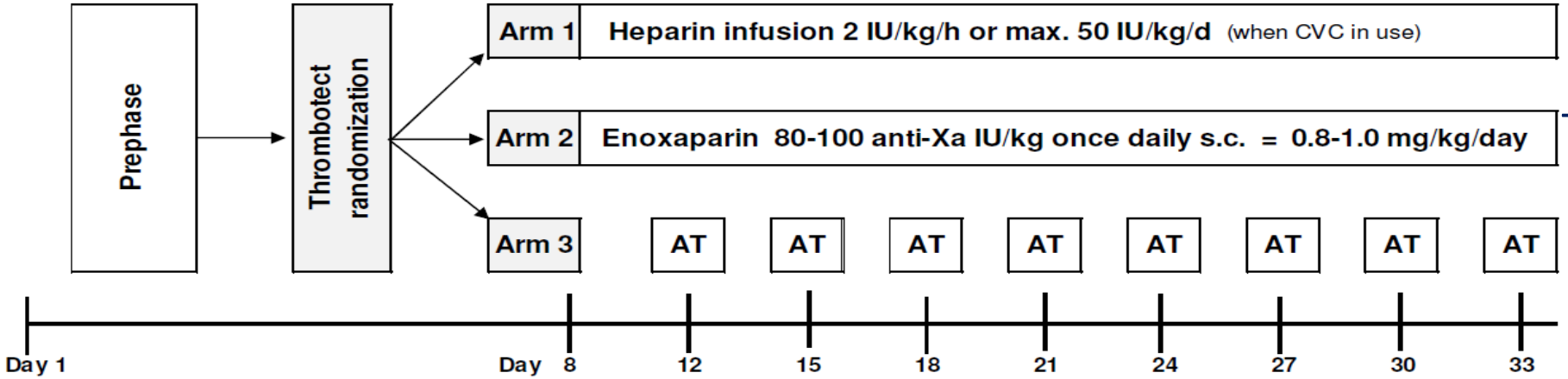
	N	Re-exposed	Not re-exposed	P
1-9 yrs	20	12 (71%)	5	NS
10-17 yrs	15	11 (79%)	3	NS
18-45 yrs	11	8 (73%)	3	NS
Total	46	31 (74%)	11*	
Median time from ALL Dx		50 days	81 days	0.03
Age/BMI/Sex/CNS2-3/Risk				NS

* 4 patients excluded due to death shortly after TE (N=3) or all Asp doses given (N=)

2 re-exposed patients developed a 2nd TE, including one CSVT (complete normalization at FU; clinically & MRI)
At FU (median: 4.5 yrs from CSVT) neurology (normal in 61%) and re-canalization (57%) did not differ between +/- re-exposed

Skipper, Br J Haematol 2022 (In press)

THROMBOTECT: Randomized thromboprophylaxis during Induction Therapy for ALL in Children and Adolescents
ALL-BFM 2000 / AIEOP-BFM ALL 2009; Dec 2002 – Dec 2011, 26 centers (Germany & Switzerland)



TE-prophylaxis until day 33 (EOI)
Observation until day 64 (EOC)

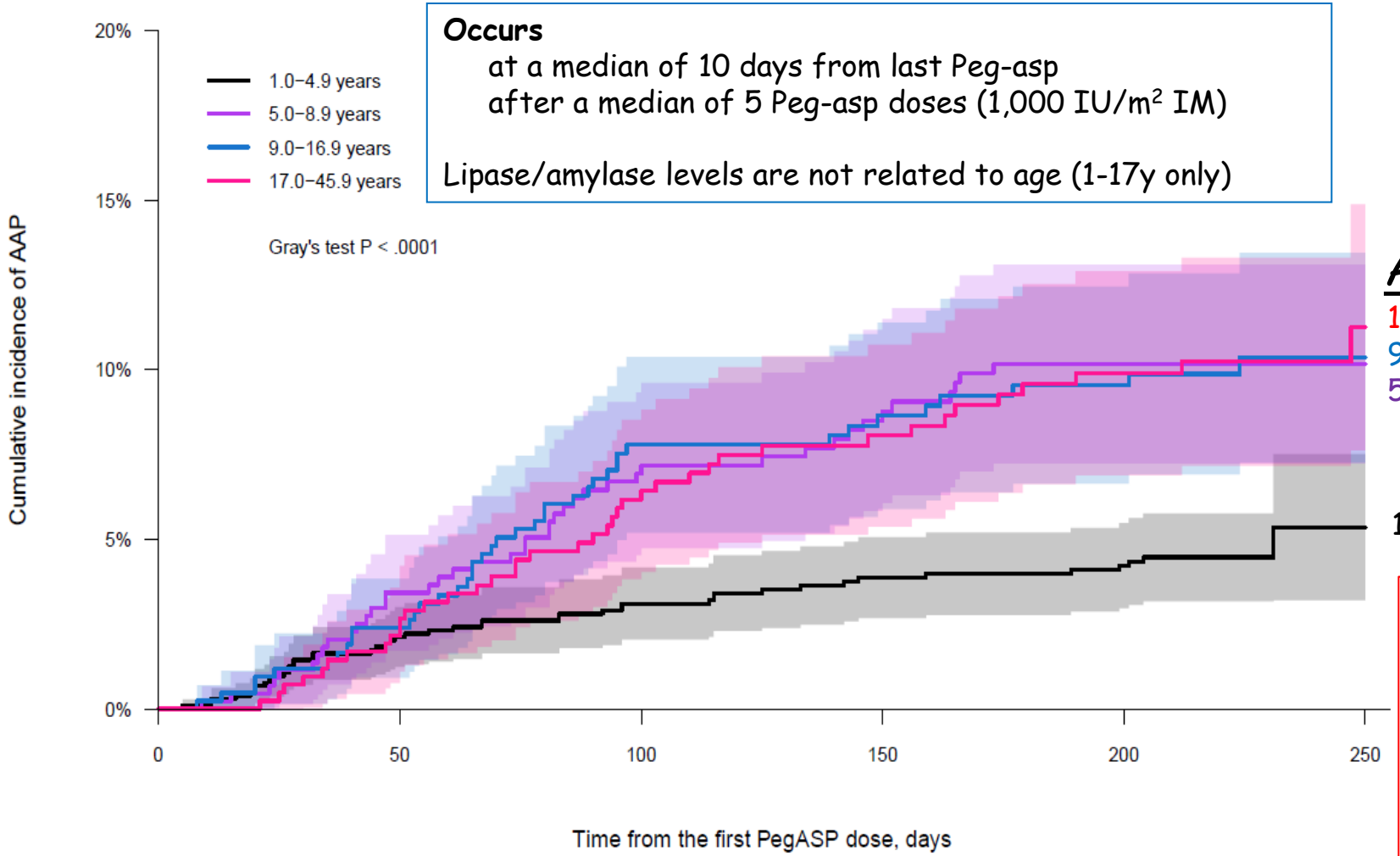
Greiner *et al.*, Haematologica 2019

Asparaginase-associated pancreatitis

NOPHO ALL2008; N = 2,448
AAP cases N=168

Occurs
at a median of 10 days from last Peg-asp
after a median of 5 Peg-asp doses (1,000 IU/m^2 IM)

Lipase/amylase levels are not related to age (1-17y only)



At risk:											
1.0–4.9 years :	1065	1023	1004	985	968	870	819	800	772	430	66
5.0–8.9 years :	453	435	419	408	384	354	329	314	307	192	32
9.0–16.9 years :	435	415	401	382	361	331	304	290	268	178	47
17.0–45.9 years :	427	417	398	377	353	326	302	280	260	222	79

Age groups:

17-45:	11.3%
9-16:	10.4%
5-8:	10.2%
1-4:	5.4%

73% SIRS; 22% needed mechanical ventilation
27% (45/167) developed pseudocysts
21% (9/43) w/ recurrent pain

11% (but 21% of 10-45y) developed IDDM

Pts 10-17y had 4.4-fold (95%CI: 1.7-11.2) risk of developing these complications (*P*=0.002)

