Dr. K. Vogt

The Genetics of CANCER

Today we are going to…

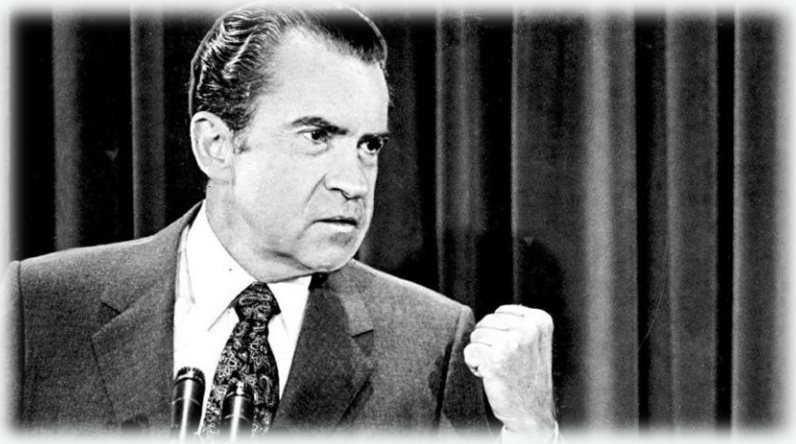
- … identify DNA repair mechanisms
- … investigate Genetic Predispositions to Cancer using selected examples
- … … explore the Chromosomal Aberrations in (Haematopoietic) Cancers

MBBS learning outcomes

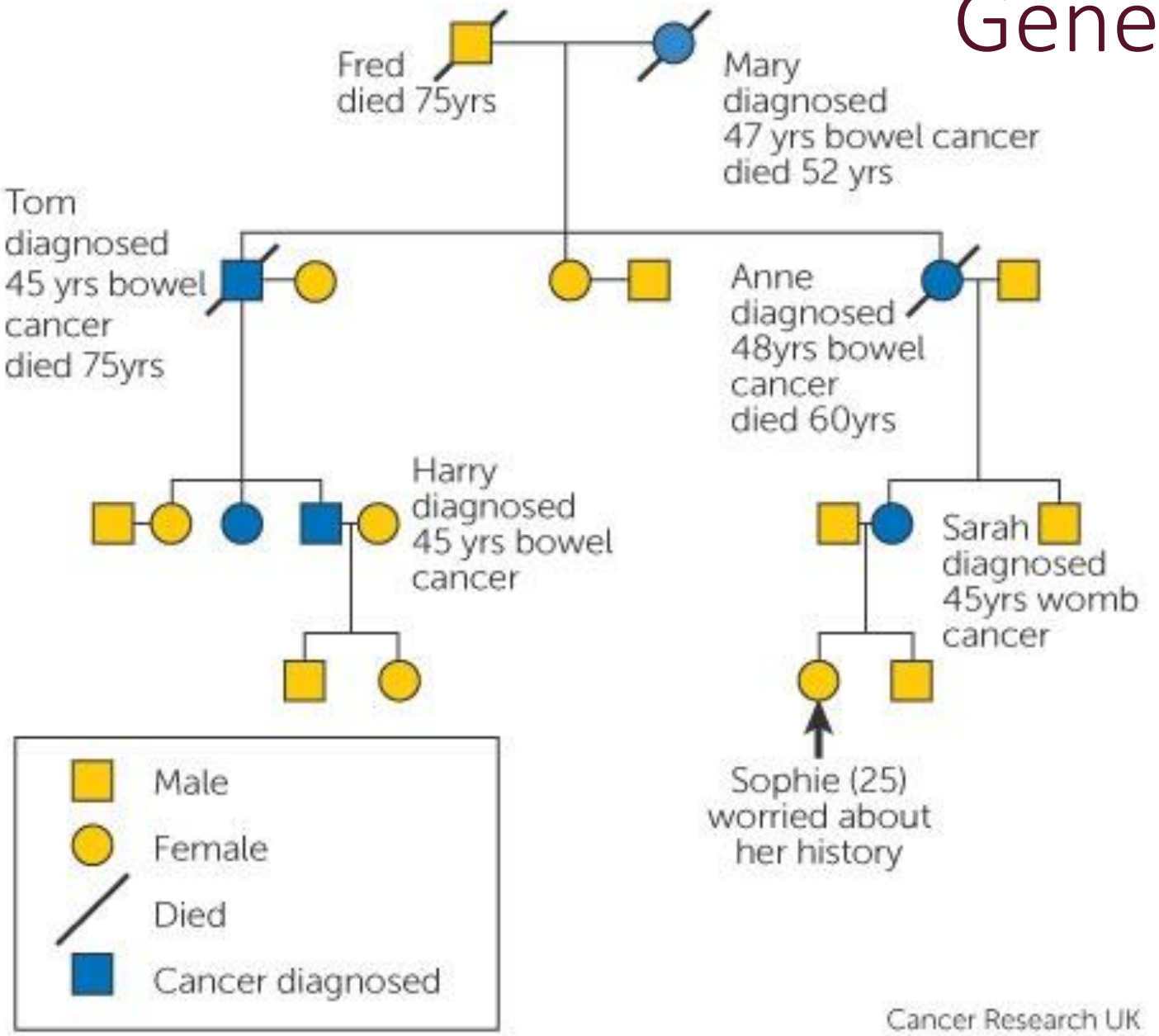
- Recognise the basic concepts of cancer, including the Hallmarks of cancer, cell cycle checkpoints, oncogenes and tumour suppressor genes
- Explain the principles of invasion and metastasis, including cancer staging
- Describe the stepwise progression of carcinogenesis using bowel cancer as an example

What is Cancer?

- Uncontrolled cell proliferation
- Cancer is more than one disease
- Cancer is caused by the accumulation of genetic mutation



Genetic predispositions to Cancer

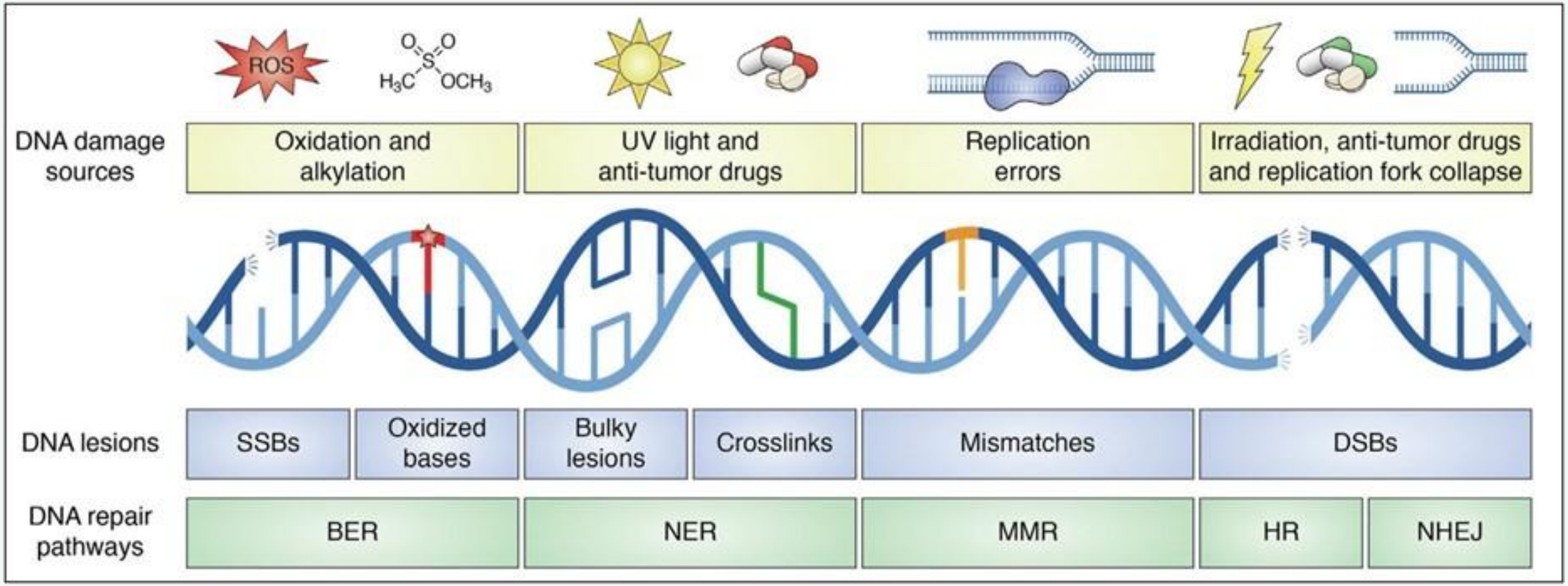


- Most cancers are not linked to inherited mutated genes
- Only around 5% of cancers are linked to an inherited faulty gene
- Cancer in older people is less likely to be due to an inherited cancer gene

How does DNA get mutated?

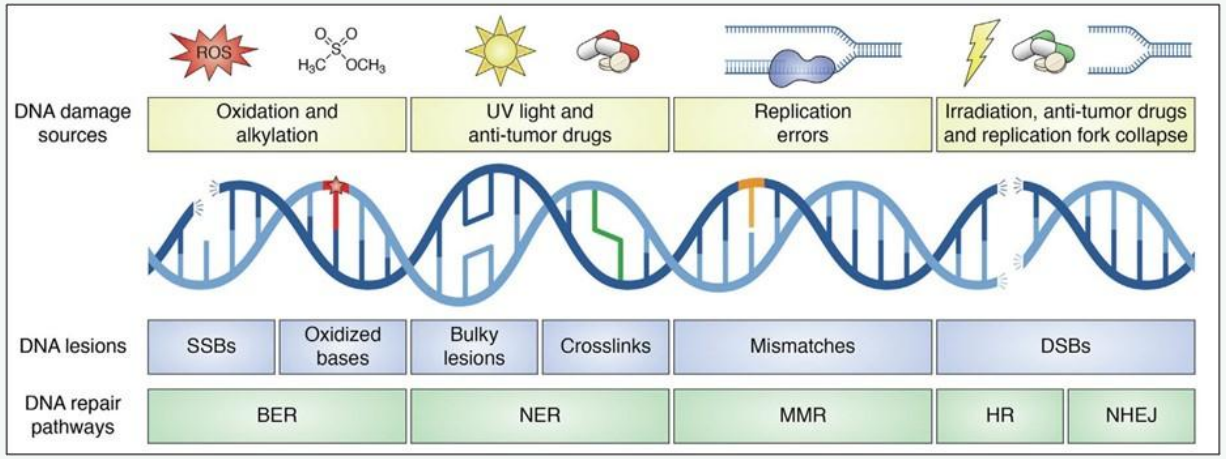
- Environmental factors
  - UV light
  - Smoke
  - Obesity
  - Drugs
- Errors in replication
- Errors in chromosome segregation

