

# DANSKE KRÆFTFORSKNINGSDAGE 2023

## Børnekræft:

# En kontinuerlig rejse imod bedre overlevelse og en bedre fremtid

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#DKD2023

#SamarbejdeOmKræft



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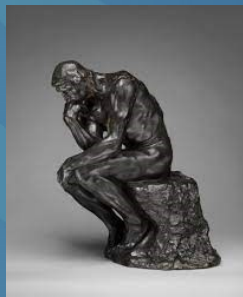
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# DANSKE KRÆFTFORSKNINGSDAGE 2023

## Børnekræft:

# ”Lang nats rejse mod dag”

*Eugene O’Neill*



#DKD2023

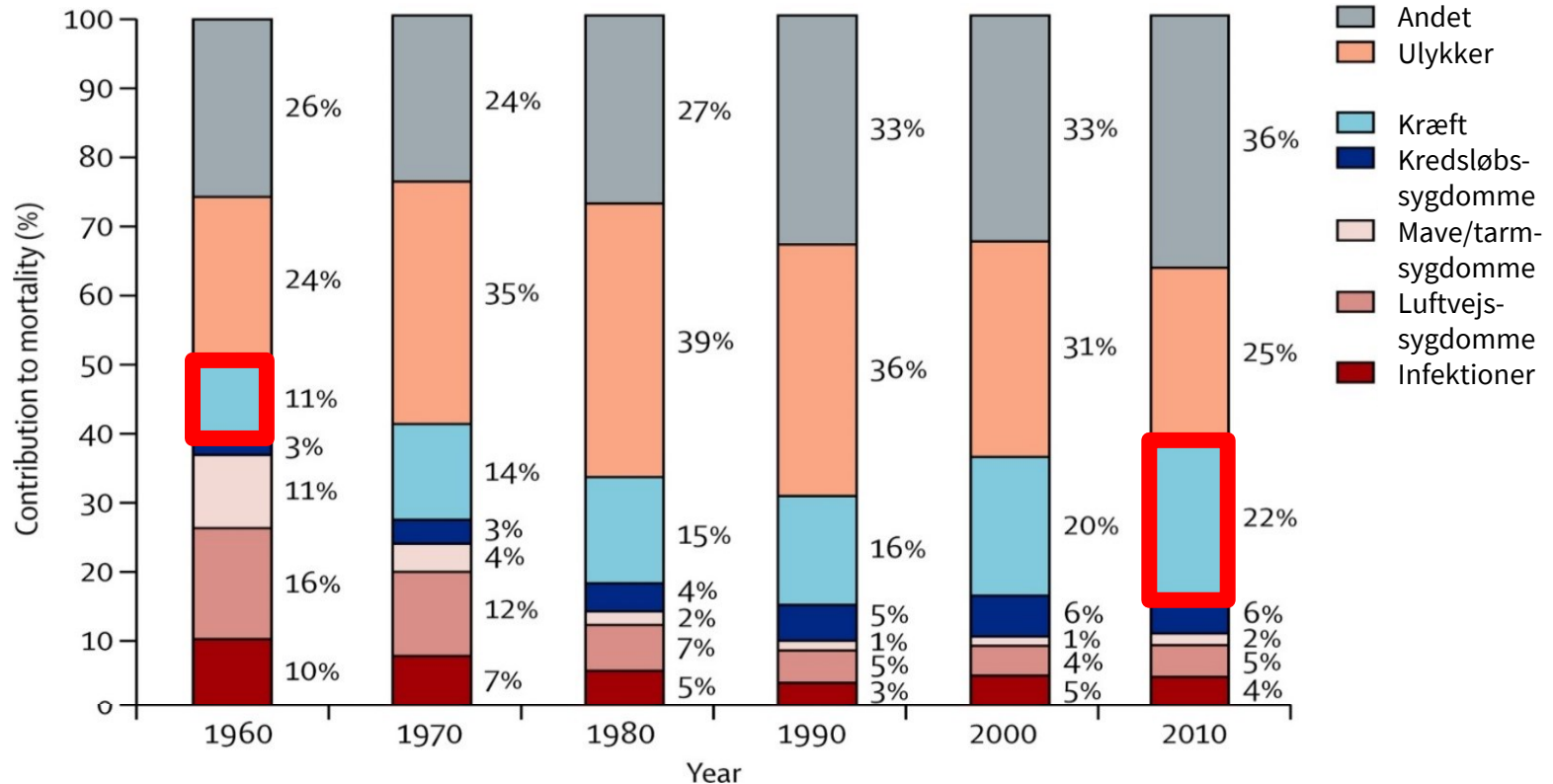
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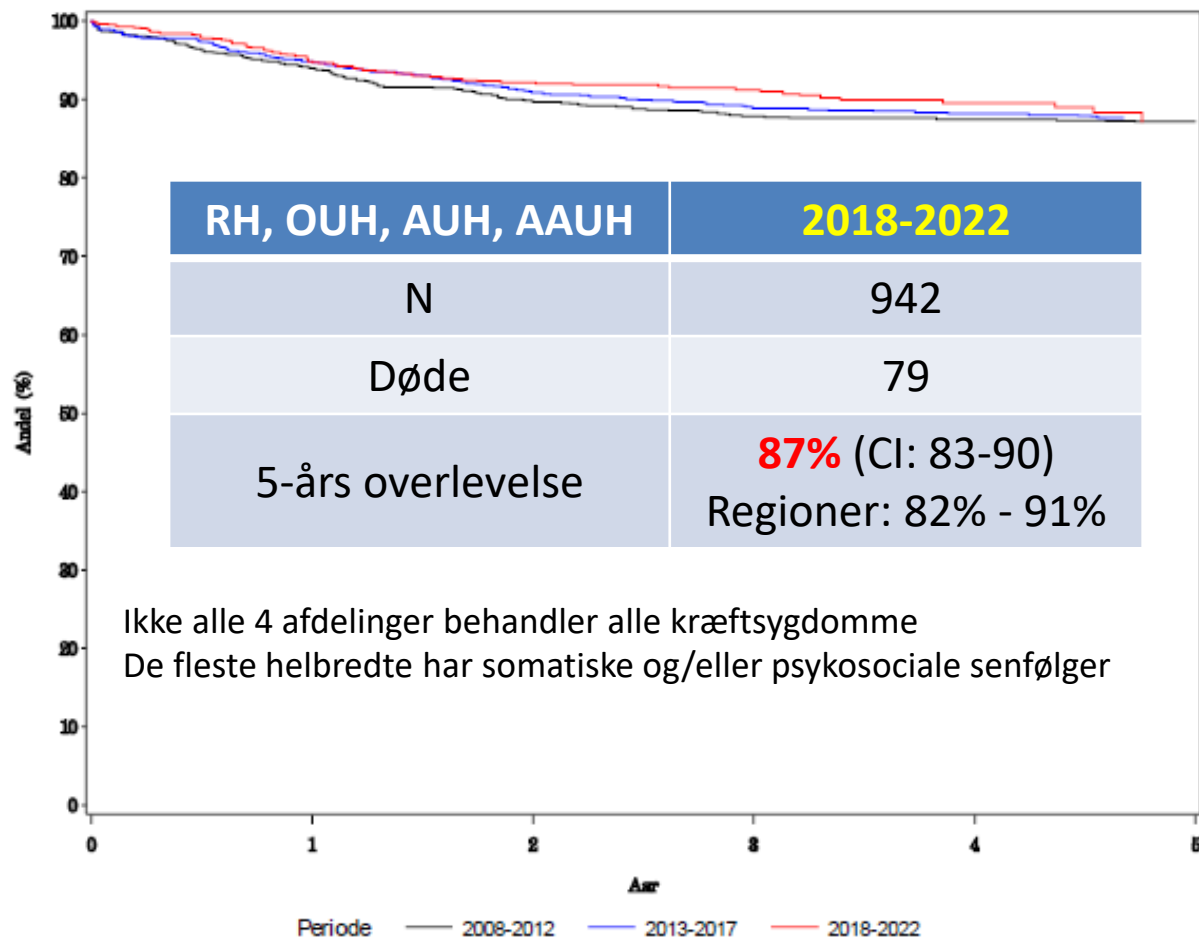
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# Børnedødelighed i Europa



