

Secrets within the genomes of cancer cells

Michael Stratton

Incidence and mortality of cancer

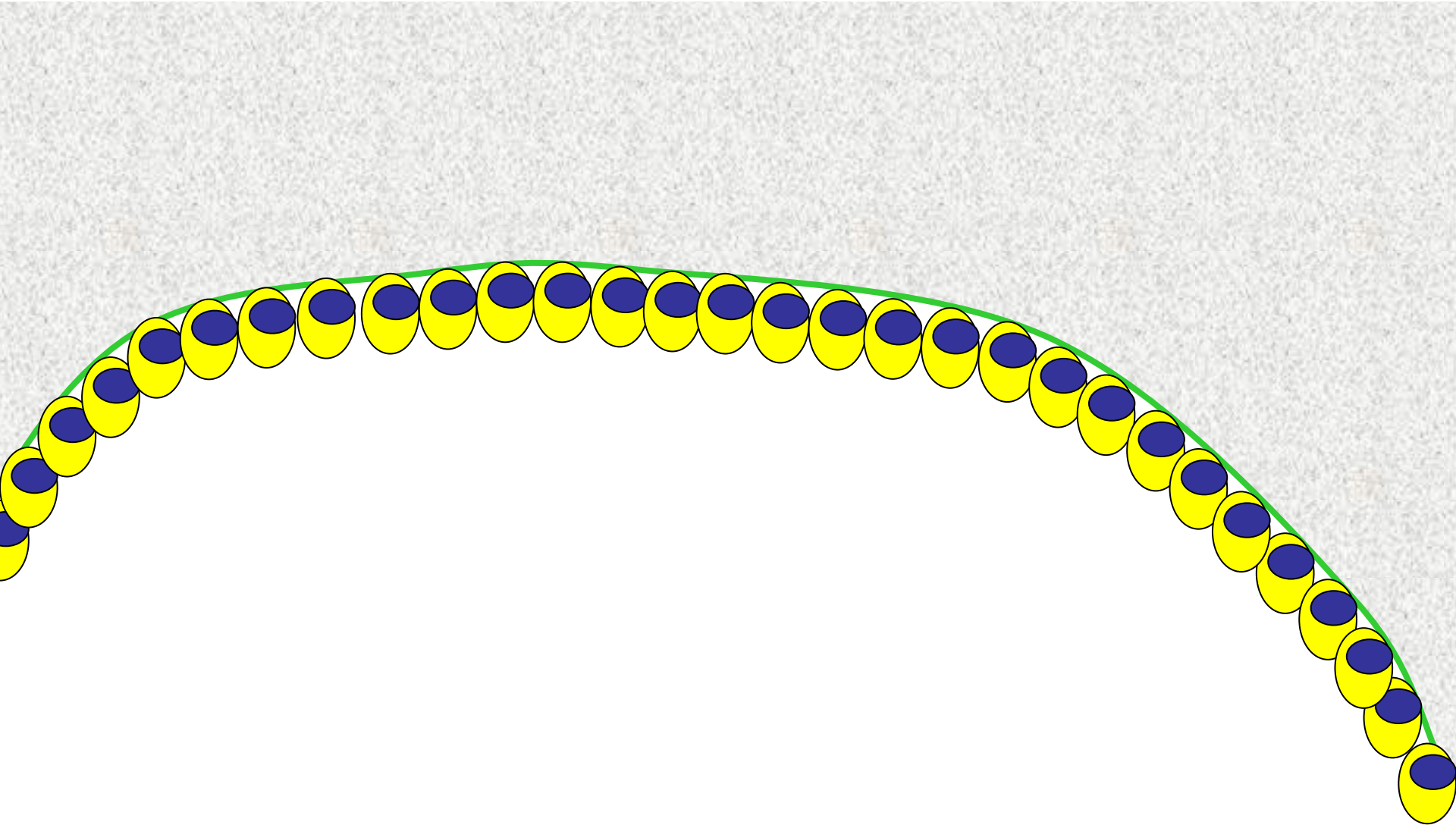
1:3 develop cancer

1:5 die of cancer

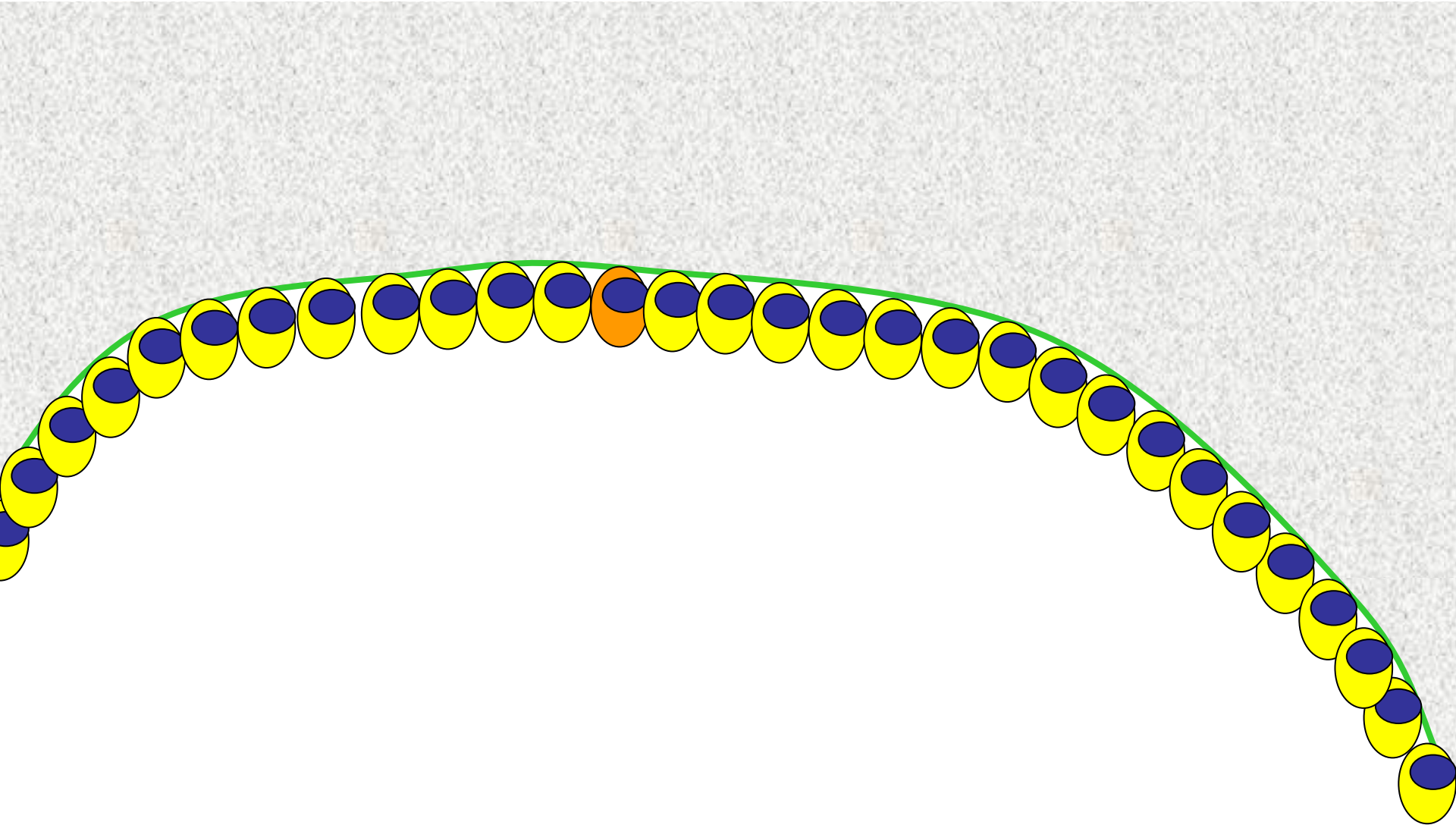
100-200 different types of cancer



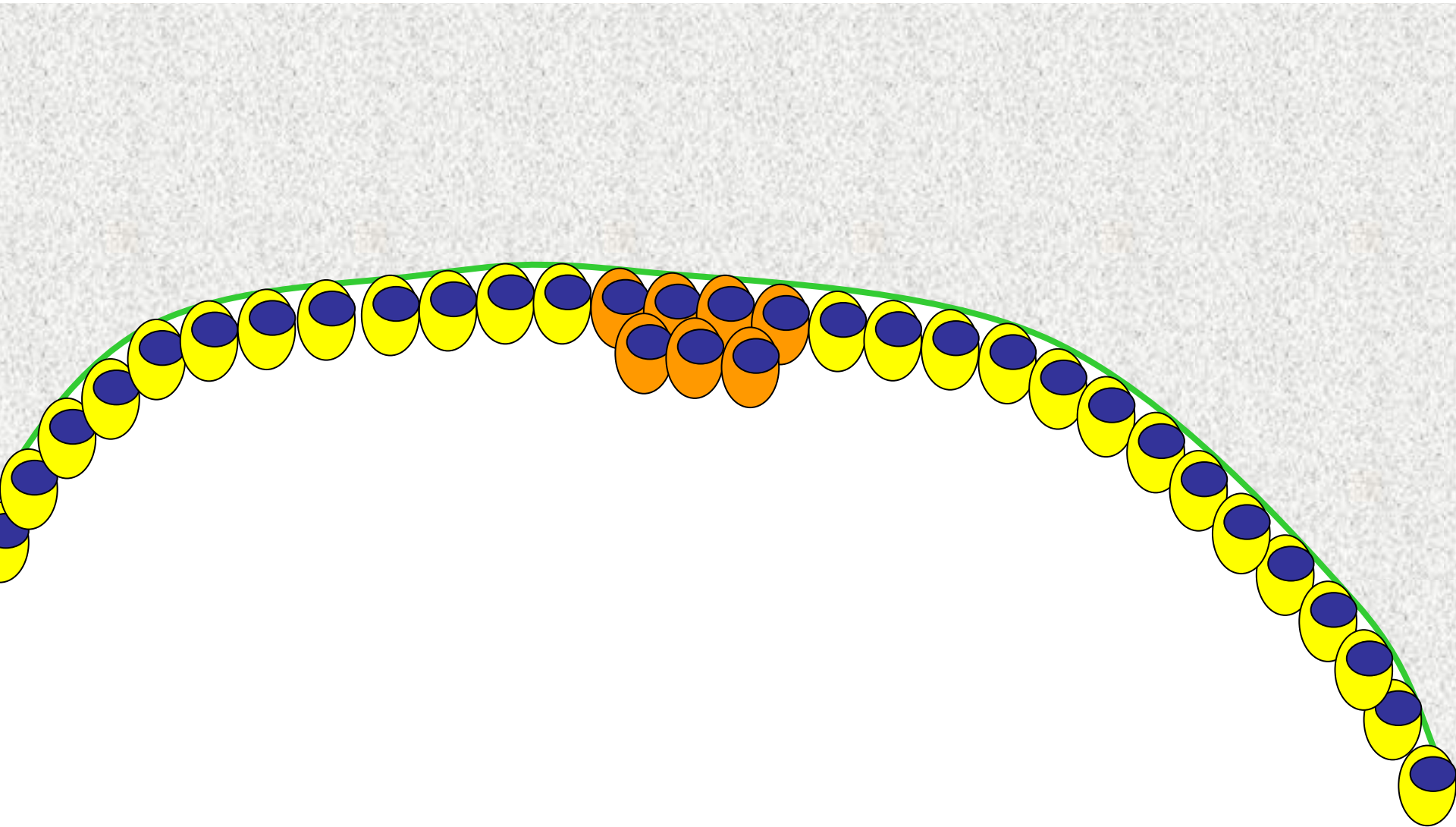
A cancer is a clone of cells which is growing in an unregulated manner