DNA repair mechanisms



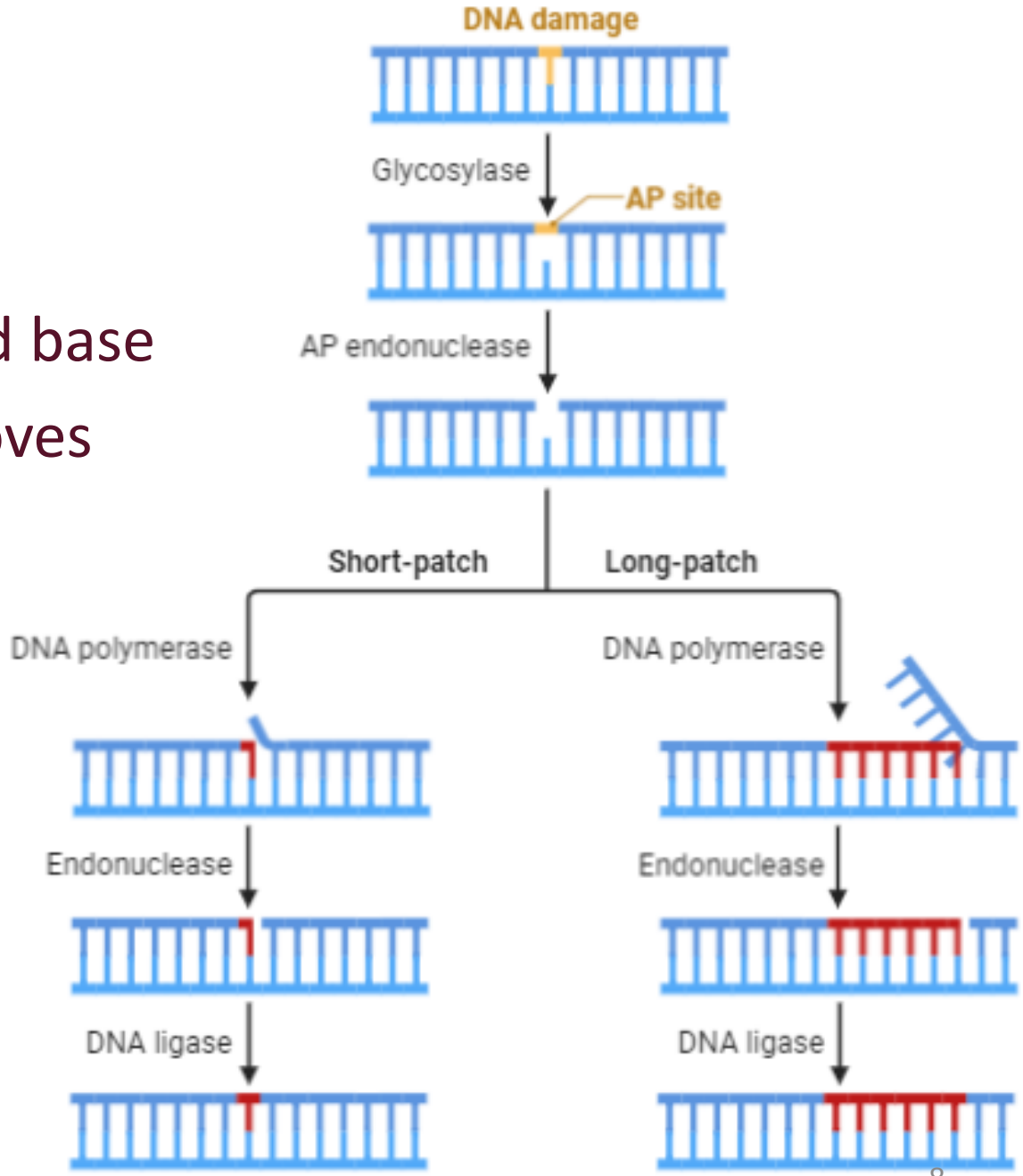
DNA repair mechanisms

- Base excision repair (BER)
- Nucleotide excision repair (NER)
- Mismatch repair (MMR)
- Non-homologous end joining (NHEJ)
- Homologous recombination repair (HRR)



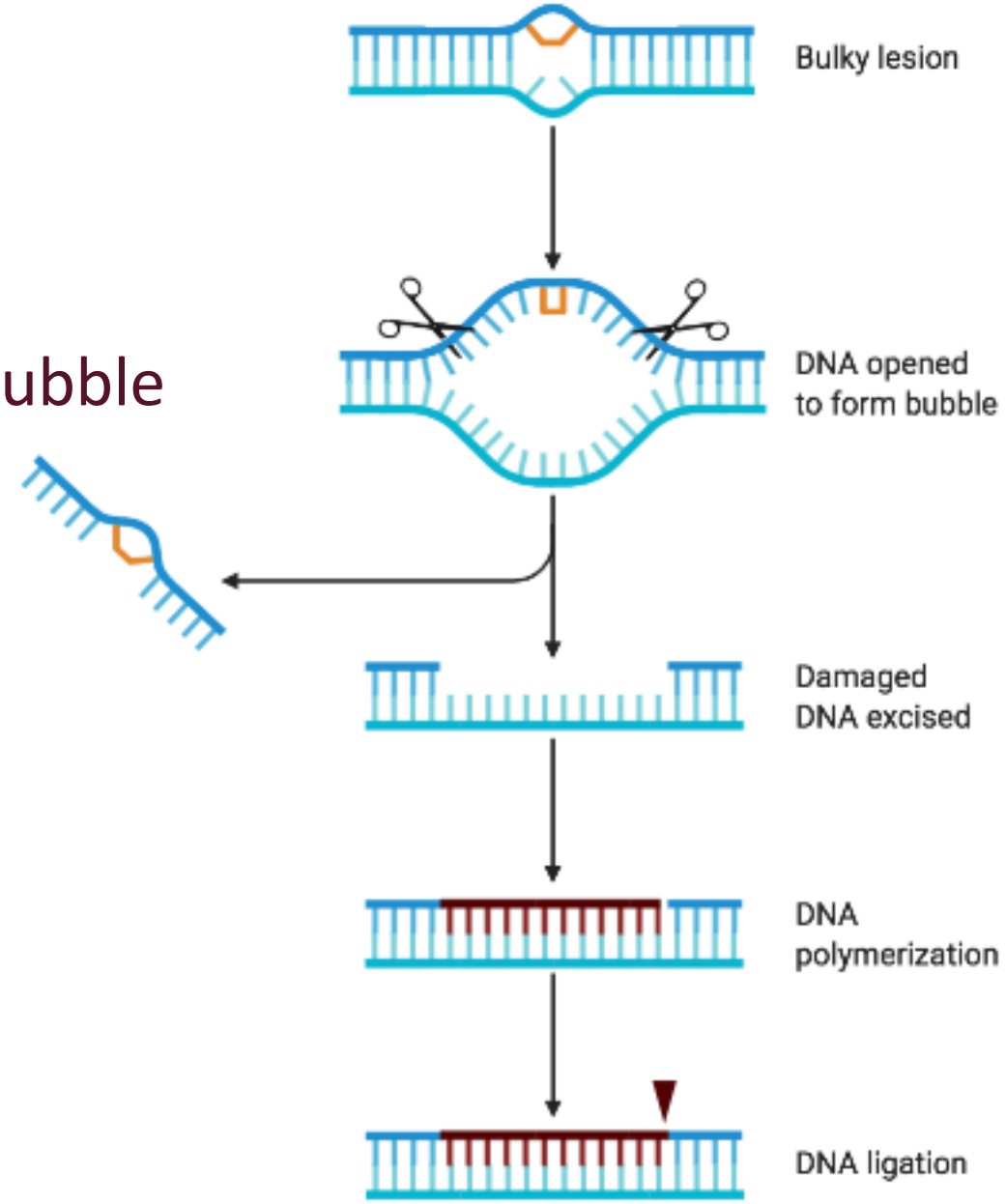
Base excision repair

- Removal and replacement of modified base
- DNA Glycosylase binds DNA and removes damaged base
- AP endonuclease nicks the backbone
- DNA polymerase fills the gap



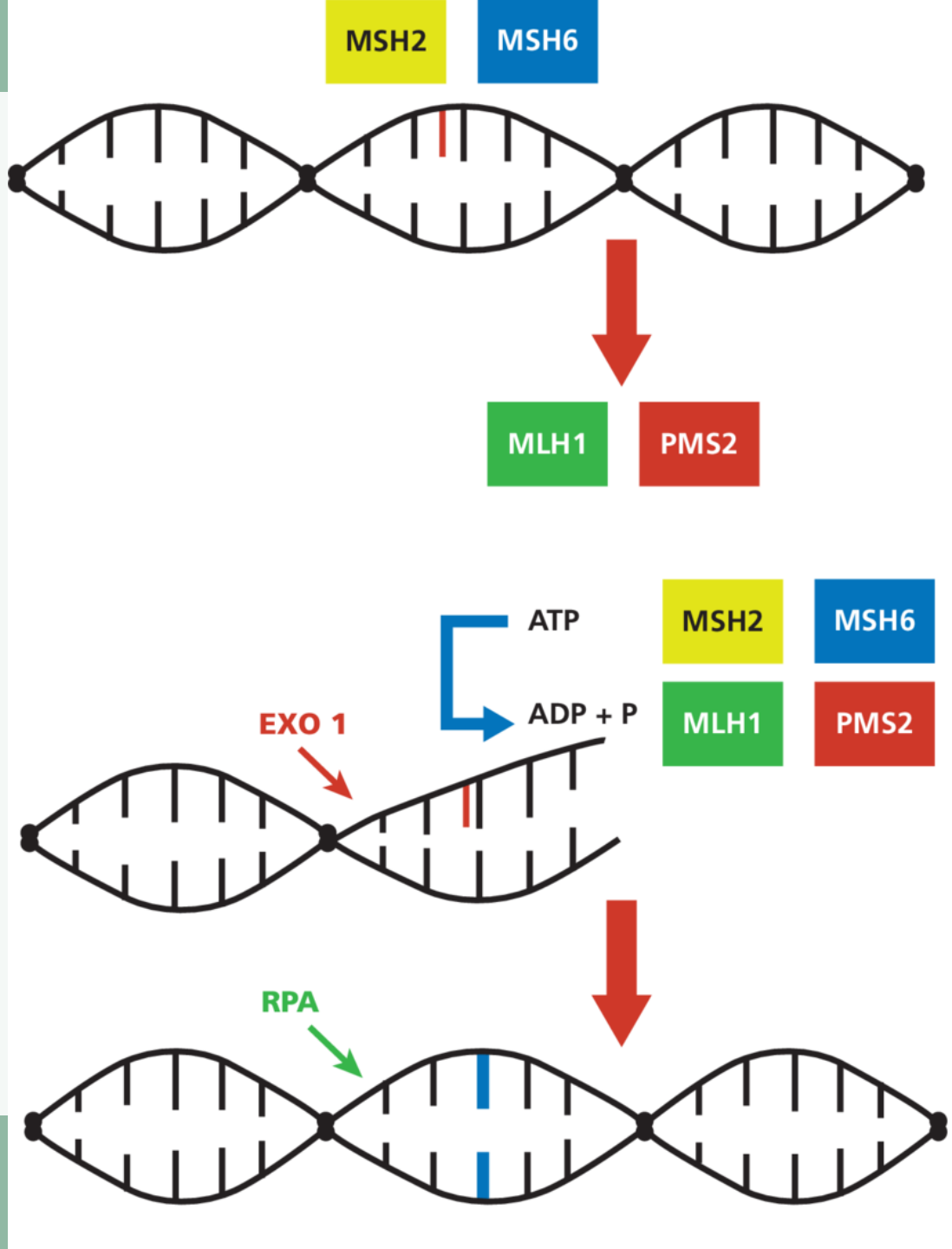
Nucleotide excision repair

- Bulky dimer is detected
- Surrounding DNA is opened to form a bubble
- Enzymes cut the damaged region
- DNA polymerase replaces DNA
- Ligase seals the backbone



