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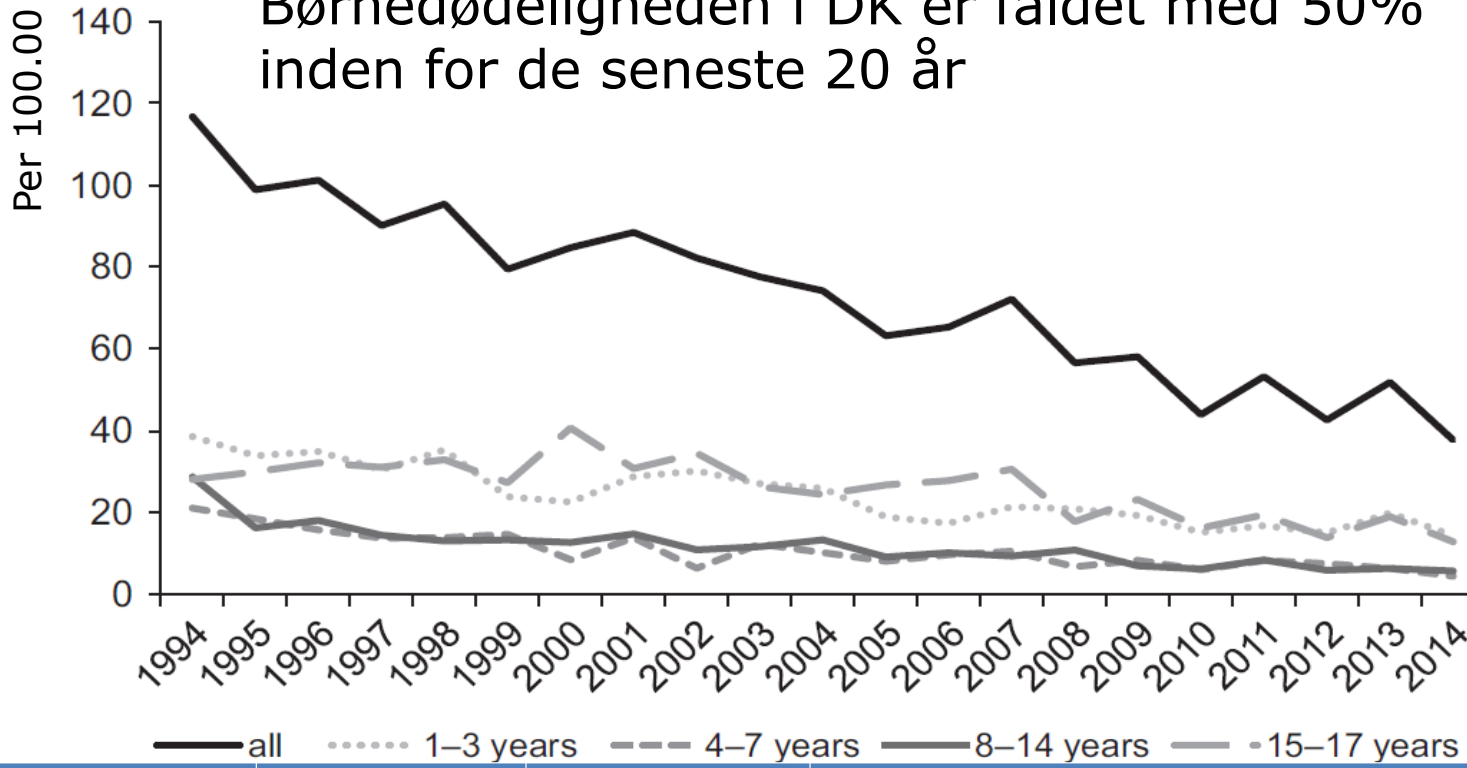
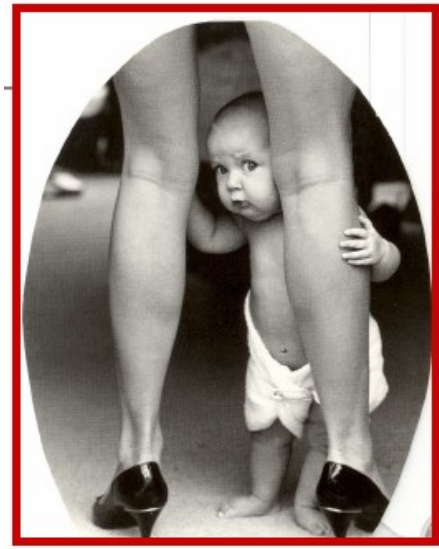
Hvorfor er personlig medicin *særlig* vigtigt til børn med kræft?

