Introduction to next-generation sequencing

Pre-IMPAKT 2015

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Honorary Consultant Clinical Geneticist

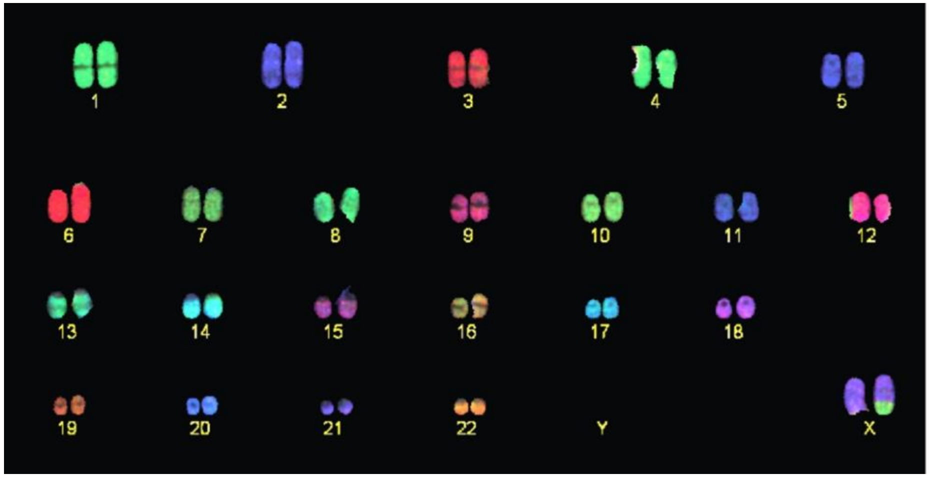
wellcome trust sanger institute

Cambridge University Hospitals NHS

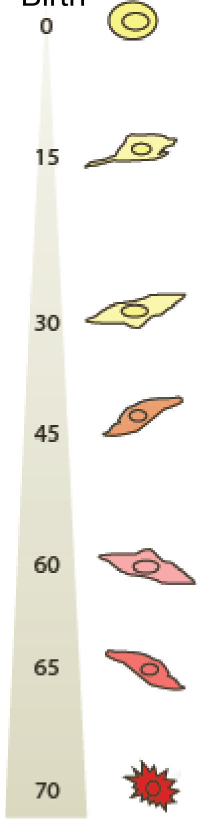
NHS Foundation Trust

International Cancer Genome Consortium

Time
(years)
Birth



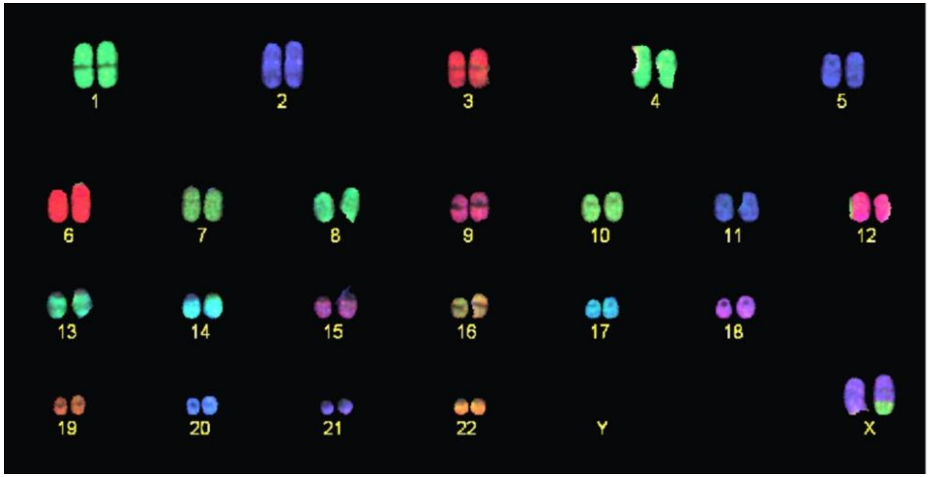
Time
(years)
Birth

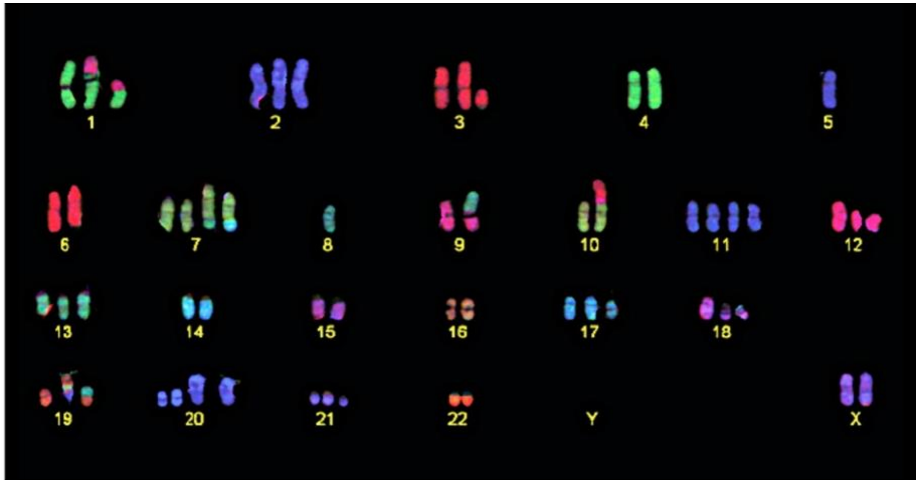


cancer
initiation

progressio
n

metastasis

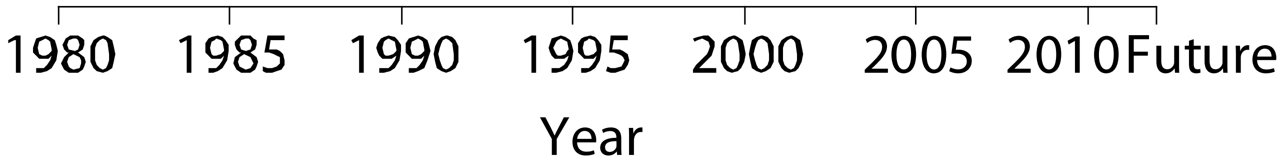




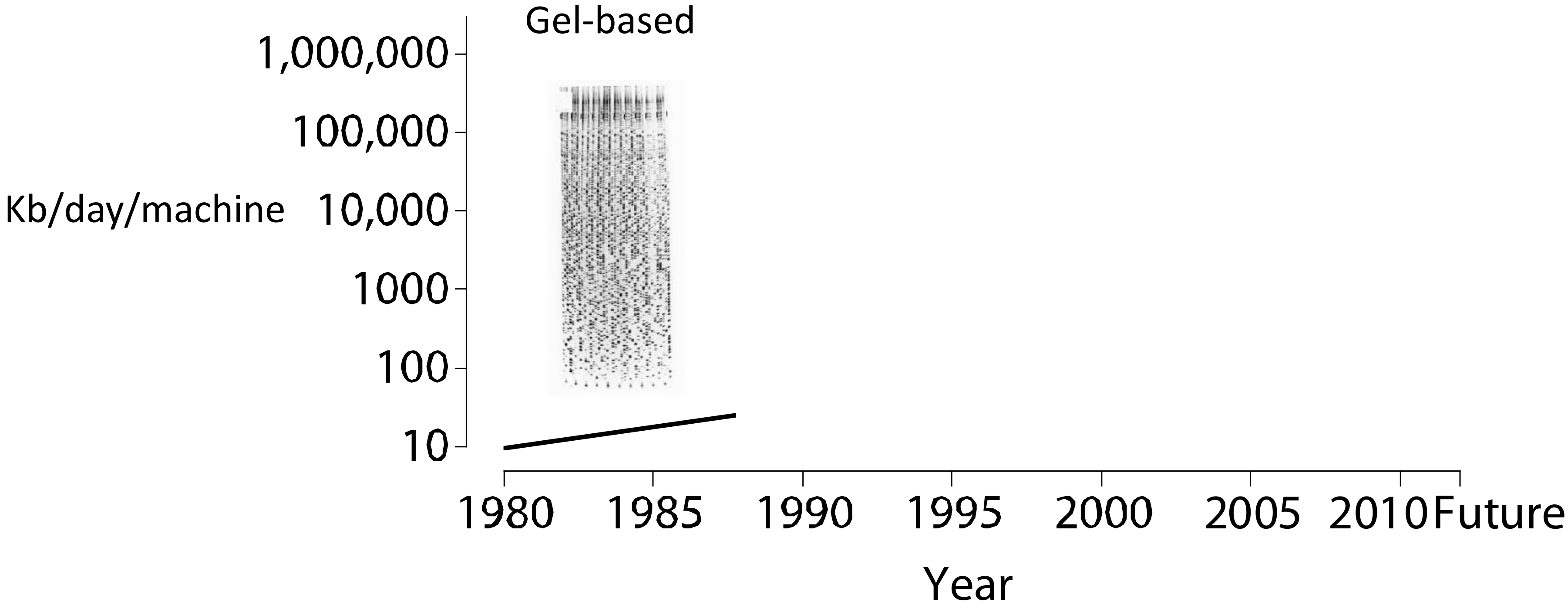
Part I: What’s all the fuss about?

MASSIVELY PARALLEL SEQUENCING

Massively-parallel sequencing



Massively-parallel sequencing



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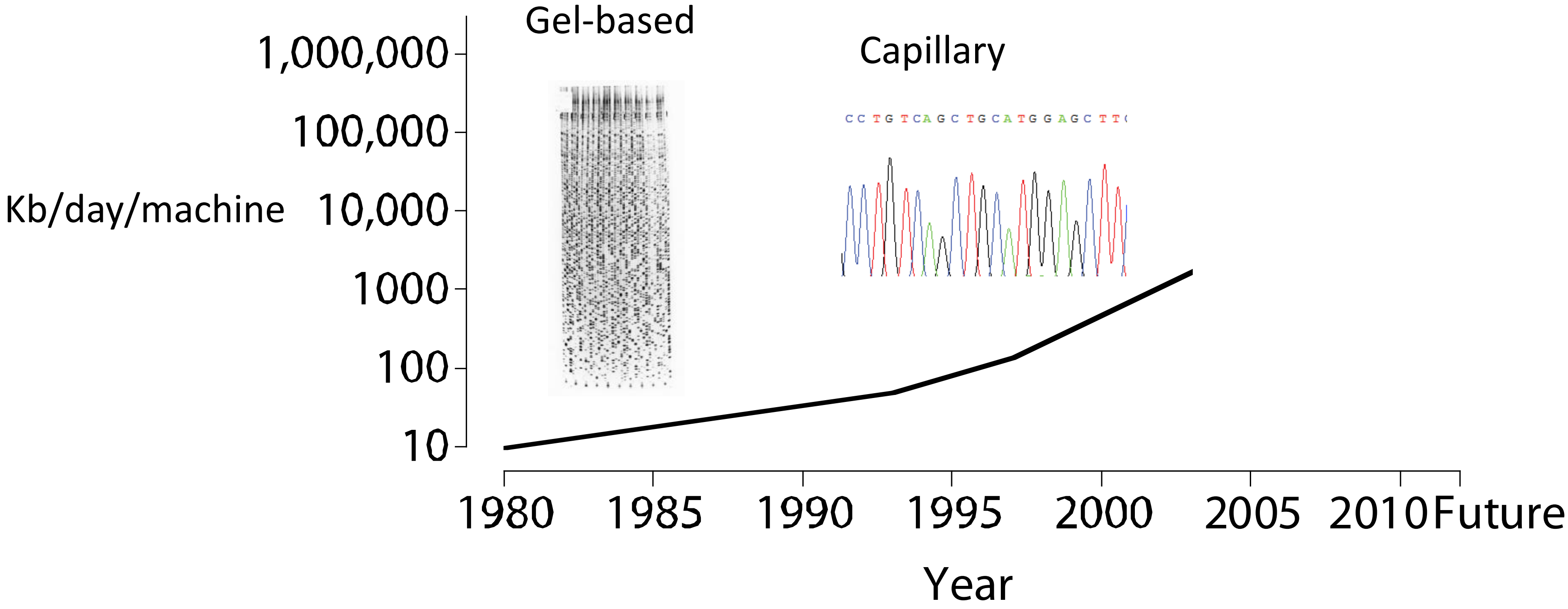

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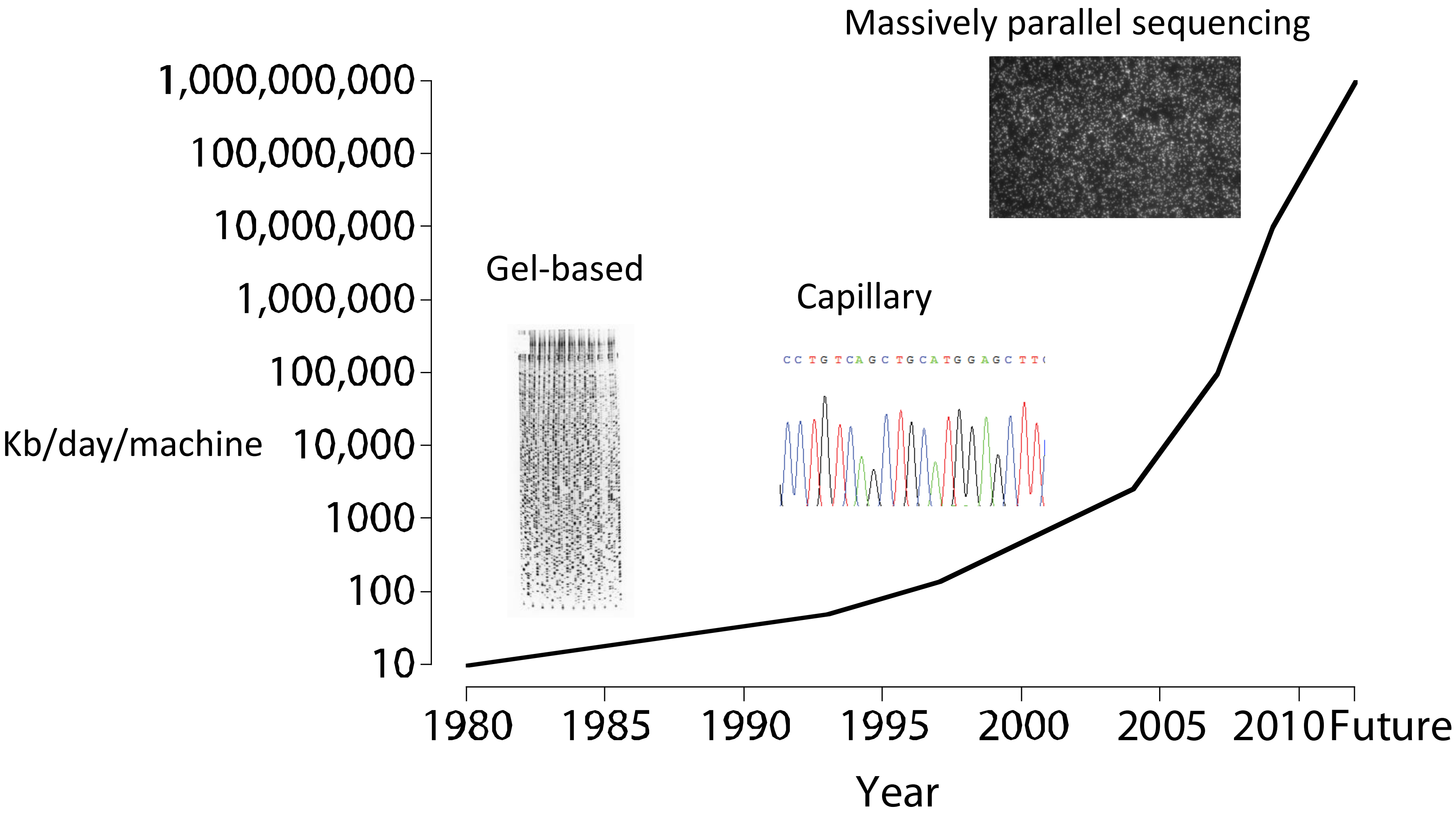
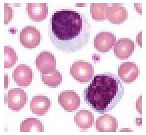


DNA Samples

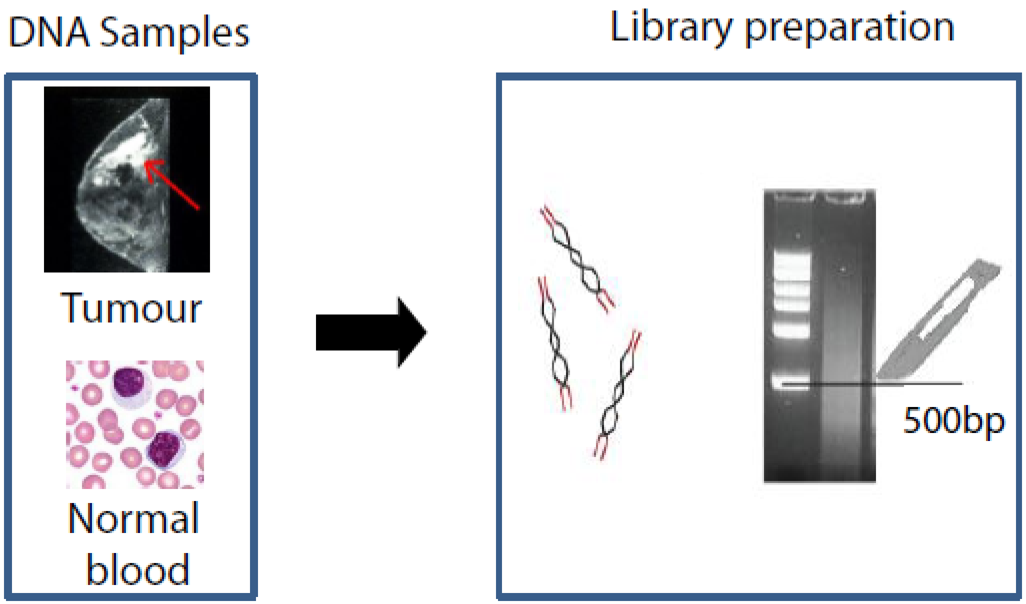
Tumour

DNA Samples

Tumour



Normal blood



DNA Samples

Tumour

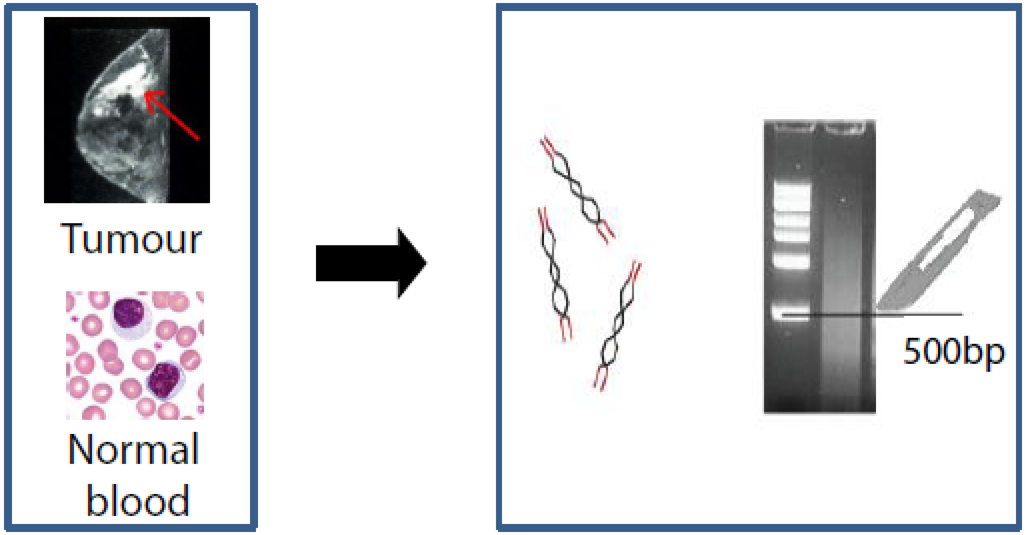
Normal blood

Library preparation

500bp

DNA Samples

Library preparation



Tumour

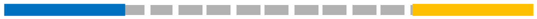
Normal blood

500bp

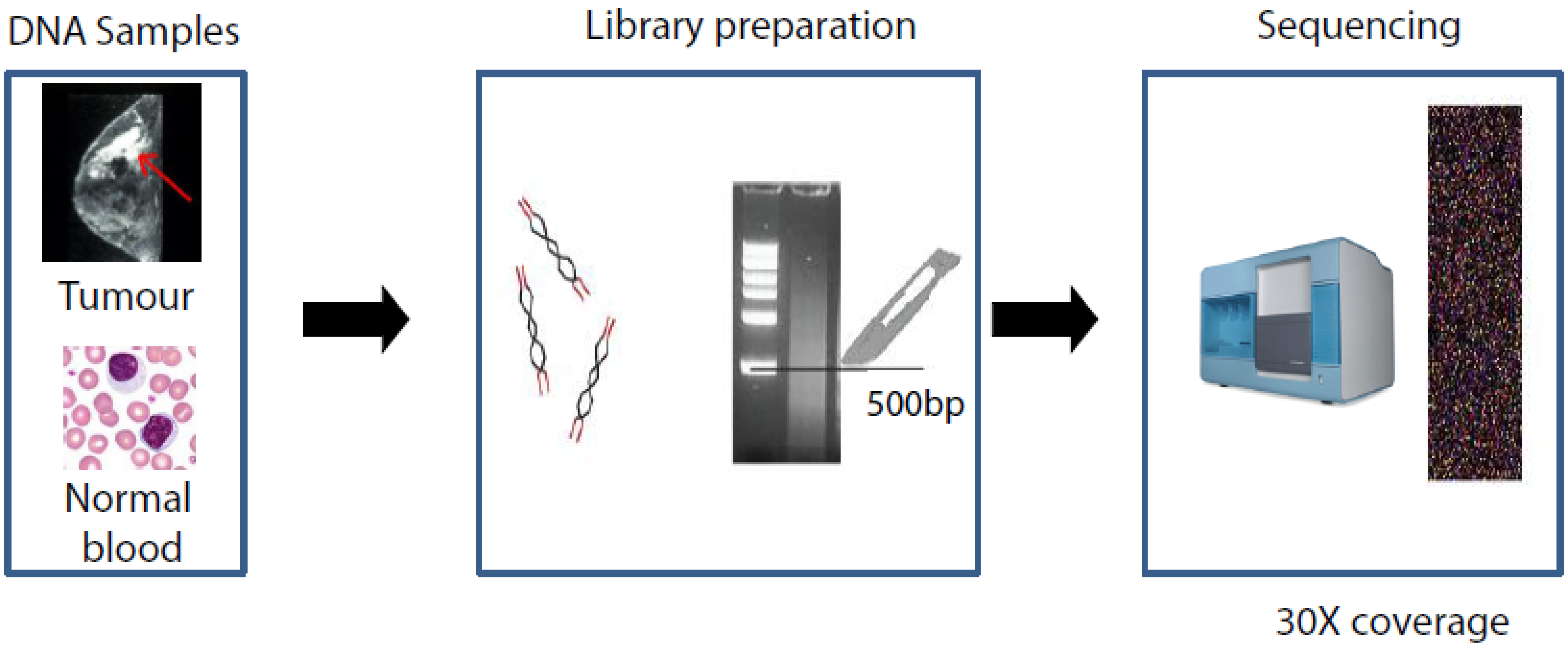
Sequenced 100 bps

500 bp

Sequenced 100 bps



Paired-end high-coverage next-generation sequencing experiment



DNA Samples

Tumour

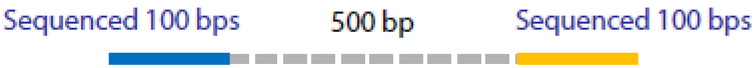
Normal blood

Library preparation

500bp

Sequencing

30X coverage



Sequenced 100 bps

500 bp

Sequenced 100 bps

Massively-parallel sequencing

sequencing experiment	**genomic footprint**
• Whole genome sequencing	3,000,000,000 base pairs

Massively-parallel sequencing

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• Whole genome sequencing	3,000,000,000 base pairs
• Exome sequencing	50,000,000 base pairs

