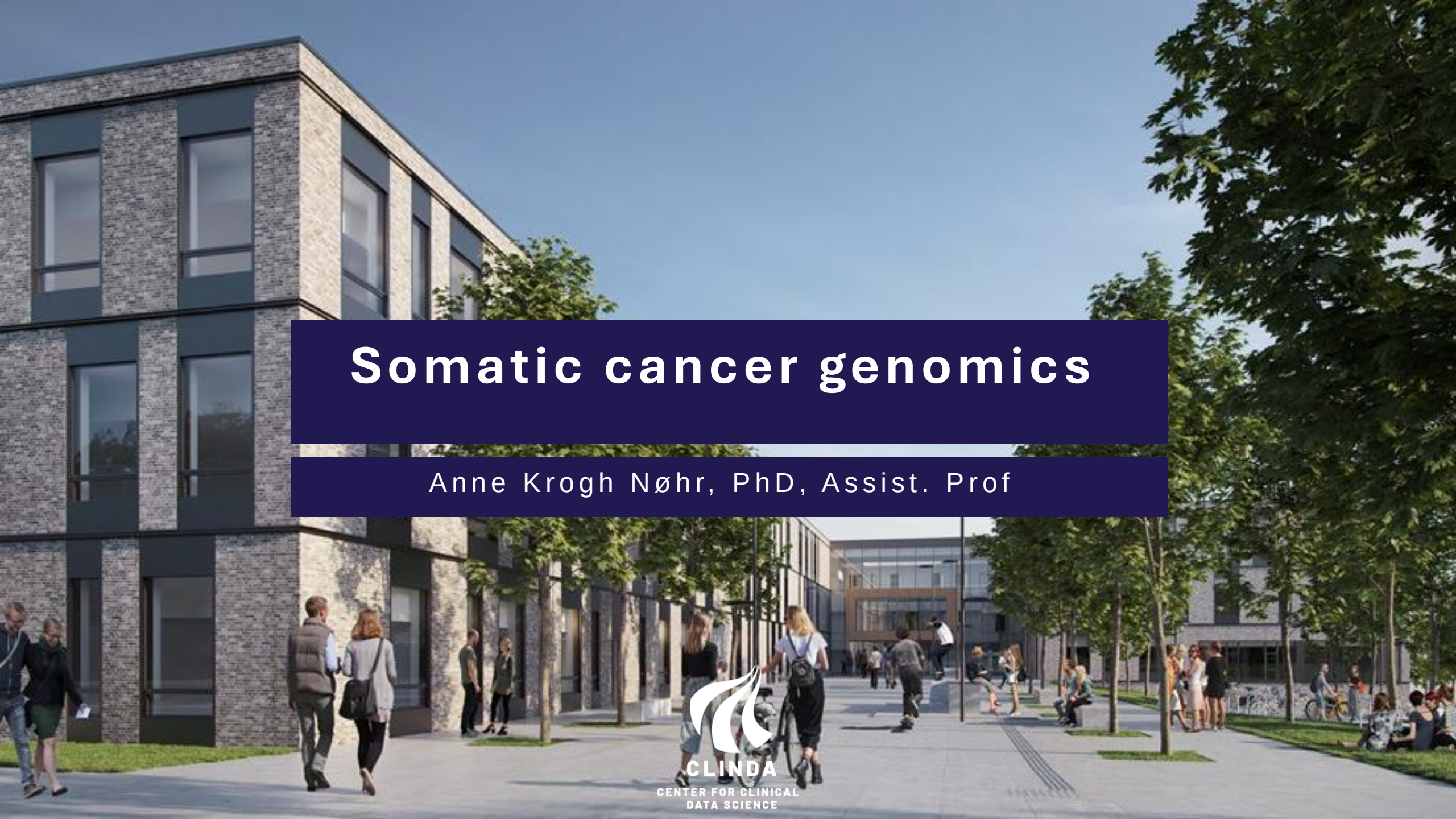


Somatic cancer genomics

Anne Krogh Nøhr, PhD, Assist. Prof

CLINDA
CENTER FOR CLINICAL
DATA SCIENCE

LETS GET STARTED

AGENDA

08:15 – 08:30	Recap [*Somatic cancer genomics*]
08:30 – 09:00	Group work
09:00 – 09:15	Break
09:15 – 09:45	Lecture 1 [Rare and common germline variants]
09:45 – 10:15	Exercise 1
10:15 – 10:30	Break
10:30 – 10:45	Lecture 2 [*Combining common and rare germline variants and cancer risk prediction*]
10:45 – 11:55	Exercise 2 - 6
11:55 – 12:00	Evaluation at Moodle

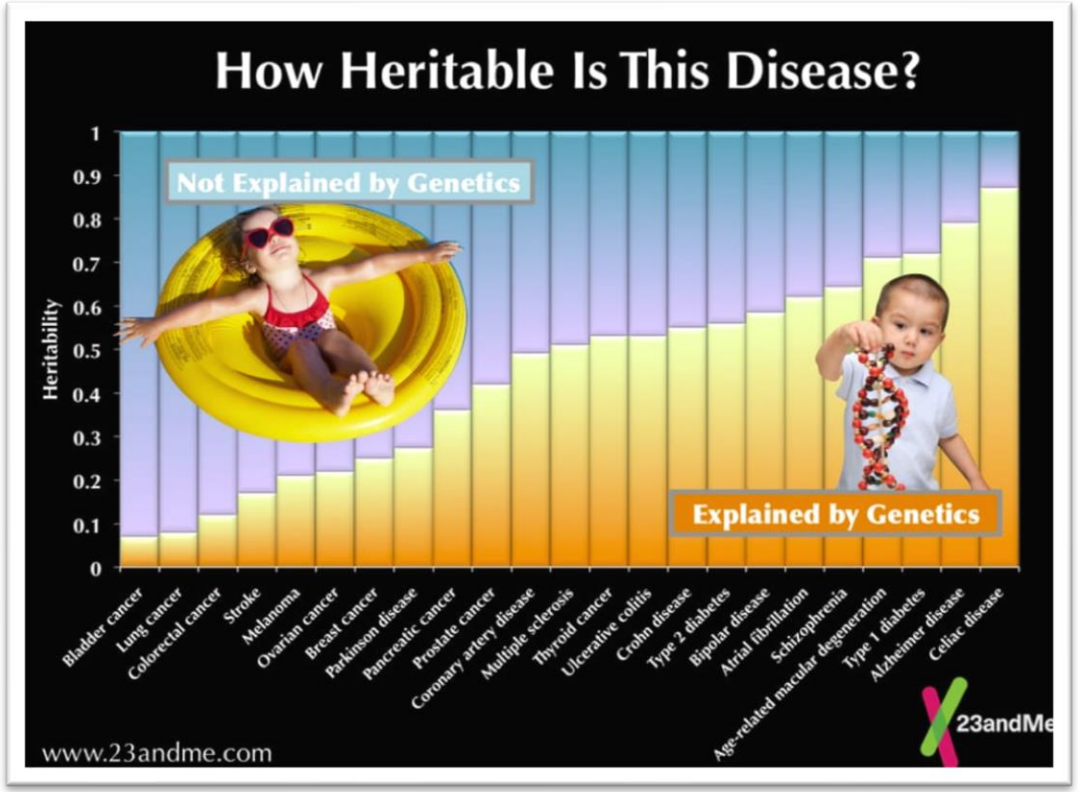
Last time

Common features of all cancers:

- Caused by uncontrolled growth of abnormal cells
- Multifactorial, influenced by both environmental and polygenic factors

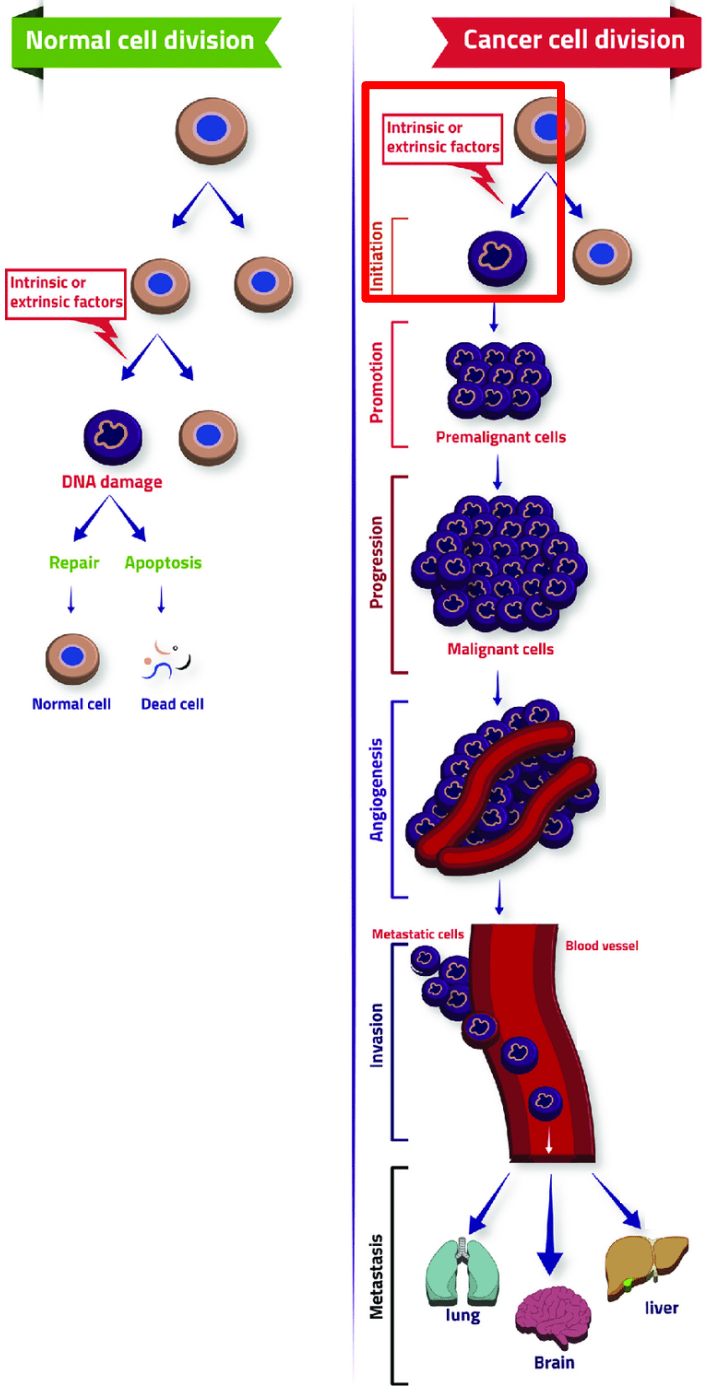
How cancers differ:

- Varying environmental factors
- Different high-penetrance genetic variants
- Differences in heritability



Cancer is a genetic disease

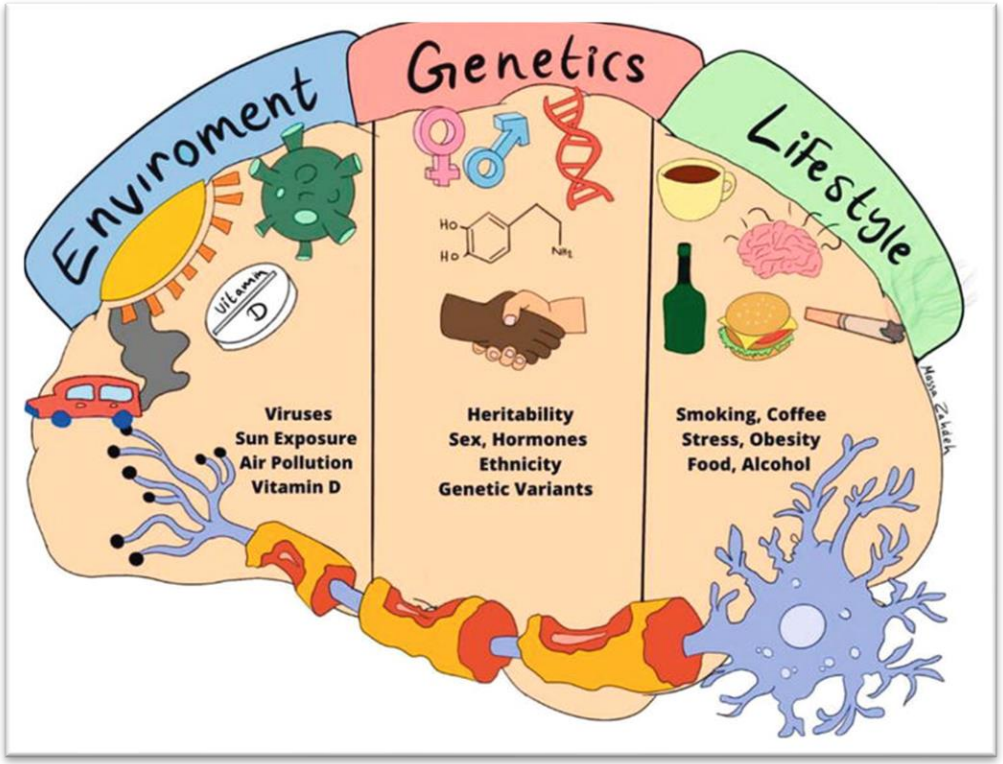
- A group of diseases caused by uncontrolled growth of abnormal cells.
- The DNA in a human cell undergoes thousands to a million harmful events per day.
- Normal Cell Division
  - In case of cellular damage, the cell undergoes repair or apoptosis.
- Cancer Cell Division
  1. Initiation: Cellular damage → somatic mutation in a cell.
  2. Promotion: Stimulated increased cell division → large number of clones.
  3. Progression: Gradual transformation from a benign tumor to a malignant tumor.
  4. Angiogenesis: Tumors form blood vessels by releasing chemical signals.
  5. Invasion: Cancer cells invade nearby tissue.
  6. Metastasis: Spread of cancer cells through the circulatory system or the lymphatic system.



What cause cancer?

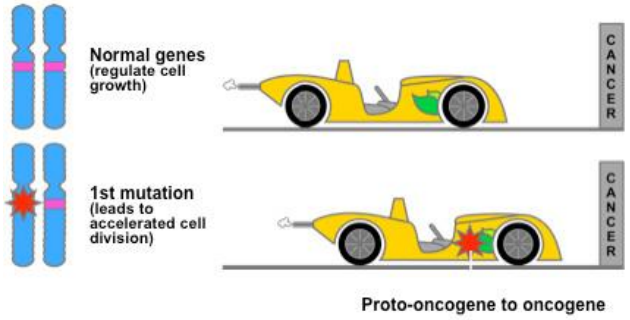
Mutations caused by:

- Environmental factors
- Inherited
- Random mistakes
- Cancer form when mutations occure in cancer-causing genes regulating growth and differentiation

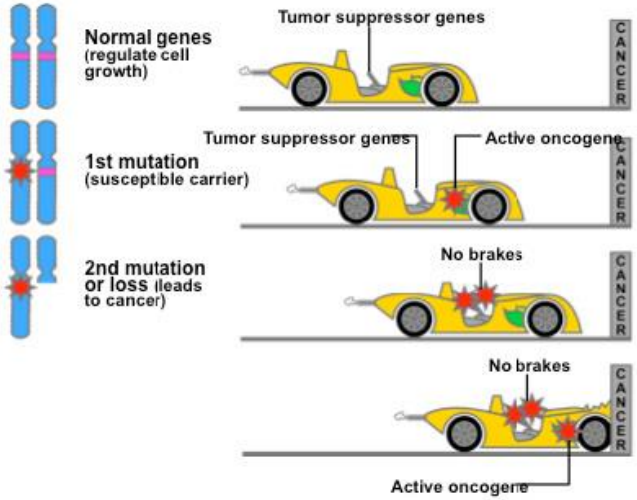


Three major classes of cancer-causing genes

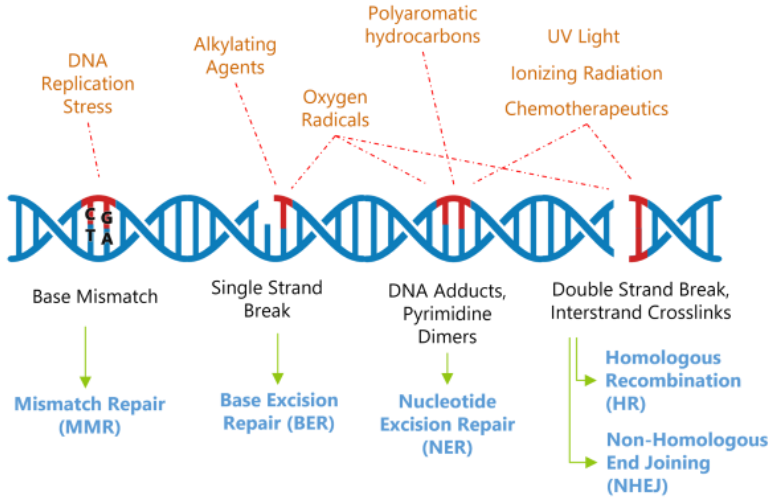
Oncogenes:
The bad guys, turn on unregulated growth (gas pedal)



Tumor suppressor genes:
The good guys, control cell division (brake pedal)

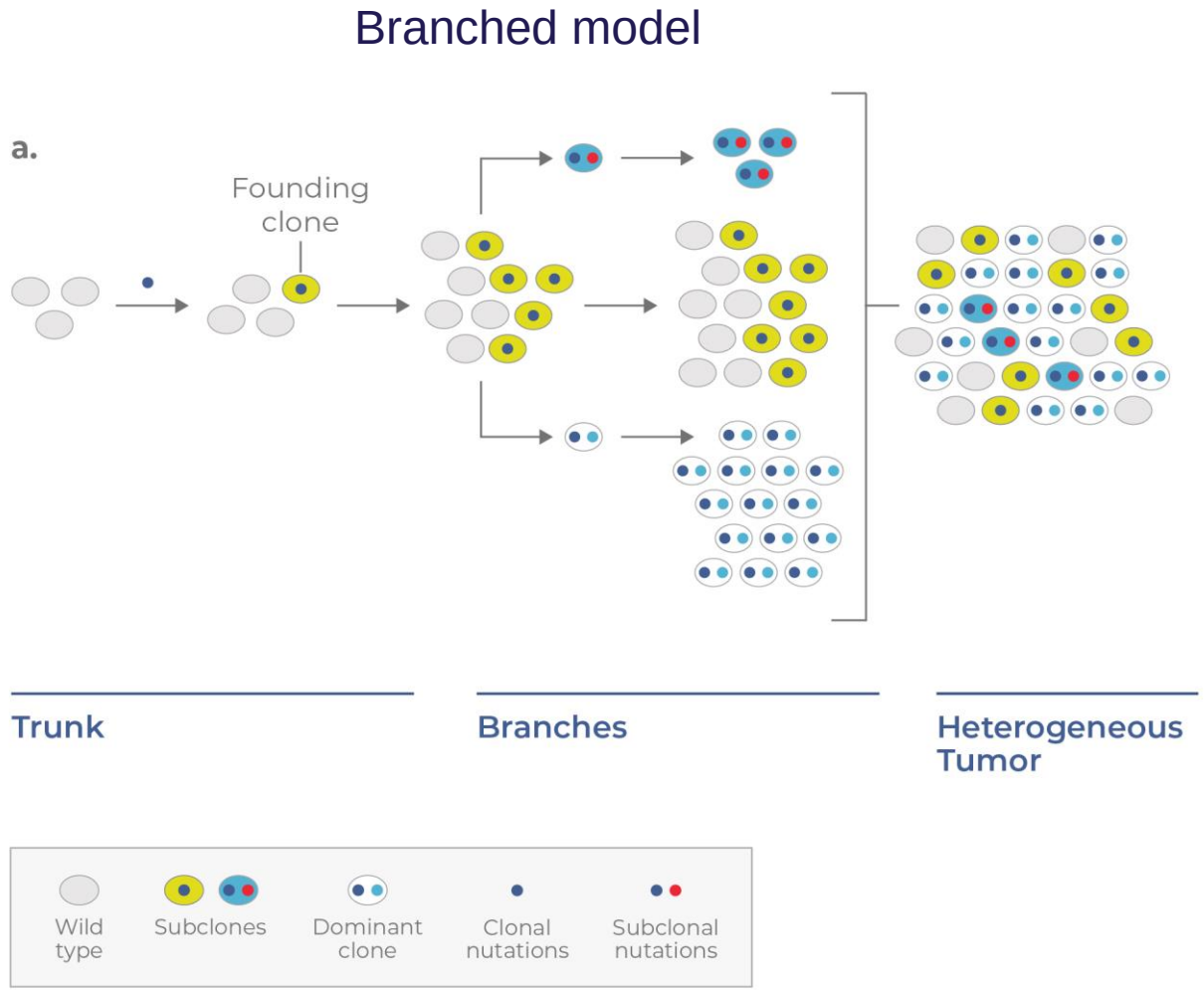


DNA repair genes:
More good guys- repair genes



Clonal evolution drives tumor heterogeneity

- **Clones**: Cells that are genetically identical.
- **Founder clone**: A healthy cell that acquires a driver mutation.
- **Subclone**: A clone that originates from another clone but has acquired additional mutation(s).
- **Dominant clone**: The clonal population that occurs with the highest frequency in the tumor.