Danske kræftforskningsdage

Odense August 29-30, 2019

Børnedødeligheden i DK er faldet med 50% inden for de seneste 20 år

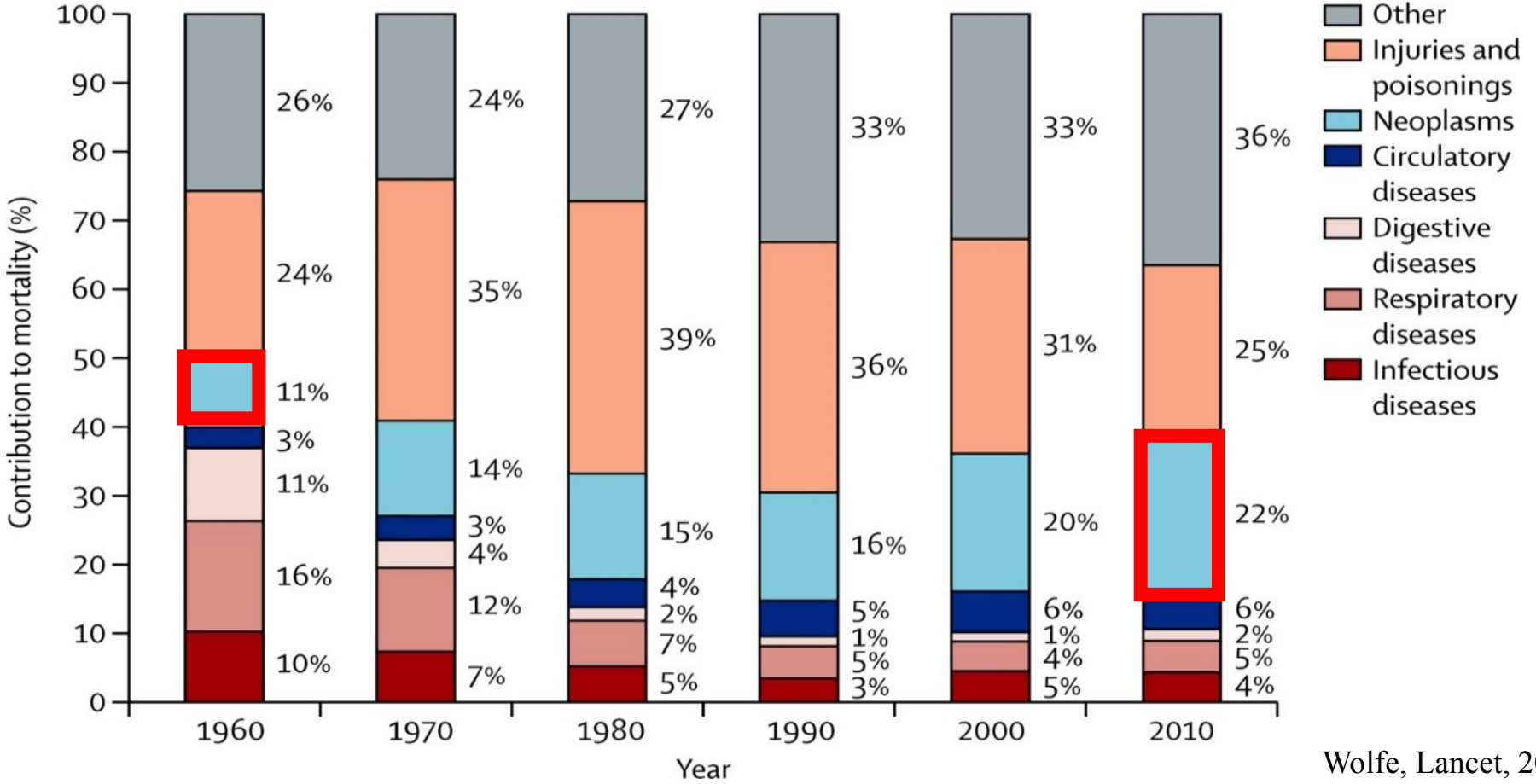




Lykke, Acta Pædiatrica 2018

Alder (år)	Proportion	Fald i mortalitet	Primære årsager til faldet
0.0-0.9	61%	26%	Medfødte misdannelser og kromosomfejl (68%) & perinatale dødsfald (30%)
1.0-17.9	39%	65%	Ydre årsager (ulykker, vold, selvmord) (75%) & **KRÆFT (57%)**

Børnedødelighed (1.0-14.9 år) i Europa

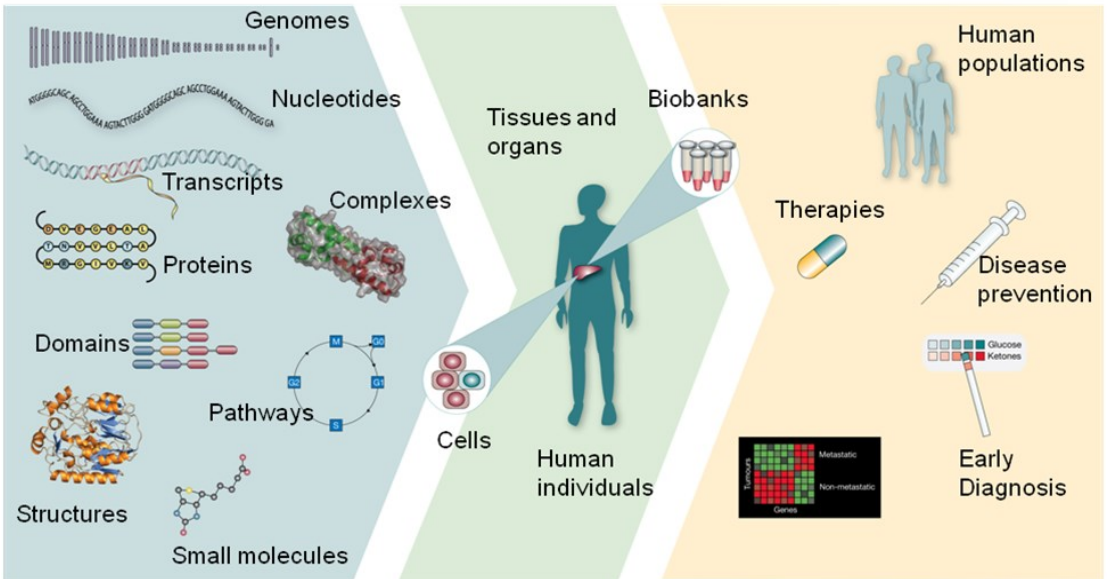


Wolfe, Lancet, 2013

Ætiologi	Tumorbiologi	Frontlinje behandling	Farmakologi	Fase 1&2 behandling	Akut toksicitet	Over-levelse	Senfølger & rehabilitering
Værts genom	Tumor genom	Tumor genom	Værts genom	Tumor genom	Værts genom	Tumor & værts genomer	Værts genom

Helbredelse og liv

Præcisionsmedicin og/eller personlig medicin



- Cancer disposition / ætiology
- Tumor -omics (diagnose/prognose)
- Fase 1 & fase 2 forsøg
- Farmaka-monitorering (TDM)
- Akutte toksiciteter
- Senfølger
- Genotype -> fænotype vs fænotype -> fænotype??

Hvornår skal vi overveje et cancersyndrom?