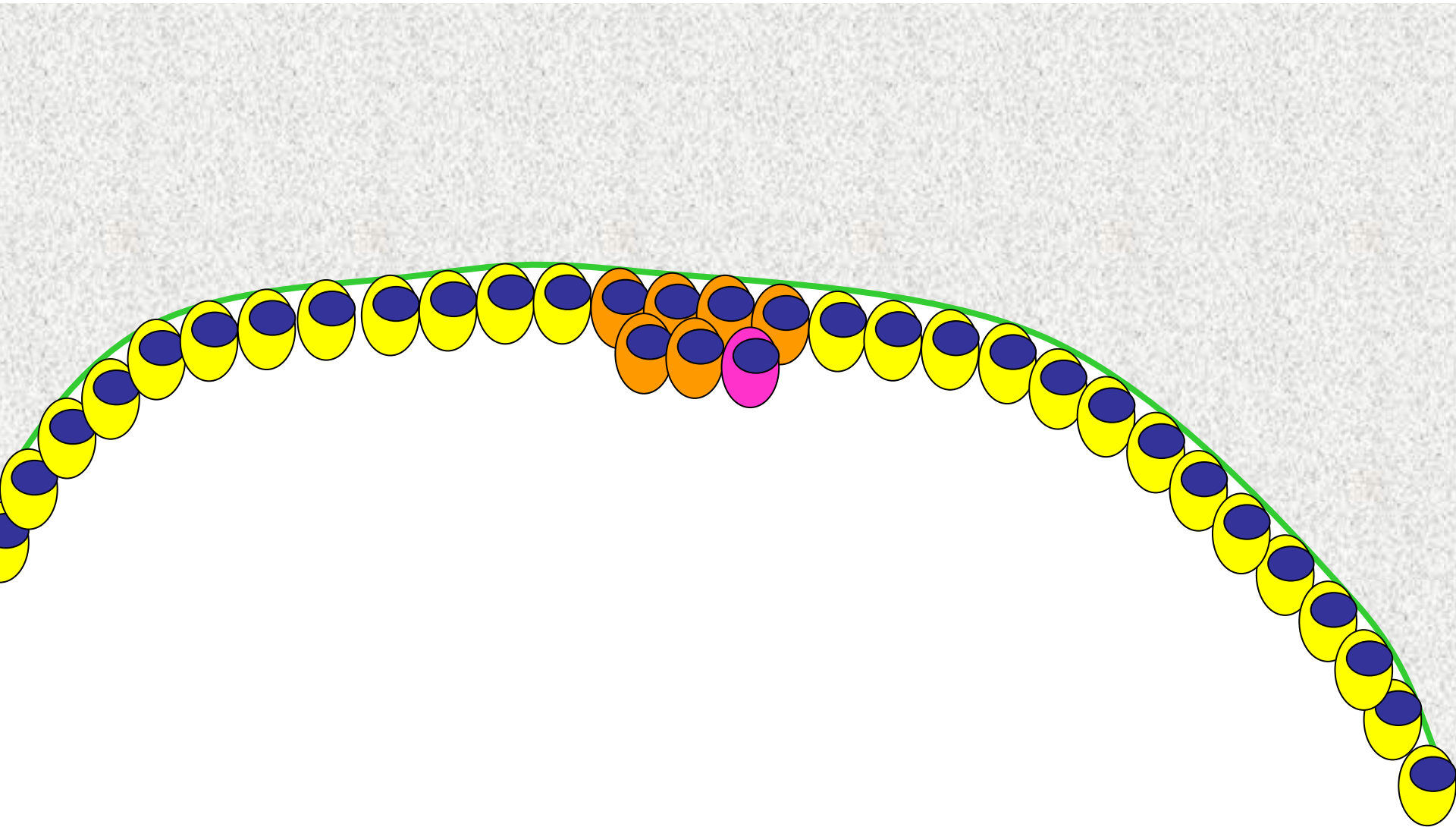
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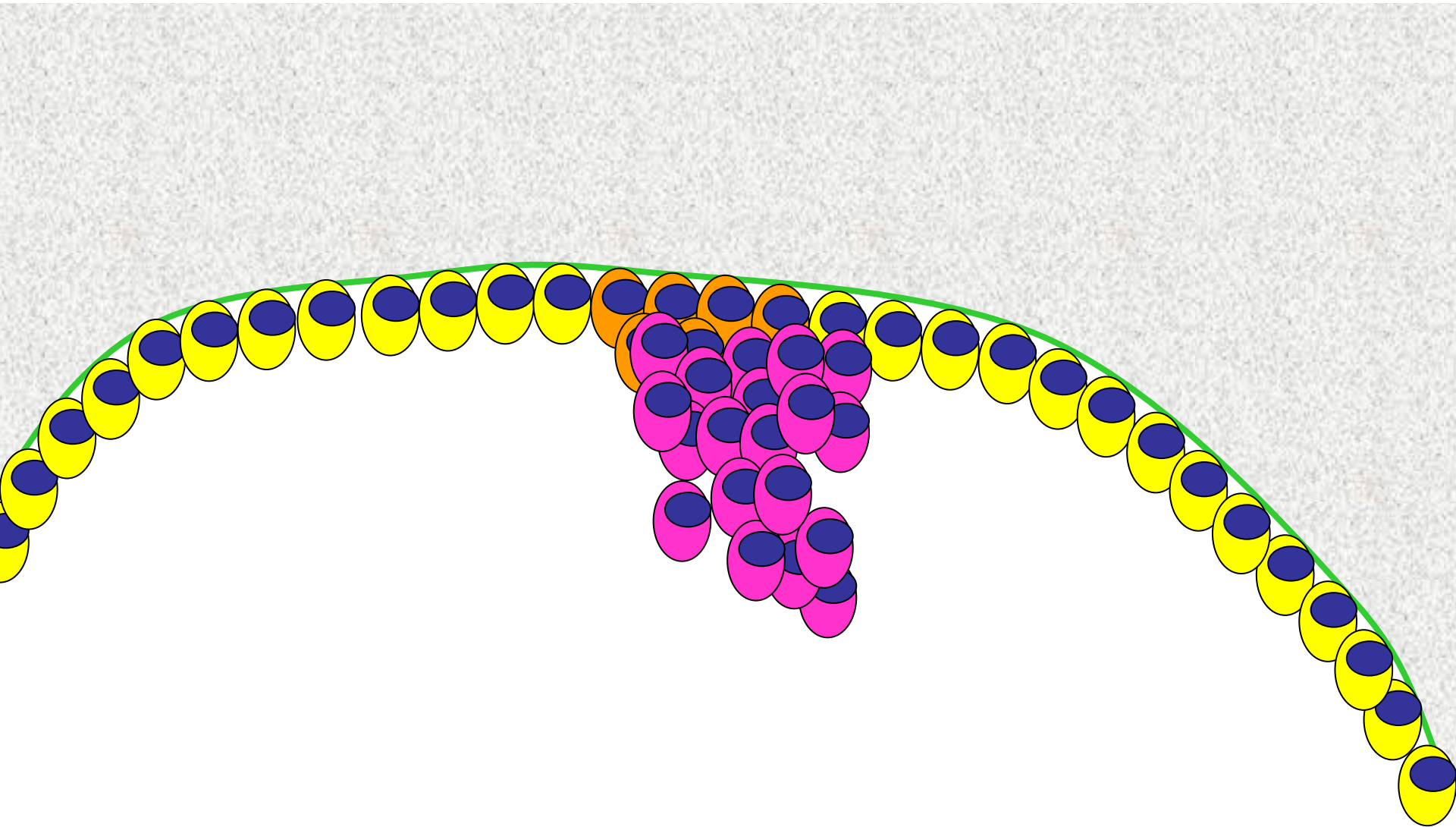
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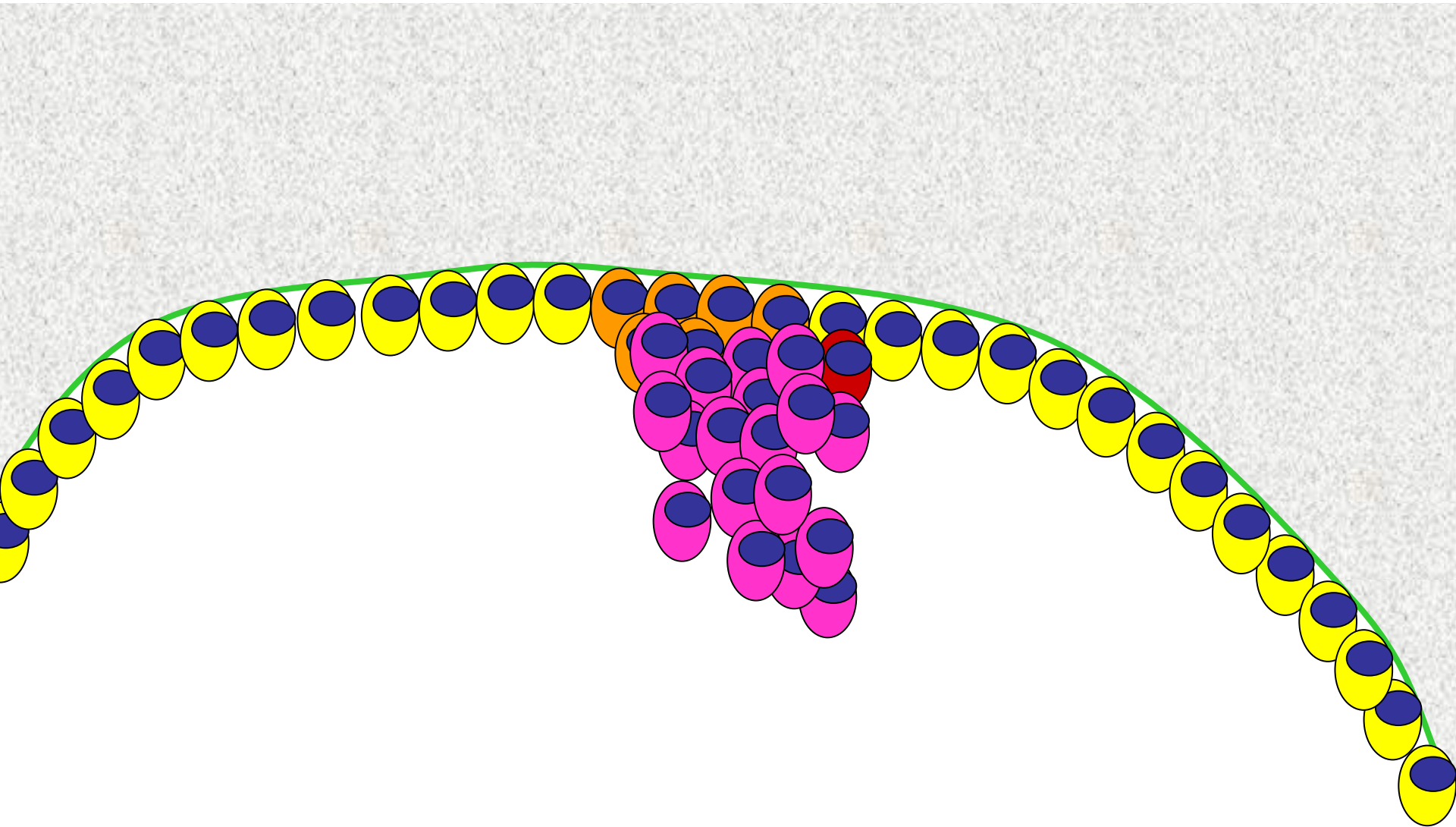
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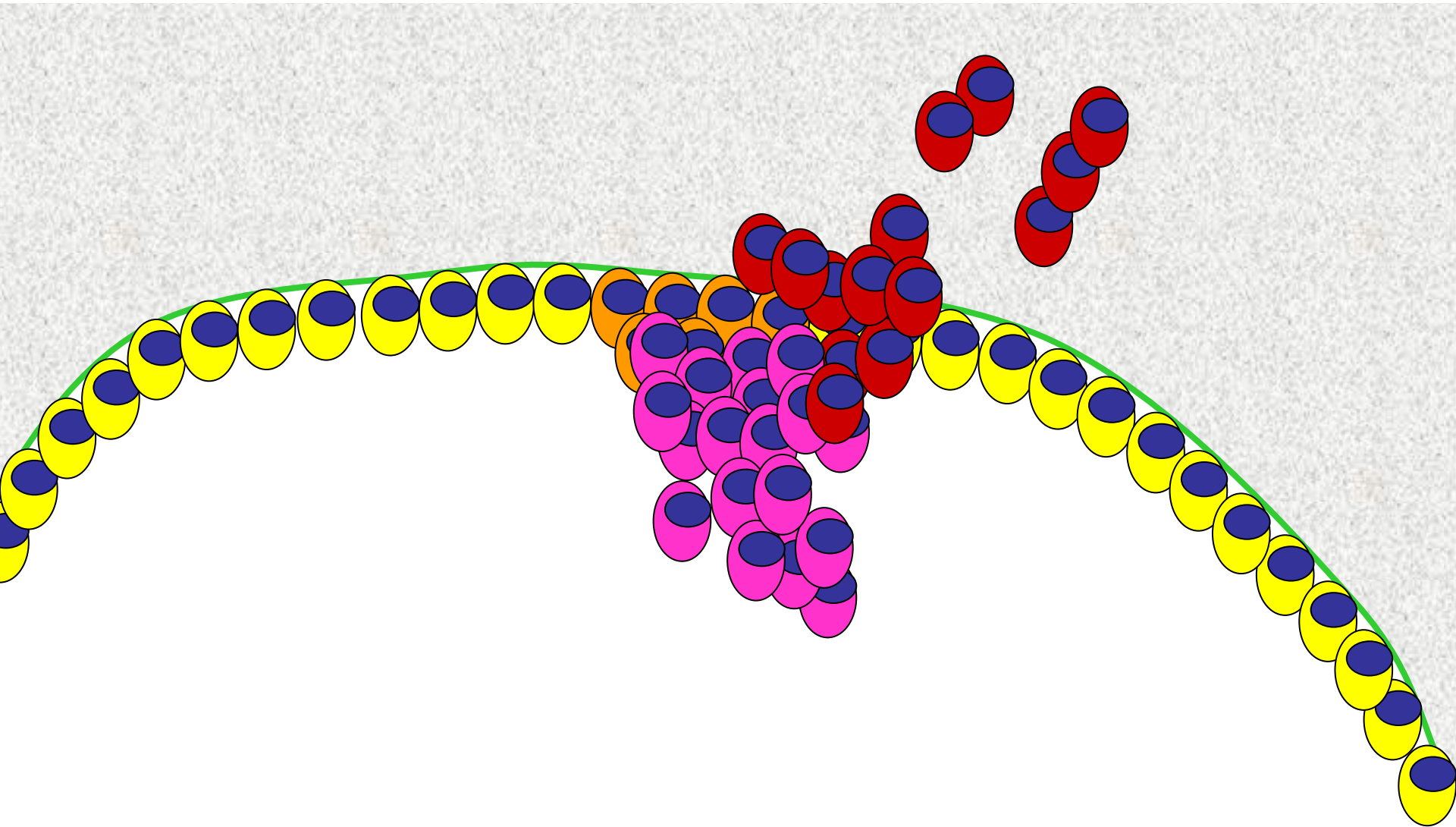
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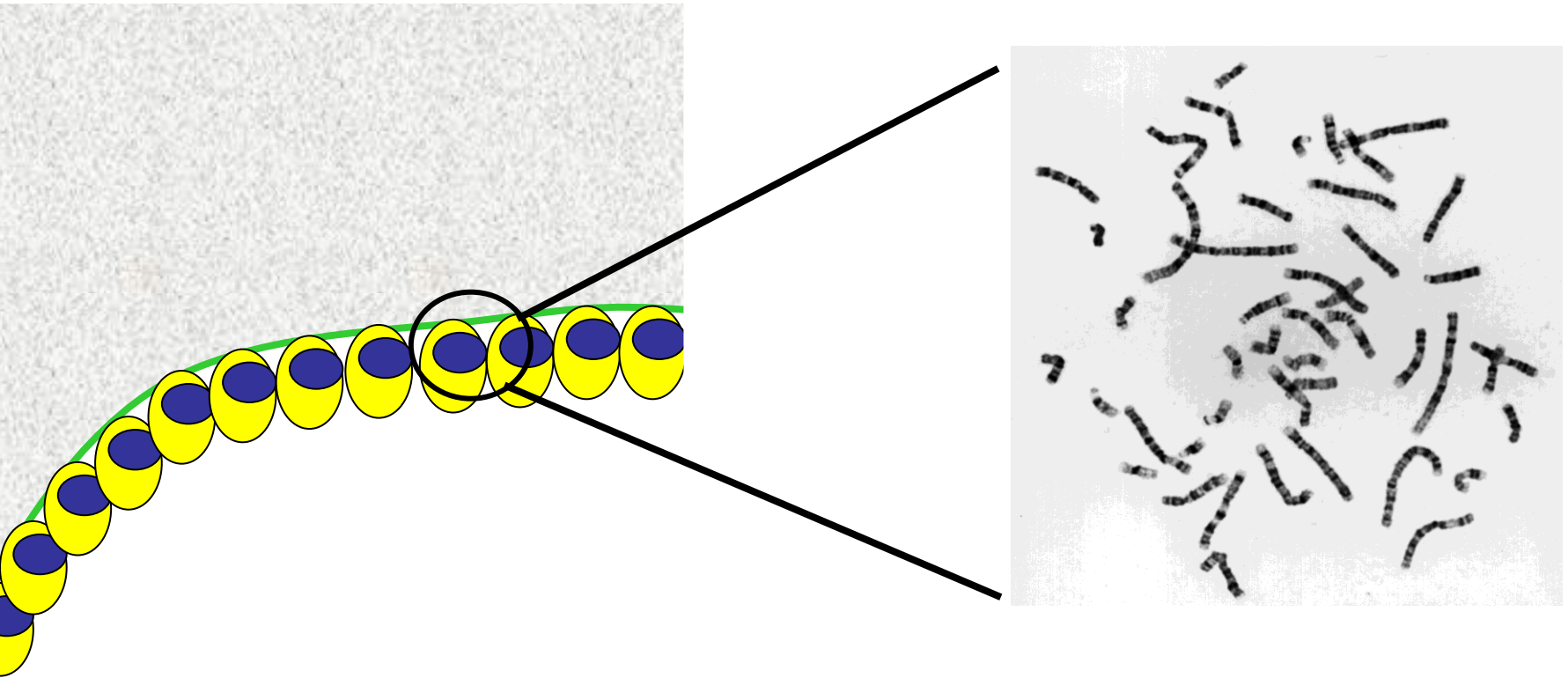
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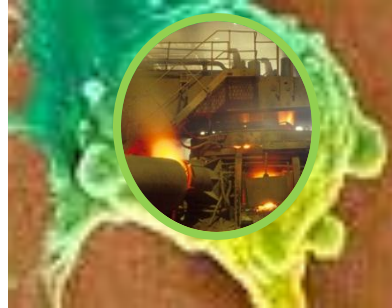
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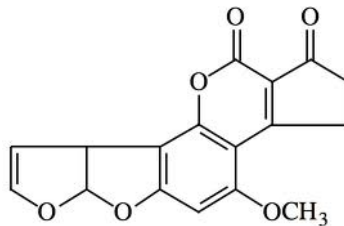
Somatic mutations occur in all cells of the body throughout life