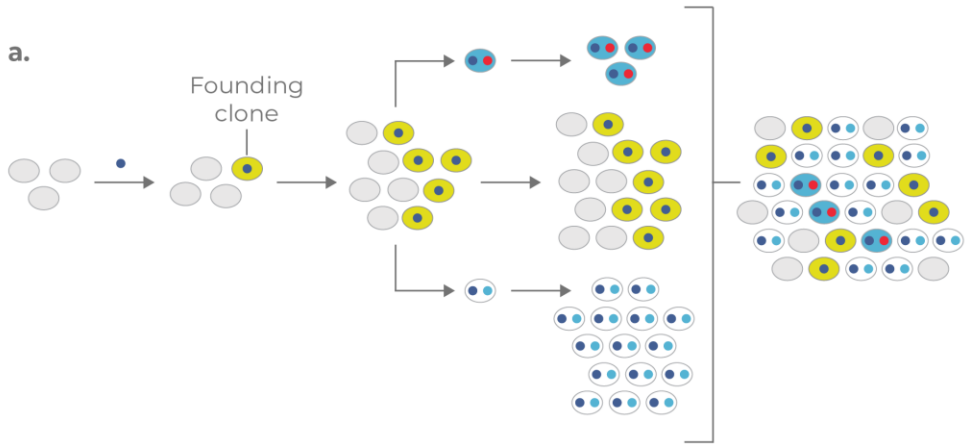
Driver mutations

Driver mutations: induce cell proliferation and tumour growth advantage - provide a selective advantage to the clone

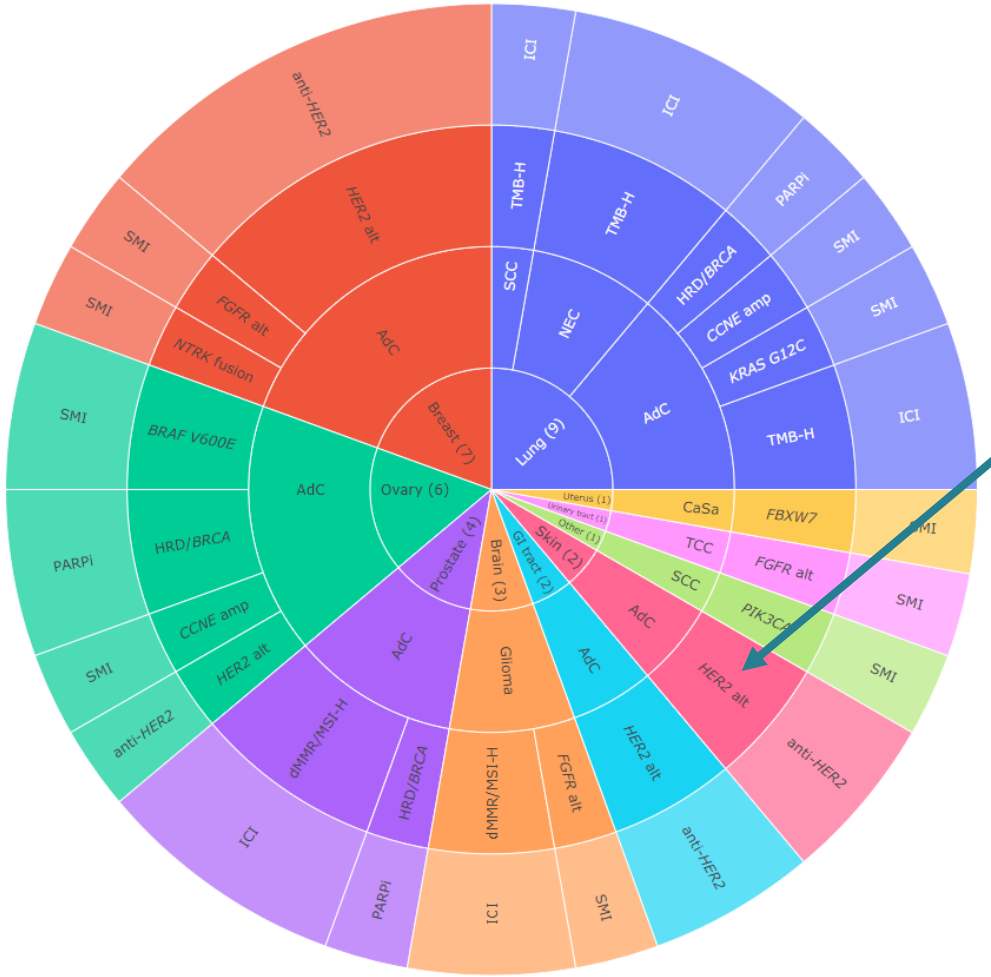
- Cancer genomes contained 4–5 driver mutations.
- In around 5% of cases no drivers are identified.

Passenger mutations: have no direct effect on cell proliferation and tumour growth

- The number of passenger mutations far exceeds the number of driver mutations.

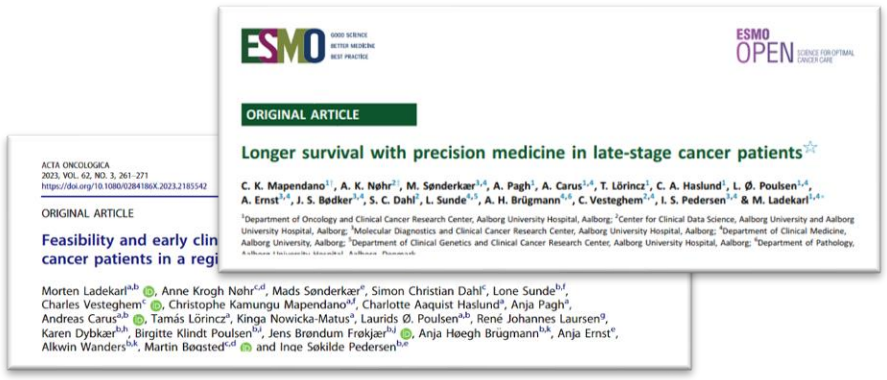


Cancer-causing genes in personalized medicine



HER2 oncogene (growth factor receptor)

Treatment = anti-HER2



ESMO OPEN

ORIGINAL ARTICLE

Longer survival with precision medicine in late-stage cancer patients☆

C. K. Mapendano[1], A. K. Nøhr[2], M. Sønderkær[3,4], A. Pagh[1], A. Carus[1,4], T. Lörincz[1], C. A. Haslund[1], L. Ø. Poulsen[1,4], A. Ernst[3,4], J. S. Bødker[3,4], S. C. Dahl[2], L. Sunde[4,5], A. H. Brügmann[4,6], C. Vesteghem[2,4], I. S. Pedersen[3,4] & M. Ladekarl[1,4]*

ACTA ONCOLOGICA
2023, VOL. 62, NO. 3, 261–271
https://doi.org/10.1080/0284186X.2023.2185542

ORIGINAL ARTICLE

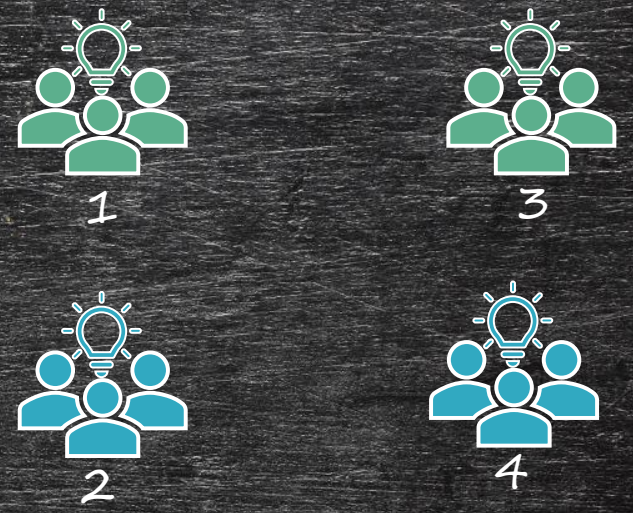
Feasibility and early clin
cancer patients in a regi

Morten Ladekarl[a,b], Anne Krogh Nøhr[c,d], Mads Sønderkær[e], Simon Christian Dahl[c], Lone Sunde[b,f], Charles Vesteghem[c], Christophe Kamungu Mapendano[a,f], Charlotte Aaquist Haslund[a], Anja Pagh[a], Andreas Carus[a,b], Tamás Lörincz[a], Kinga Nowicka-Matus[a], Laurids Ø. Poulsen[a,b], René Johannes Laursen[g], Karen Dybkær[h,i], Birgitte Klindt Poulsen[h,i], Jens Brøndum Frøkjær[h,i], Anja Høegh Brügmann[b,k], Anja Ernst[e], Alkwin Wanders[b,k], Martin Bøgsted[c,d] and Inge Søkilde Pedersen[b,e]

CENTER FOR CLINICAL DATA SCIENCE

GROUP WORK

THE HERITABILITY OF HUMAN DISEASE

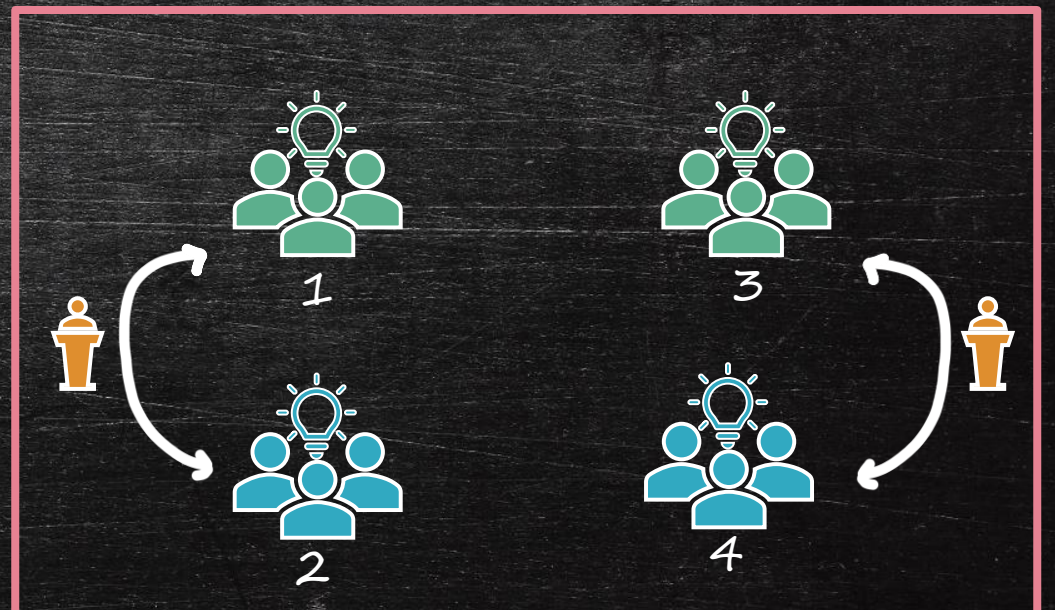


PART 1

1) Make 4 groups & prepare a 5-7 min presentation
   - ❑ Feasibility and early clinical impact of precision medicine for late-stage cancer patients in a regional public academic hospital
   - ❑ Longer survival with precision medicine in late-stage cancer patients

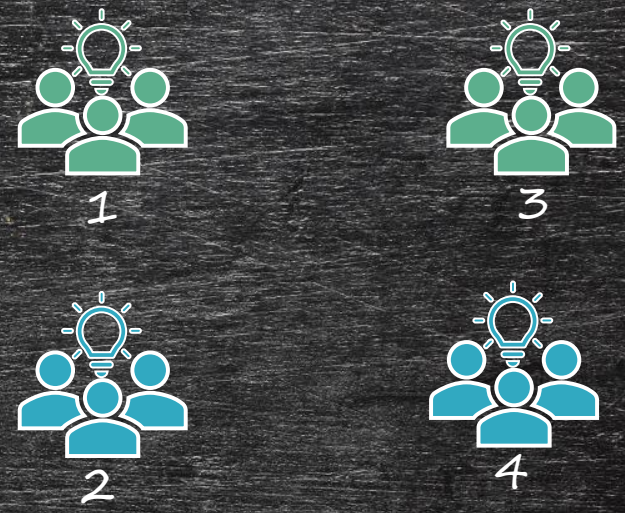
PART 2 – *next time (7/6)*

- ❑ Group 1 present to group 2 and *vise versa*
- ❑ Group 3 present to group 4 and *vise verse*



GROUP WORK

THE HERITABILITY OF HUMAN DISEASE



All should include:

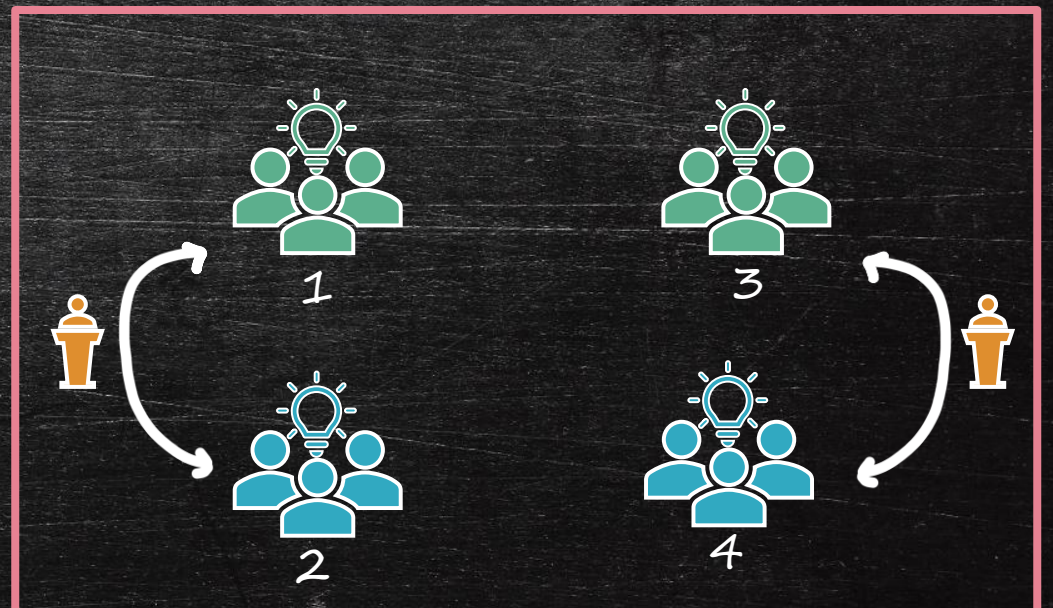
- Brief description of the study
- Limitations
- Conclusion

Feasibility and early clinical impact of precision medicine for late-stage cancer patients in a regional public academic hospital:

- The flow of patients from inclusion to treatment recommendation and NMTB recommendations (figure 1)
- Treatment duration and response for targeted treatments (figure 3)

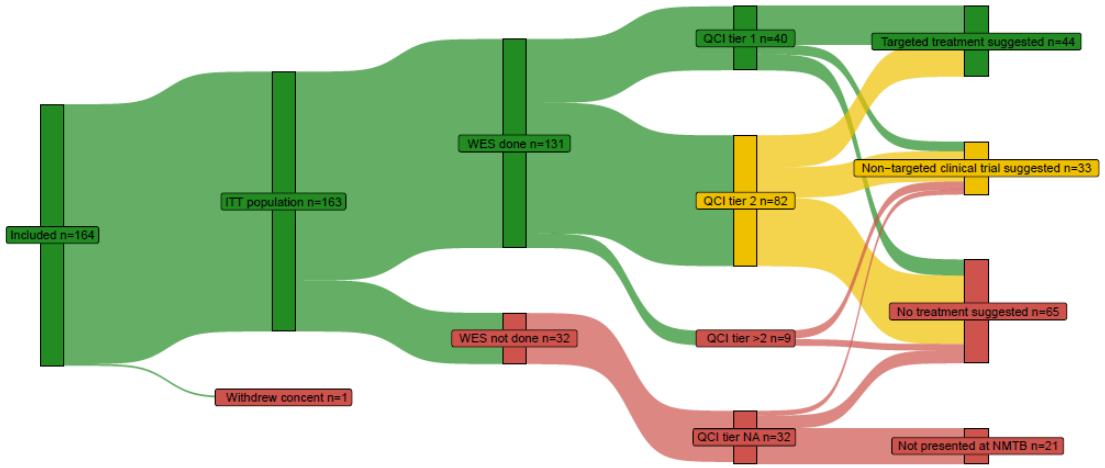
Longer survival with precision medicine in late-stage cancer patients

- Describe the 196 molecularly profiled patients (table 1)
- Overall survival of the patients (figure 4)

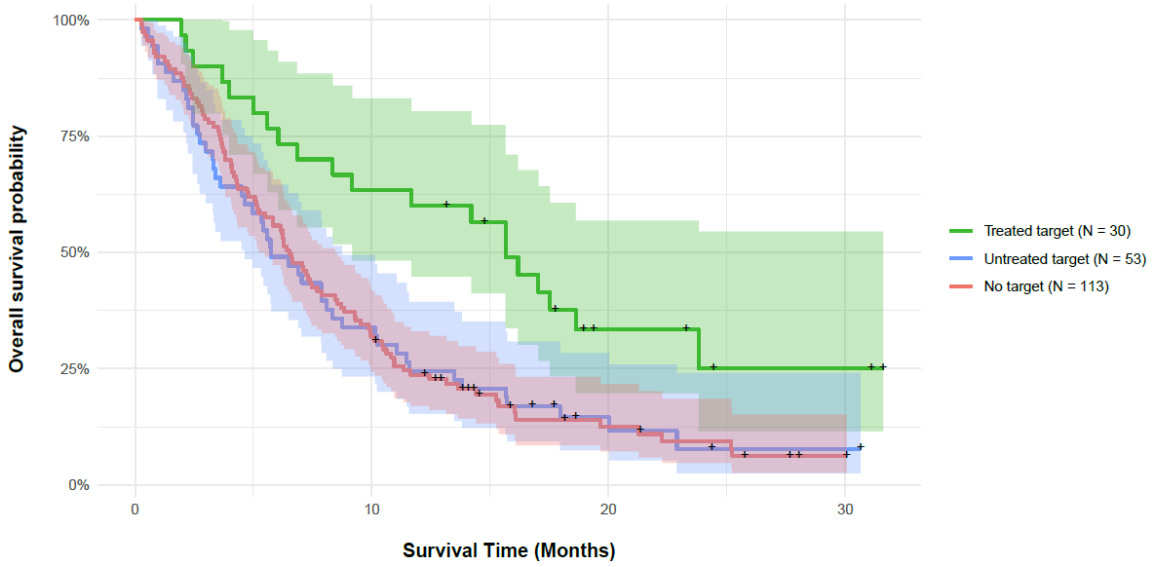


What did you learn?