## Udviklingen i 5-års overlevelsen for børnekraft i Danmark 2008-2022.



# CONTROL

## De 17 work-packages (WPs)



**Ledelse**  
Sikrer integrering af  
forskningsområderne.

-omics



**Værts-genomet**  
Finder årsager til  
børnekraft.



**Cancer screening  
& tidlig diagnostik**  
Øger overlevelse og  
reducerer morbiditet.



**Tumor-genomet &  
tumorbiologi**  
Målretter behandling  
ud fra tumorforståelse.



**CNS-tumorer &  
metastasering**  
Non-invasiv diagnose og  
målrettet behandling.

Farma



**Monitorering af  
behandling**  
Forbedrer måling af  
behandlingsrespons.



**Farmakologi**  
Optimerer læge-  
middel dosering via  
sensitive analyser.



**Immunoterapi**  
Introducerer nye  
behandlinger med  
CAR-T celleterapi.



**Fase 1 & fase 2  
forsøg**  
Adgang til ny  
experimental medicin.

Toksicitet



**Akutte bivirkninger**  
Standardiserer og  
reducerer bivirkninger.



**Senfølger**  
Undersøger senfølger  
og sikrer et bedre liv  
efter kræft er kureret.



**Palliation**  
Minimerer smerter og  
lidelse via tidlig  
palliativ indsats.

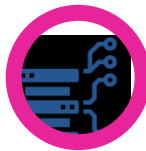


**Social ulighed**  
Identificerer sociale  
uligheders påvirkning  
af overlevelse.

Helheden



**Leg & fysisk  
træning**  
Sikrer fysisk aktivitet  
og mulighed for leg.



**Databaser**  
Styrker mulighederne  
for koblinger af data  
fra multiple kilder.



**Biostatistik &  
modellering**  
Integrerer avancerede  
algoritmer i klinikken.



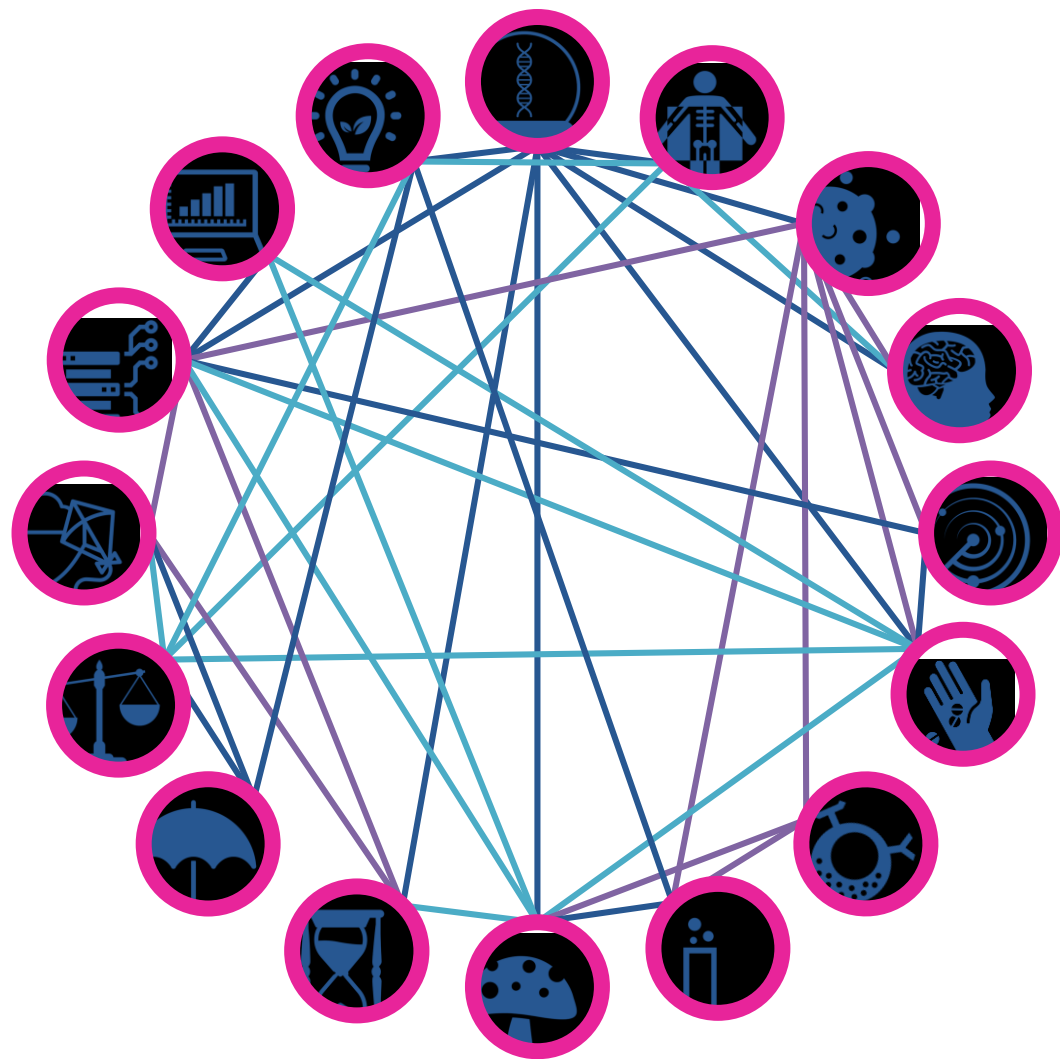
**Bioetik**  
Fokuserer specifikt på  
etiske problemstillinger i  
forbindelse børnekraft.