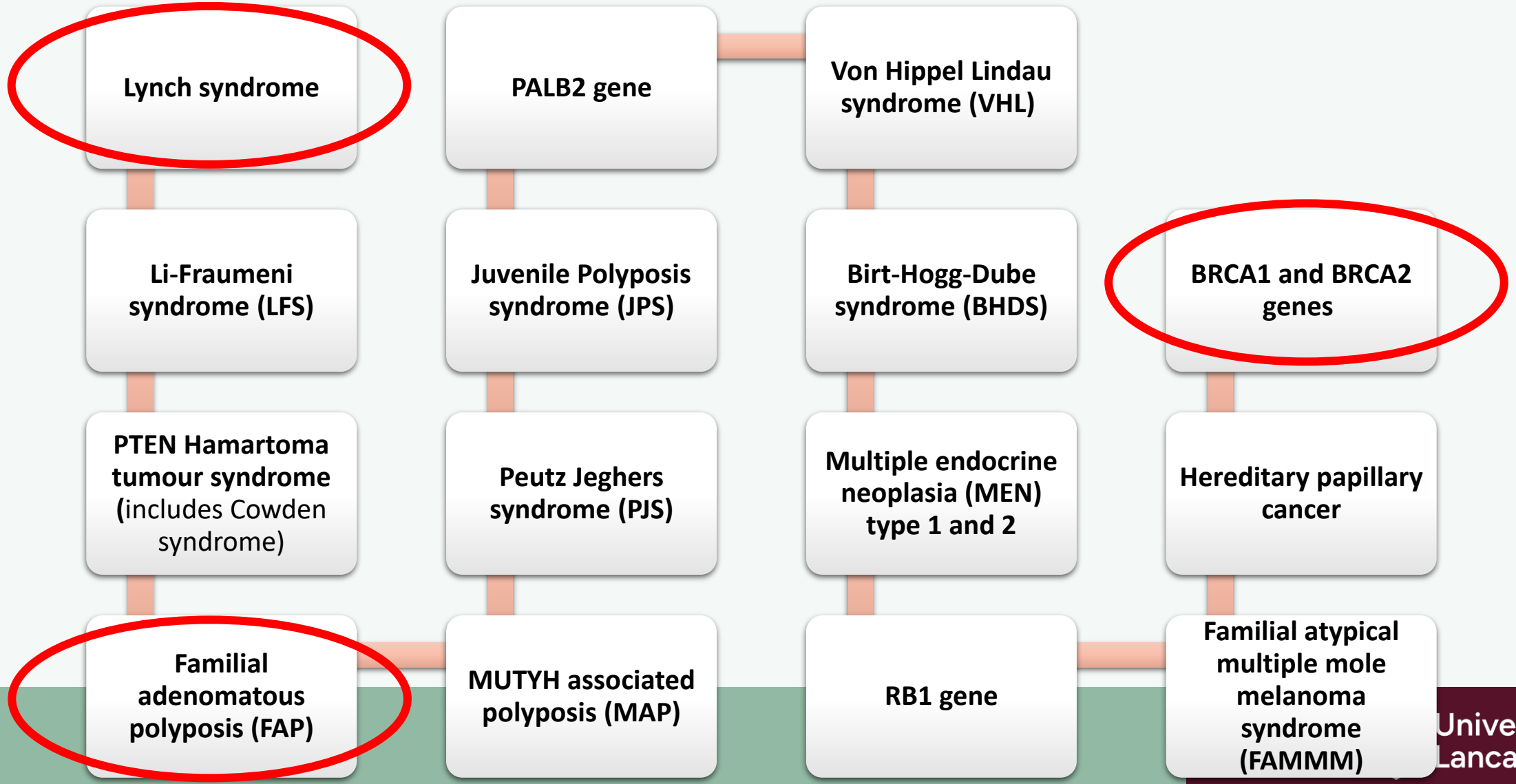
Mismatch repair

- Mismatch is detected
- Surrounding DNA is opened
- Enzymes cut the damaged region
- DNA polymerase replaces DNA
- Ligase seals the backbone



Genes and Syndromes associated with familiar cancer cases

Dr Katja Vogt

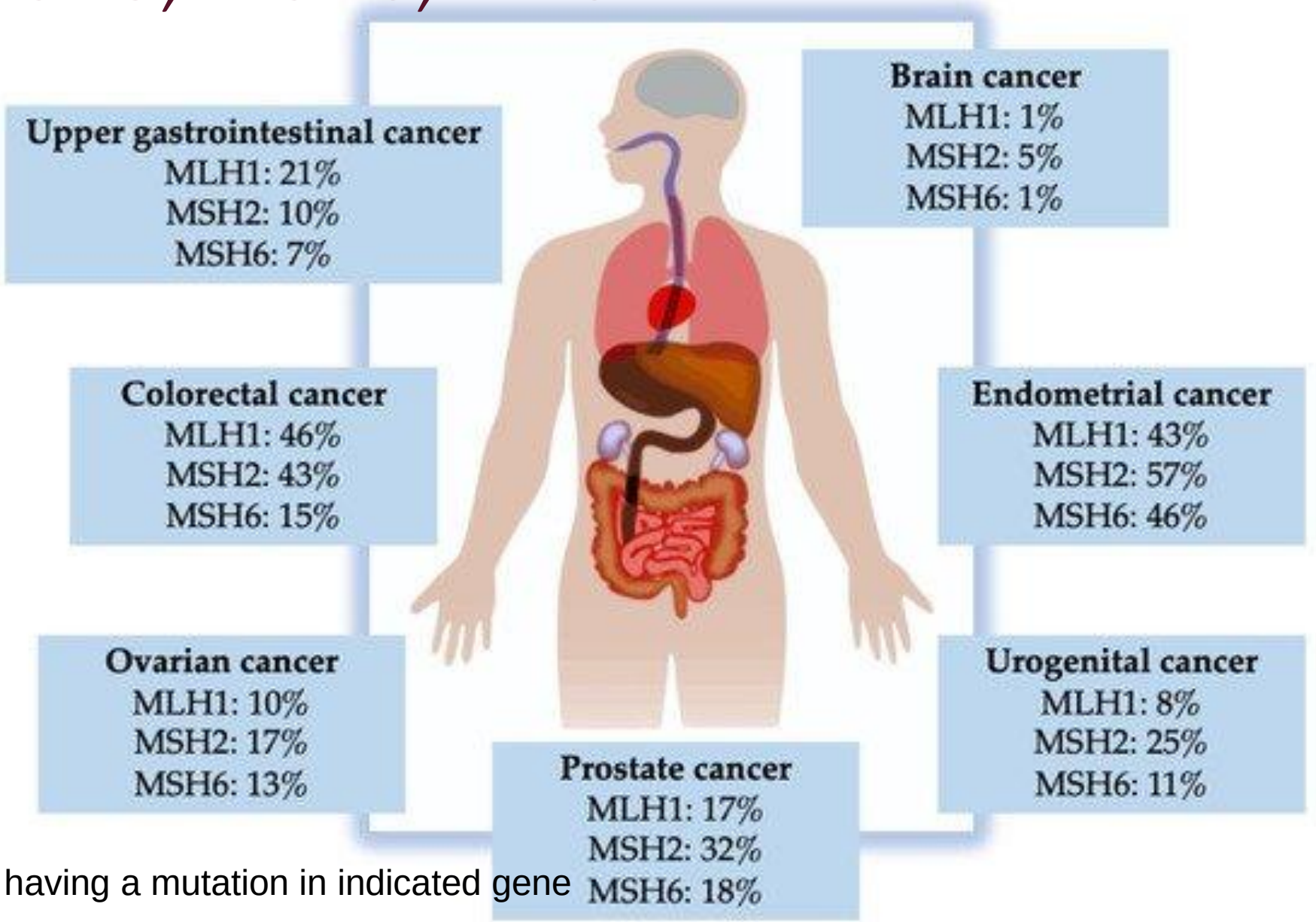


Lynch syndrome

- Also called hereditary non polyposis colon cancer (HNPCC)
- Autosomal dominant changes in one of the genes or MLH1, MSH2, MSH3, MSH6 or PMS2
- Increased risk of developing **bowel cancer,** womb-, ovarian-, stomach-, gallbladder- or prostate cancer, also cancer of the urinary tract such as bladder cancer
- Estimated: 1 in 300 people (US and Western Europe)

MLH1, MSH2, MSH3, MSH6, PMS2

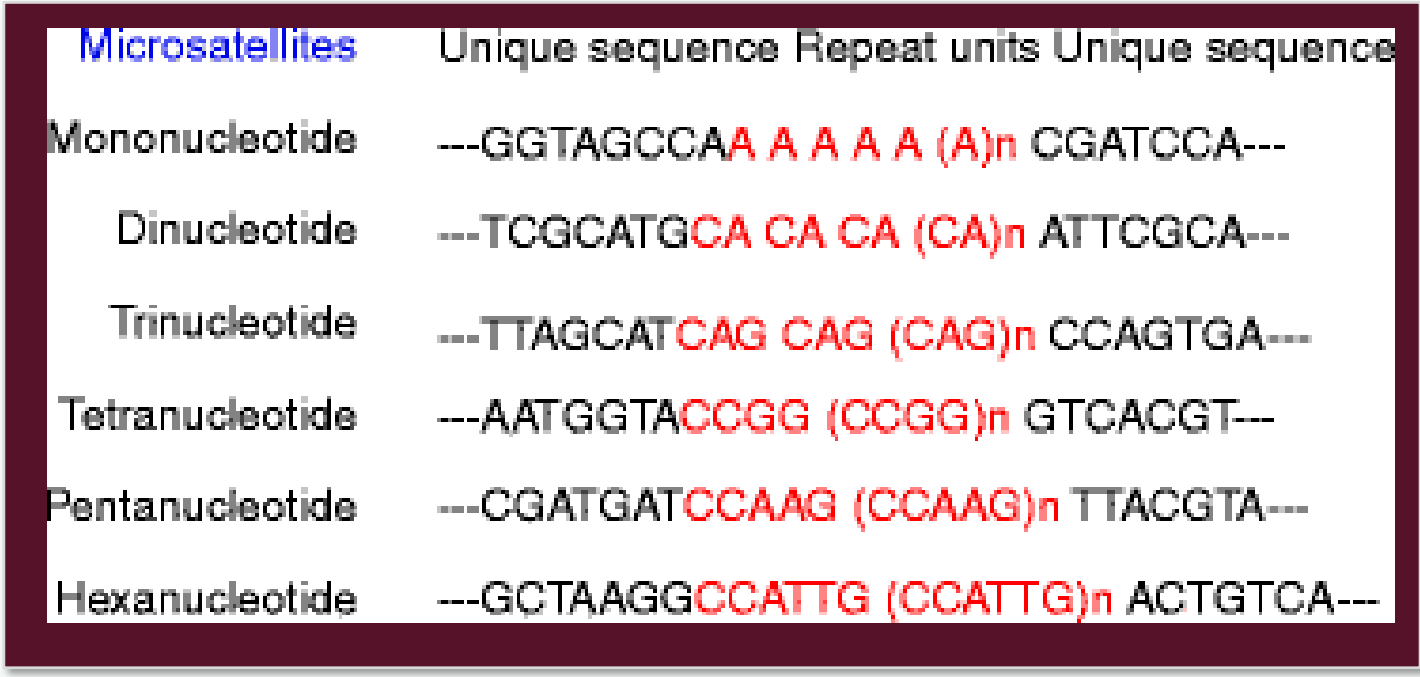
- Constitute the DNA mismatch repair system