Feasibility and early clinical impact of precision medicine for late-stage cancer patients in a regional public academic hospital



Longer survival with precision medicine in late-stage cancer patients




BREAK

AGENDA

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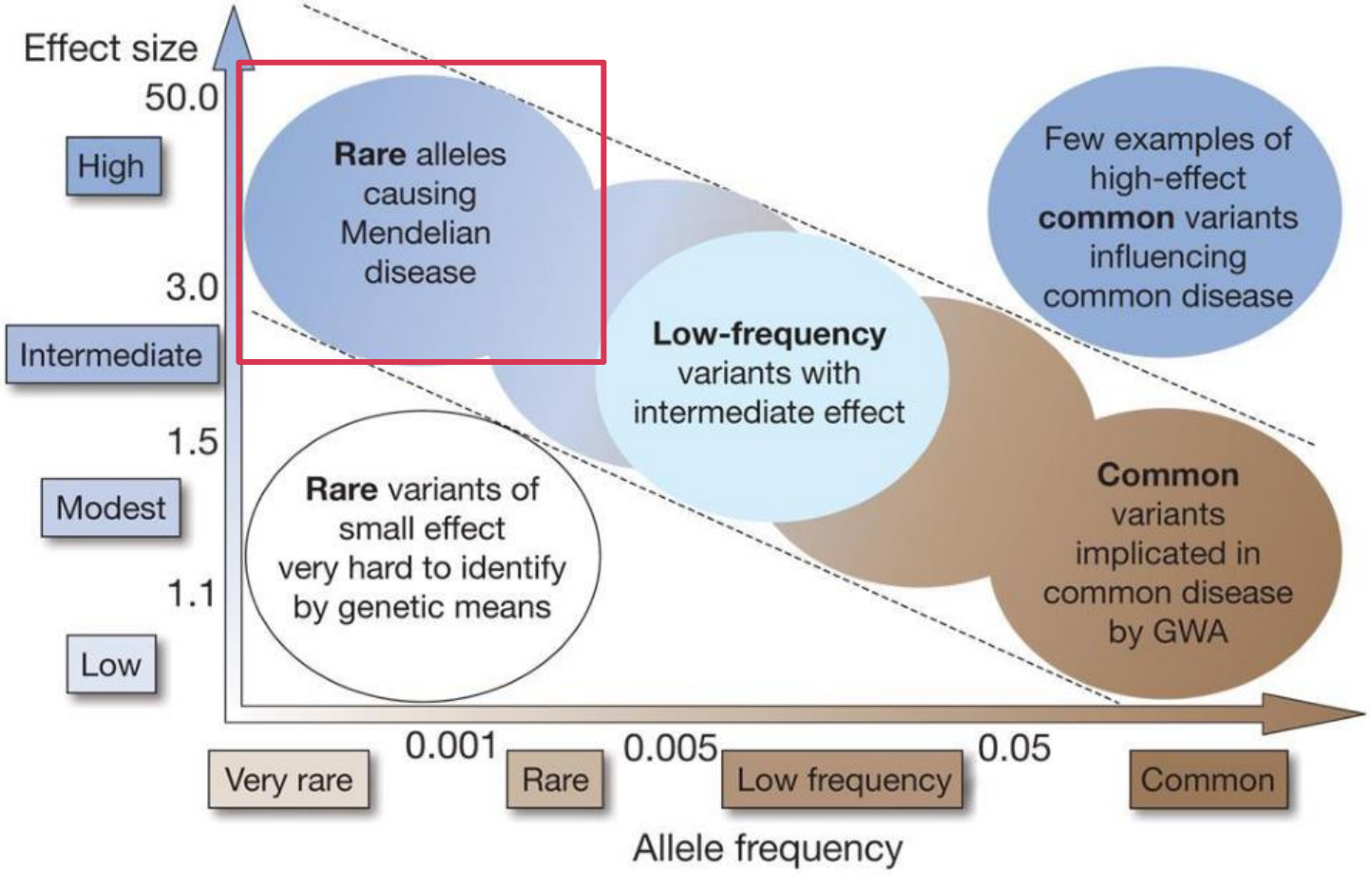
Rare germline cancer-causing variants

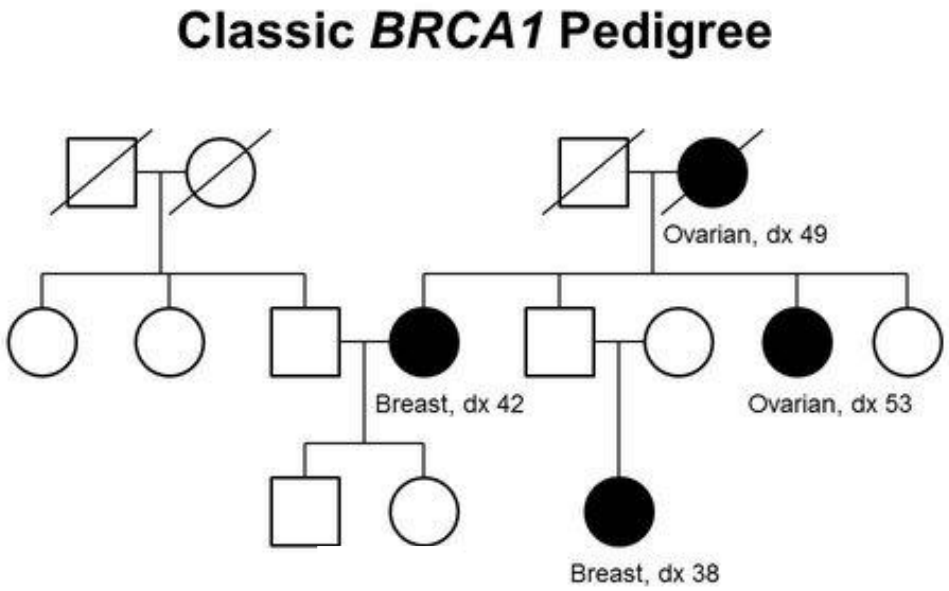


Driver mutations – facts

- Cancer genes show:
  - ~10% germline and somatic mutations
  - ~80% only somatic mutations
  - ~10% only germline mutations
- Classic examples of inherited driver mutations
  - BRCA1 and BRCA2 mutations in familial breast and ovarian cancer
  - APC mutations in familial adenomatous polyposis.
- Driver mutations in the germline demonstrates that somatic driver mutations can be acquired decades before the cells become cancerous.
- This is possible because a cell requires multiple mutations to become cancerous - acquired gradually over time.

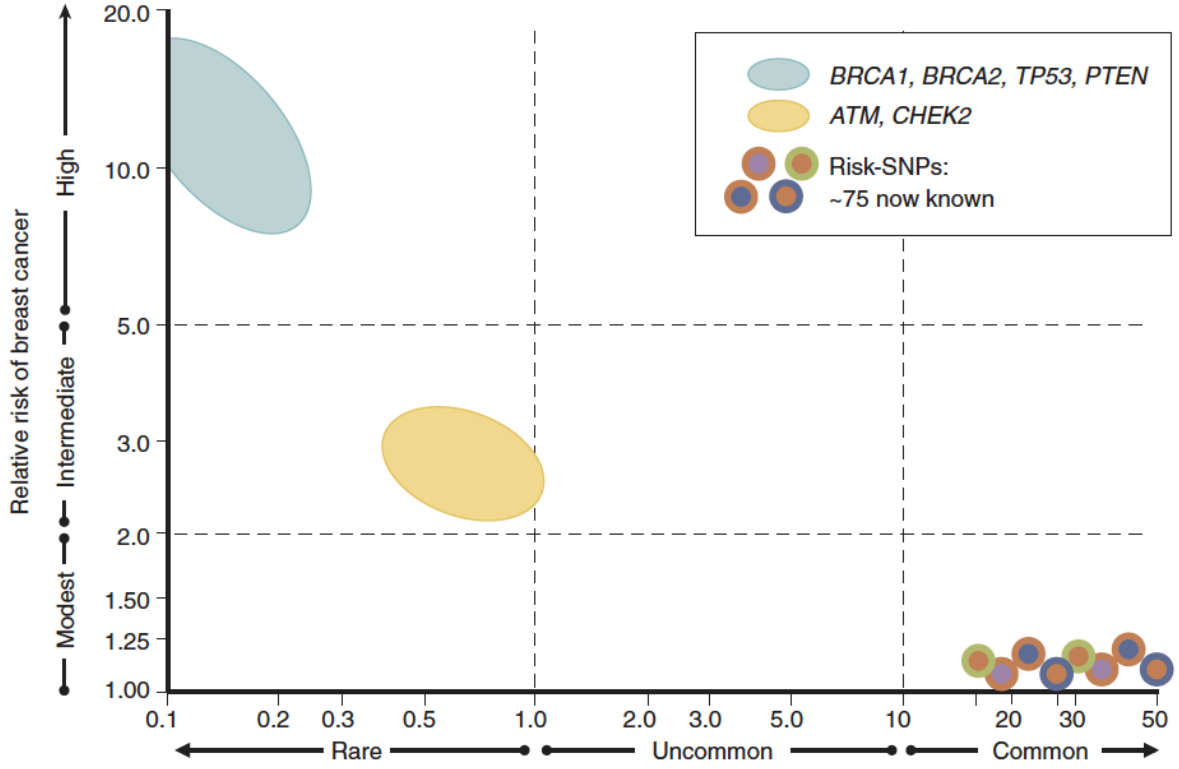
Rare variants with high penetrance

- Nearly 10% of all cancers are inherited.
- The majority are inherited in an autosomal dominant manner with incomplete penetrance.
- How does inherited cancer present?
  - Early age of onset
  - Occurrence of the disorder often in all generations (vertical transmission)
  - Cancer occurring in a gender in which it does not commonly occur
  - Bilaterally affected organs

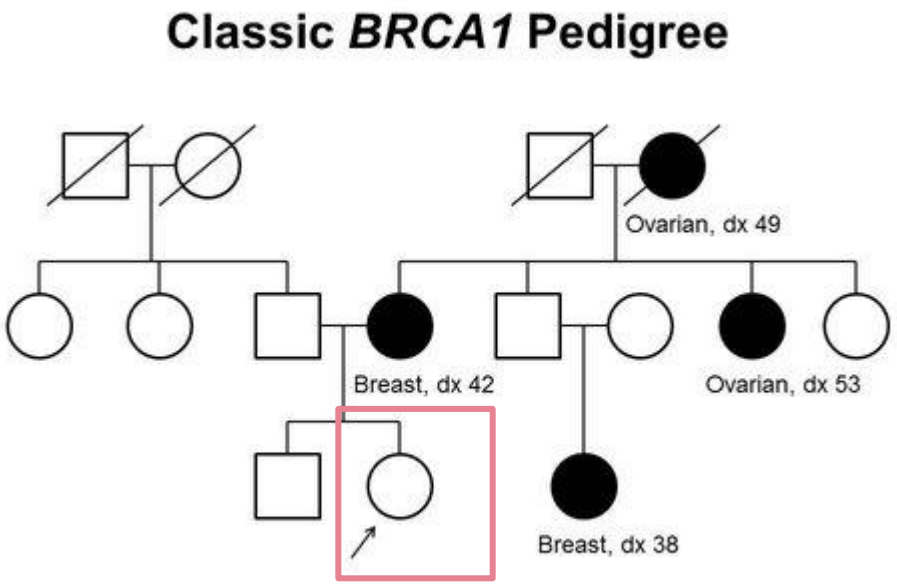


Breast cancer

- The lifetime prevalence of breast cancer in women is 1 in 8.
- 1-3% of cases are due to inherited mutations in BRCA1 and BRCA2.
- Women with a positive family history of both breast and ovarian cancer have inherited a BRCA1 or BRCA2 mutation in 60-80% of cases.
- Lifetime risk of breast cancer:
  - BRCA1 mutation: 50%-80%
  - BRCA2 mutation: 50%



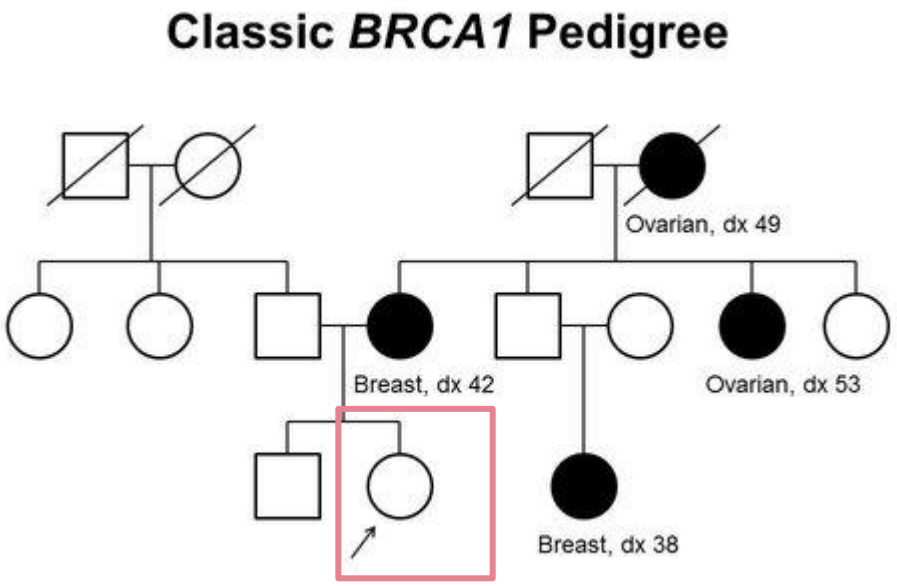
Complete vs. incomplete penetrance



Assuming complete penetrance and autosomal dominant inherence.

What is the risk that this person is affected?

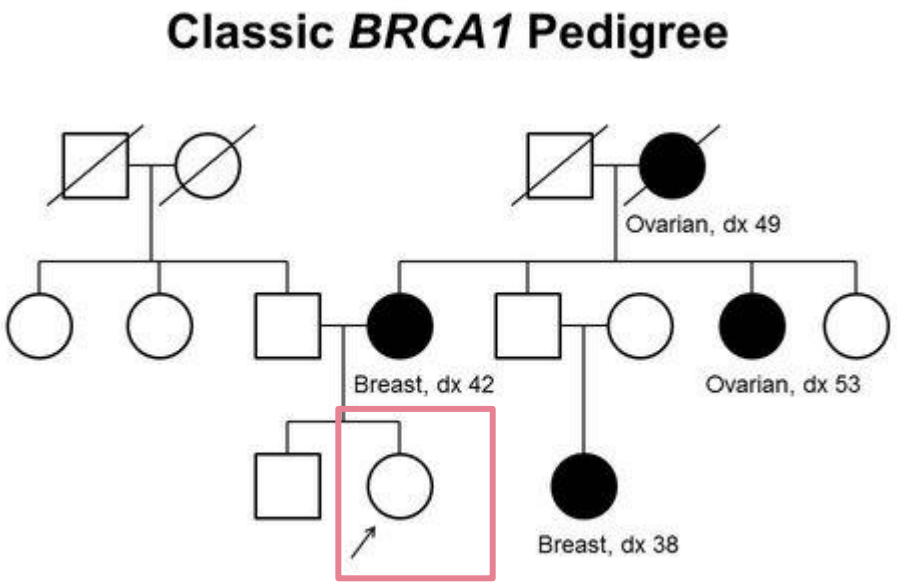
Complete vs. incomplete penetrance



Assuming 70% penetrance and autosomal dominant inherence.

What is the risk that this person is affected?

Complete vs. incomplete penetrance



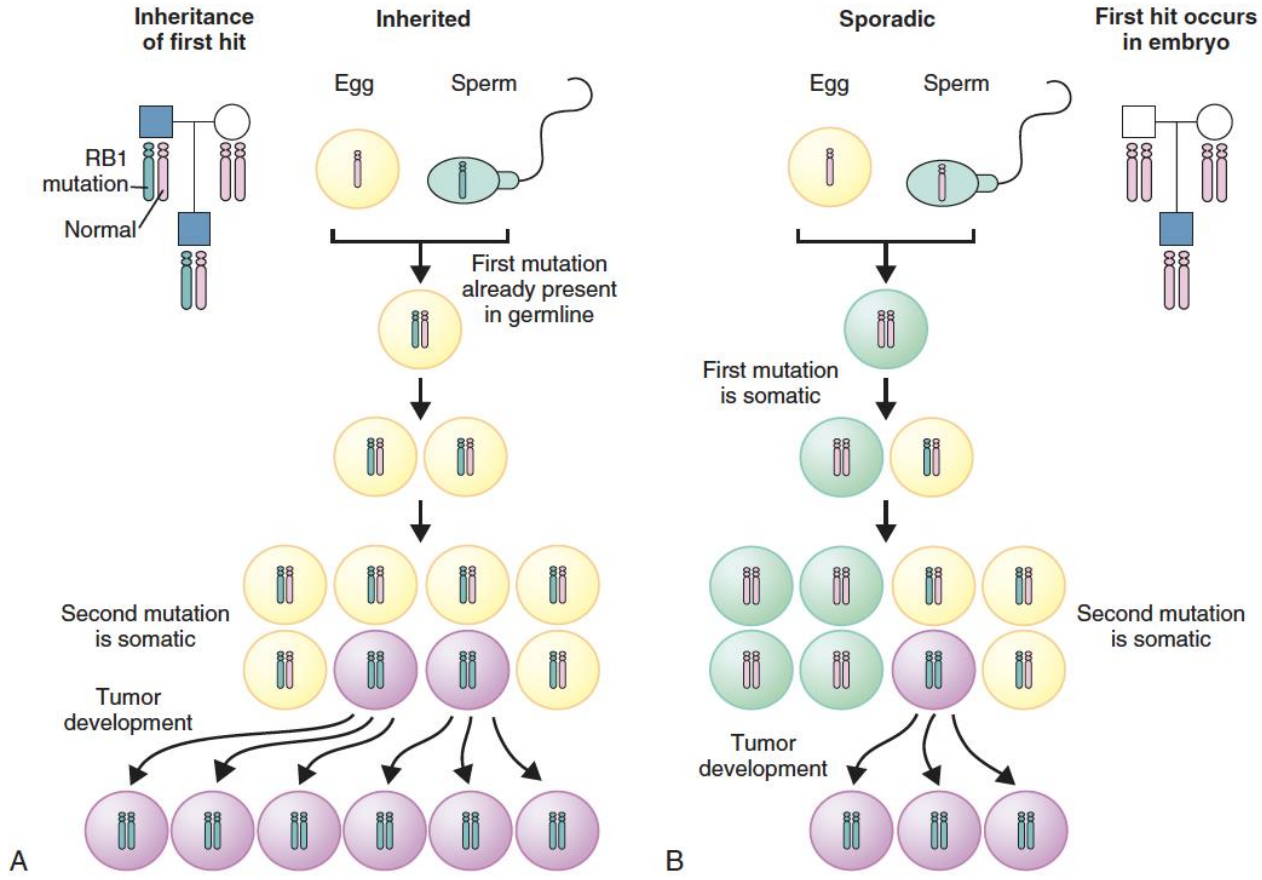
Assuming 70% penetrance and autosomal dominant inherence.