# CONTROL

## WP interaktioner organisering

### WP2 Værts-genomet

- ✓ Disposition/screening
- ✓ Tumor-genom/biologi
- ✓ Hjernetumorer
- ✓ Medicinomsætning
- ✓ Bivirkninger
- ✓ Immunterapi
- ✓ CONTROL database
- ✓ Etik



**DRUG** **FDA approved**

Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Busulfan	1959
Vincristine	1964
Thioguanine	1966
Cytarabine	1969
Asparaginase	1978
Daunorubicin	1979
Etoposide	1983
Doxorubicin	1986
Idarubicin	1990
Fludarabine	1991
Peg-asparaginase	1994
Rituximab	1997
Imatinib Mesylate	2001
Clofarabine	2004
Nelarabine	2005
Dasatinib	2006
Erwinaze	2011
Vincristine sulfacte liposomes	2012
Ponatinib	2016
Blinatumomab ▼	2016
Inotuzumab ozogamicin ▼	2017
Tisagenlecleucel ▼ (CAR-T)	2017

Generally non-specific

More targeted therapy

# Leukemia therapy 1953–2017

**Induction**  
 Glucocorticosteroid  
 Vincristine  
 Asparaginase a/o  
 Anthracycline

Remission induction & chemosensitivity testing

**Consolidation-1**  
 Cyclophosphamide  
 Cytarabine  
 Mercaptopurine  
 HD-Methotrexate

Deepening of remission; CNS-directed Tx

**Delayed intensification (x1-2)**  
 Dexamethasone  
 Vincristine  
 Asparaginase  
 +/- Anthracycline

Deepening of remission

**Consolidation-2**  
 Cyclophosphamide  
 Cytarabine  
 Thioguanine

Deepening of remission

**Maintenance therapy**  
 Thiopurines  
 Methotrexate  
 (VCR/steroid pulses)

Until 2-3 years from Dx (girls longer)

▼These medicinal products are subject to additional monitoring. All suspected adverse reactions to be reported

# Therapeutic drug monitoring in ALL

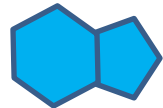
Antileukemic agent	Relevant biomarker	Routine TDM in ALLTogether-1	Target	Key PG biomarker
Vincristine				<i>CEP72</i> promotor
Prednisolone/Dexa	Cellular Drug Resistance			
Asparaginase	p-ASNase activity		100 IU/L	No
Doxorubicine				
Cytarabine				
Cyclophosphamide				
Thiopurines	DNA-TG			<i>TPMT/NUDT15</i>
HD-MTX	p-MTX		Duration >1 $\mu$ M before leukovorin	<i>SLCO1B1</i> (5-10%)
Oral MTX	Ery-MTXpg		Unknown	<i>DHFR/FPGS</i>
Imatinib	p-Imatinib		>1,000 ng/ml	<i>CYP3A4</i>
Busulfan (conditioning)	p-Busulfan (AUC)		AUC 85-95 mg x h/L	