Kun kræft (e.g. *TP53*) (5-10%) ← Ukendt → (10%) Non-malign fænotype

1. Stamtræ (3 generat.)
   - ≥ to med cancer før 18 års alderen
   - forældre/søskende cancer <45 år
   - ≥ to 1./2. grads slægtninge med cancer <45 år
   - indgifte forældre
2. Cancer der indikerer syndrom
   - N=60+ & stigende; fx binyrebark carcinom (LFS)
3. Tumor genetik

   Fx chromotripsis ved Li-Fraumeni syndrom
4. Patient med ≥2 cancere
   - 2., bilateral, multifokal, metakron
5. Cancer & syndrom-stigmata
   - Misdannelser, ansigts dysmorfologi, metal retardering, abnorm vækst, hud-elementer (fx cafe au lait), dys-hæmatologi, immundefekt, endokrin sygdom
6. Udtalte bivirkninger

Childhood cancer: Indication for genetic counseling?*

*updated Jongmans criteria [Jongmans et al., 2016]

If at least one criterion is fulfilled, your patient may benefit from genetic counseling

1. Family history (3 generation pedigree)

- O ≥2 malignancies occurred in family members before age 18 years, including index patient
- O Parent or sibling with current or history of cancer before age 45 years
- O ≥2 first or second degree relatives in the same parental lineage with cancer before age 45 years
- O The parents of the child with cancer are consanguineous

2. One of the following Neoplasms was diagnosed:

- O Adrenocortical carcinoma / adenoma
- O ALL (low hypodiploid)
- O ALL (ring chromosome 21)
- O ALL (Robertsonian translocation 15;21)
- O ALL relapse (TP53 mutated)
- O AML (Monosomy 7)
- O Basal cell carcinoma
- O Botryoid rhabdomyosarcoma of the urogenital tract (fusion-negative)
- O Chondromesenchymal hamartoma
- O Choroid plexus carcinoma / tumor
- O Colorectal carcinoma
- O Cystic nephroma
- O Endolymphatic sack tumor
- O Fetal rhabdomyoma
- O Gastrointestinal stromal tumor
- O Glioma of the optic pathway (with signs of NF1)
- O Gonadoblastoma
- O Hemangioblastoma
- O Hepatoblastoma (*CTNNB1* wildtype)
- O Hepatocellular carcinoma
- O Infantile myofibromatosis
- O Juvenile myelomonocytic leukemia
- O Keratocystic odontogenic tumor
- O Large cell calcifying Sertoli cell-tumor
- O Malignant peripheral nerve sheath tumor
- O Medullary thyroid carcinoma
- O Medulloblastoma (SHH activated)
- O Medulloblastoma (WNT activated, *CTNNB1* wildtype)
- O Medullary renal cell carcinoma
- O Medulloepithelioma
- O Melanoma
- O Meningioma
- O Myelodysplastic syndrome
- O Myeloproliferative neoplasms (except CML)
- O Myxoma
- O Neuroendocrine tumor
- O Paraganglioma / pheochromocytoma
- O Parathyroid carcinoma / adenoma
- O Pineoblastoma
- O Pituitary adenoma / tumor
- O Pituitary blastoma
- O Pleuropulmonary blastoma
- O Renal cell carcinoma
- O Retinoblastoma
- O Rhabdoid tumor
- O Rhabdomyosarcoma with diffuse anaplasia
- O Schwannoma
- O Schwannomatosis
- O Sertoli-Leydig cell tumor
- O Sex cord stromal tumor with annular tubules
- O Small cell carcin. of the ovary hypercalcemic type
- O Squamous cell carcinoma
- O Subependymal giant cell astrocytoma
- O Thyroid carcinoma (non-medullary)
- O Transient myeloproliferative disease
- O **Other rare cancers or cancers that typically occur in adults, unusually early manifestation age**

3. O Genetic tumor analysis reveals defect suggesting a germline predisposition

4. O A patient with ≥2 malignancies (e.g. secondary, bilateral, multifocal, metachronous)

5. O A child with cancer and congenital or other anomalies

Sign	*Think of*
O Congenital anomalies	Abnormal organs, skeletal anomalies, oral clefting, abnormal teeth, urogenital anomalies, abnormal hearing or vision, etc.
O Facial dysmorphism	
O Mental impairment, developmental delay	Abnormal behavior, learning difficulties
O Abnormal growth	Height, head circumference, birth weight, hemihyperplasia, growth chart
O Skin anomalies	Abnormal pigmentation such as ≥2 café-au-lait spots, vascular lesions, hypersensitivity to sun, benign tumors, etc.
O Hematological abnormalities (not explained by current cancer)	Pancytopenia, anemia, thrombocytopenia, neutropenia, leukopenia, macrocytic erythrocytes
O Immune deficiency	Frequency of infections, lymphopenia
O Endocrine anomalies	Primary hyperparathyroidism, precocious puberty, gigantism/acromegaly, Cushing syndrome

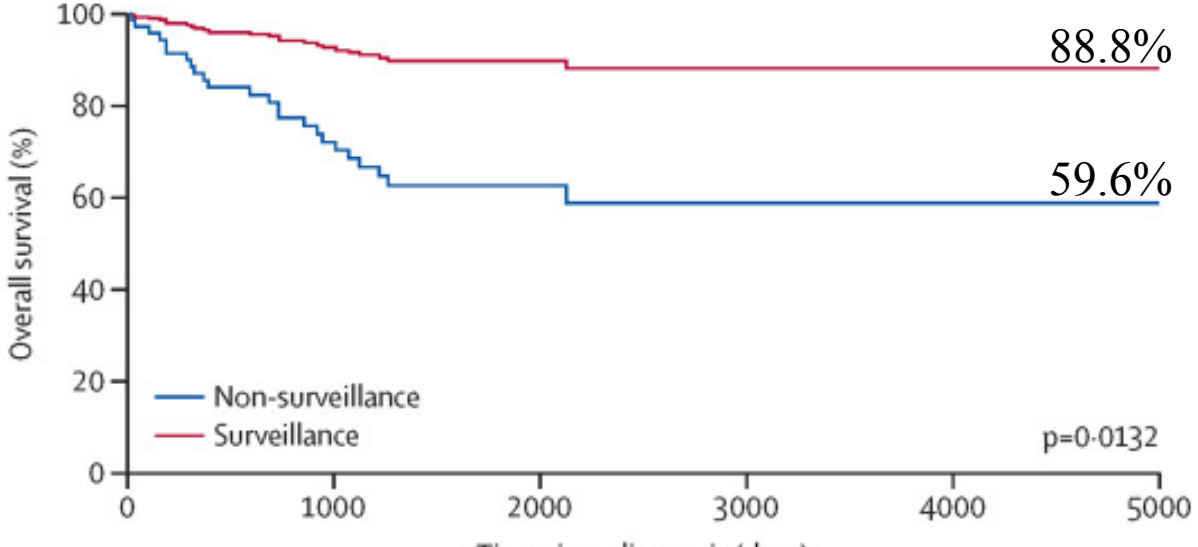
6. O The patient suffers from excessive toxicity of cancer therapy