What is the risk that this person is affected?

What indicates this is a BRCA1?

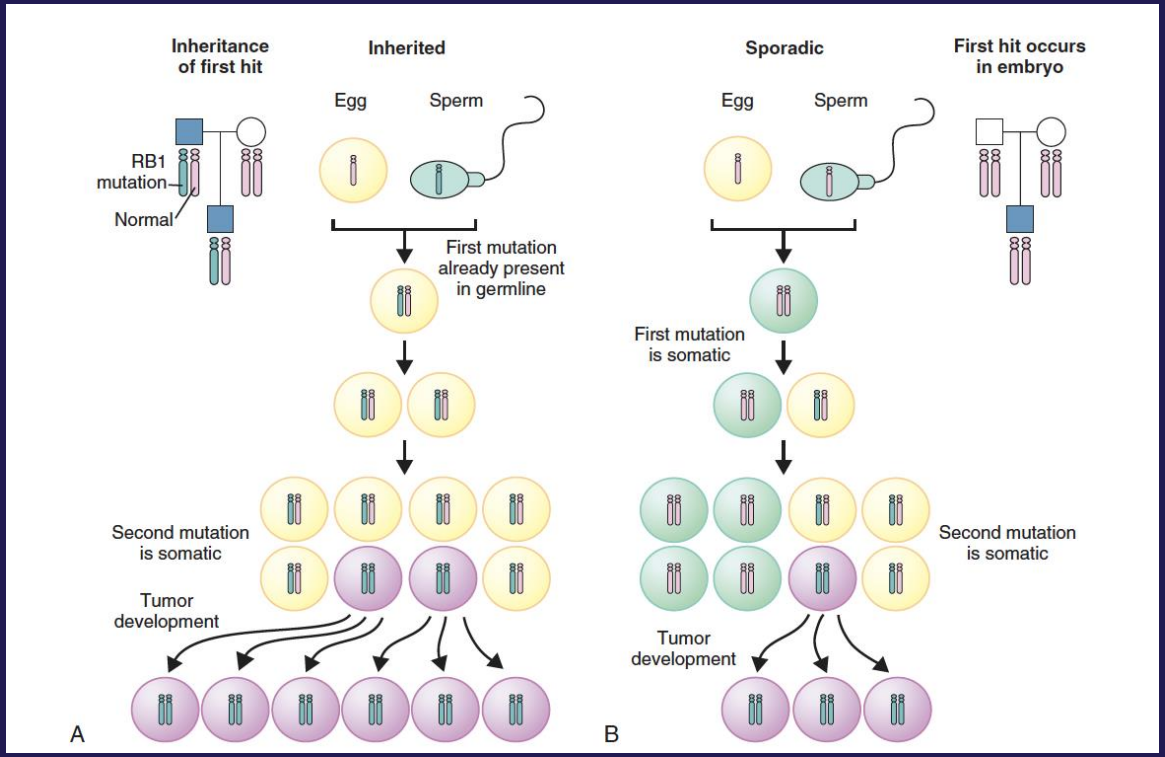
Rare variants with high penetrance – Breast cancer

- BRCA1 and BRCA2 follow the "two-hit" model for tumor suppressor genes.
- If inherited:
  - Dominant at the individual level
  - Recessive at the cellular level

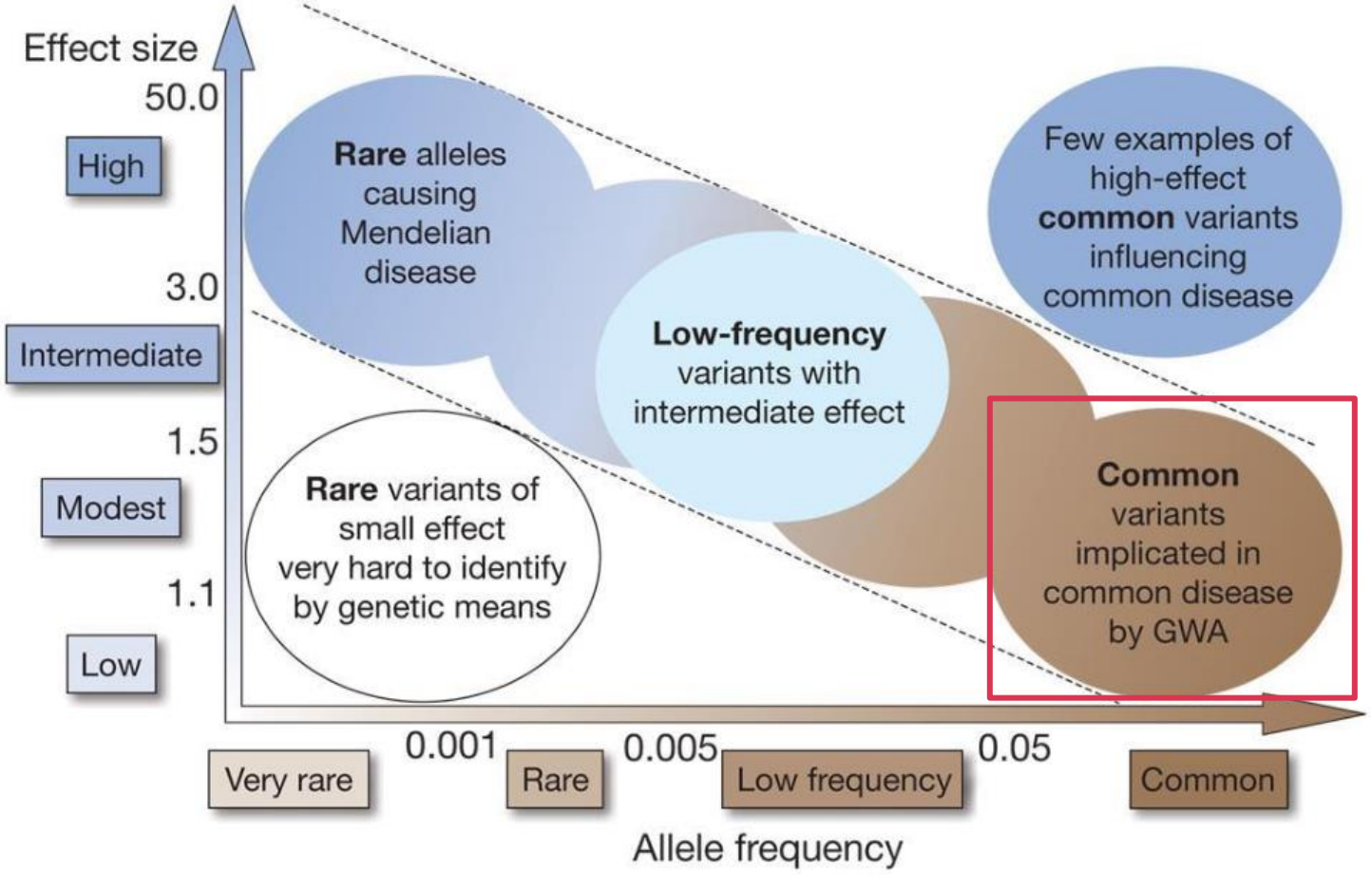


Take one minute each to explain to your neighbor:

- How does the "two-hit" model for tumor suppressor genes differ between inherited and sporadic cancer?

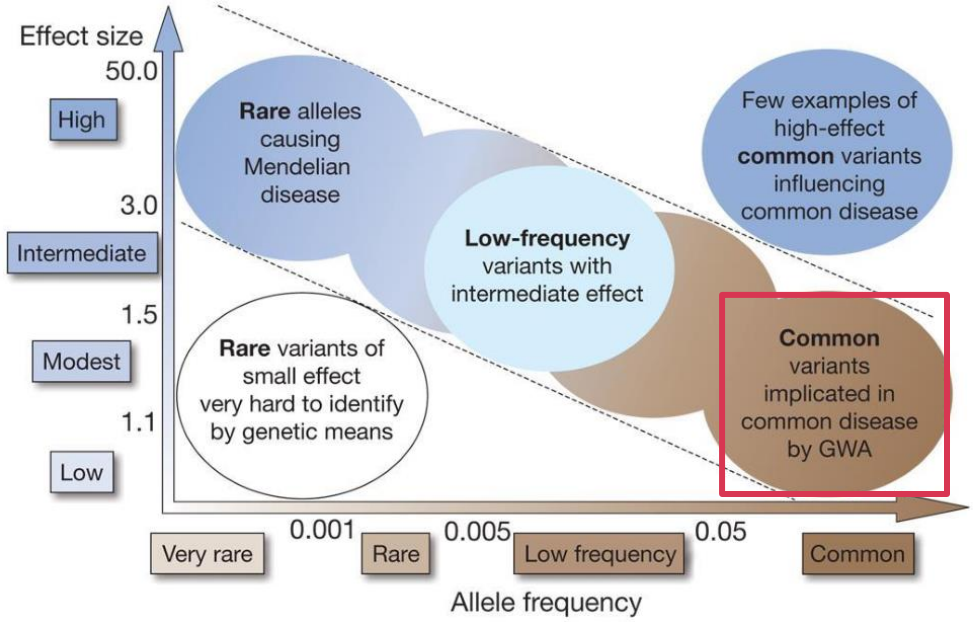


Common germline variants



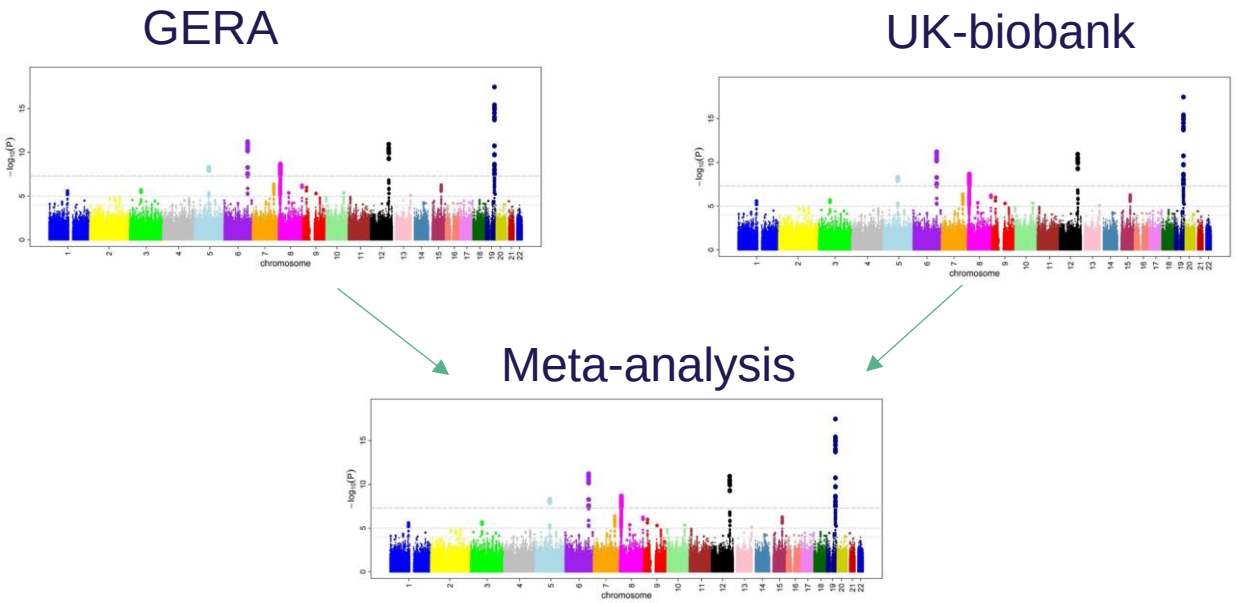
Common germline variants in cancer

- Driver mutations are typically defined as having a large impact on fitness
- SNPs do not have a strong enough effect on fitness to be considered driver mutations
- We can use SNPs to estimate cancer risk



Rashkin et al. 2020

- 64,962 cases and 410,350 controls
- Meta-analysis of 18 cancers



nature COMMUNICATIONS

ARTICLE

Check for updates

https://doi.org/10.1038/s41467-020-18246-6 OPEN

Pan-cancer study detects genetic risk variants and shared genetic basis in two large cohorts

Sara R. Rashkin[1,8], Rebecca E. Graff[1,2,8], Linda Kachuri[1], Khanh K. Thai[2], Stacey E. Alexeeff[2], Maruta A. Blatchins[2], Taylor B. Cavazos[1,3], Douglas A. Corley[2], Nima C. Emami[1,3], Joshua D. Hoffman[1], Eric Jorgenson[2], Lawrence H. Kushi[2], Travis J. Meyers[1], Stephen K. Van Den Eeden[2,4], Elad Ziv[5,6,7], Laurel A. Habel[2], Thomas J. Hoffmann[1,2,5], Lori C. Sakoda[2,9✉] & John S. Witte[1,4,5,7,9✉]

For each cancer:
- SNPs
- Heritability

Pan-cancer:
- Pleiotropy
- Genetic correlation

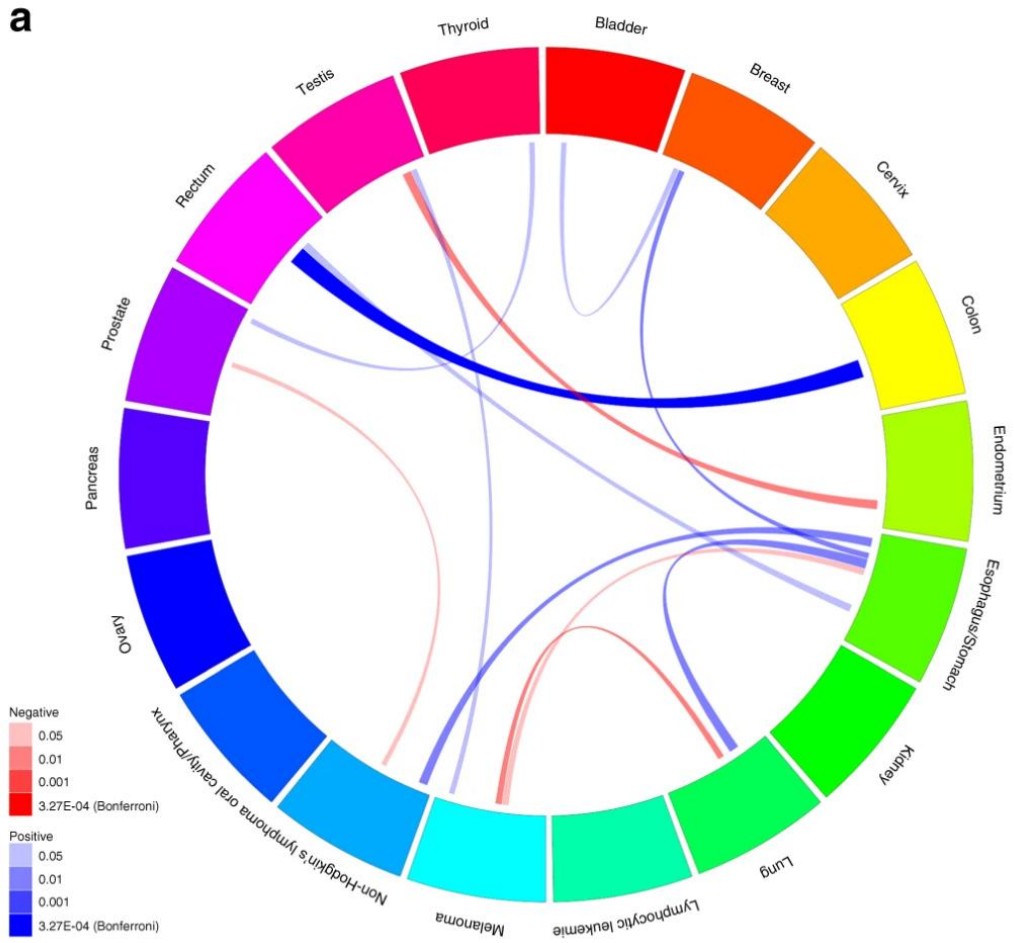
How many common variants were found?

- Heritability estimates range between 4%-26%
- No. of variants associated with the risk of individual cancers differs
  - Colorectal cancer: 205 variants
  - Breast cancer: 210 variants
  - Oral cavity/pharynx: 29 variants
- Have we discovered all variants yet?