Rank, J Clin Oncol 2020

ASP RE-EXPOSURE AFTER PANCREATITIS

	PdL study[a]	NOPHO 1-45 y[b]
AAP cases	465	168
Re-exposure	96	34
2nd AAP	44 (46%)	15 (44%)
Severe 2nd AAP	22 (52%)	6 (40%)
Age risk factor?	No	No (power issue?)
Severity of 1st AAP risk factor?	No	No
Median No./% of PEG-Asp before 2nd AAP	3.5	14% < 10 y after 1st dose 33% AYA after 1st dose

- Asp re-exposure should be determined by the anticipated risk of ALL relapse!!
  - AYA pts 21% risk for IDDM[a], but also increased risk of relapse
- Risk for AAP: initially ~1% per dose, increases to ~10% per dose at re-exposure after AAP

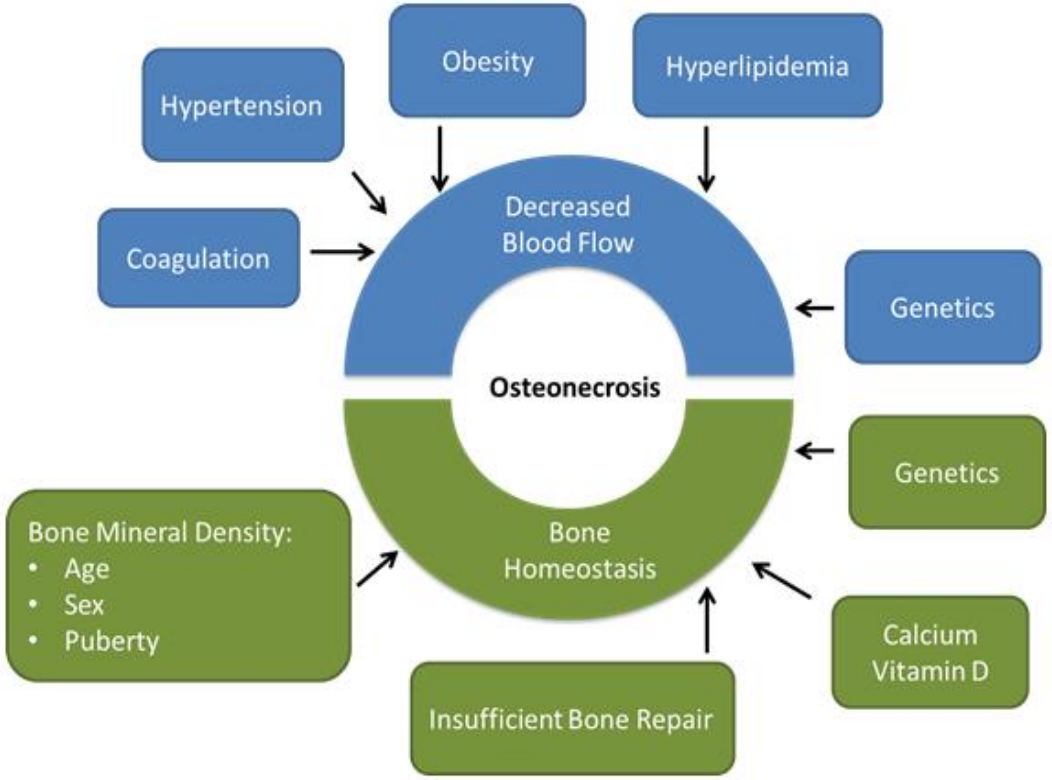
[a] Wolthers, *Lancet Oncol* 2017
[b] Rank, *J Clin Oncol* 2020

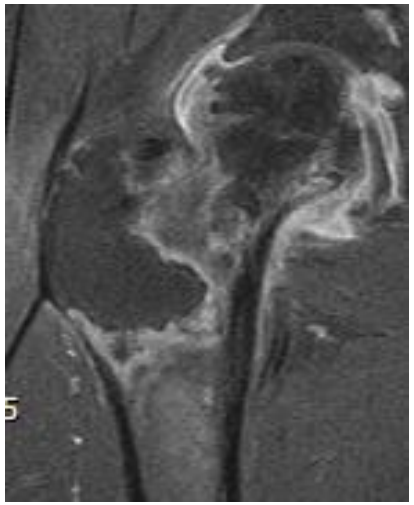
Osteonecrosis

Incidence: 2-50+ %; most subclinical (only on MRI)
Of the symptomatic 60% gr 3-4

Late effects: Among patients with severe ON (grade 4) >90% have persistent pain (30% always – every day!!).

Risk factors for ON: Older age, female gender, steroids (dexa>>predn), host genome variants, hyperlipidemia





	N (%) Total= 785*
Phase of ALL treatment ON diagnosed	
Induction	18 (2%)
Intensification/Consolidation	140 (18%)
Maintenance/Continuation	389 (50%)
After Treatment Completion	123 (16%)
Unknown/Missing	114 (14%)

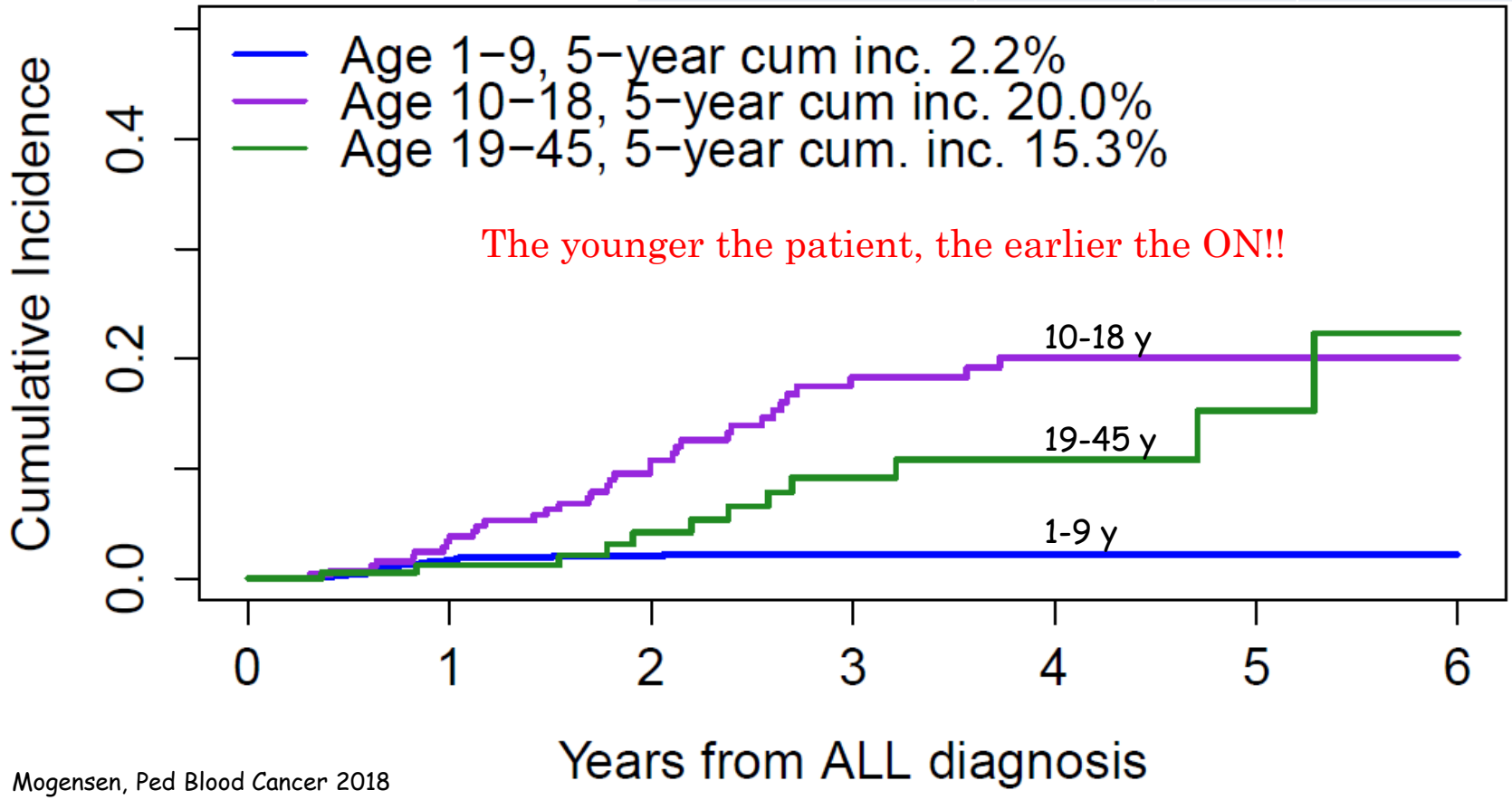
* Lynda Vrooman, Ponte di Legno Toxicity Working Group (unpublished – not to be distributed)