Villani; Lancet Oncol 2016 (3 cancercentre i USA og Canada)

Biokemi og billeddiagnostik for bærere af TP53 germline mutation (=Li-Fraumeni syndrom)

11 års opfølgning i prospektivt, observationalt studie

Helkrops MR skanning, mammografi, abdominal ultralyd, kolonoskopi, blod- og urinprøver, klinisk kontrol



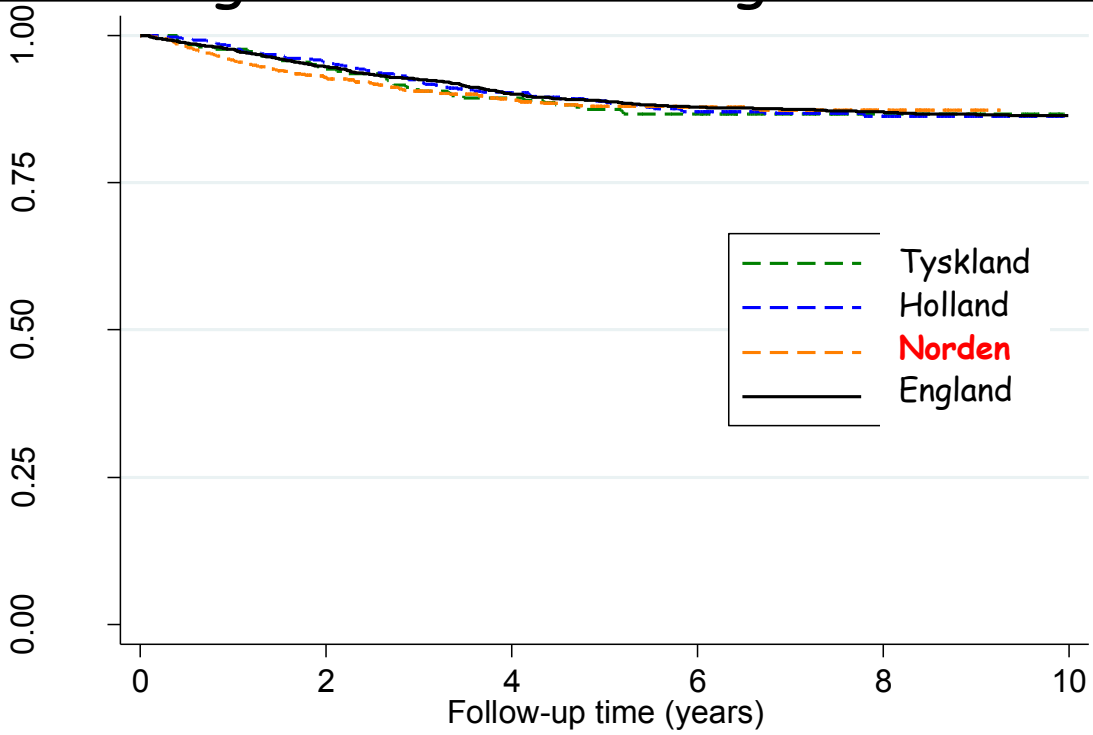
Number at risk (censored)						
Non-surveillance	61 (0)	36 (8)	17 (16)	5 (10)	0 (5)	0 (0)
Surveillance	42 (0)	22 (19)	12 (8)	5 (7)	1 (4)	0 (1)

89 TP53 mutations bærere i 39 familier

Overvågning: N=59; 40 tumorer hos 19 patienter (+2 ”falsk” negative)

Uden overvågning: N=49; 61 tumorer hos 43 patienter

Behandling ALL: Danmark og Norden blandt de bedste i verden!



Numbers at risk

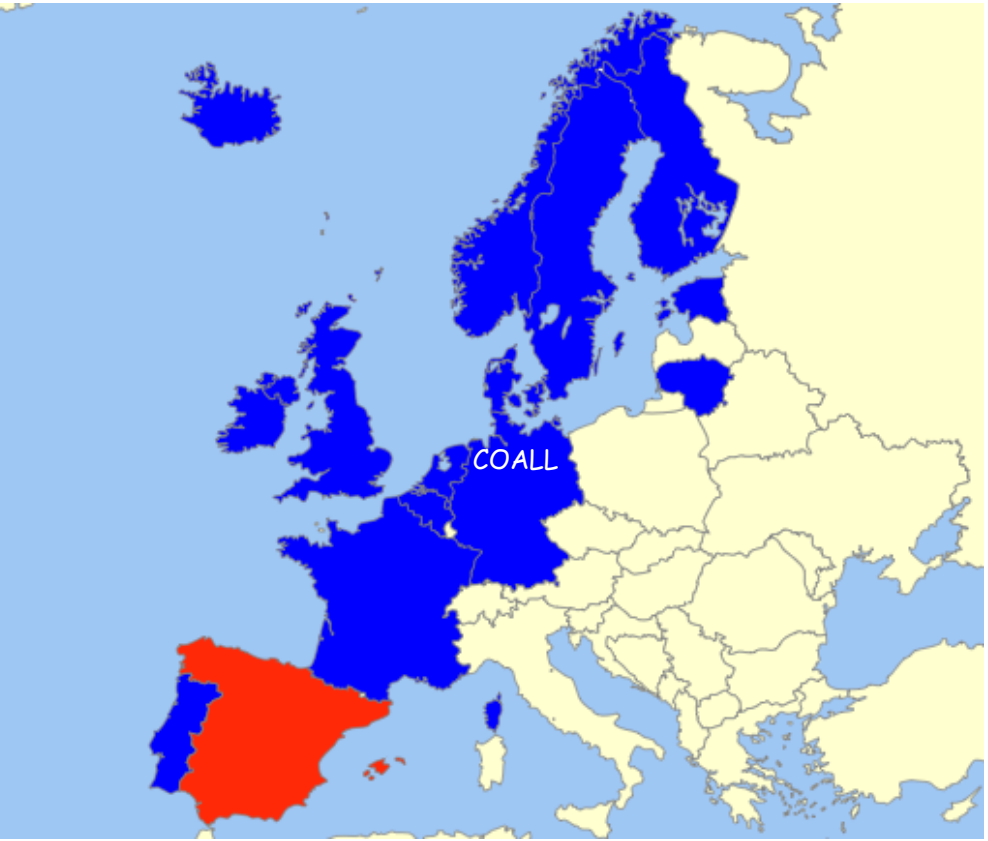
COALL	264	249	236	220	93	26
DCOG	655	625	502	345	190	33
Norden	1550	1307	892	487	127	0
UK	2533	2394	2198	1587	876	295