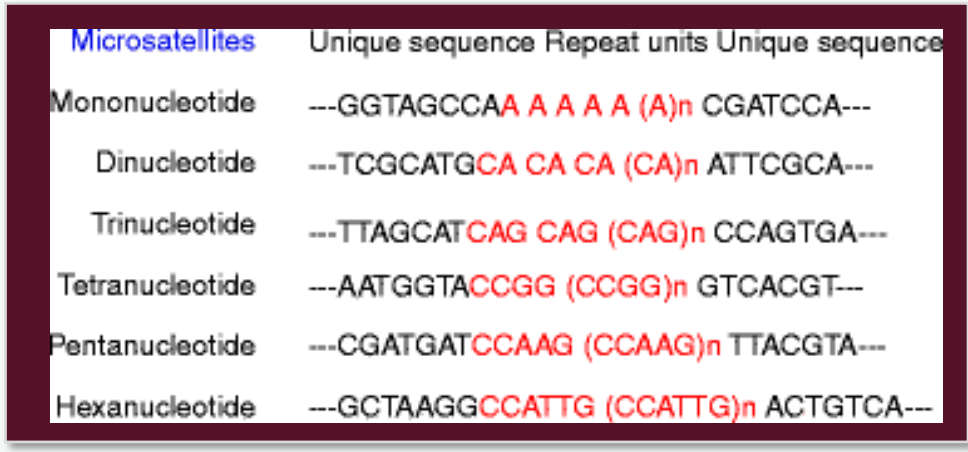
Numbers represent the % of cancers having a mutation in indicated gene

Microsatellite

- **Microsatellites**: short repetitive motifs of 1–6 nucleotides in length
- Tandemly repeated 10–60 times and flanked by unique sequences



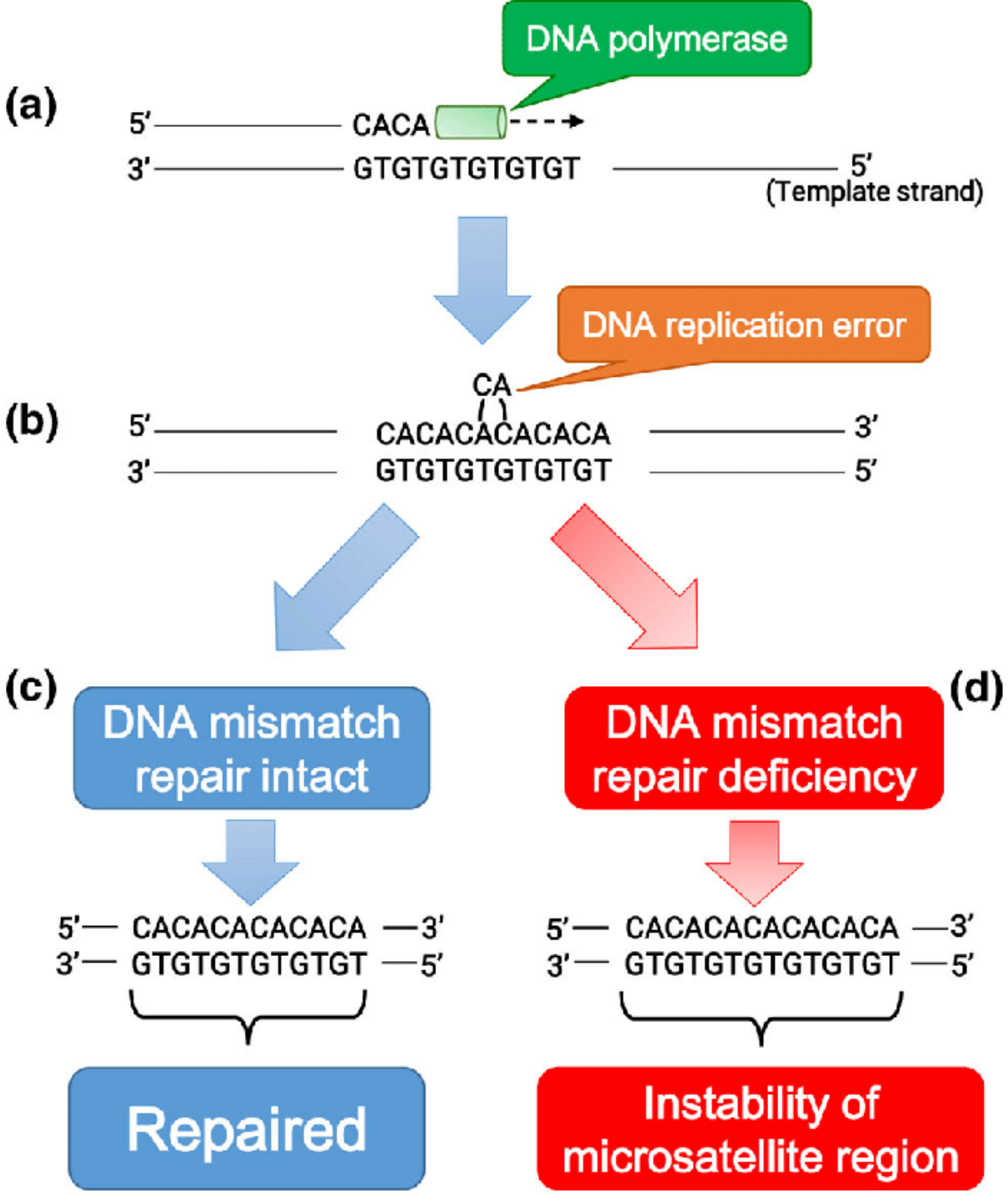
Microsatellite instability (MSI)

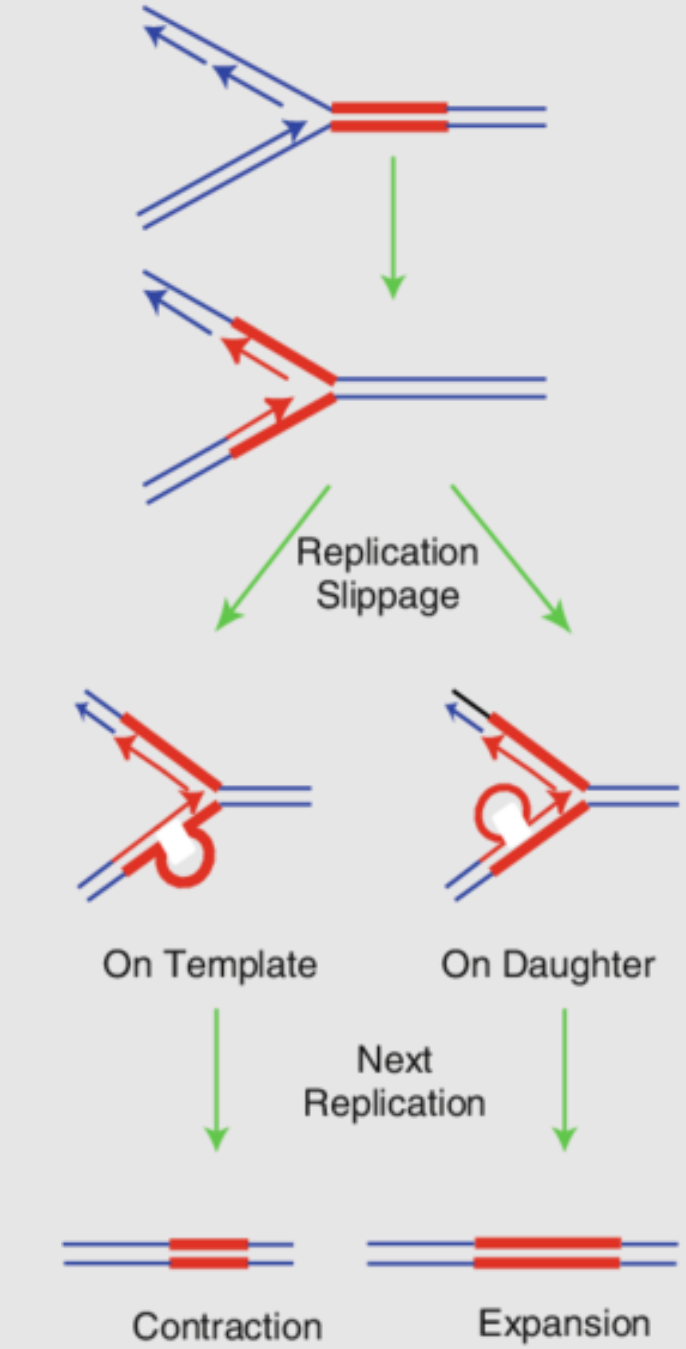


Microsatellites	Unique sequence Repeat units Unique sequence
Mononucleotide	---GGTAGCCAA A A A A A (A)n CGATCCA---
Dinucleotide	---TCGCATGCA CA CA CA (CA)n ATTCGCA---
Trinucleotide	---TTAGCATCAG CAG CAG (CAG)n CCAGTGA---
Tetranucleotide	---AATGGTACCGG (CCGG)n GTCACGT---
Pentanucleotide	---CGATGATCCAAG (CCAAG)n TTACGTA---
Hexanucleotide	---GCTAAGGCCATTG (CCATTG)n ACTGTCA---

- Is caused by defective MMR
- Strand slippage can occur leading to microsatellite instability, if unrepaired.
- In cells, lacking repair mechanism, mutations at coding microsatellites accumulate leading to:
  - Loss of function
  - May also trigger translation of highly immunogenic neo-peptides (antigens)

