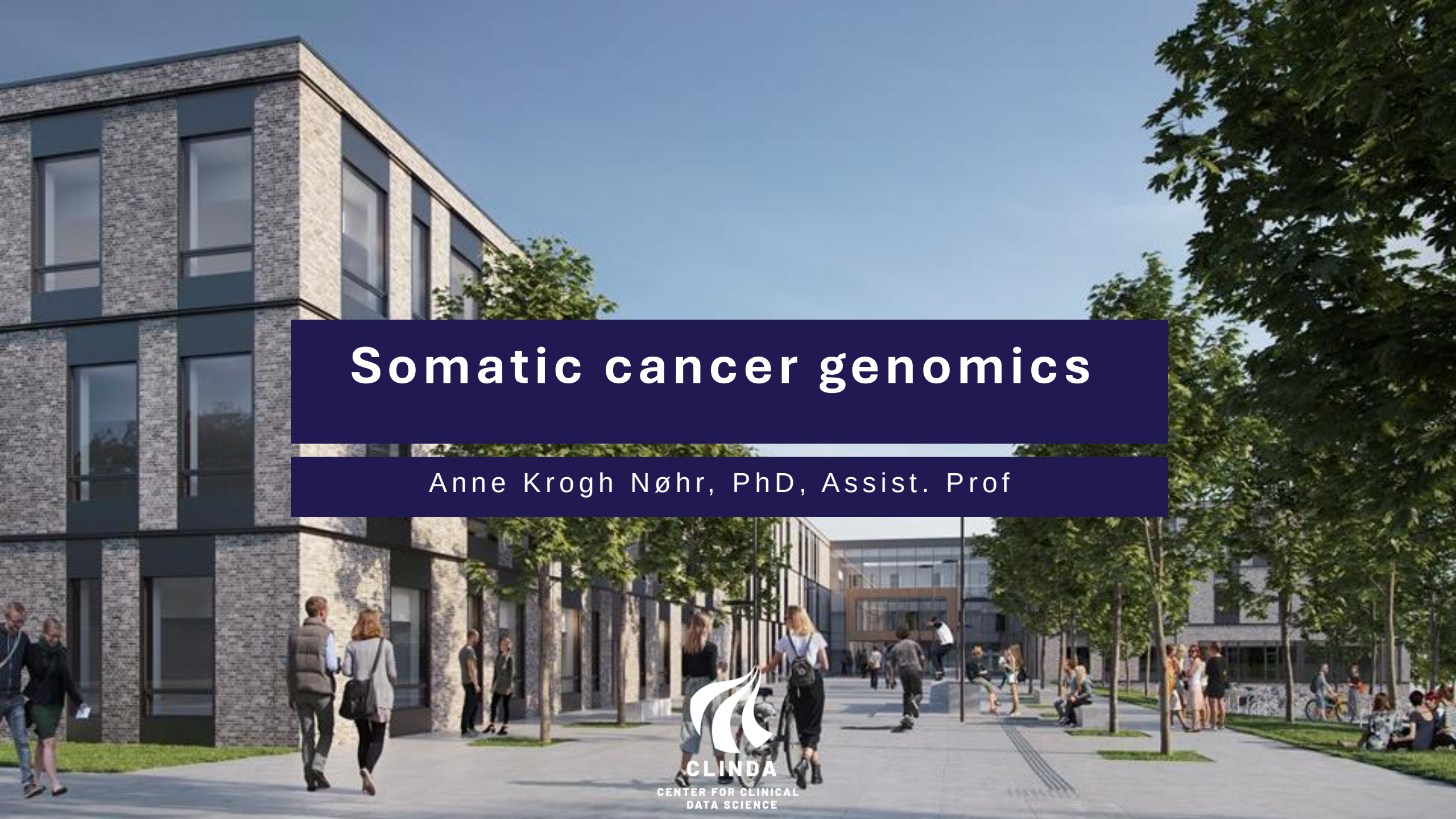

Somatic cancer genomics

Anne Krogh Nøhr, PhD, Assist. Prof

CLINDA
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Who am I?

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LETS GET STARTED

AGENDA

08:15 – 08:45	Recap [*Risk estimation from genome wide data*]
08:45 – 09:00	Lecture 1 [*Cancer Introduction*]
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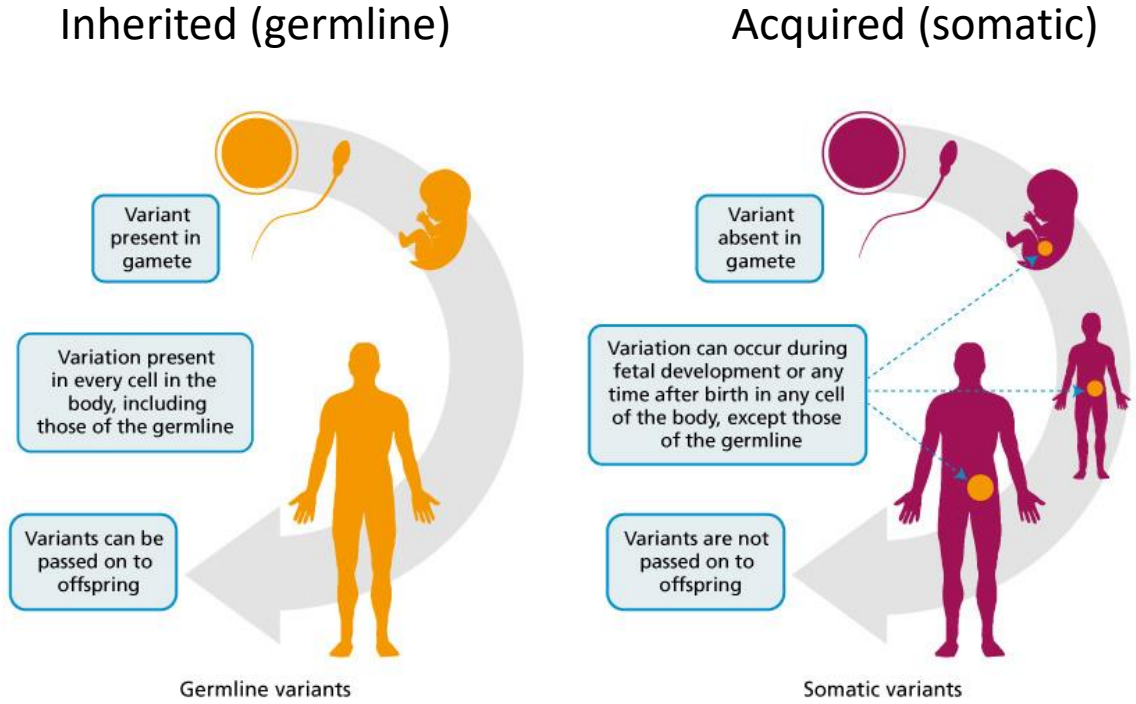
Why cancer genomics?

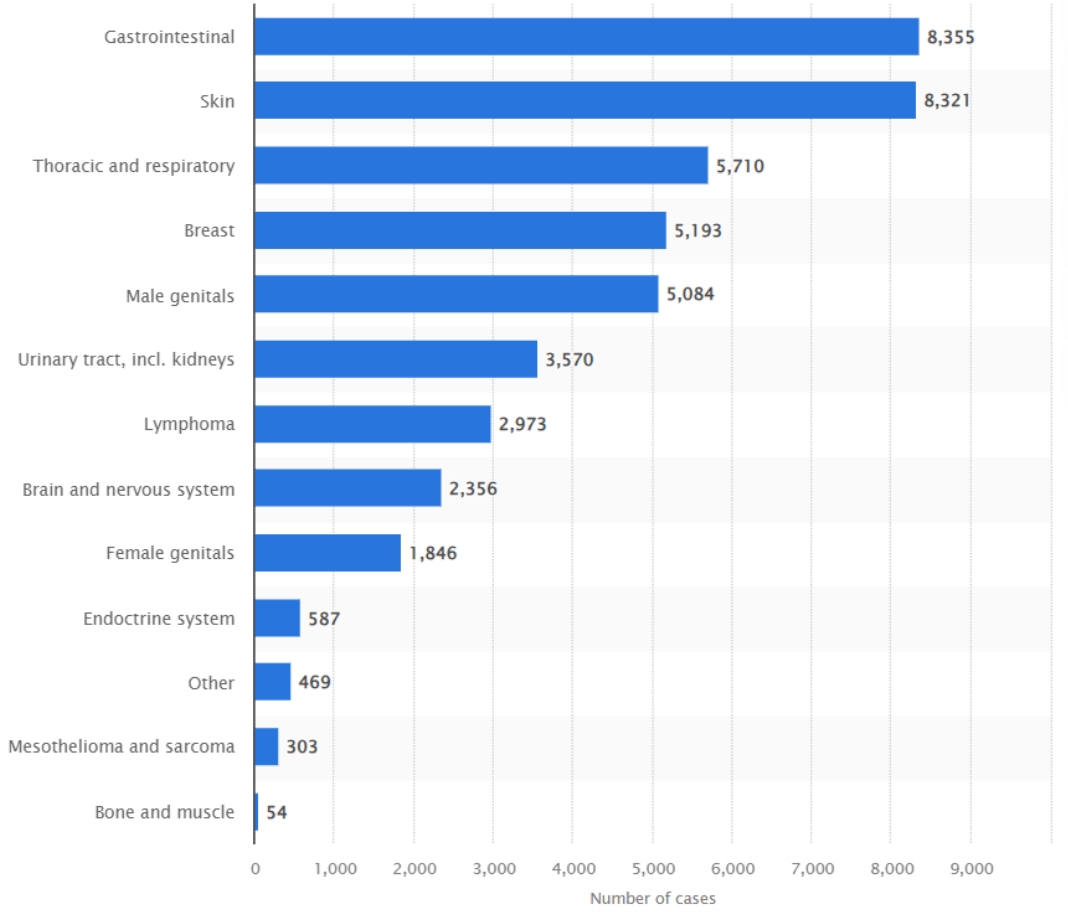
- Cancer affects millions of people worldwide
- Cancer is a disease of the genome
- Cancer is a Multifactorial disease
- Personalized medicine is already implemented in clinical practice