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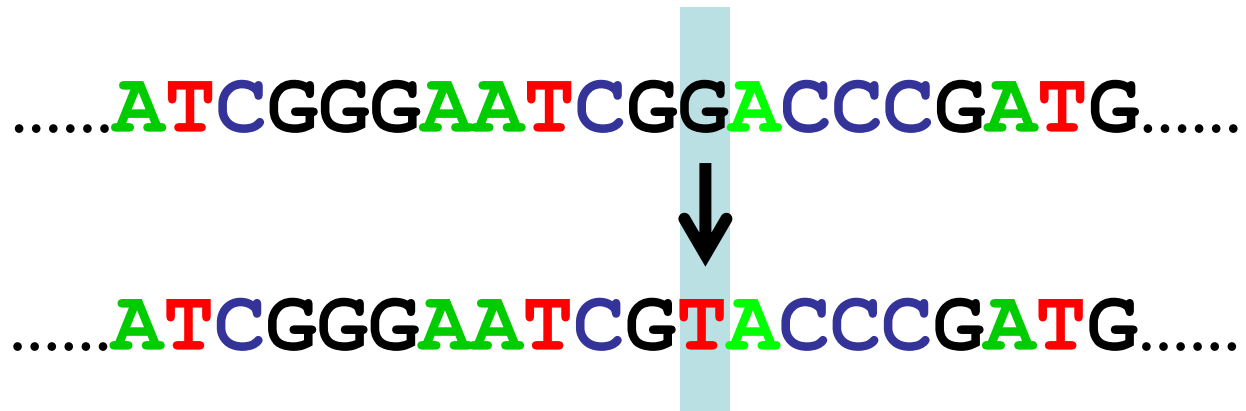
.....ATCGGGAATCGGACCCGATG.....



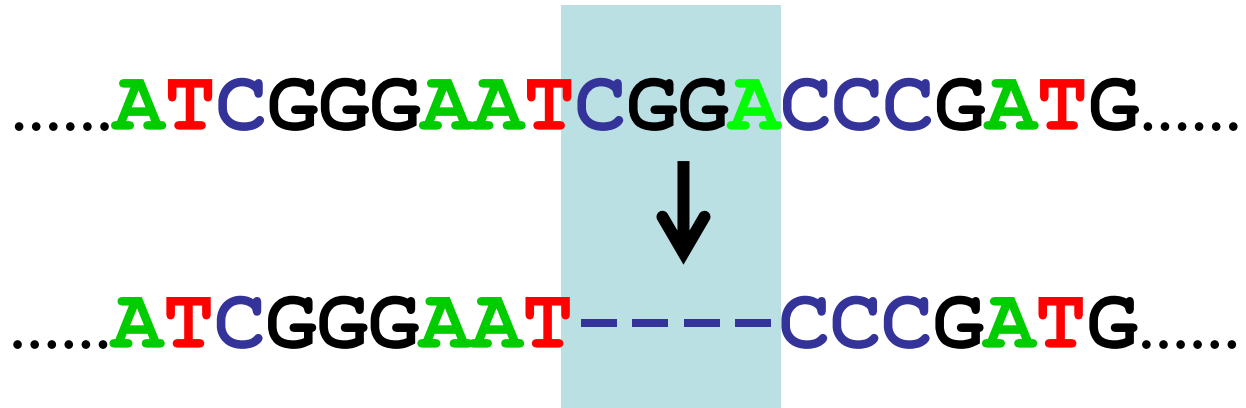
Types of somatic mutations

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Types of somatic mutations



Types of somatic mutations



Types of somatic mutations

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Types of somatic mutations

.....ATCGGGAAATCGG-

Types of somatic mutations

.....ATCGGGAAATCGG--CTGAGTTTTGAGGG.....

Driver and Passenger mutations



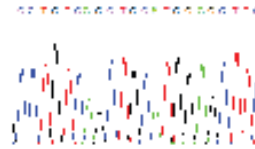
Cancer genes

Driver and Passenger mutations

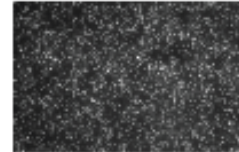


Cancer genes

Progress in the generation of DNA sequence 1980-2010

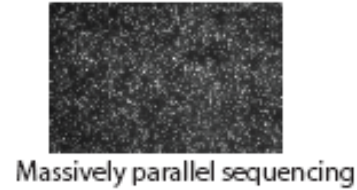
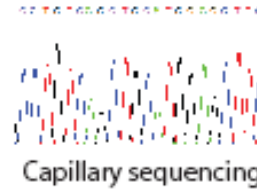


Capillary sequencing

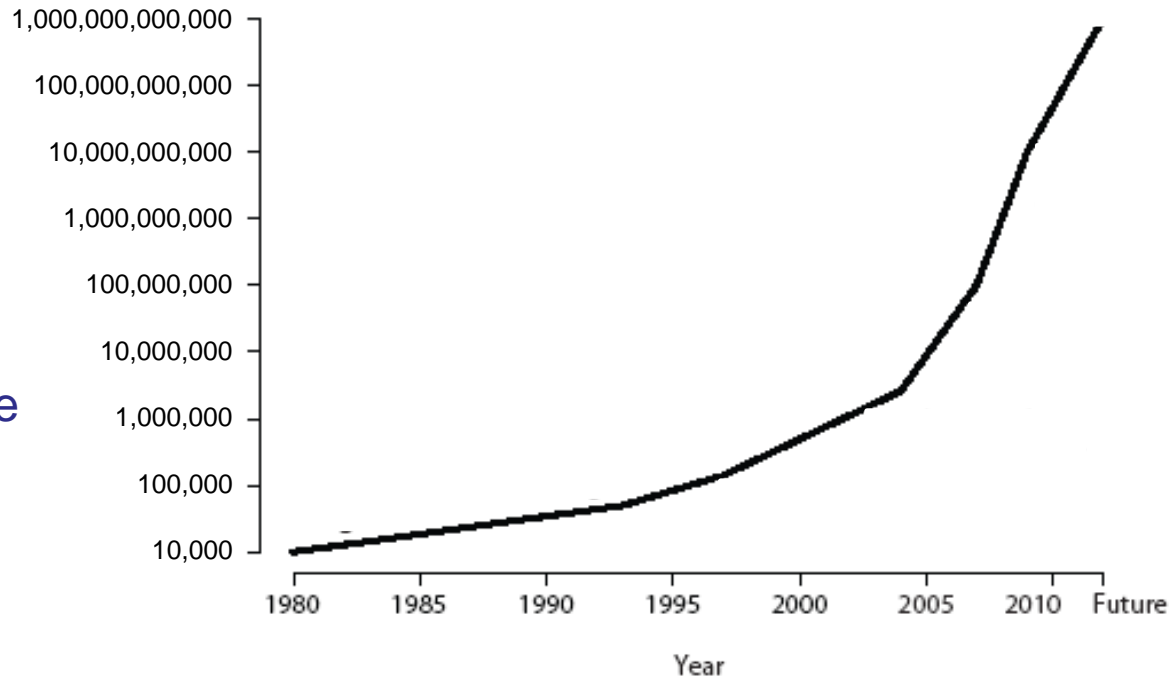


Massively parallel sequencing

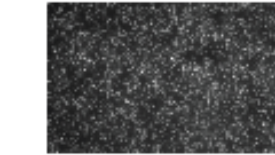
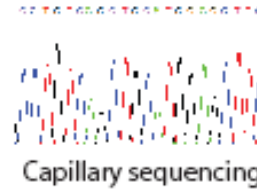
Progress in the generation of DNA sequence 1980-2010



bases
per day
per machine



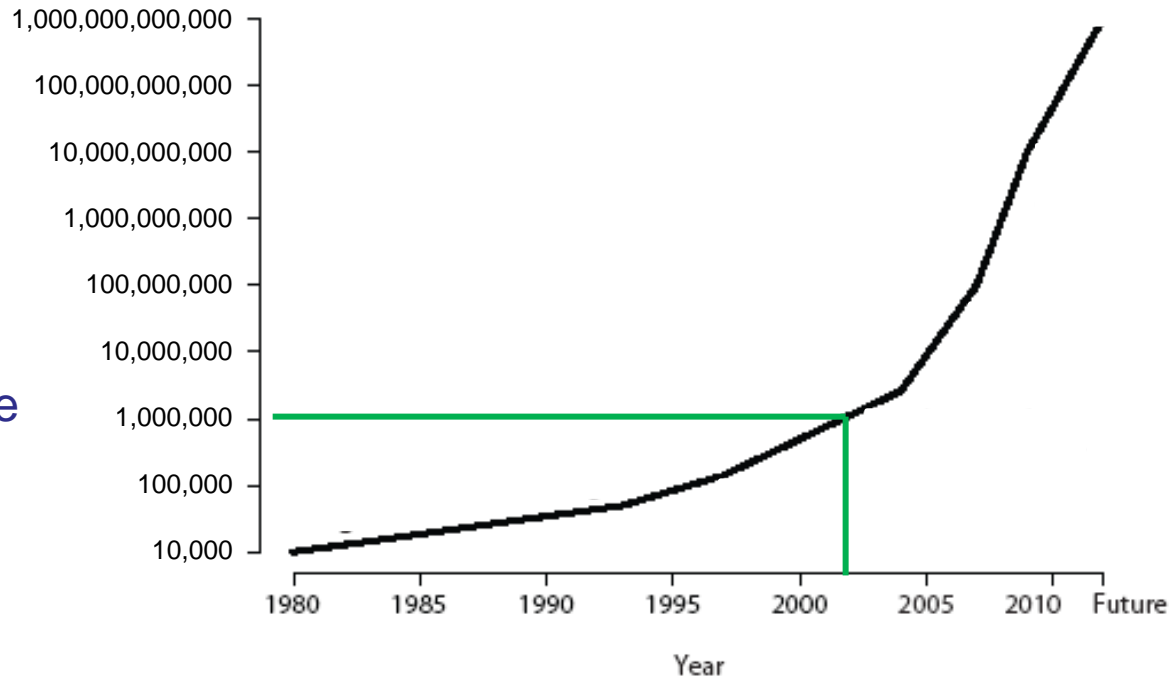
Progress in the generation of DNA sequence 1980-2010