Cancer site	Current study (array based)
Bladder	0.08 (0.04–0.12)
Breast	0.10 (0.08–0.13)
Cervix	0.07 (0.02–0.12)
Colon	0.07 (0.04–0.10)
Endometrium	0.13 (0.07–0.18)
Esophagus/stomach	0.14 (0.07–0.21)
Kidney	0.09 (0.04–0.15)
Lung	0.15 (0.10–0.20)
Lymphocytic leukemia	0.14 (0.05–0.23)
Melanoma	0.08 (0.04–0.11)
Non-Hodgkin's lymphoma	0.13 (0.03–0.23)
Oral cavity/pharynx	0.04 (0.00–0.13)
Ovary	0.07 (0.01–0.13)
Pancreas	0.06 (0.00–0.18)
Prostate	0.16 (0.13–0.20)
Rectum	0.11 (0.07–0.16)
Testis	0.26 (0.15–0.38)
Thyroid	0.21 (0.09–0.33)

Pleiotropic variants

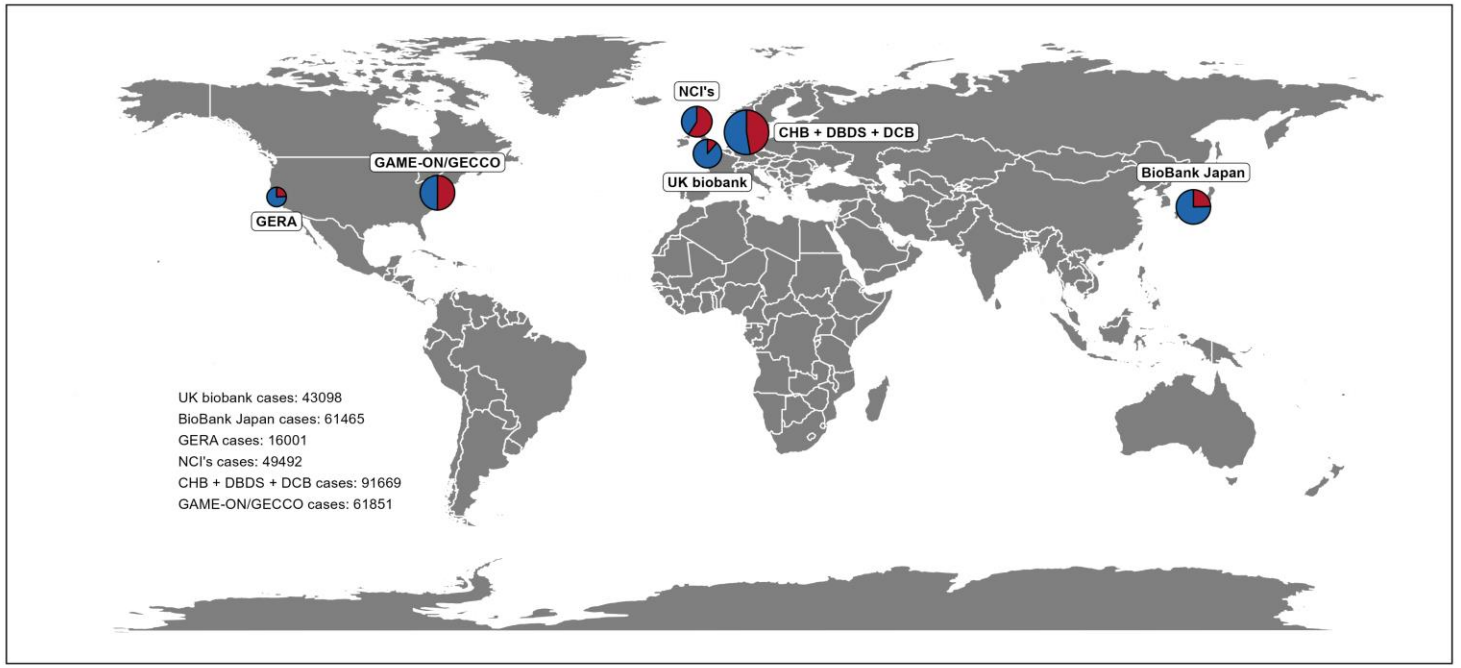
- One-directional pleiotropic variants = 85
  - 84/85 were in regions previously associated with cancer
  - 68/85 were associated with at least one cancer not previously reported
- Bidirectional pleiotropic associations = 15
  - all were in regions that have previously been associated with cancer
  - all were associated with at least one cancer not previously reported
- 1 significant genetic correlation



Importance of sample size

Not all cancers are equally represented:

Rashkin et al. 2020**:** **663 (pancreas)** – 17,881 (breast)



Adjusting for multiple testing

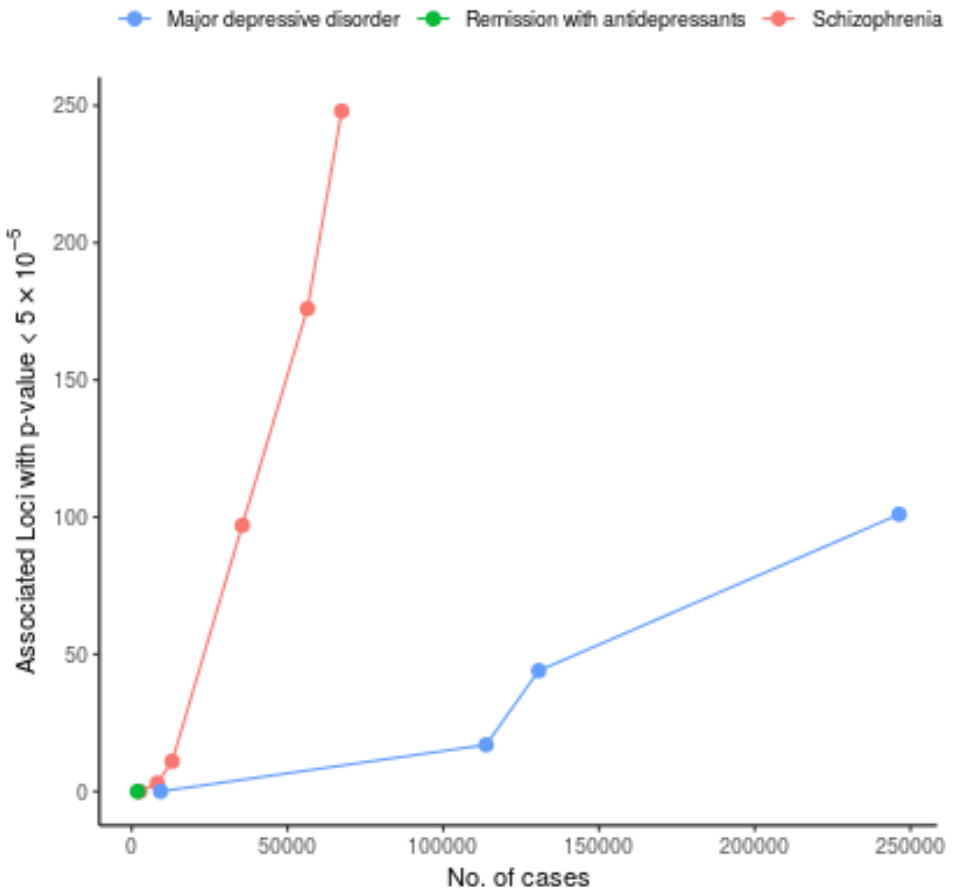
How many cases do you need?

That will depend on:

- No. of controls
- MAF
- Effect size

Breast cancer:

- Large GWAS: 210 variants (N = 118,474)
- This study: 105 variants (N = 17,881)



Exercise 1


BREAK

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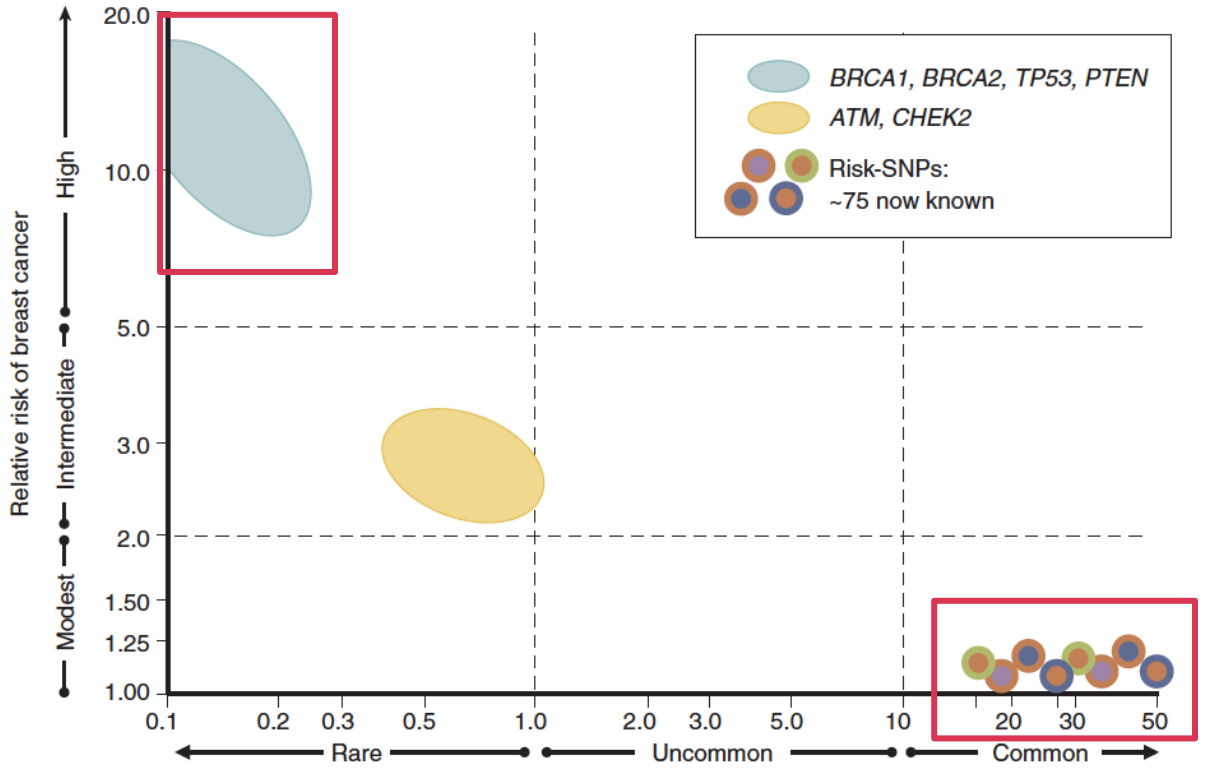
Can we combine common and rare germline variants?

- BRCA1 and BRCA2 less common in Finns
- Two frameshift mutations in tumor suppressor genes have high allele frequency in Finns
  - PALB2
  - CHEK2
- Mutations in the high penetrante genes account for less than 25% of the overall inherited predisposition
- GWAS have identified:
  - 210 common variants
  - Heritability of 16%
- 122,978 women in FinnGen, 8401 with breast cancer



Can we combine common and rare germline variants?

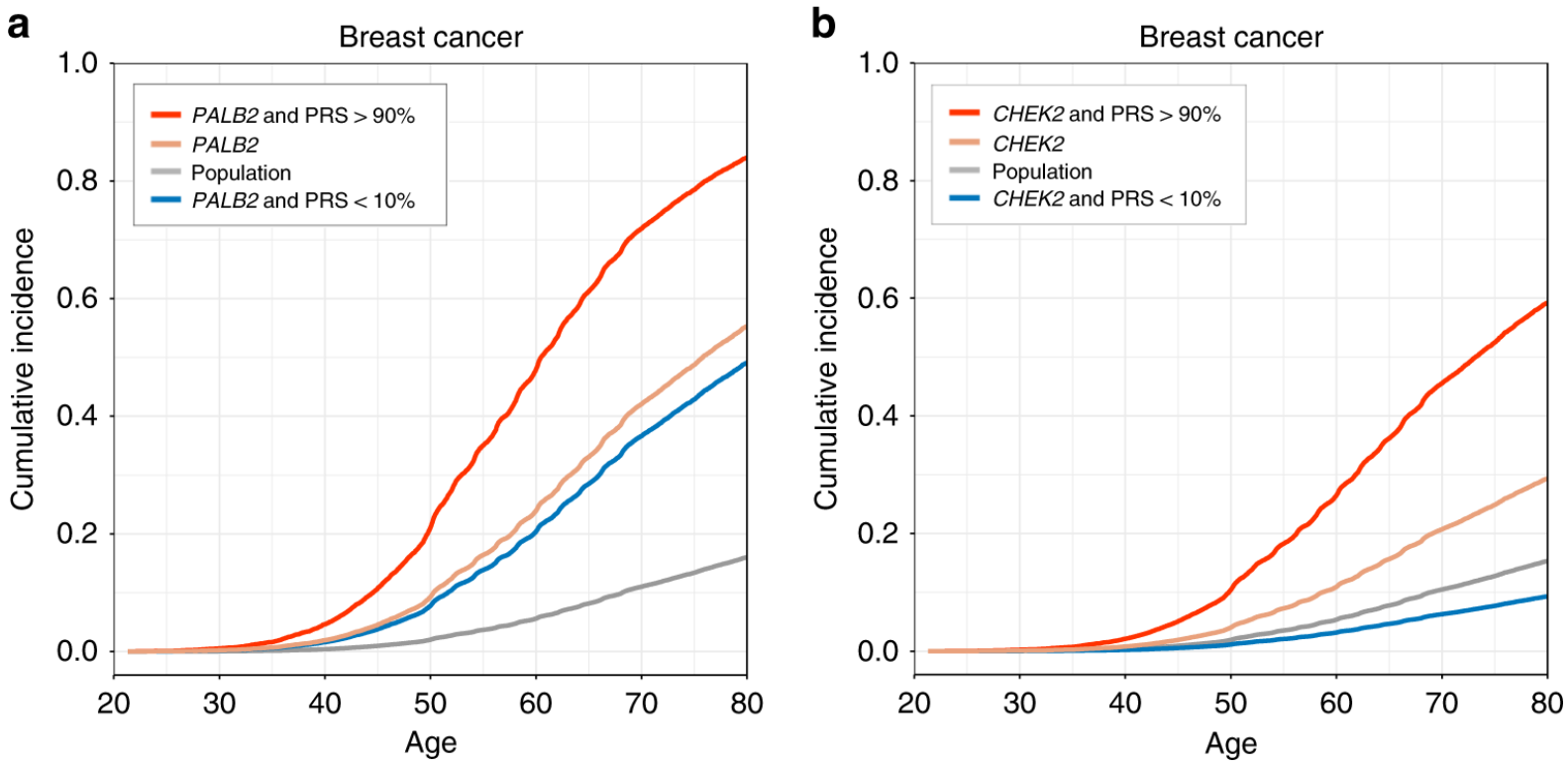
Table 2 Risk for breast cancer events in the population in carriers of the *PALB2* and *CHEK2* frameshift mutations, and in the top decile of the polygenic risk score (PRS).

From: The role of polygenic risk and susceptibility genes in breast cancer over the course of life

	PALB2	*CHEK2*	PRS > 90%
Number of individuals	336	1648	12,298
Number of cases	84	214	1821
Lifetime risk of breast cancer, % (95% CI)	56.1 (50.8–61.4)	31.7 (29.5–33.9)	32.5 (31.6–33.4)
Mean age at disease onset in cases (SD)	53.1 (10.4)	56.5 (12.0)	57.8 (11.3)

Lifetime risk was estimated by age 80. The variants were rs180177102 (c.1592delT) for *PALB2* and rs555607708 (c.1100delC) for *CHEK2*. The *PALB2* analysis was done in 109,371 women, and the *CHEK2* and PRS analyses in 122,978 women.
CI confidence interval, *SD* standard deviation.

PRS modifies the risk in PALB2 and CHEK2 mutation carriers



Population level was defined as women with PRS between the 10th and 90th percentiles. The *PALB2* analysis was done in 109,371 women and *CHEK2* analysis in 122,978 women. Adjusted survival curves Cox proportional hazards model.

Is there an interaction?

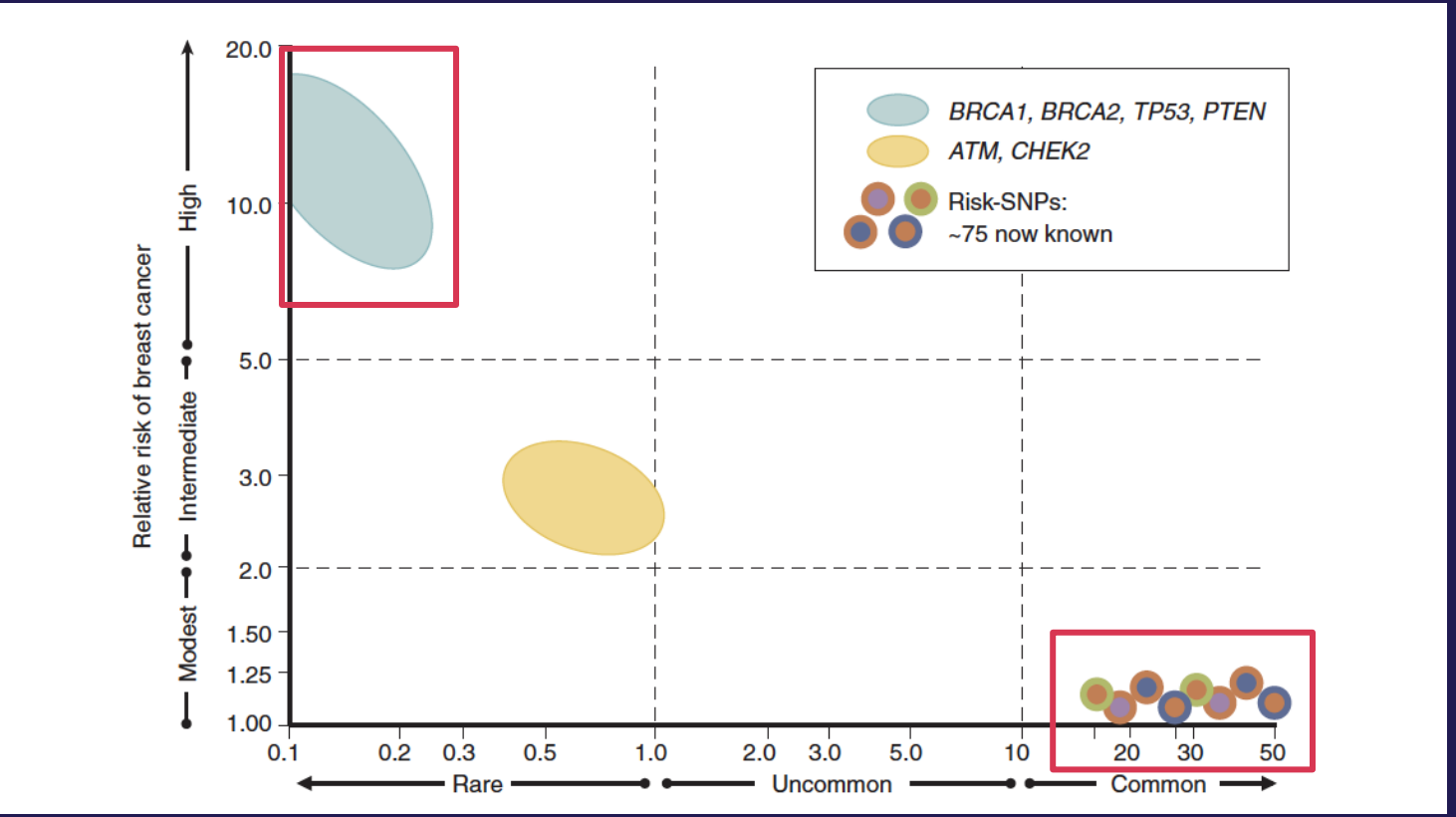
Table 5 To test for interaction in all 122,978 women, we compared the polygenic risk score (PRS) effect size in pooled mutation carriers (pooling *PALB2* and *CHEK2*) and in non-carriers.

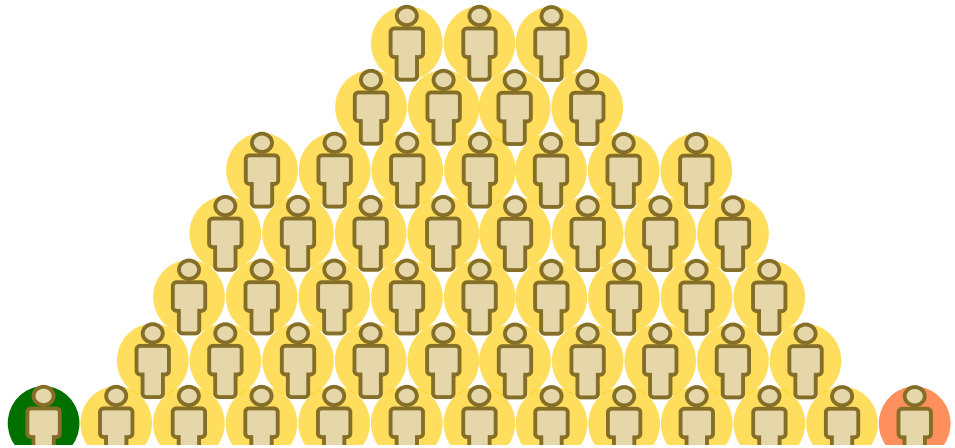
From: The role of polygenic risk and susceptibility genes in breast cancer over the course of life

	PRS < 10%	PRS 10–90%	PRS > 90%
Mutation	0.42 (0.23–0.79)	1.00 (reference)	2.44 (1.82–3.28)
No mutation	0.38 (0.34–0.43)	1.00 (reference)	2.37 (2.25–2.50)

The table shows the hazard ratios and 95% confidence intervals for the bottom and top deciles, comparing them to women with an average risk (PRS between the 10th and 90th percentiles).