Introduction to cancer

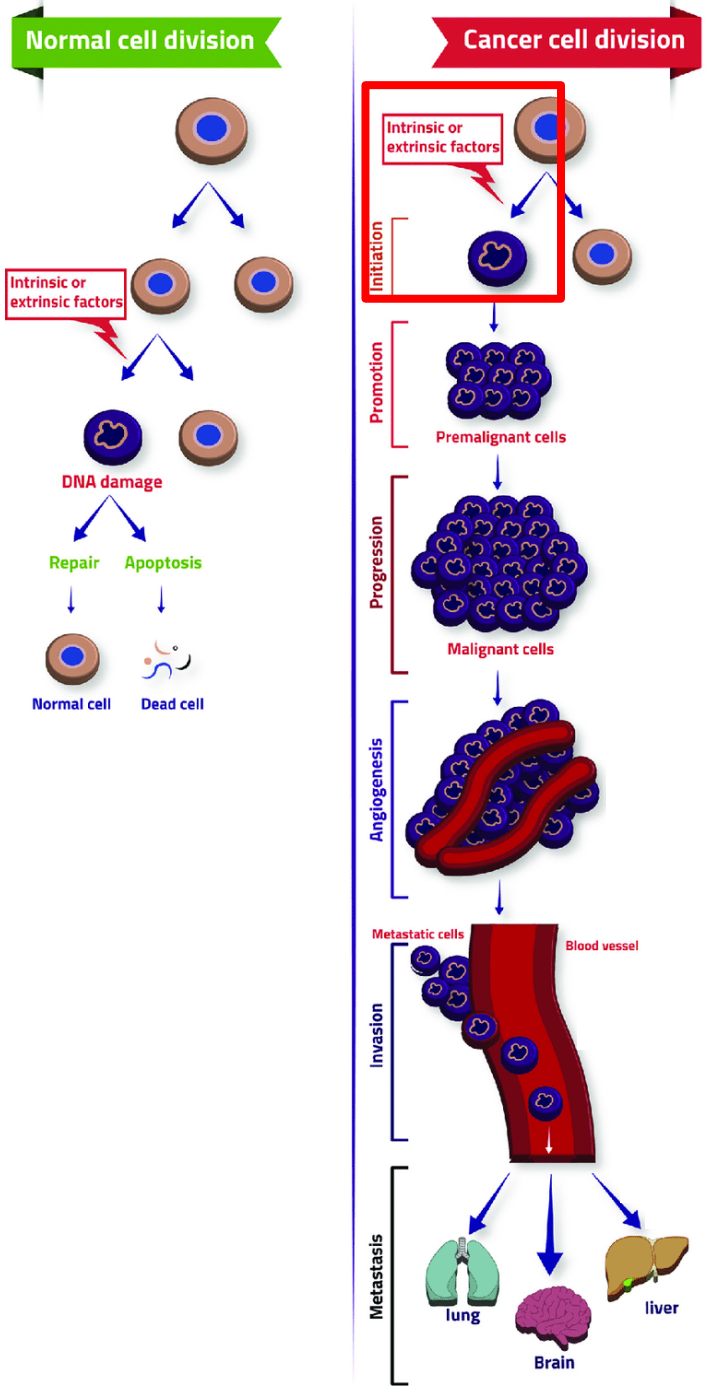
- Every third person in Denmark is diagnosed with cancer before turning 75.
- Two out of three have a family member suffering from cancer.
- In 2022, 47,755 people were diagnosed with cancer in Denmark.
- In 2023, the number had risen to 48,372.

Number of new cancer cases in Denmark in 2022 by cancer type



Cancer is a genetic disease

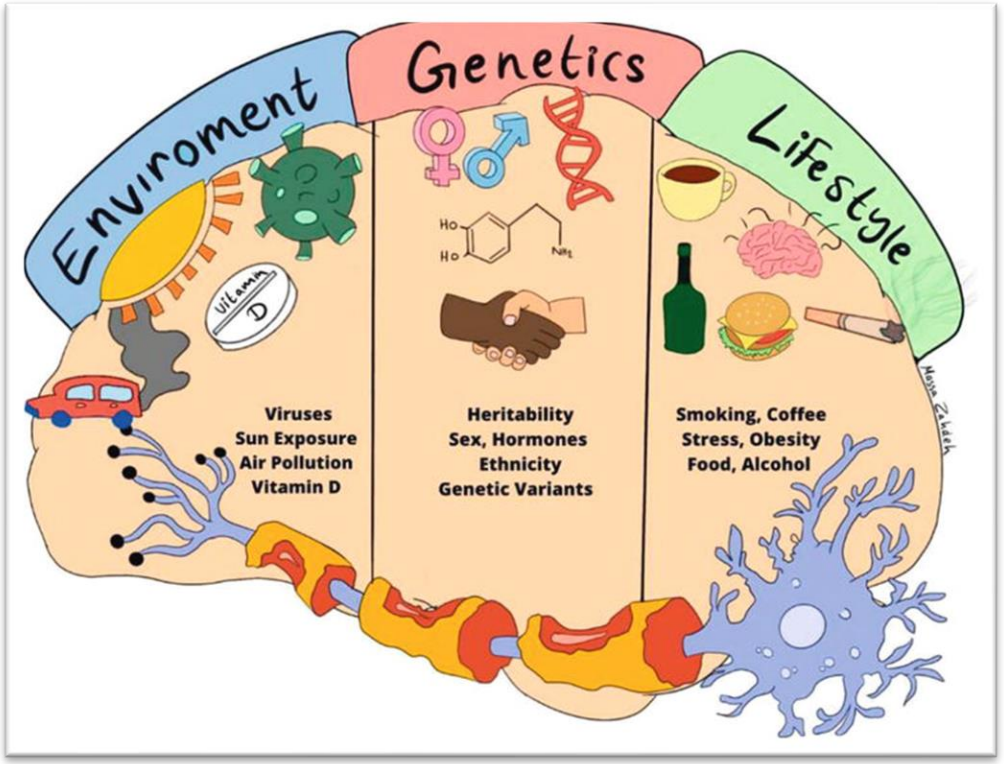
- A group of diseases caused by uncontrolled growth of abnormal cells.
- The DNA in a human cell undergoes thousands to a million harmful events per day.
- Normal Cell Division
  - In case of cellular damage, the cell undergoes repair or apoptosis.
- Cancer Cell Division
  1. Initiation: Cellular damage → 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:

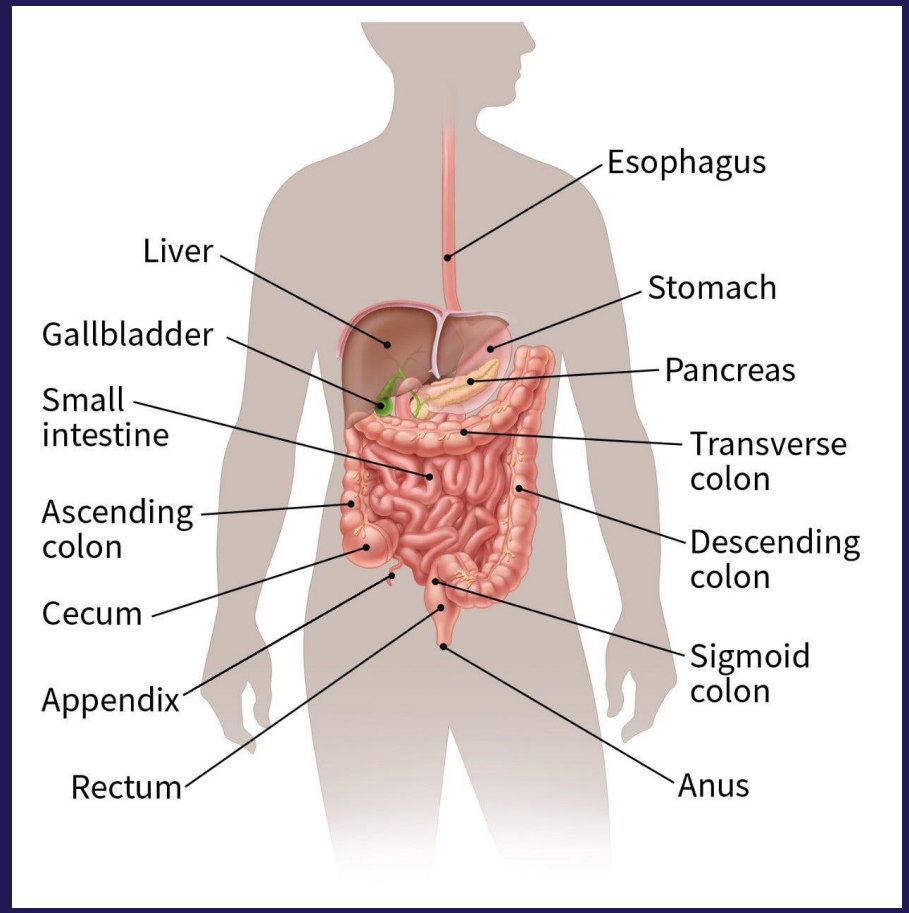
- Environmental factors - epidemiological studies
- Random mistakes made during normal DNA replication
- Inherited - twin studies and GWAS



