Genetiske årsager til børnekræft

Ulrik Kristoffer Stoltze, MD, PhD

Magnus

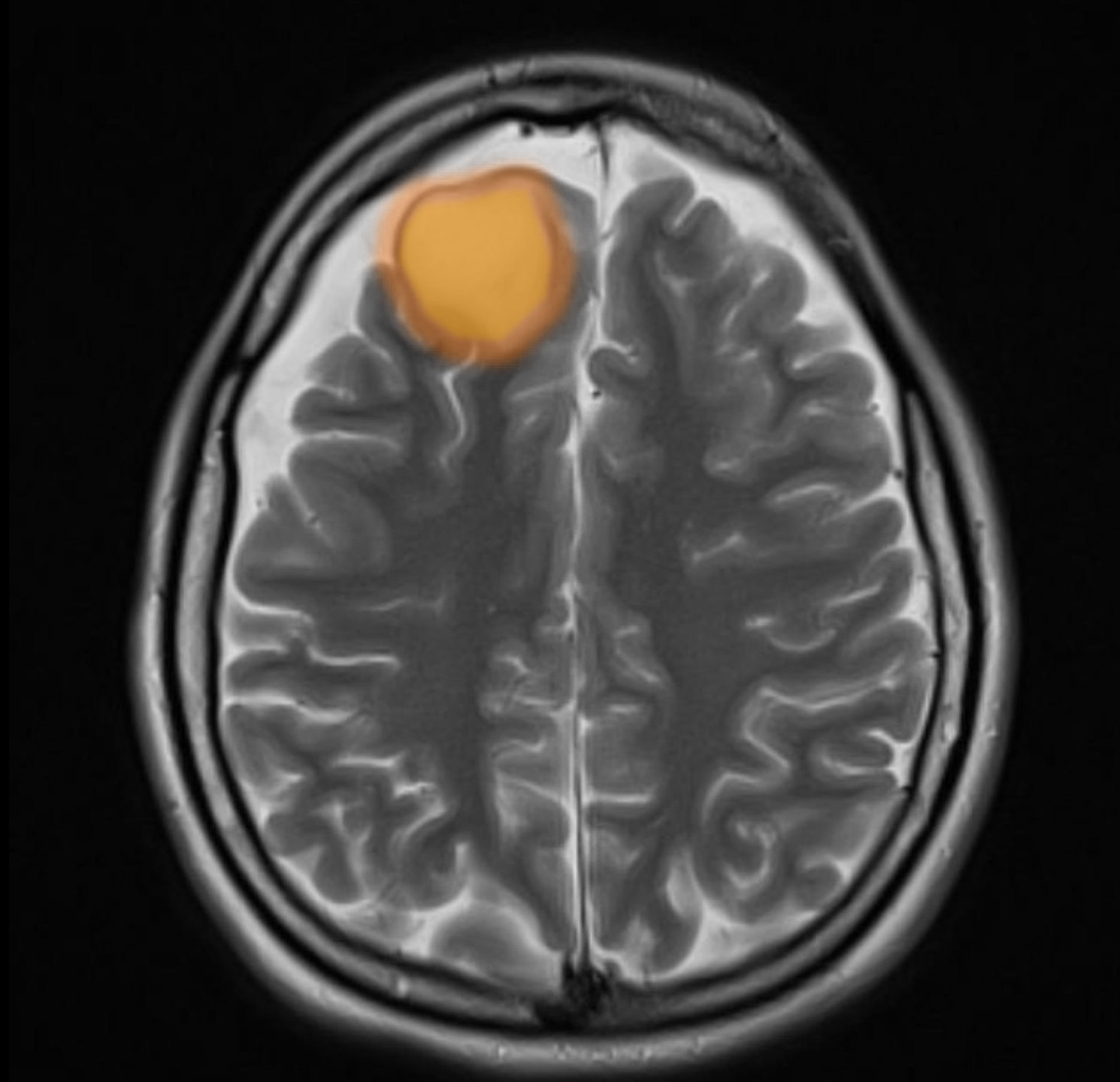
Går i 9. klasse og elsker teater…

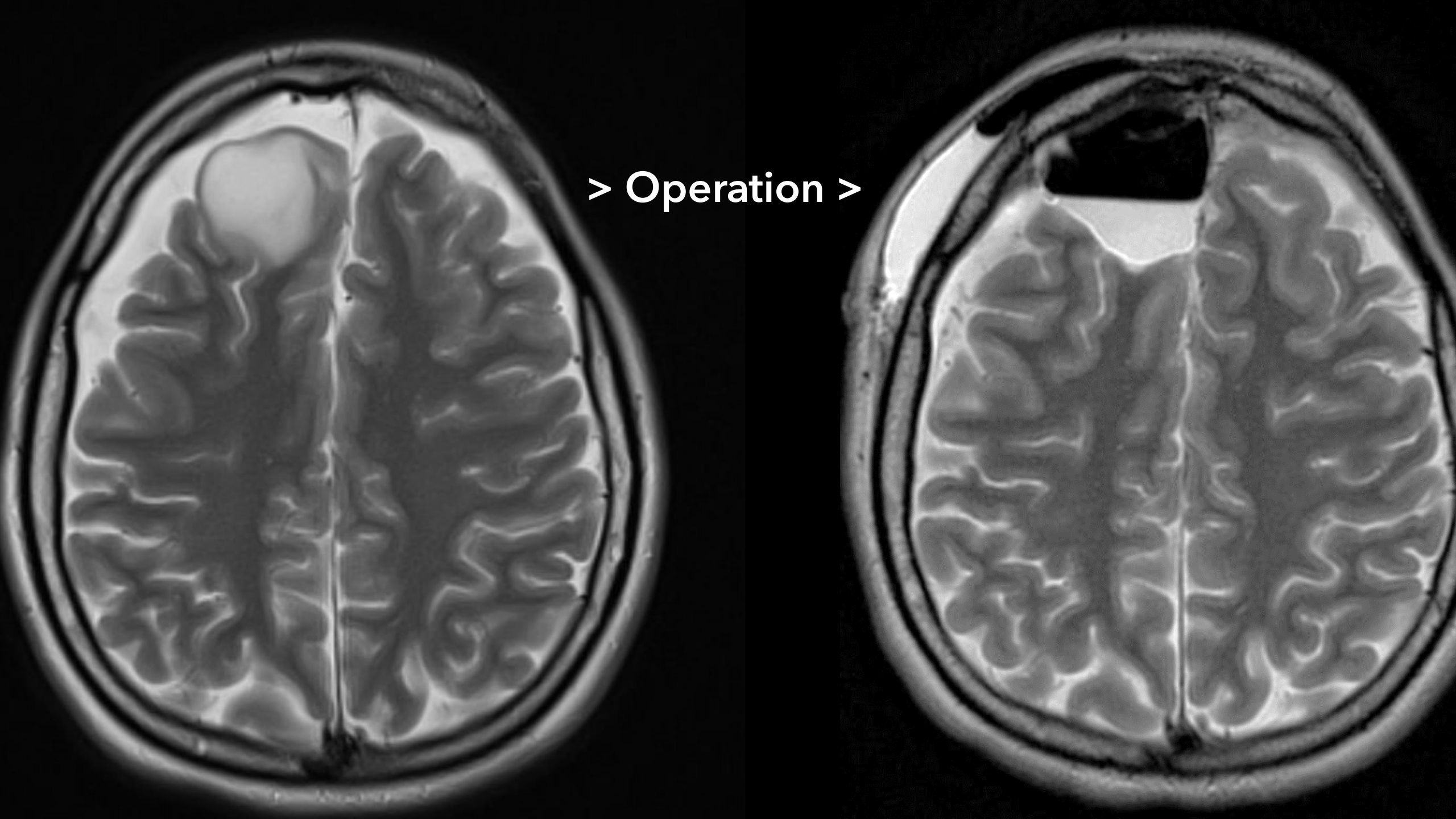
Germline TP53 variant GGCCTCT **Li-Fraumeni Syndrom**

Risiko for børnekræft:

<40%

Magnus

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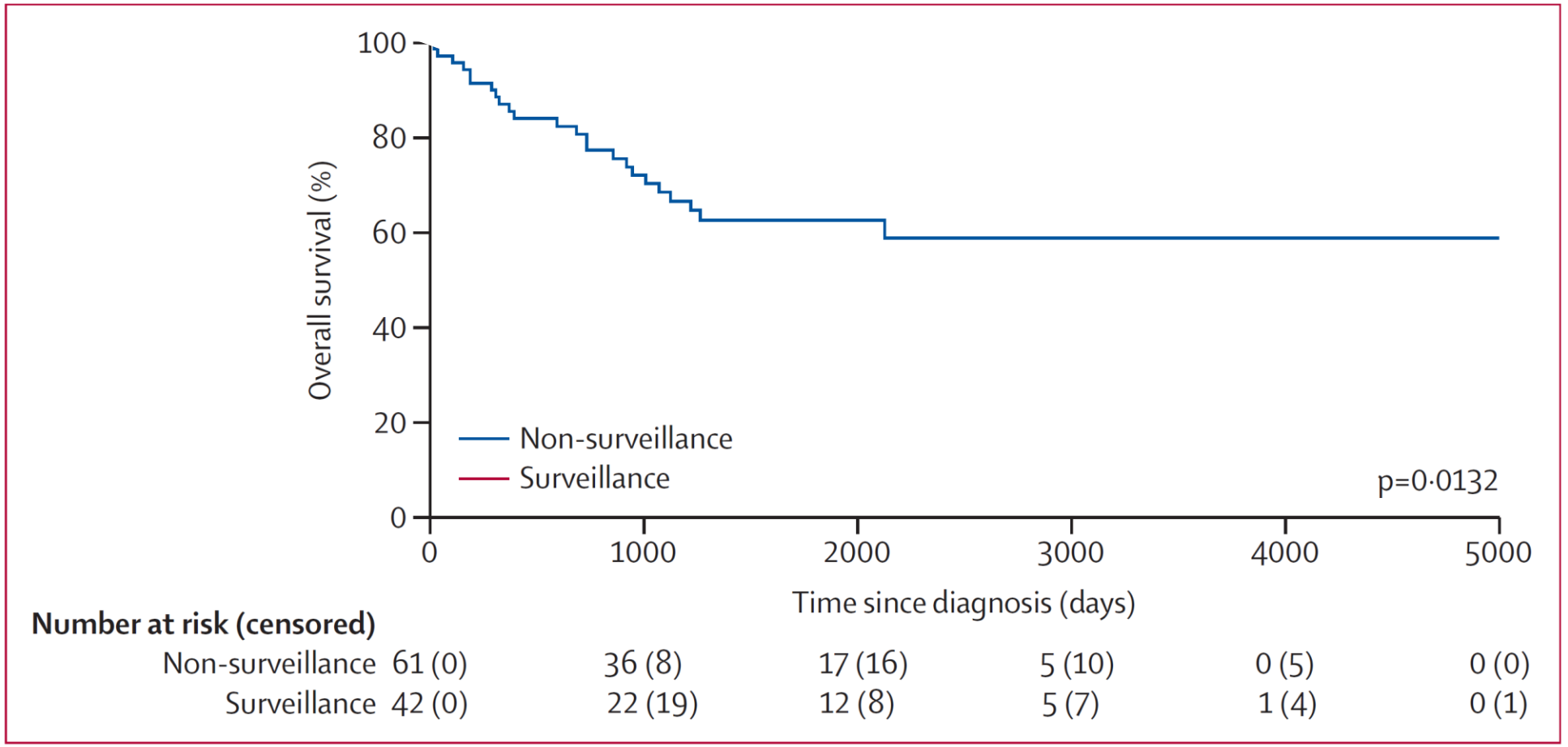
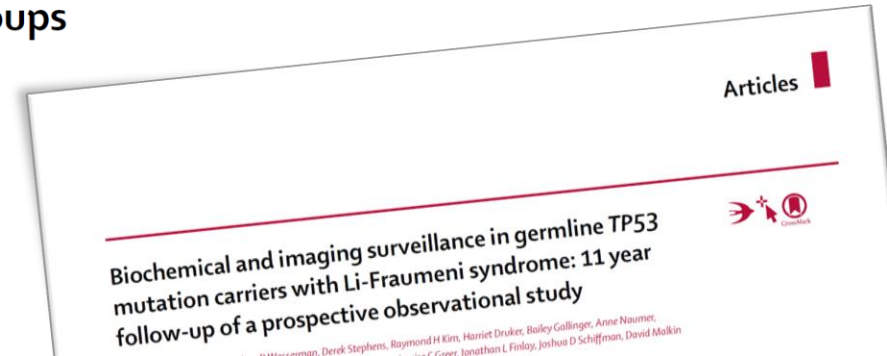
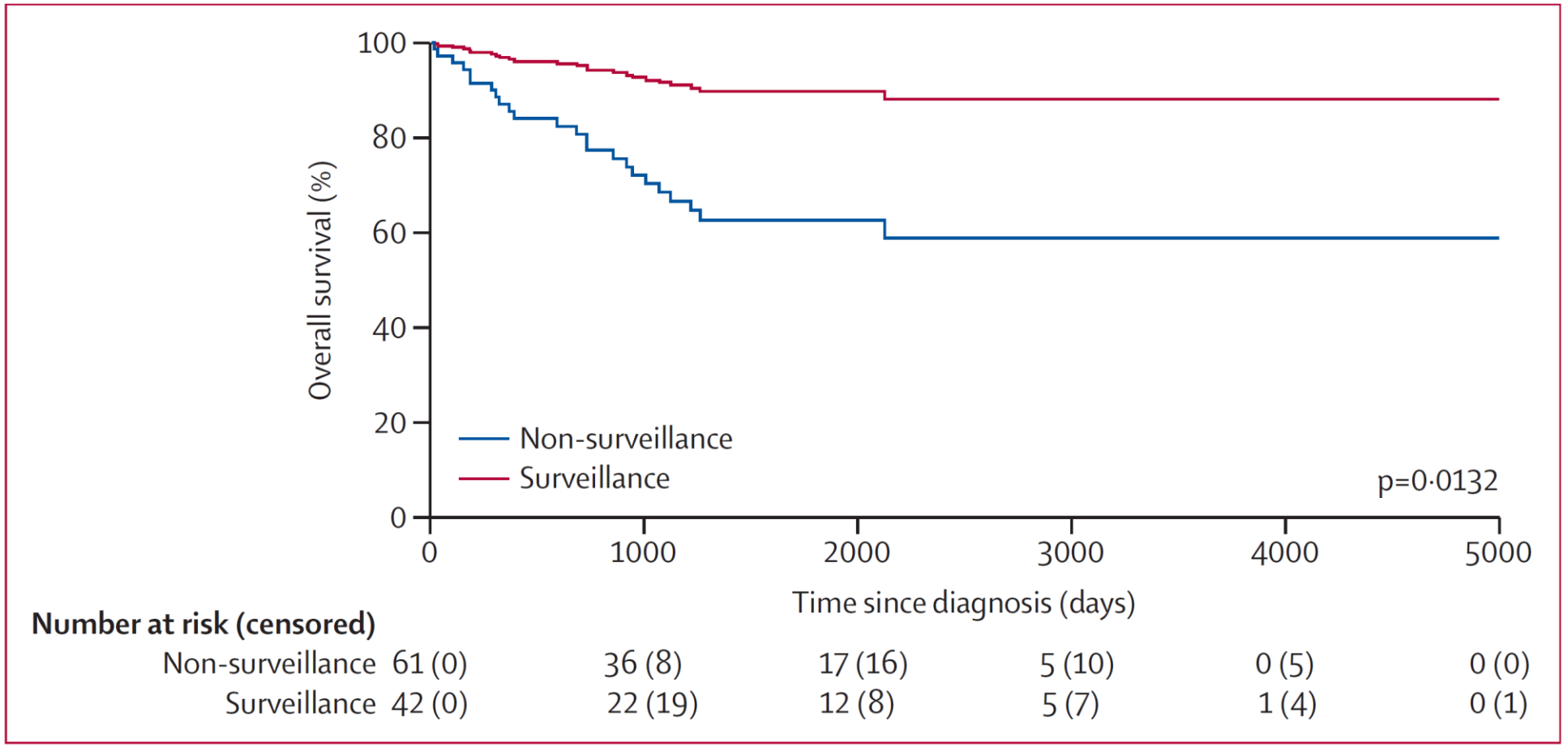


Figure 1: **Overall survival in the surveillance and non-surveillance groups**
Number at risk refers to the number of tumours, not individuals.


Articles

Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study



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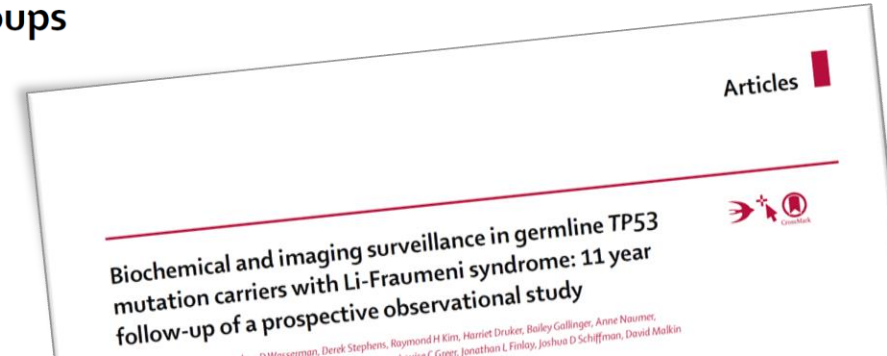

Articles

Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study

1 Hvad fortæller 140.000 voksnes genetik om kræftrisikoens evolution?

2 Hvor meget børnekræft skyldes genetik direkte?

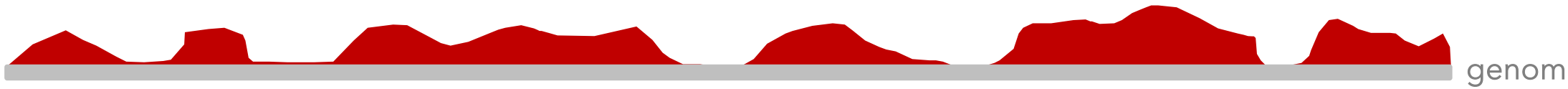
3 Hvordan kan vi finde risikoen inden kræften opstår?