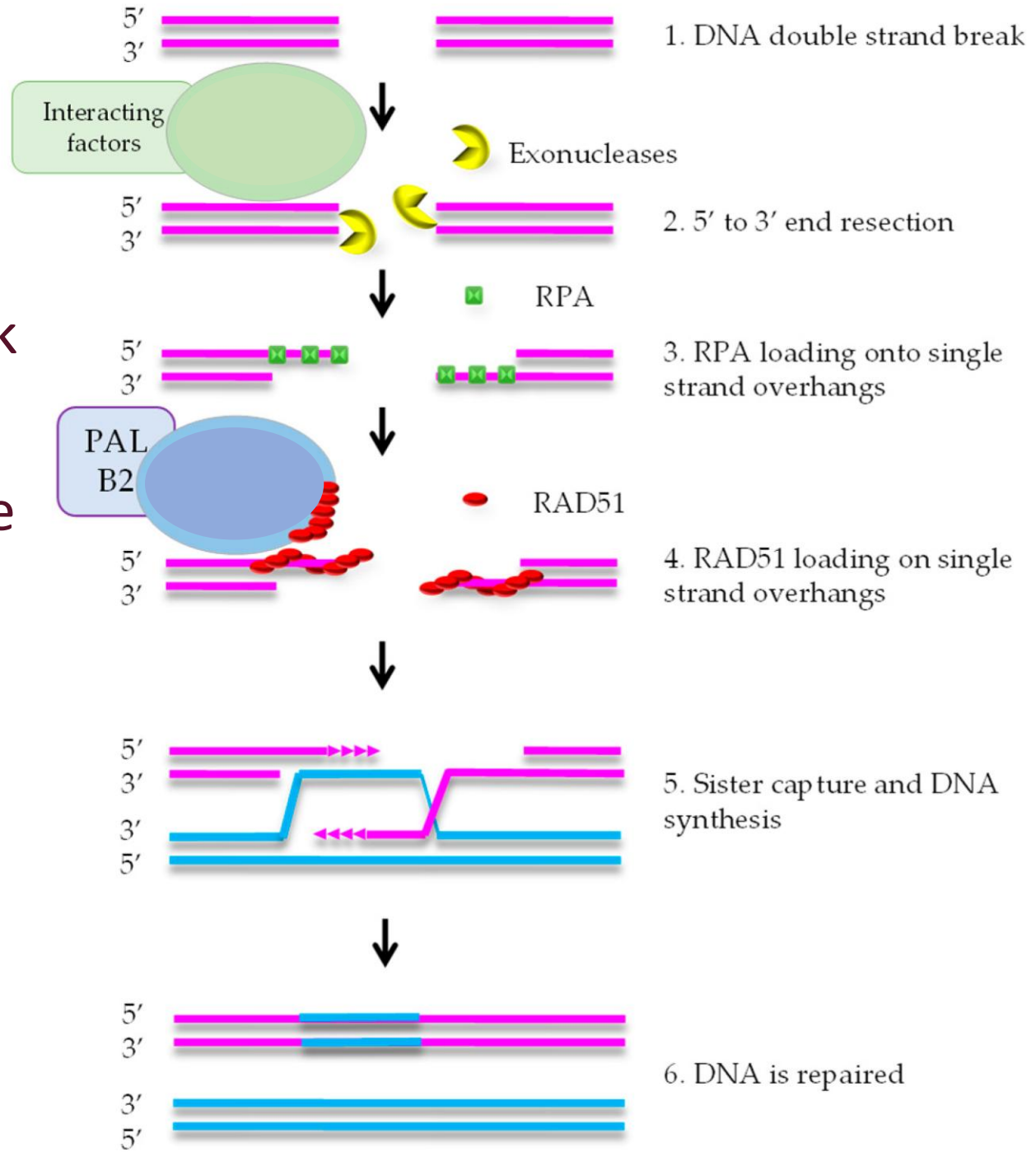
Microsatellite instability





Homologous recombination repair

- Recognition of double strand break
- 5’ to 3’ resection
- RPA and RAD51 loading onto single strand overhangs
- Sister capture and DNA synthesis
- During mitosis



BRCA1 and BRCA2

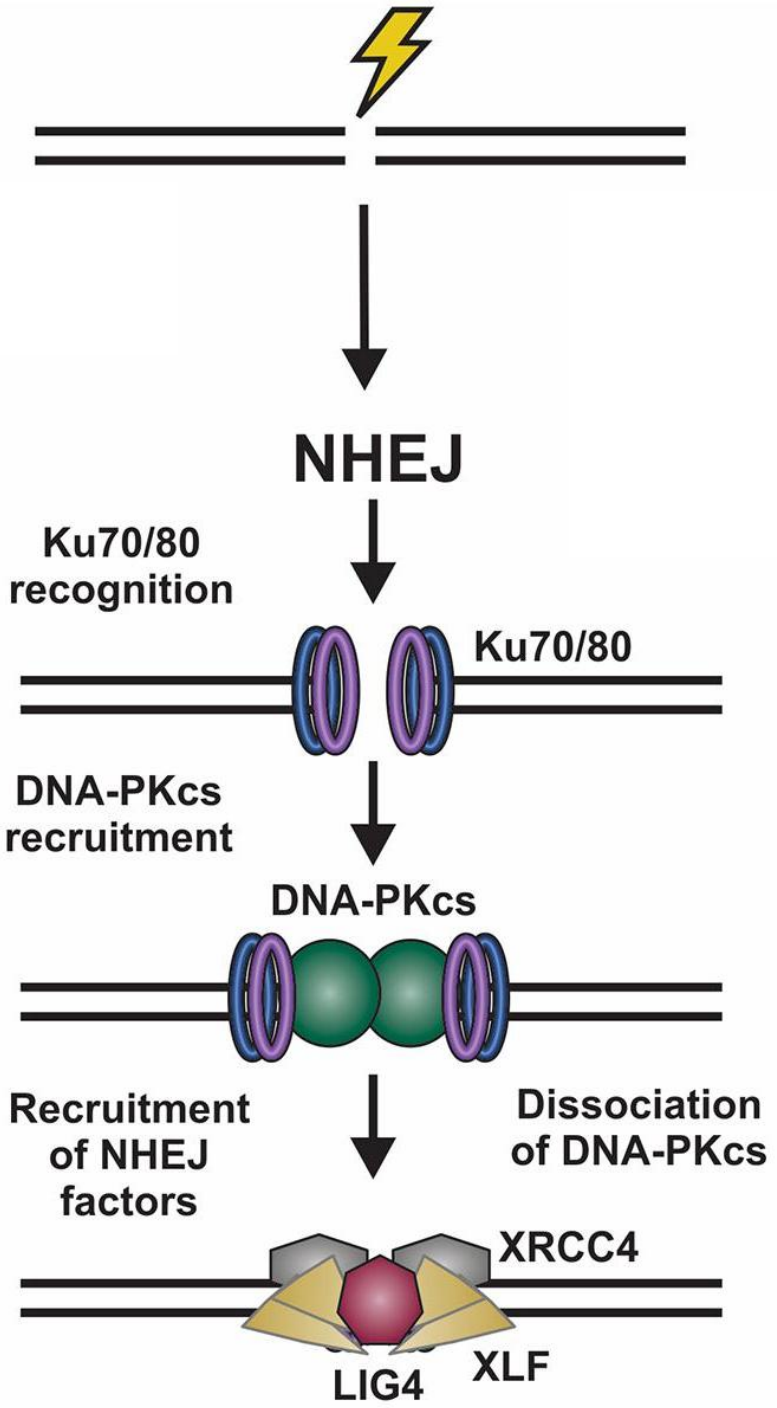
- BRCA stands for BReast CAncer gene
- Tumour suppressor
- Hereditary low (1 in 400)
- **BUT**:
  - around 70% and 45% of women with a BRCA1/BRCA2 mutated gene will develop breast cancer or ovarian cancer by the age of 80
- Encode multi-domain proteins that function in a number of cellular pathways to maintain genomic stability
  - Cell cycle checkpoint activation
  - Transcriptional regulation
  - Apoptosis
  - **DNA double strand break repair**

Familial Breast Cancer

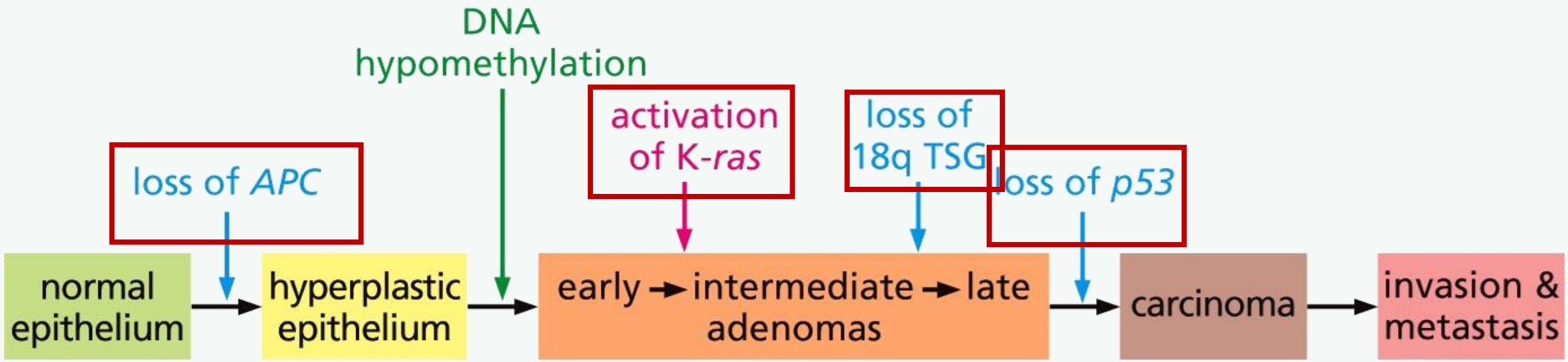
- ~5% to 10% of breast cancer cases are thought to be hereditary
- 8 genes have significant association with breast cancer risk
  - **BRCA1, BRCA2**, PALB2, BARD1, RAD51C, RAD51D, ATM and CHEK2
- ~2.5 of Ashkenazi Jewish women have a BRCA gene mutation.
  - High proportion of mutations found in Icelandic population

Non-homolougous end-joining

- Recognition of DS break by Ku complex
- Trimming and filling of DNA as needed
- Ends ligated back together
- Error prone