Colorektal cancer

Disease characteristics

- Third most common cancer worldwide
- Lifetime risk is about 1 in 24 for men and 1 in 26 for women
- A type of cancer that affects the colon (large intestine) or rectum
- Common symptoms include:
  - often no symptoms in the early stages
  - blood in the stool (rectal bleeding)
  - abdominal cramps, pain or bloating that won't go away
  - unexplained weight loss
- The incidence and impact of colorectal cancer have been significantly reduced by early diagnosis through screening



Colorektal cancer

Environmental factors

- Low intake of calcium and vitamin D (protective effect)
- Pollution and chemicals
- Smoking
- Alcohol consumption
- Obesity
- Diet high in red meat and low in fiber, fruits, and vegetables

Genetic factors

- Common variants
  - SNP-Heritability ~ 12% (MAF >1%)
  - 205 SNPs
- Rare variants
  - Heritability ~ 10% (MAF <1%)
  - 2-5% are inherited as autosomal dominant, high-penetrance syndromes (lynch syndrome often MSH2-gene)

Group work 1: Disease characteristics, environmental factors, and genetic factors

You will be divided into 4 groups, with each group assigned one of the following four cancers: breast cancer, melanoma, lung cancer, or Non-Hodgkin lymphoma.

For your assigned cancer, you should describe:

- Disease characteristics
- Environmental factors
- Genetic factors

Use your computer to research the information and write it down on a piece of paper to display on the wall. Drawings are welcome! ☺

Each group will give a 5-minute presentation on their assigned disease.


BREAK

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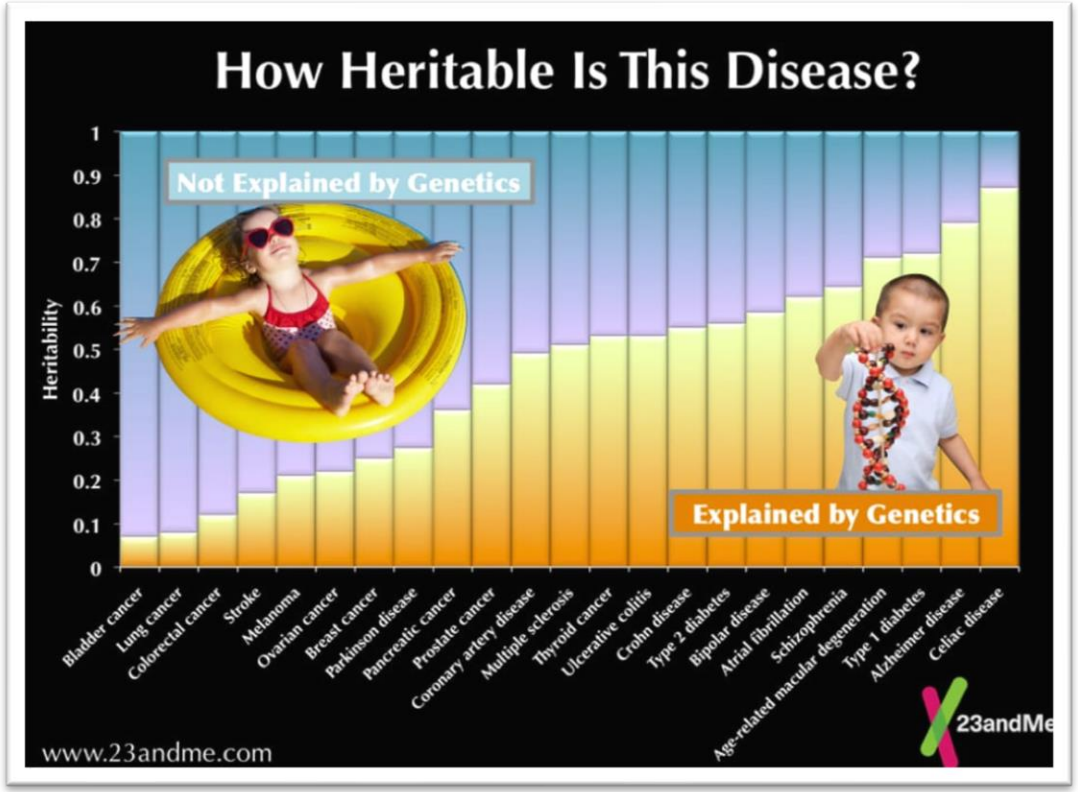
Take home messages

Common features of all cancers:

- Caused by uncontrolled growth of abnormal cells
- Multifactorial

How cancers differ:

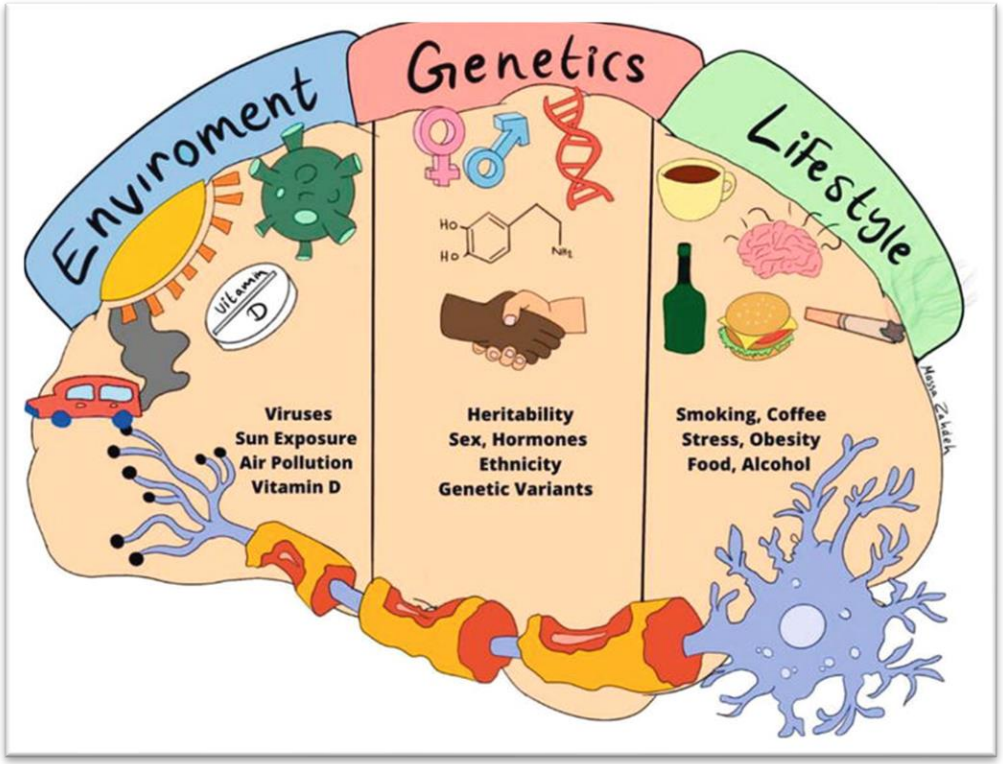
- Environmental factors
- Heritability
- Common variants
- Rare variants



What cause cancer?