ON and maintenance therapy:
NOPHO ALL2008 study
1,234 patients, 17,854 blood samples

Ery-MTXpg/TGN/MeMP & DNA-TG not associated w/ MTX/6MP PK
Toksvang, Cancer Chem Pharm 2021

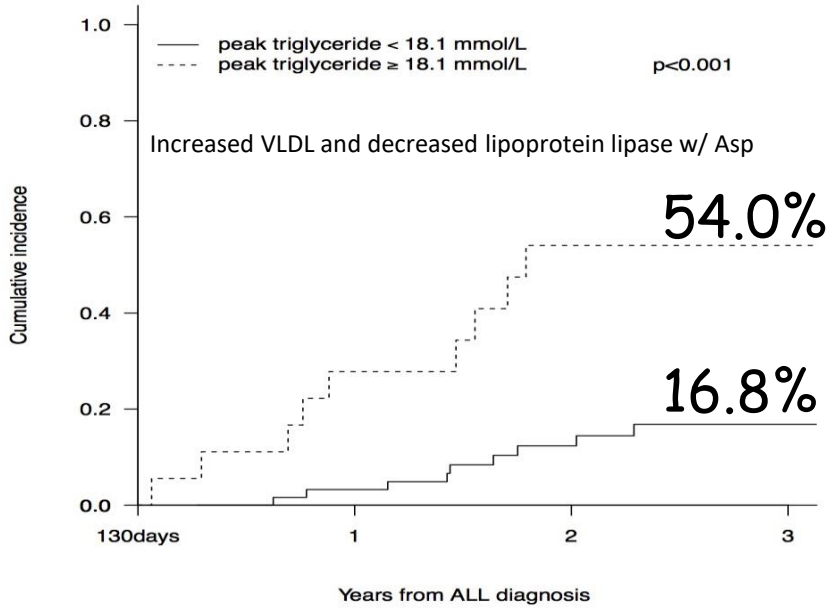
Osteonecrosis
NOPHO ALL2008
1-45y

	Pts	ON	Median time to ON	Males	Females	P
1-9y	1010	20	0.9 yrs	1.2%	3.2%	0.08
10-17y	282	35	1.8 yrs	15%	28%	0.03
18-45y	197	12	2.2 yrs	17%	12%	0.84
Median age				14.9 y	12.1 y	



Mogensen, Ped Blood Cancer 2018

Peak triglyceride and risk of subsequent osteonecrosis



Mogensen, Haematologica 2017

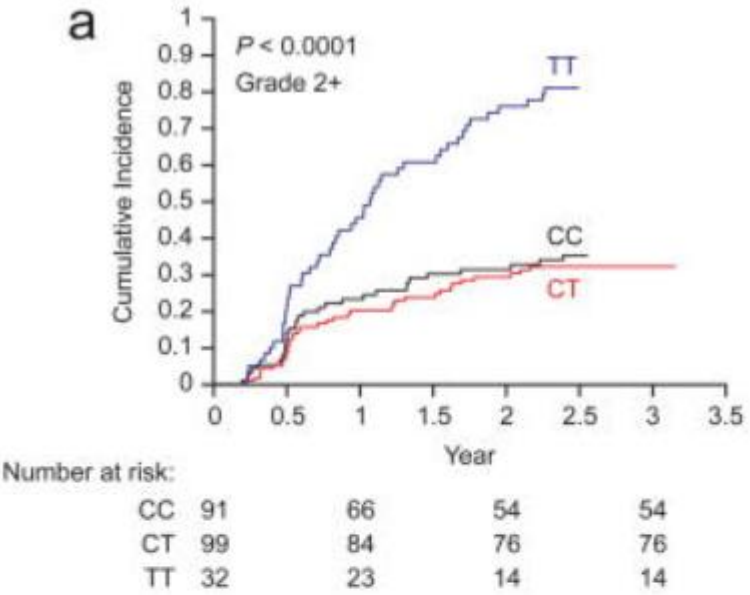
Asparaginase: Hypertriglyceridemia in ALL

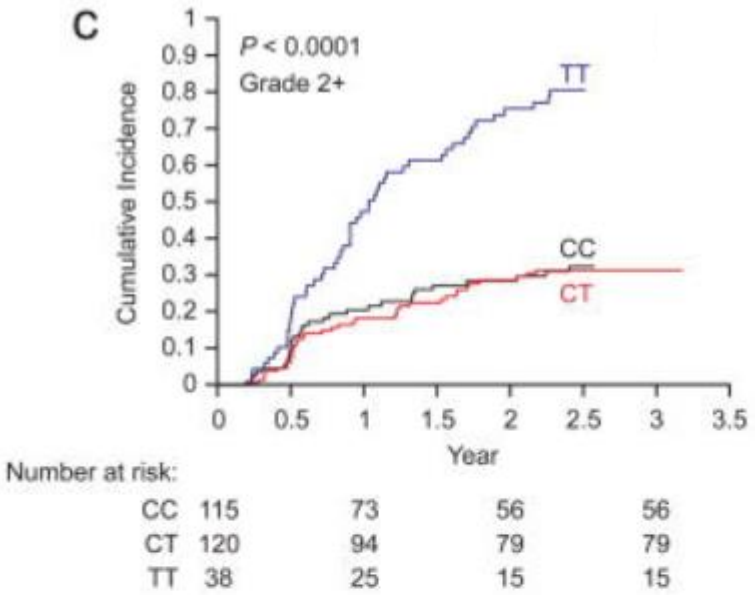
- Frequent – 15-50% of adults (10% in pediatric ALL)
  - Altered lipid metabolism resulting in increased LDL synthesis
  - Steroids contribute
- Mostly w/o symptoms (but lipemic serum may compromise routine lab-work)
- Manageable w/
  - Almost never requires alteration in treatment (no change in diets)
  - Fibrates (increase lipoprotein lipase & educe hepatic triglyceride synthesis)
  - Insulin (increases lipoprotein lipase)
  - Plasmaferese (in emergency situations)
  - Omega-3 (reduces triglycerides, VLDL & chylomicrons)
    - Nordic Rx trial (+/- fish oil (long-chained omega-3); N=100; NCT04209244)
- Linked to osteonecrosis risk; but not Asp-associated pancreatitis or thromboembolism

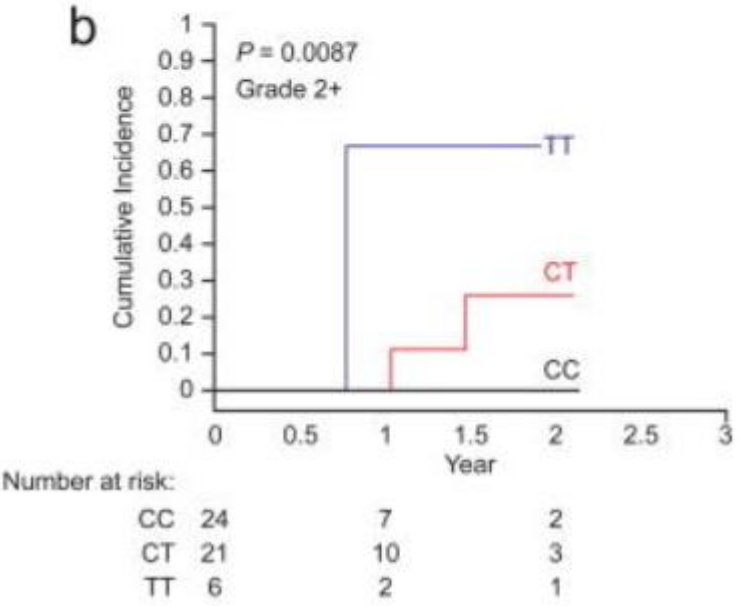
GWAS: CEP72* (promotor) variant and risk of Vincristine-associated peripheral neuropathy