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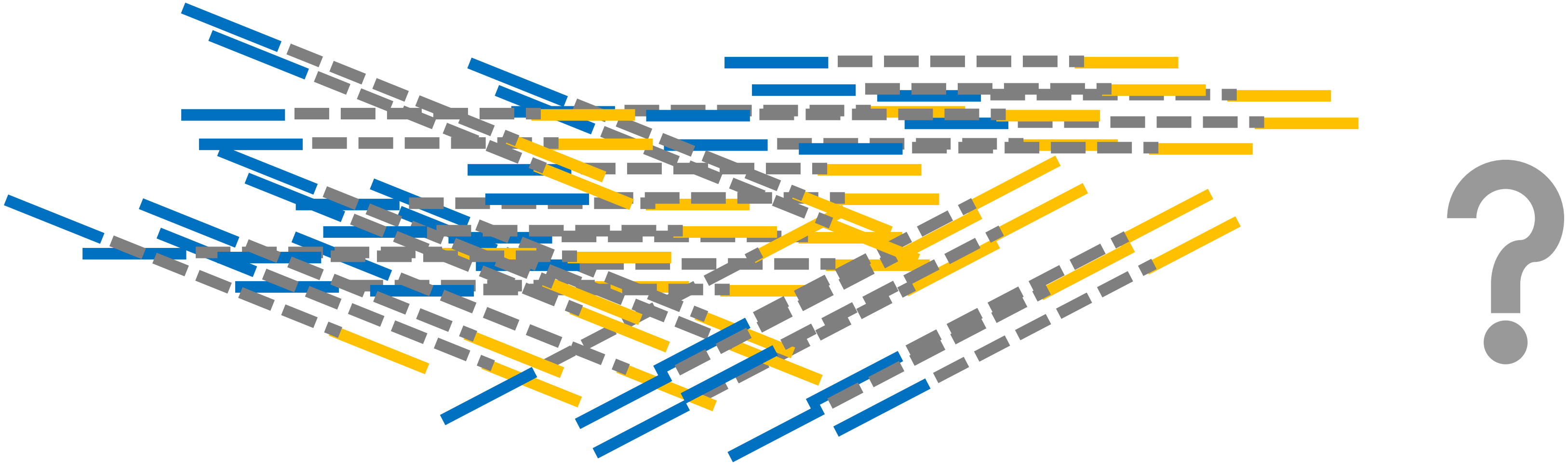
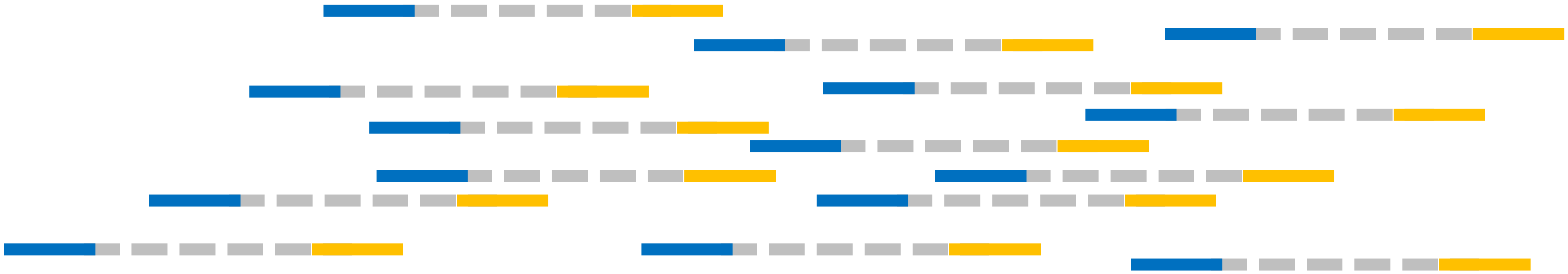
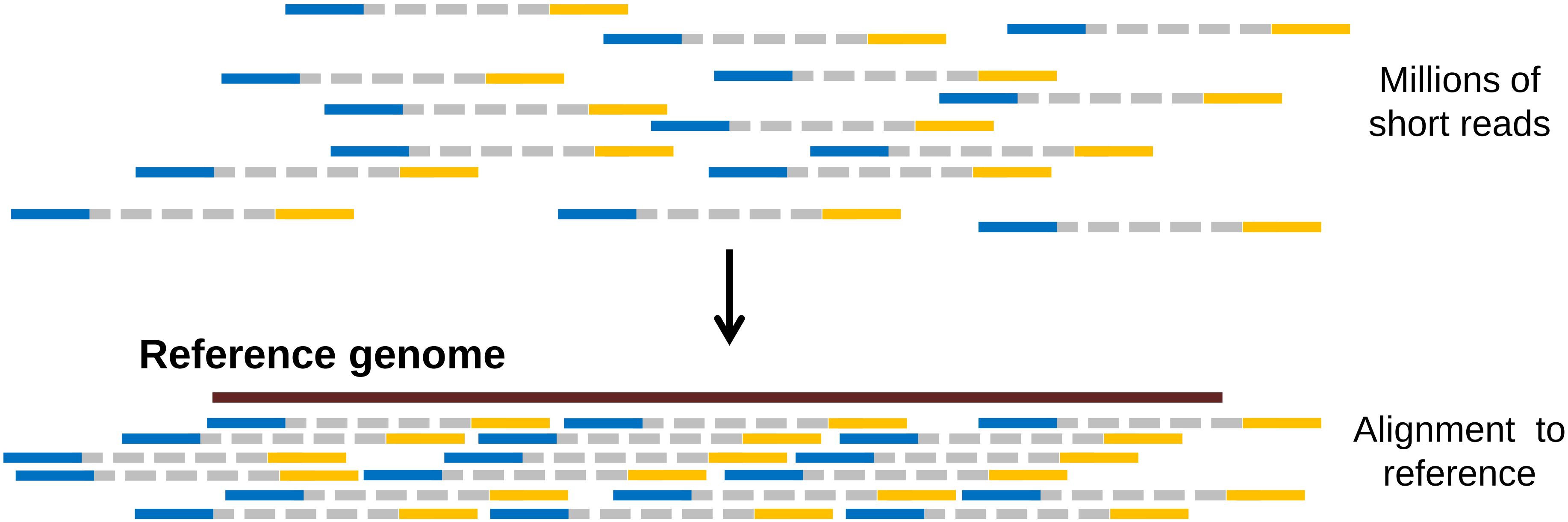


Basic principle for calling somatic mutations



Millions of short reads

Basic principle for calling somatic mutations

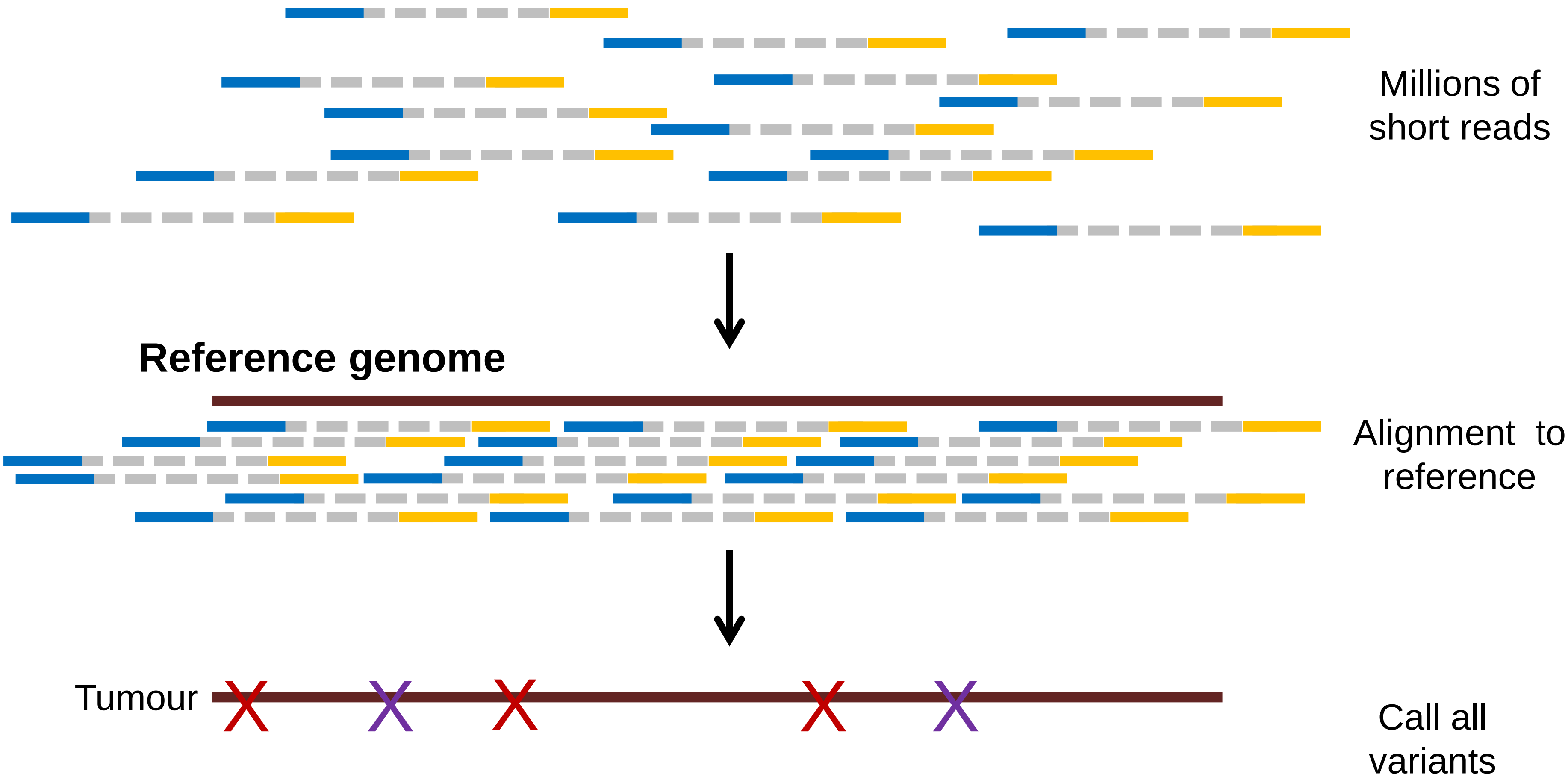


Millions of short reads

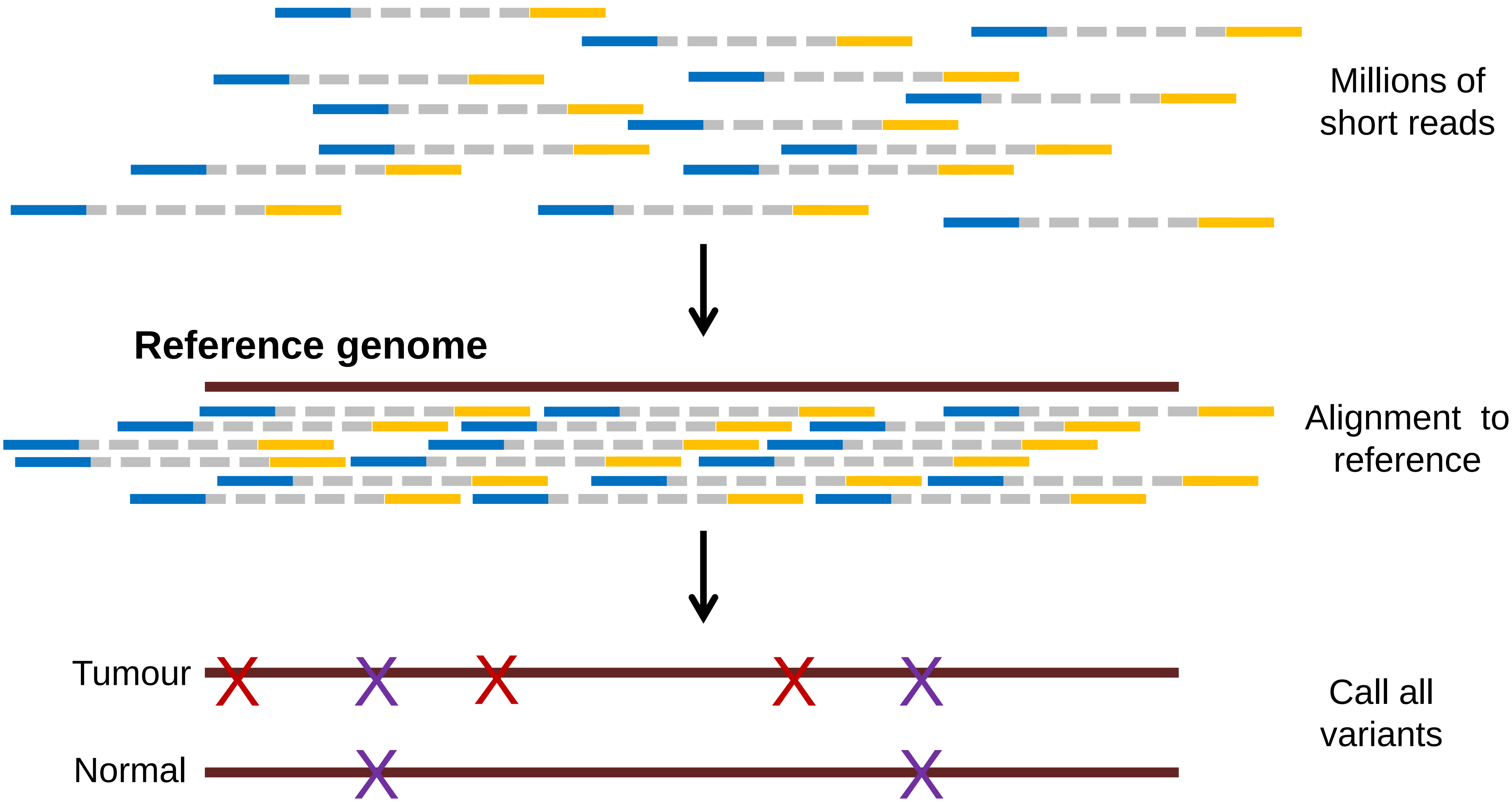
Reference genome

Alignment to reference

Basic principle for calling somatic mutations



Basic principle for calling somatic mutations



Millions of short reads

Reference genome

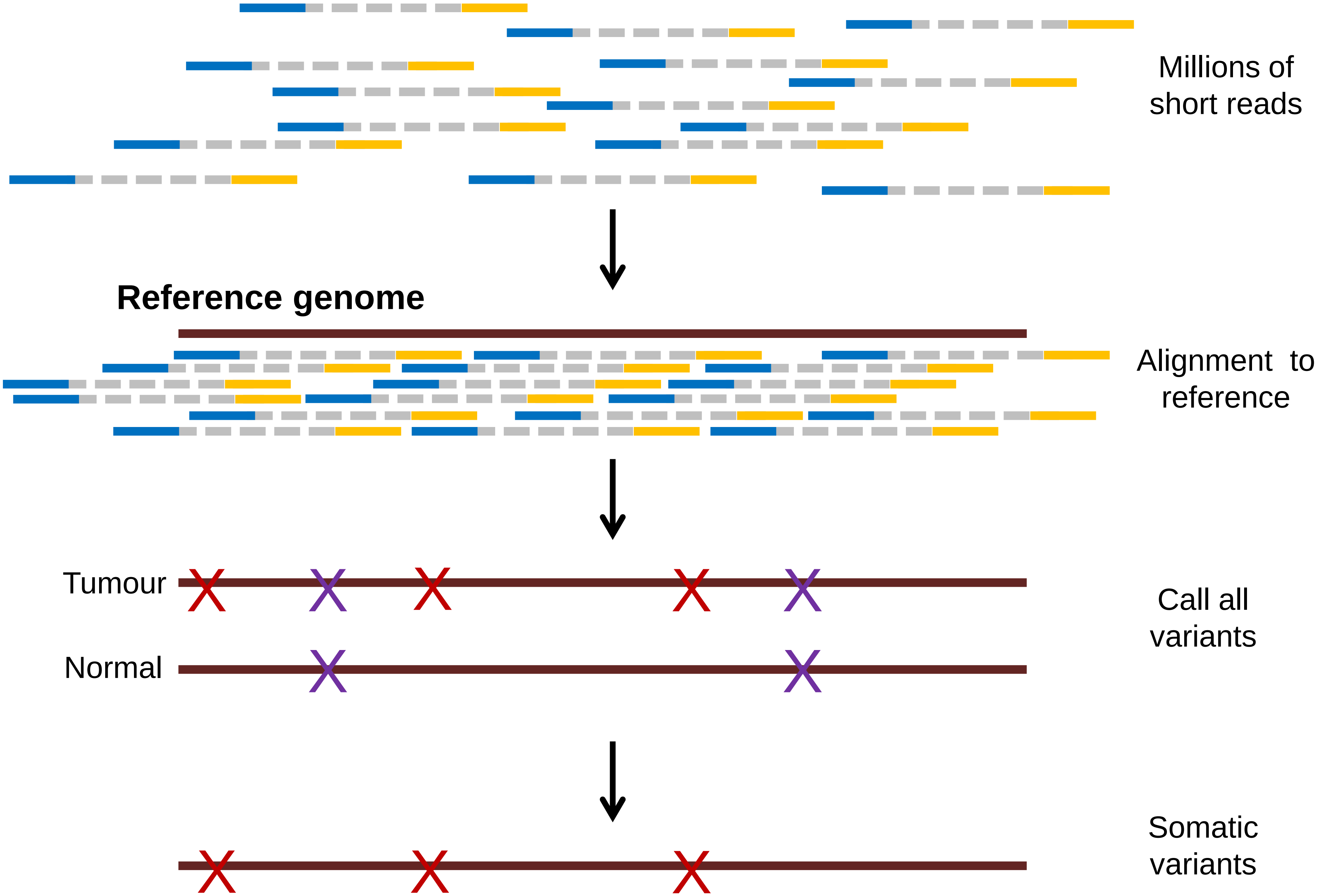
Alignment to reference

Tumour

Normal

Call all variants

Basic principle for calling somatic mutations



Millions of short reads

Reference genome

Alignment to reference

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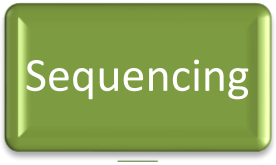
Normal