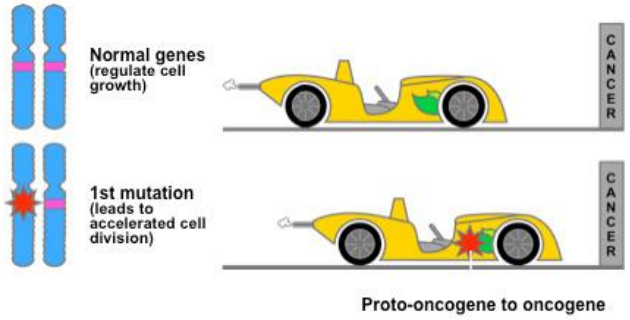
Mutations caused by:

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

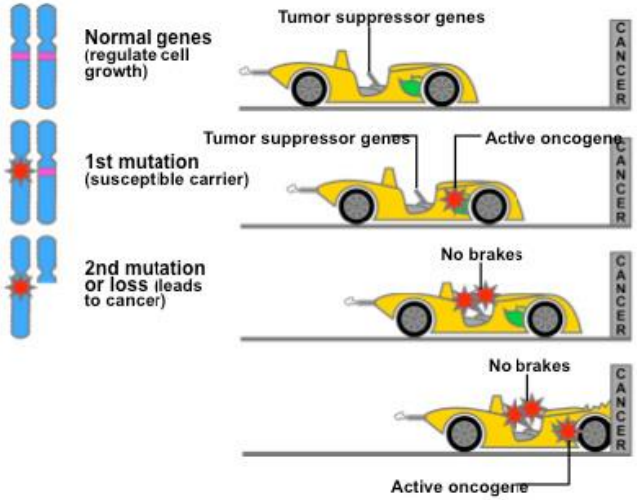


Three major classes of cancer-causing genes

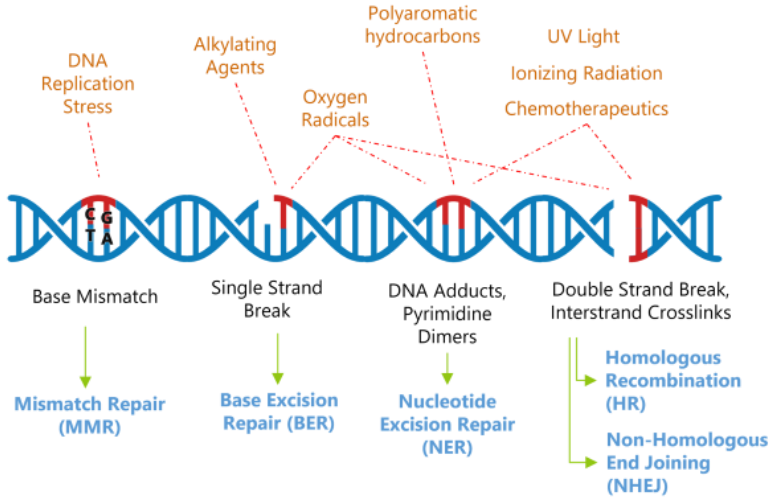
Oncogenes:
The bad guys, turn on unregulated growth (gas pedal)



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



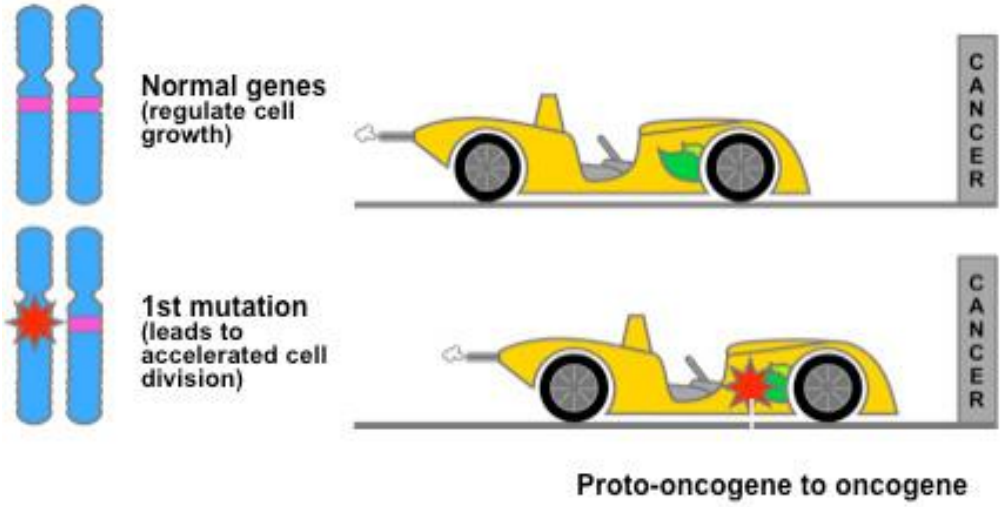
DNA repair genes:
More good guys- repair genes



Oncogenes

- Normal function: Pronto-oncogenes promotes cell growth and cell devision
- Mutation: Dominant - Only a single copy of a mutated oncogene is required. Turns pronto-oncogenes to oncogene
- Effect: Gain of function

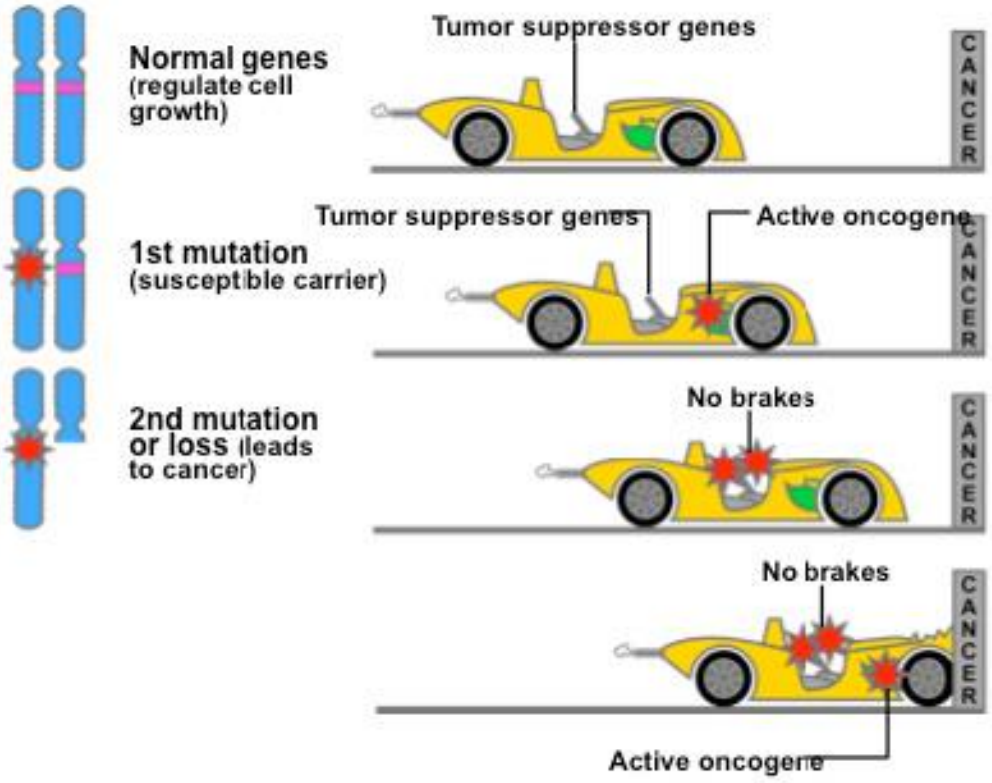
The bad guys, turn on unregulated growth (gas pedal)



Tumor suppressor genes

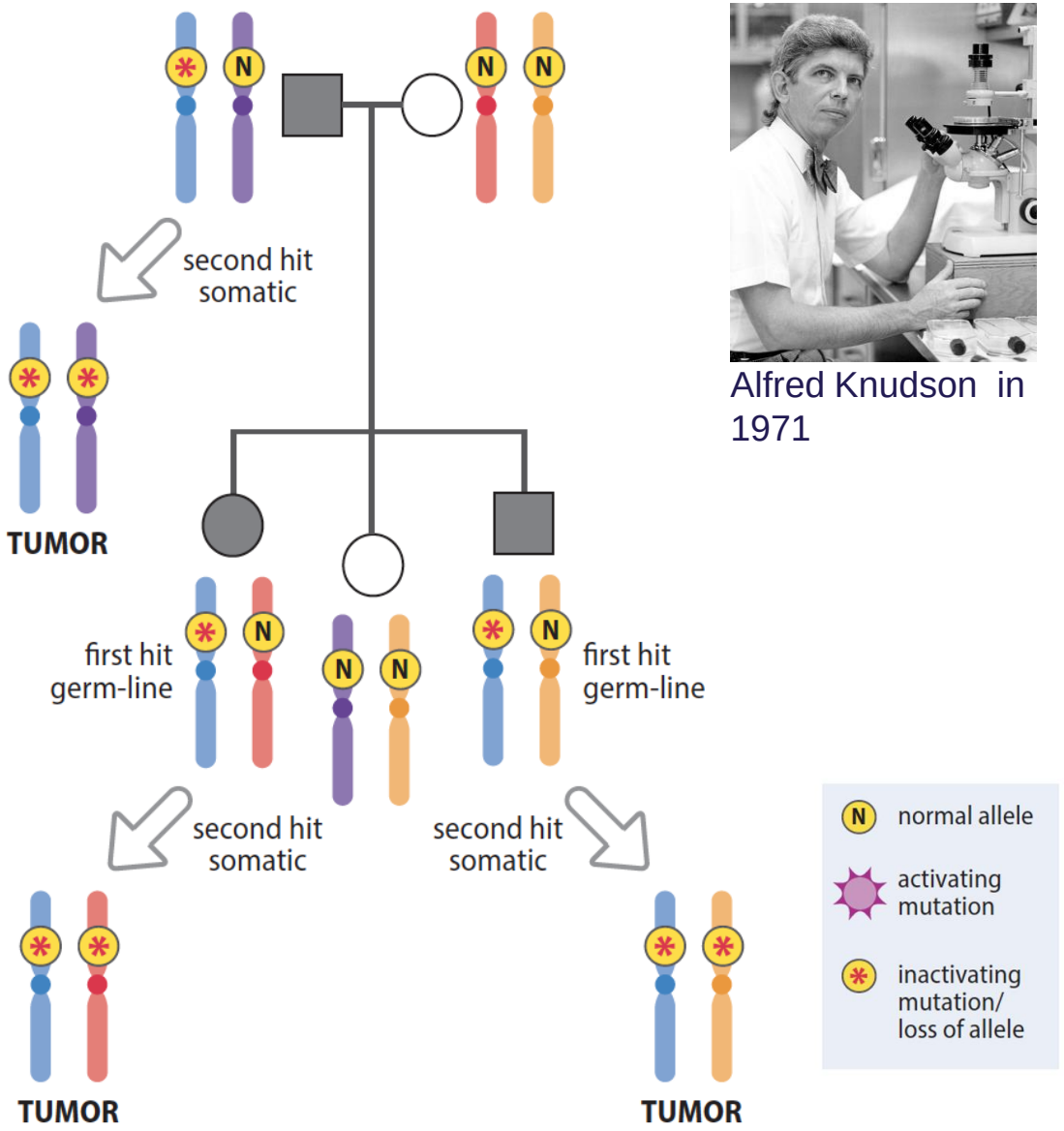
- Normal function: Regulates cell growth, cell division, induce apoptosis, and DNA repair mechanisms
- Mutation: Recessive on the cellular level - both copies of the gene inactivated
- Effect: Loss of function