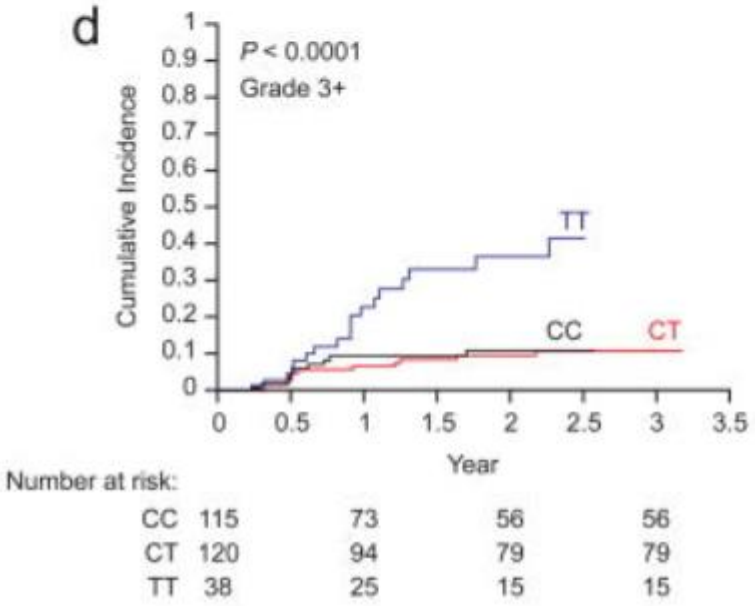
**CEP72* encodes centrosomal protein involved in microtubule formation*

GWAS P: 6.3×10^{-9}









Patients: N=321 on SJCRH XIIIB or COG AALL0433
36–39 doses of vincristine
Leukemia cell lines and pluripotent stem cell neurons assessed effects of low *CEP72* expression on VCR sensitivity.
Grade 2 to 4 VCR neuropathy (22-29%) during maintenance

Reducing CEP72 expression in human neurons and leukemia cells increased their sensitivity to vincristine

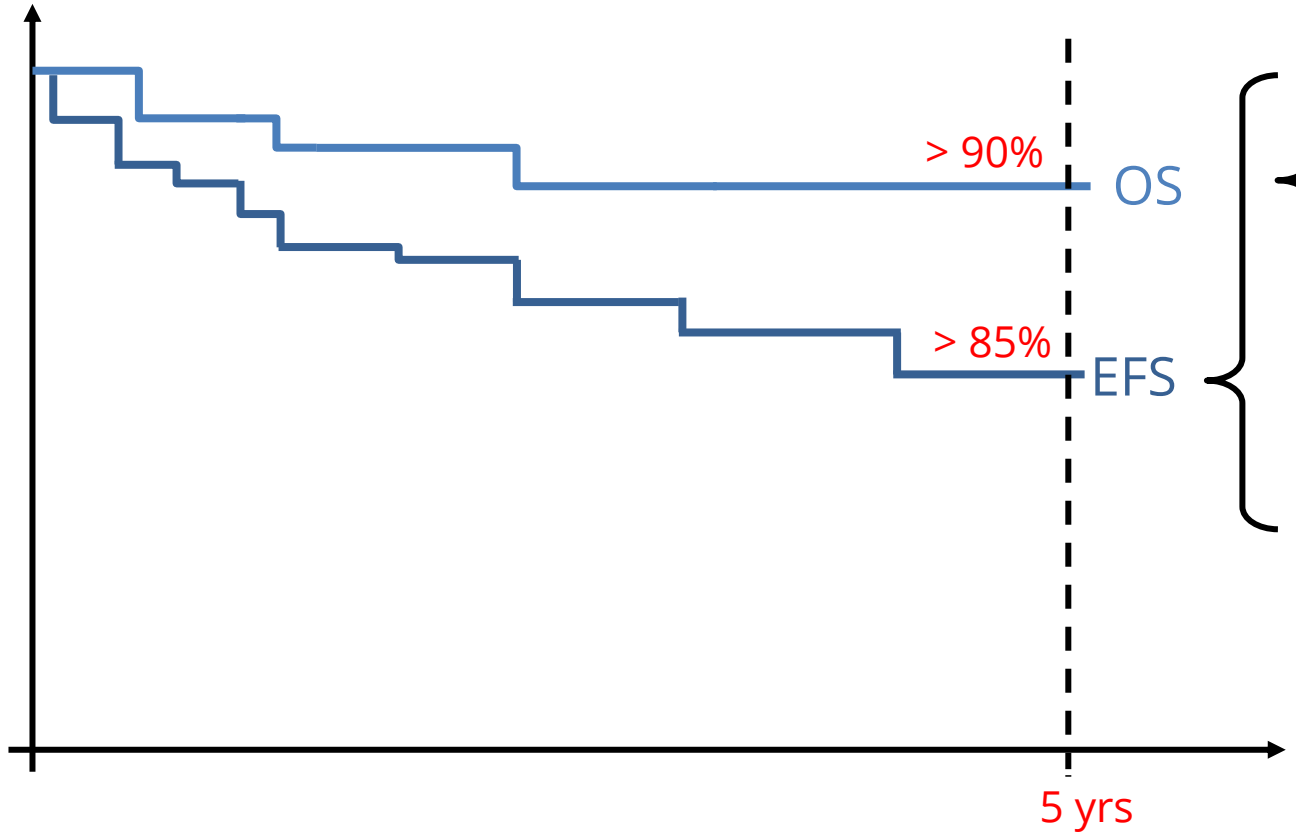
NCT03117751: SJCRH randomisation

Lower or shorter VCR dosage

Diouf, JAMA 2015
Stock, Clin Pharmacol Ther 2017 (adults)
Goodenough, Leukemia 2022
Uittenboogaard, Cancers 2022 (Systematic review and meta-analysis)

Severe toxicity-free survival

Traditional evaluation of cancer treatment outcome



- death (leukemia/TRM)

- resistant disease
- relapse
- SMN

Review

Severe toxicity free survival: physician-derived definitions of unacceptable long-term toxicities following acute lymphocytic leukaemia

Liv Andrés-Jensen, Andishe Attarbaschi, Edit Bardi, Shlomit Barzilai-Birenboim, Deepa Bhojwani, Melanie M Hagleitner, Christina Halsey, Arja Harila-Saari, Raphaele R L van Litsenburg, Melissa M Hudson, Sima Jeha, Motohiro Kato, Leontien Kremer, Wojciech Młynarski, Anja Möricke, Rob Pieters, Caroline Piette, Elizabeth Raetz, Leila Ronceray, Claudia Toro, Maria Grazzia Valsecchi, Lynda M Vrooman, Sigal Weinreb, Naomi Winick, Kjeld Schmiegelow, on behalf of the Ponte di Legno Severe Toxicity Working Group*

Lancet Haematol 2021; 8: e513-23

*Members are listed in the appendix (pp 2–3)