BROAD INSTITUTE

Konrad Karczewski

141,456 individer

Karczewski et al., 2020, Nature



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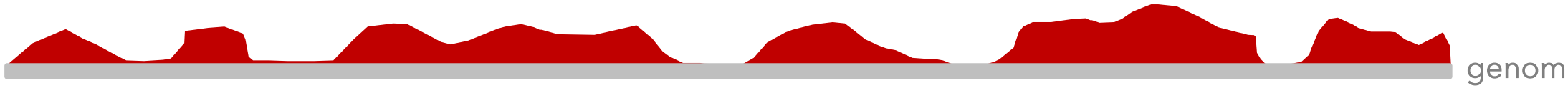
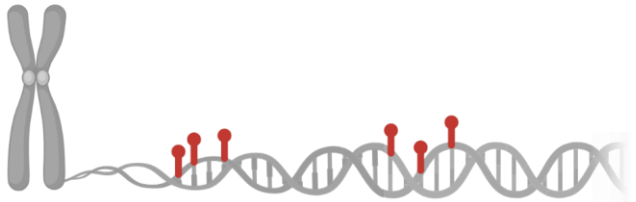
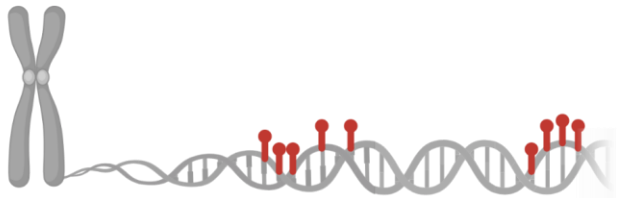




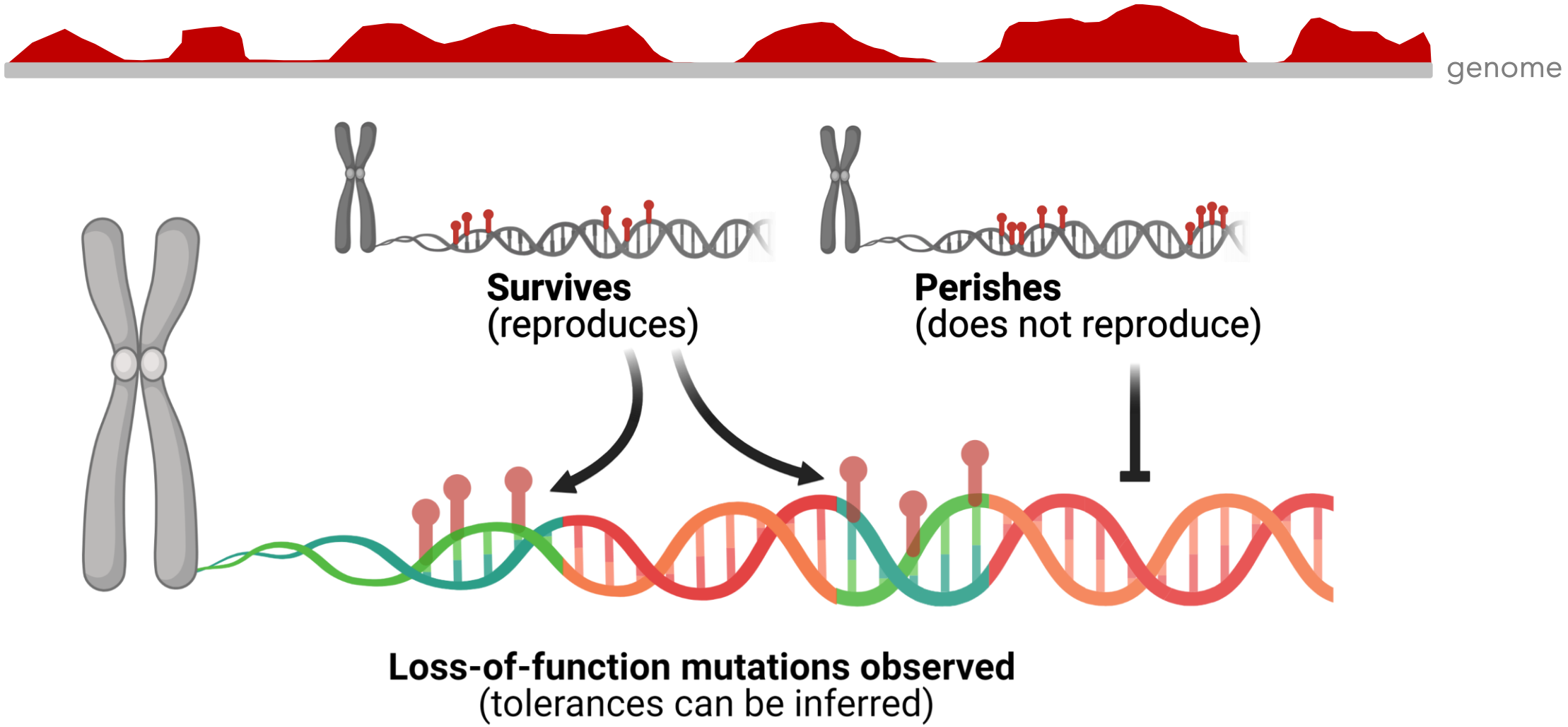
Survives
(reproduces)



Perishes
(does not reproduce)

141,456 individuals

Karczewski et al., 2020, Nature



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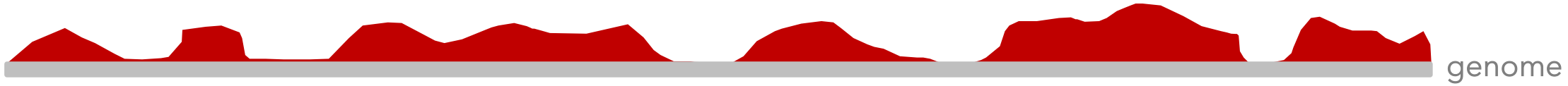
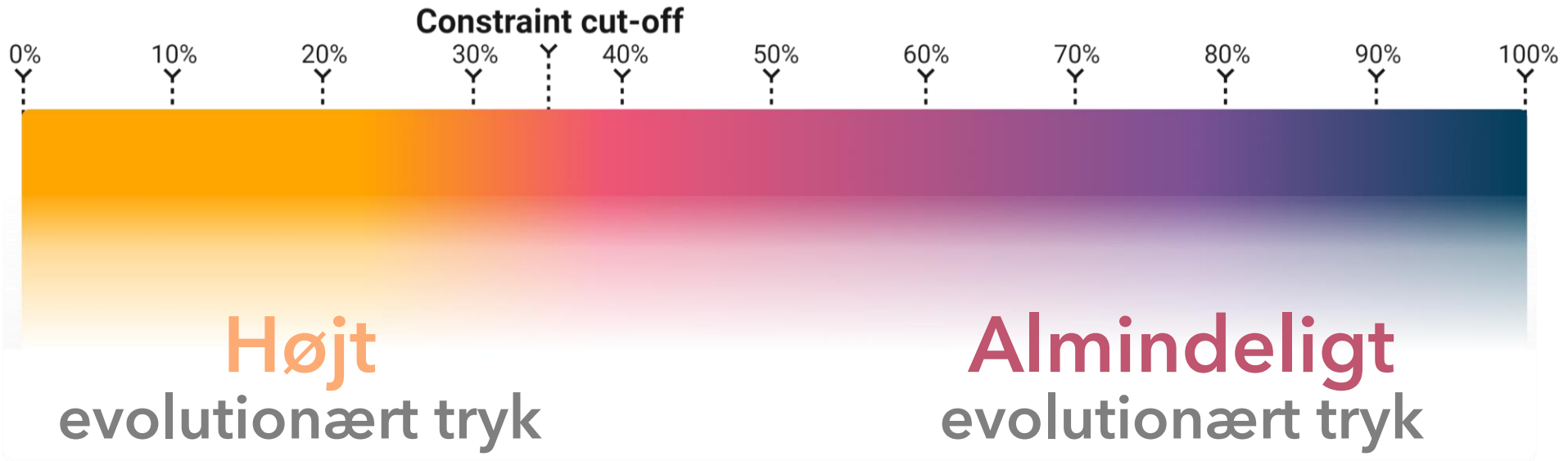