The good guys, control cell division (brake pedal)



Knudson's two-hit teori

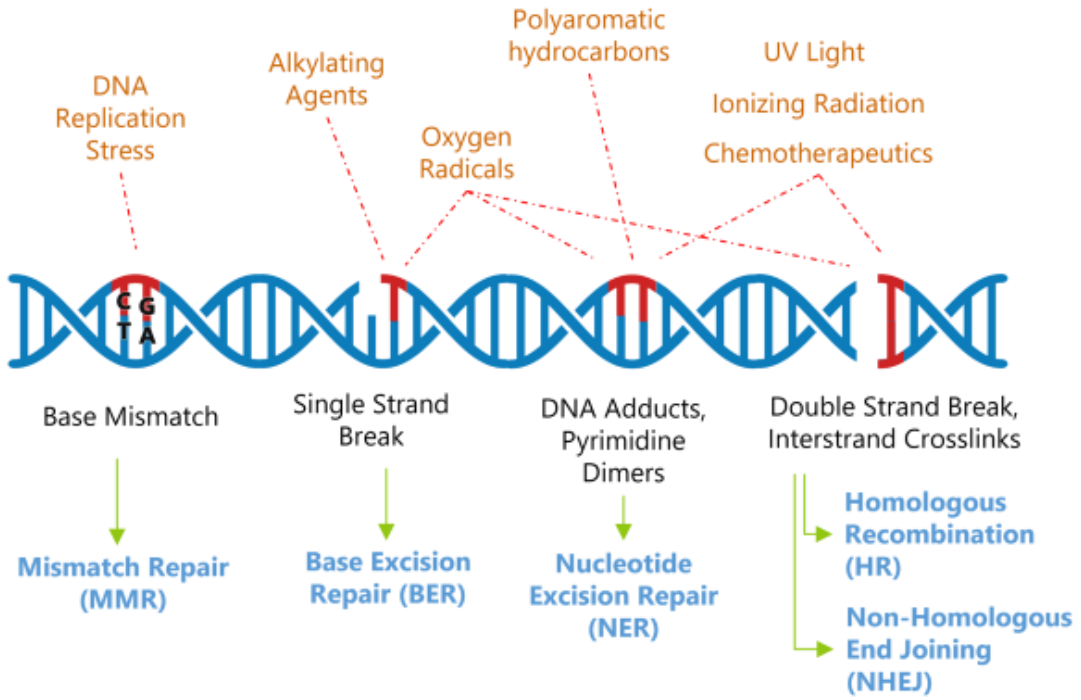
- Most of our current knowledge of tumor suppressor genes originates from Knudson's work on eye cancer:
  - Inherited: usually affects both eyes and often an affected parent – dominant
  - Sporadic: usually affects one eye and no affected parents
  - Originally found in the RB1 gene
- Knudson's two-hit teori: Two hits/mutations are required
- Tumor suppressor genes: dominant at individual level, recessive on the cellular level



Alfred Knudson in 1971

DNA repair genes

- Is often classified as a tumor supressor gene
- E.g. BRCA1 and BRCA2
- In hereditary cancers, loss of DNA repair genes can lead to genome instability
- Genomic instability: The increased tendency for somatic mutations and other genetic changes to occur during cell division.



Take three minutes to discuss with your neighbor:

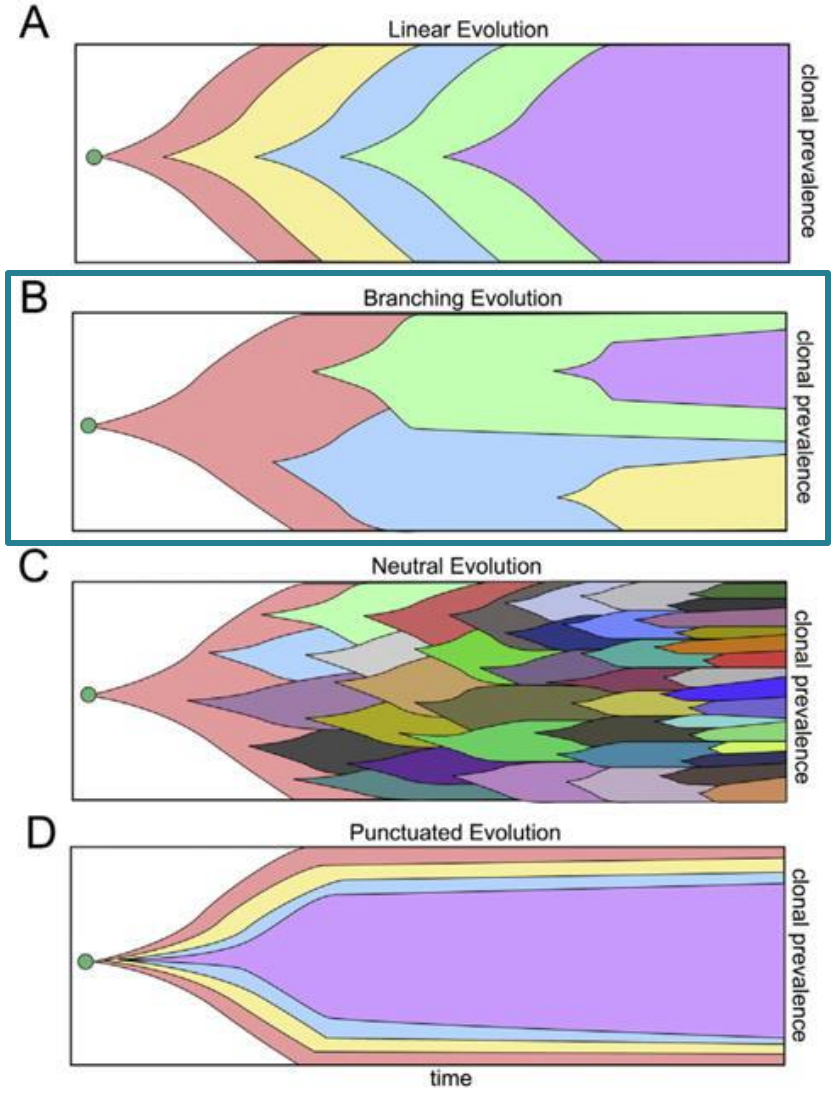
1. What is an oncogene?
2. What is a tumor suppressor gene?

Take three minutes to discuss with your neighbor:

1. Do you expect to find tumor suppressor genes or oncogenes in families with a genetic predisposition to cancer?
2. And why does the other type of genes not predispose?