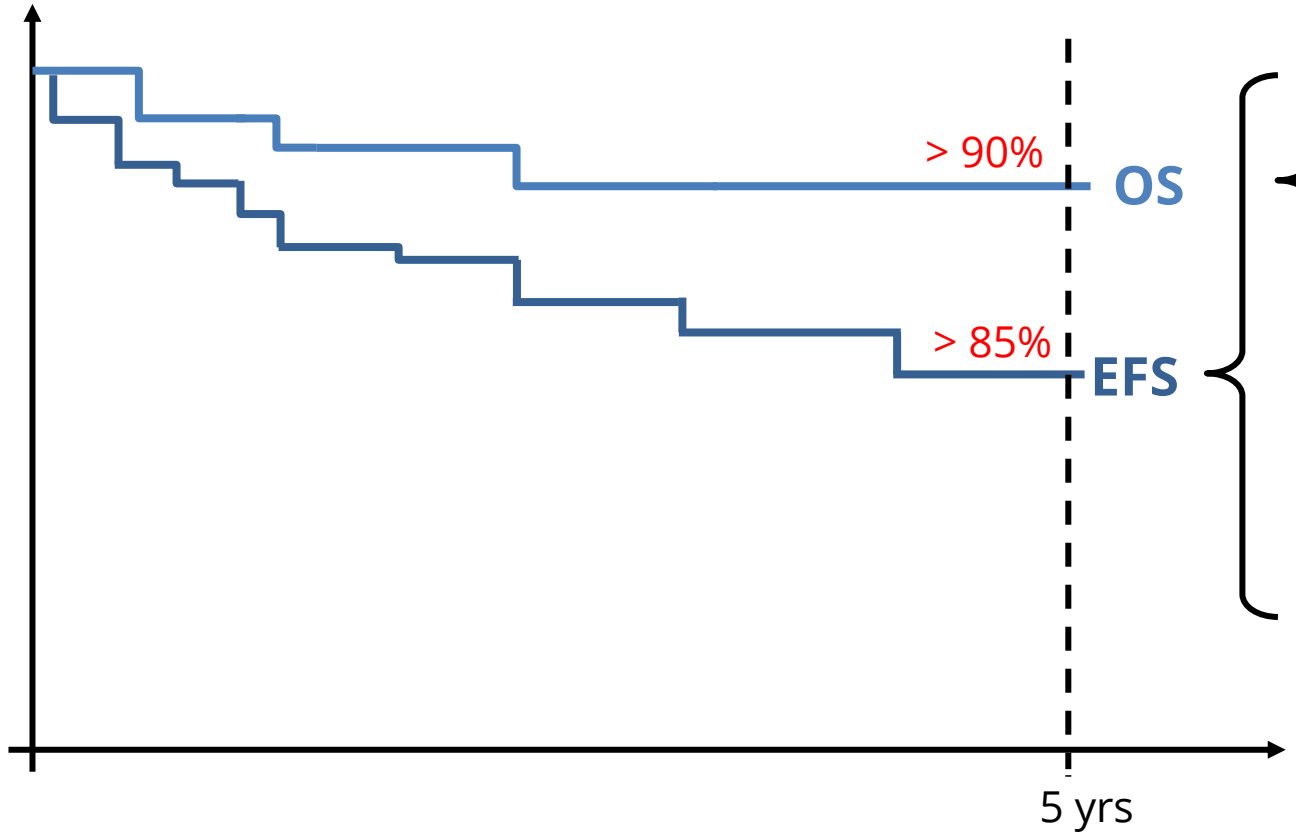
Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (L Andrés-Jensen MD, Prof K Schmiegelow MD); Department of Pediatric Hematology-Oncology, St Anna Children's Hospital, Medical University of Vienna, Vienna, Austria (A Attarbaschi MD, E Bardi MD, L Ronceray MD); Department of Pediatric Oncology and Immunology, Kepler University Clinic, Linz, Austria (E Bardi); Department of Pediatric Hematology-Oncology, Schneider Children's Medical Center of Israel, Petah Tikva,

5-year overall survival rates have surpassed 90% for childhood acute lymphocytic leukaemia, but survivors are at risk for permanent health sequelae. Although event-free survival appropriately represents the outcome for cancers with poor overall survival, this metric is inadequate when cure rates are high but challenged by serious, persistent complications. Accordingly, a group of experts in paediatric haematology–oncology, representative of 17 international acute lymphocytic leukaemia study groups, launched an initiative to construct a measure, designated severe toxicity-free survival (STFS), to quantify the occurrence of physician-prioritised toxicities to be integrated with standard cancer outcome reporting. Five generic inclusion criteria (not present before cancer diagnosis, symptomatic, objectifiable, of unacceptable severity, permanent, or requiring unacceptable treatments) were used to assess 855 health conditions, which resulted in inclusion of 21 severe toxicities. Consensus definitions were reached through a modified Delphi process supplemented by two additional plenary meetings. The 21 severe toxicities include severe adverse health conditions that substantially affect activities of daily living and are refractory to therapy (eg, refractory seizures), are without therapeutic options (eg, blindness), or require substantially invasive treatment (eg, cardiac transplantation). Incorporation of STFS assessment into clinical trials has the potential to improve and diversify treatment strategies, focusing not only on traditional outcome events and overall survival but also the frequencies of the most severe toxicities. The two major aims of this Review were to: prioritise and define unacceptable long-term toxicity for patients with childhood acute lymphocytic leukaemia, and define how these toxicities should be combined into a composite quantity to be integrated with other reported outcomes. Although STFS quantifies the clinically unacceptable health tradeoff for cure using childhood acute lymphocytic leukaemia as a model disease, the prioritised severe toxicities are based on generic considerations of relevance to any other cancer diagnosis and age group.

Andres-Jensen; Lancet Haematol Vol 8 July 2021

Severe toxicity-free survival

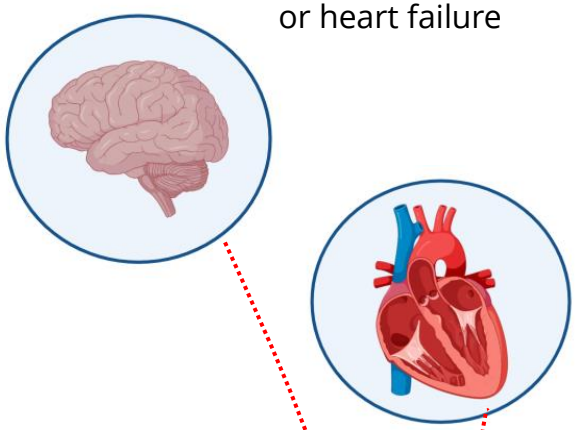
Traditional evaluation of cancer treatment outcome



- death

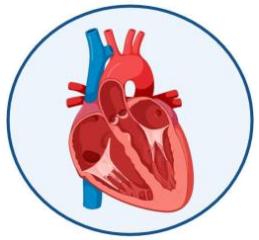
- resistant disease
- relapse
- SMN
- severe long-term toxicities

e.g., severe neurocognitive impairment or heart failure

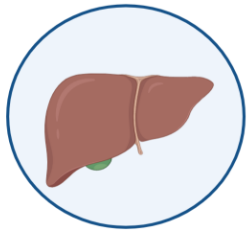


Andres-Jensen; Lancet Haematol Vol 8 July 2021

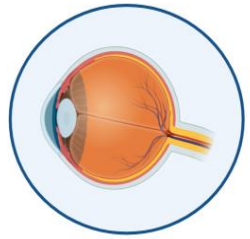
STFS: 21 prioritized Severe Toxicities



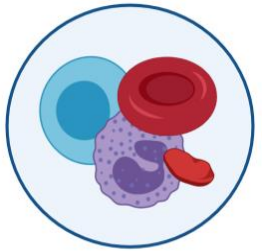
Heart failure
Coronary artery disease
Arrhythmia
Valve disease