Identiske resultater
(DFS, OS, recidiv risik)
Men:
Ikke identisk kemoterapi

ALL Together

Nyt Europæisk ALL konsortium

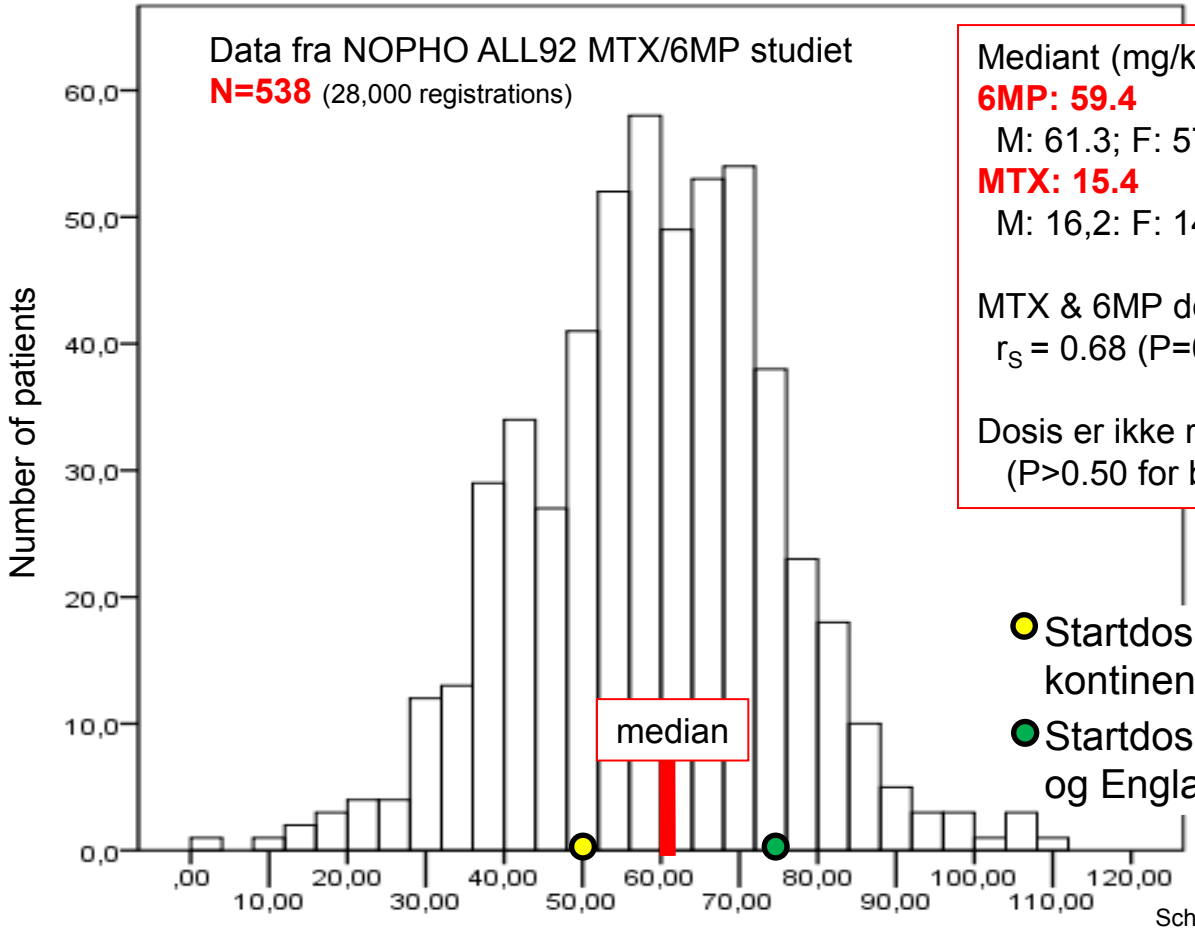
ALLTogether: 14 lande; 1400 pat. /år



Hyppigt anvendte Cytostatika til ALL	Godkendt FDA	
*Mercaptopurine	1953	
*Methotrexate	1953	
Prednisone	1955	
Dexamethasone	1958	
Cyclophosphamide	1959	
*Busulfan	1959	
Vincristine	1964	
Thioguanine	1966	Traditionelle
Cytarabine	1969	
*Asparaginase	1978	
Daunorubicin	1979	
Etoposide	1983	
Doxorubicin	1984	
Idarubicin	1990	
Fludarabine	1991	
*Imatinib	2001	
Clofarabine	2004	
Nelarabine	2005	Targeteret
Inotuzumab ozogamicin	2017	Behandling
CAR-T (Tisagenlecleucel)	2017	
Blinatumomab	2018	