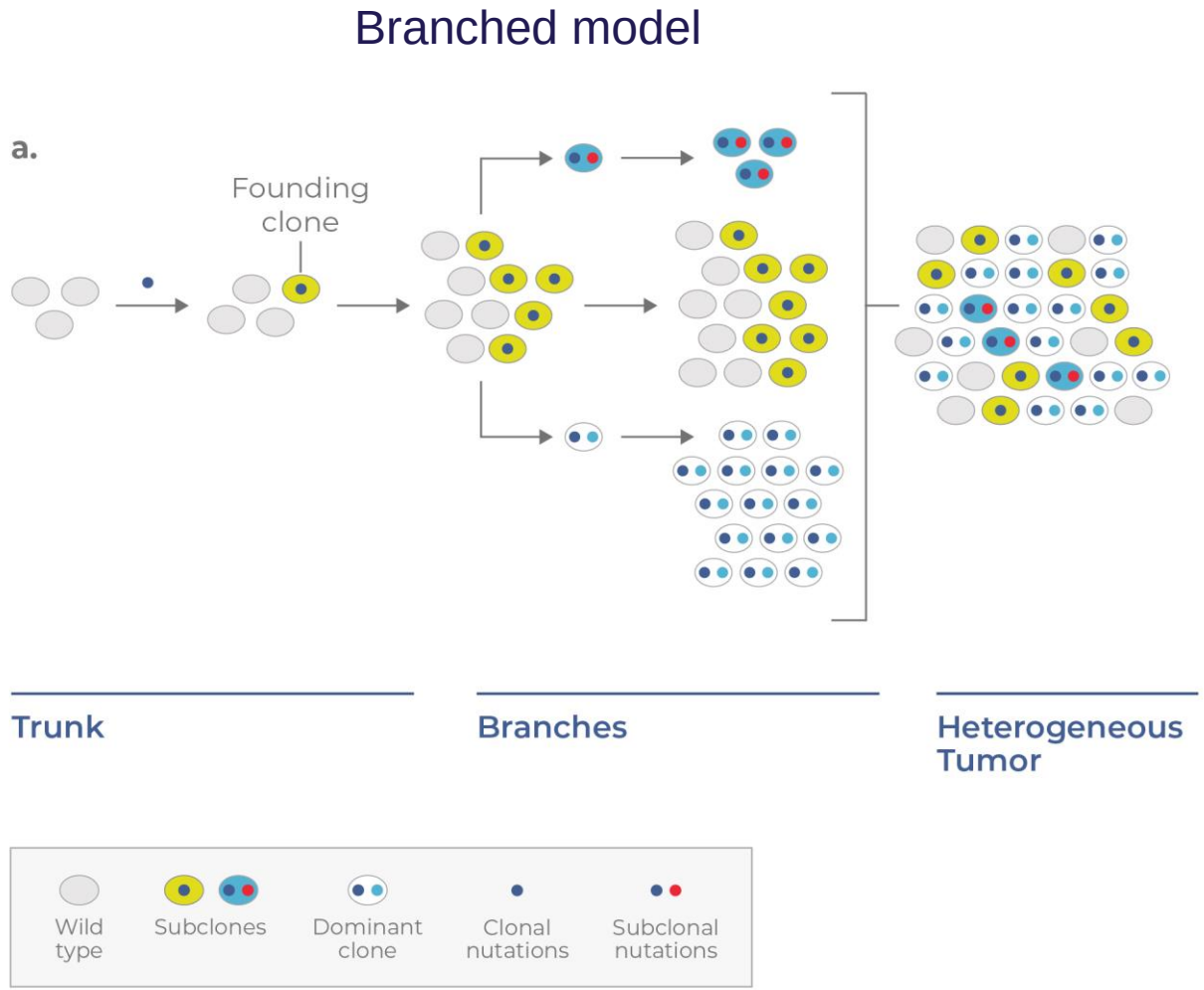
Clonal evolution drives tumor heterogeneity

- **Clonal evolution**: A process that describes how cancer develops, becoming more aggressive and difficult to treat over time through multiple mutations and selection.
- **Challenging to study** – difficult to collect longitudinal samples.
- There are several competing models of tumor evolution: **linear, branched, neutral, and punctuated**.
- Literature supports a **branched model** for point mutations and a **punctuated model** for copy number variation.



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.



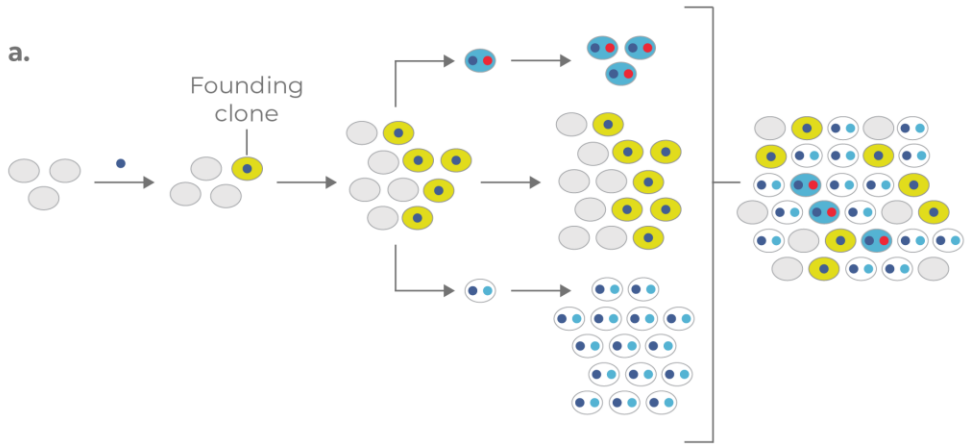
Driver mutations

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

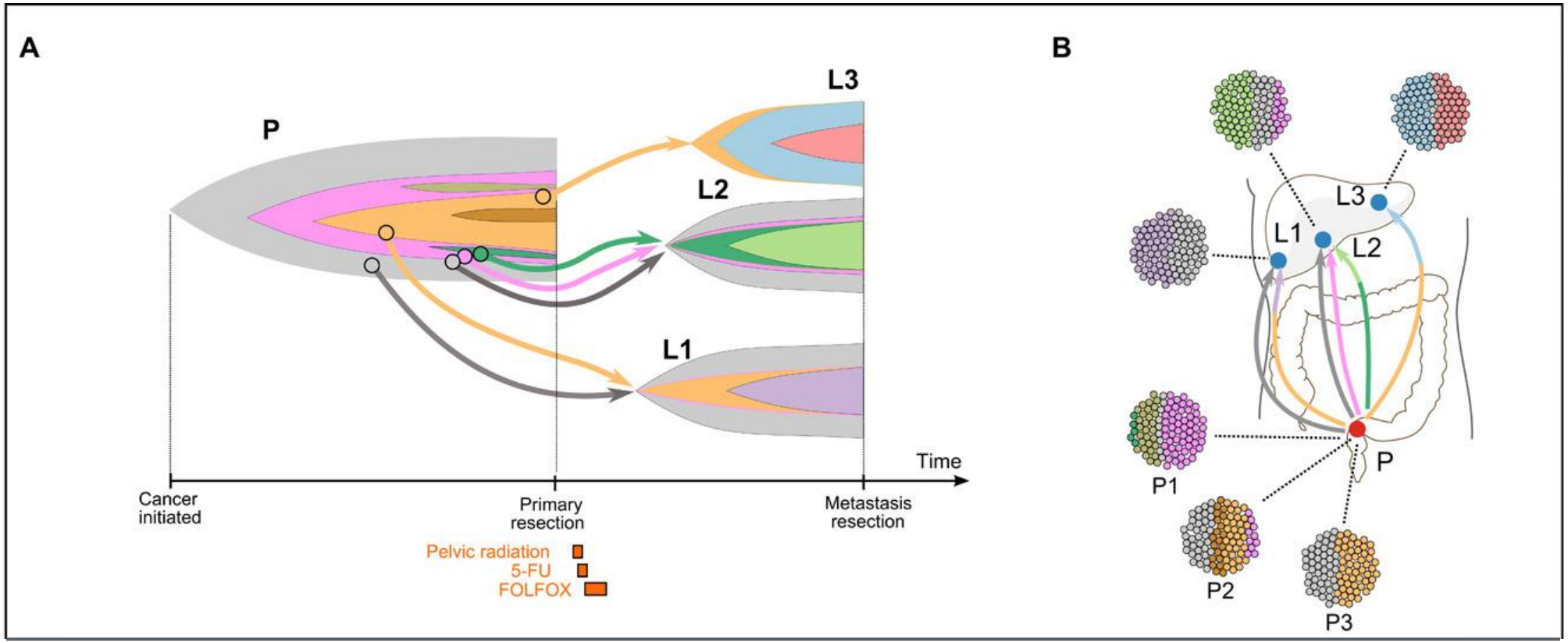
- Cancer genomes contained 4–5 driver mutations.
- In around 5% of cases no drivers are identified.

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

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



From primary tumor to metastases



(P, primary rectum cancer; L, liver metastasis) https://www.science.org/doi/10.1126/sciadv.aay9691

Driver mutations – what do we know?

- Frequency of somatic CNVs and the frequency of somatic SNVs were inversely correlated across 12 cancer types.
- In breast and ovarian cancer - predominantly CNVs.
- In kidney cancer, glioblastoma, acute myeloid leukemia, and colorectal cancer - predominantly SNVs.
- Translocations and inversions are [illegible] of all cancer cases.
- SNPs, even though they may be [illegible] based cancer risk, are not typically considered drivers.