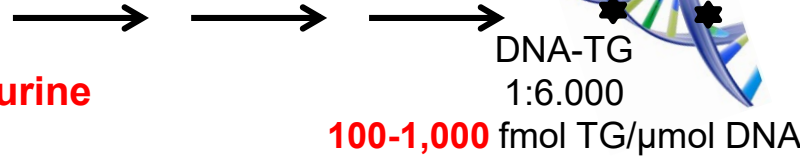
# NOPHO ALL-2008 918 **non-HR patients** (>10,000 blood samples)

## Risk of **relapse** by DNA-TG levels during maintenance therapy

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

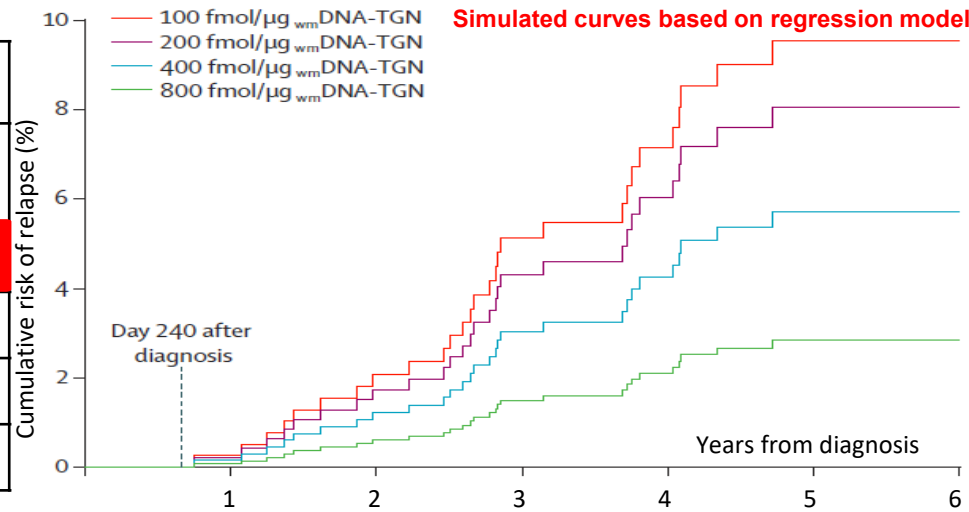


**Mercaptopurine**



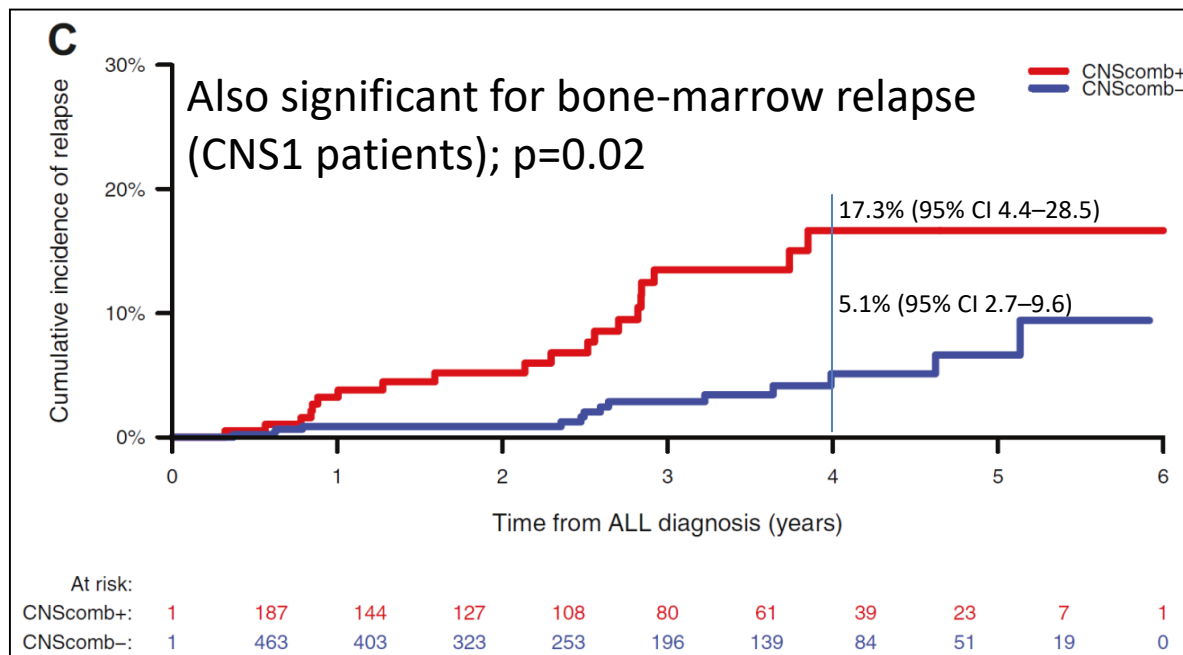
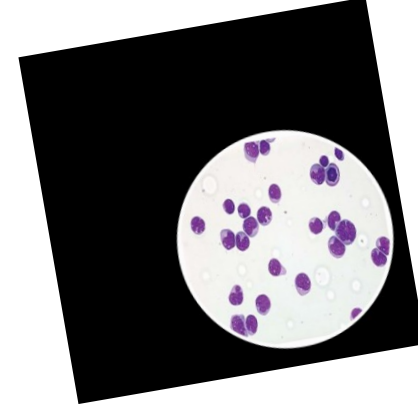
Parameters in time-weighted Cox regression model	Positive MRD day 29 (EOI) n = 526, 31 relapses		
	Relapse specific HR	95% CI	p-value
DNA-TG per 100 <sup>a</sup>	<b>0.723</b>	<b>0.572–0.913</b>	<b>0.0065</b>
Age at diagnosis	1.118	1.037–1.205	0.0035
Female sex	1.036	0.511–2.100	0.92
WBC at Dx per 10 x10 <sup>9</sup> /L	1.001	0.998–1.005	0.56