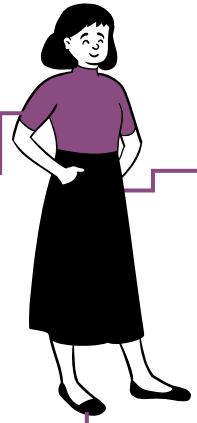


Børnekræft:
Wilms Tumor

REST mutation

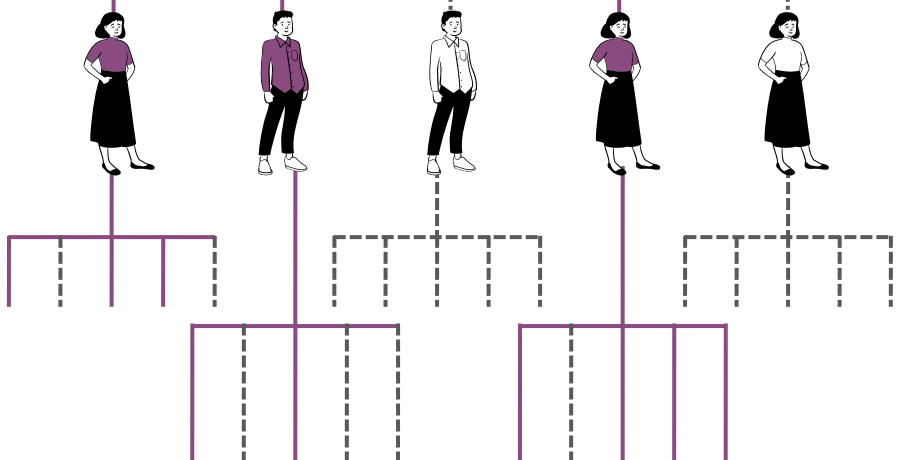
Mutationen nedarves ikke

Voksenkræft:
Bryst Tumor



BRCA1 mutation

Mutationen nedarves




REST

Familial Cancer (2021) 20:279–287
https://doi.org/10.1007/s10689-021-00254-0

ORIGINAL ARTICLE

Selection criteria for assembling a pediatric cancer predisposition syndrome gene panel

Anna Byrjalsen[1] · Illja J. Diets[2] · Jette Bakhuizen[3,4] · Thomas van Overeem Hansen[1,5] · Kjeld Schmiegelow[5] · Anne-Marie Gerdes[1] · Ulrik Stoltze[5] · Roland P. Kuiper[3,4] · Johannes H. M. Merks[3] · Karin Wadt[1] · Marjolijn Jongmans[3,4]

Received: 14 September 2020 / Accepted: 7 April 2021 / Published online: 1 June 2021

Abstract
Increasing use of genomic sequencing enables standardized screening of all childhood cancer predisposition syndromes (CPS) in children. Gene panels currently used often include adult-onset CPS genes and genes without substantial evidence link... We have developed criteria to select genes relevant for childhood-onset CPS and assembled a gene panel... applied our criteria to 381 candidate genes, which were selected through two in-house panels (n=... assessing two Genomics England's PanelApp panels... evaluation criteria that... childhood cancer by... onset CPS gene... evidence supporting a causal relation... developed criteria to compile patients reported carrying a pathogenic variant in this gene and ca... development. 138 genes... panel which might ultimately... the speci... childhood cancer... prospective study. The panel... tric-cancer-predisposition-genepanel.nl) and will be... gene selection...

Keywords Childhood cancer predisposition syndrome · Gene panel · Genetic predisposition

Anna Byrjalsen and Illja J. Diets shared first authorship

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85 gener forbundet med markant øget børnekræftrisiko

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Keywords Childhood cancer predisposition syndrome · Gene panel · Genetic predisposition

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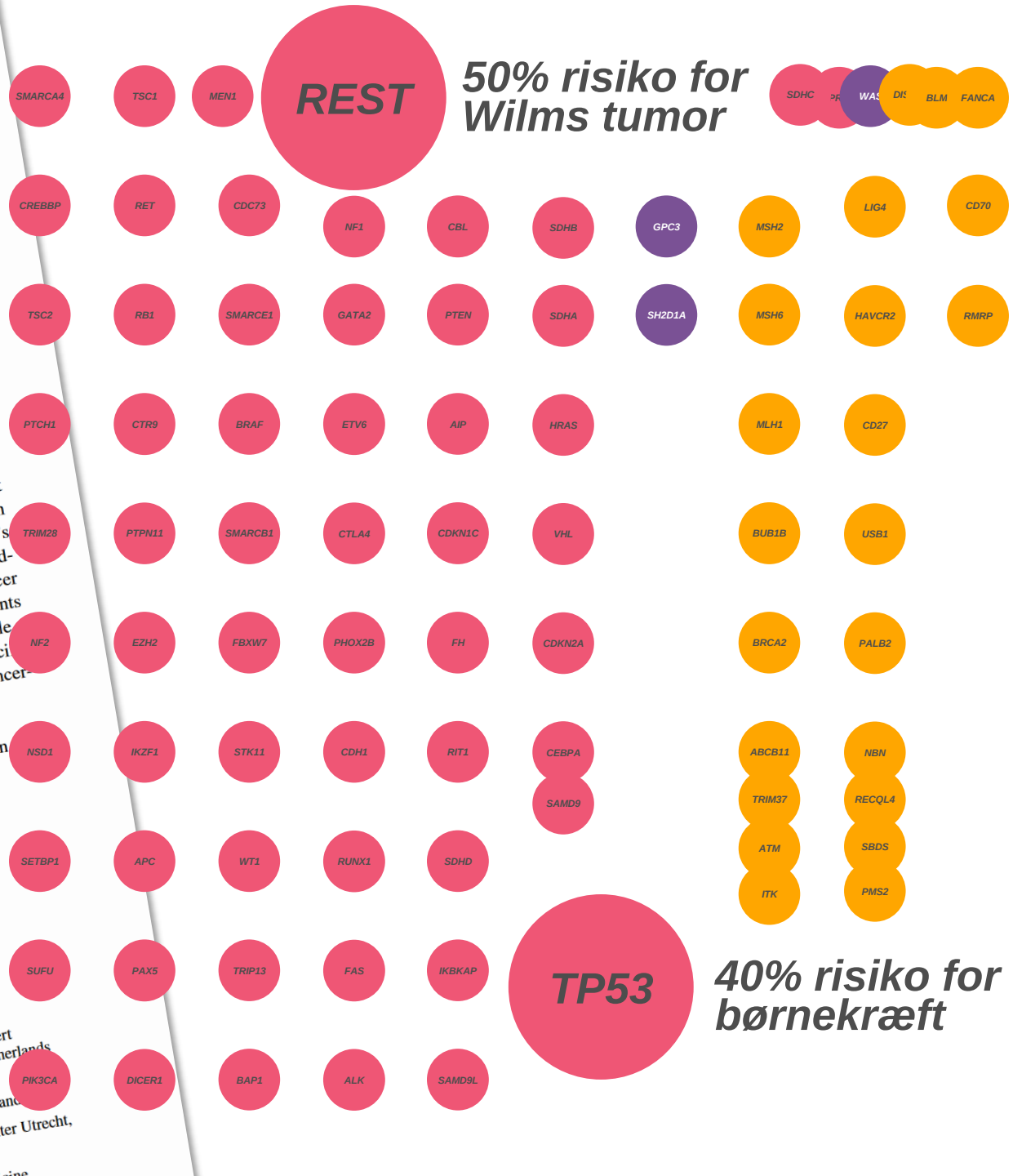
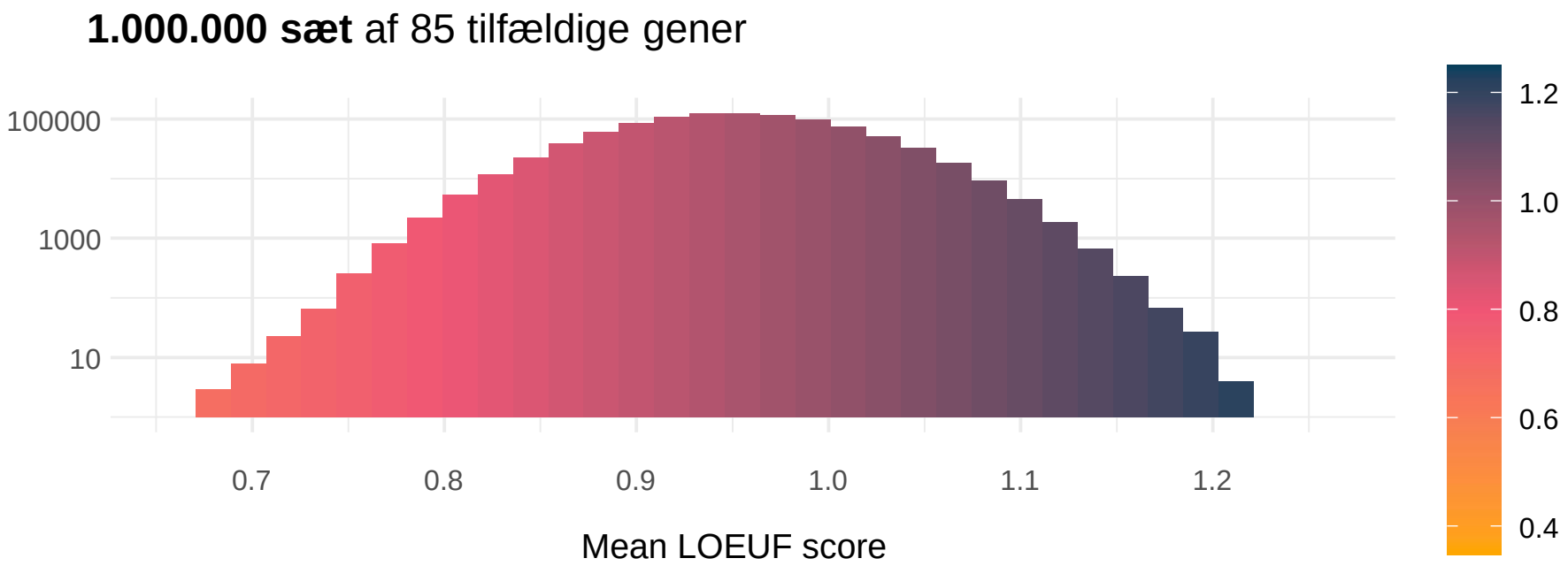