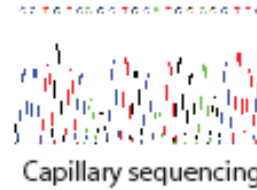
Capillary sequencing

Massively parallel sequencing

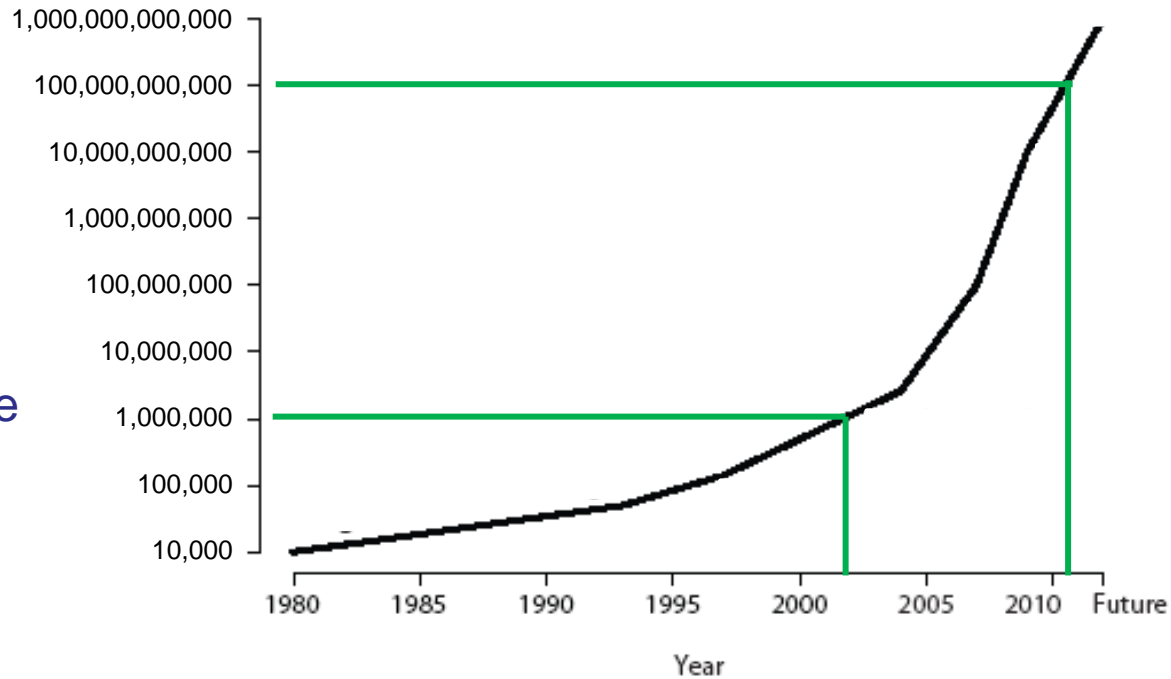
bases
per day
per machine



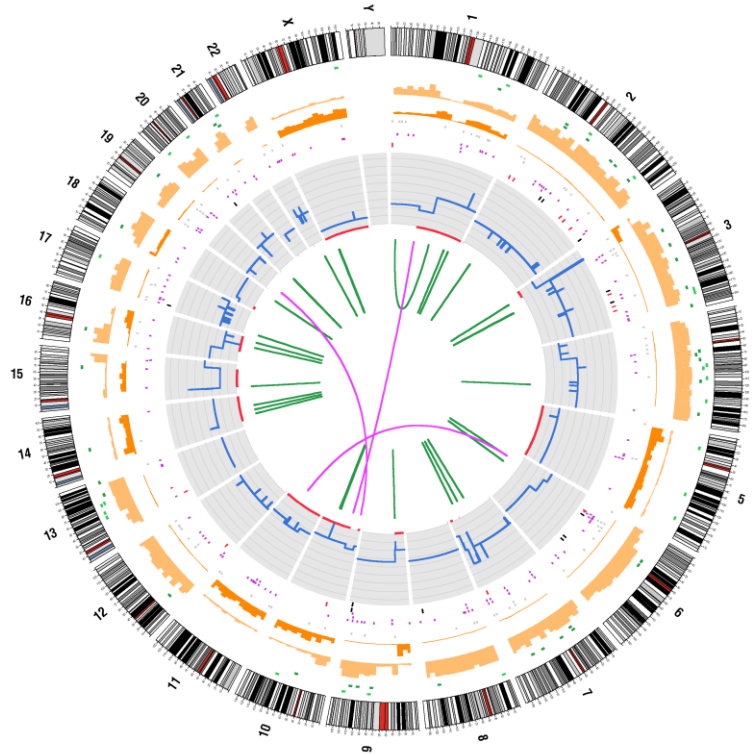
Progress in the generation of DNA sequence 1980-2010



bases
per day
per machine



A comprehensive catalogue of somatic mutations in a malignant melanoma



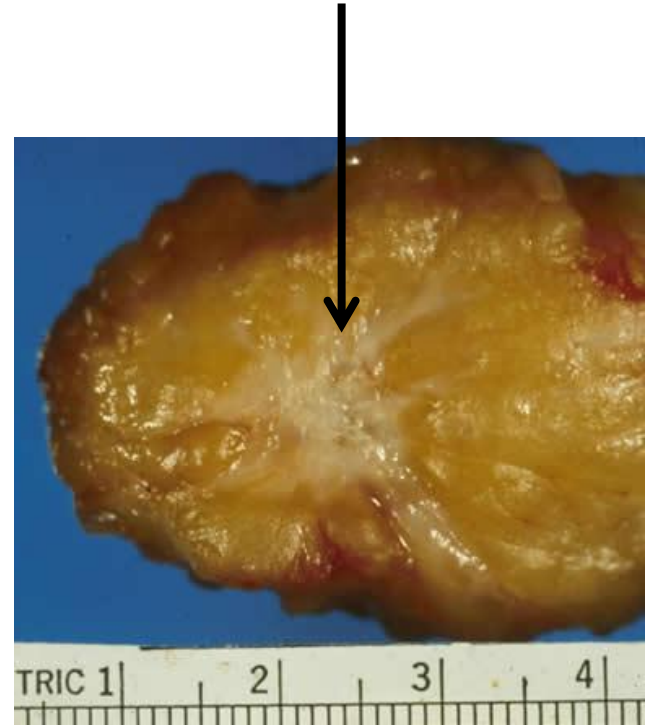
33,345 base changes
66 insertions / deletions
37 rearrangements

Key questions we can now ask about cancers and their genomes

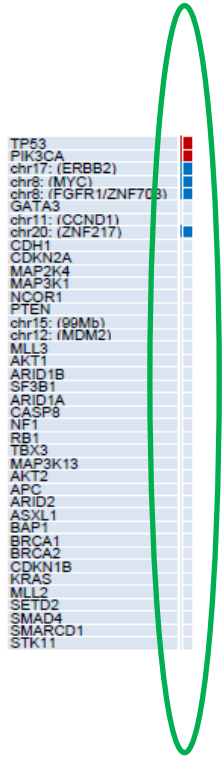
- What are the mutated cancer genes and how different are individual cancers in their mutated cancer genes?
- What causes the somatic mutations in the first place?
- How do cancers spread?
- How can we use all this information to help patients?

Breast Cancer

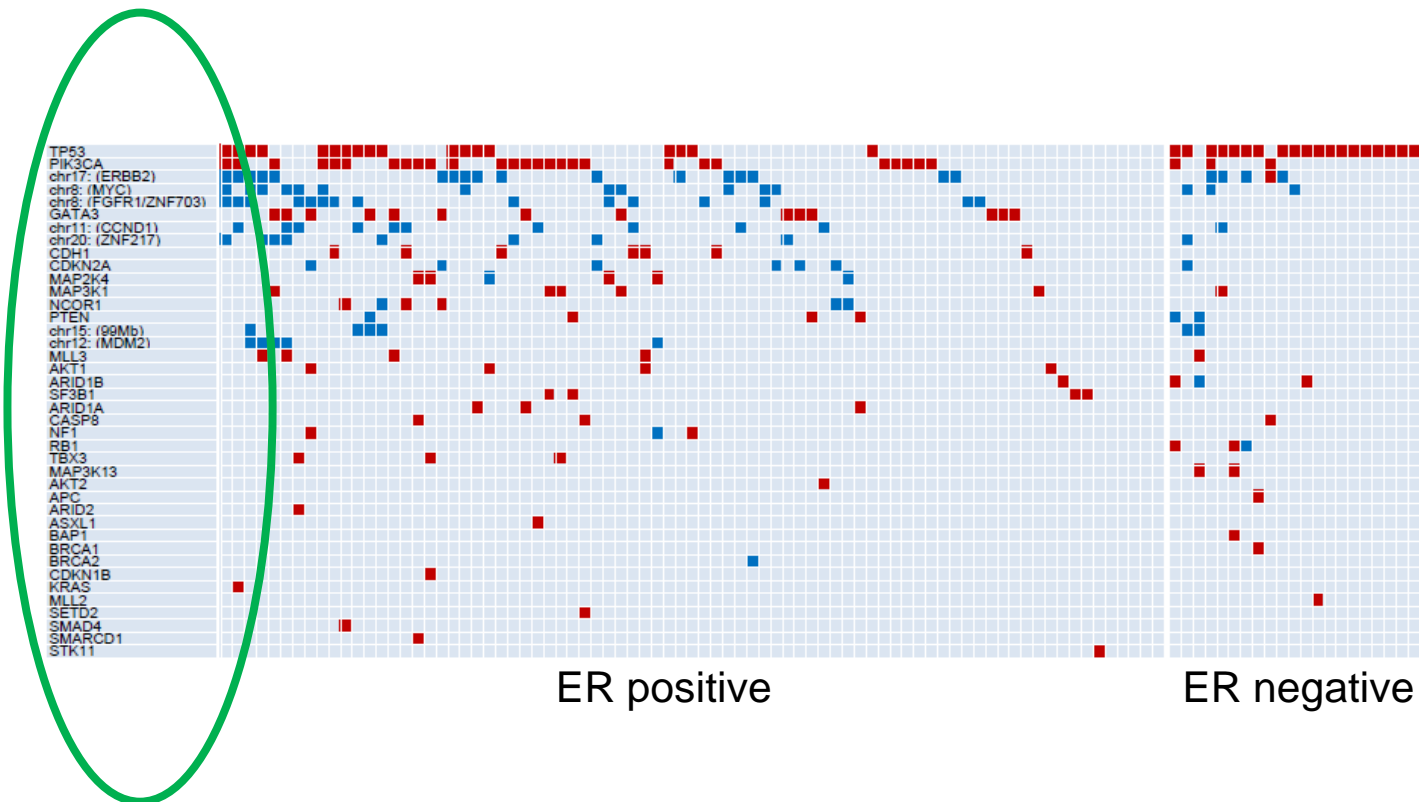
- In UK:
 - 50,000 cases per year
 - 12,000 deaths per year



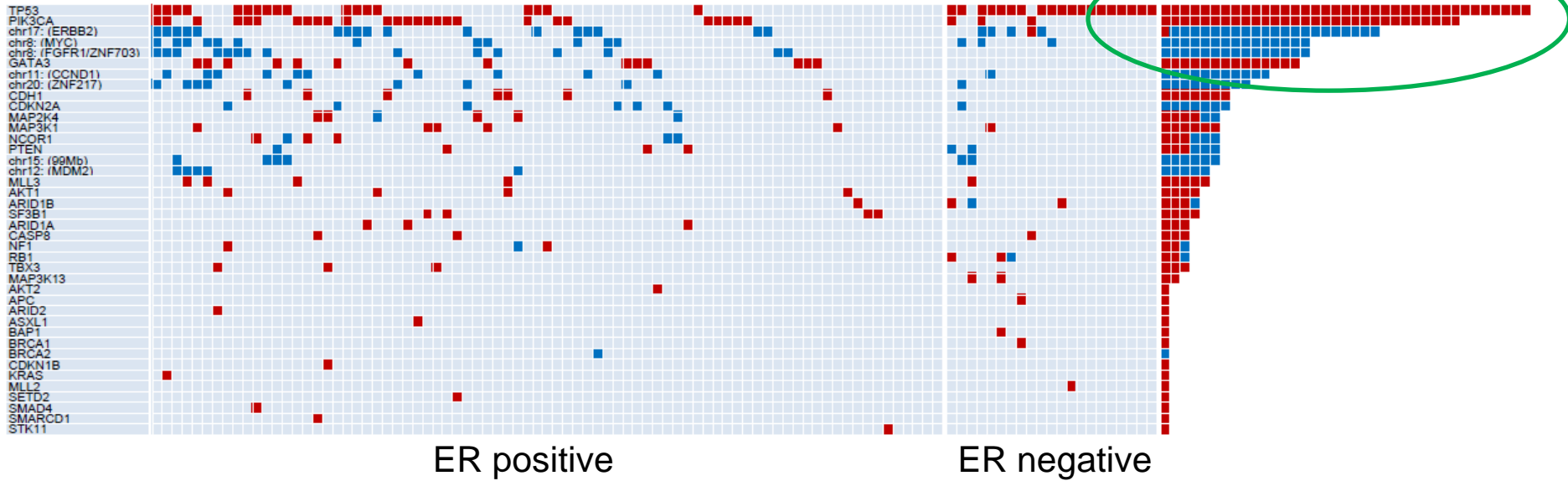
The landscape of driver mutations in breast cancer



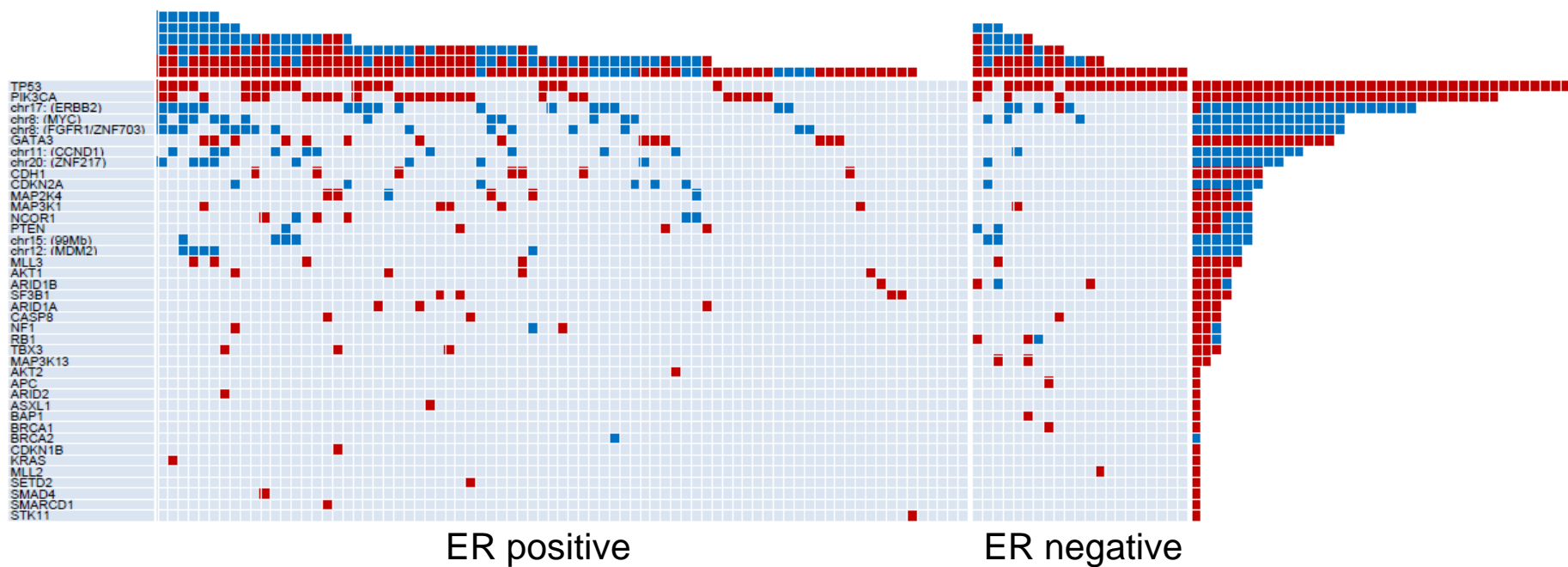
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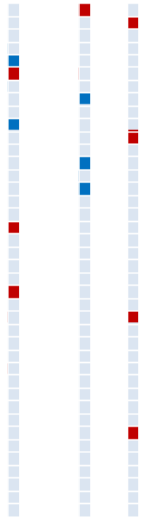