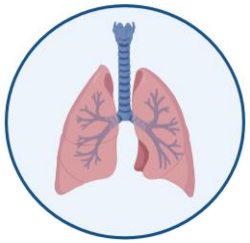
Liver failure



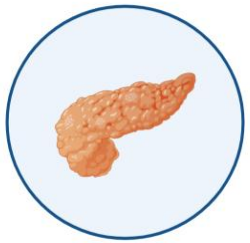
Blindness



Cytopenia

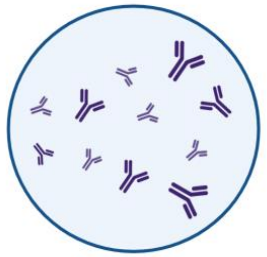


Lung failure

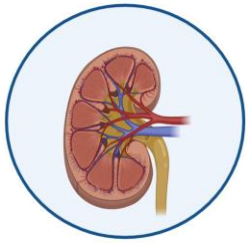


IDDM

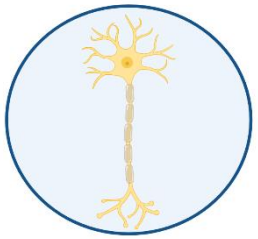
Hearing loss



Immune deficiency

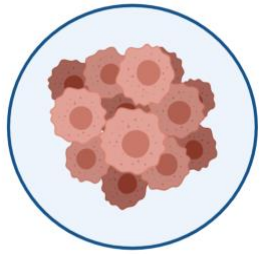


Kidney failure

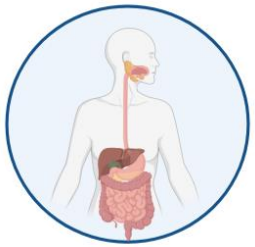


Vocal cord paralysis
Paralytic-, neuropathic-, myopathic, and movement disorders

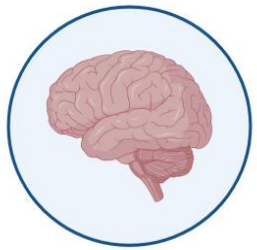
Osteonecrosis



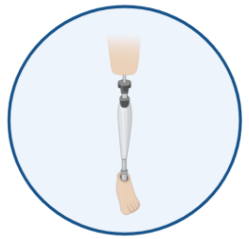
SMN and benign CNS tumors



GI failure



Seizures
Cognitive dysfunction
Psychiatric disease



Amputation and physical deformation

Andres-Jensen; Lancet Haematol Vol 8 July 2021

ST data capture in five ALL cohorts

Fall 2022

NOPHO

Same protocol
across seven countries

St Jude

Single-institution
Extensive, systematic
clinical evaluations

DCOG

National,
single-institution cohort

Poland
Australia

National cohorts
Distinct protocol

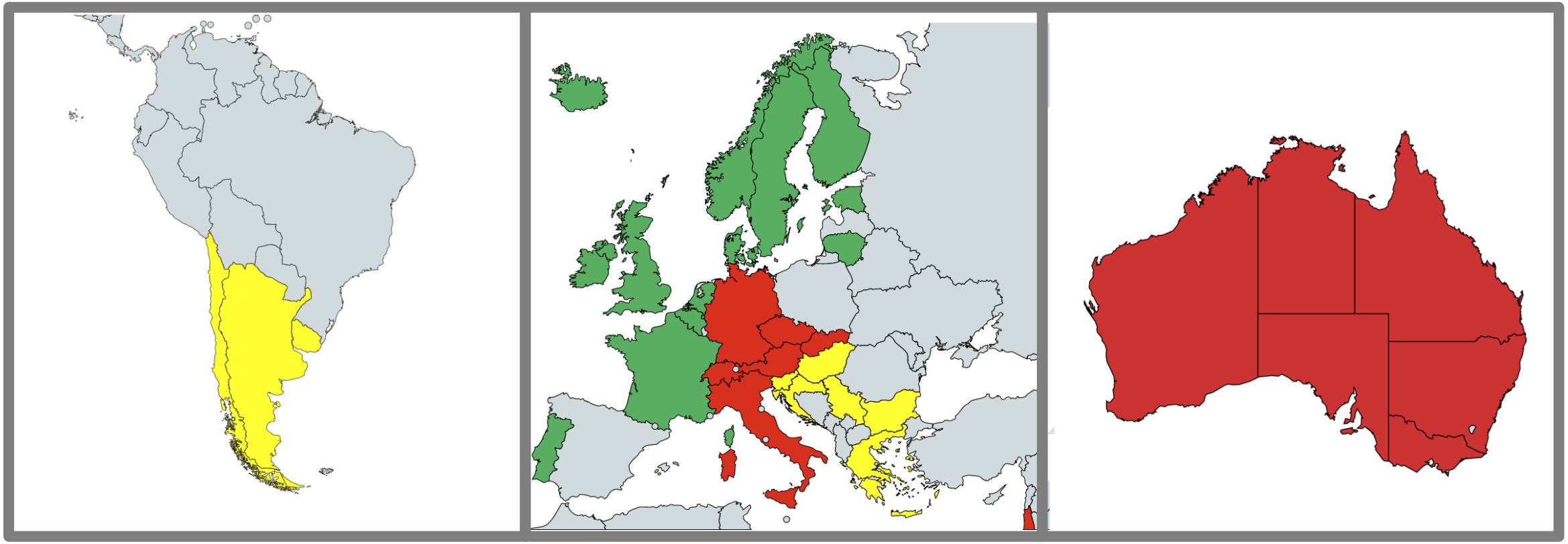
→ **Results can guide the strategy for global implementation incl. reporting of outcomes**

? Incidence across protocols / Tx strategies
? Association with subjective measures
? Influence of ”culture” on perceived burden of toxicities

Andres-Jensen; Lancet Haematol Vol 8 July 2021

ELEGANT – ALL host DNA (SNP) profiling

Exploring Leukemia: Education, Genetics And Novel Technologies



33 countries. 500 mio+ population. 6 mio+ births and >3,000 cases of ALL annually; Target: N=15-20,000 cases

AIEOP/BFM:	Australia, Austria, Czech Republic, Germany, Israel, Italy, Slovakia, Switzerland
ALLIC:	Argentina, Bulgaria, Chile, Croatia, Greece, Hungary, Russia (Moscow single center), Serbia, Slovenia, Uruguay
ALLTogether:	Belgium, Denmark, Estonia, Finland, France, Germany (COALL group), Holland, Iceland, Ireland, Lithuania, Norway, Portugal, Sweden, United Kingdom

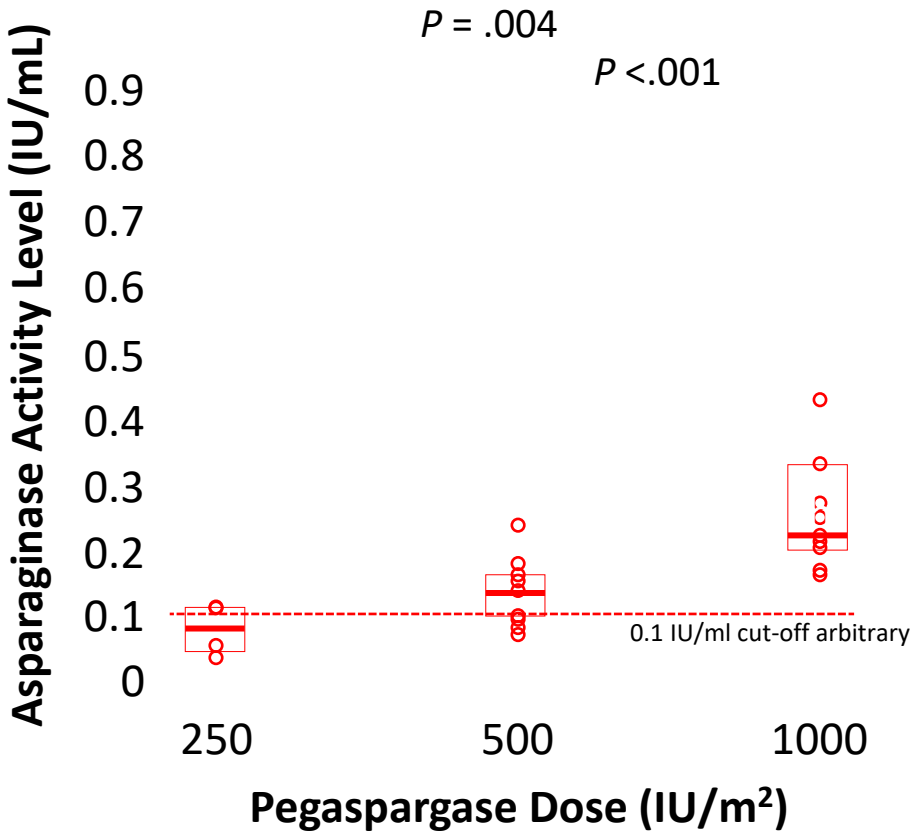
Challenges & requiremens for toxicity prevention in ALL

Summary:

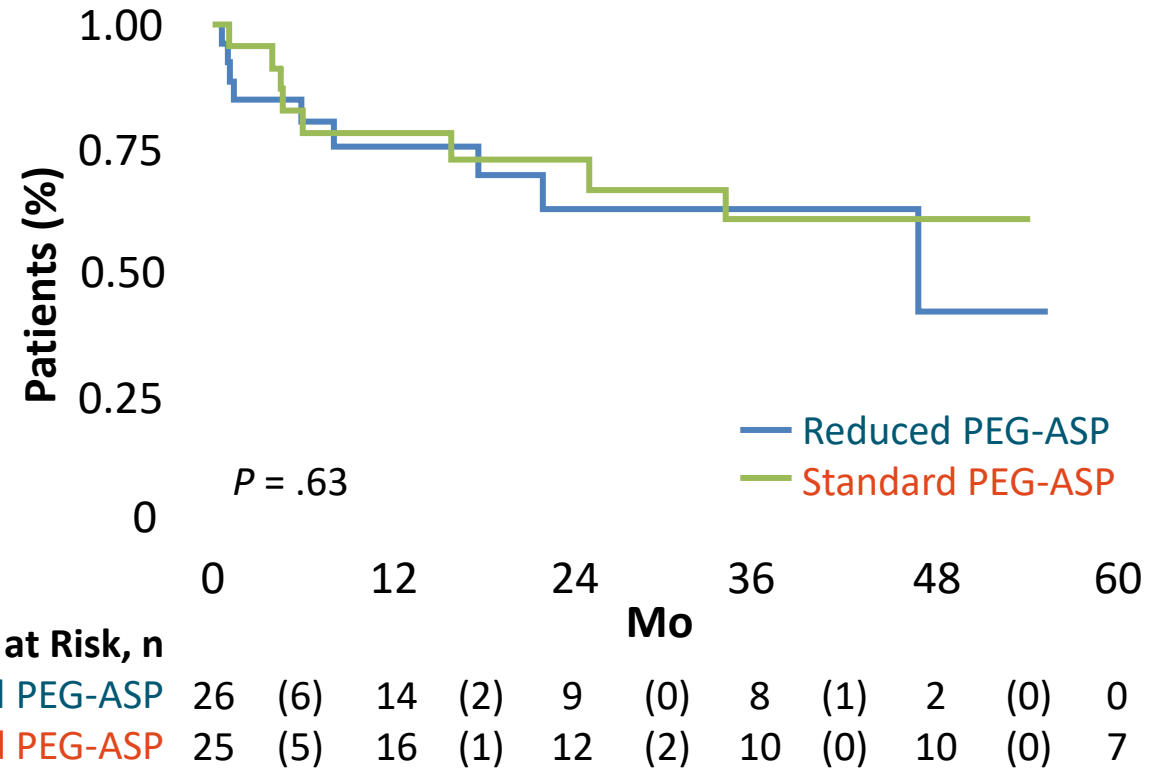
- **Deep phenotyping of the most significant parameters**
  - & consensus definitions
- **Clinically relevant odds ratios**
- (Optional) **registration of ”exposome”**
  - Age and pubertal stage
  - Exposures: Chemotherapy, inflammation, endothelial dysfunction, nutrition, microbiome, supportive care
- **Detailed mapping of our –omics**
- **Complex bioinformatics strategies** (Machine learning / AI)
- **Reproducible associations across cohorts**
- (Optional) **Biological validation**
- **Clinically applicable and acceptable interventions**

Empiric Dose-Reduction of Pegaspargase in ALL

Activity of Pegasparagase at Reduced Doses



Relapse-Free Survival



Patients at Risk, n											
Reduced PEG-ASP	26	(6)	14	(2)	9	(0)	8	(1)	2	(0)	0
Standard PEG-ASP	25	(5)	16	(1)	12	(2)	10	(0)	10	(0)	7

Retrospective study of consecutive patients aged ≥18 yr with Ph-negative ALL who received ≥1 dose of pegaspargase during induction thherapy

Slide credit: clinicaloptions.com

Derman. Leuk Lymphoma. 2020;61:614.

Candidate gene approach: Thromboembolism

Four genes selected based on adult GWAS meta-analysis (7,507 VTE cases; 52,632 controls)*

Cox regression (time to TE)**	Single-SNP			Multiple-SNP		
	HR	95% CI	p-value	HR	95% CI	p-value
F5 rs6025	1.06	0.44-2.55	0.89	1.16	0.48-2.83	0.75
ABO rs8176719***	0.99	0.75-1.37	0.94	1.03	0.76-1.40	0.83
FGG rs2066865	1.36	0.98-1.89	0.065	1.37	0.99-1.91	0.058
F11 rs2036914	1.51	1.11-2.06	0.009	1.52	1.11-2.07	0.009

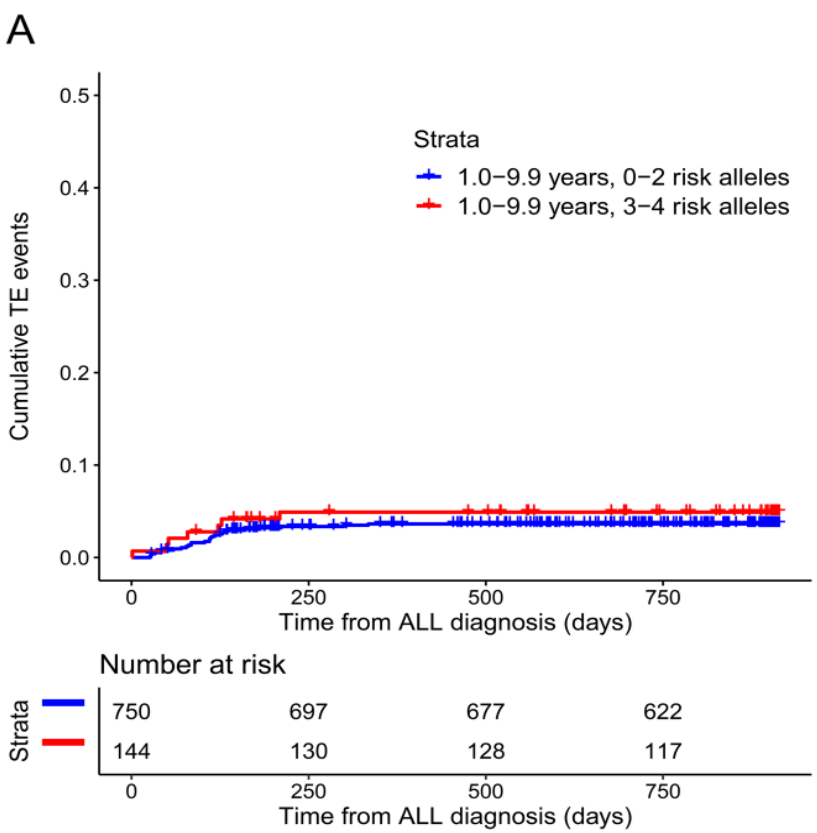
**Controling for age, gender, mediastinal mass, lymph nodes and the first two principal components.