Almindeligt evolutionstryk

nature communications

Article

https://doi.org/10.1038/s41467-024-45975-9

The evolutionary impact of childhood cancer on the human gene pool

Received: 16 March 2023

Accepted: 8 February 2024

Published online: 29 February 2024

Check for updates

Ulrik Kristoffer Stoltze[1,2,3] ✉, Jon Foss-Skiftesvik[1,4], Thomas van Overeem Hansen[2,5], Simon Rasmussen[6,7], Konrad J. Karczewski[3,7,8,9], Karin A. W. Wadt[2,5] & Kjeld Schmiegelow[1,5] ✉

Germline pathogenic variants associated with increased childhood mortality must be subject to natural selection. Here, we analyze publicly available germline genetic metadata from 4,574 children with cancer [11 studies; 1,083 whole exome sequences (WES), 1,950 whole genome sequences (WGS), and 1,541 gene panel] and 141,456 adults [125,748 WES and 15,708 WGS]. We find that pediatric cancer predisposition syndrome (pCPS) genes [n = 85] are highly constrained, harboring only a quarter of the loss-of-function variants that would be expected. This strong indication of selective pressure on pCPS genes is found across multiple lines of germline genomics data from both pediatric and adult cohorts. For six genes [*ELP1*, *GPR161*, *VHL* and *SDHA/B/C*], a clear lack of mutational constraint calls the pediatric penetrance and/or severity of associated cancers into question. Conversely, out of 23 known pCPS genes associated with biallelic risk, two [9%, *DIS3L2* and *MSH2*] show significant constraint, indicating that they may monoallelically increase childhood cancer risk. In summary, we show that population genetic data provide empirical evidence that heritable childhood cancer leads to natural selection powerful enough to have significantly impacted the present-day gene pool.

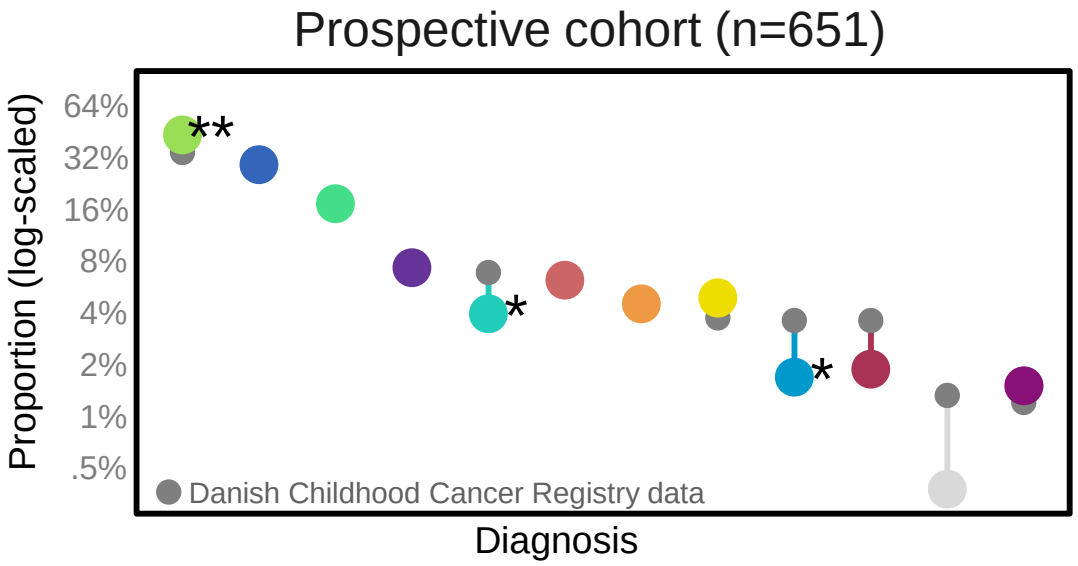
TAKE-HOME MESSAGES

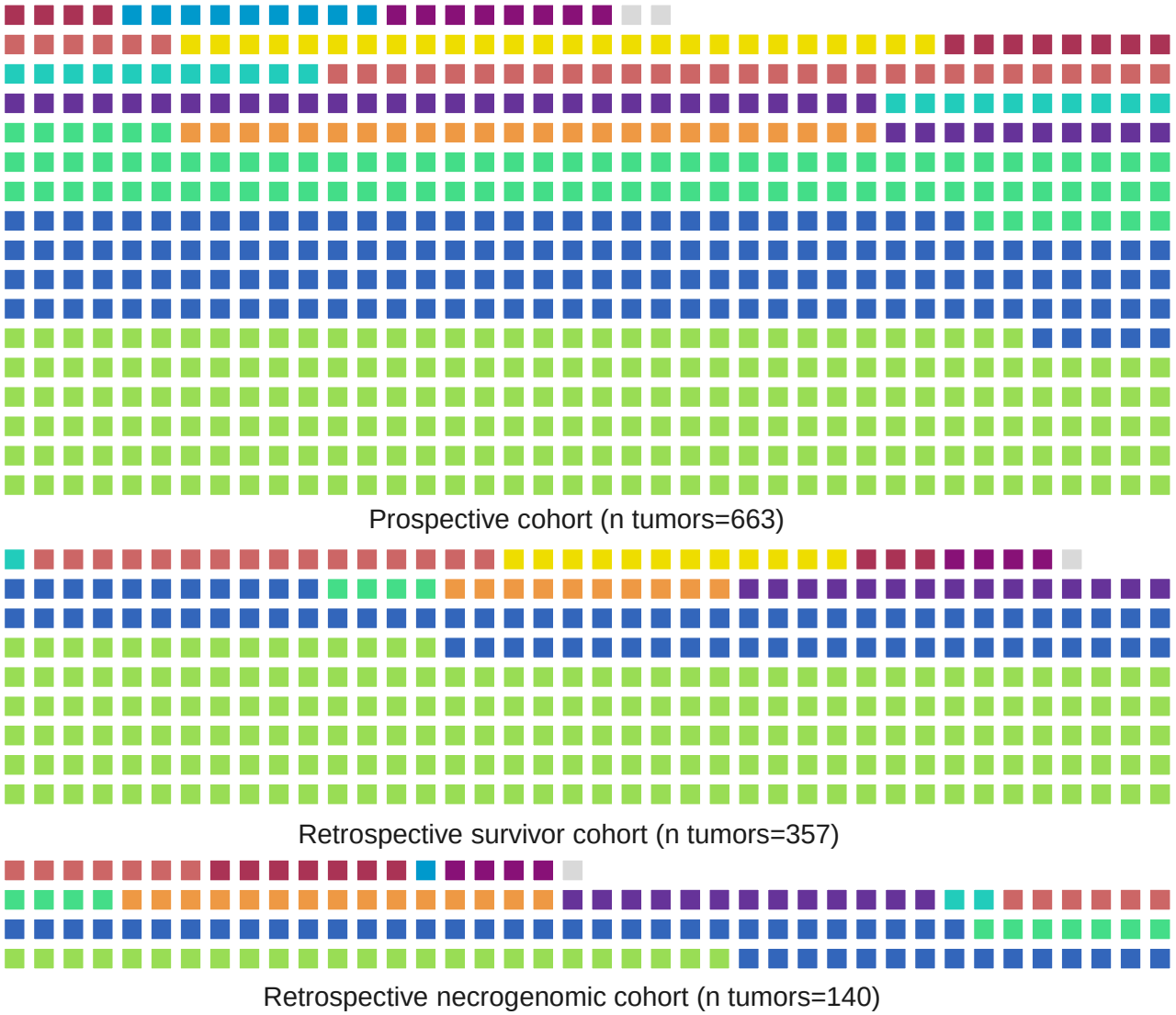
- Genetisk børnekræftrisiko har været udsat for massivt og nu målbart **evolutionært selektionstryk**.
- *Hvor stor en andel af børnekræftforekomst skyldes genetik?*