The landscape of driver mutations in breast cancer

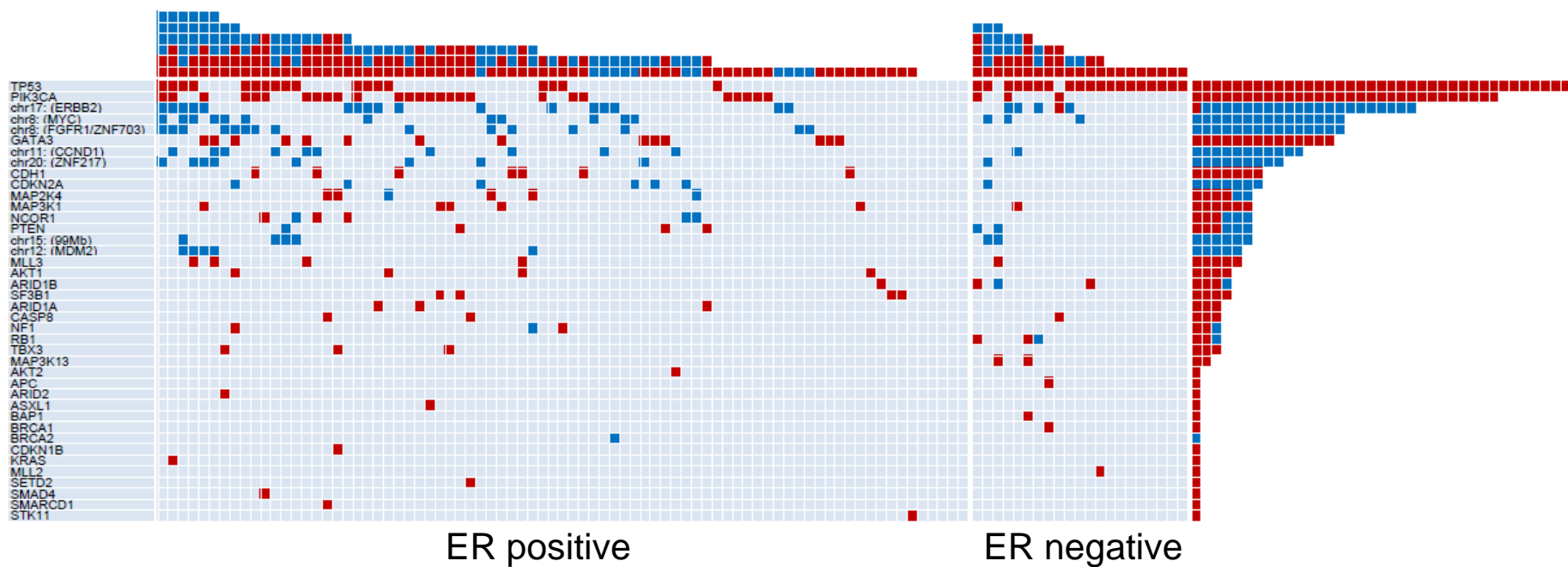


The landscape of driver mutations in breast cancer

TP53
PIK3CA
chr17: (ERBB2)
chr8: (MYC)
chr8: (FGFR1/ZNF)
GATA3
chr11: (CCND1)
chr20: (ZNF217)
CDH1
CDKN2A
MAP2K4
MAP3K1
NGOR1
PTEN
chr15: (99Mb)
chr12: (MDM2)
MLL3
AKT1
ARID1B
SF3B1
ARID1A
CASP8
NF1
RB1
TBX3
MAP3K13
AKT2
APC
ARID2
ASXL1
BAP1
BRCA1
BRCA2
CDKN1B
KRAS
MLL2
SETD2
SMAD4
SMARCD1
STK11



The landscape of driver mutations in breast cancer



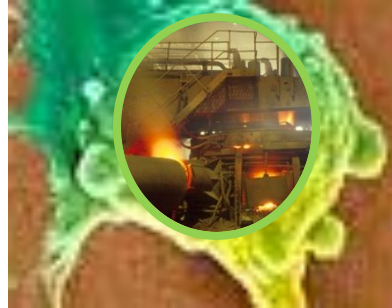
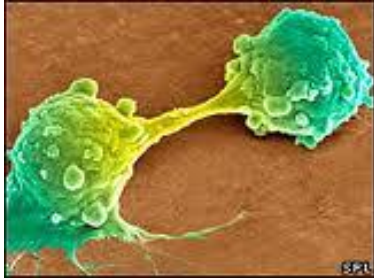
How many cancer genes with driver mutations across all types of cancer?

- ~20,000 genes that make proteins in the human genome
- ~550 are cancer genes carrying driver mutations involved in causing human cancer

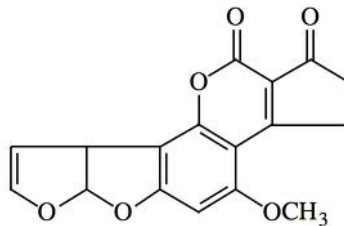
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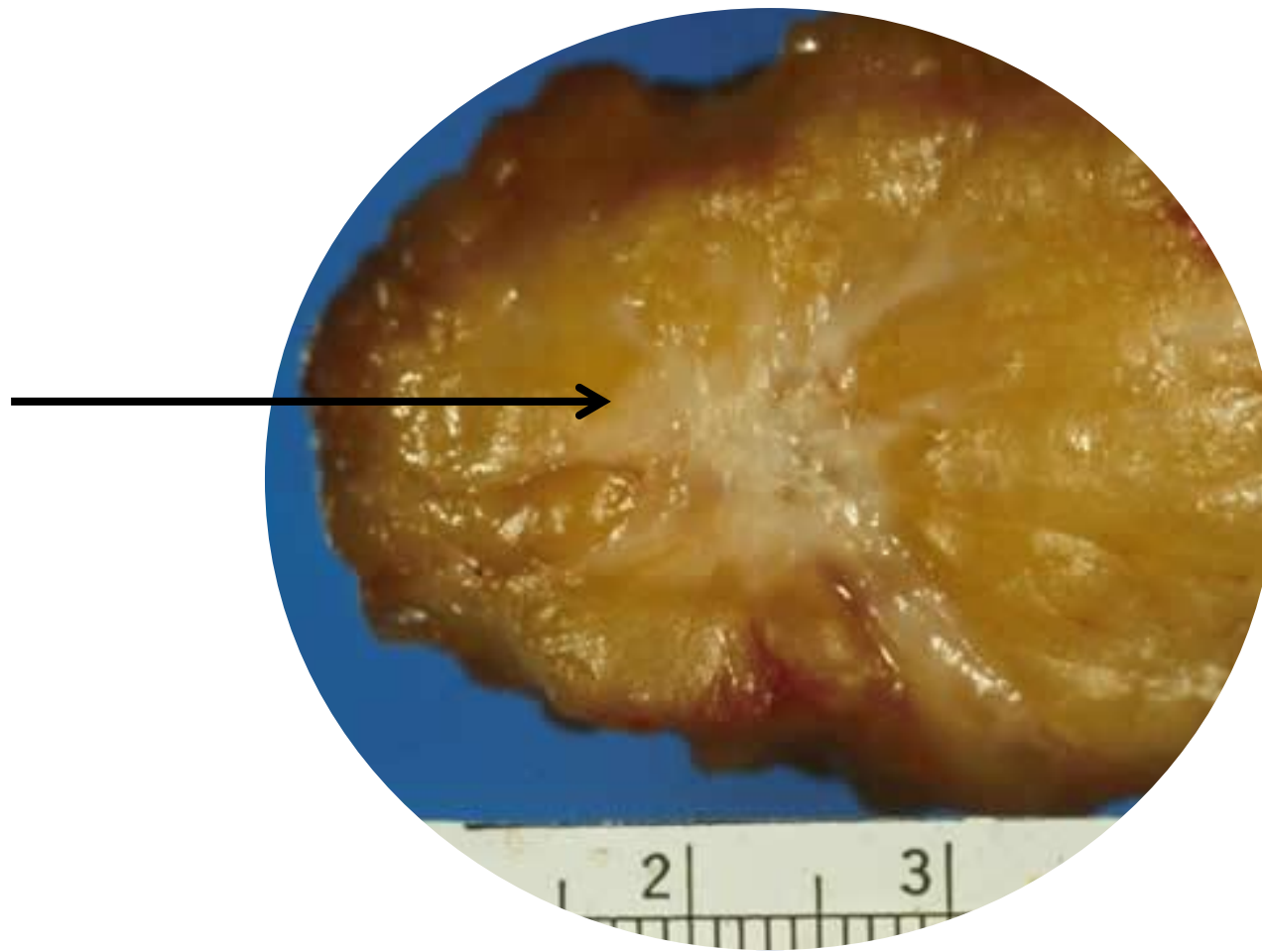
Known causes of somatic mutations



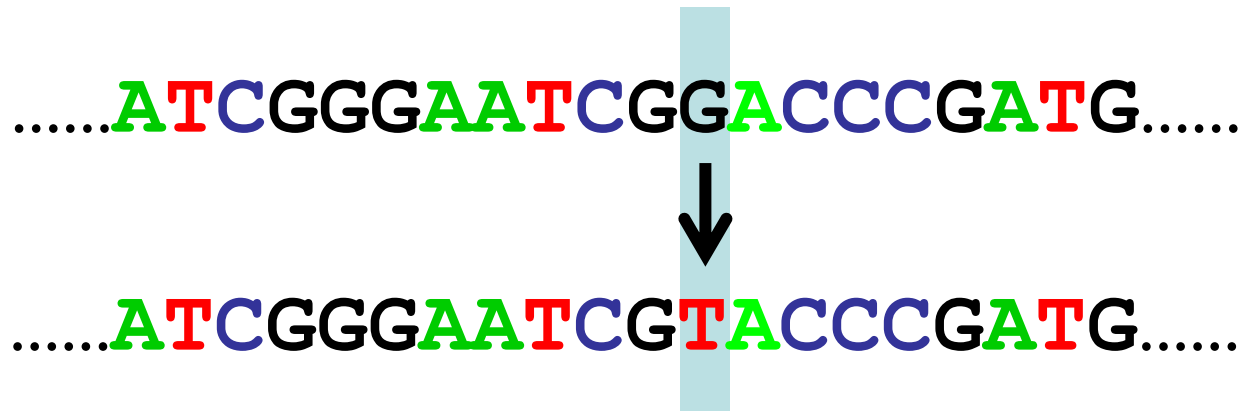
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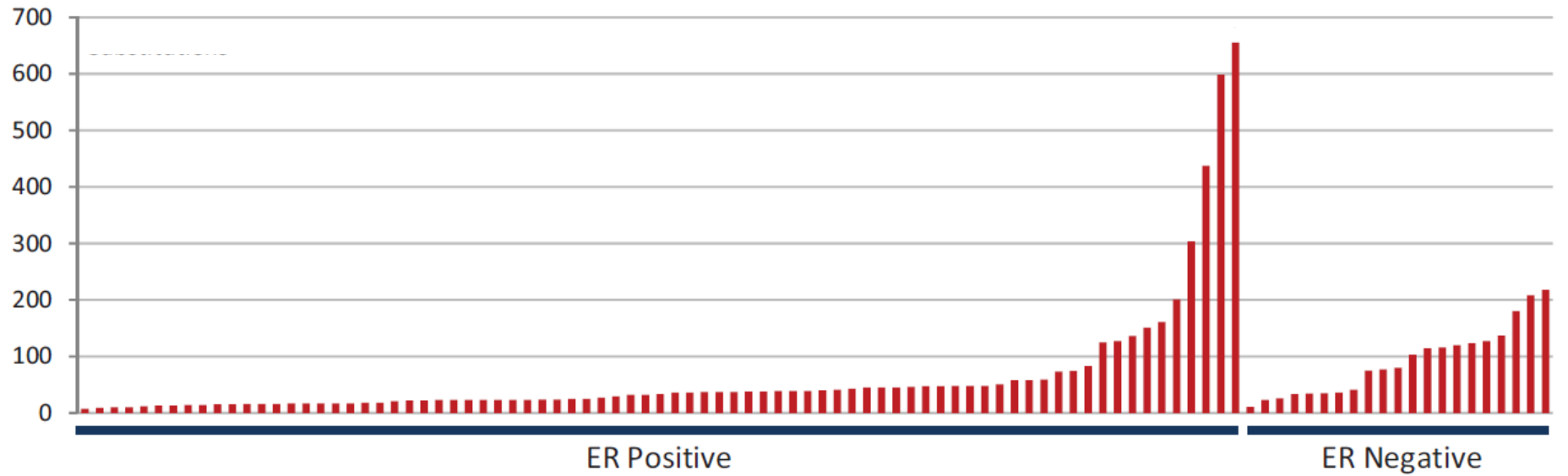
What causes the somatic mutations in breast cancer?