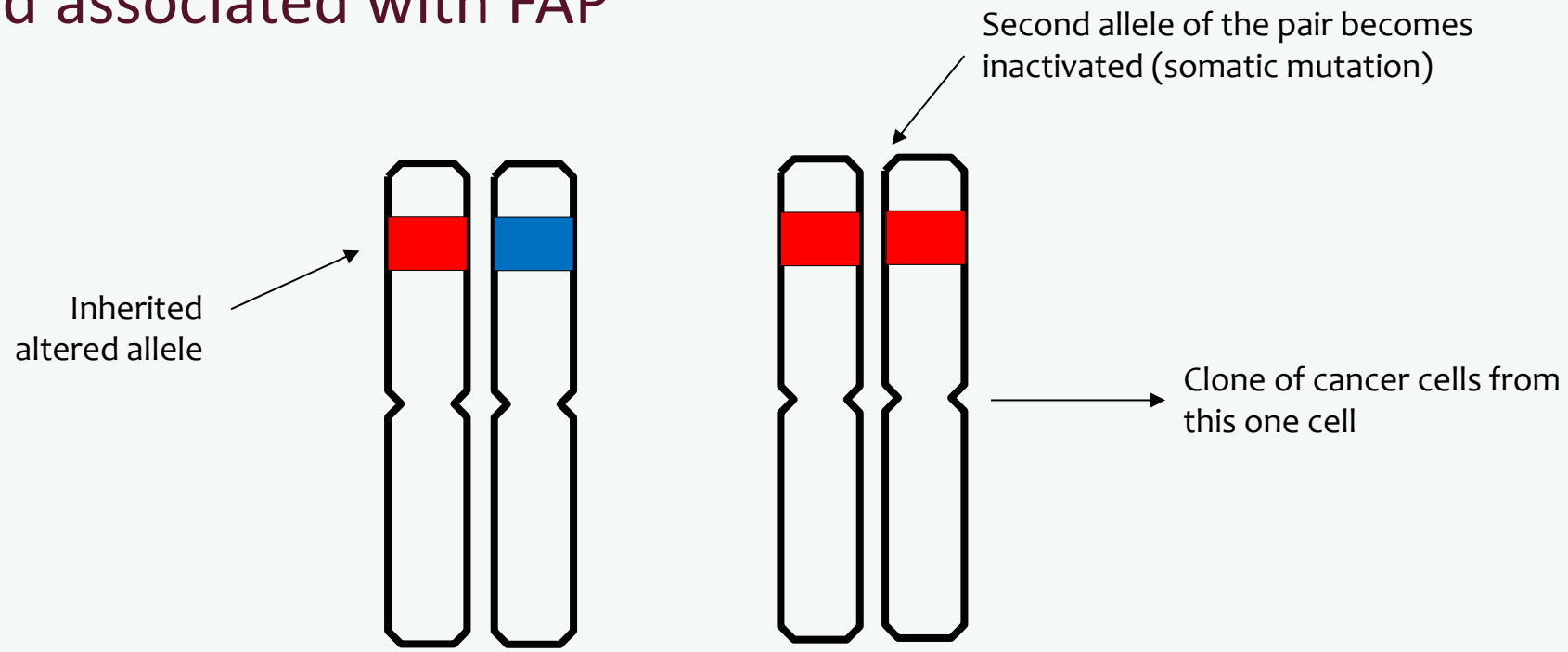


Multistage Model of Bowel Cancer

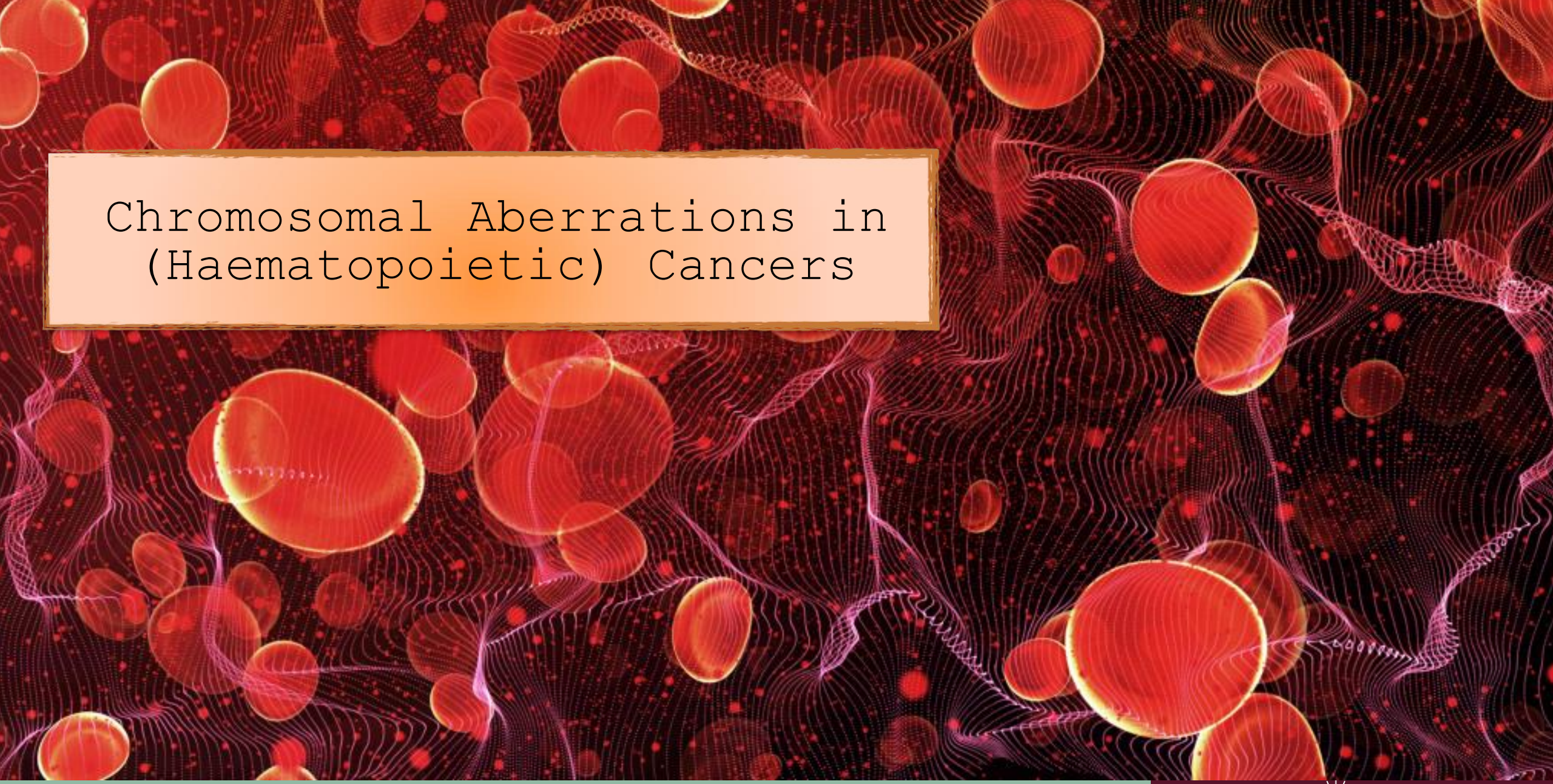


Familial Adenomatous Polyposis (FAP)

- APC first discovered associated with FAP



Chromosomal Aberrations in (Haematopoietic) Cancers



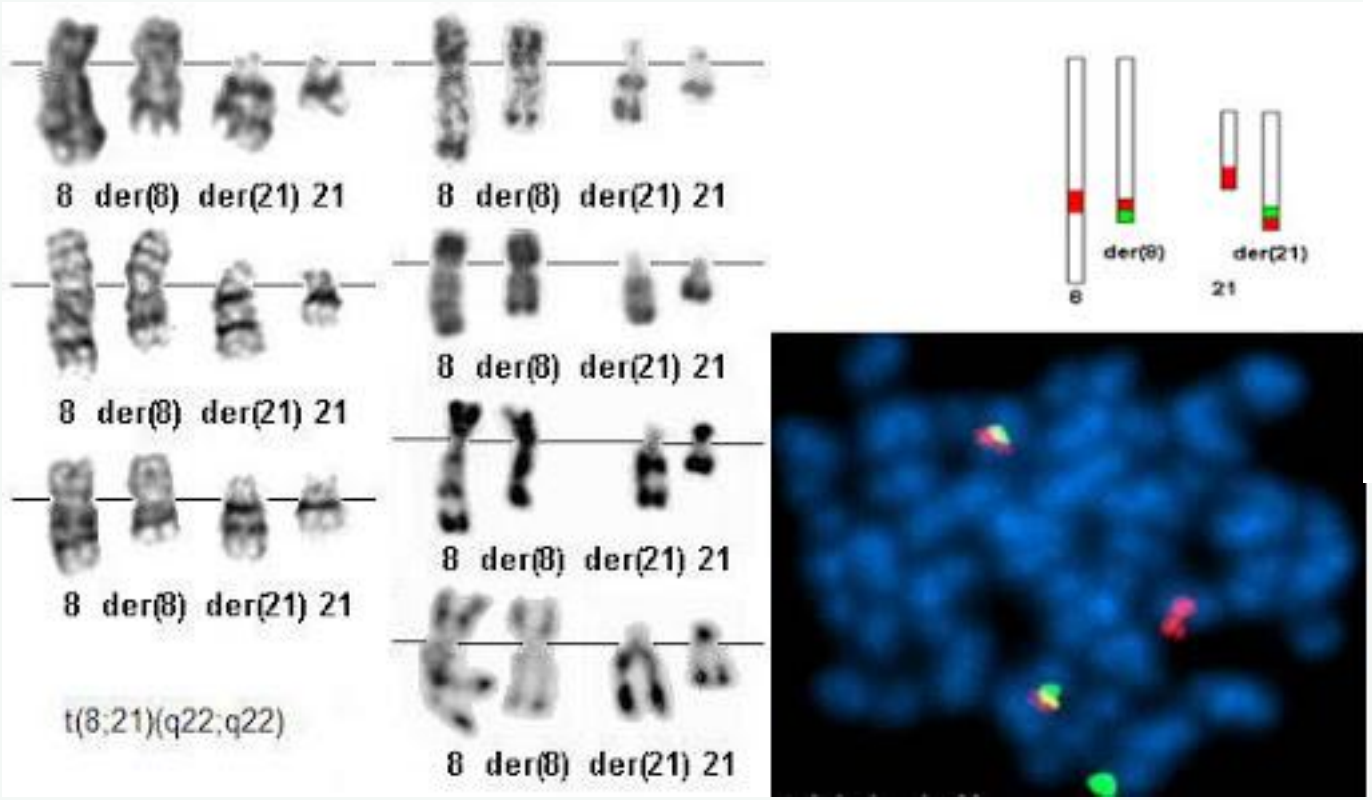
University of Lancashire

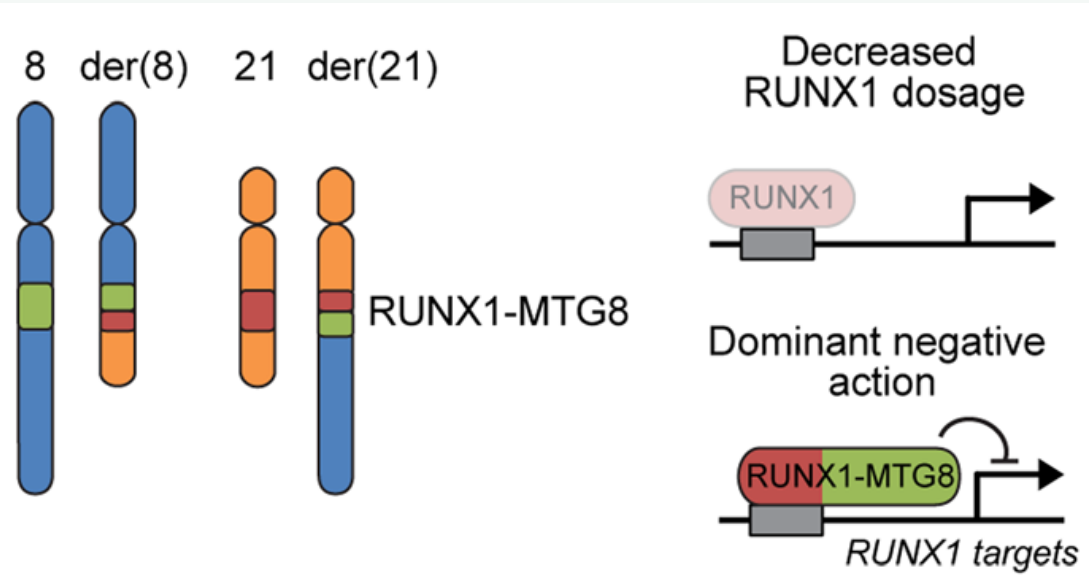
A quick overview

- Targeting Runx1
- Philadelphia chromosome
- C-Myc translocation
- JAK/STAT signalling