Call all variants

Somatic variants

Bioinformatics

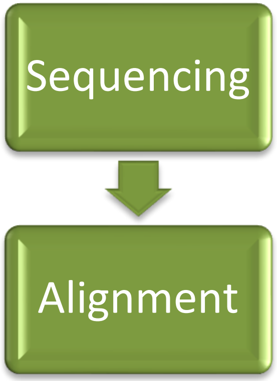
- Data processing



Sequencing

Bioinformatics

- Data processing

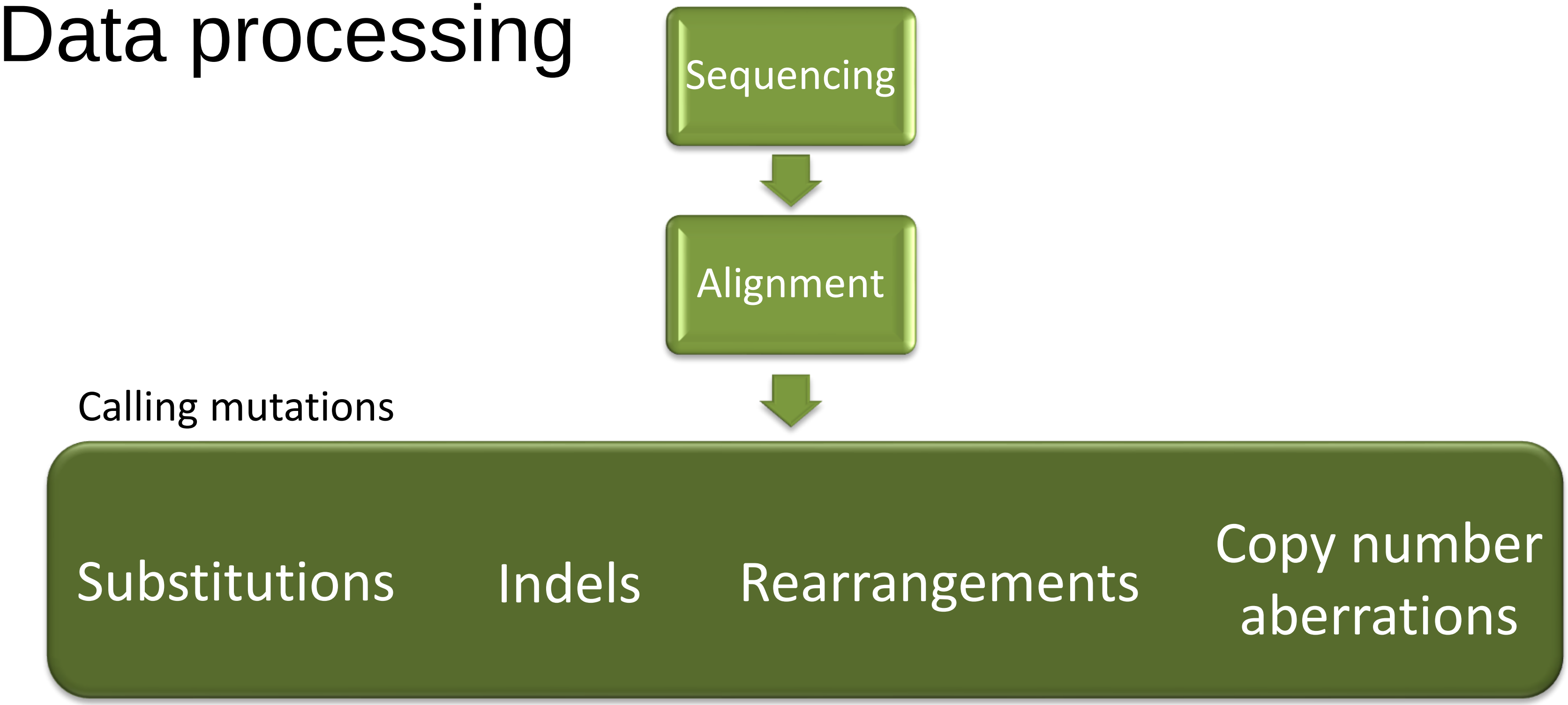


Sequencing

Alignment

Bioinformatics

- Data processing



Sequencing

Alignment

Calling mutations

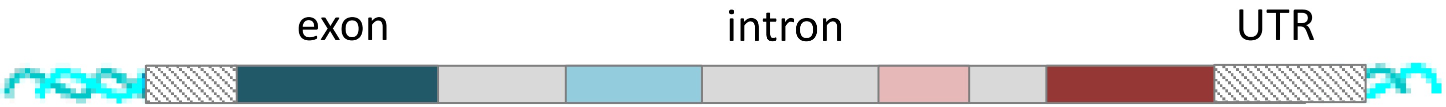
Substitutions

Indels

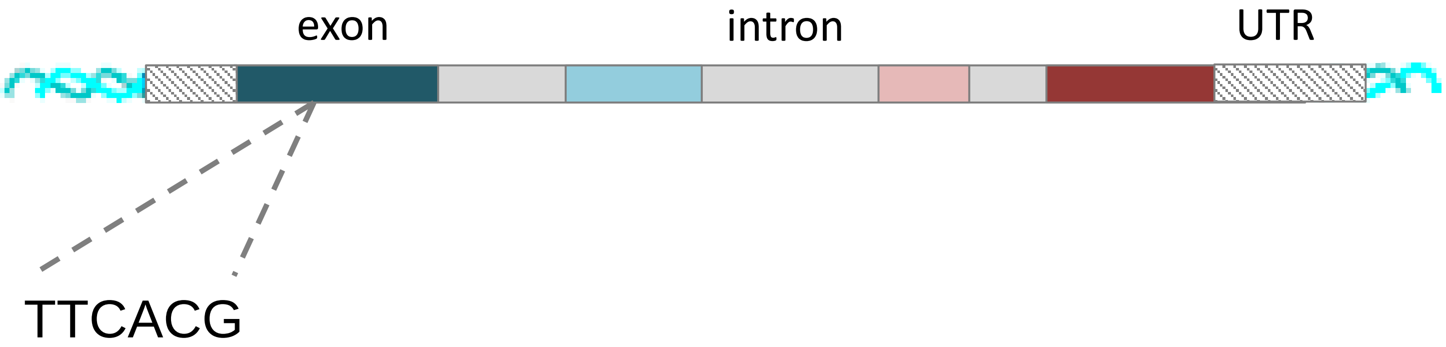
Rearrangements

Copy number aberrations

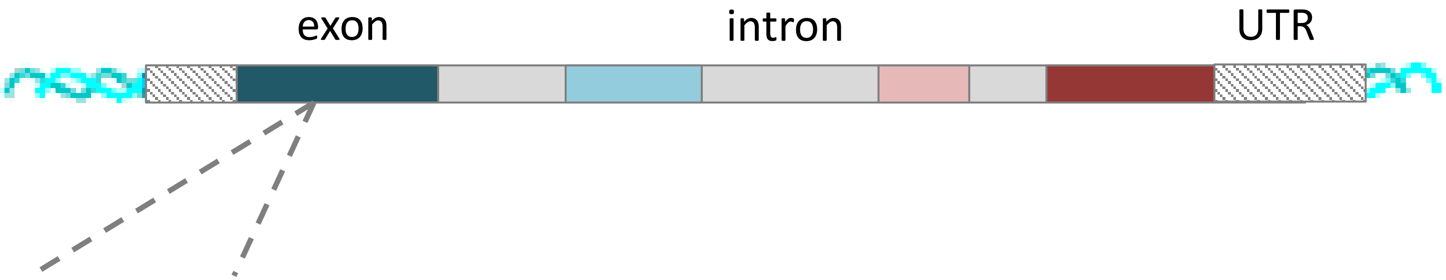
Genomic abnormalities



Genomic abnormalities



Genomic abnormalities



exon

intron

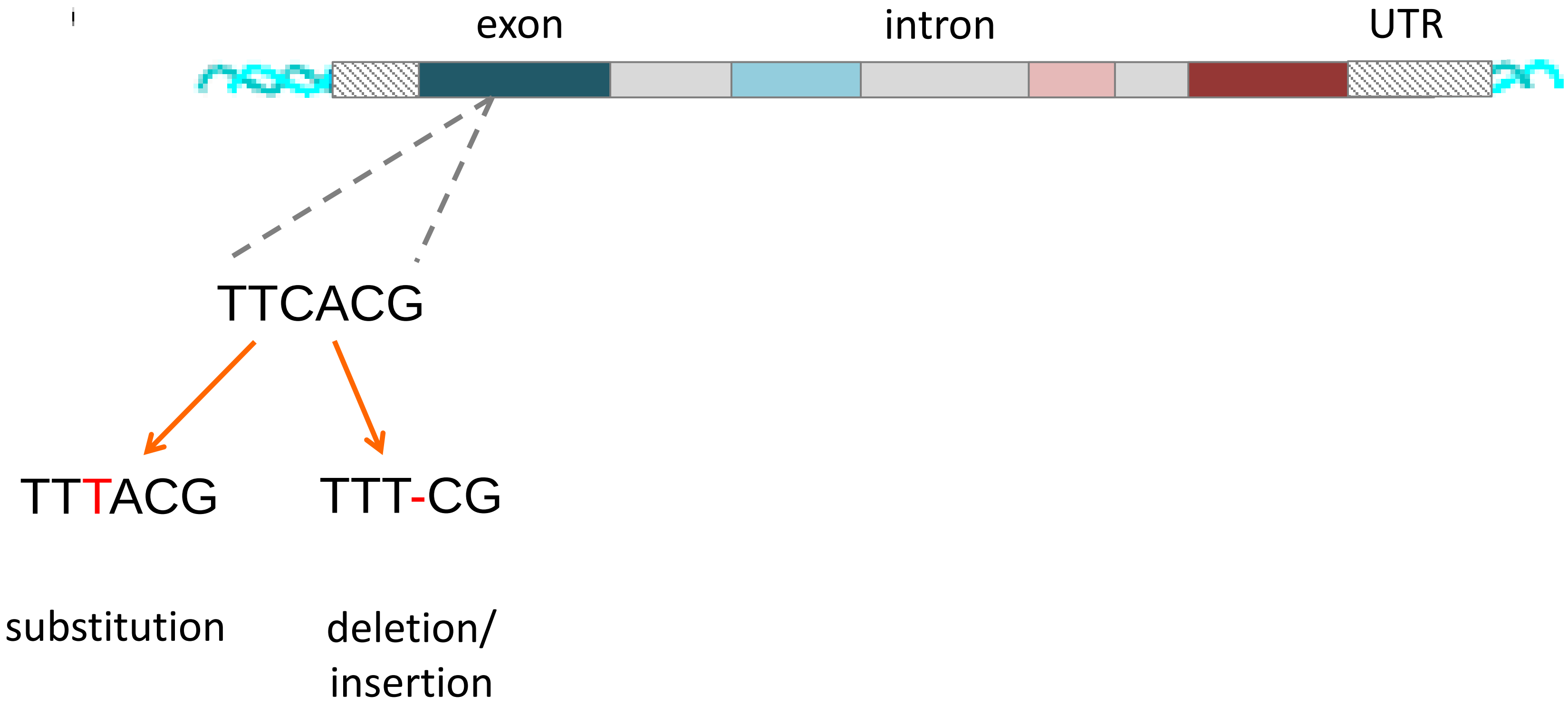
UTR

TTCACG

TTTACG

substitution

Genomic abnormalities



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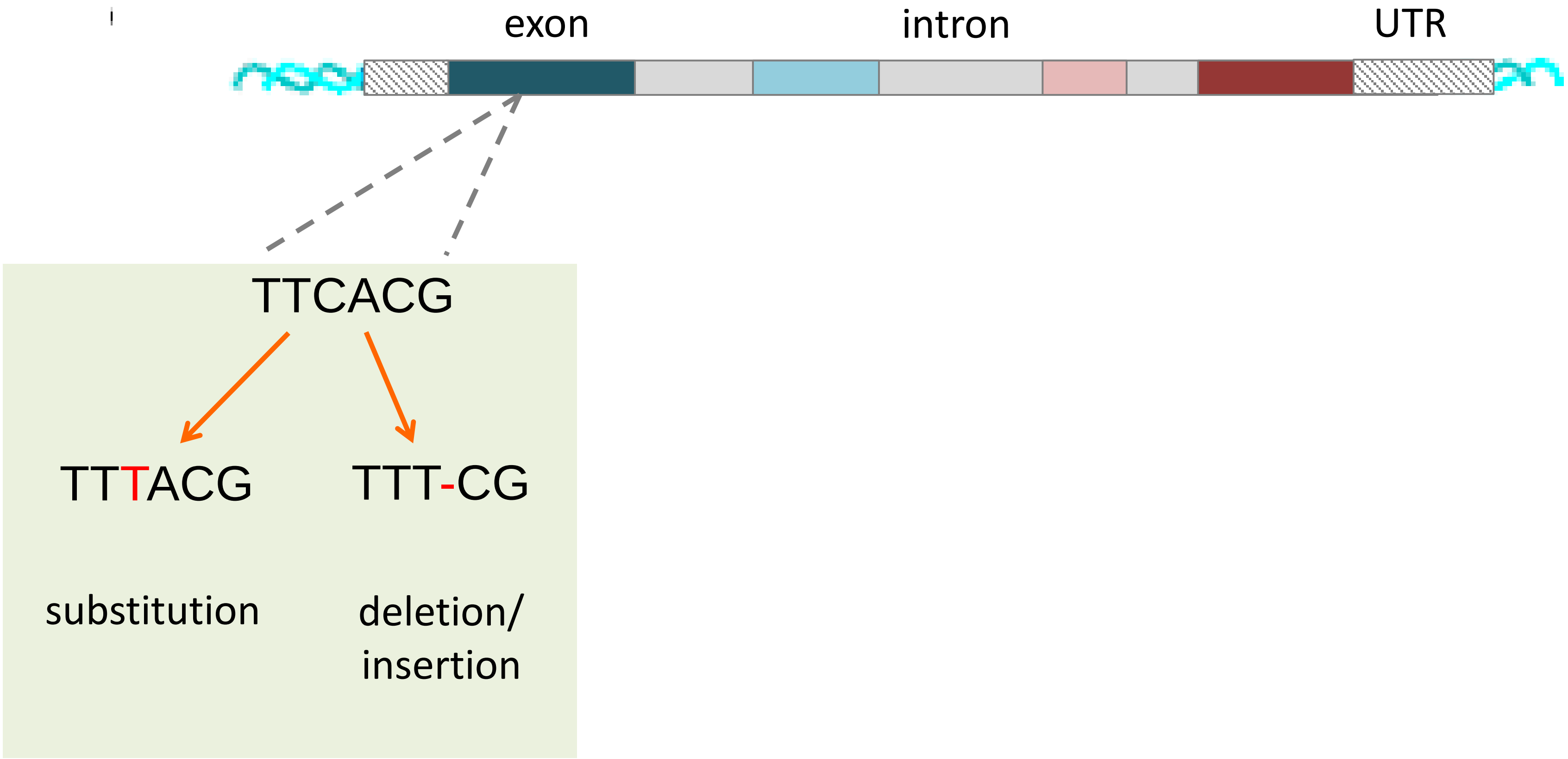
substitution

deletion/
insertion

Genomic abnormalities



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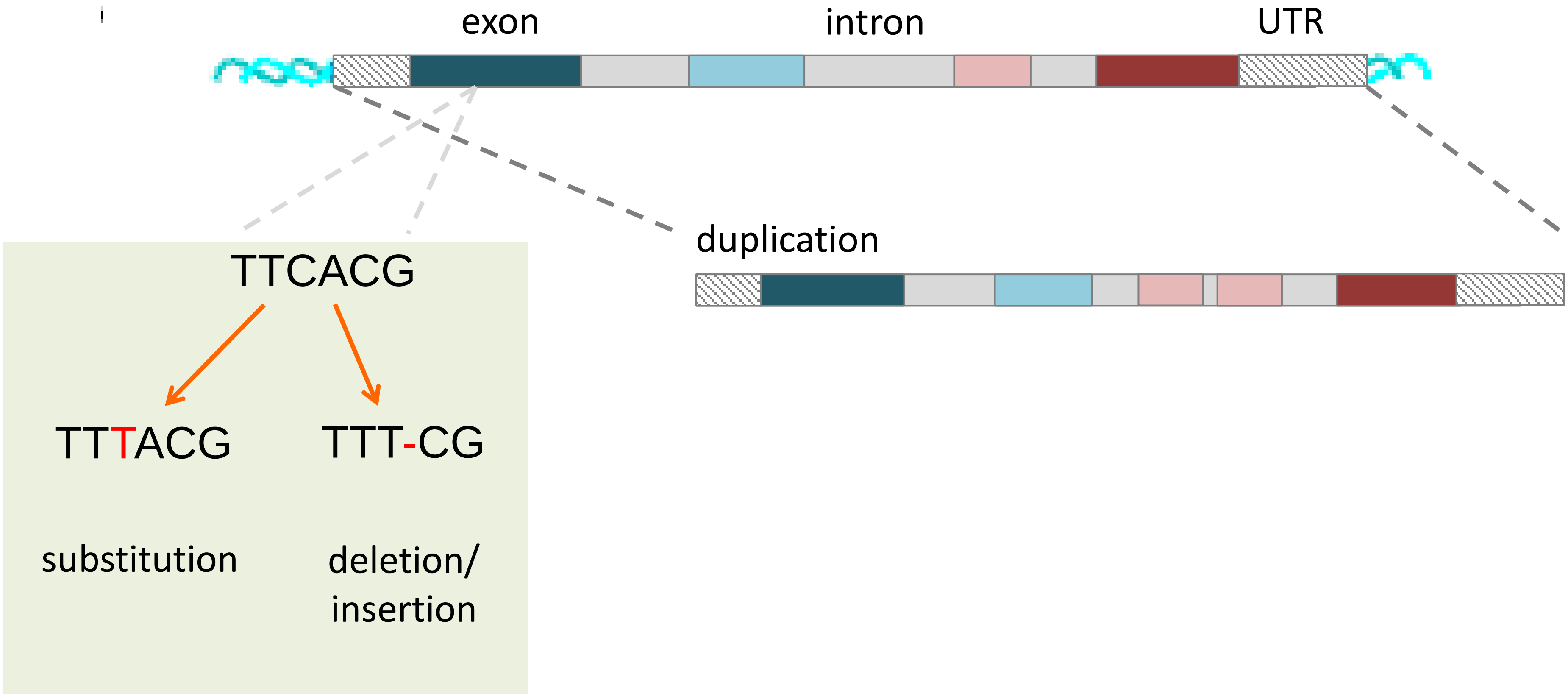
substitution

deletion/ insertion

base pair resolution

Genomic abnormalities



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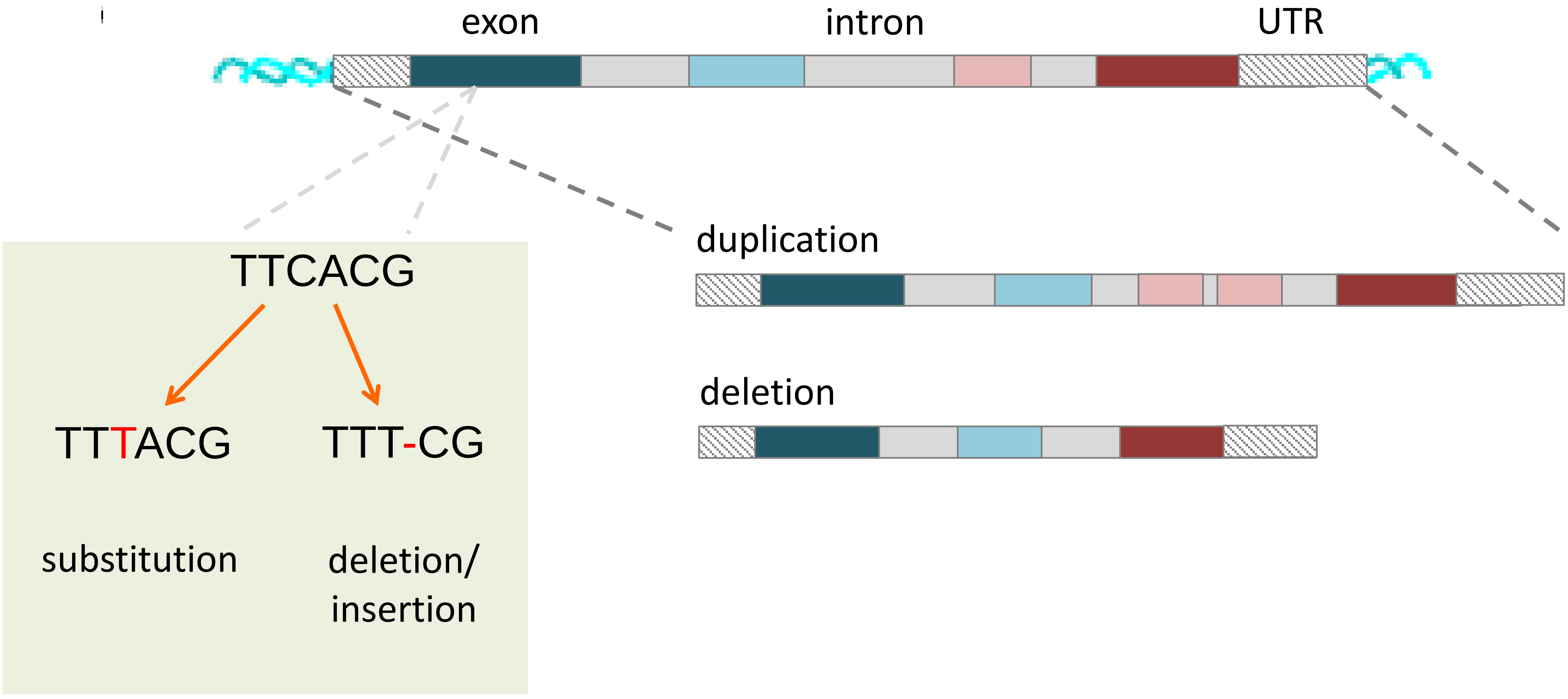

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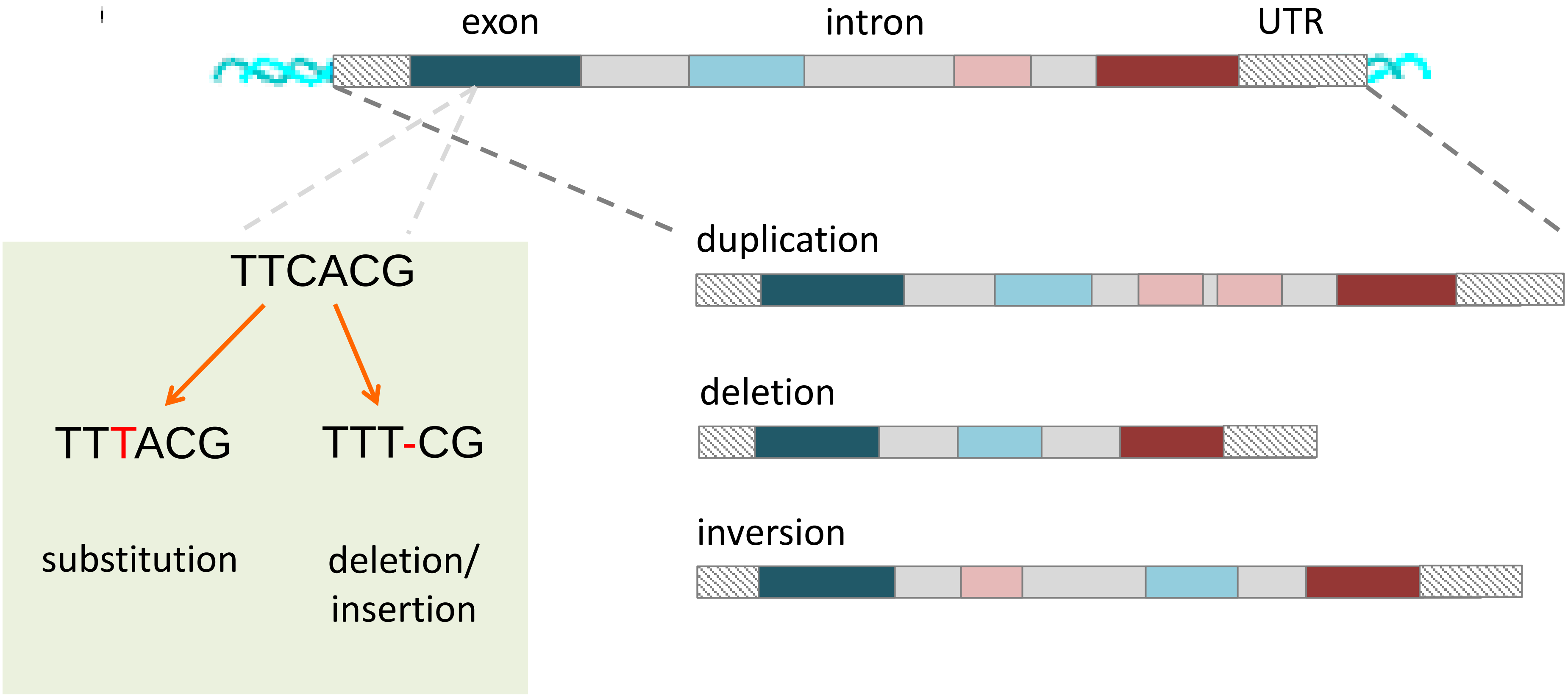

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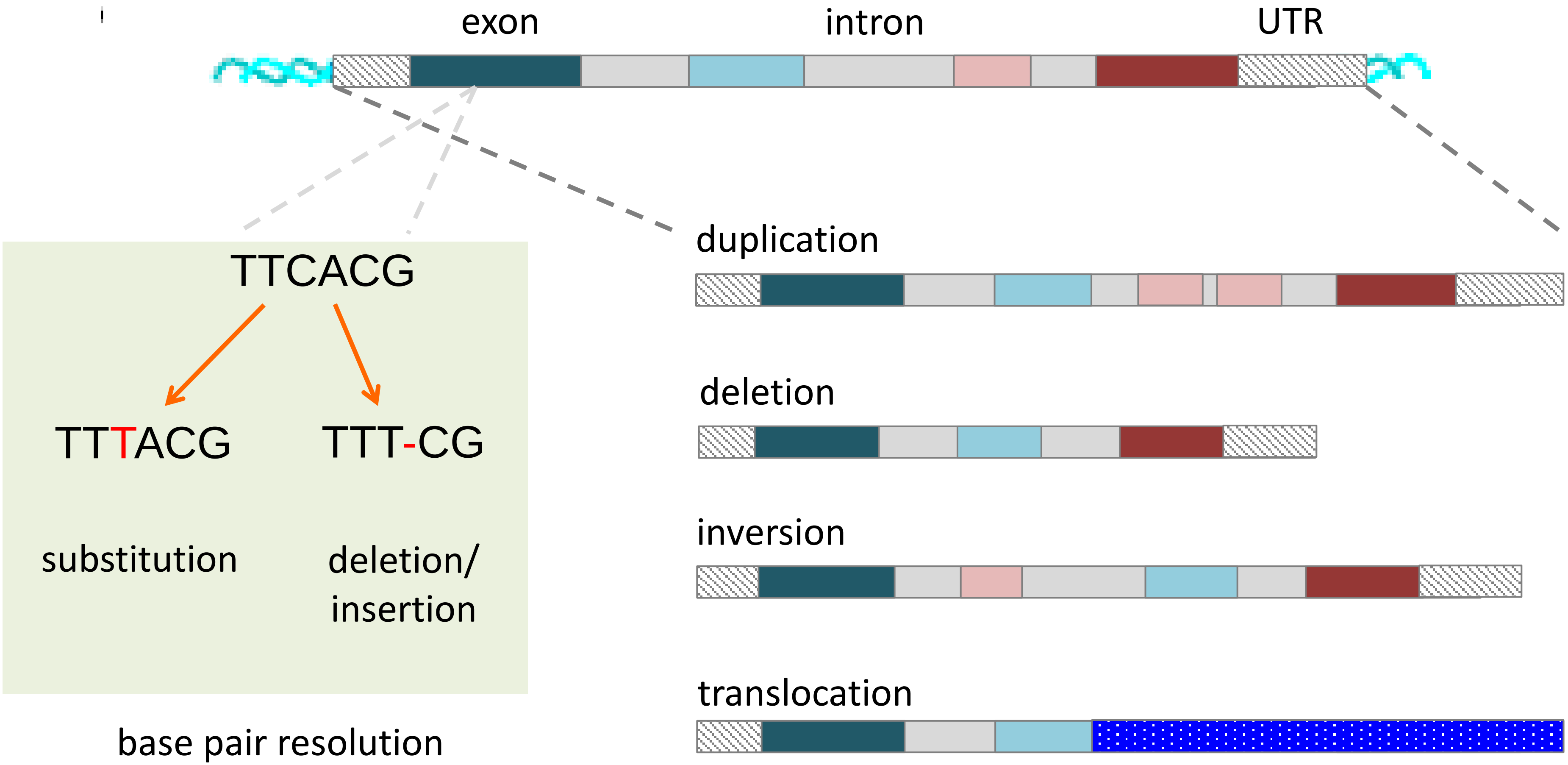

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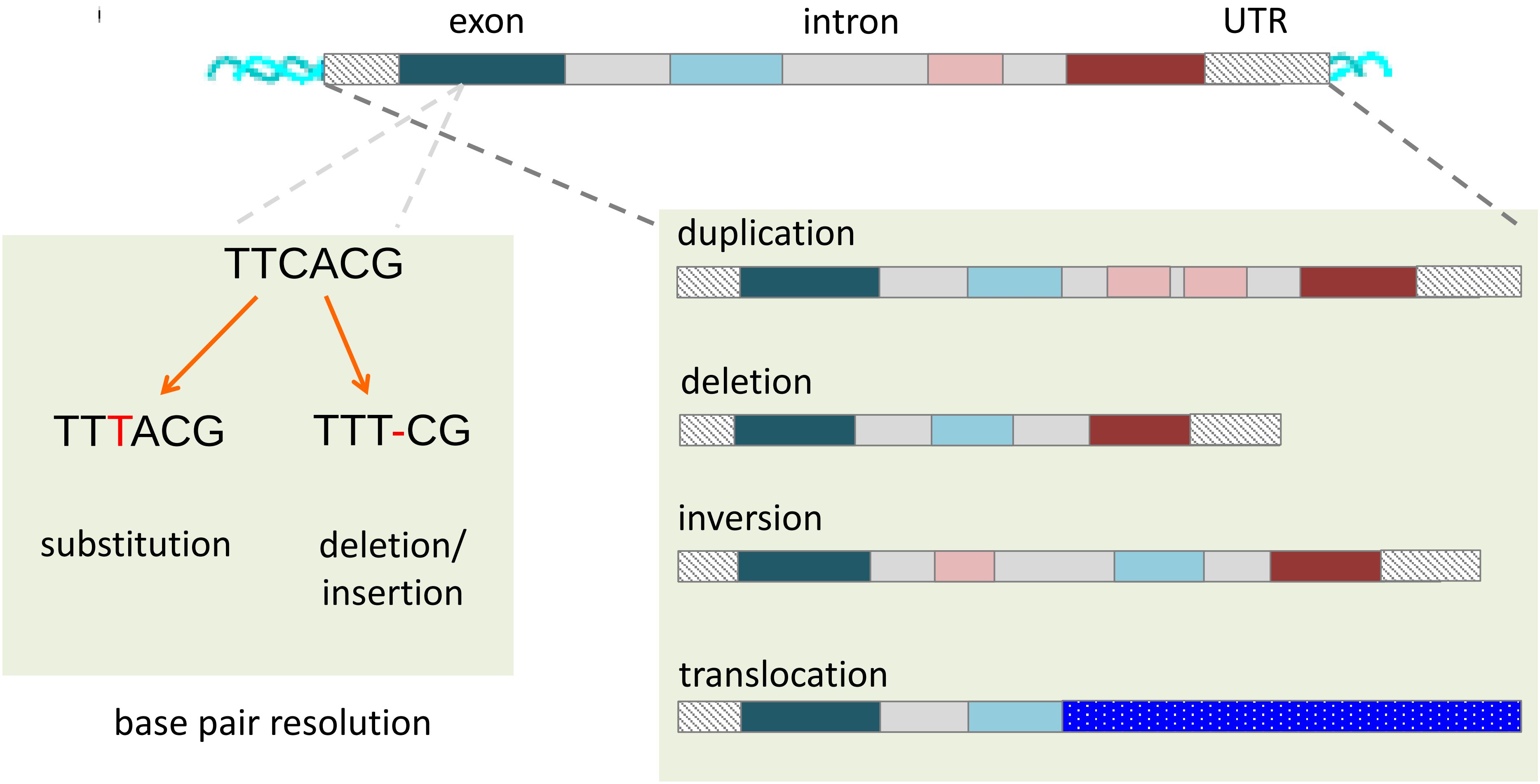
translocation