*Måles på Bonkolab, Rigshospitalet

Merkaptopurin (6MP) doser under vedligeholdelsesbehandling af ALL



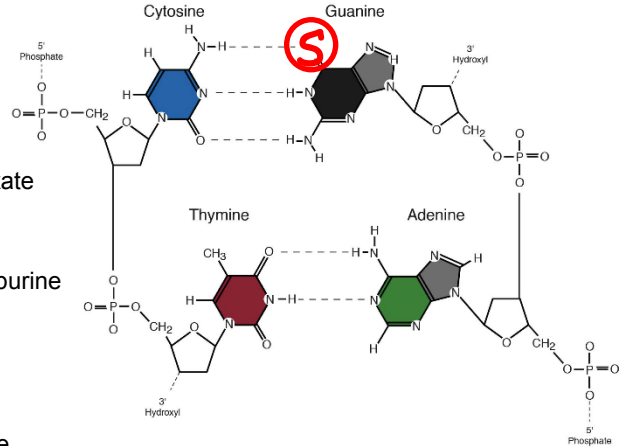
Mediant (mg/kvm):
6MP: 59.4
M: 61.3; F: 57.4 (P=0.006)
MTX: 15.4
M: 16,2: F: 14.6 (P=0.001)

MTX & 6MP doser er korrelerede
r_S = 0.68 (P=0.000)

Dosis er ikke relateret til recidiv-risiko
(P>0.50 for både 6MP og MTX)

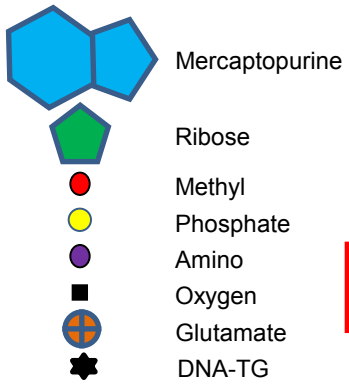
- Startdosis i kontinental Europa
- Startdosis i Norden, og England

Schmiegelow, JCO 2003
Schmiegelow, JPHO 2014
Schmiegelow, PBC 2016



DNA-TG:

- TG matcher normalt med C
- Når TG metylerer mismatcher TG med with T (S^6-MeTG·T)
- Mismatch repair er forgæves, da mismatch fortsætter, hvilket medfører apoptose eller mutation (fx C->T)



Mismatch repair reducerer DNA kopifejl fra 600 til 0-3 per celledeling
Bi-allel MMR defekt: 600 mut/celledeling (*Tabori, Clin Can Res 2017)*

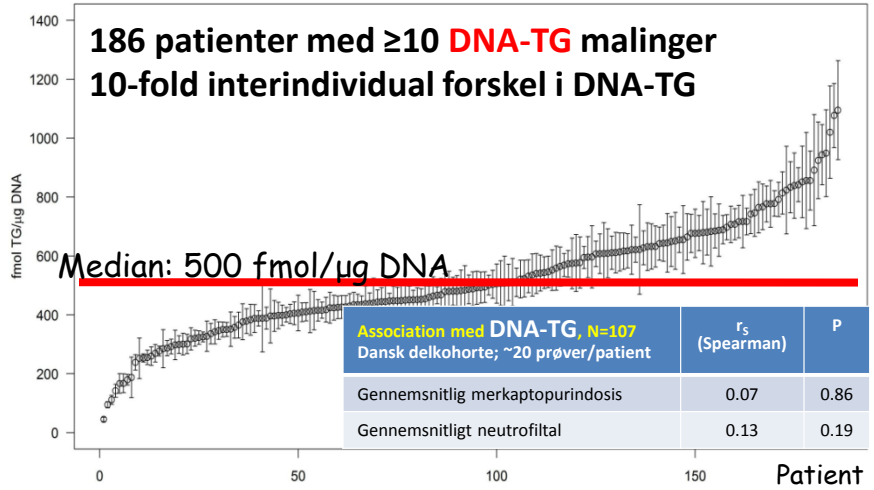
Høj "first-pass-effect" i tarm og lever
Biotilgængelighed 5-95% (Mediant:16%)

chmiegelow, J Ped Hematol Oncol 2014 (review)

*Jacobsen, J Chromatogr B Analyt Technol Biomed Life Sci 2012

NOPHO ALL2008 DNA-TG studie

- **918 børn med ALL** (7 Nordiske/Baltiske lande)
  - 89% af alle der opfyldte inklusionskriterier
  - 526 MRD-positive dag 29
  - 390 MRD-negative dag 29
  - 2 ingen dag 29 MRD status
- 5 års EFS: 92.4% (40 recidiver)
- >10.000 blodprøve
  - Ery-TGN/-MeMP/-MTXpg, **DNA-TGN**
- Klinikeren kendte ikke resultaterne



	Patients (n=918)
Age at diagnosis (years)	4·2 (2·9–7·3)
Sex	
Male	489 (53%)
Female	429 (47%)
White blood cell count at diagnosis (×10⁹ cells per L)	9·2 (4·3–30·9)
Risk group	
Standard	549 (60%)
Intermediate	369 (40%)
Immunophenotype	
B-precursor leukaemia	854 (93%)
T-cell leukaemia	64 (7%)

Data are n (%) or median (IQR).

Nielsen, Lancet Oncol 2017

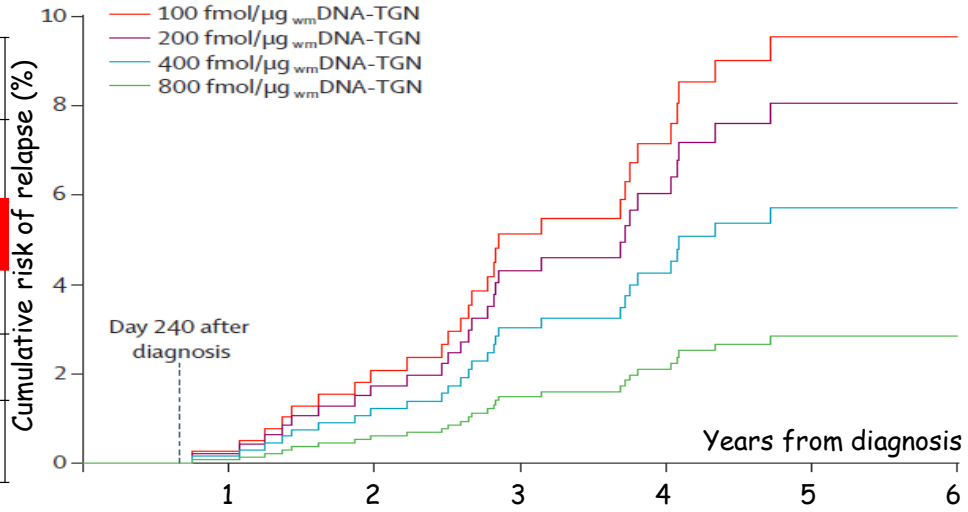
NOPHO ALL-2008 918 **non-HR patienter** (>10,000 blodprøver)