Targeting Runx1

1. t(8;21) → RUNX1

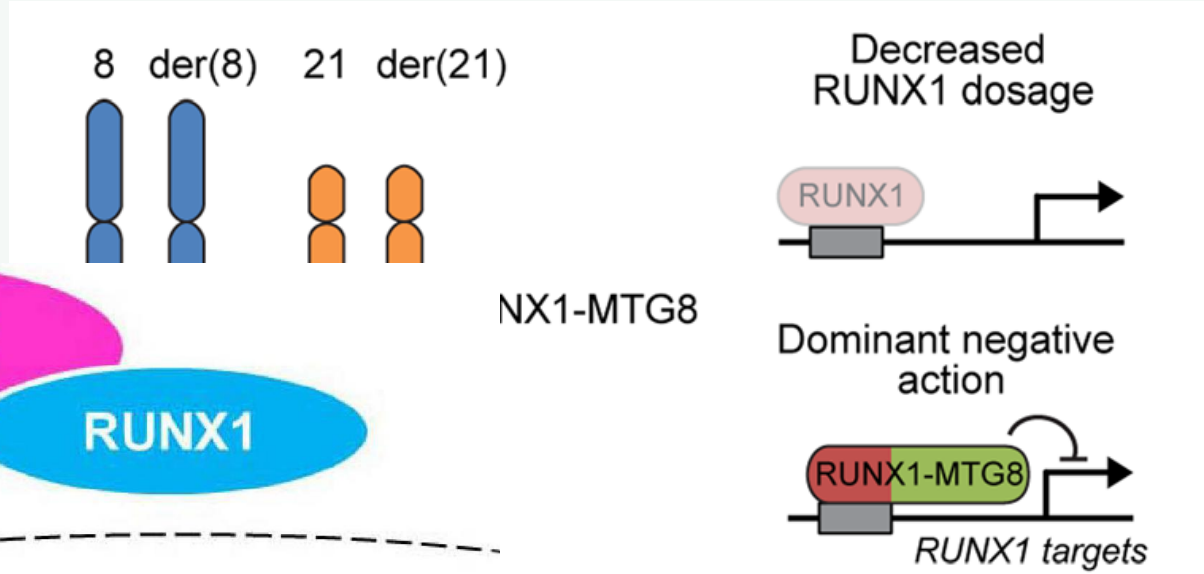


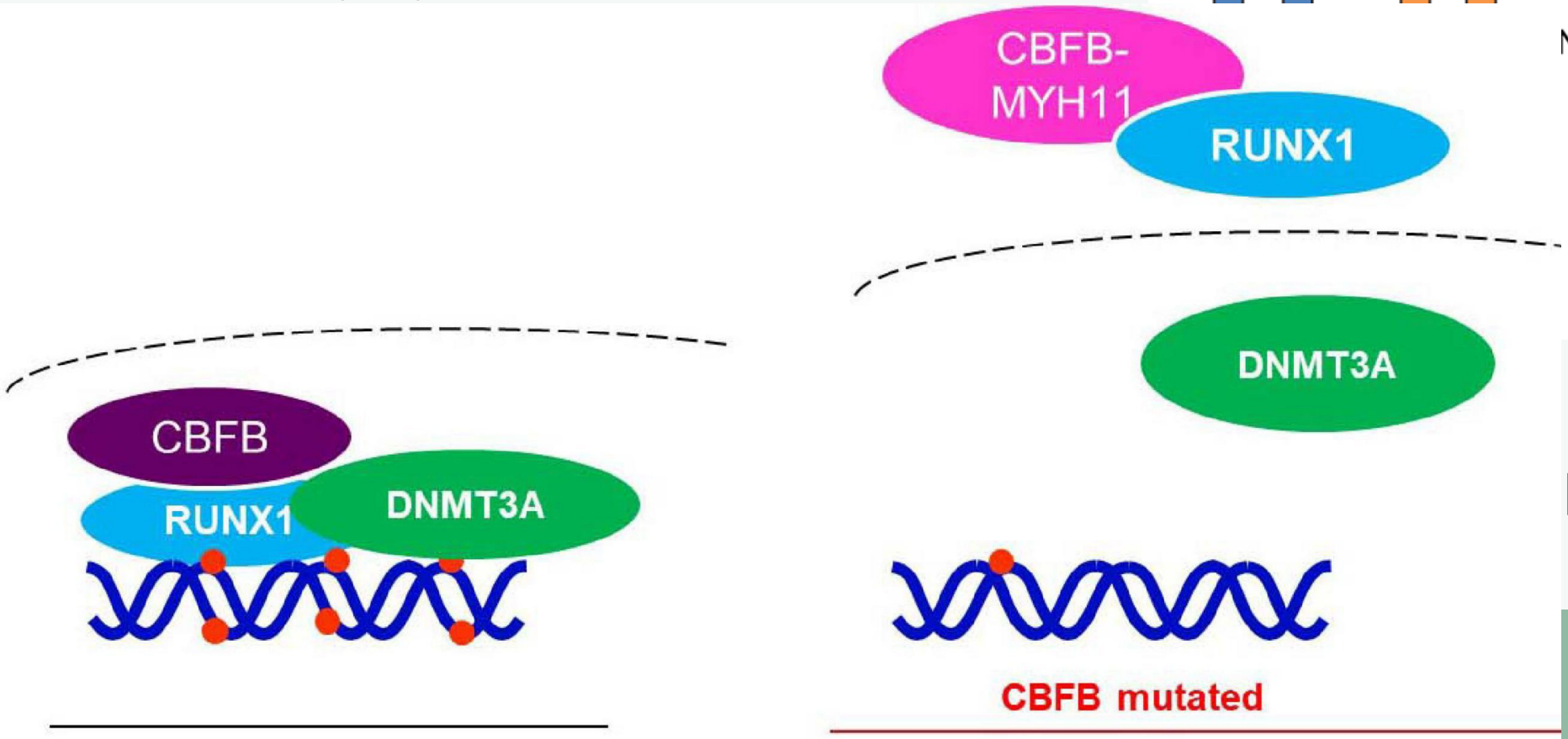


Runx1 defines hematopoiesis

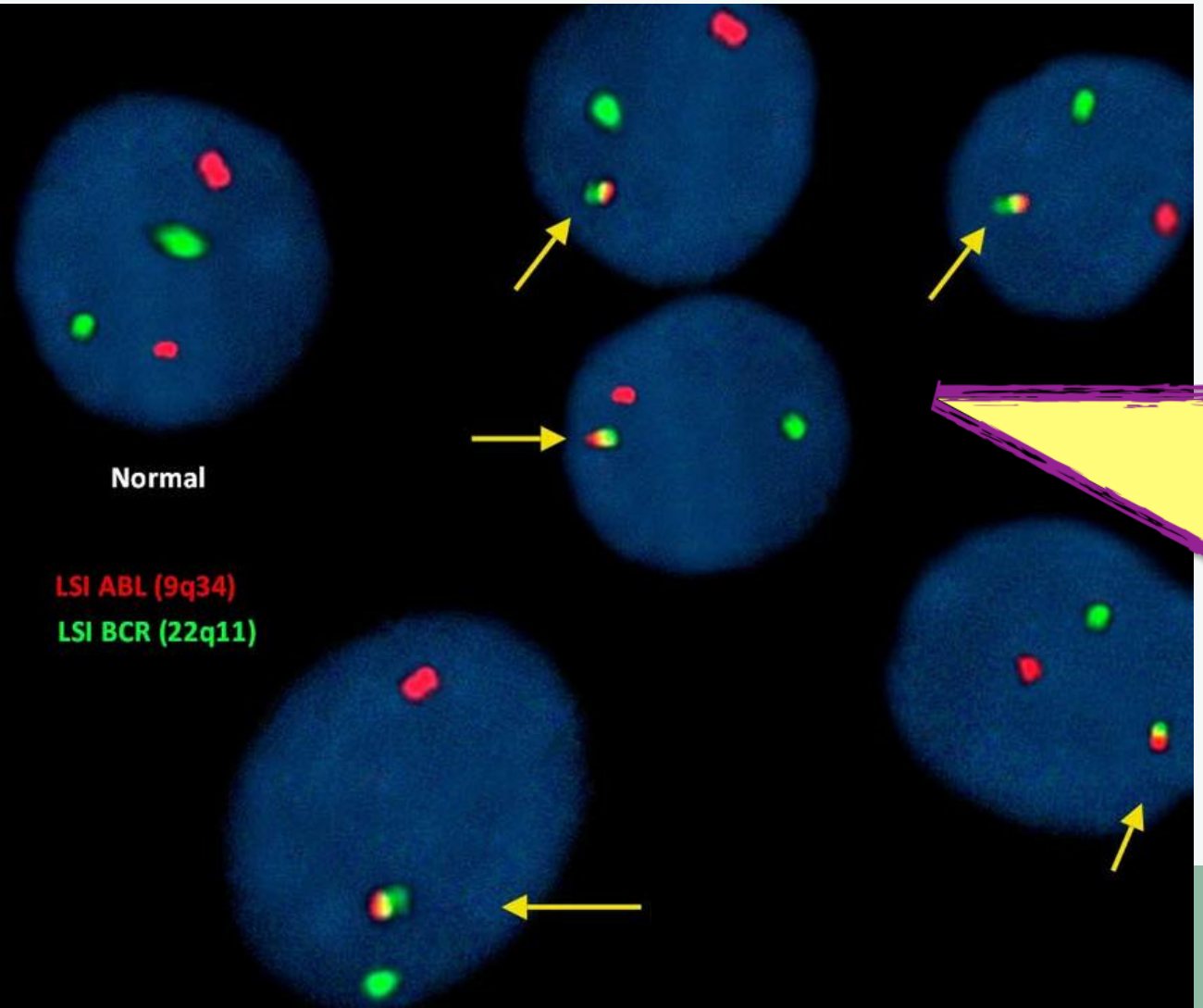
Targeting Runx1

1. t(8;21) → RUNX1
2. inv(16) → RUNX1/ CBFB





Runx1 defines hematopoiesis

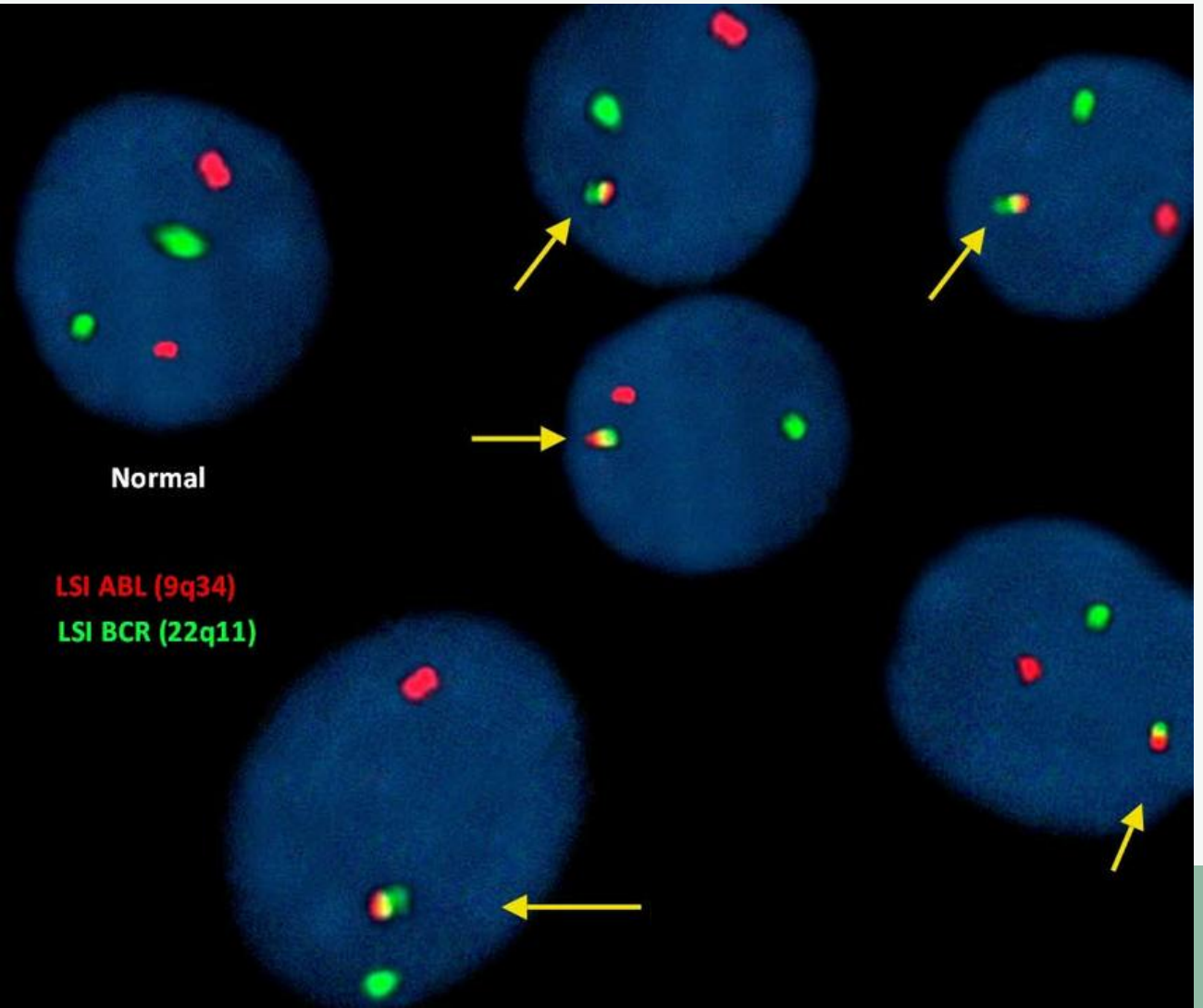


Question:

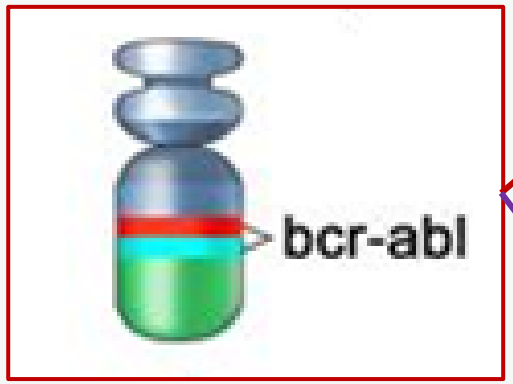
What what do the yellow arrows point to?

-

Philadelphia chromosome



Philadelphia chromosome



Bcr gene:

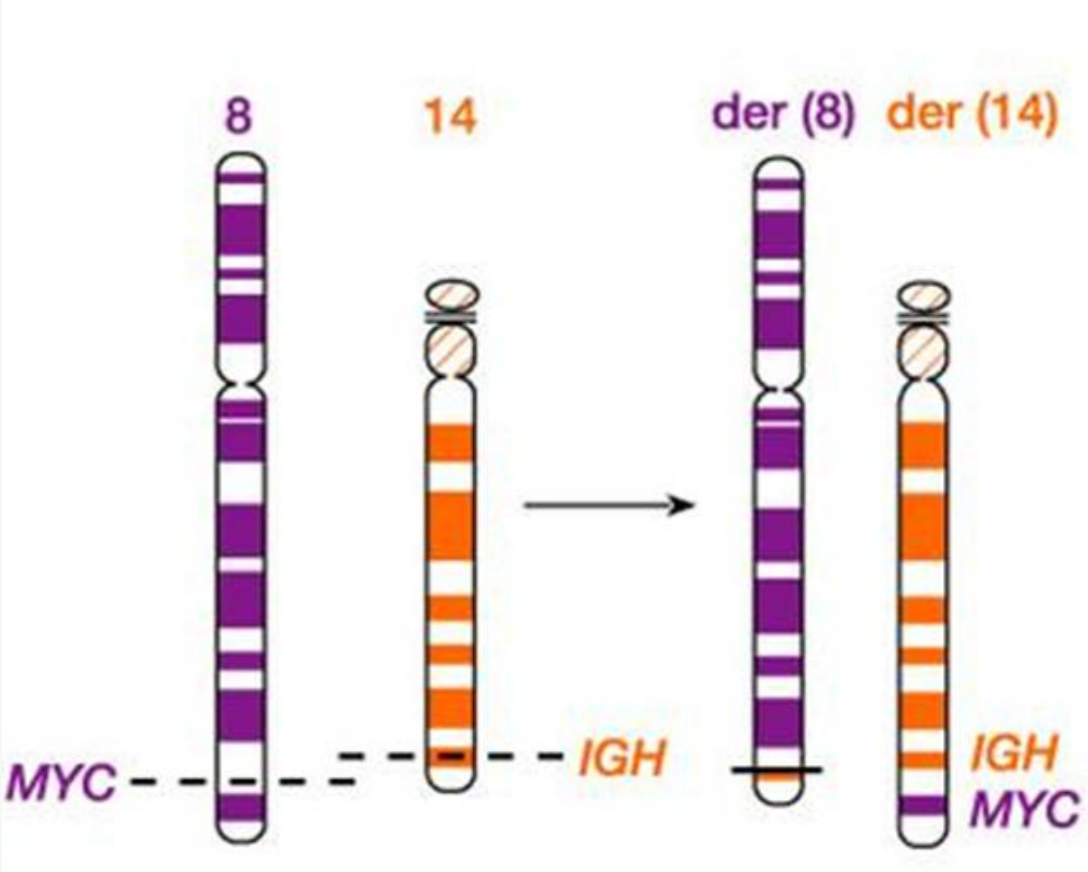
Normal function as yet unknown. Protein has serine/threonine kinase activity and GTPase activity so is involved in signalling.

Abl gene:

Originally found in a leukaemia virus. Tyrosine kinase which promotes cell division.

BCR-ABL fusion protein acts as a constitutively active signalling molecule which promotes cell division leading to chronic myeloid leukaemia