Genomic abnormalities



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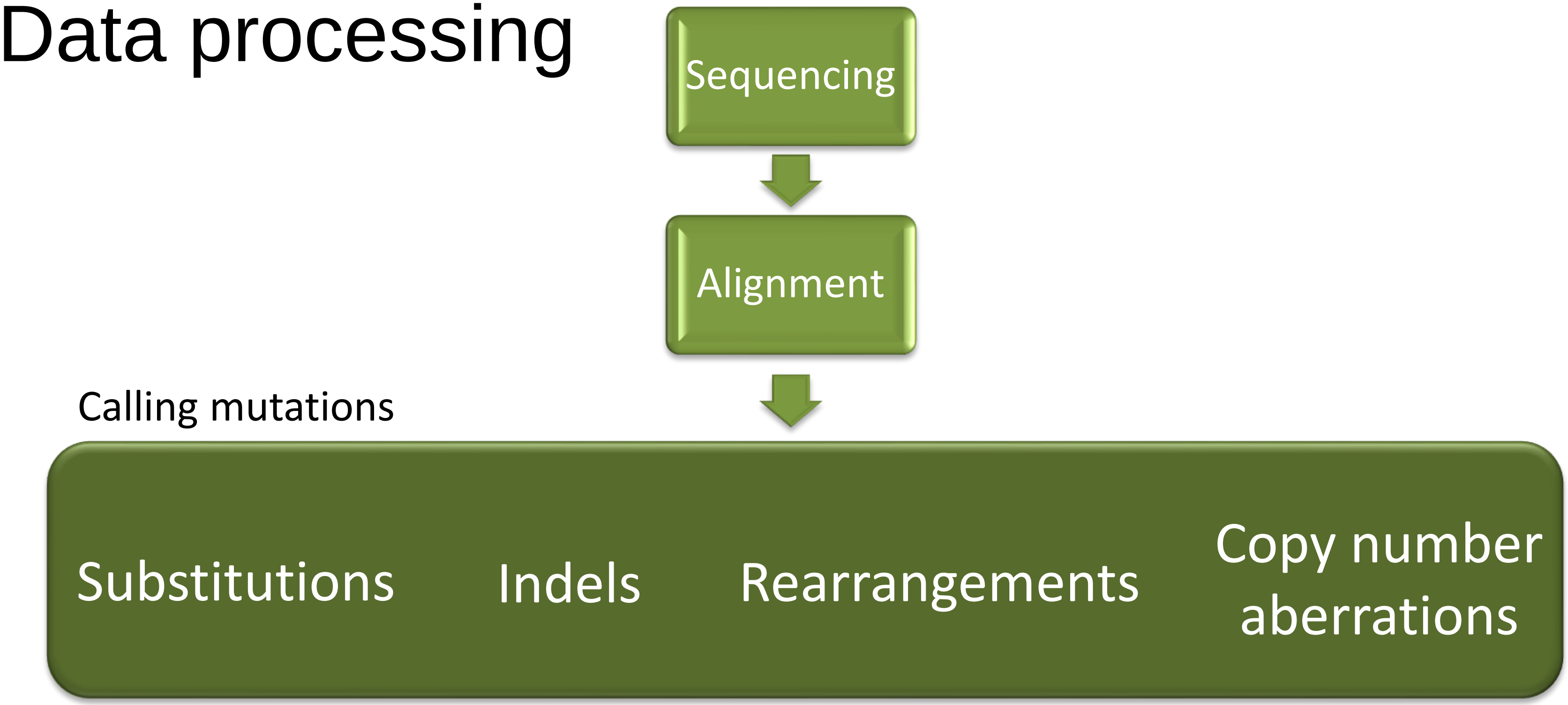
translocation

chromosomal scale

Bioinformatics

- Data processing



Sequencing

Alignment

Calling mutations

Substitutions

Indels

Rearrangements

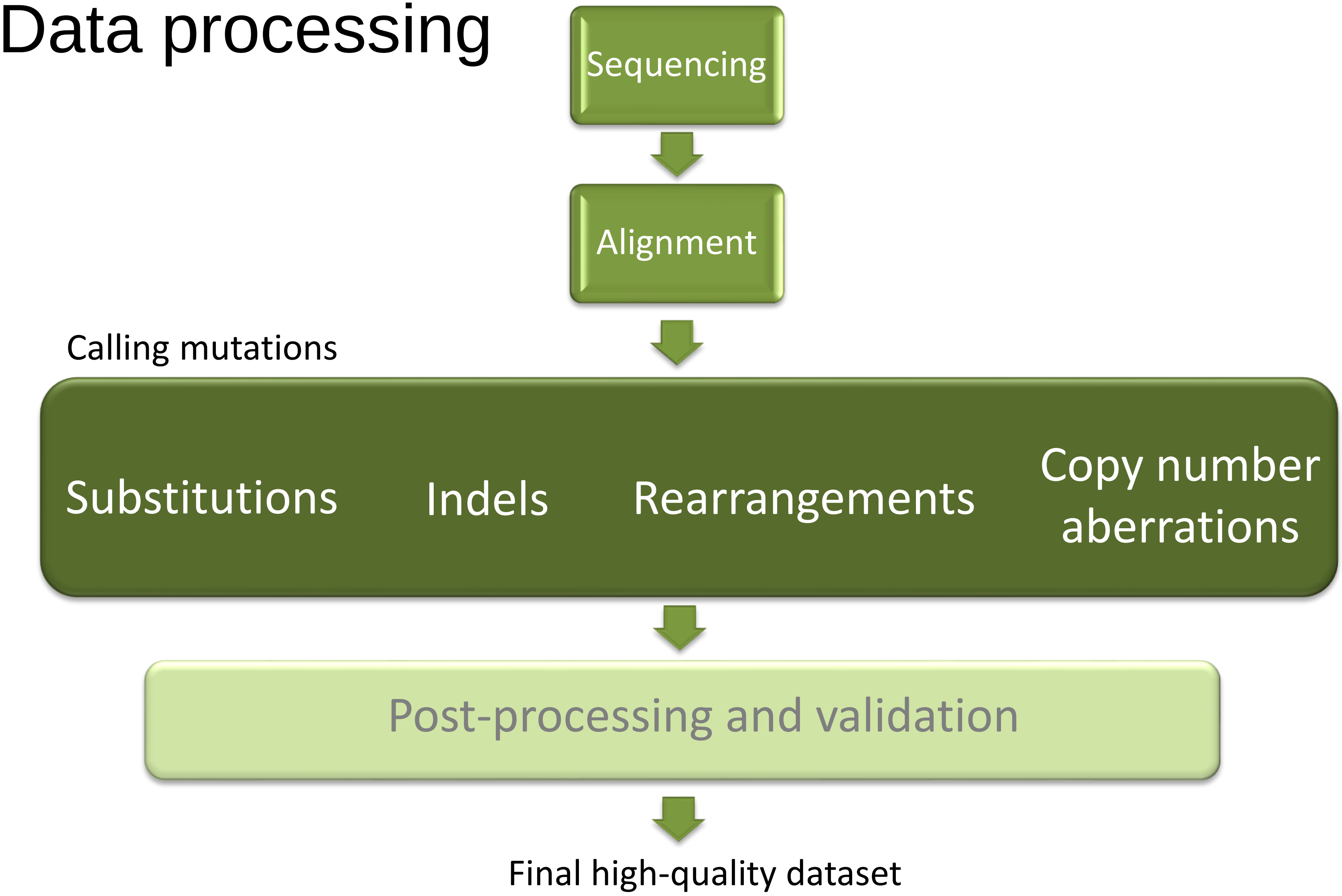
Copy number aberrations

Limitations

- DNA
  - Quality of DNA (Fresh frozen, FFPE)
  - Ploidy of DNA
  - Normal cell “contamination”
- Sequencing
  - Variation in coverage
  - Systematic sequencing artefacts
- Reference genome
  - Poorly-defined parts of the genome
  - Repeats
- Mutation-calling
  - Sensitivity
  - Specificity

Bioinformatics

- Data processing



Sequencing

Alignment

Calling mutations

Substitutions

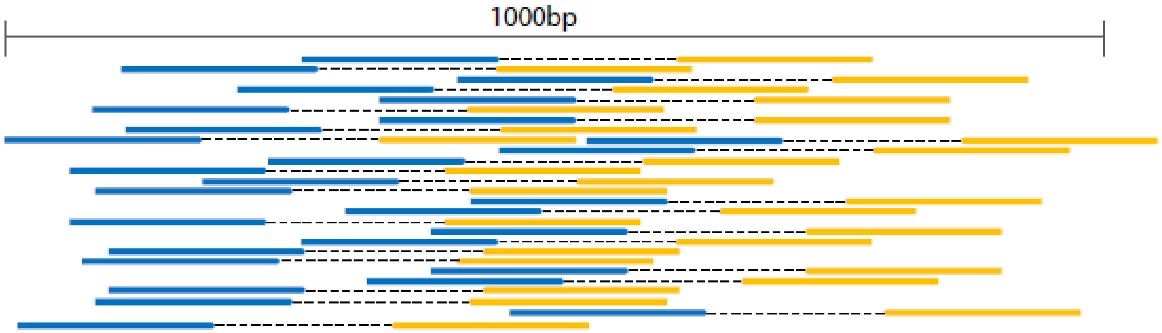
Indels

Rearrangements

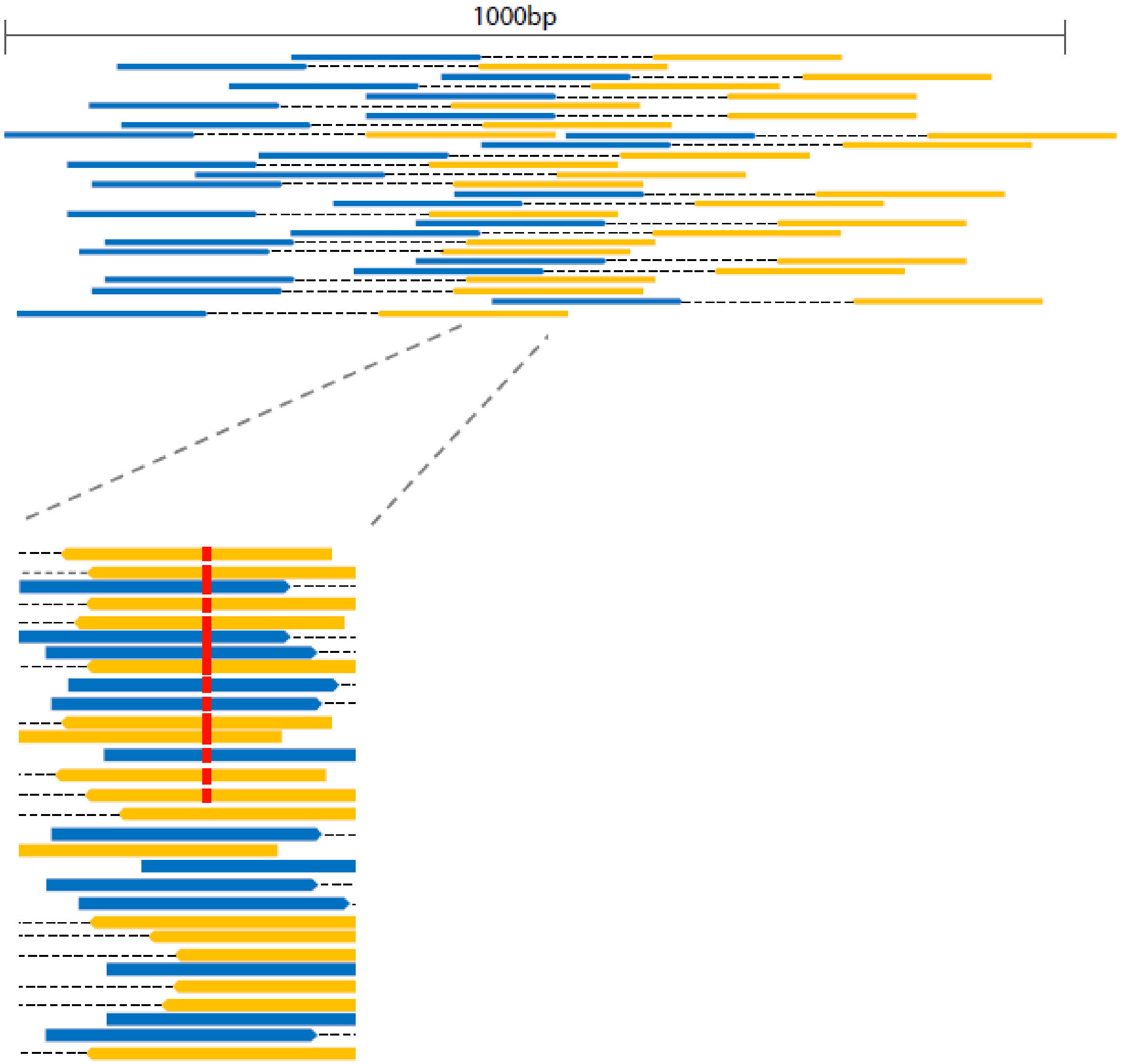
Copy number aberrations

Post-processing and validation

Final high-quality dataset



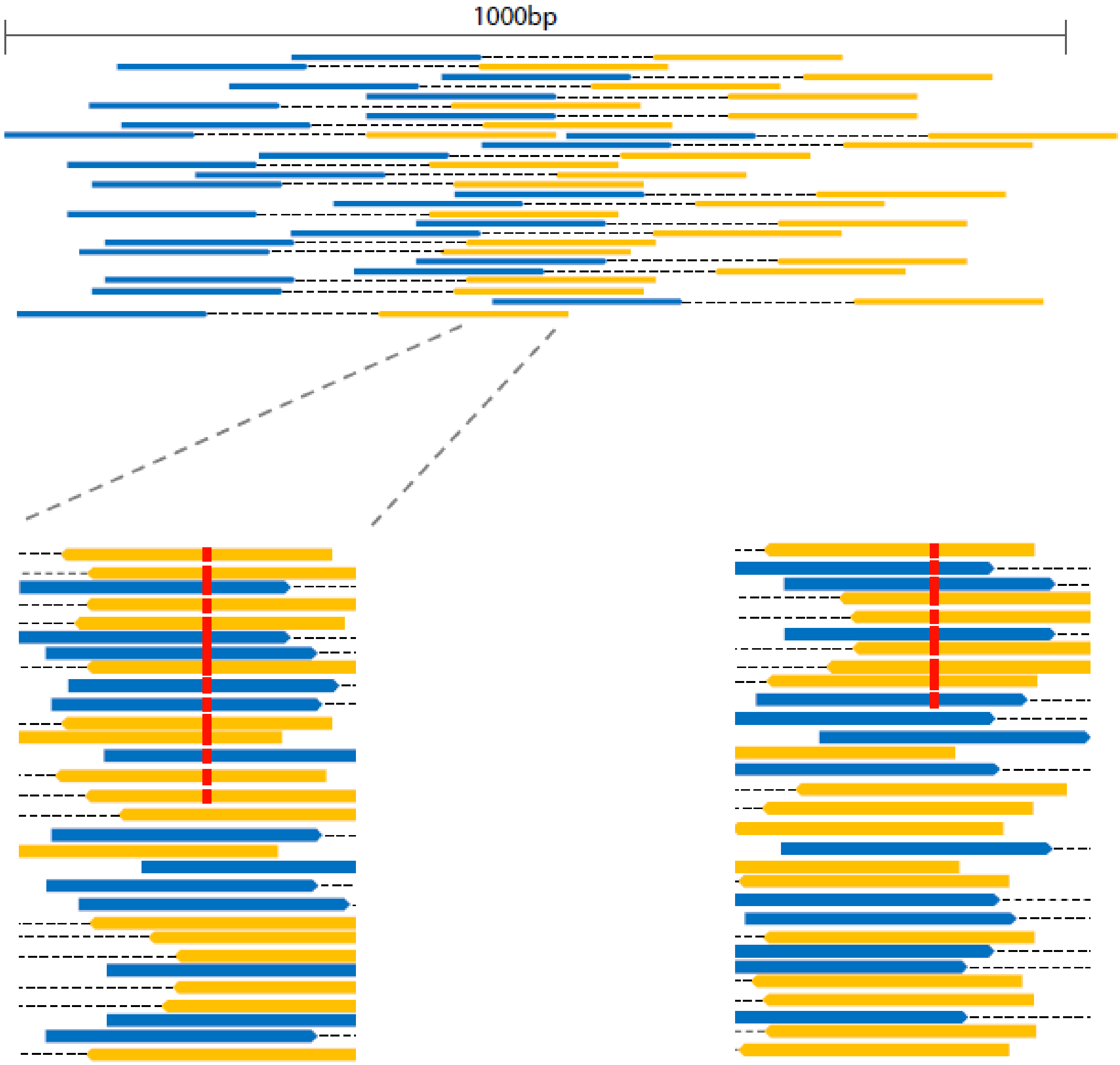
Align billions of NGS sequenced read pairs back to the reference genome



Align billions of NGS sequenced read pairs back to the reference genome

Fraction of reads 50%

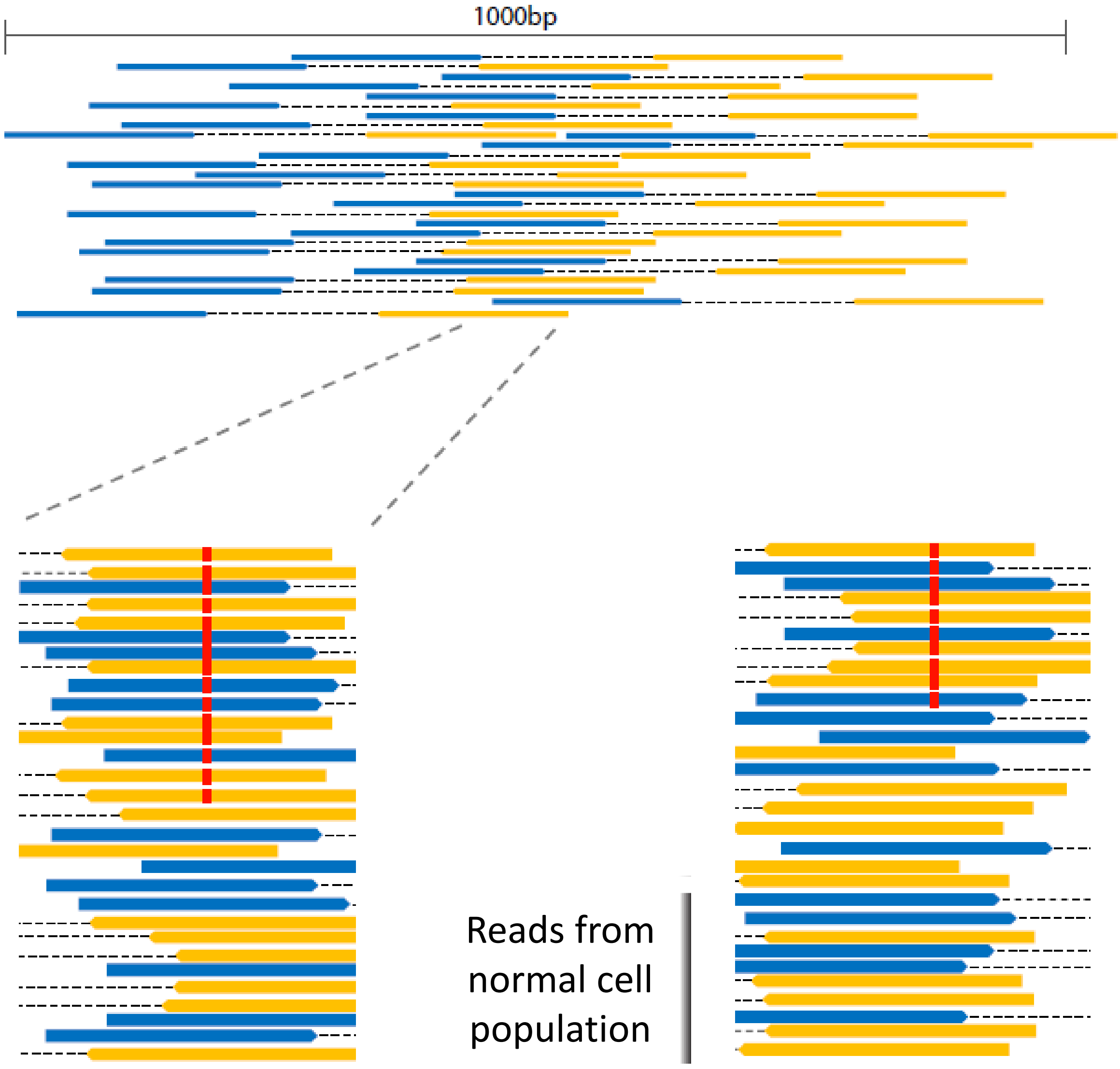
Germline



Fraction of reads 50%

Germline

Tumour

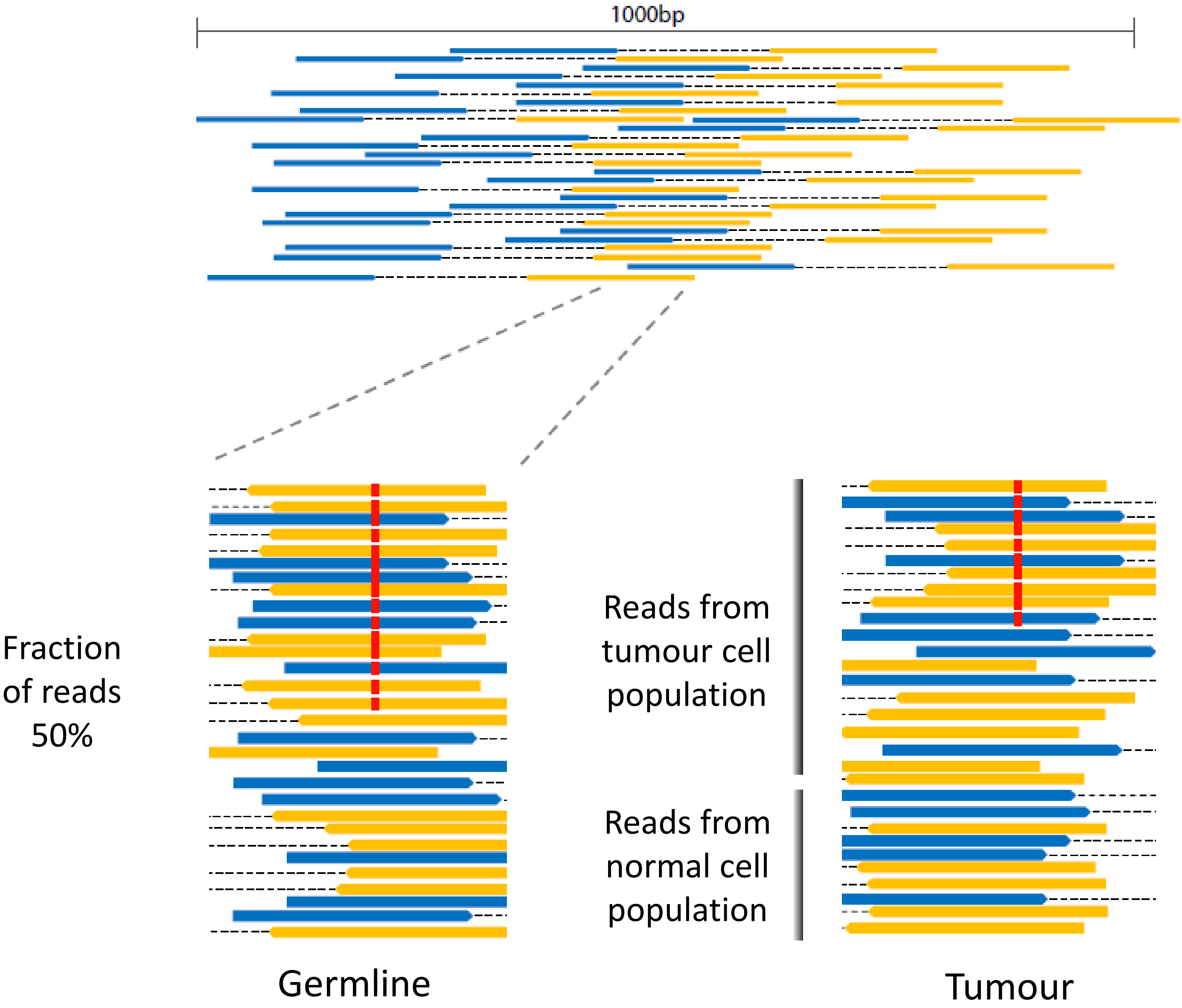


Fraction of reads 50%

Reads from normal cell population

Germline

Tumour



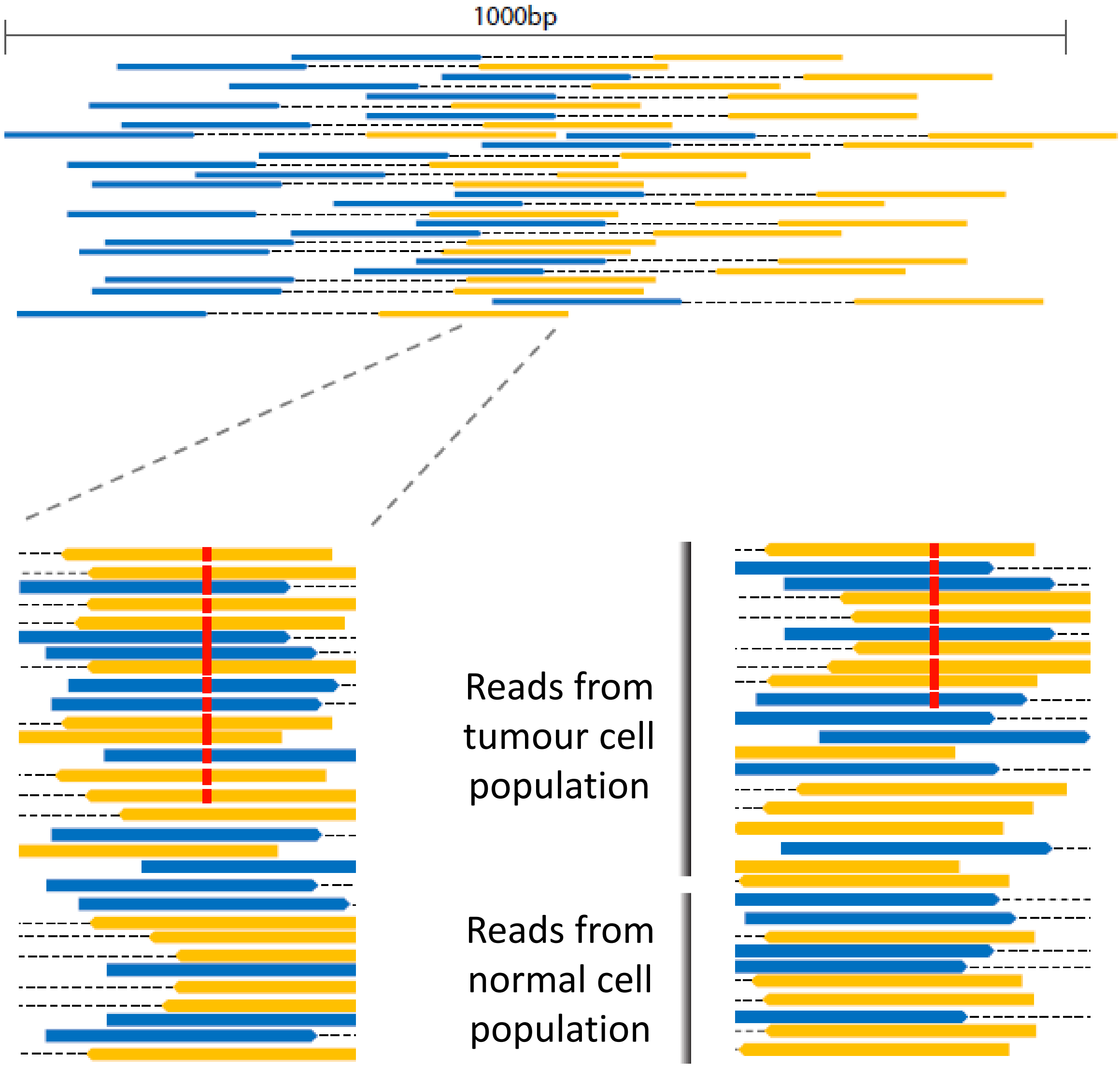
Fraction of reads 50%

Reads from tumour cell population

Reads from normal cell population

Germline

Tumour



Fraction
of reads
50%

Reads from
tumour cell
population

Reads from
normal cell
population

Fraction
of reads
35%

Germline

Tumour

Summary I

- Advances in sequencing chemistry has led to a vast increase in scale and speed of sequencing, permitting unprecedented access to all parts of the human genome