Types of somatic mutations



Numbers of base substitution mutations in 100 breast cancers

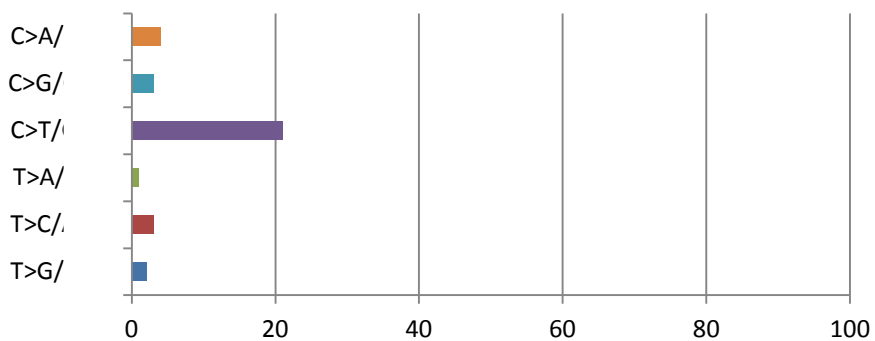


Types of substitution mutations

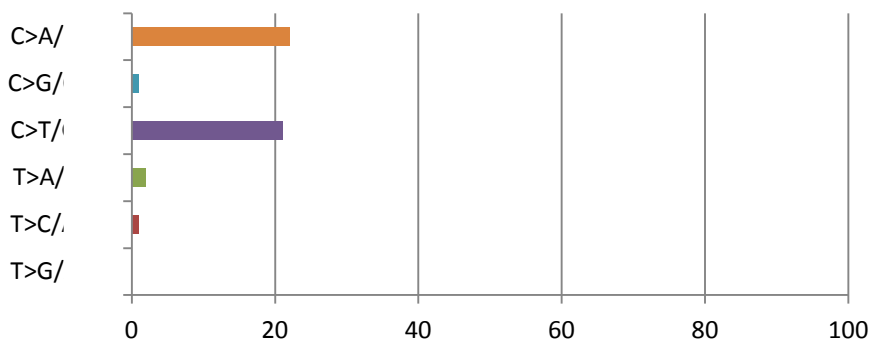
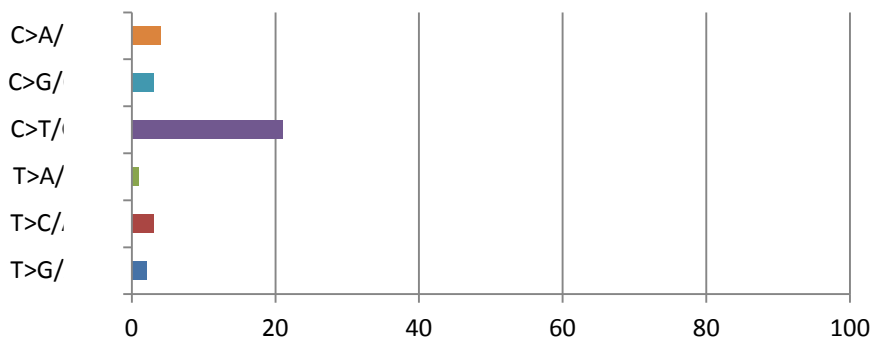
C → T
C → A
C → G
F → C
F → A
F → G

G → A
G → T
G → C
A → G
A → T
A → C

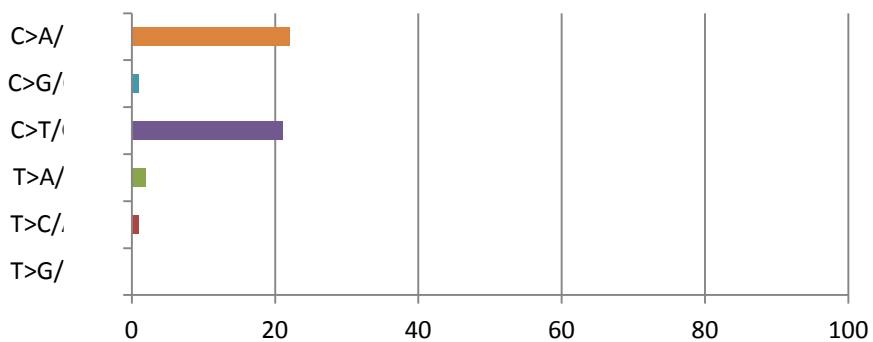
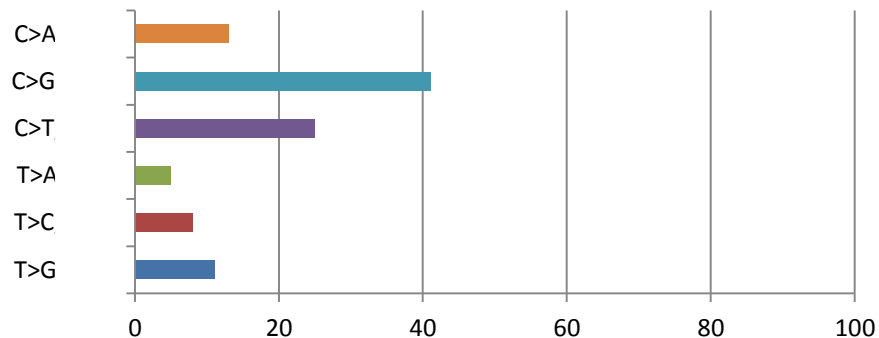
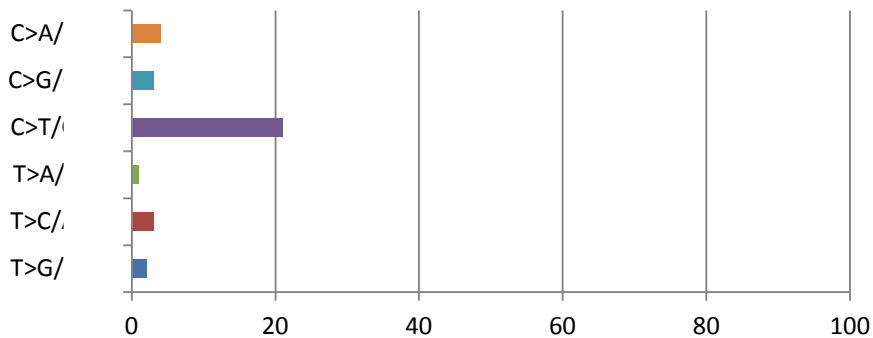
Variation in base substitution patterns among breast cancers



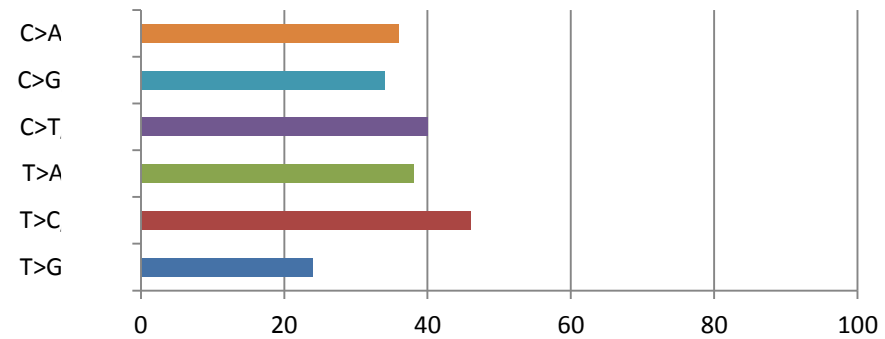
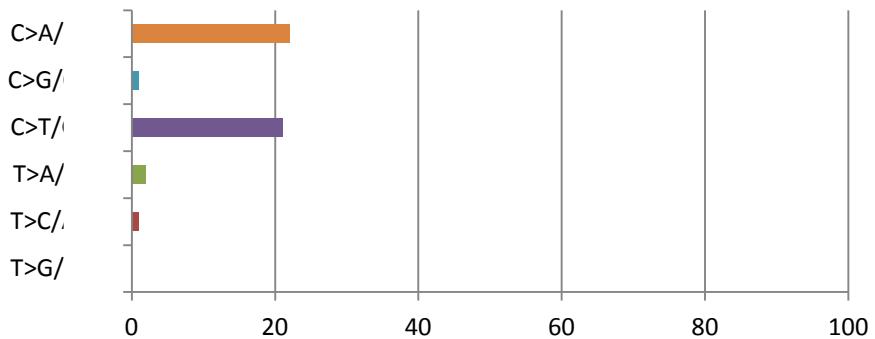
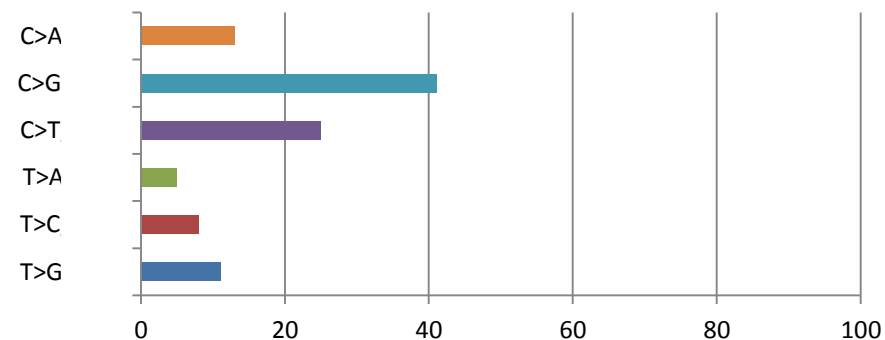
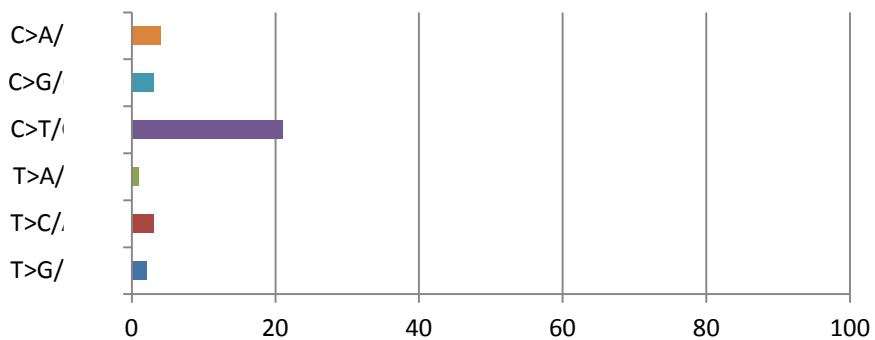
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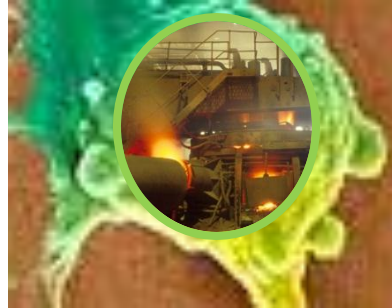
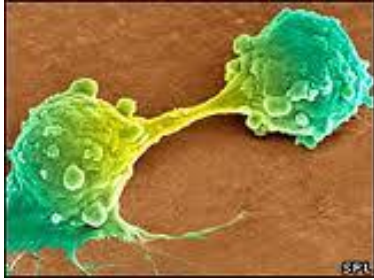
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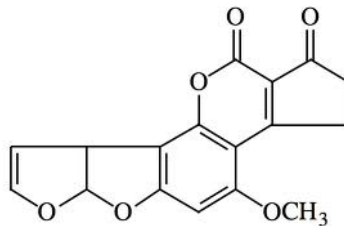
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Known causes of somatic mutations



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Liver metastases from a primary ductal carcinoma of the pancreas



Types of somatic mutations

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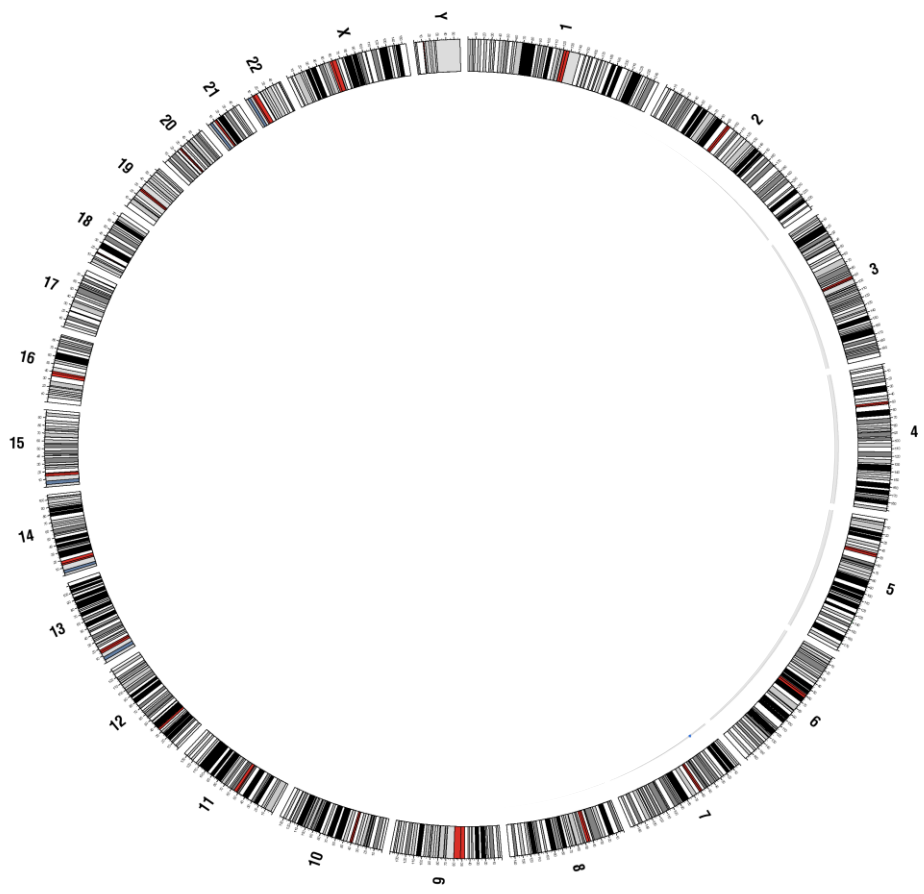
Types of somatic mutations