More info next monday

→ Driver mutations varies between cancer types and between samples within the same cancer type.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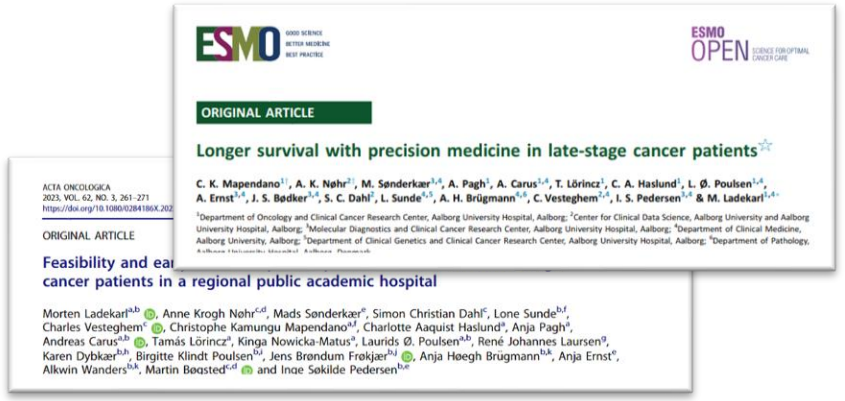
Precision medicine program at Aalborg University Hospital

Patients are from the ongoing Proseq Cancer trial

- Started in June 2020
- Aims to assess the value of precision medicine in patients with advanced and incurable malignancies
- Based on in-house whole exome sequencing (WES) and RNA sequencing
- Presented weekly at a National Molecular Tumor Board (NMTB) for discussion of targeted treatment.



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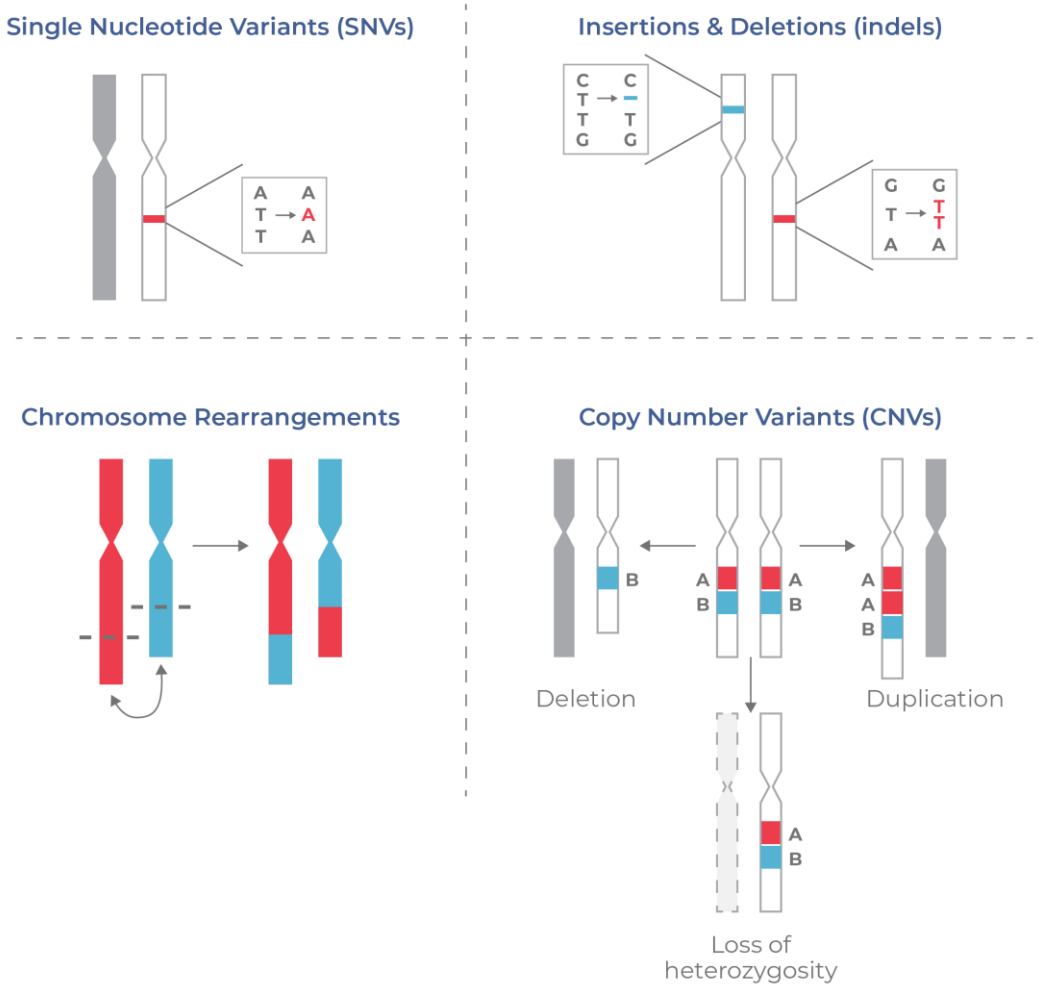
How can we detect somatic mutations

Whole exome sequencing (WES)

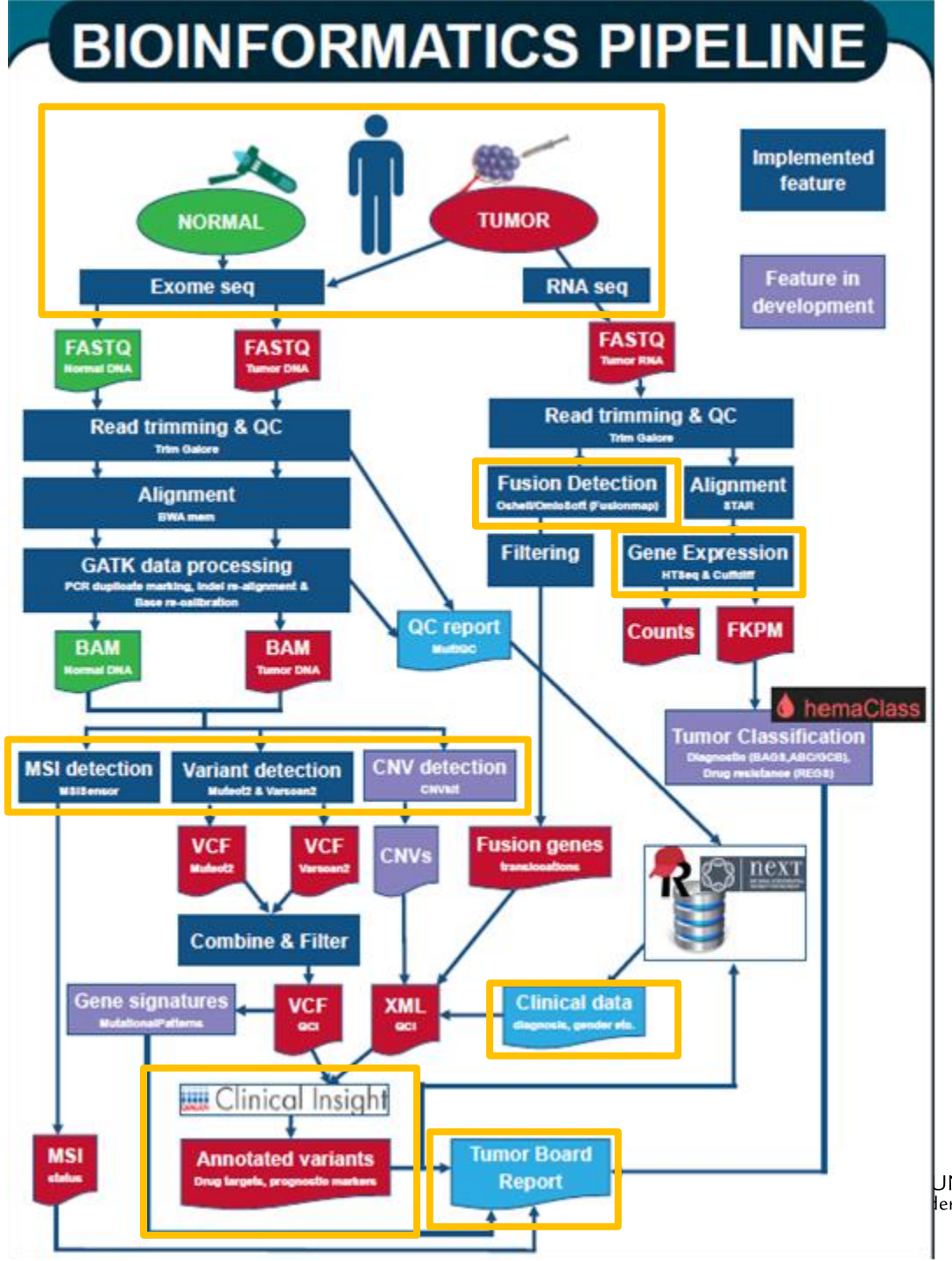
- Single nucleotide variants (SNV)
- Indels
- Copy number variants (CNV)

RNA sequencing (RNAseq)

- Gene expression
- Gene fusion: hybrid gene formed from two previously independent genes. Fusion genes are often oncogenes.



Bioinformatic pipeline for sampels



> Cancers (Basel). 2020 Jan 29;12(2):312. doi: 10.3390/cancers12020312.