Translocation



- Reciprocal translocation between chromosomes 8 and 14.
- C-myc gene under the control of the Ig heavy chain enhancer leading to c-myc upregulation
- C-myc is a transcription factor involved in the regulation of proliferation, apoptosis and differentiation.

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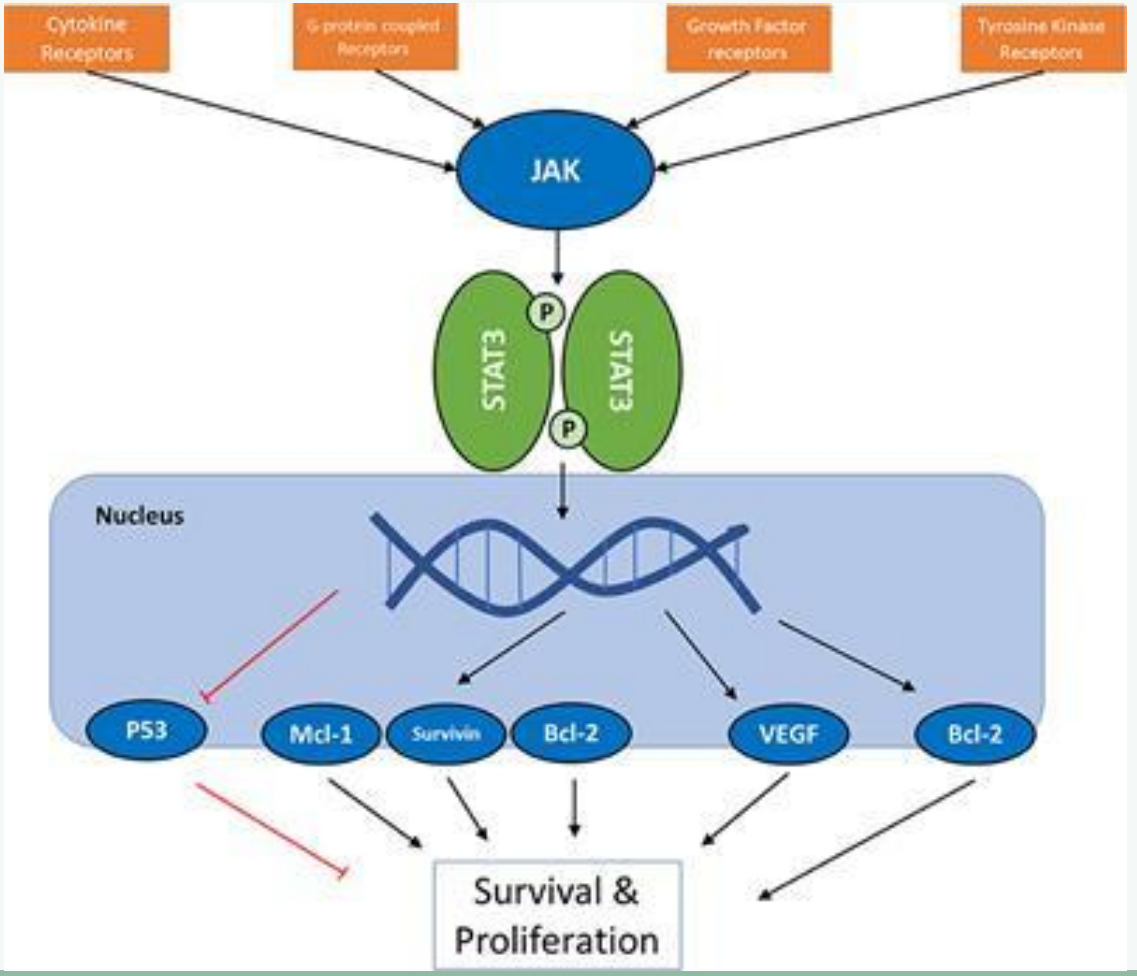
JAK/STAT signalling



- Myeloproliferative disorders
- Broad variety of solid tumours
- Inhibitors are used in many different types of cancer

Today we looked at …

- … DNA repair mechanisms
- … Genetic Predispositions to Cancer using selected examples
- … the Chromosomal Aberrations in (Haematopoietic) Cancers

MBBS learning outcomes

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