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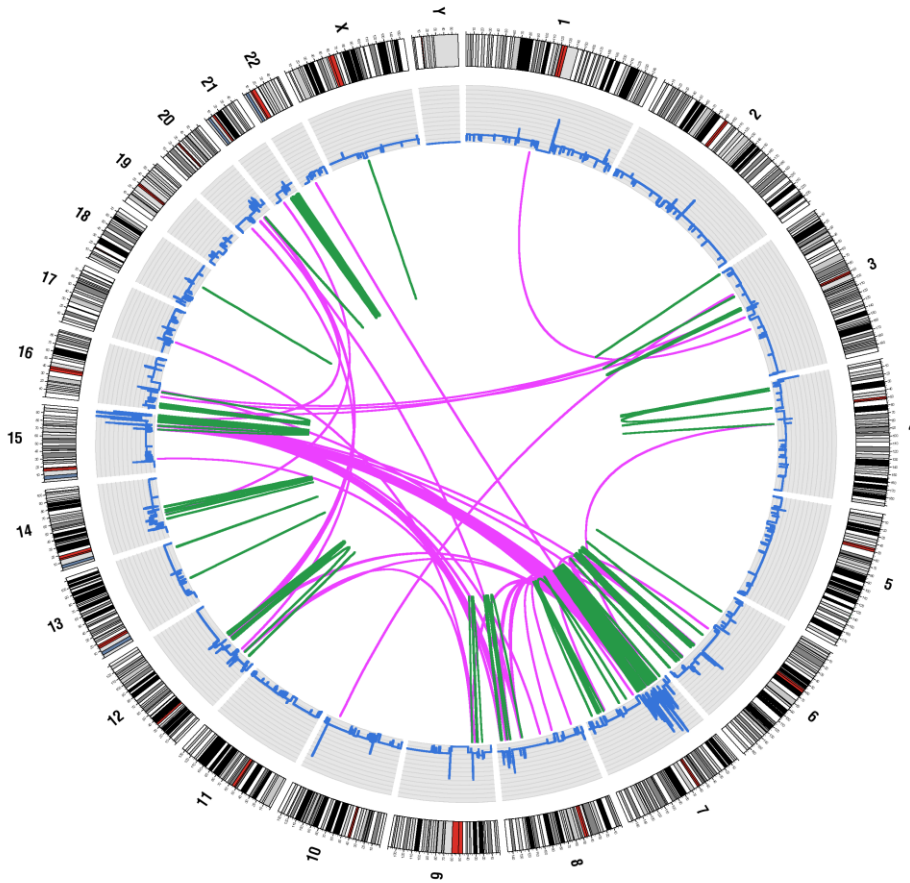
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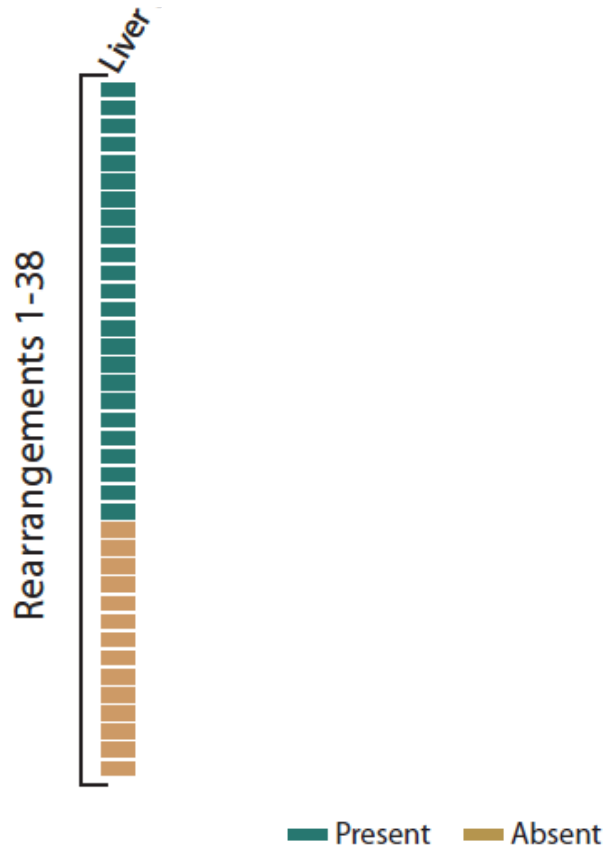
Genome-wide detection of rearrangements



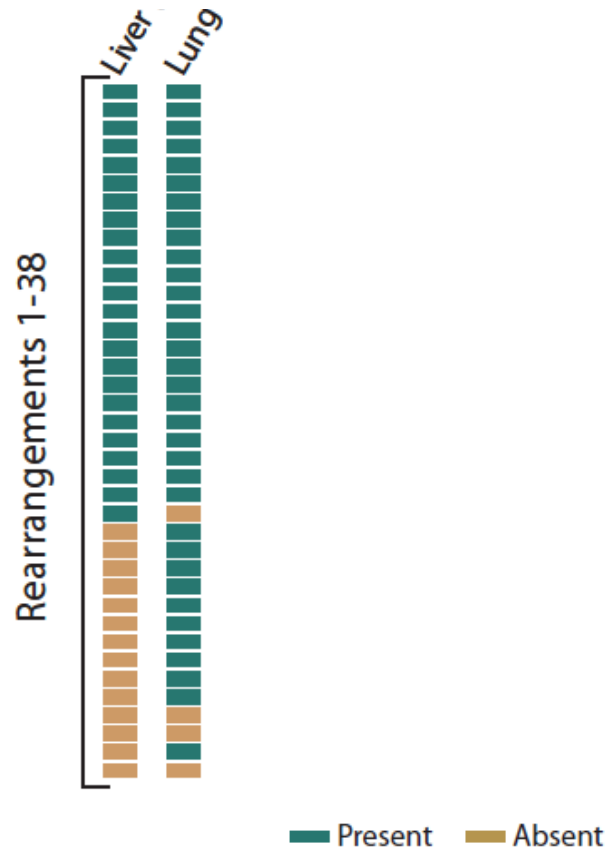
Genome-wide detection of rearrangements



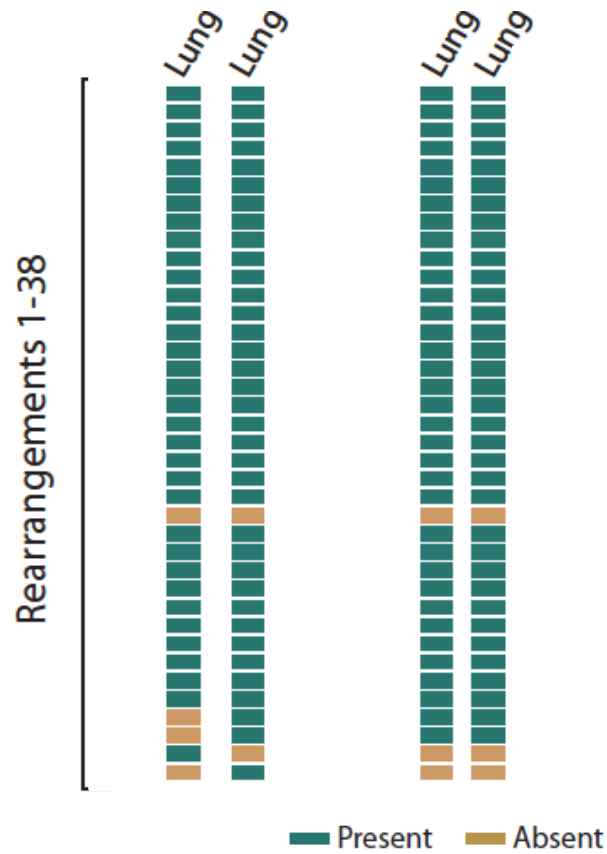
Analysis of rearrangements in metastases from pancreatic cancer



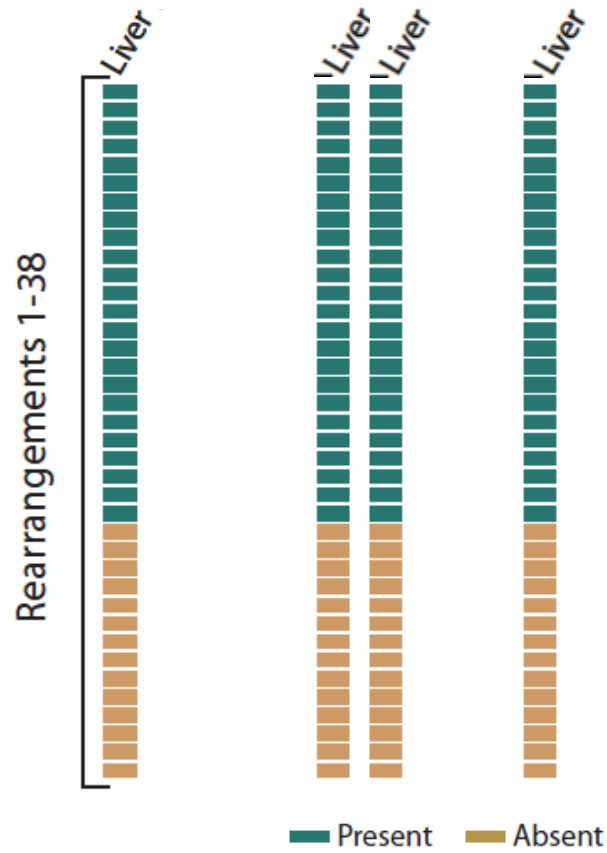
Analysis of rearrangements in metastases from pancreatic cancer



Analysis of rearrangements in metastases from pancreatic cancer



Analysis of rearrangements in metastases from pancreatic cancer



Liver metastases from a primary ductal carcinoma of the pancreas



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Malignant Melanoma

- Develops from melanocytes in skin
- In the UK
 - 11,000 cases per year
 - 2,000 deaths per year