- This technology is digital, providing quantifiable information for every mutation seen

- A huge amount of compute is required for processing and for storage of raw data

- A considerable amount of computational expertise is required to ensure high quality datasets with high sensitivity and high specificity

Part II: Making the most out of NGS data

DATA ANALYSIS

Bioinformatics

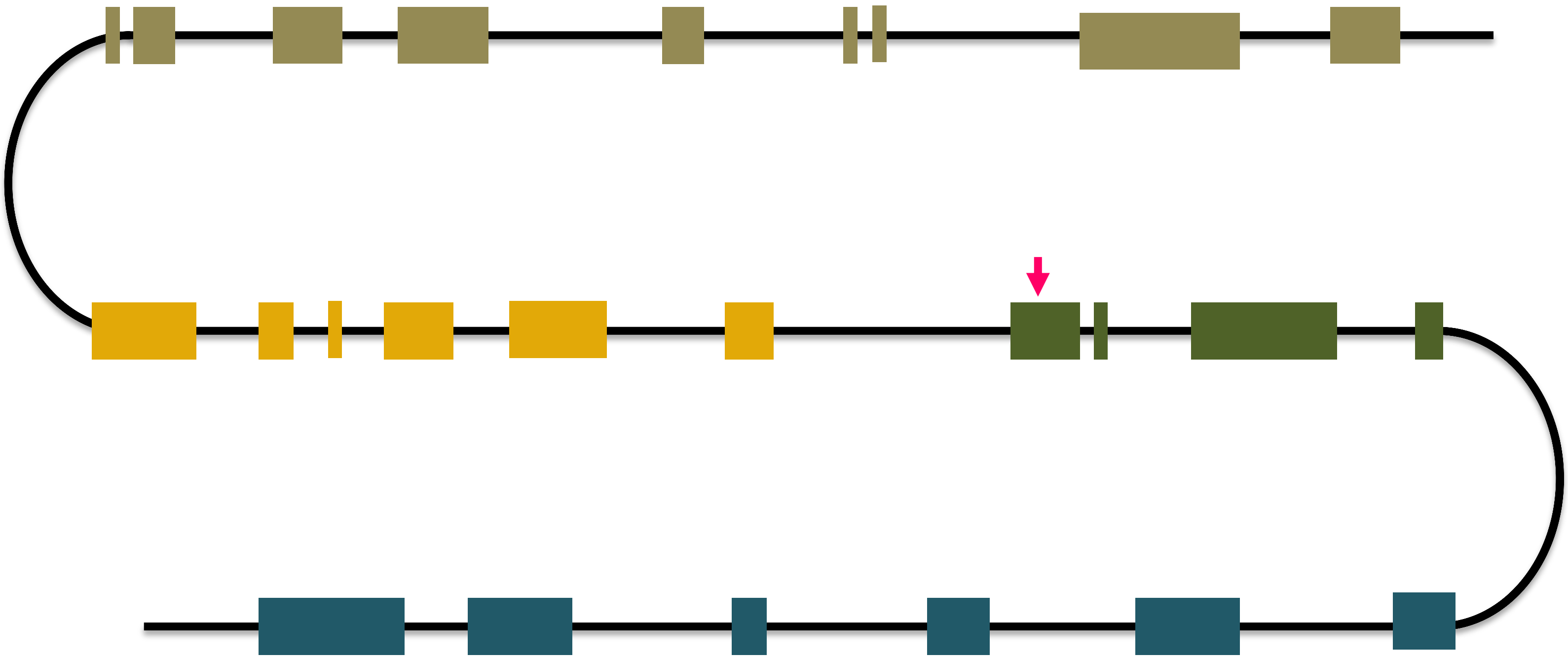
- Data processing

Bioinformatics

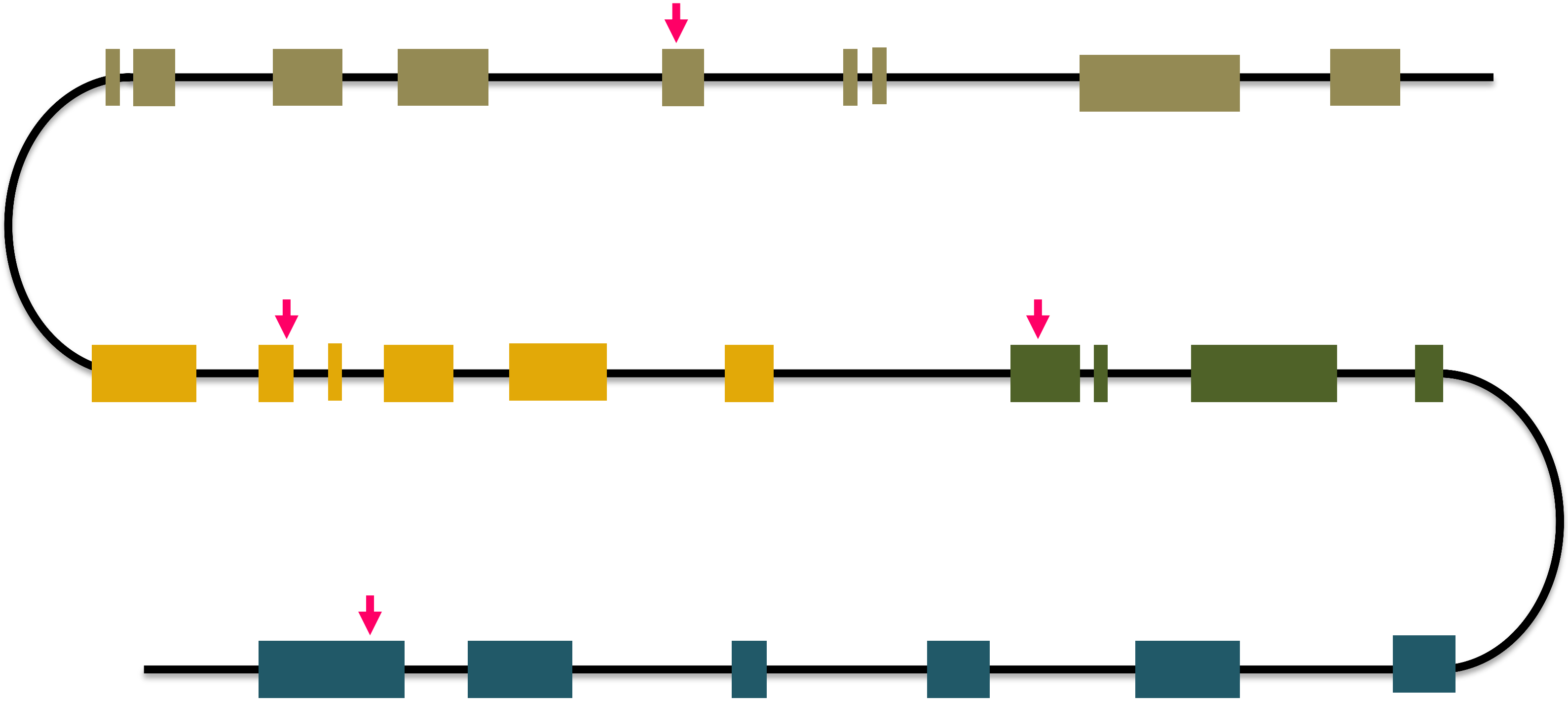
- Data processing

- Downstream analysis
  - Cancer genes
  - Somatic mutation signatures
  - Cancer evolution

DRIVERS



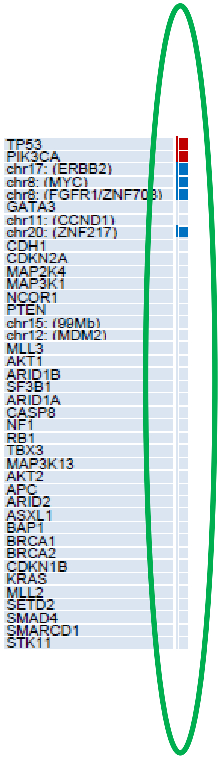
DRIVERS



Downstream analysis: Cancer genes I

Genomic scenario	Targeted drug
ERBB2 Amplification – (Breast Cancer)	Herceptin & Lapatinib
BCR-ABL – (CML)	Imatinib (and others)
EGFR – *(NSCLC)*	Erlotinib, Gefitinib
EML4-ALK – *(NSCLC)*	Crizotinib
KRAS-negative – (colorectal cancer)	Cetuximab
BRAF(V600E) – *(Metastatic Melanoma)*	Vemurafenib

Downstream analysis: Cancer genes I

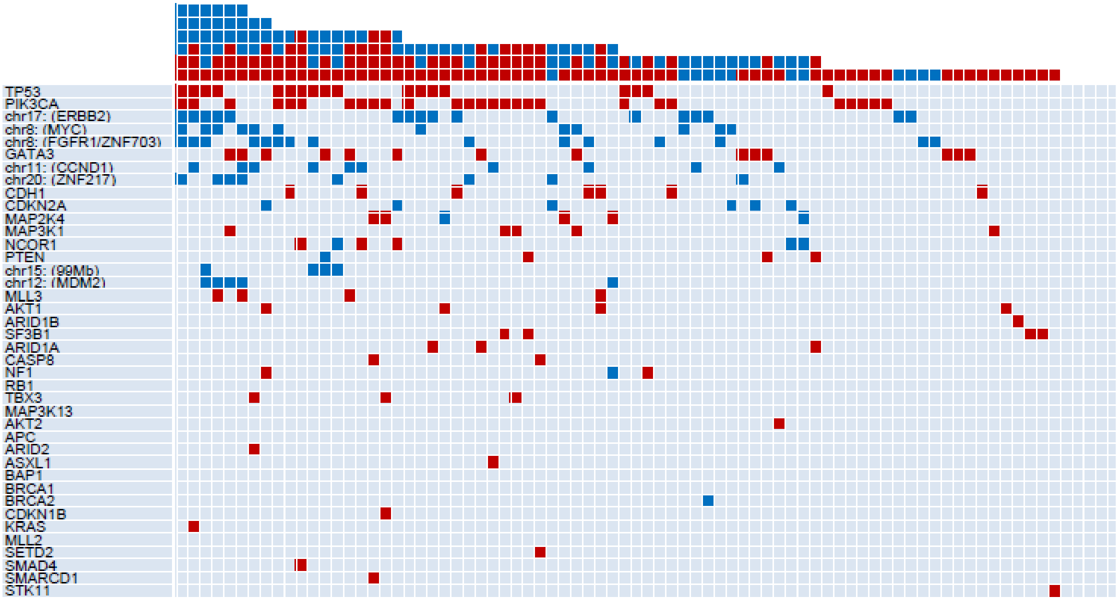


🟦 Copy number changes

🟥 Point mutations

Stephens et al 2012

Downstream analysis: Cancer genes I



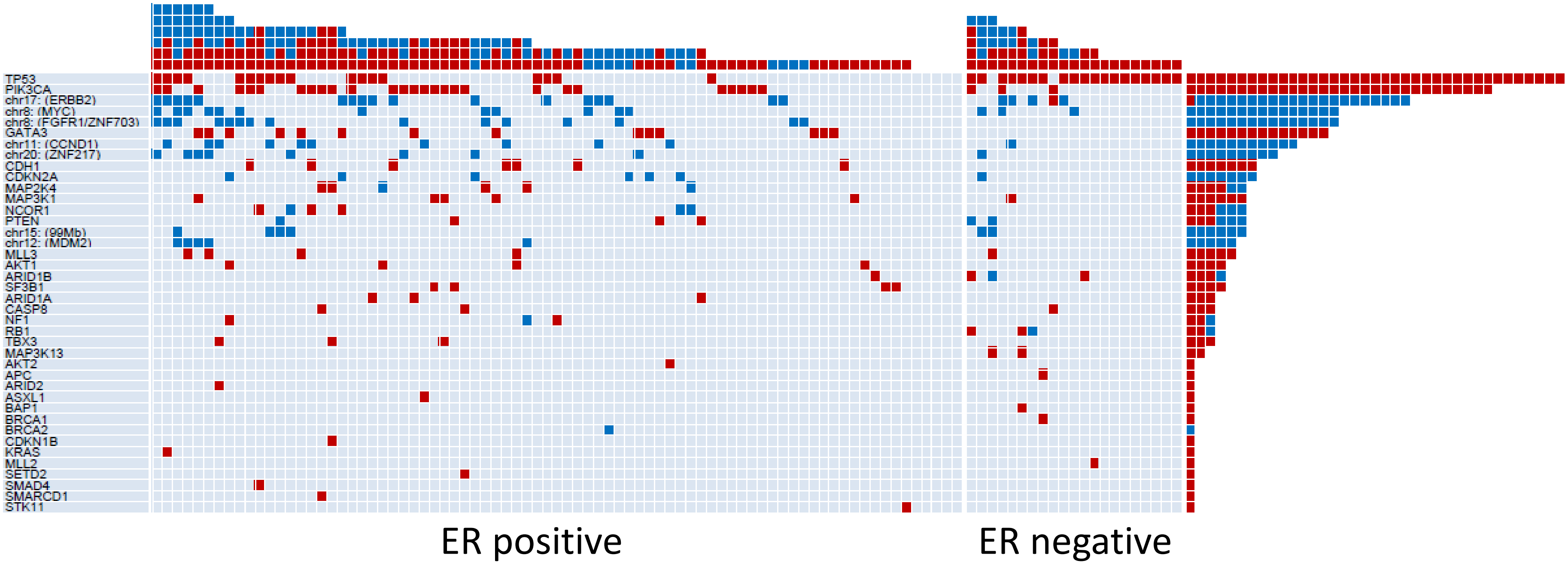
ER positive

🟦 Copy number changes

🟥 Point mutations

Stephens et al 2012

Downstream analysis: Cancer genes I



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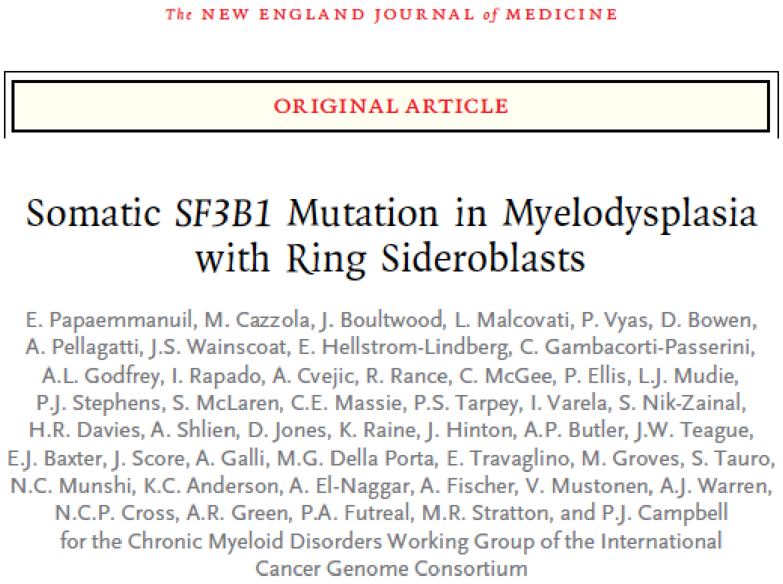
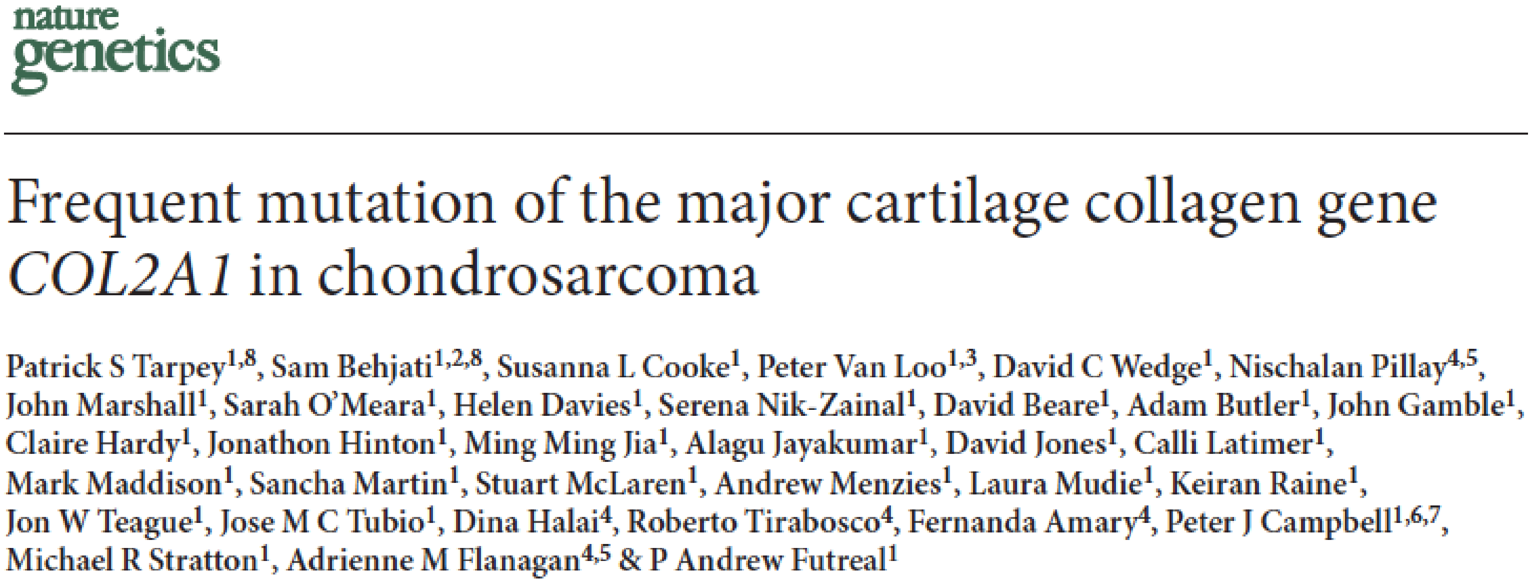


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic *SF3B1* Mutation in Myelodysplasia with Ring Sideroblasts

E. Papaemmanuil, M. Cazzola, J. Boultwood, L. Malcovati, P. Vyas, D. Bowen, A. Pellagatti, J.S. Wainscoat, E. Hellstrom-Lindberg, C. Gambacorti-Passerini, A.L. Godfrey, I. Rapado, A. Cvejic, R. Rance, C. McGee, P. Ellis, L.J. Mudie, P.J. Stephens, S. McLaren, C.E. Massie, P.S. Tarpey, I. Varela, S. Nik-Zainal, H.R. Davies, A. Shlien, D. Jones, K. Raine, J. Hinton, A.P. Butler, J.W. Teague, E.J. Baxter, J. Score, A. Galli, M.G. Della Porta, E. Travaglino, M. Groves, S. Tauro, N.C. Munshi, K.C. Anderson, A. El-Naggar, A. Fischer, V. Mustonen, A.J. Warren, N.C.P. Cross, A.R. Green, P.A. Futreal, M.R. Stratton, and P.J. Campbell for the Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium

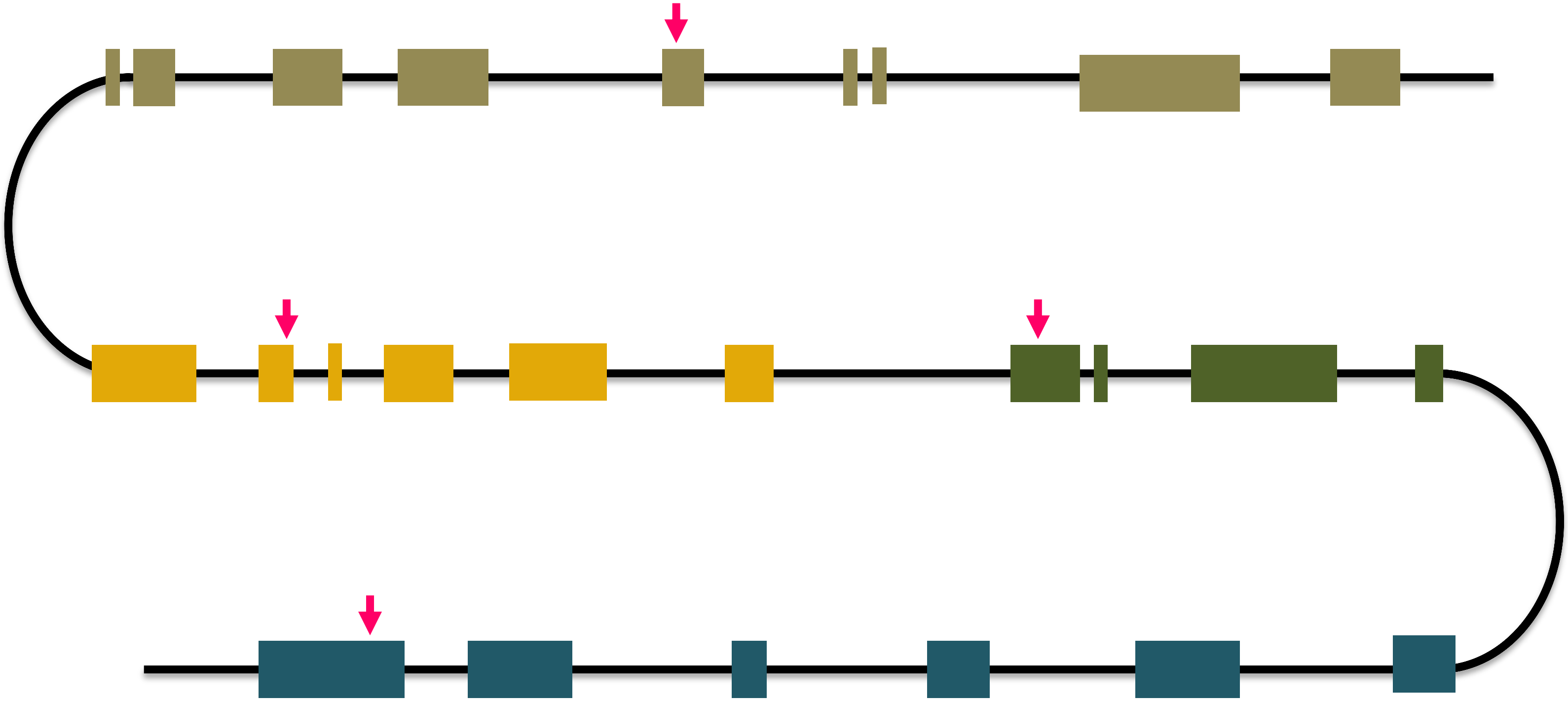


nature genetics

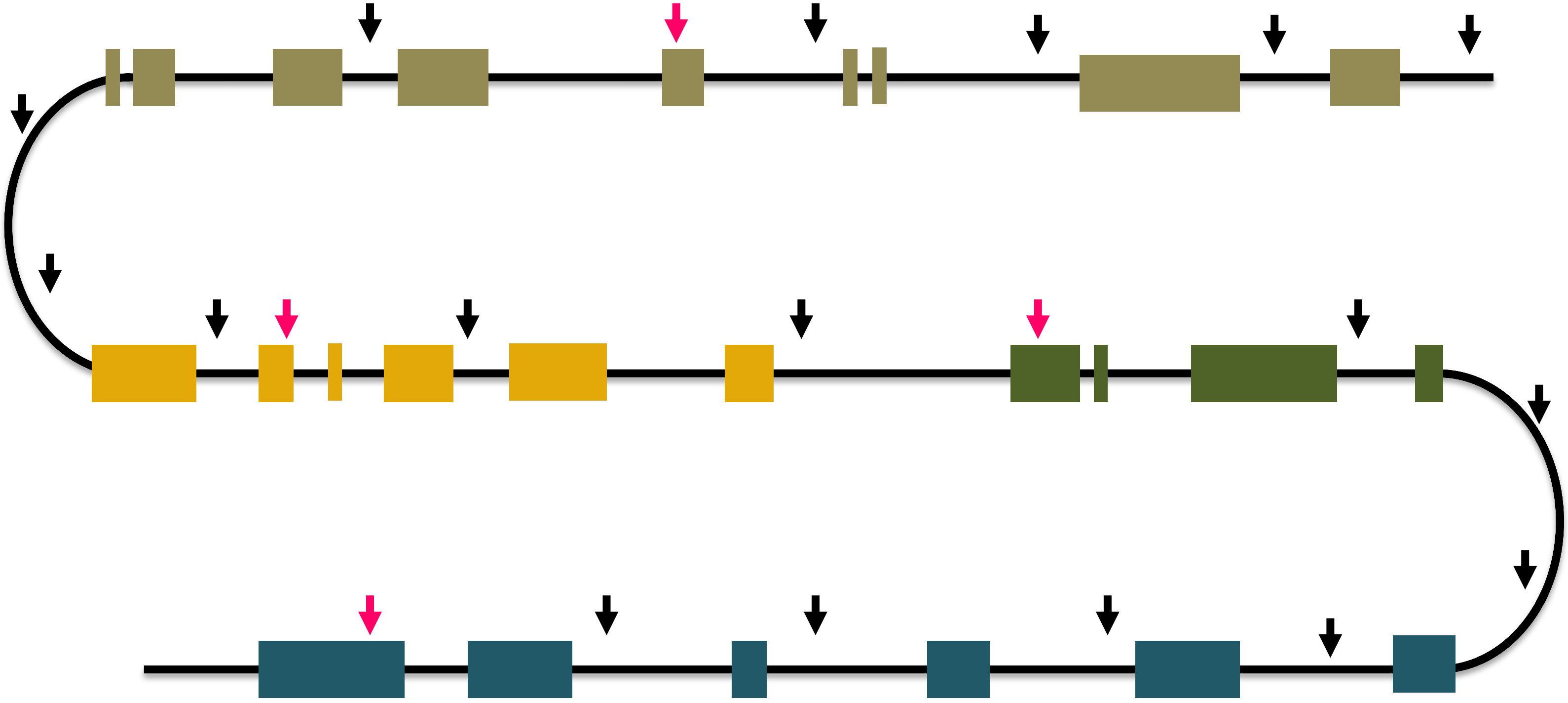
Frequent mutation of the major cartilage collagen gene *COL2A1* in chondrosarcoma