1127 included patients with NGS data

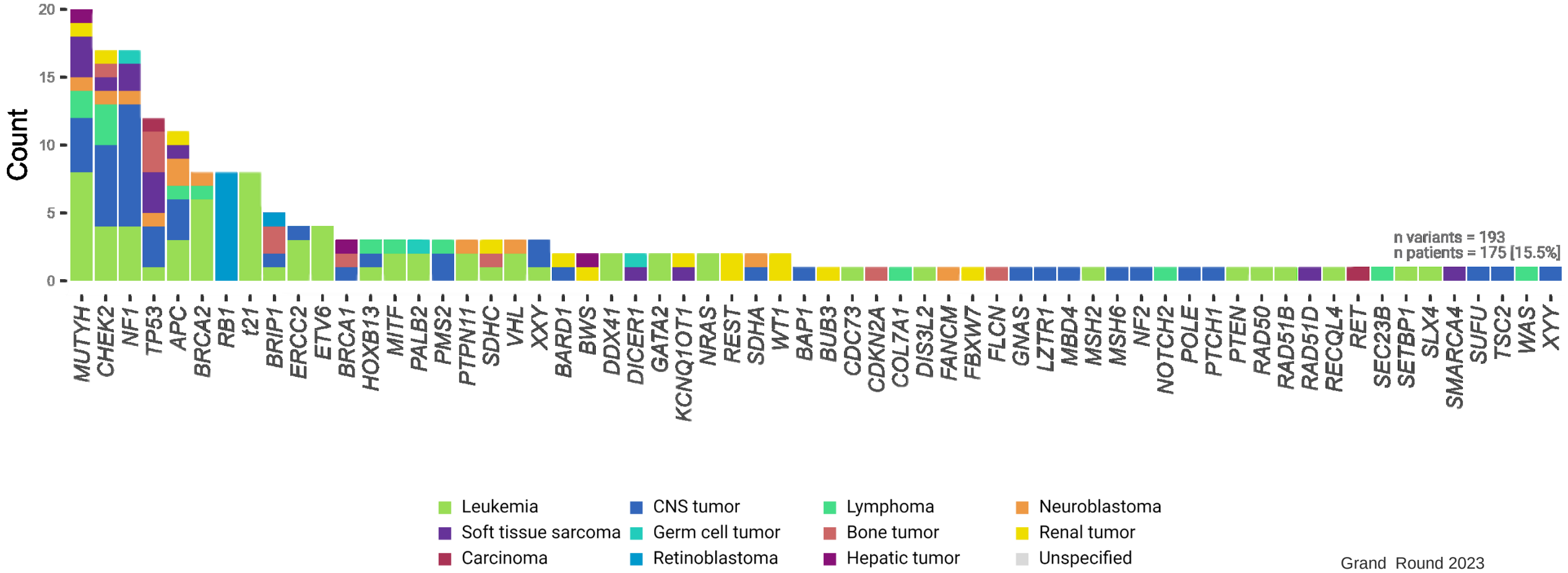
1160 tumors

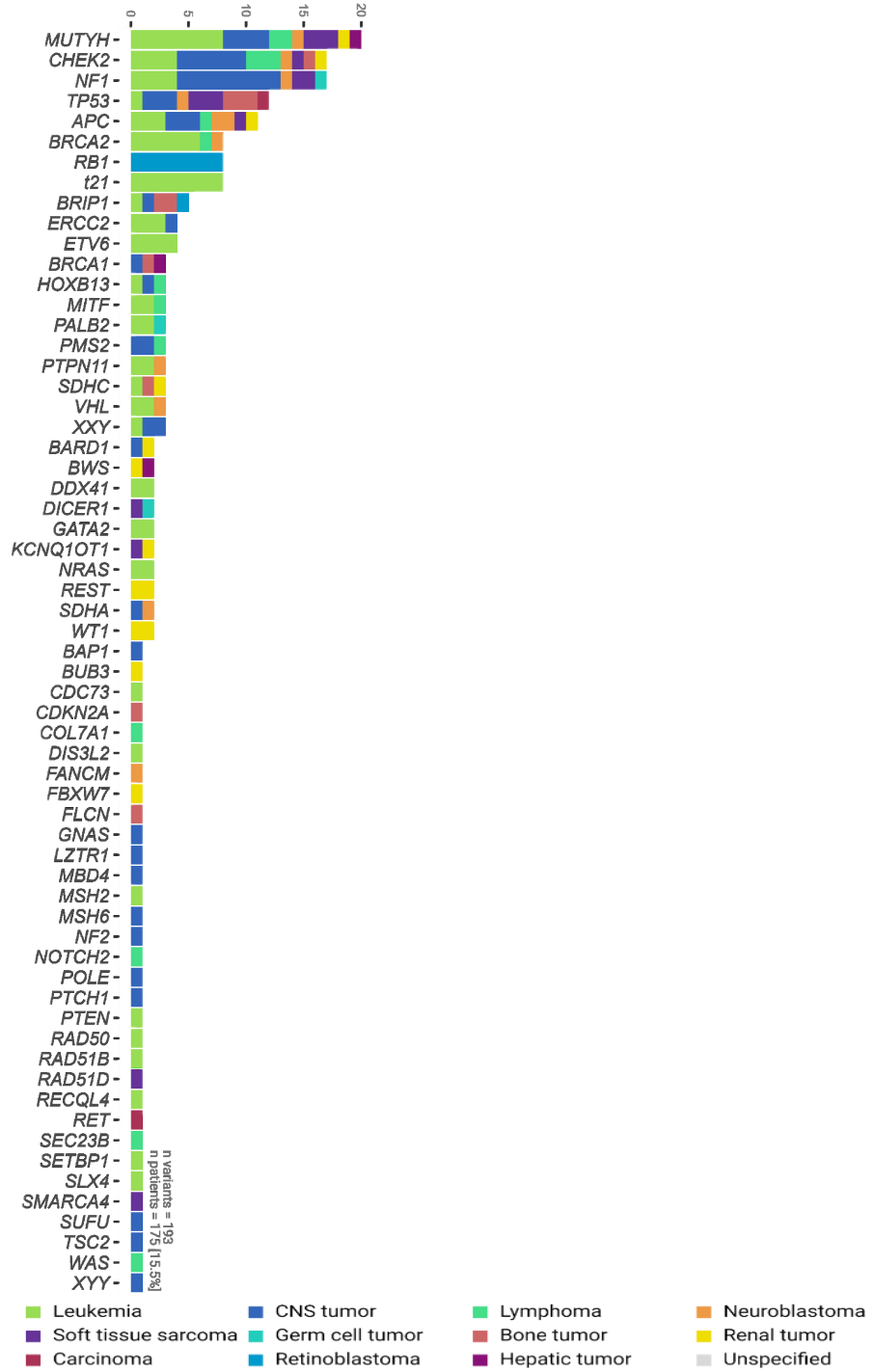
- Leukemia
- CNS tumor
- Lymphoma
- Neuroblastoma
- Soft tissue sarcoma
- Germ cell tumor
- Bone tumor
- Renal tumor
- Carcinoma
- Retinoblastoma
- Hepatic tumor
- Unspecified