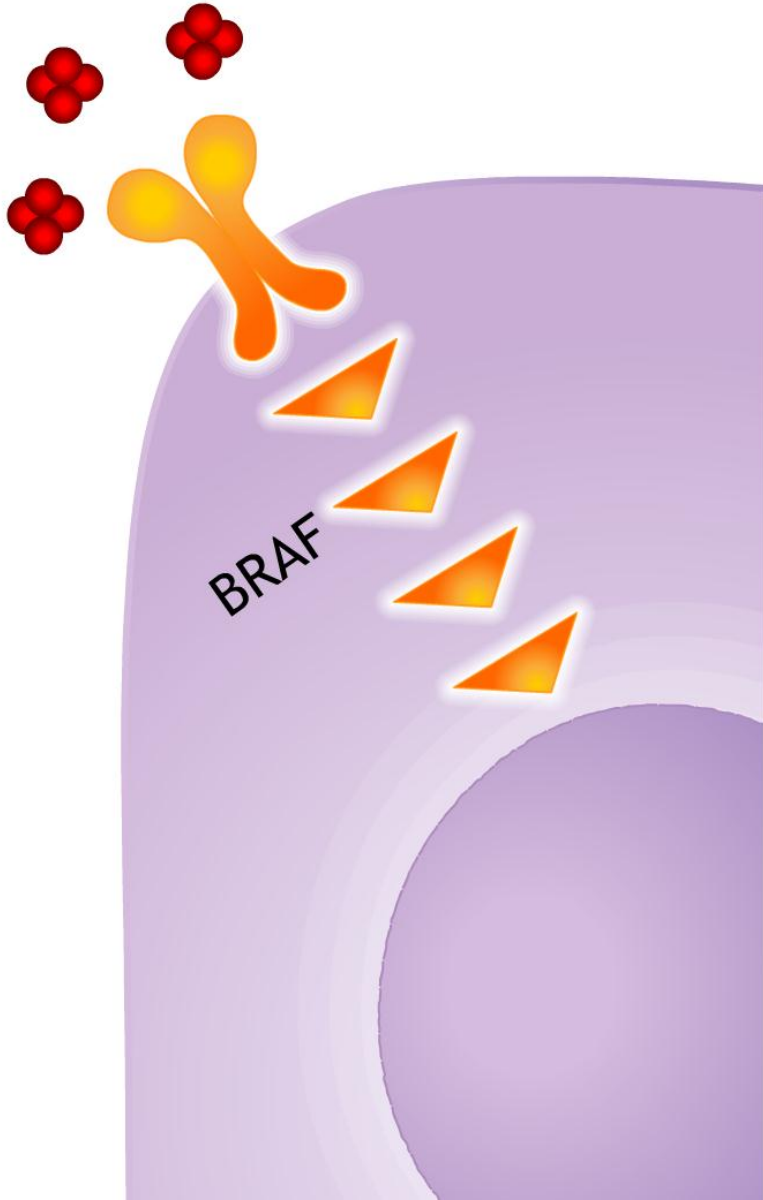


Mutations of **BRAF** found in malignant melanoma and other cancers

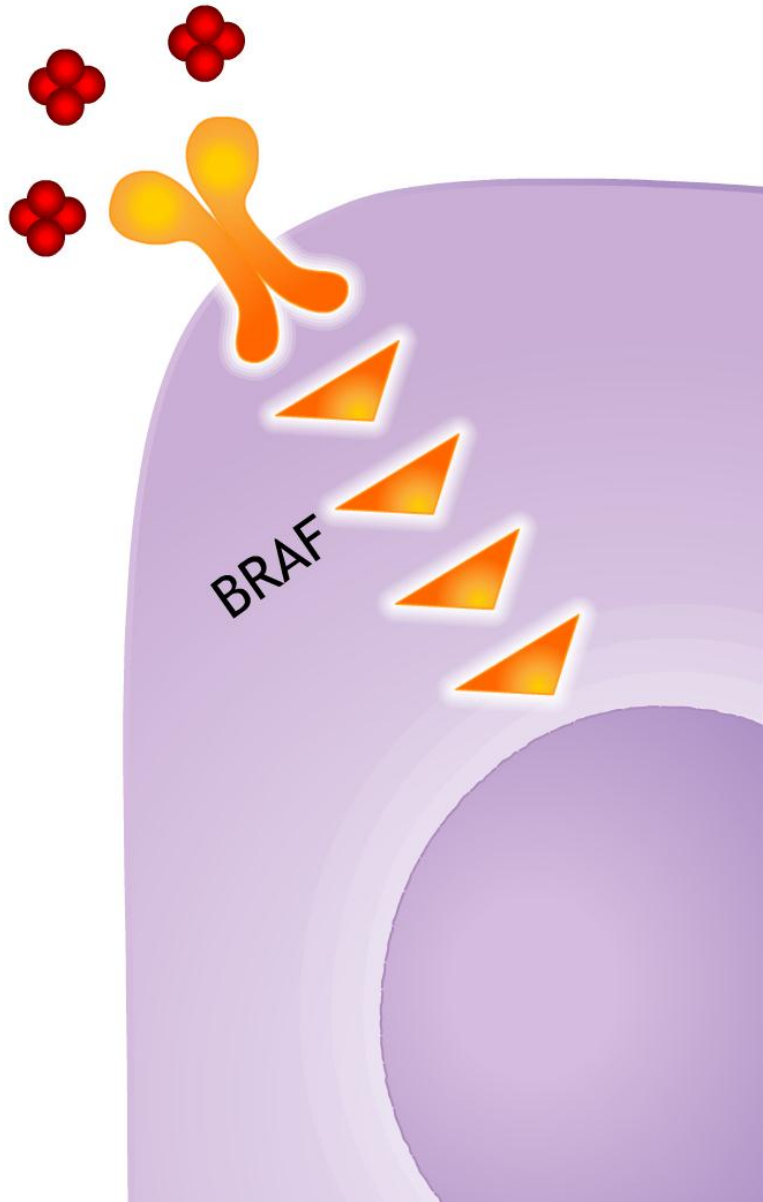
- Driver mutations of **BRAF** found in
 - 70% malignant melanoma
 - 30% thyroid cancer
 - 10% colorectal cancer



Normal cell



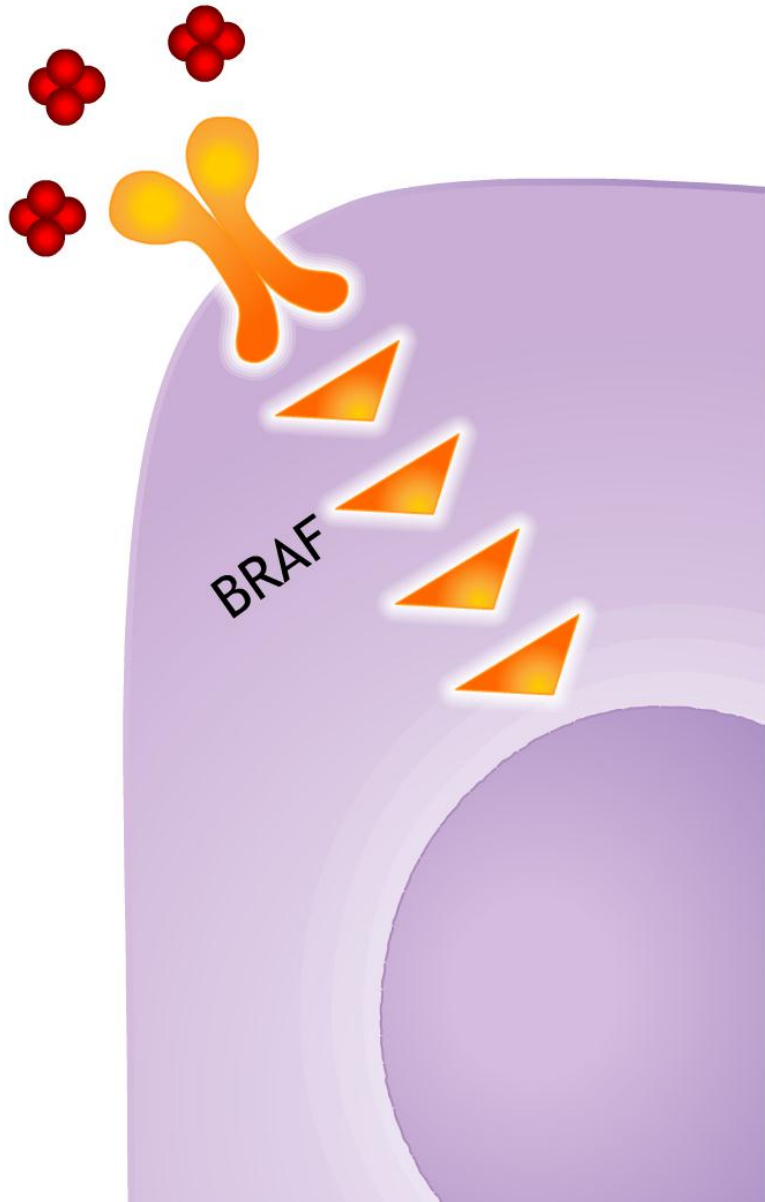
Normal cell



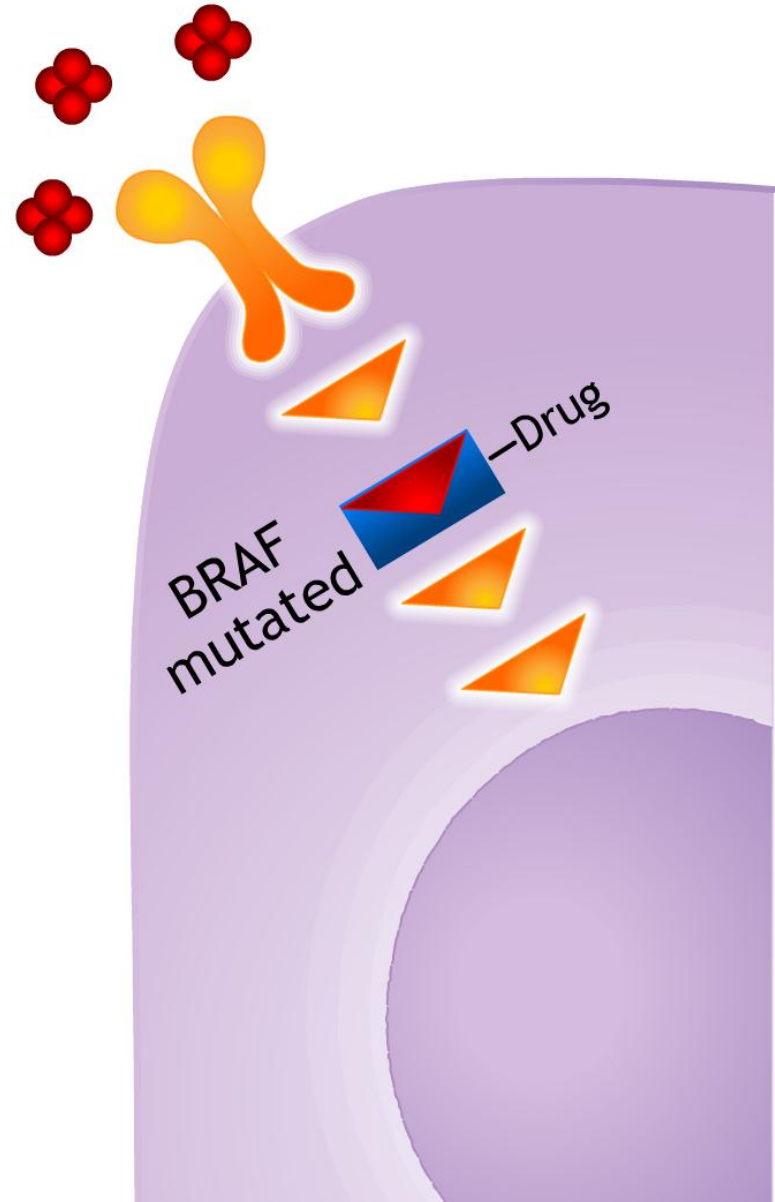
Cancer cell



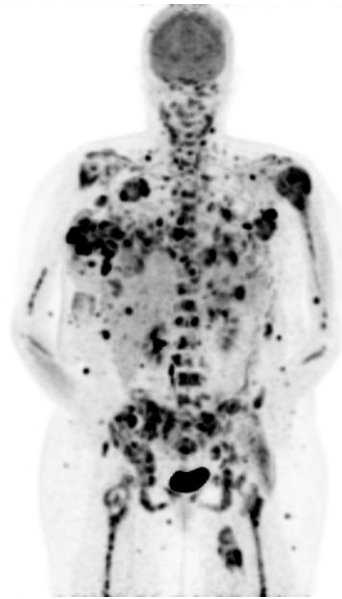
Normal cell



Cancer cell

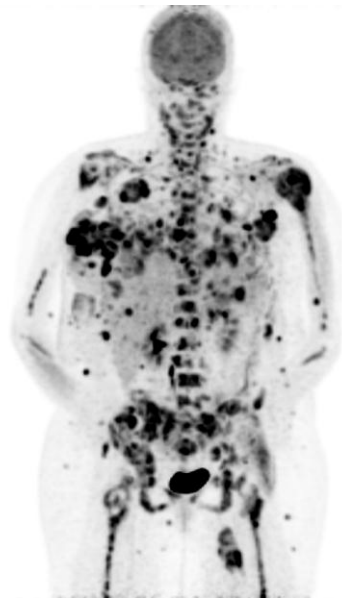


Treatment of metastatic malignant melanoma with a selective inhibitor of mutated BRAF (Vemurafenib)

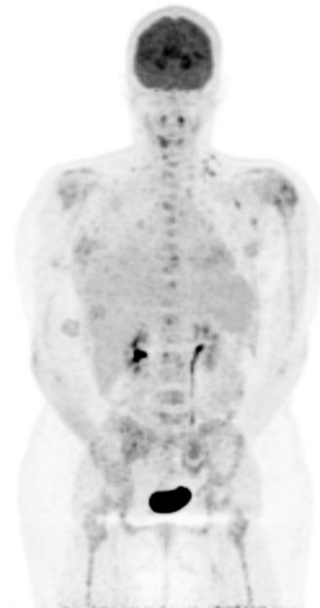


Before

Treatment of metastatic malignant melanoma with a selective inhibitor of mutated BRAF (Vemurafenib)

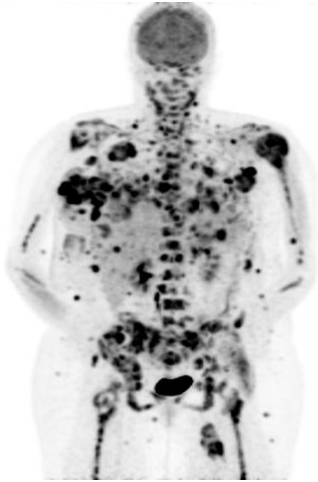


Before

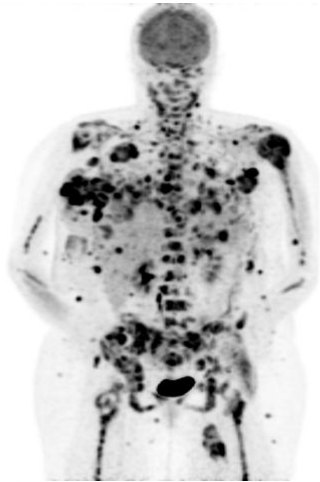


15 days after

Personalised treatment with Vemurafenib



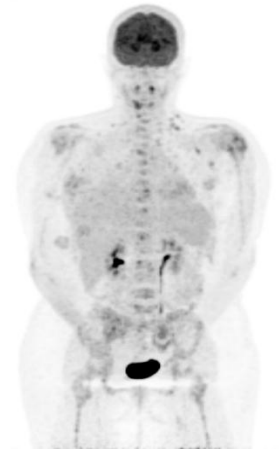
Personalised treatment with Vemurafenib



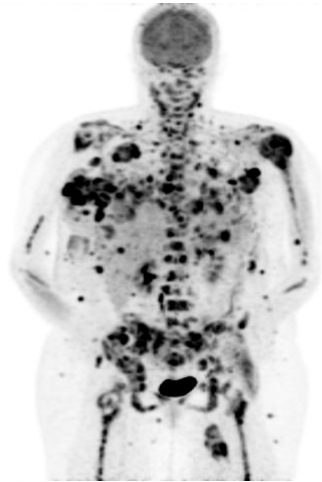
With BRAF mutation

....TACAGTTGAAA.....

....TACAGAGAAA.....



Personalised treatment with Vemurafenib



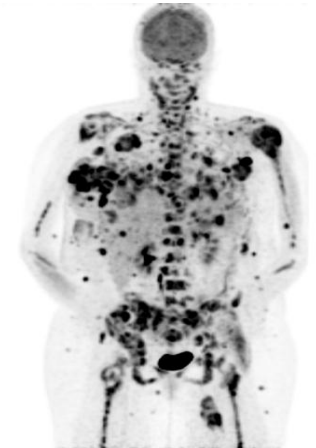
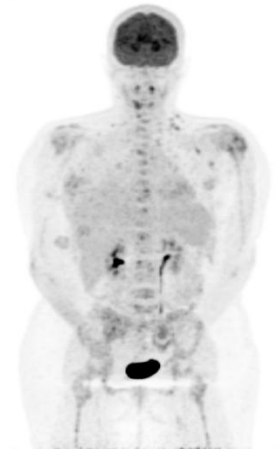
With BRAF mutation

.....TACAGT**T**GAAA.....

.....TACAG**A**GAAA.....

Without BRAF mutation

.....TACAG**T**GAAA.....



Key questions we can now ask about cancers and their genomes

- How diverse are individual cancers in their driver mutations?
- What causes the somatic mutations?
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International Cancer Genome Consortium Projects