Patrick S Tarpey[1,8], Sam Behjati[1,2,8], Susanna L Cooke[1], Peter Van Loo[1,3], David C Wedge[1], Nischalan Pillay[4,5], John Marshall[1], Sarah O'Meara[1], Helen Davies[1], Serena Nik-Zainal[1], David Beare[1], Adam Butler[1], John Gamble[1], Claire Hardy[1], Jonathon Hinton[1], Ming Ming Jia[1], Alagu Jayakumar[1], David Jones[1], Calli Latimer[1], Mark Maddison[1], Sancha Martin[1], Stuart McLaren[1], Andrew Menzies[1], Laura Mudie[1], Keiran Raine[1], Jon W Teague[1], Jose M C Tubio[1], Dina Halai[4], Roberto Tirabosco[4], Fernanda Amary[4], Peter J Campbell[1,6,7], Michael R Stratton[1], Adrienne M Flanagan[4,5] & P Andrew Futreal[1]

DRIVERS



DRIVERS AND PASSENGERS



Downstream analysis II: Using passengers

BRCA1 null	5
BRCA2 null	4
ER+, HER2-	5
ER+, HER2+	2
ER-, HER2+	2
ER-, HER2-	3
Total	21 whole-genome sequenced breast cancers

Nik-Zainal et al, Cell, 2012a

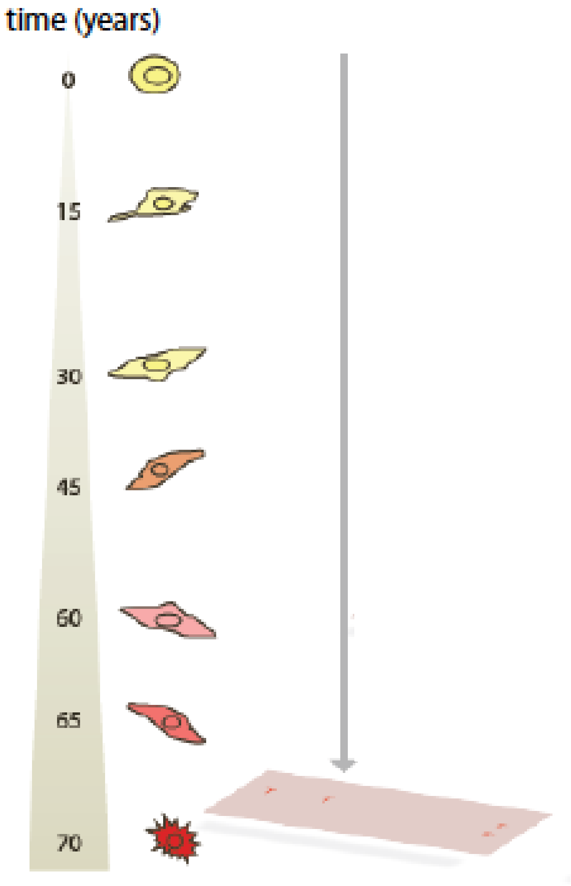
Downstream analysis II: Using passengers

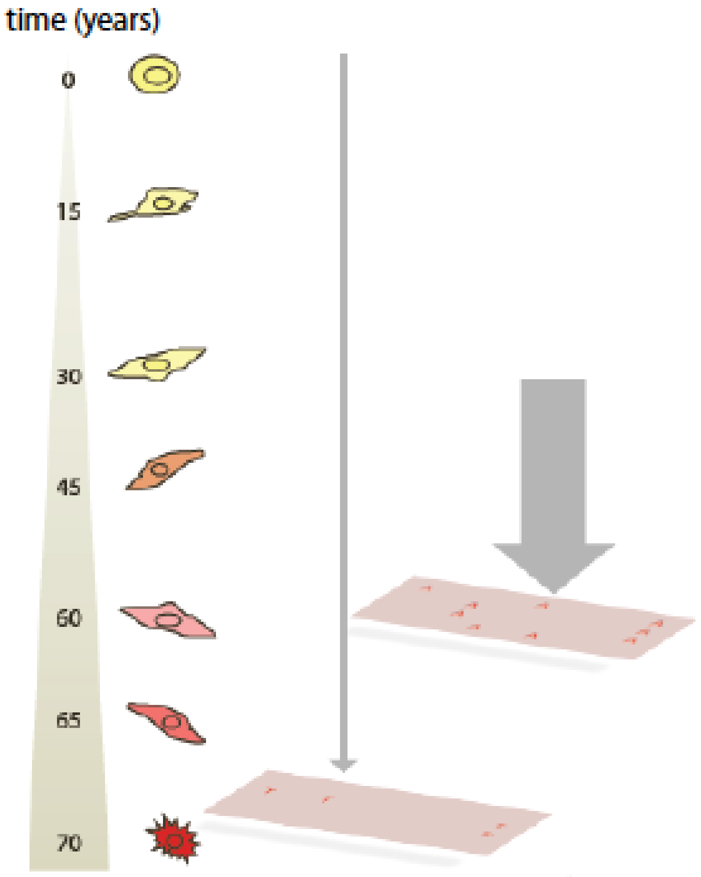
BRCA1 null	5
BRCA2 null	4
ER+, HER2-	5
ER+, HER2+	2
ER-, HER2+	2
ER-, HER2-	3

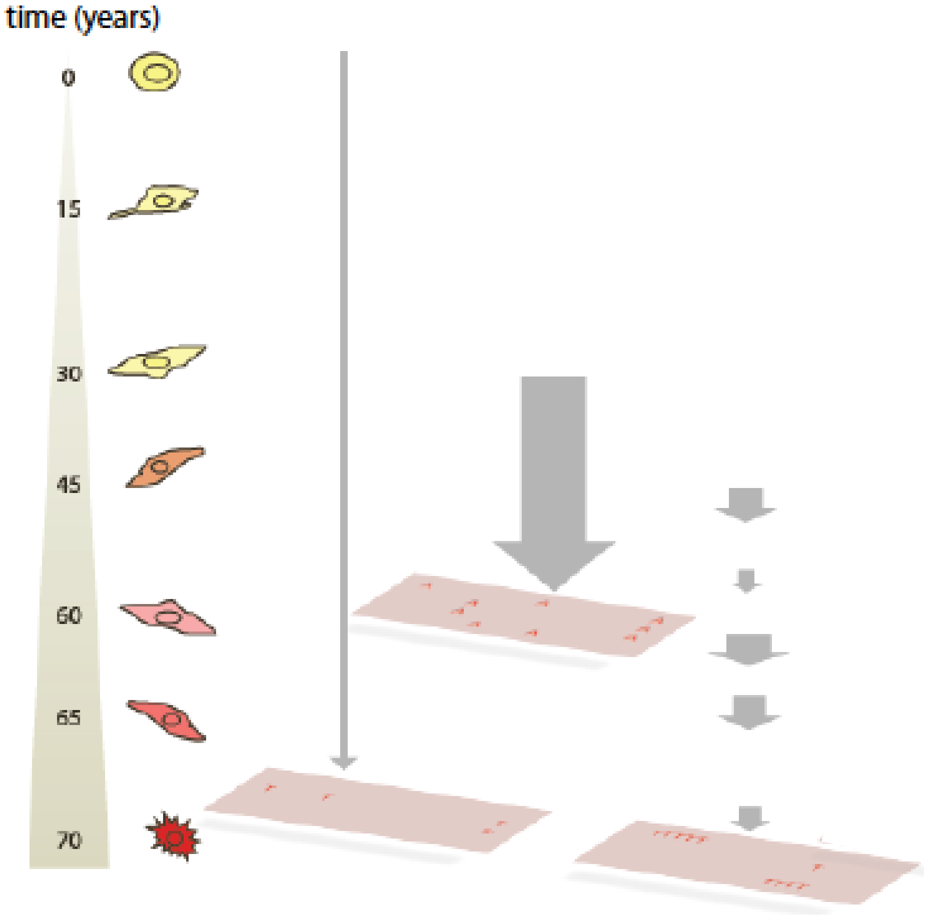
Somatic substitutions	183,916
Somatic indels	2,869
Somatic rearrangements	1,192

Total 21 whole-genome sequenced breast cancers

Nik-Zainal et al, Cell, 2012a


time (years)
0
15
30
45
60
65
70


time (years)
0
15
30
45
60
65
70


time (years)
0
15
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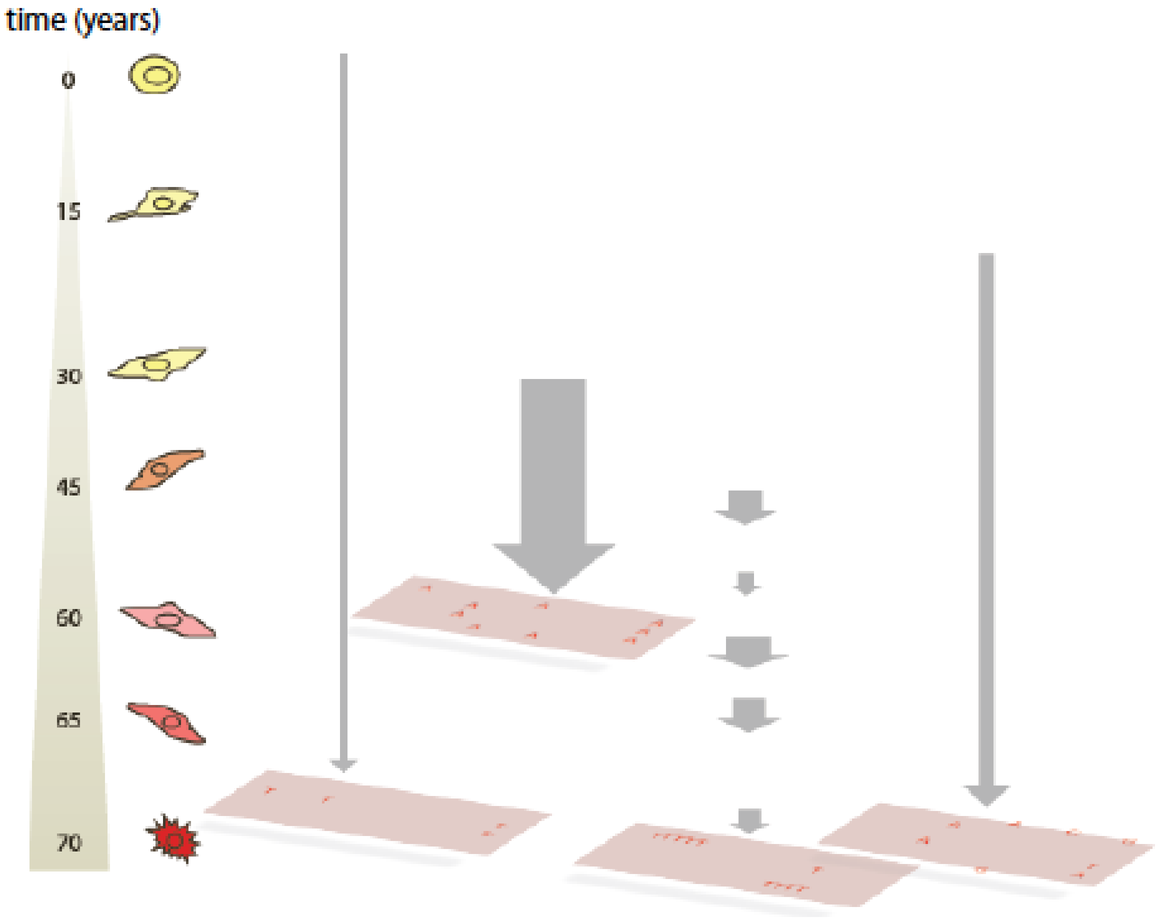
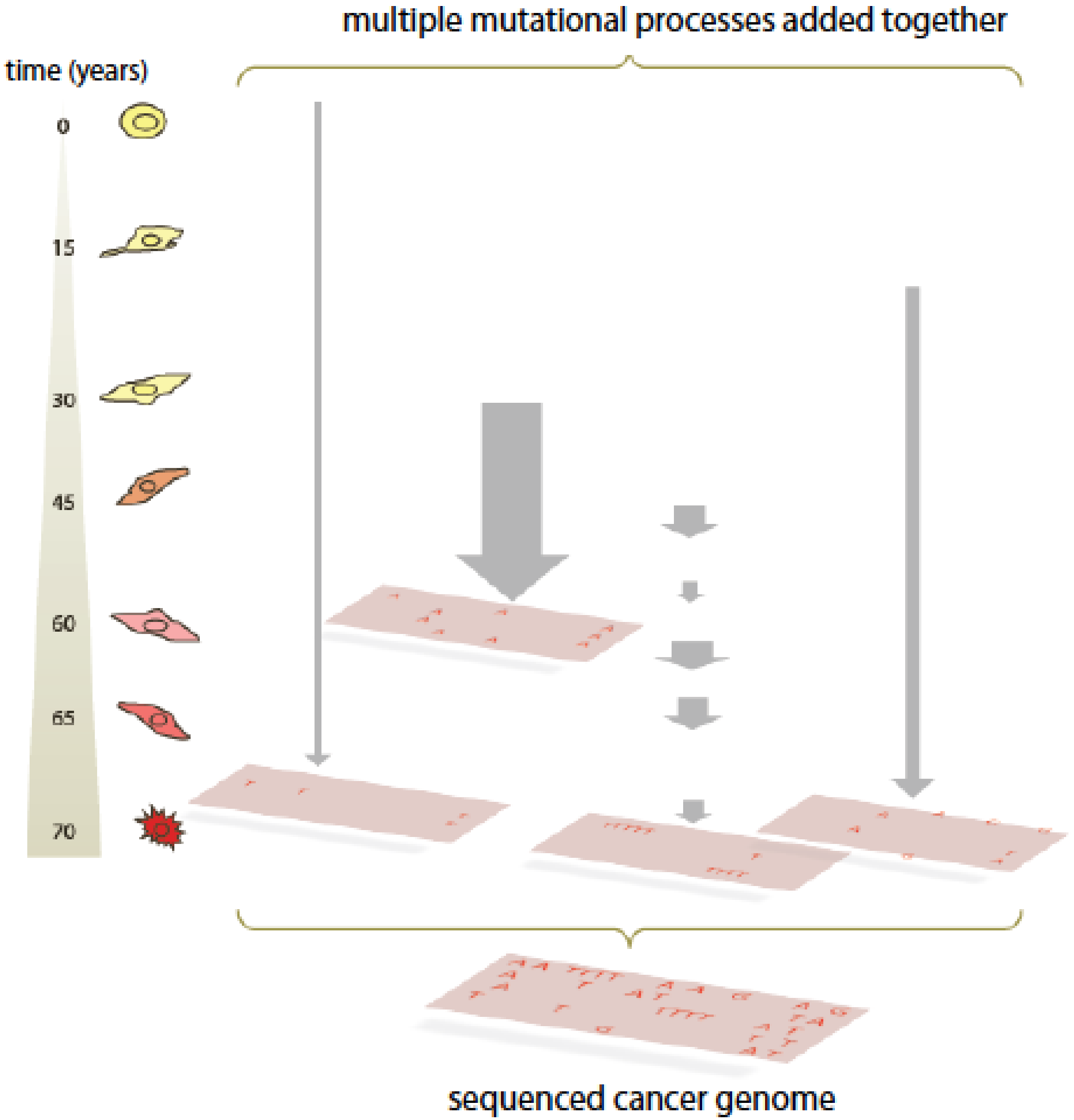
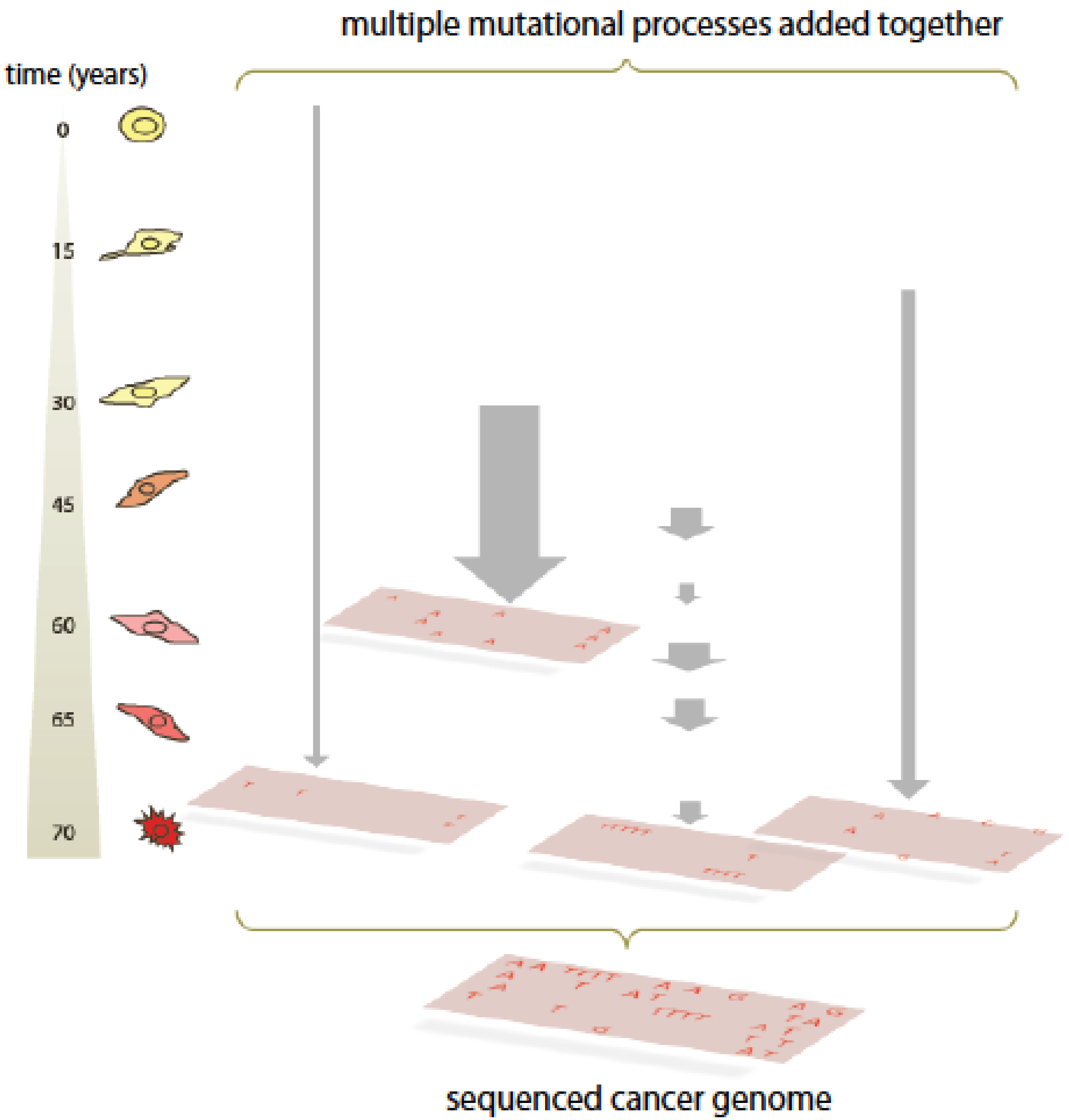

time (years)
0
15
30
45
60
65
70



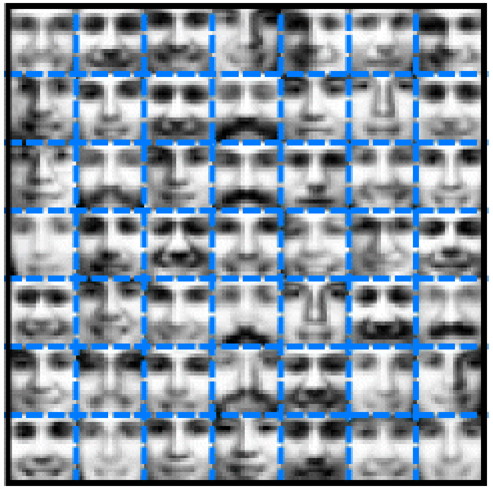
multiple mutational processes added together