<sup>a</sup> Time-dependent mDNA-TG levels are re-calculated at time point of each event



**28% reduction in relapse hazard risk per increment of DNA-TG of 100 fmol/μg DNA**

Centralized, blinded results	Cytospin (register data)		Flowcytometry Study	
<i>CNS leukemia</i>	Positive	Negative	Positive (Median: 25/ml)	Negative
BCP-ALL	171 (10.7%)	1427 (89.3%)	122 (20.8%)	464 (79.2%)
T-ALL	65 (27.1%)	175 (72.9%)	49 (56.3%)	38 (43.7%)



COX REGRESSION			
	Adj. HR	95% CI	P value
<b>CNS status</b> CNScomb+ vs. CNScomb-	2.2	1.0–4.7	<b>0.042</b>
<b>Sex</b> Female vs. male	0.5	0.2–1.1	0.085
<b>Age</b> Per one year	1.1	1.1–1.2	<b>&lt;0.001</b>
<b>WBC</b> Per doubling	1.4	1.1–1.6	<b>&lt;0.001</b>

Immunophenotype (BCP-ALL vs T-cell ALL) and MRD day 29 status (positive vs negative) were included as stratification factors



# Severe Toxicity Free Survival (STFS)

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To prioritize **unacceptable long-term severe toxicities** for the future reporting of Severe Toxicity Free Survival

To construct **consensus-based definitions** of these toxicities

855 → 21 Severe Toxicities


## Generic criteria


- I. Not present prior to diagnosis of ALL
- II. Symptomatic
- III. Objective
- IV. Unacceptable severity
- V. Permanent or only correctable by unacceptable treatments