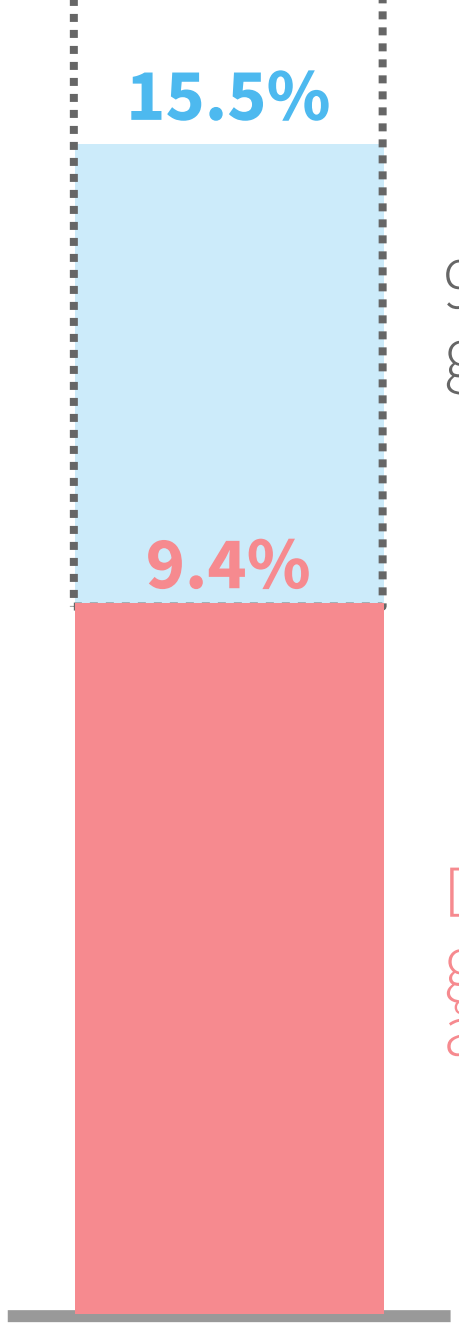




Sygdomsdisponerende genforandringer i kræftgener



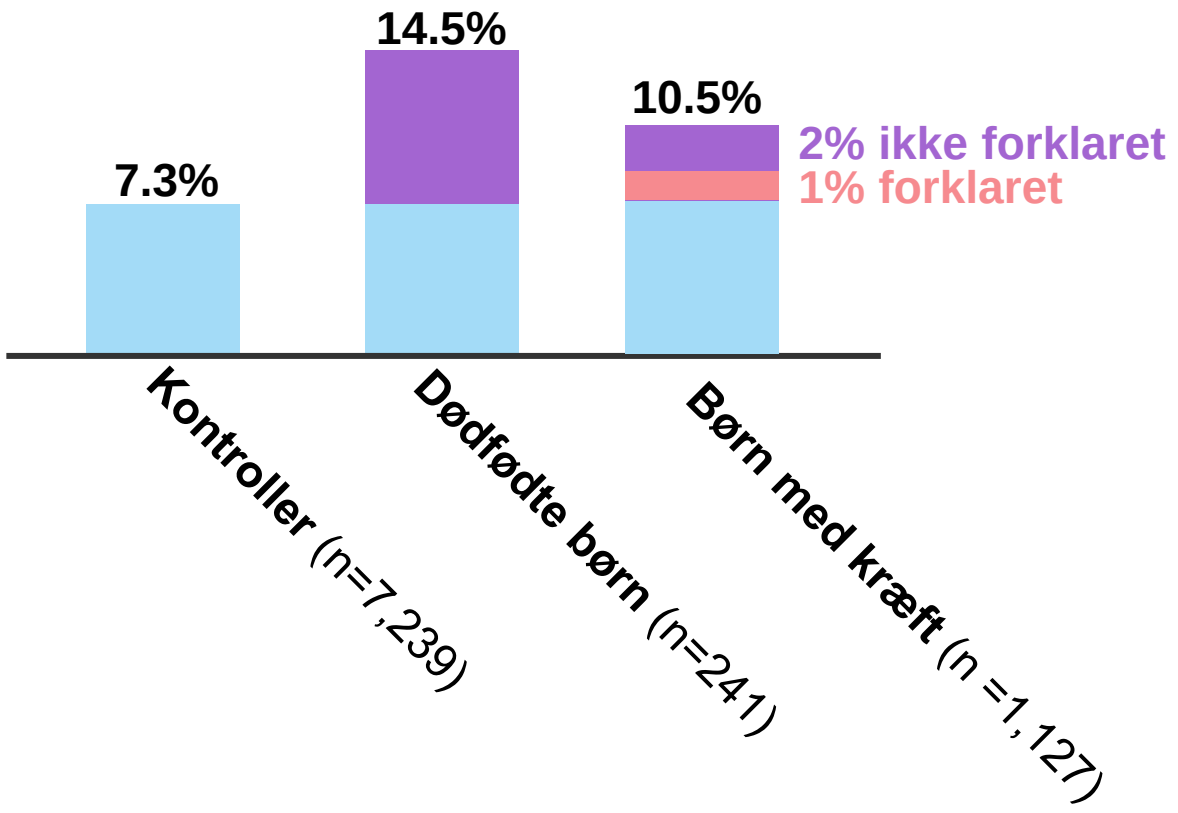




90% uden genetisk årsag?

Direkte genetisk årsag

Mutationsrate i evolutionært trykkede gener:



TAKE-HOMES

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- *Hvor stor en andel af børnekræftforekomst skyldes genetik?*

TAKE-HOMES

- Genetisk børnekræftrisiko har været udsat for massivt og nu målbart **evolutionært selektionstryk**.
- **9.4% af børn med kræft** har en underliggende genetisk tilstand. Dog tyder den nye evolutionsbaserede analyse på at tallet **kan være tre gange højere**.
- *Kan vi finde børnekræftforårsagende genforandringer hos raske børn?*

Stoltze et al. Genome Medicine (2023) 15:17
https://doi.org/10.1186/s13073-023-01167-6

Genome Medicine

RESEARCH

Open Access

Combinatorial batching of DNA for ultralow-cost detection of pathogenic variants

Ulrik Kristoffer Stoltze[1,2*], Christian Munch Hagen[3], Thomas van Overeem Hansen[2,4], Anna Byrjalsen[2], Anne-Marie Gerdes[2], Victor Yakimov[3], Simon Rasmussen[5], Marie Bækvad-Hansen[3], David Michael Hougaard[3], Kjeld Schmiegelow[1,4], Henrik Hjalgrim[4,6,7,8], Karin Wadt[2] and Jonas Bybjerg-Grauholm[3*]

Abstract

Background Next-generation sequencing (NGS) based population screening holds great promise for disease prevention and earlier diagnosis, but the costs associated with screening millions of humans remain prohibitive. New methods for population genetic testing that lower the costs of NGS without compromising diagnostic power are needed.

Methods We developed double batched sequencing where DNA samples are batch-sequenced twice — directly pinpointing individuals with rare variants. We sequenced batches of at-birth blood spot DNA using a commercial 113-gene panel in an explorative ($n = 100$) and a validation ($n = 100$) cohort of children who went on to develop pediatric cancers. All results were benchmarked against individual whole genome sequencing data.

Results We demonstrated fully replicable detection of cancer-causing germline variants, with positive and negative predictive values of 100% (95% CI, 0.91–1.00 and 95% CI, 0.98–1.00, respectively). Pathogenic and clinically actionable variants were detected in *RB1*, *TP53*, *BRCA2*, *APC*, and 19 other genes. Analyses of larger batches indicated that our approach is highly scalable, yielding more than 95% cost reduction or less than 3 cents per gene screened for rare disease-causing mutations. We also show that double batched sequencing could cost-effectively prevent childhood cancer deaths through broad genomic testing.

Conclusions Our ultracheap genetic diagnostic method, which uses existing sequencing hardware and standard newborn blood spots, should readily open up opportunities for population-wide risk stratification using genetic screening across many fields of clinical genetics and genomics.

Keywords Germline, Genomics, Population, Neonatal, Screening, Frugal science, Pediatrics, Cancer predisposition, Rare disease, Health care economics

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jogr@ssi.dk
Full list of author information is available at the end of the article

INDIVIDUEL DNA SEKVENTERING

>900.000.000 DKK

>9.000 DKK / individ

~30.000.000 DKK

~100 DKK / individ

DNA FRA ÉT INDIVIDUAL

PA Media: Science

New £105m scheme aims to speed up diagnosis of rare genetic diseases in newborns

Lucas Cumiskey, PA

13 December 2022 · 3-min read

Thousands of babies born with treatable rare genetic diseases each year could get faster access to treatment if a new genomic sequencing research programme proves successful.

Genomics England will sequence the genomes of 100,000 newborn children – which involves the study of people's DNA – for rare conditions, after the Government provided £105million in funding for the research, it was announced on Tuesday.

Programme will assess the feasibility

TRENDING

1. How a house price crash will crush retirement dreams for millions

British retirement has peaked – it's only

DOUBLE BATCHED SEQUENCING

DOUBLE BATCHED SEQUENCING

- Opstil prøver sv.t. et Excel ark

DOUBLE BATCHED SEQUENCING

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- Bland DNA fra 48 personer sammen
  - Sv.t. rækker

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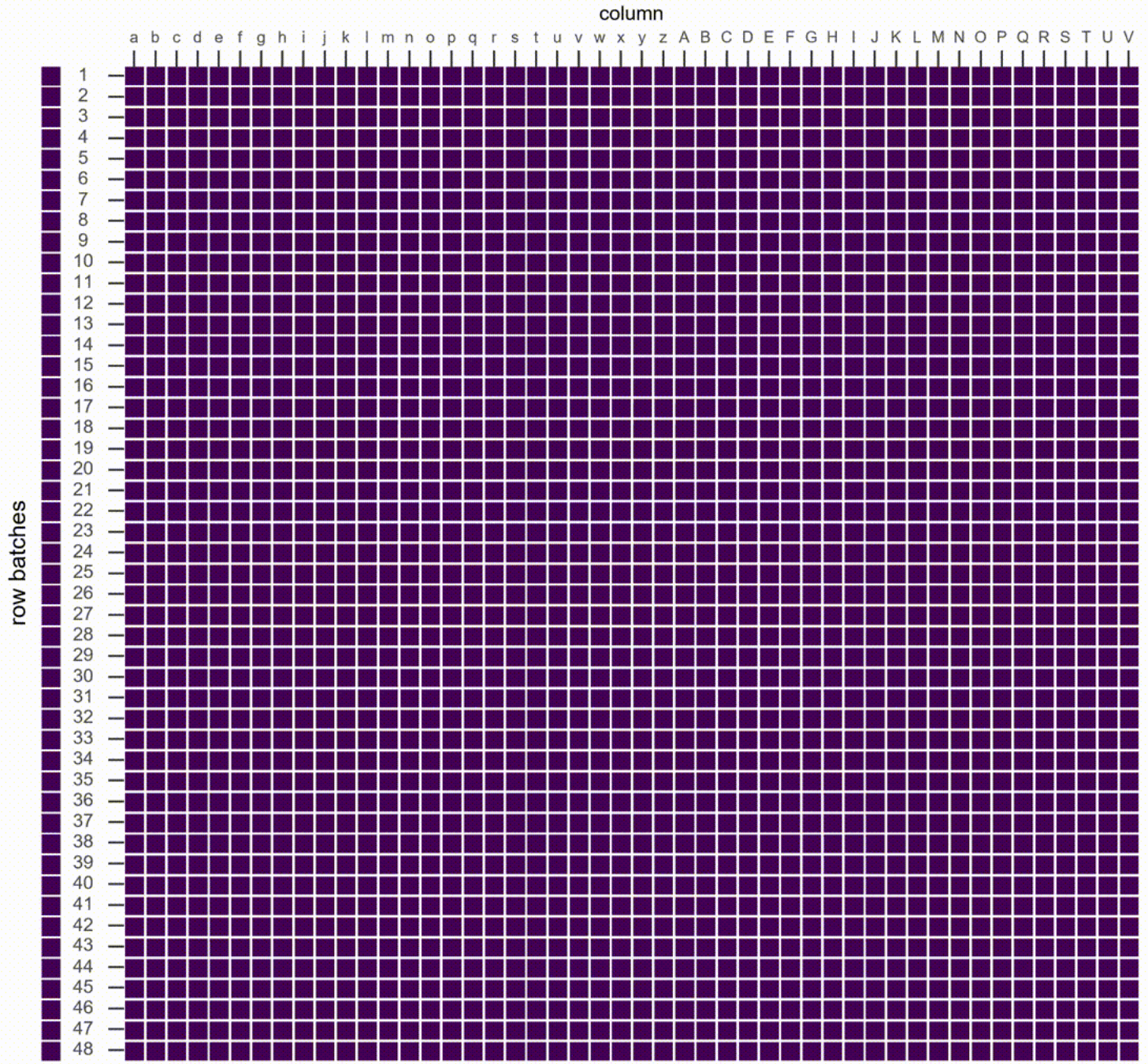