Jarvis, Thrombosis Res 2019

*Germain, Am J Hum Genet 2015

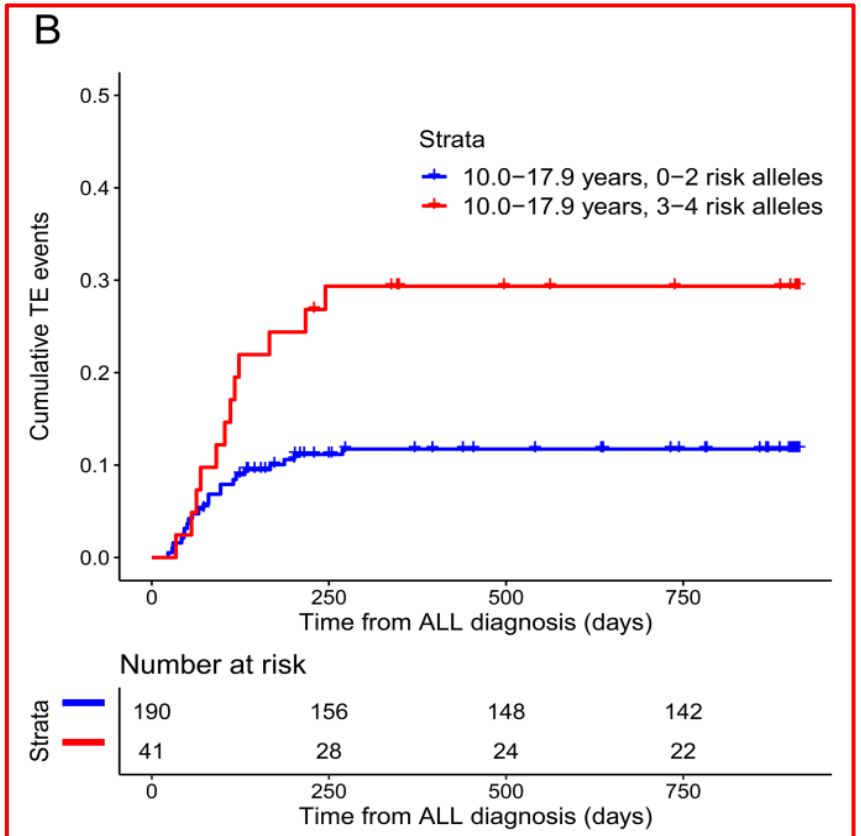
***Athale, Ped Blood Cancer 2022

Incidence of TE with <3 or ≥3 FGG/F11 risk alleles*



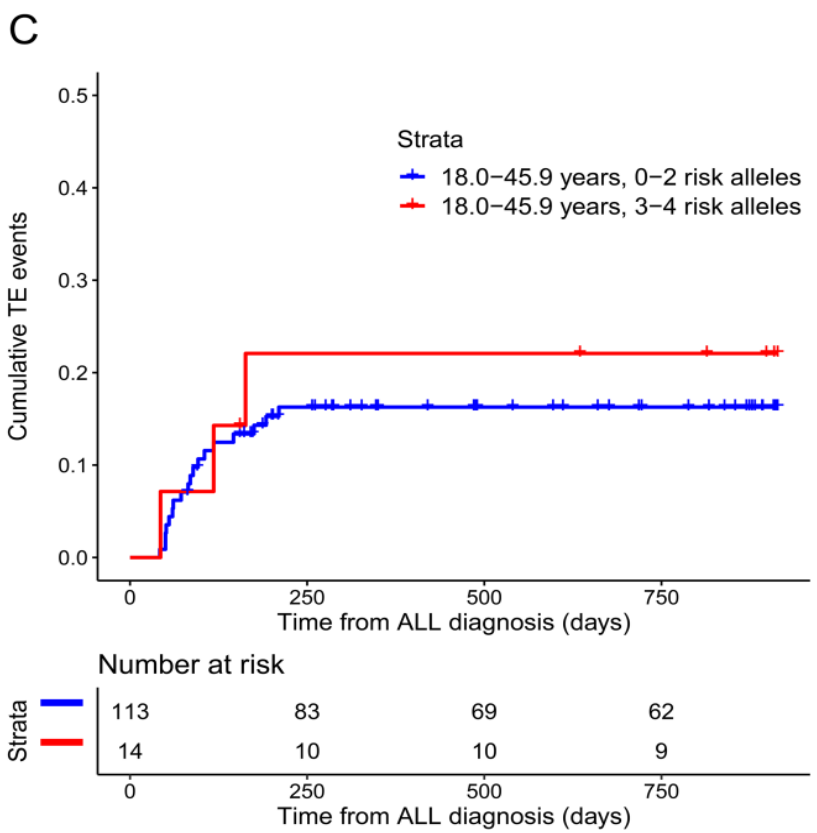
1.0-9.9 years

p 0.48, N = 894



10.0-17.9 years

p 0.006, N = 231



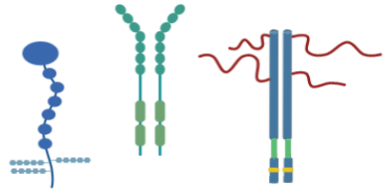
18.0-45.9 years

p 0.59, N = 127

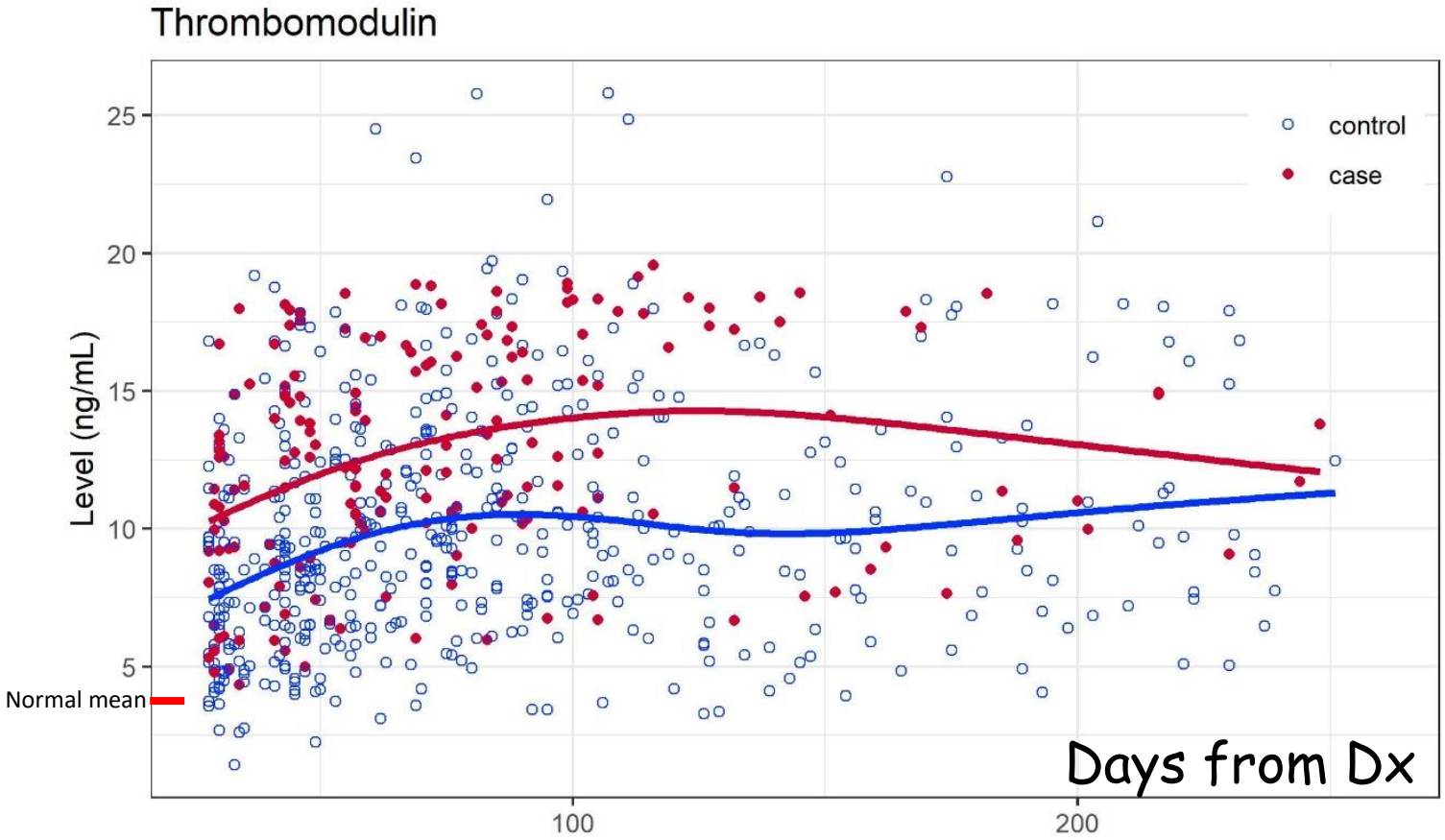
*No association with ABO or F5 rs6025 (Factor V Leiden)

Jarvis, Trombosis Res 2019

Results ASSOCIATION BETWEEN BIOMARKERS ANI



Thrombomodulin*: 37% increase in TE odds per 1 ng/mL (p<0.0001) (increases w/ Asp Tx)
Syndecan**: 12% increase in TE odds per 10 ng/mL (p=0.005)
VEGFR-1: No association



Andres-Jensen, Leukemia 2022

Sensitivity analysis:

1. Same results when using mean rather than median
2. Additive effect of TM and VEGFR-1
3. Same results when using only samples drawn > 30 days prior to TE

* Endothelial anticoagulant (reflects endohelial injury)
** Co-receptor for extracellular signal transfer