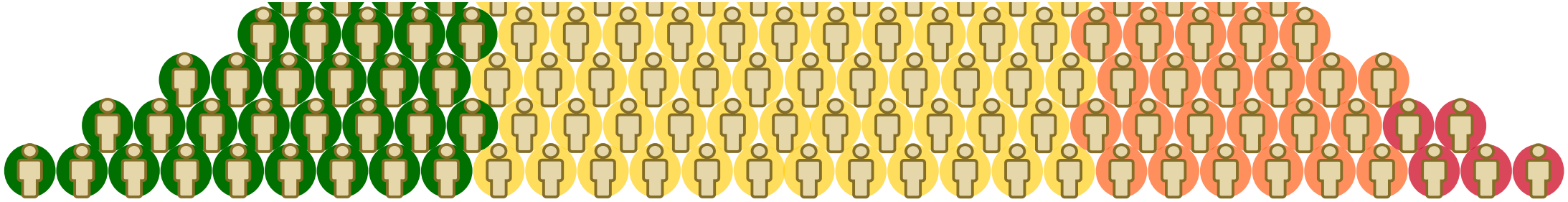
Are you surprised by the impact of the PRS?



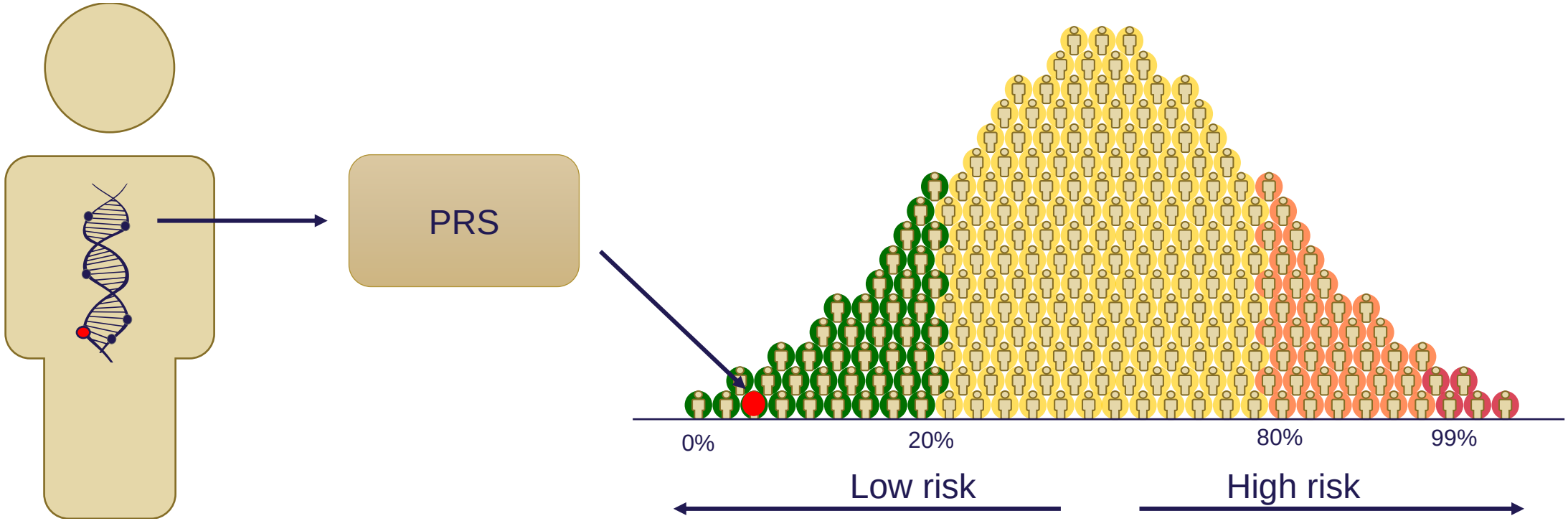


Cancer risk prediction

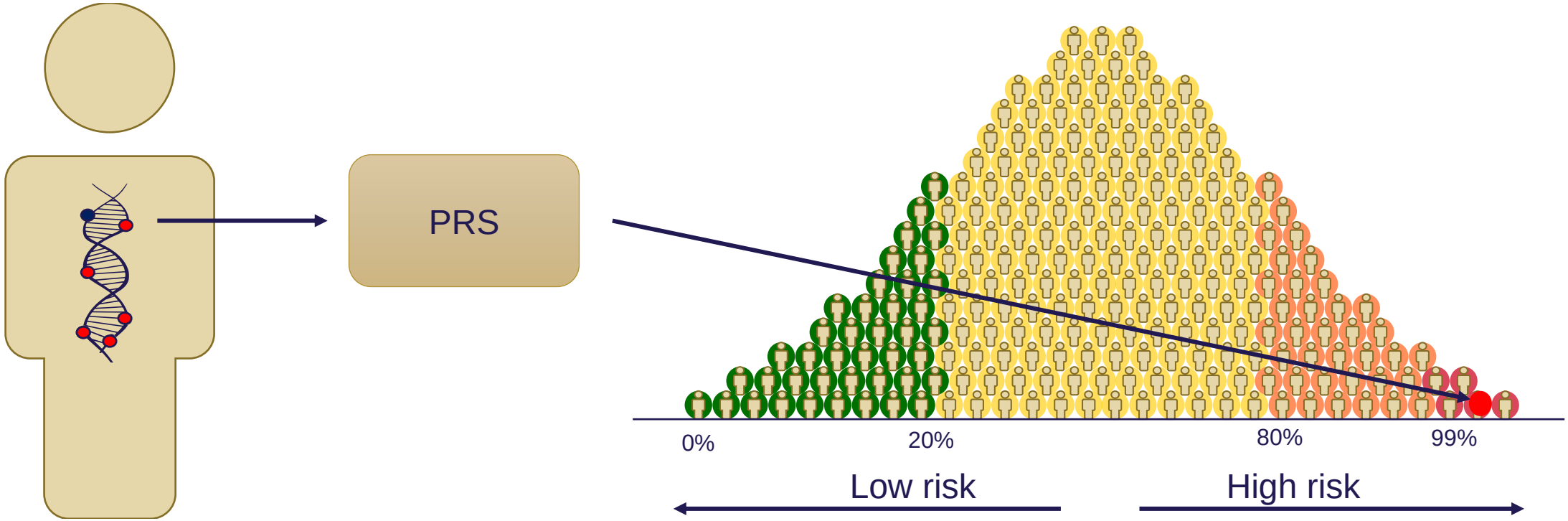
- ***Can we improve the current colorectal cancer screening program by combining genetic data with registry data?***



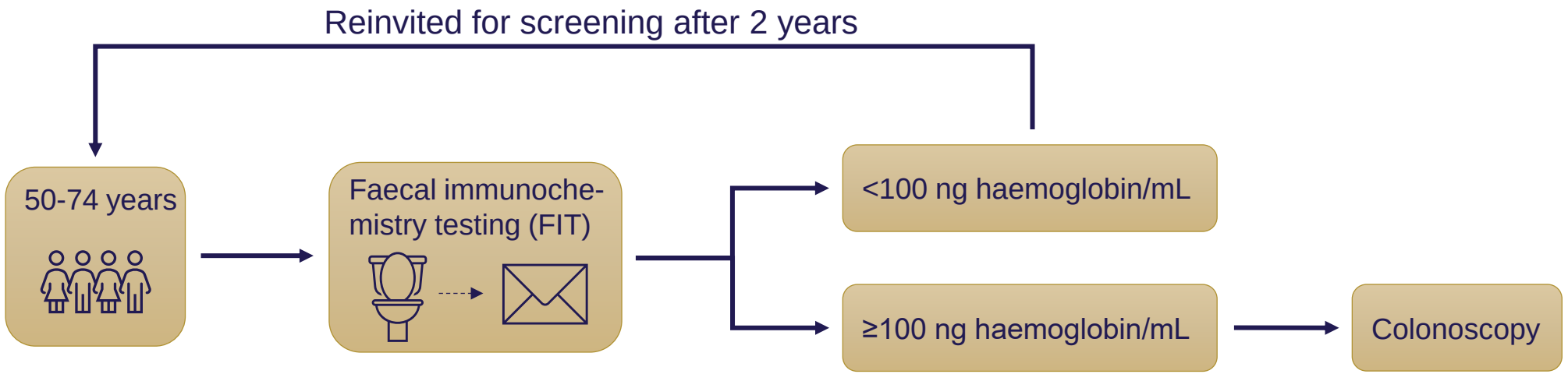
Genetic risk and common variants



Genetic risk and common variants



Why improve the current screening program?



Njor SH, Friis-Hansen L, Andersen B, et al. Three years of colorectal cancer screening in Denmark. *Cancer Epidemiol*. 2018;57:39-44. doi:10.1016/j.canep.2018.09.003.

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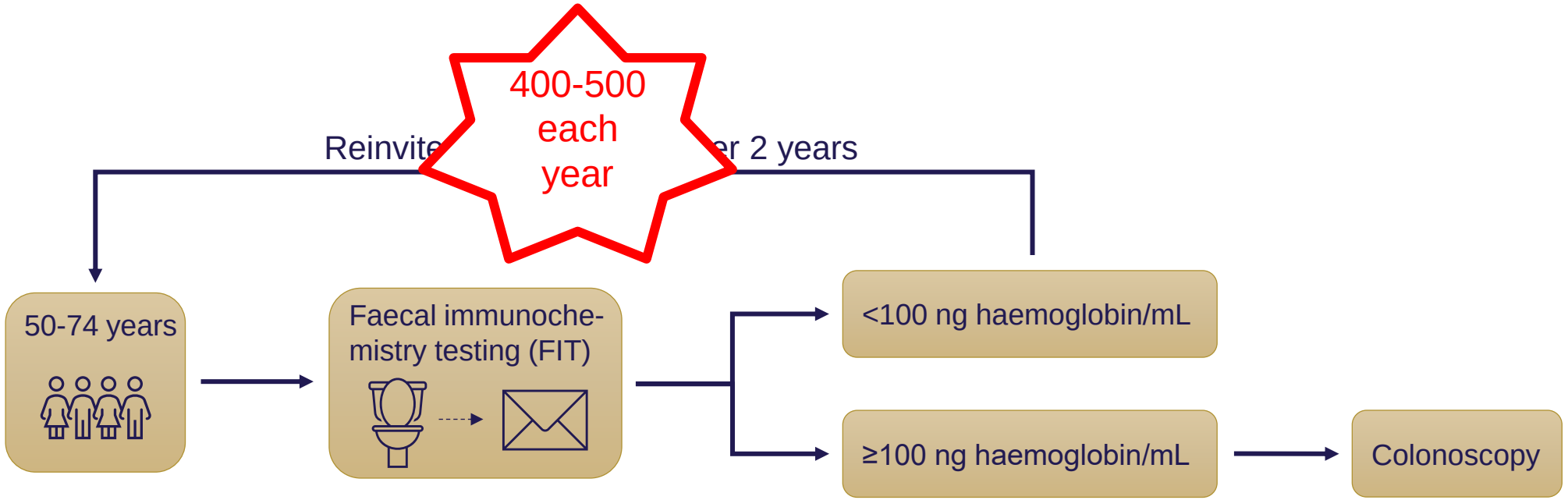
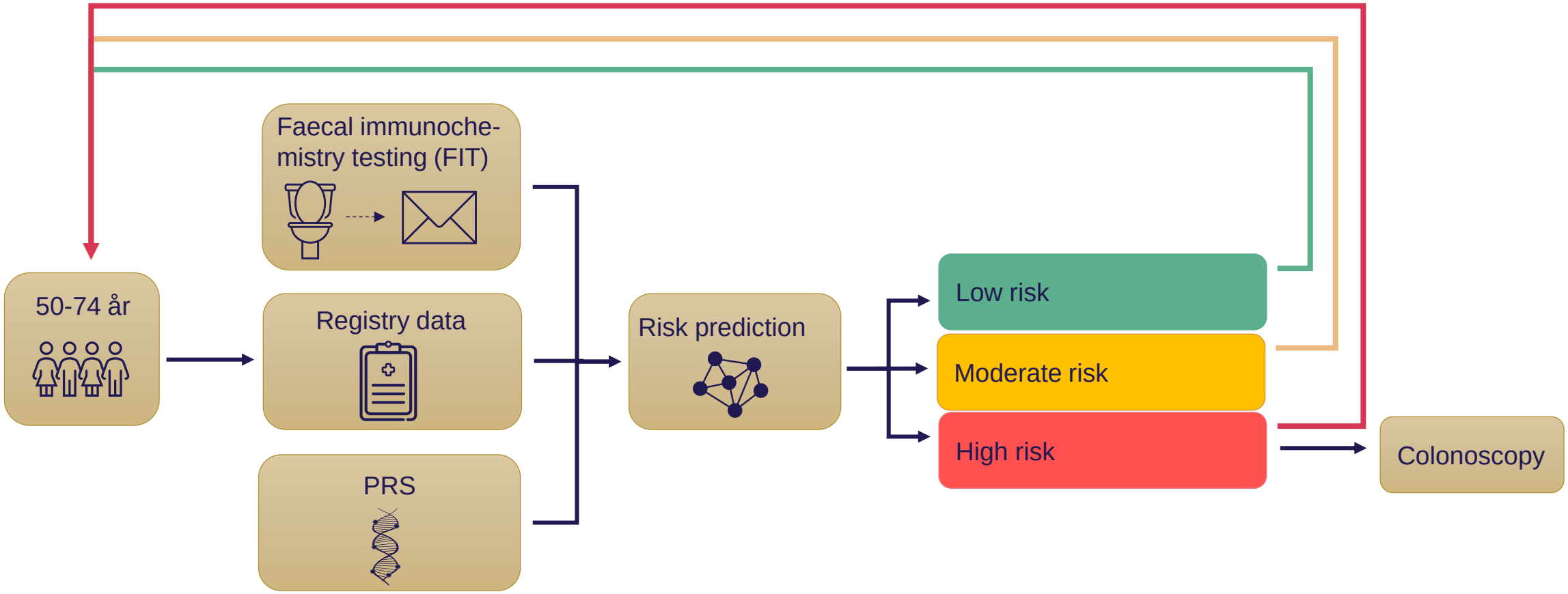
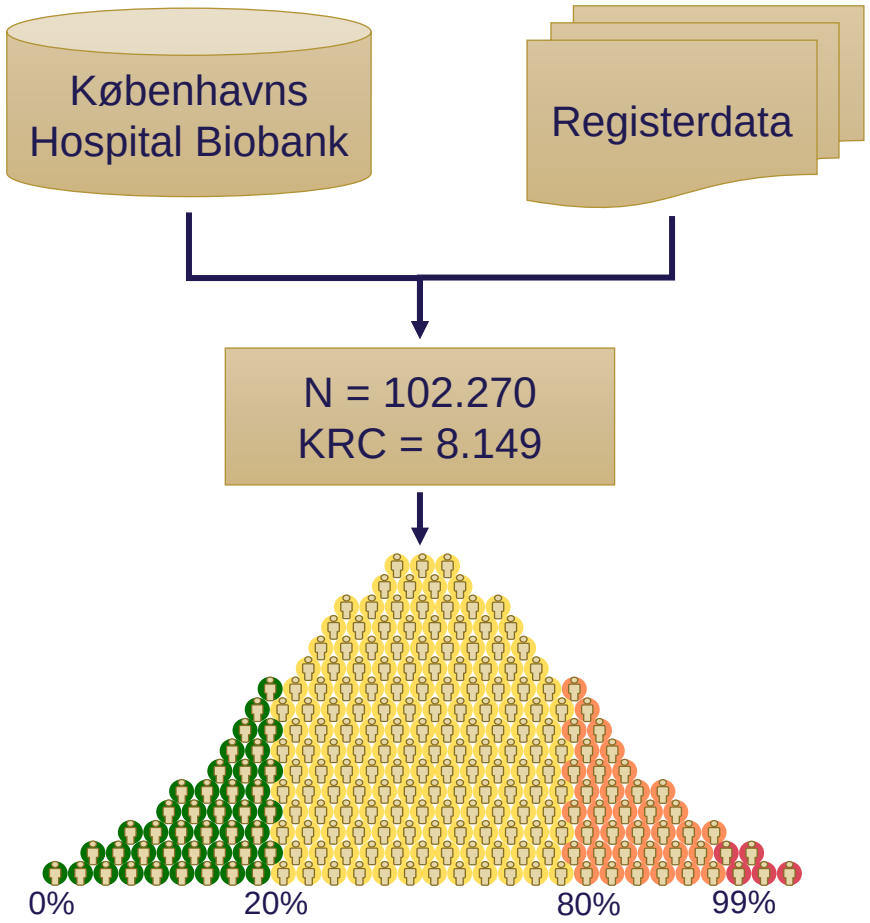


Njor SH, Friis-Hansen L, Andersen B, et al. Three years of colorectal cancer screening in Denmark. *Cancer Epidemiol*. 2018;57:39-44. doi:10.1016/j.canep.2018.09.003.

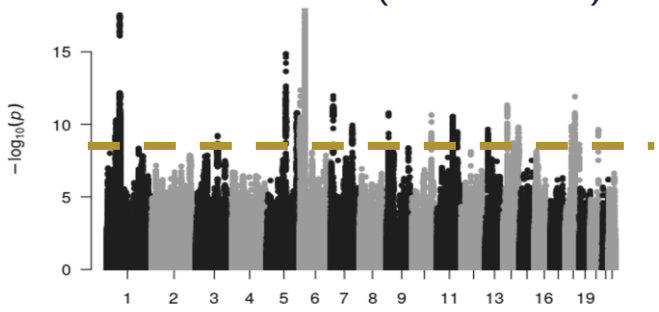
Why improve the current screening program?