Risiko for **recidiv ift** DNA-TG niveauer under vedligeholdelsesbehandling

Antal målinger per patient: median N=9 (1-56)

	Positiv MRD day 29 n = 526, 31 recidiver		
	Recidiv specific HR	95% CI	P
DNA-TG per 100[a]	**0.723**	**0.572–0.913**	**0.0065**
Alder ved diagnose	1.118	1.037–1.205	0.0035
Køn: Pige vs dreng	1.036	0.511–2.100	0.92
Leukocyttal ved diagnose per 10 x10^9/L	1.001	0.998–1.005	0.56

[a] Time-dependent mDNA-TG levels are re-calculated at time point of each event

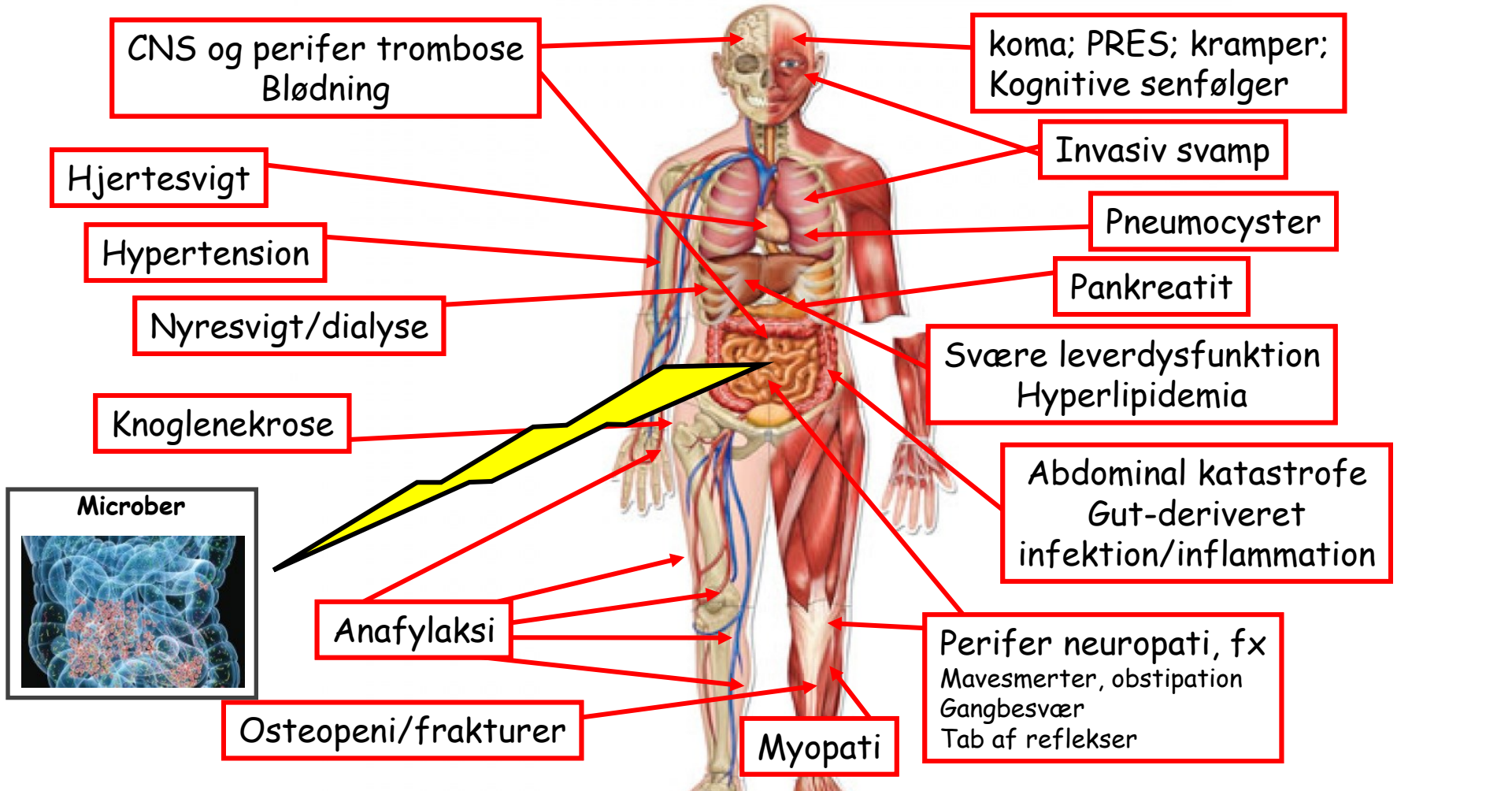


28% reduktion i recidiv hazard (HR) per stigning i DNA-TG (100 fmol/µg DNA)

ALLTogether randomiseret studie: Dosis justering af vedligeholdelsesbehandling efter graden af myelotoksicitet (traditionelt / kontroller) eller strategi der øger DNA-TG

Nielsen, Lancet Oncol 2017

1 patient; 1 cancer; multiple organer; 25000+ gener; 100 mio varianter



TOXICITIES BEING ADDRESSED (√)	Schmiegelow, Lancet Oncol 2016 (konsensus definitioner)
Hypersensitivity to asparaginase √	
Hyperlipidemia	
Osteonecrosis (N ~1,000) √	
Asparaginase-associated pancreatitis √	Wolthers, Lancet Oncol 2017 (fænotype); Haematology 2018 (genotyper)
Arterial hypertension	
Posteror reversible encephalopathy syndrome √	
Seizure √	
Depressed level of consciousness √	
Methotrexate-related stroke-like syndrome √	
Peripheral neuropathy	
High-dose methotrexate related nephrotoxicity √	
Sinusoidal obstruction syndrome	
Thromboembolism (N ~1,000) √	
Invasive fungal infections √	