Novel international measure of the unacceptable biological burden of therapy




## Severe Toxicity Free Survival


 Hearing loss


 Hepatic failure


 Seizures


 Blindness


 Insulin dependent diabetes


 Psychiatric disease


 Heart failure


 Renal failure


 Paralytic, neuropathic, myo-pathic and movement disorders


 Coronary artery disease


 Pulmonary failure


 Vocal cord paralysis


 Arrhythmia

 Osteonecrosis


 Chronic cytopenia


 Heart valve disease

 Amputation, physical deformation

 Immunodeficiency

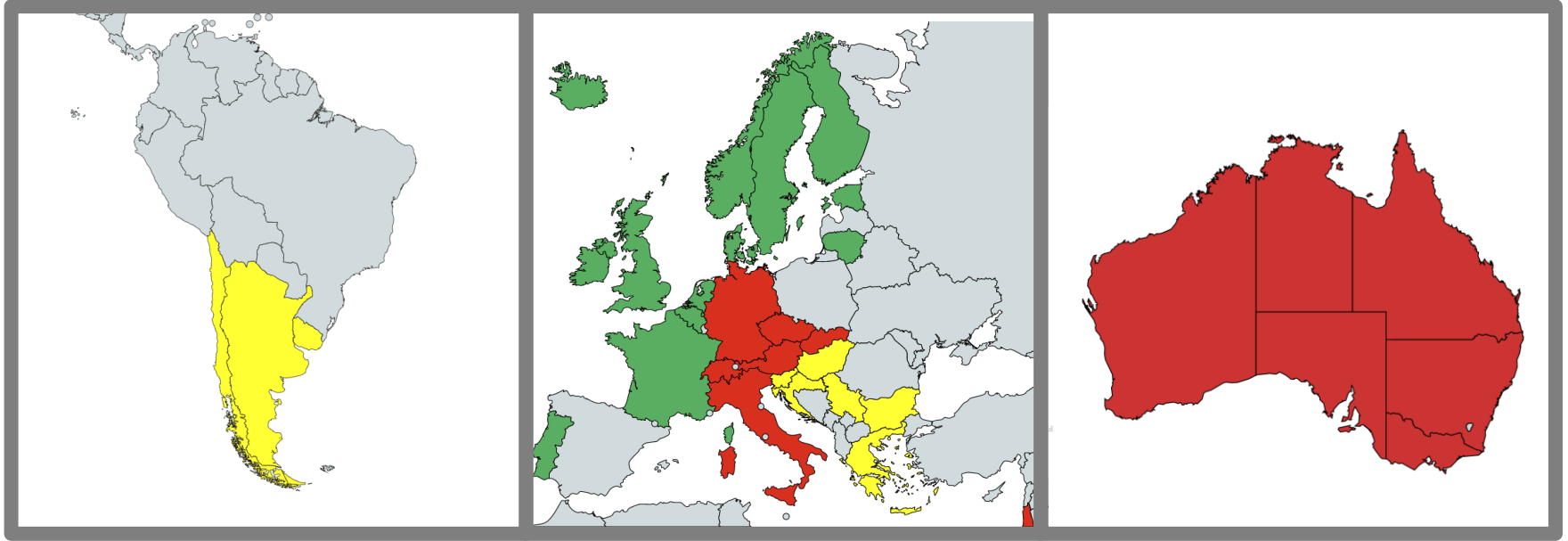
 Gastrointestinal failure

 Cognitive dysfunction

 SMN & benign CNS tumours

# ELEGANT - Exploring Leukemia: Education, Genetics, And Novel Technologies

COMMON variants associated w/ Leukemia risk, pharmacology, efficacy, toxicity



33 countries. 500 mio+ population. 6 mio+ births and >3,000 cases of ALL annually

Target: SNP-profiling 15,000 - 20,000 ALL cases (Children and Young adults); SNP data repository

**AIEOP/BFM:** Australia, Austria, Czech Republic, Germany (BFM group), Israel, Italy, Slovakia, Switzerland

**GMALL:** German adult ALL group

**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

**Japan, Poland, StJude/COG:** Validation of findings

# PREDiSPOSED

Population-based Retro- & prospective Evaluation of Diagnostic Sequencing for Pediatric & Oncogenetic Syndromes ' Early Detection



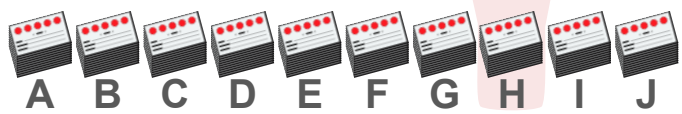
**Li-Fraumeni Syndrome**  
Muscle cancer at 3 years old. Died 4 years old.  
*De novo* mutation found after cancer.