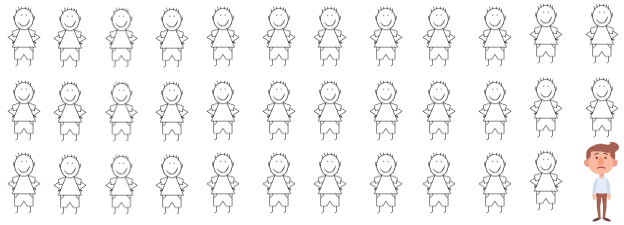
Preliminary results



CRC GWAS (205 variants)



Copenhagen hospital biobank

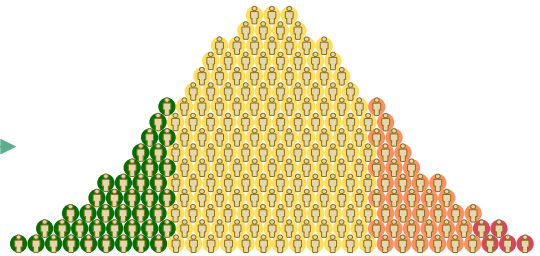


Allele	T	C	T	A
Effect	-0.5	1	-1.5	2

	SNP 1	SNP 2	SNP 3	SNP 4
Individual 1	TT	AG	TG	CA
Individual 2	AT	CT	GG	CC
Individual 3	TC	TT	CC	AG

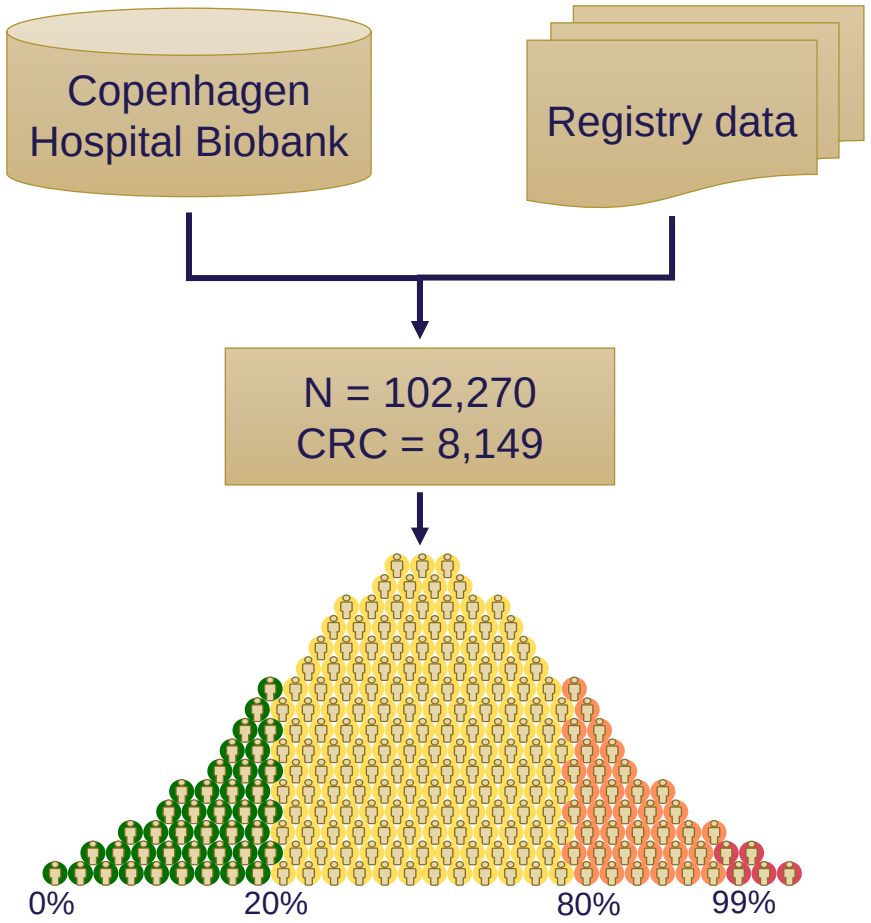
CRC PRS

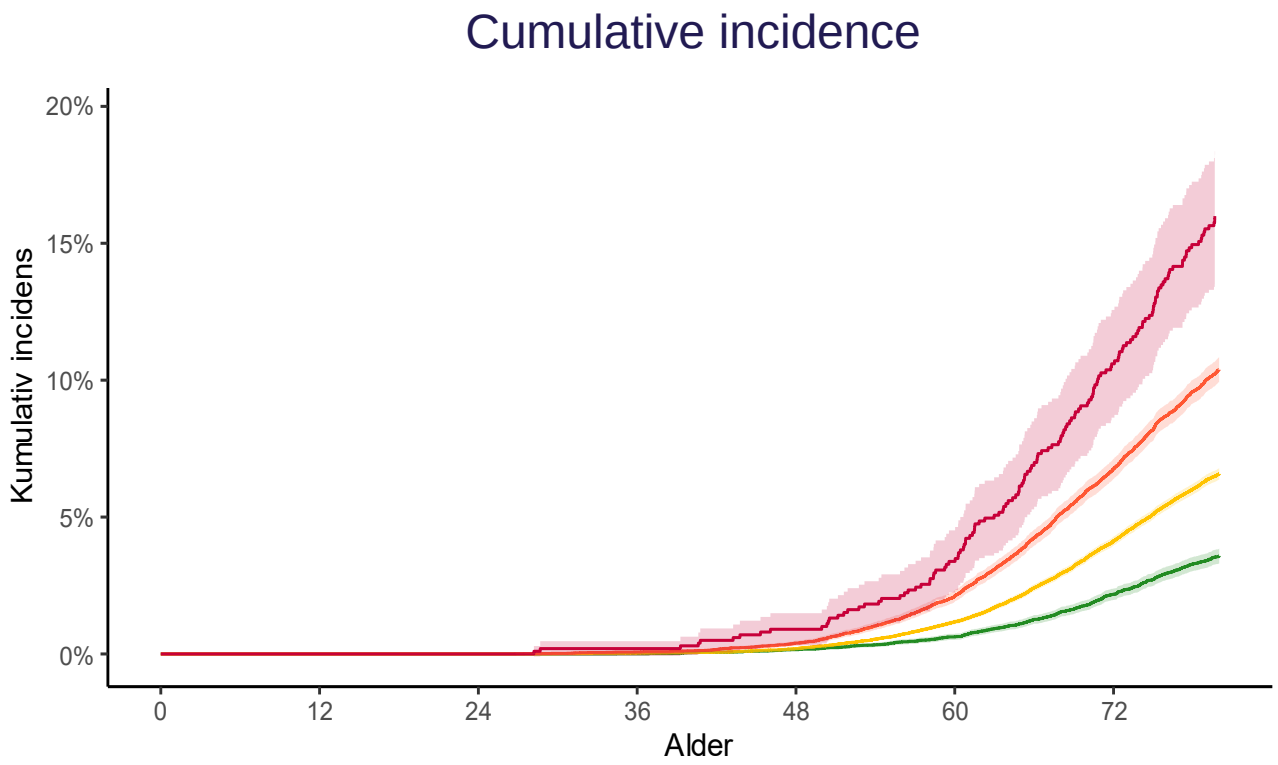
Individual 1	-1	+	0	-	1.5	+	2	=	**-0.5**
Individual 2	-0.5	+	1	-	0	+	0	=	**0.5**
Individual 3	-0.5	+	0	-	0	+	2	=	**1.5**



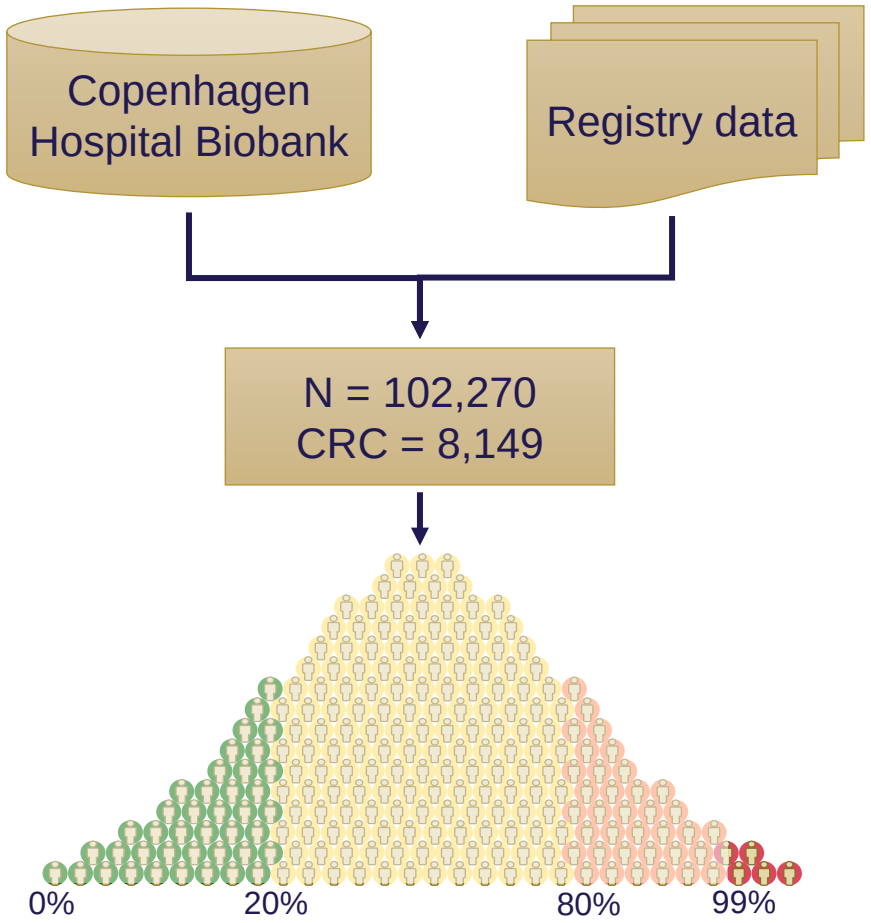
Why did I not use one of the new fancy LD-based methods?

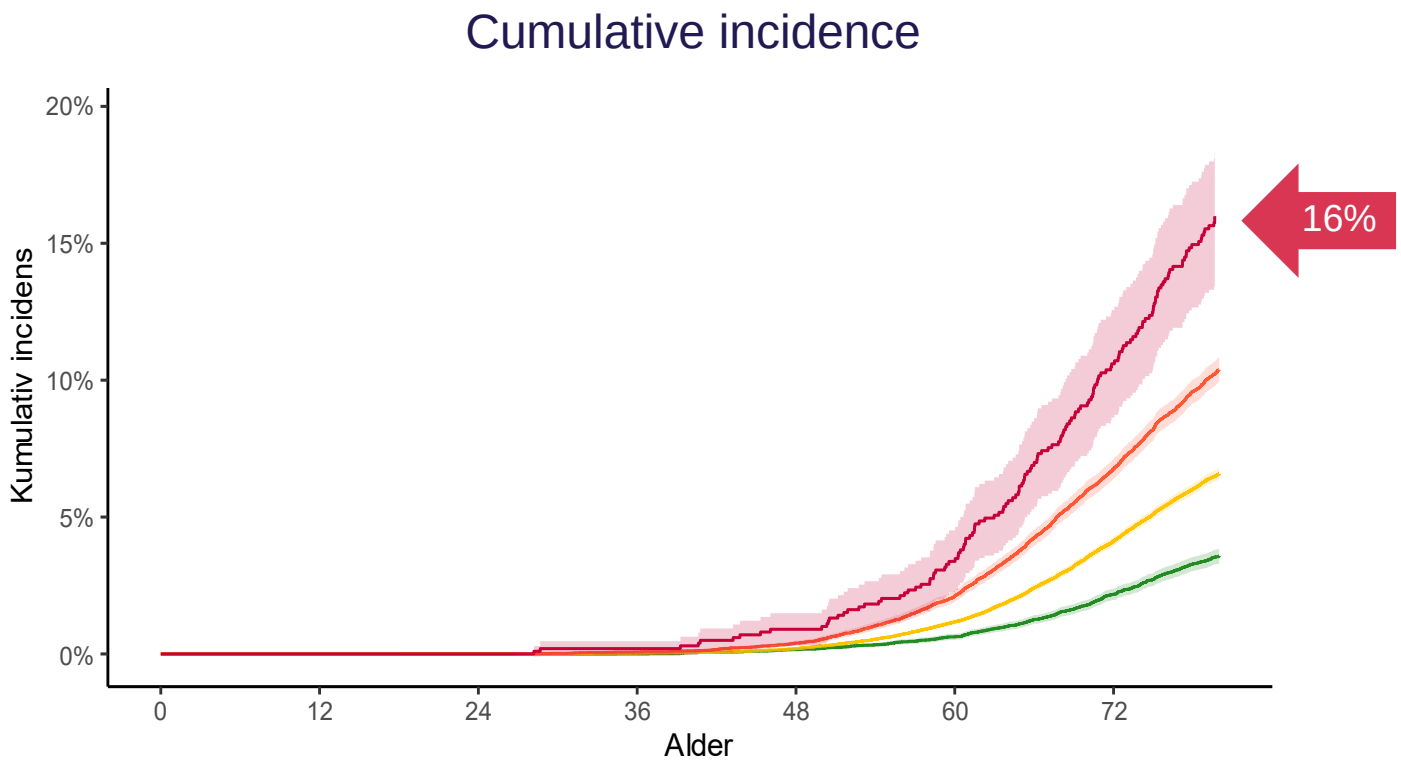
Preliminary results





Preliminary results





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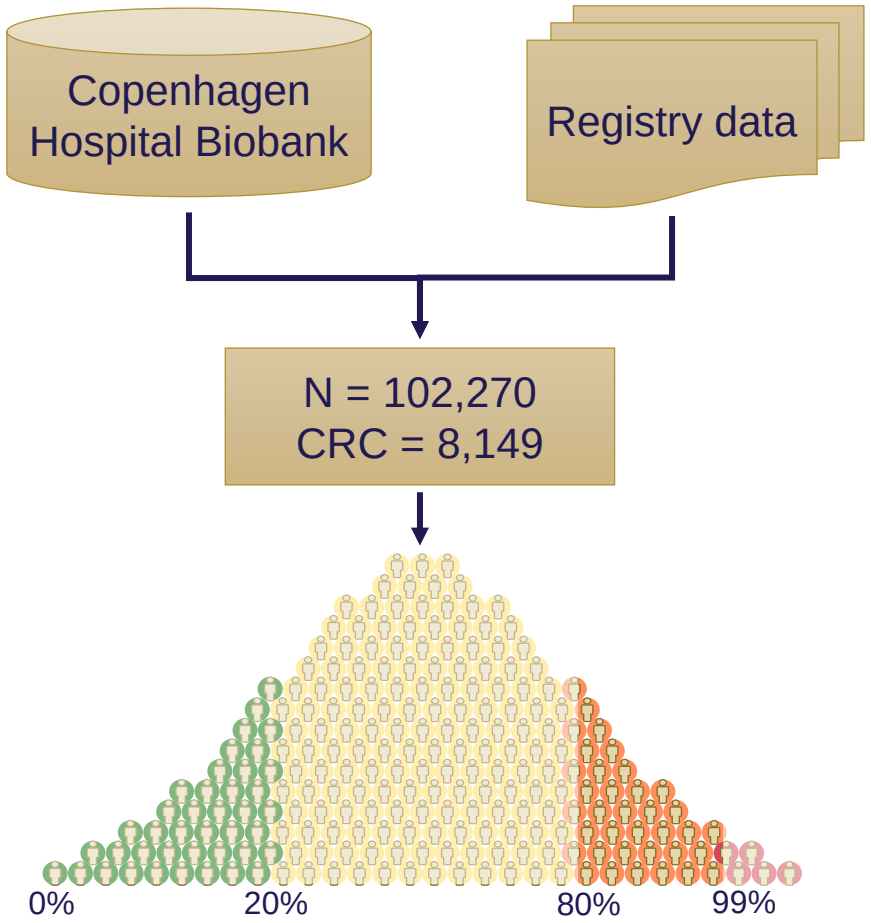

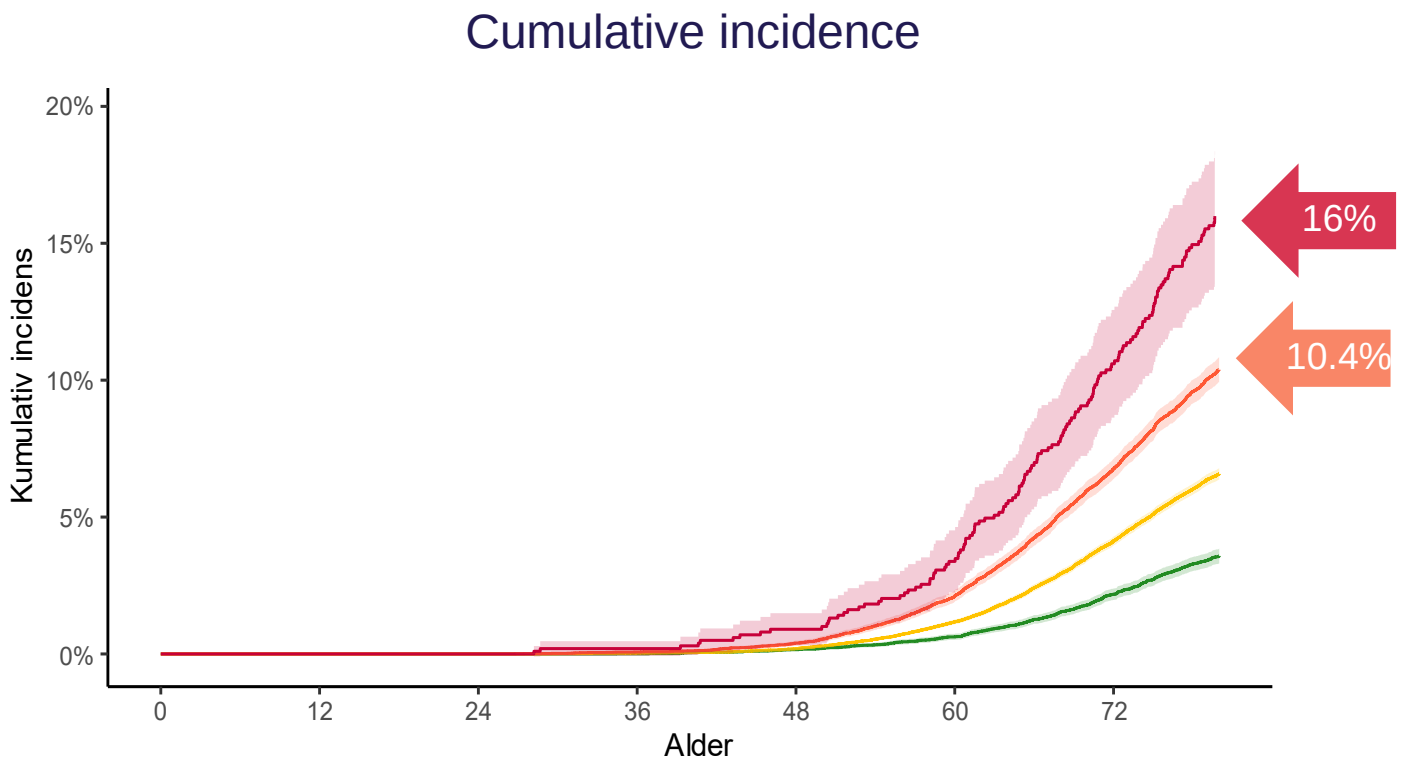

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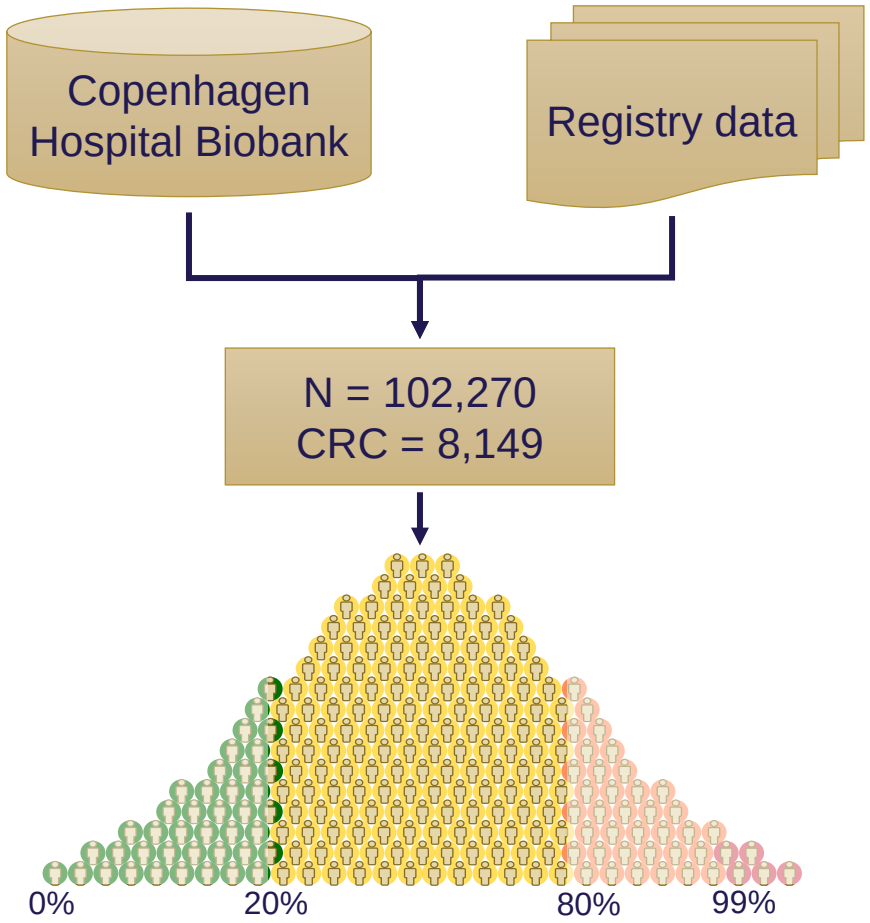