NOPHO ALL2008 kohorten:

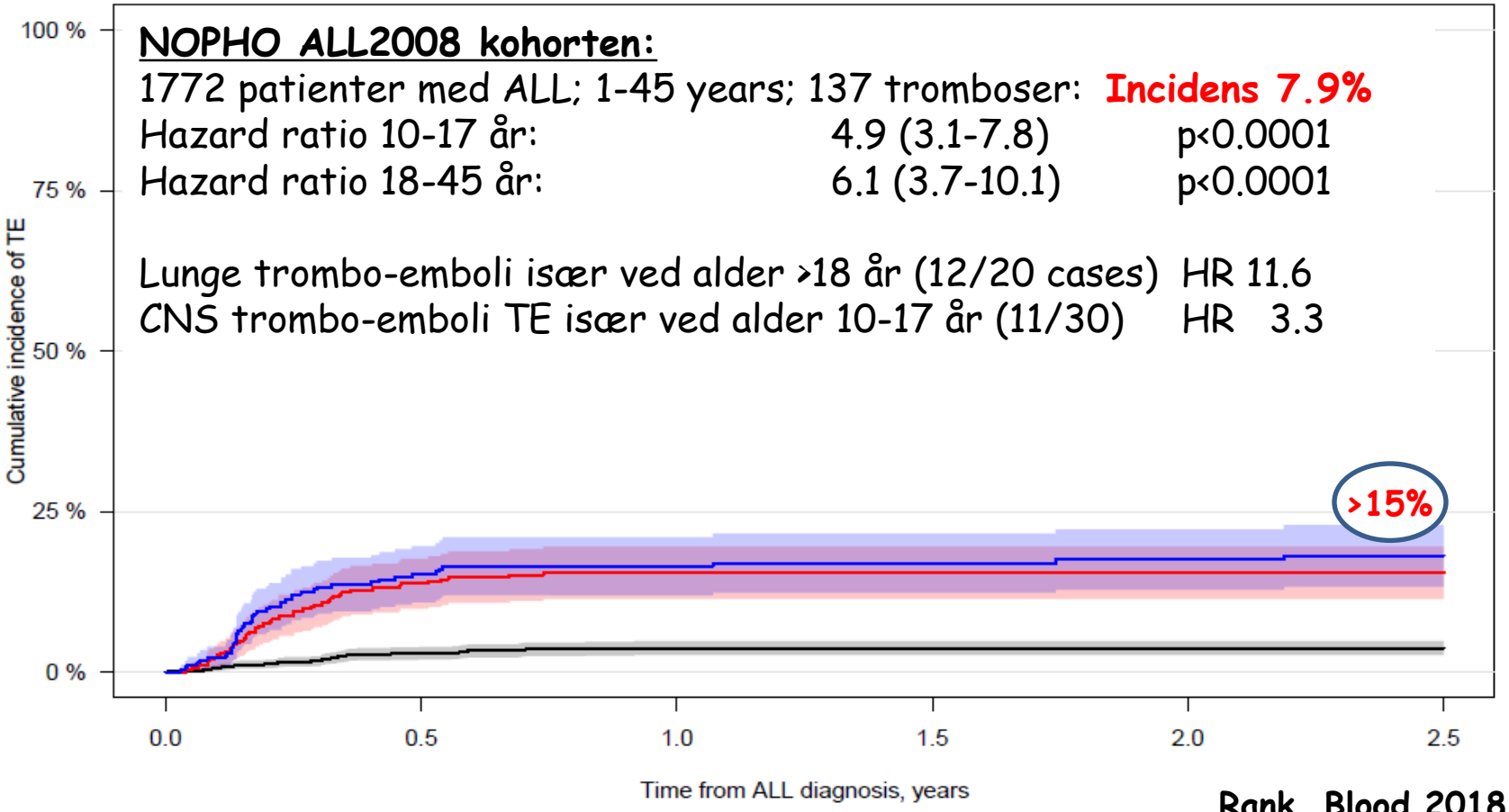
1772 patienter med ALL; 1-45 years; 137 tromboser: **Incidens 7.9%**

Hazard ratio 10-17 år: 4.9 (3.1-7.8) p<0.0001

Hazard ratio 18-45 år: 6.1 (3.7-10.1) p<0.0001

Lunge trombo-emboli især ved alder >18 år (12/20 cases) HR 11.6

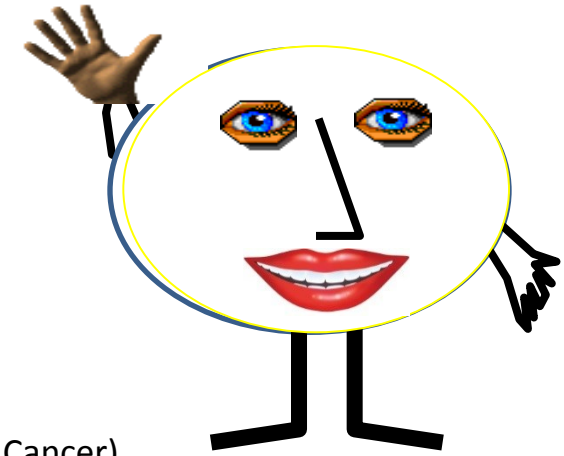
CNS trombo-emboli TE især ved alder 10-17 år (11/30) HR 3.3



Rank, Blood 2018

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

Konklusioner/forudsigelser:



- 0.2% af nyfødte er disponerede for cancer (CPS)
  - Fremtidig national neonatal screening vil inkludere CPS
- International forskning får en tiltagende rolle
  - Ikke mindst for fase 1 og 2 behandling
  - Rigshospitalet ITCC-medlem (Innovative Therapy for Children with Cancer)
- Dyb *fænotypering + genotypering* vil generere personlig medicin dvs bedre behandling; individualiseret dosering; reduktion af bivirkninger
- Monitorering af medicinomsætning øger effekt & reducerer toksicitet
- Personlig medicin mhp reduktion af senfølger vil spille en tiltagende rollle