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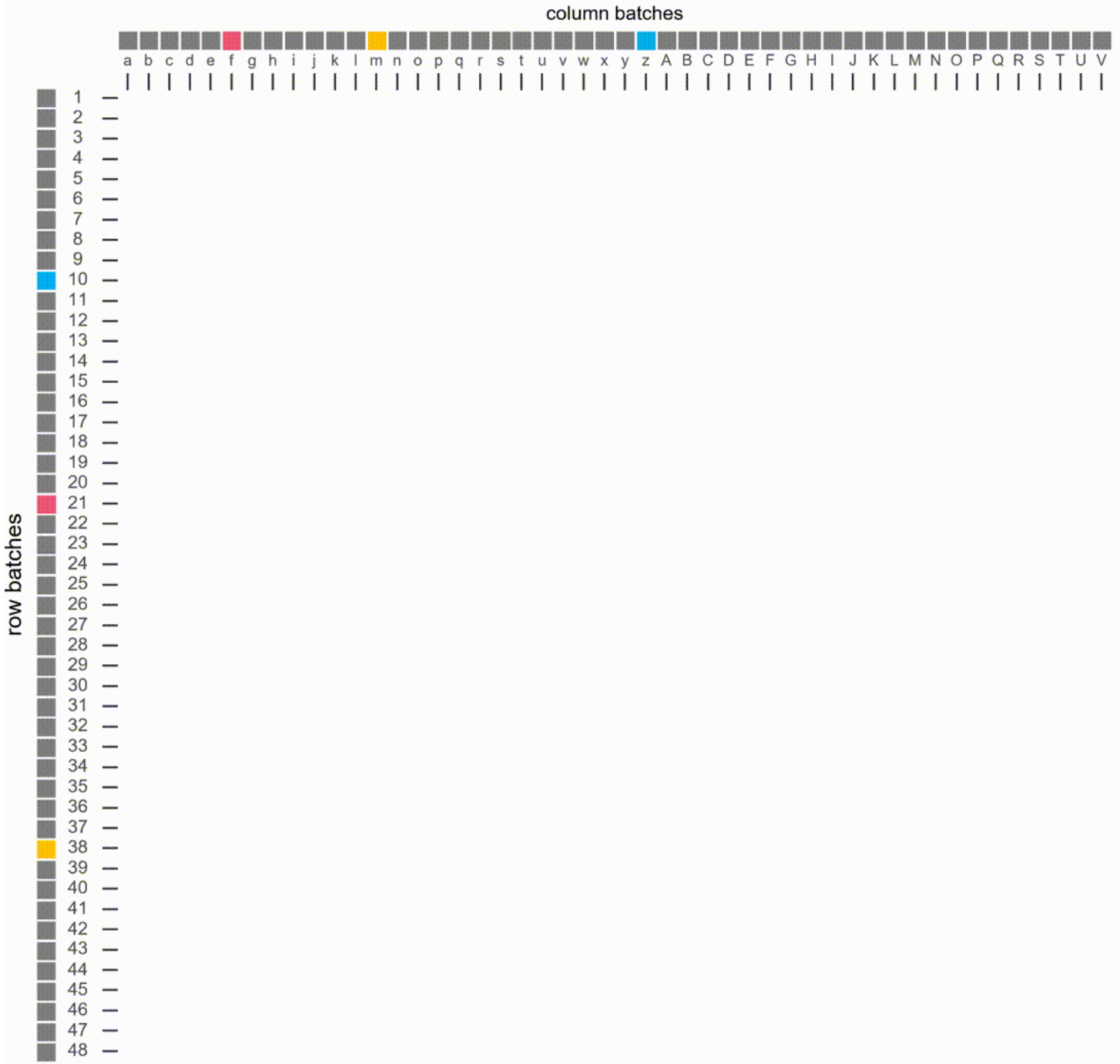
  - Sv.t. kolonner
- Sekventér blandingerne
- Krydsreferér for at finde bærere



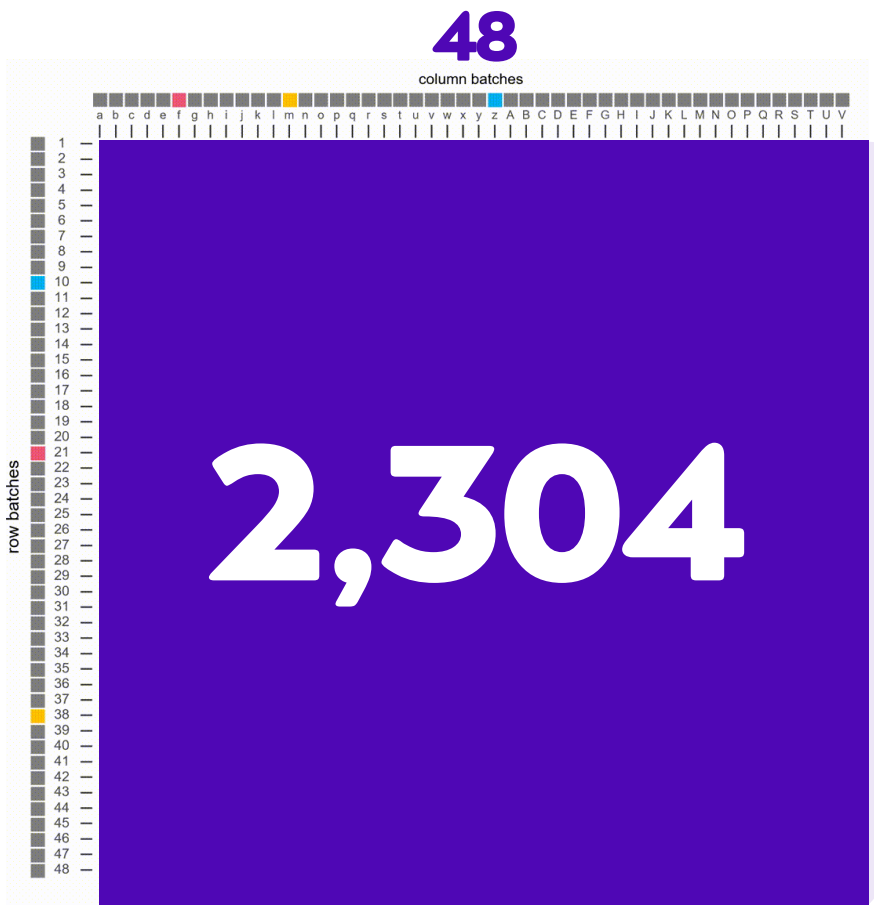
PREDISPOSED

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

Innovation Fund Denmark

børne cancer fonden

novo nordisk foundation
Benefitting people and society



VOKSNE

BØRN

Sekventere **301,824 prøver**. I form af **131 matricer**.

- **Overgang til klinik.** Front-line helgenomsekventering på alle landets patienter med børnekræft.
- **Klinik for børnekræftscreening.** Sikre enartet og evidens-baseret follow-up til børn med høj risiko for kræft.
- **Evolutionær linse.** En ny type evidens for børnekræftrisiko som nu udforskes i andre lande.
- **Et spin-off projekt.** PREDiSPOSED projektet, der ønsker at teste 300.000 borgere med en billig genetisk metode.

THANK YOU TO...


Kjeld Schmiegelow


Karin Wadt


Thomas v. Overeem Hansen


Simon Rasmussen


Anja Hirche


Solvej Kullegaard


Jon Foss-Skiftesvik

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Jesper Brok
Sabine Grønborg
Lisa Hjalgrim
Mimi Kjærsgaard
Astrid Sehested
Vera Rasmussen
Signe Sleiborg
Helle Schack
Lillian Hauman

PREDiSPOSED:
Lene Rottensten
Signe H. Søegaard
David Hougaard
Allan M. Lund
Marie B.-Hansen
Tania n. Masmas
Jacob Tfelt-Hansen

Bonkolab staff:
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Emel Korkmaz

Genomic medicine:
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Lise Ahlborn
Christina W. Yde
Frederik O. Bagger
Filipe G. Vieira

Broad Inst.:
Konrad Karczewski
Bram Gorissen
Hannah Jacobs

Other collabs:
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Kim Dalhoff
MIPOGG group

Dept. of clinical genetics:
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Mads Bak
Elsebet Østergaard
Kirsten Grønskov
Zeynep Tümer
Mathis Hildonen
Mette Klarskov
Jack Cowland
Sophia H.-Hansen

National peds. onc.:
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Peder Skov Wehner
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Marianne Helenius
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THE PATIENTS AND THEIR FAMILIES

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