sequenced cancer genome

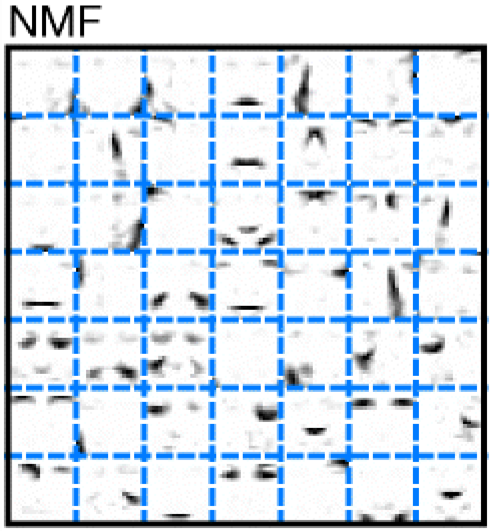
Mutation signatures in human cells

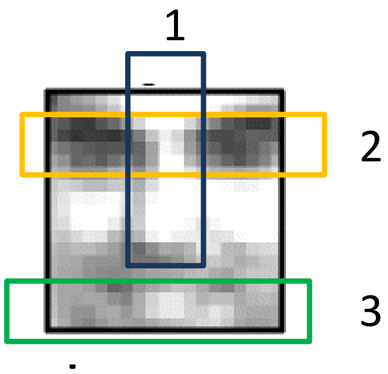


Downstream analysis II: Mutation signatures

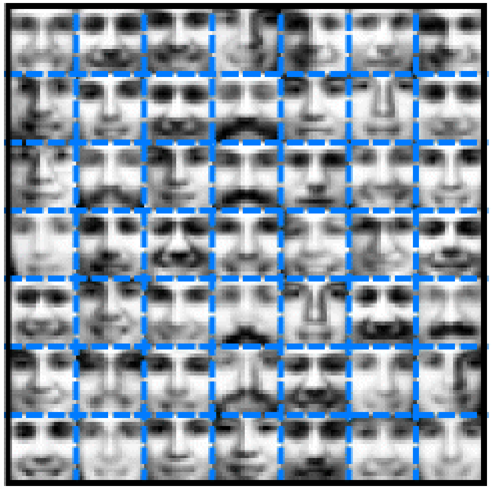


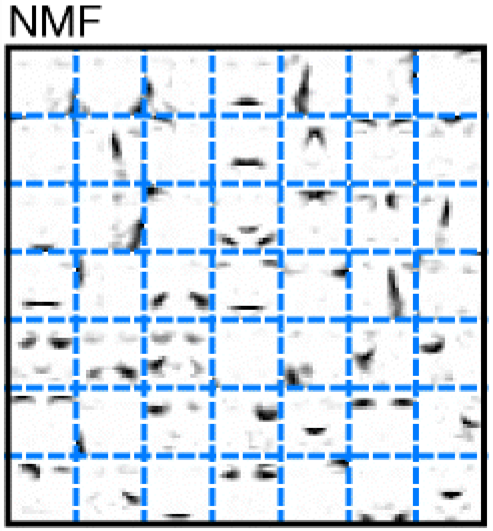
Lee & Seung 1999, Brunet et al 2004

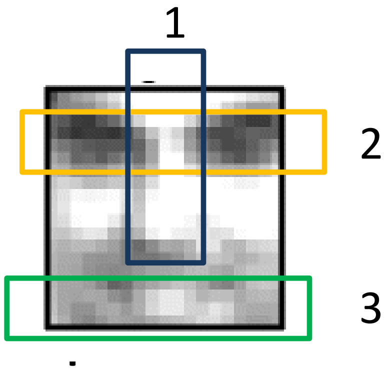




Downstream analysis II: Mutation signatures

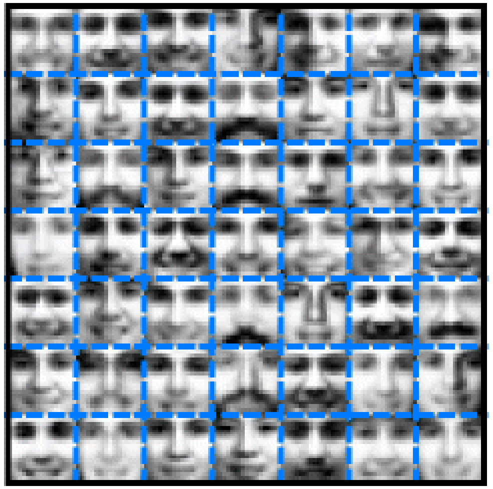




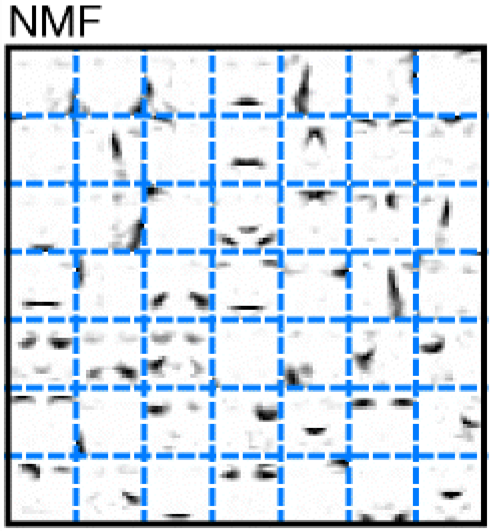


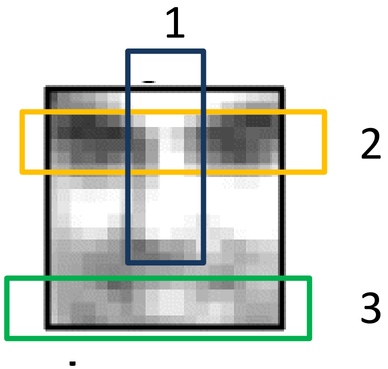
Lee & Seung 1999, Brunet et al 2004

Downstream analysis II: Mutation signatures

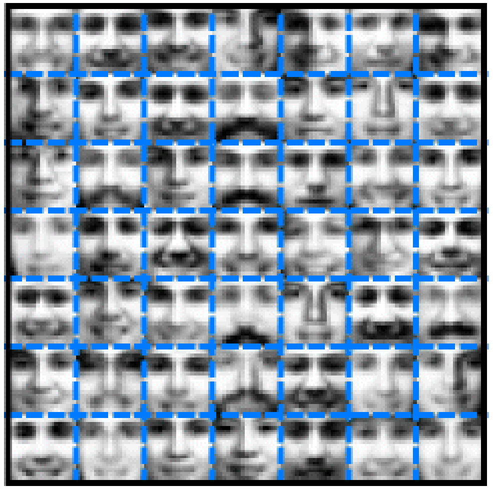


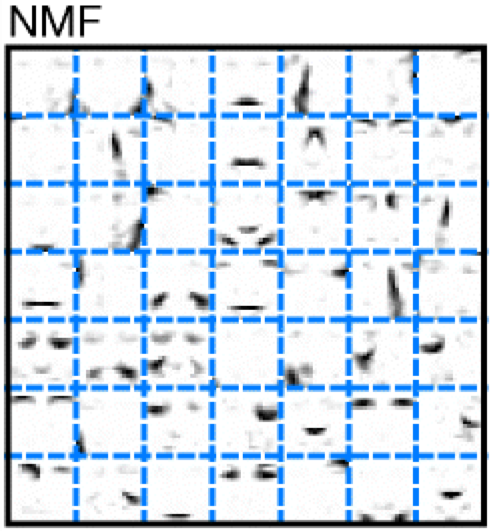
Lee & Seung 1999, Brunet et al 2004



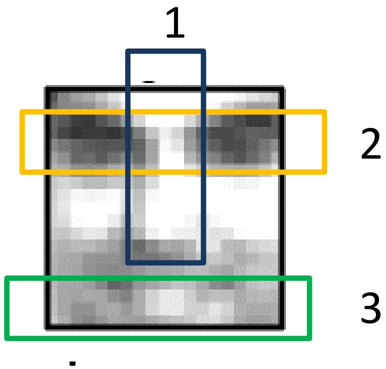


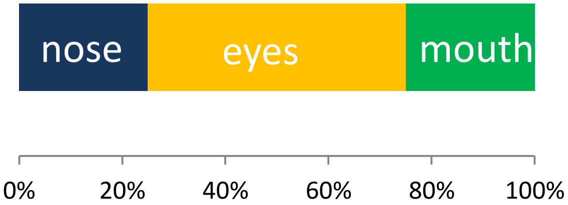
Downstream analysis II: Mutation signatures



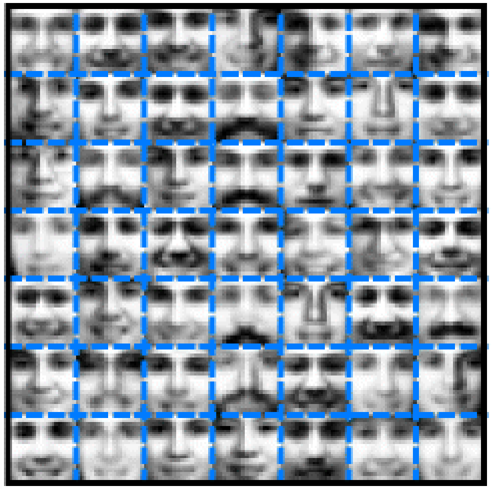


Lee & Seung 1999, Brunet et al 2004

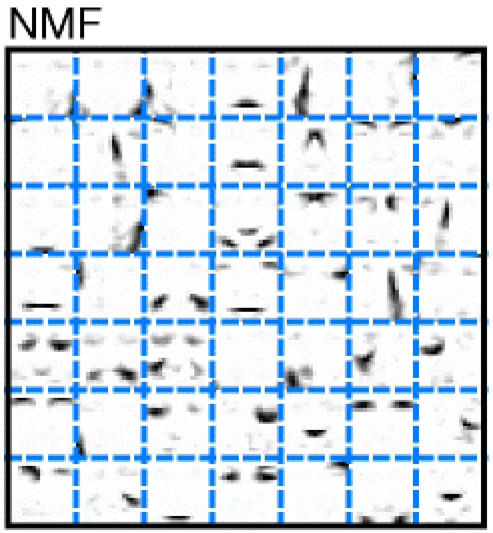


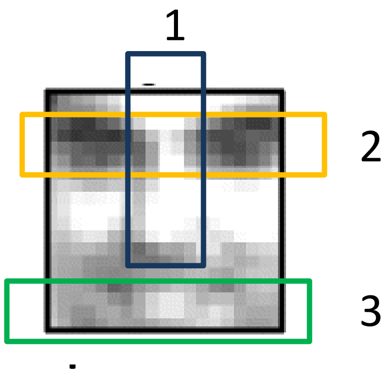


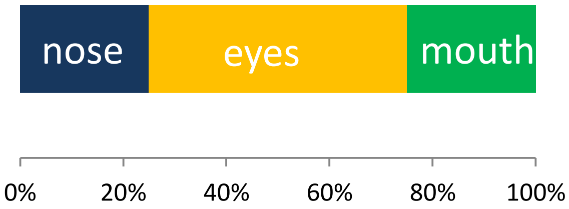
Downstream analysis II: Mutation signatures

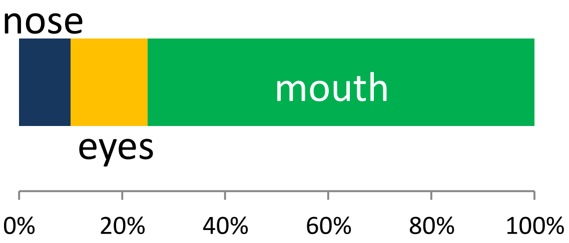


Lee & Seung 1999, Brunet et al 2004

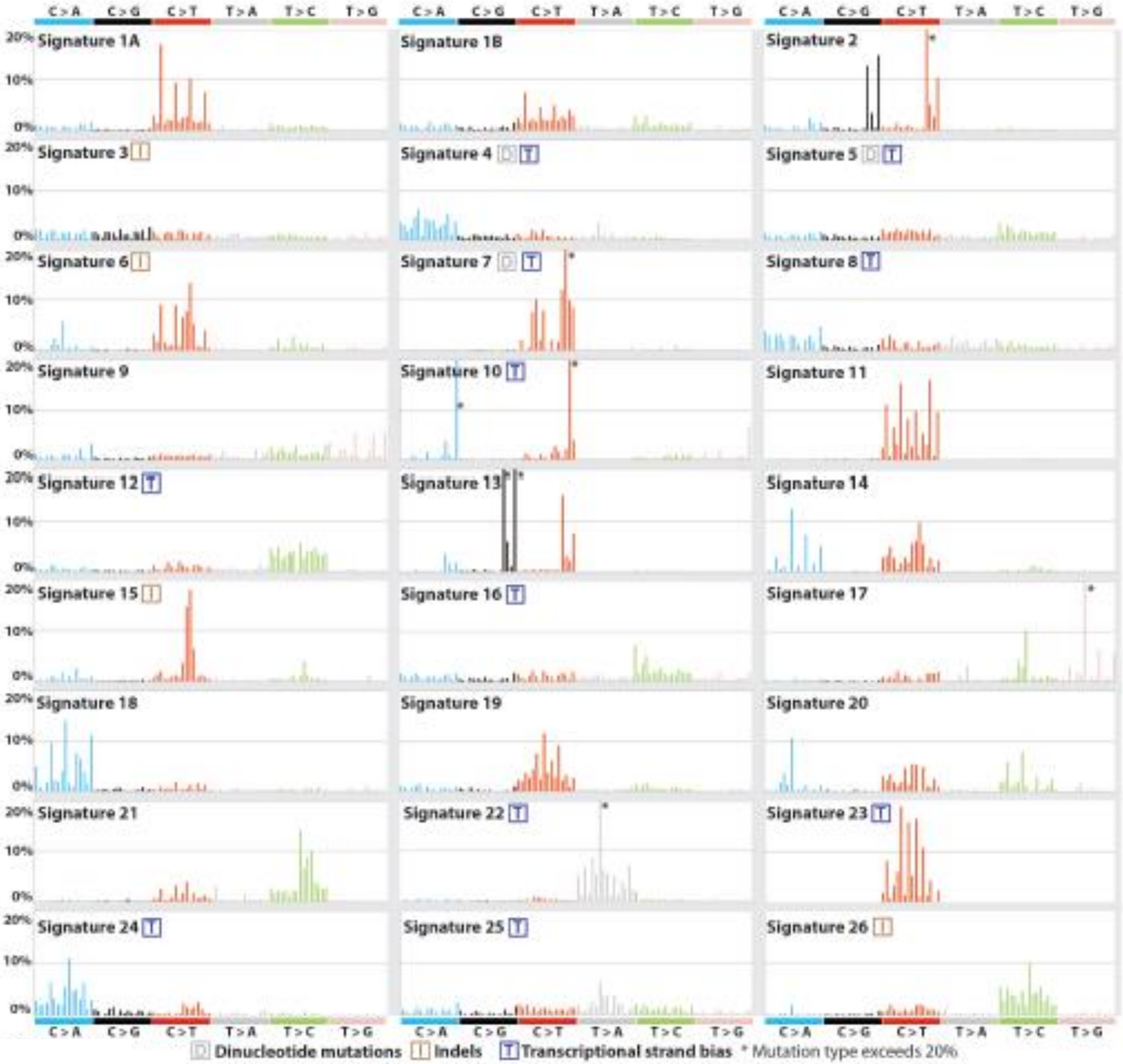




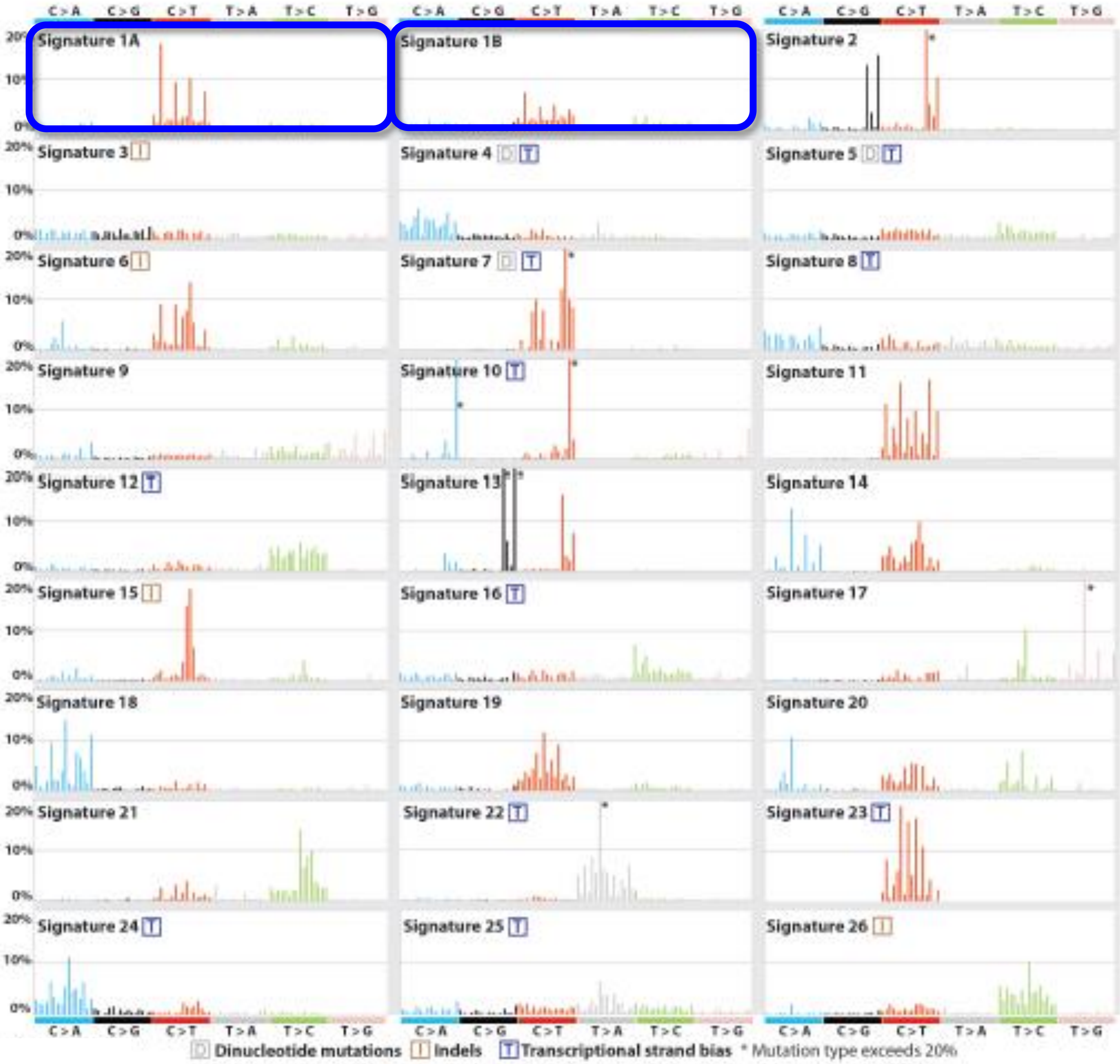




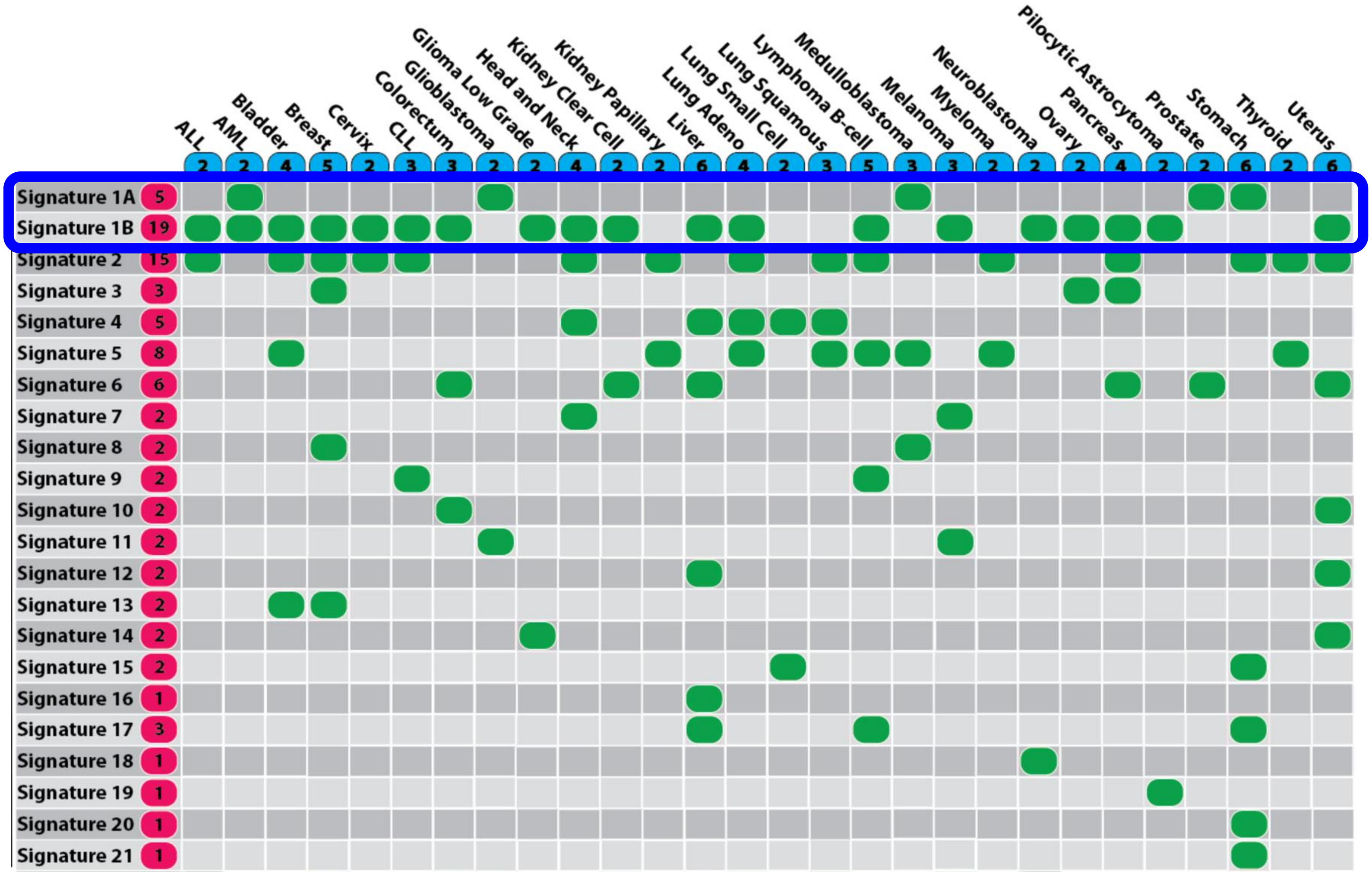
Mutation signatures in human cancers



Mutation signatures present in many cancer types



Mutation signatures present in many cancer types



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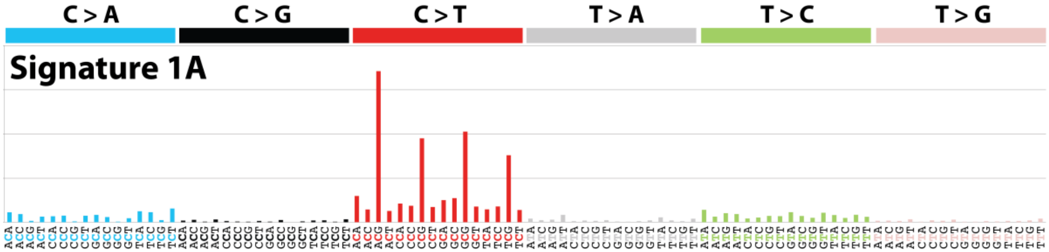
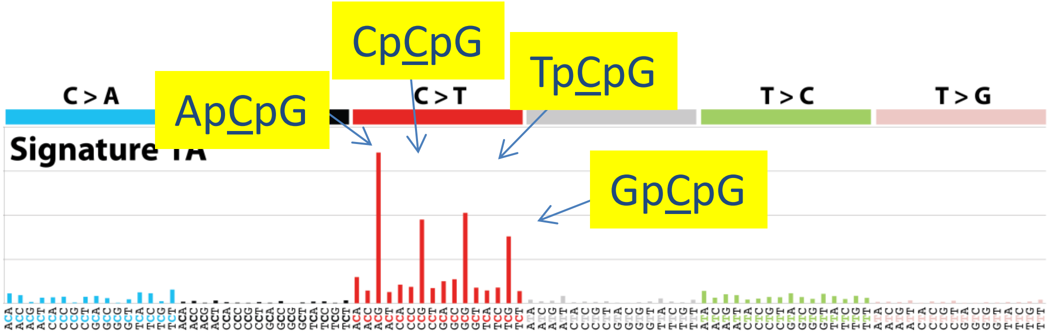
		2	2	4	5	2	3	3	2	2	4	2	2	6	4	2	3	5	3	3	2	2	2	4	2	2	6	2	6
Signature 1A	5		🟩						🟩										🟩							🟩	🟩		
Signature 1B	19	🟩	🟩	🟩	🟩	🟩	🟩	🟩		🟩	🟩	🟩		🟩	🟩			🟩		🟩		🟩	🟩	🟩	🟩				🟩
Signature 2	15	🟩		🟩	🟩	🟩	🟩				🟩		🟩		🟩		🟩	🟩			🟩			🟩			🟩	🟩	🟩
Signature 3	3				🟩																		🟩	🟩					
Signature 4	5										🟩			🟩	🟩	🟩	🟩												
Signature 5	8			🟩									🟩		🟩		🟩	🟩	🟩		🟩							🟩	
Signature 6	6							🟩				🟩		🟩										🟩		🟩			🟩
Signature 7	2										🟩									🟩									
Signature 8	2				🟩														🟩										
Signature 9	2						🟩											🟩											
Signature 10	2							🟩																					🟩
Signature 11	2								🟩											🟩									
Signature 12	2													🟩															🟩
Signature 13	2			🟩	🟩																								
Signature 14	2									🟩																			🟩
Signature 15	2															🟩											🟩		
Signature 16	1													🟩															
Signature 17	3													🟩				🟩									🟩		
Signature 18	1																					🟩							
Signature 19	1																								🟩				
Signature 20	1																										🟩		
Signature 21	1																										🟩		