Development of a Precision Medicine Workflow in Hematological Cancers, Aalborg University Hospital, Denmark

Julie S Bødker [1], Mads Sønderkær [1], Charles Vesteghem [1 2], Alexander Schmitz [1], Rasmus F Brøndum [1], Mia Sommer [1 2 3], Anne S Rytter [1], Marlene M Nielsen [1], Jakob Madsen [1], Paw Jensen [1], Inge S Pedersen [2 4], Lykke Grubach [5], Marianne T Severinsen [1 2], Anne S Roug [1 2], Tarec C El-Galaly [1 2], Karen Dybkær [1 2], Martin Bøgsted [1 2]

FULL TEXT LINKS

FULL TEXT MDPI

PMC Full text

ACTIONS

Cite

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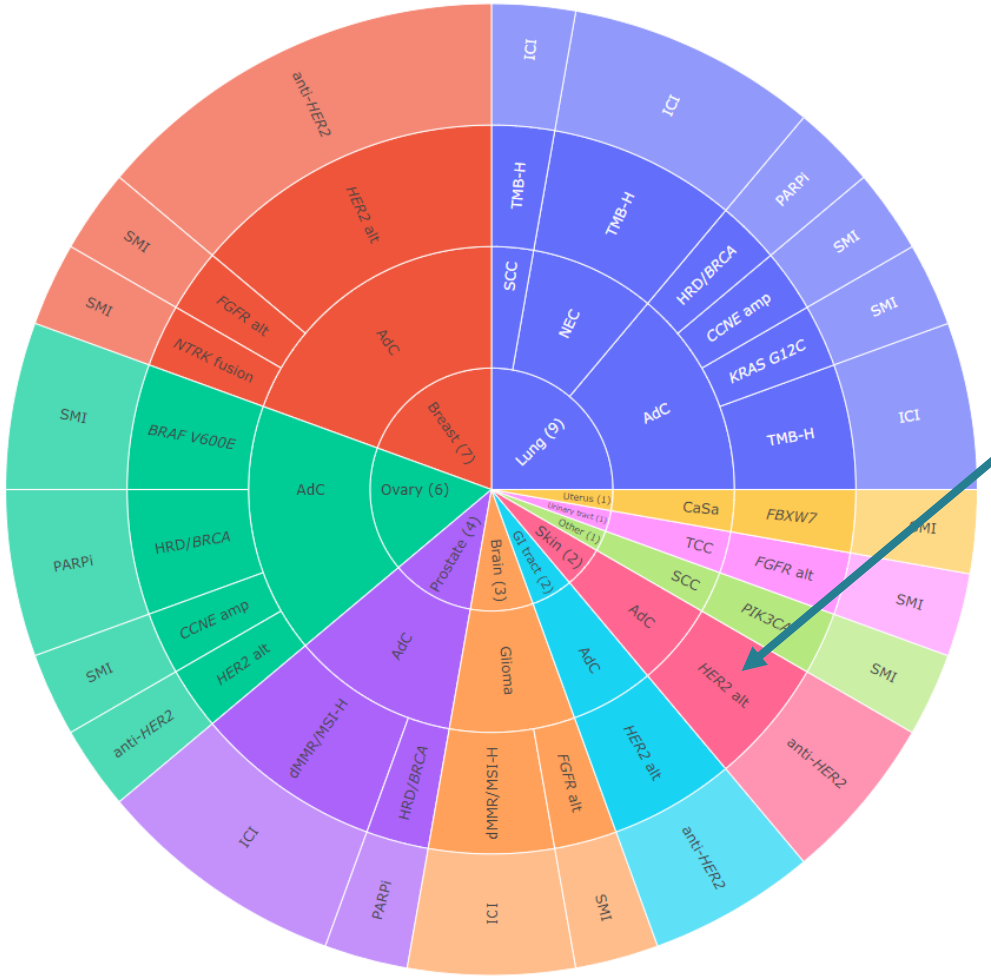
Figure 1: Overview of the bioinformatic pipeline for processing of whole exome and RNA sequencing in the Haematological Relapse Project (ProSeq). QCI Interpret is used to support classification in regards to pathogenicity and clinical relevance of detected genomic variants. These are evaluated in the context of published biomedical literature, professional association guidelines, publicly available databases, annotations, drug labels, and clinical trials. Genomic data results will be stored in a precision cancer medicine database potentially enabling results to be shared with other hospital organizations and the scientific community.

Druggable targets in personalized medicine



HER2 oncogene (growth factor receptor)

Treatment = anti-HER2

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GROUP WORK

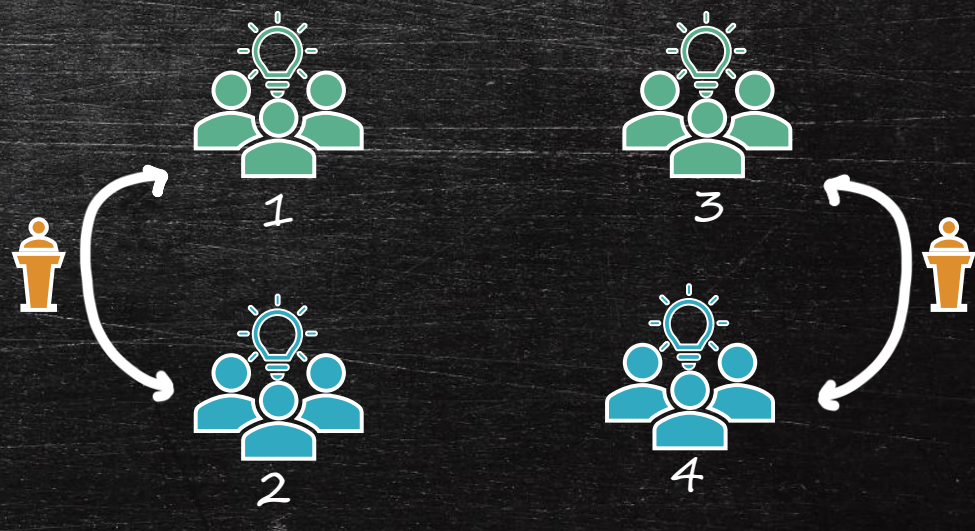
THE HERITABILITY OF HUMAN DISEASE

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

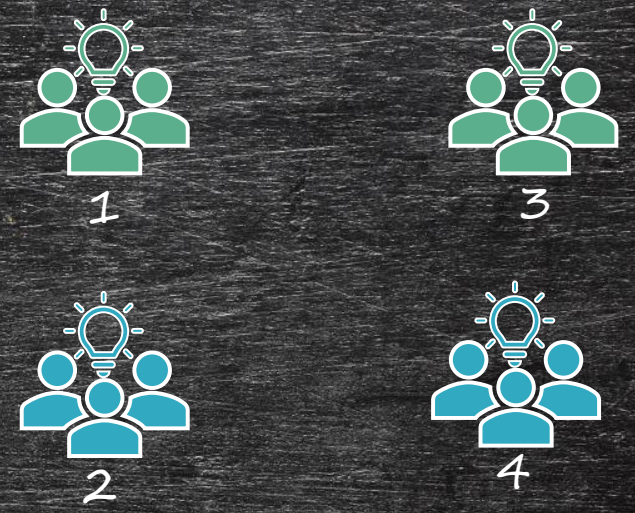
PART 2 – *next time (7/6)*

- ❑ 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

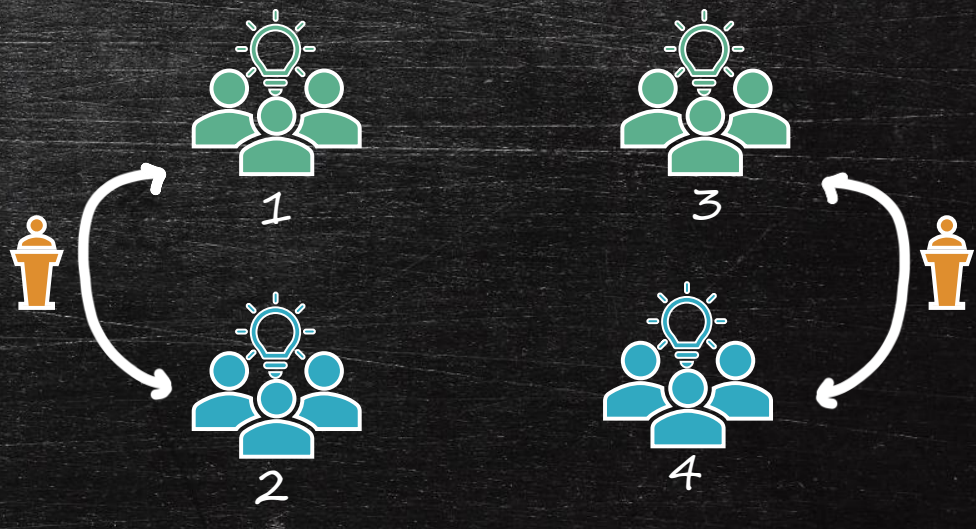


All should include:

- 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)