G A G G C C A T C G A G G T G A C C A T C A C A G T

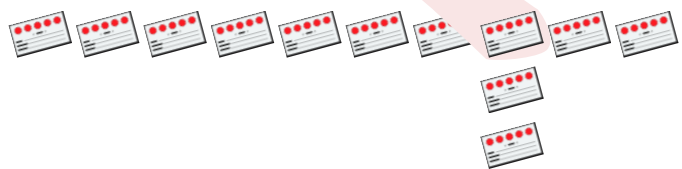
ARG ARG PRO ILE LEU TYR **THR** ILE TYR



Double Batched Sequencing

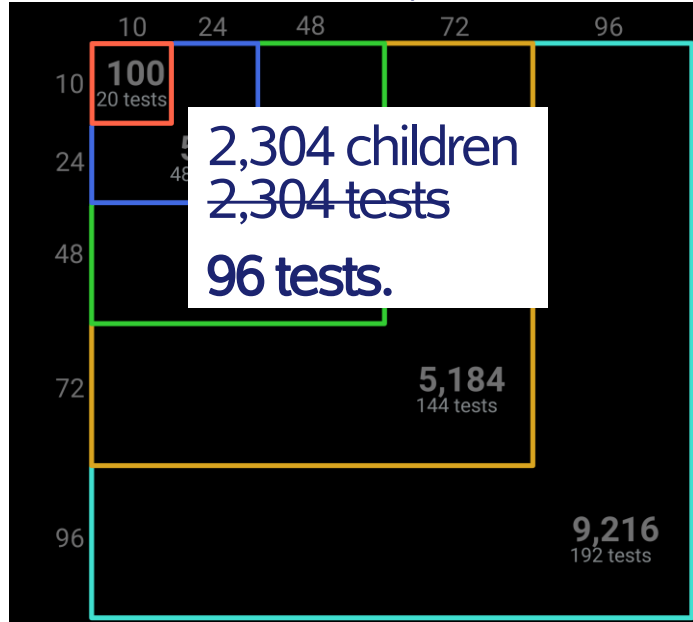


100 children  
~~100 tests~~  
20 tests.



## Designed to scale

- 10x10, 20 tests, 100 samples, 80% reduction
- 24x24, 48 tests, 576 samples, 92% reduction
- 48x48, 96 tests, 2,304 samples, 96% reduction**
- 72x72, 144 tests, 5,184 samples, 97% reduction
- 96x96, 192 tests, 9,216 samples, 98% reduction



# PREDiSPOSED will map actionable genetic diseases in 100,000 newborns and 200,000 adults

Denmark currently screen citizens for:

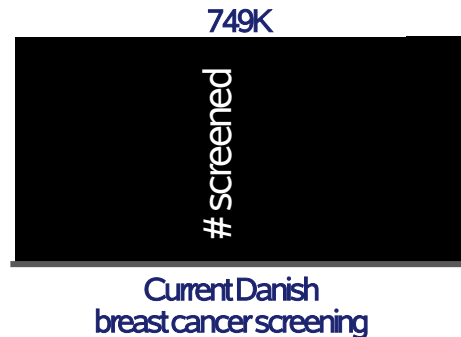
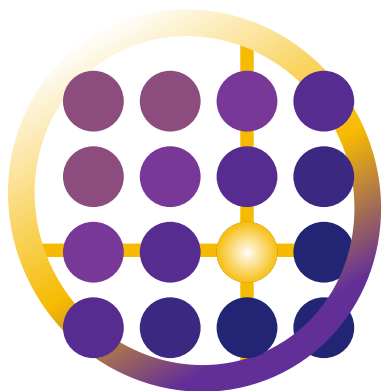
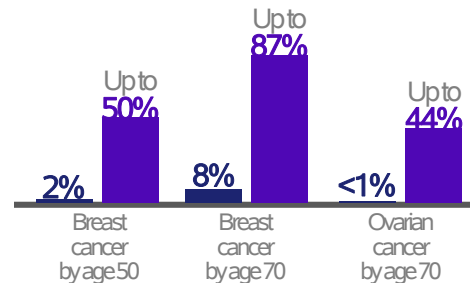
- ✓ Breast cancer
- ✓ Prenatal complications
- ✓ Colon cancer
- ✓ Metabolic diseases
- ✓ Prostate cancer
- ✓ Hearing loss
- ✓ Cervix cancer
- ✓ Much more...

**Example** Improving breast cancer screening:

749,193 DK women (50-69y) are offered breast cancer screening (low impact).

1,500 DK women with a BRCA mutation are in screening (high impact).

6,000 DK women with a BRCA mutation are currently undiagnosed.



PREDiSPOSED may shift National screening strategies towards precision, high-impact screening



# The End

**Tak til:**

100vis af kolleger

1,000vis af patienter