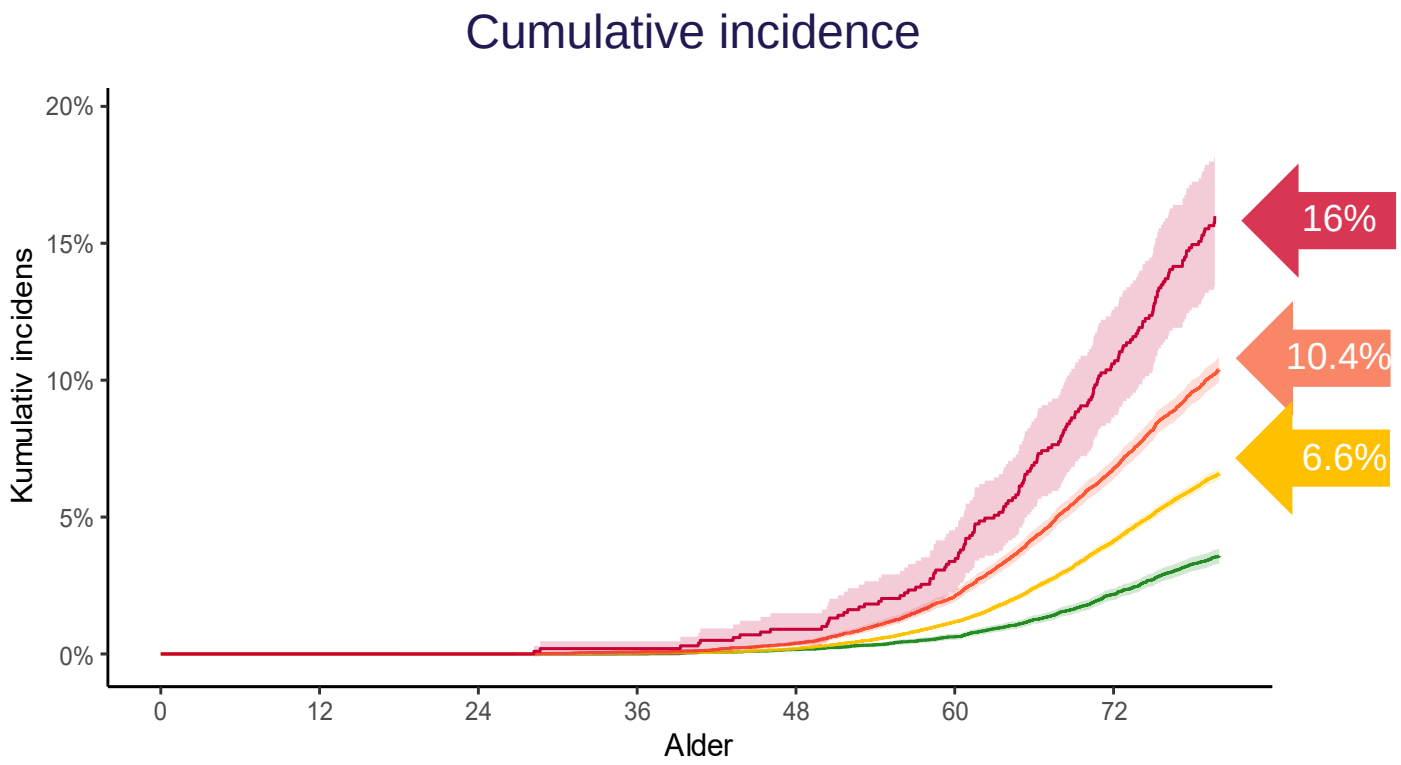

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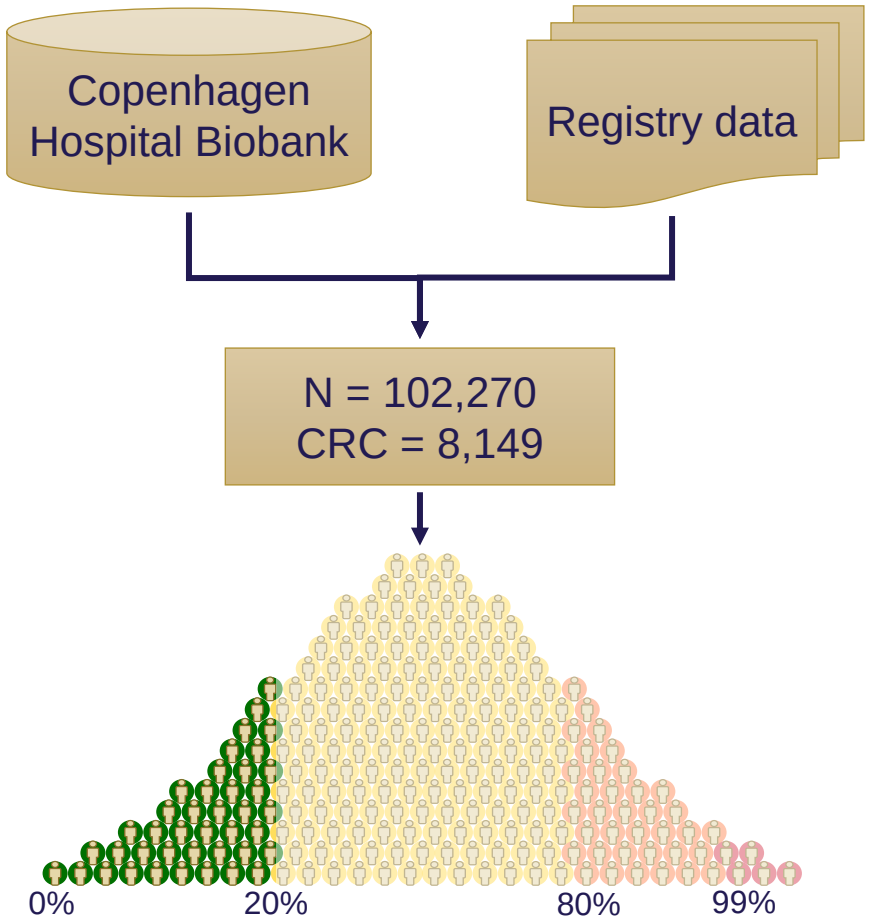

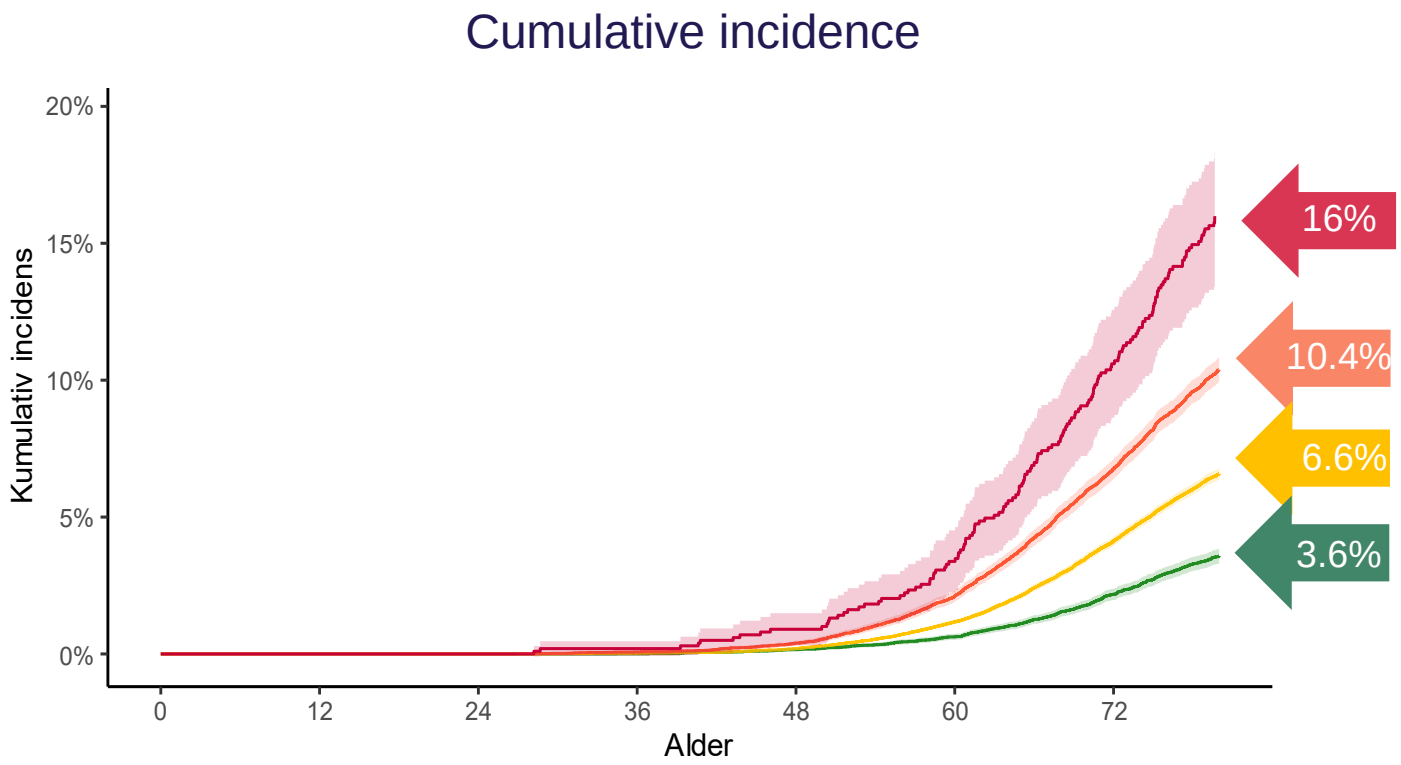

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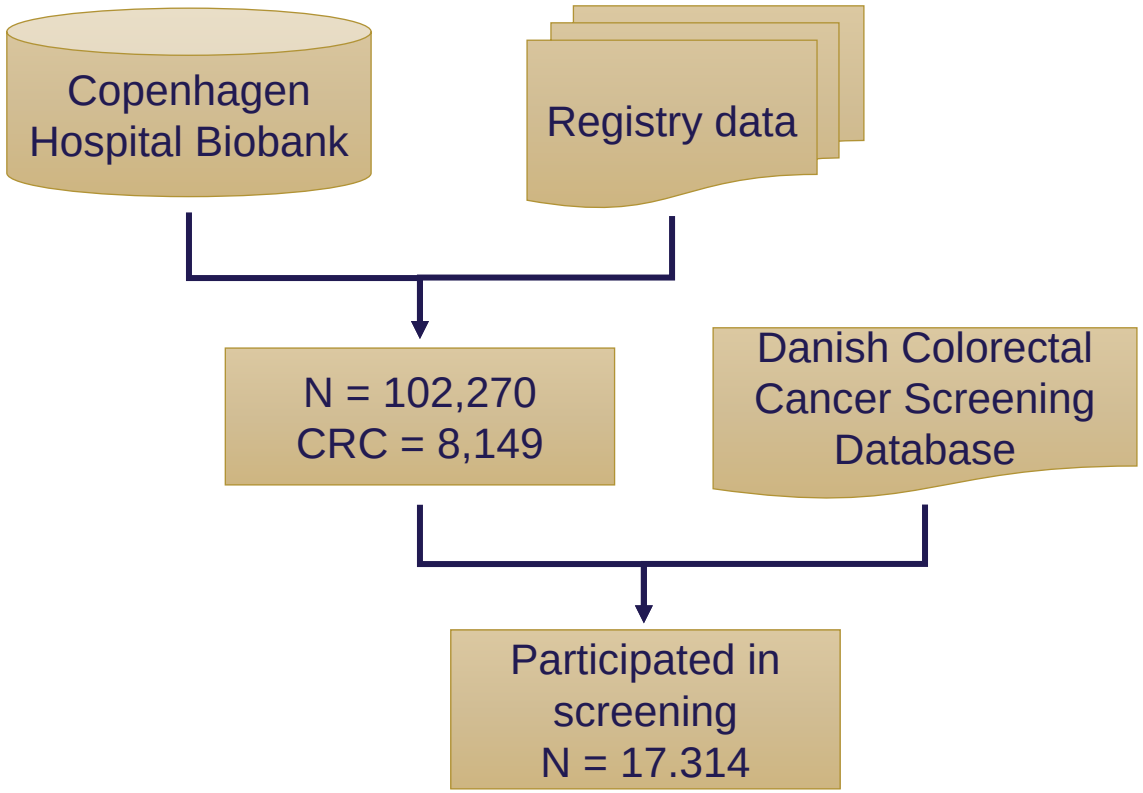
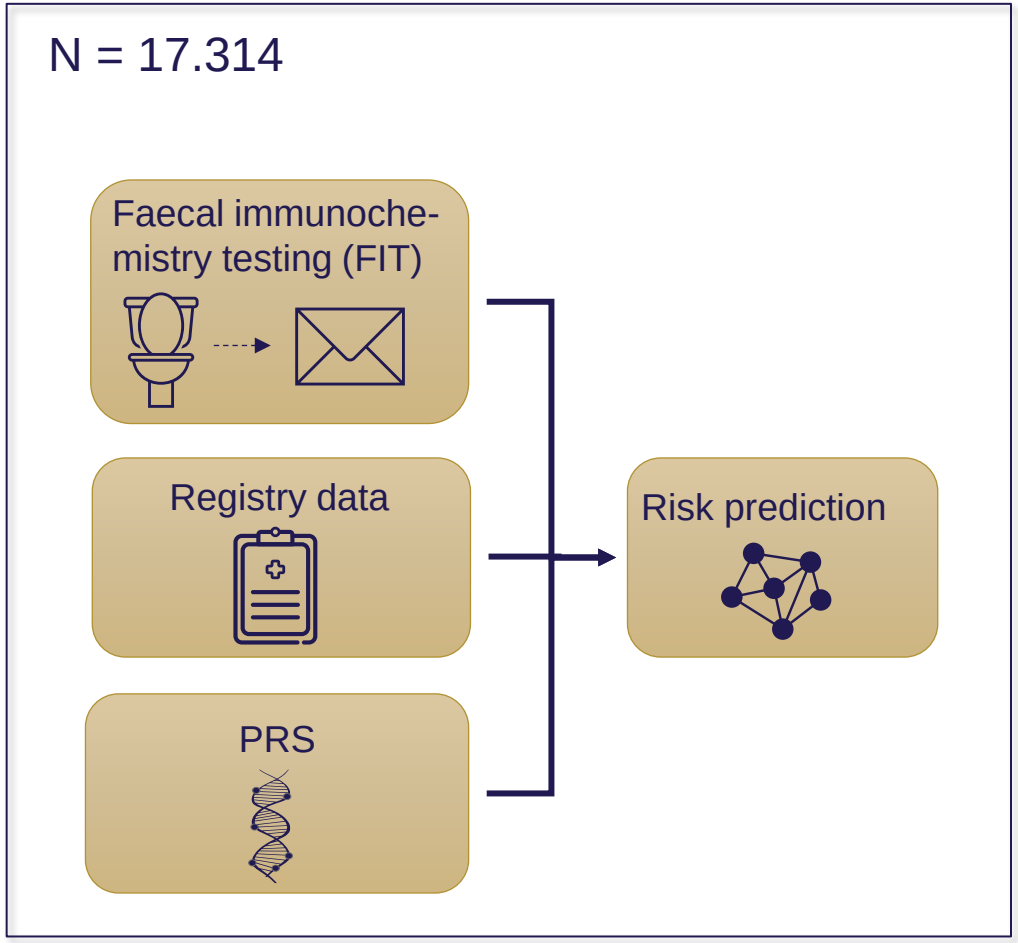
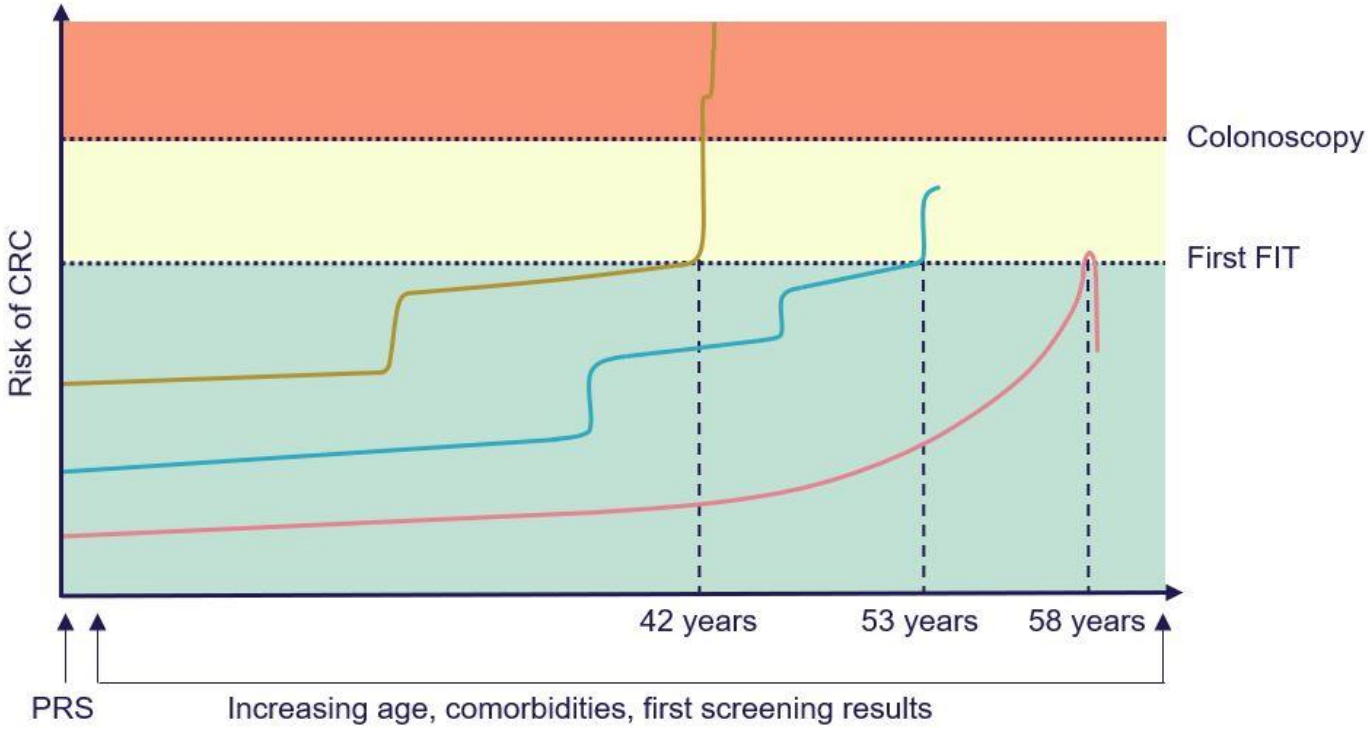




Dynamic risk prediction

- Using a unique Danish dataset including genetics and comprehensive registry data, we will develop and assess a personalized risk-based screening strategy to identify individuals at high risk across age groups



- Higher genetic risk from birth
- Diagnosed with hypertension at age 20
- Positive FIT screening at age 42
- Colonoscopy reveals CRC

- Moderate genetic risk from birth
- Diagnosed with hypertension and Type 2 diabetes
- Negative but moderately high FIT score at age 53
- Reinvited for screening after 2 years

- Low genetic risk from birth
- No clinical risk factors, but risk increases with age
- Negative FIT score at age 58
- Reinvited for screening after 6 years

What is your opinion on personal screening?

Exercise 2-6