Mutation signatures present in many cancer types



Mutation signatures present in many cancer types



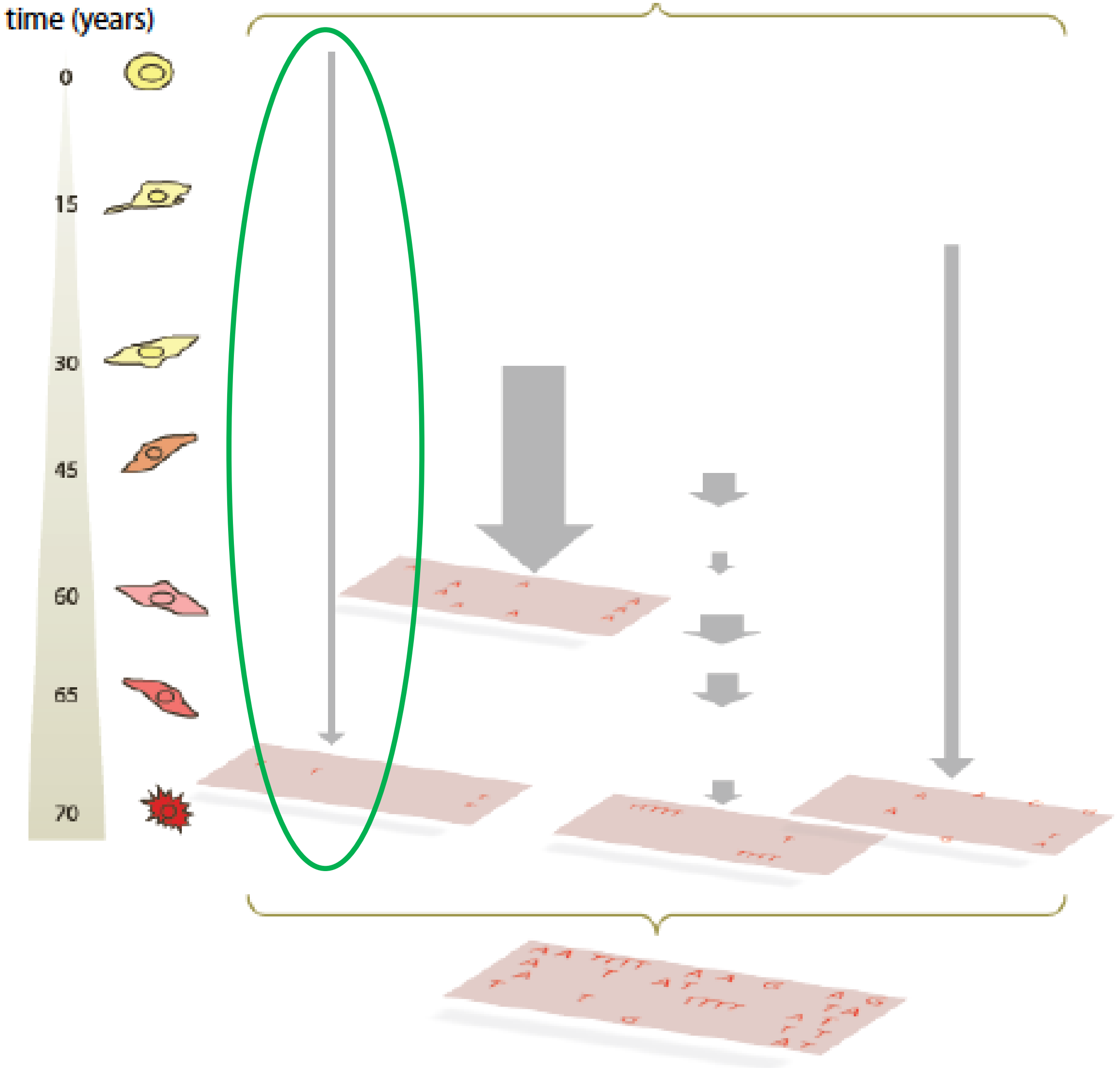
CpCpG

TpCpG

ApCpG

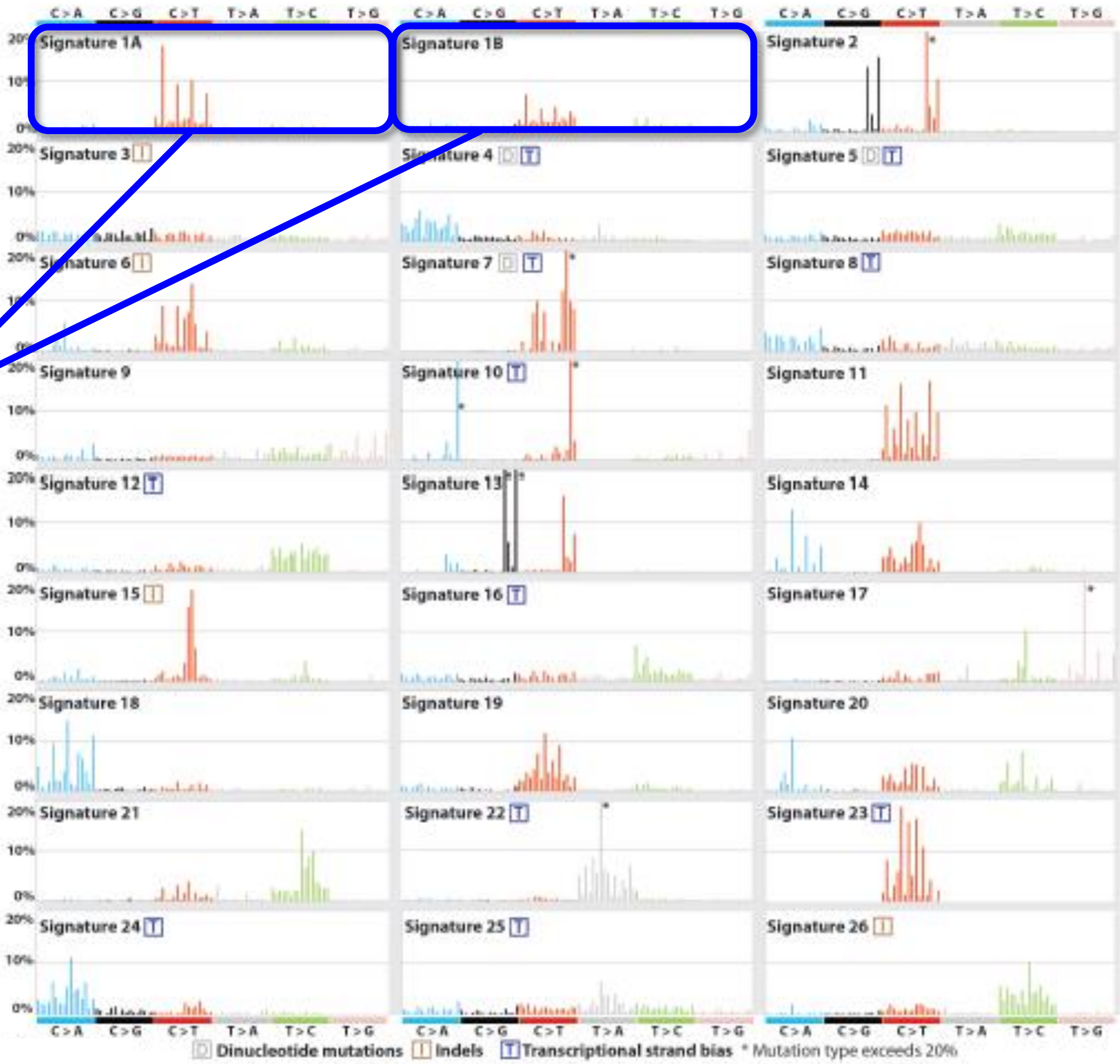
GpCpG

multiple mutational processes added together



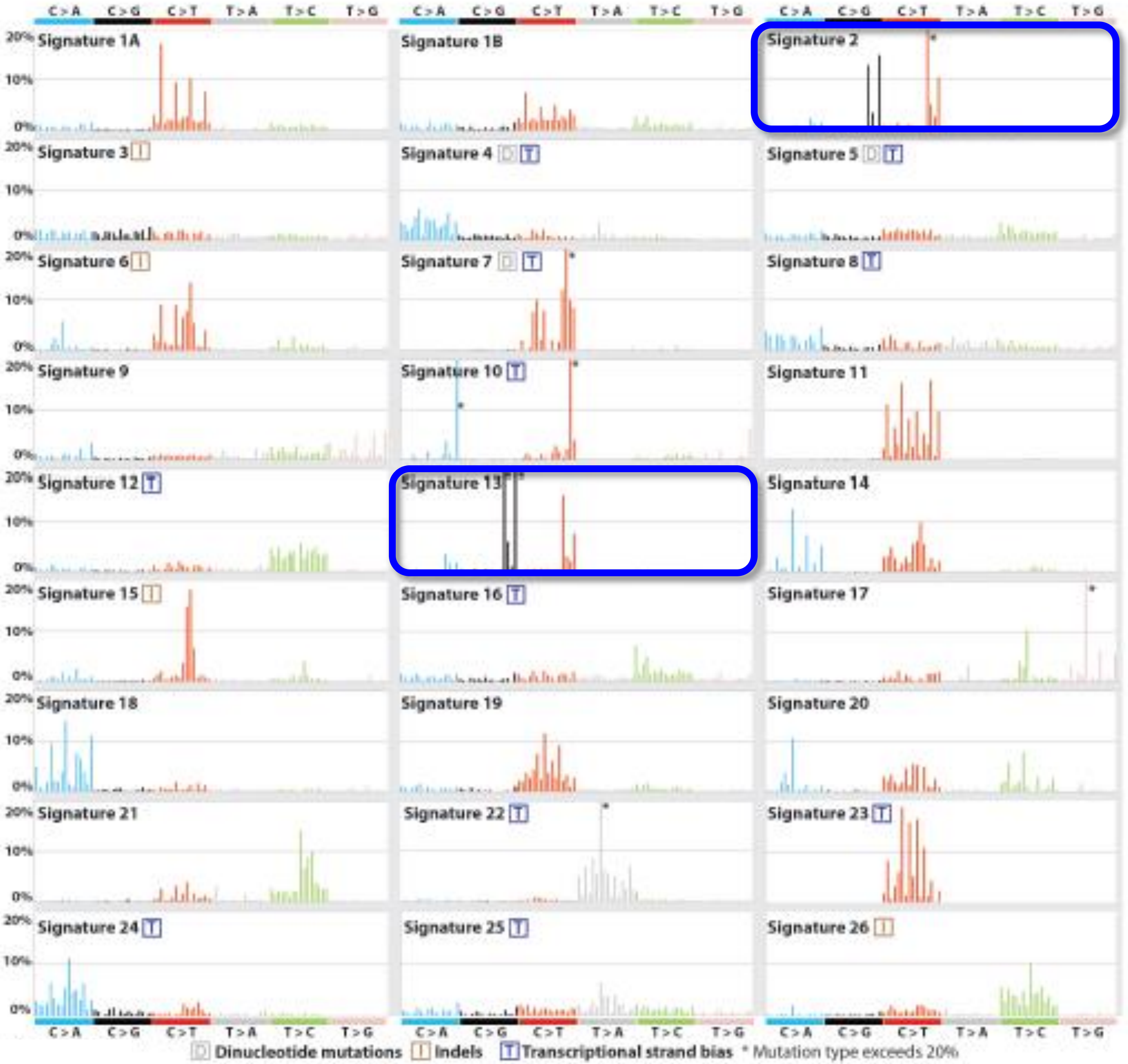
sequenced cancer genome

Mutation signatures present in many cancer types

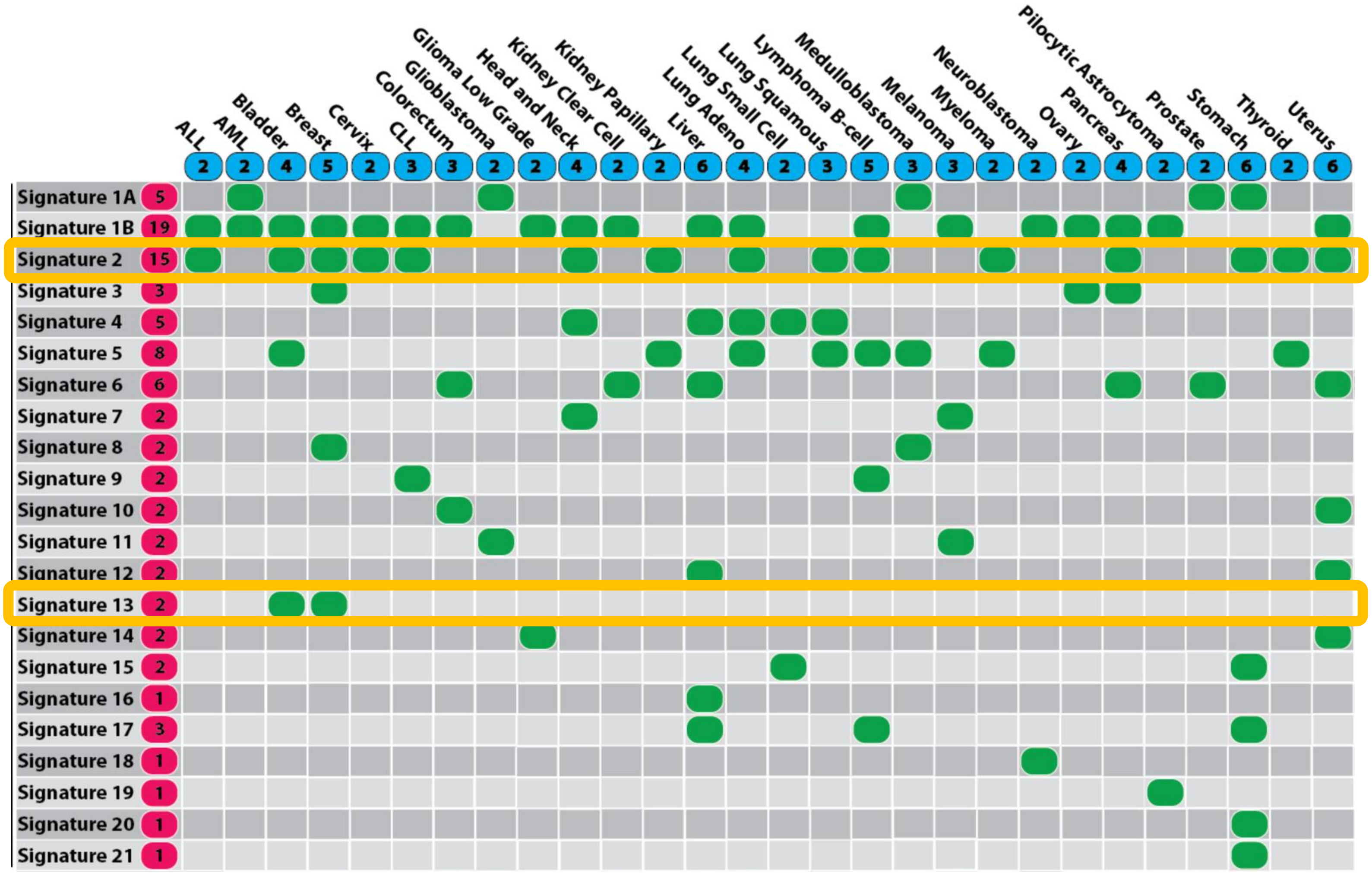


deamination of methylated cytosines

Mutation signatures present in many cancer types

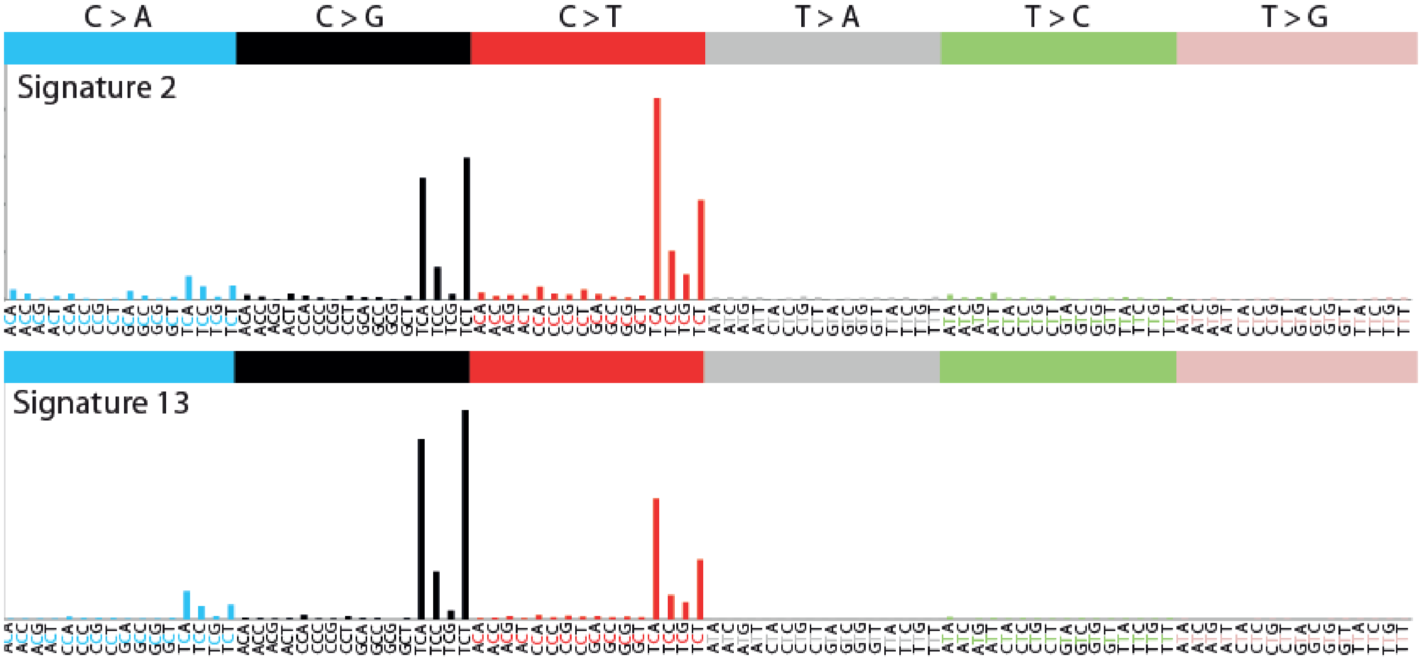


Mutation signatures present in many cancer types

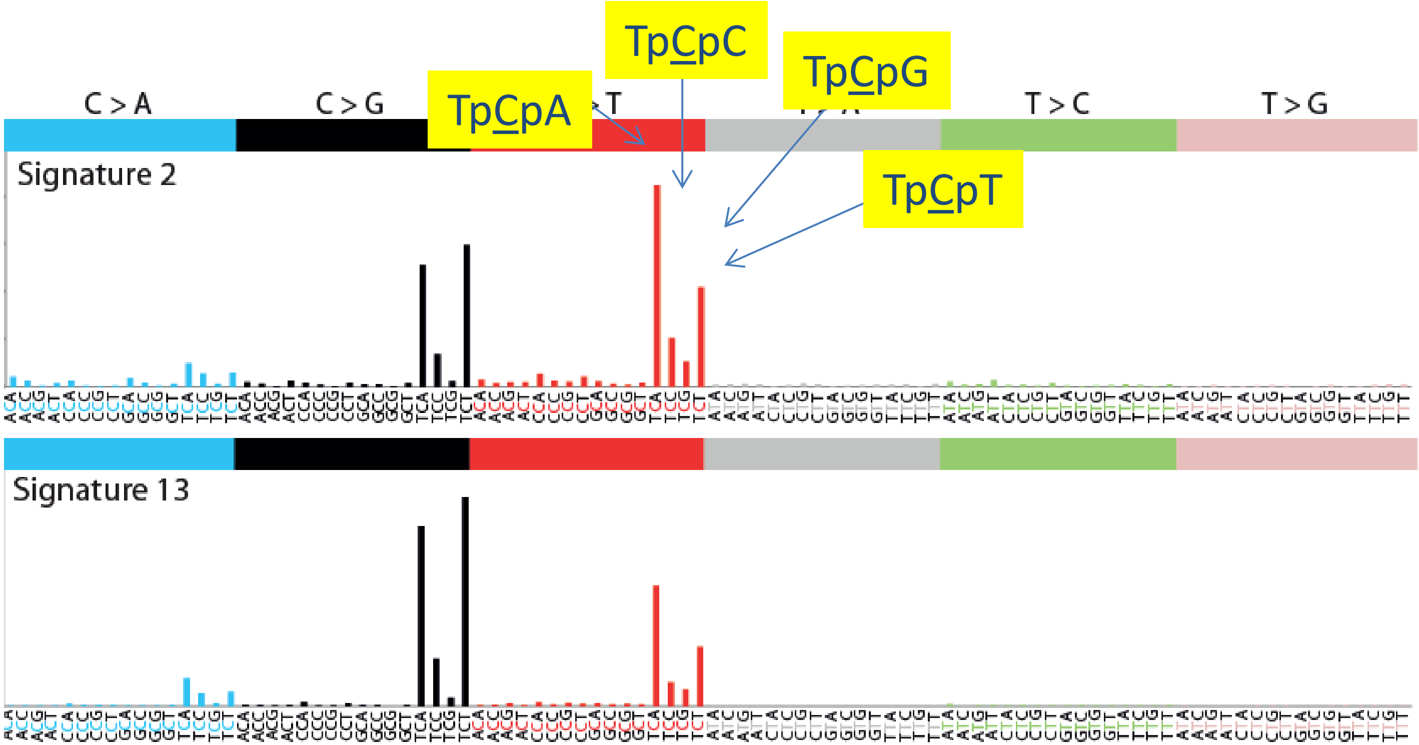


		ALL	AML	Bladder	Breast	Cervix	CLL	Colorectum	Glioblastoma	Glioma Low Grade	Head and Neck	Kidney Clear Cell	Kidney Papillary	Liver	Lung Adeno	Lung Small Cell	Lung Squamous	Lymphoma B-cell	Medulloblastoma	Melanoma	Myeloma	Neuroblastoma	Ovary	Pancreas	Pilocytic Astrocytoma	Prostate	Stomach	Thyroid	Uterus
		2	2	4	5	2	3	3	2	2	4	2	2	6	4	2	3	5	3	3	2	2	2	4	2	2	6	2	6
Signature 1A	5		✓						✓										✓							✓	✓		
Signature 1B	19	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓		✓	✓	✓	✓				✓
Signature 2	15	✓		✓	✓	✓	✓				✓		✓		✓		✓	✓			✓			✓			✓	✓	✓
Signature 3	3				✓																		✓	✓					
Signature 4	5										✓			✓	✓	✓	✓												
Signature 5	8			✓									✓		✓		✓	✓	✓		✓							✓	
Signature 6	6							✓				✓		✓										✓		✓			✓
Signature 7	2										✓									✓									
Signature 8	2				✓														✓										
Signature 9	2						✓											✓											
Signature 10	2							✓																					✓
Signature 11	2								✓											✓									
Signature 12	2													✓															✓
Signature 13	2			✓	✓																								
Signature 14	2									✓																			✓
Signature 15	2															✓											✓		
Signature 16	1													✓															
Signature 17	3													✓				✓									✓		
Signature 18	1																					✓							
Signature 19	1																								✓				
Signature 20	1																										✓		
Signature 21	1																										✓		

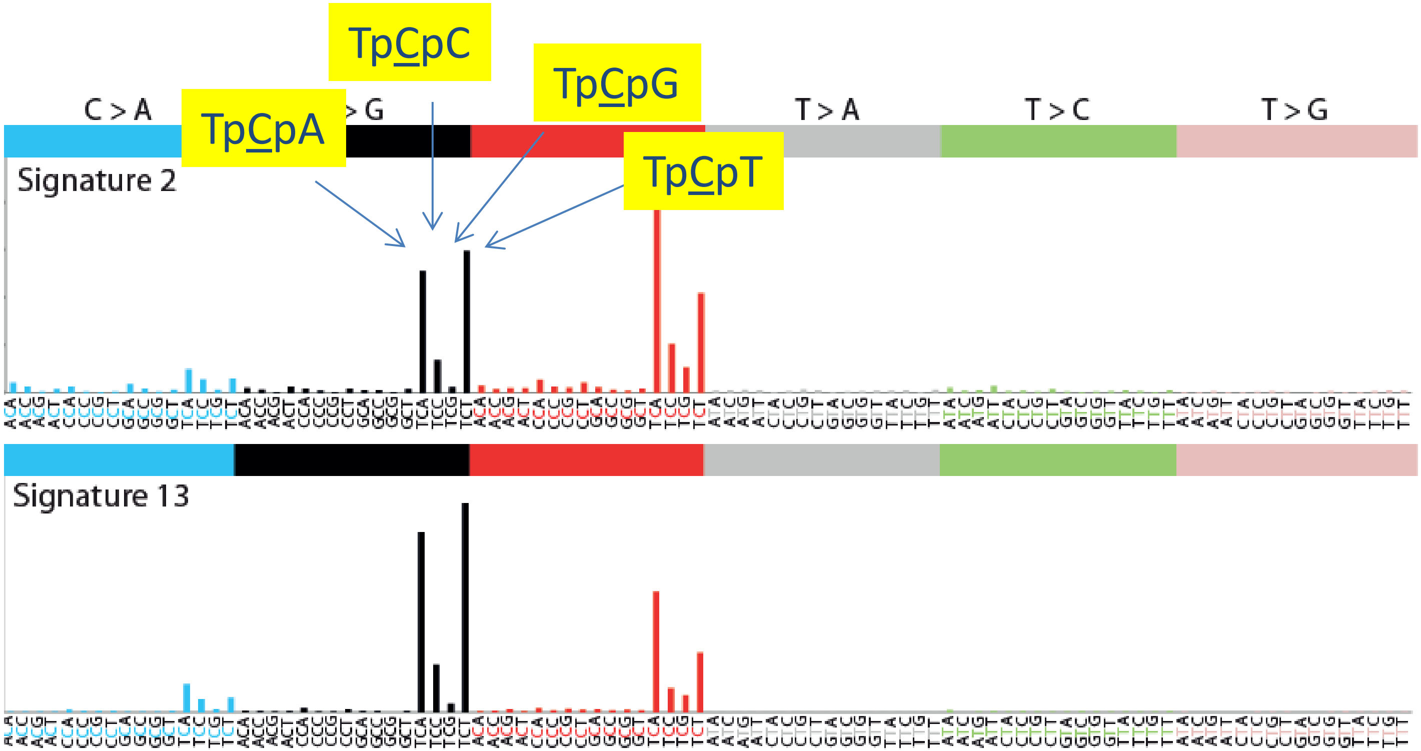
Mutation signatures present in many cancer types



Mutation signatures present in many cancer types



Mutation signatures present in many cancer types



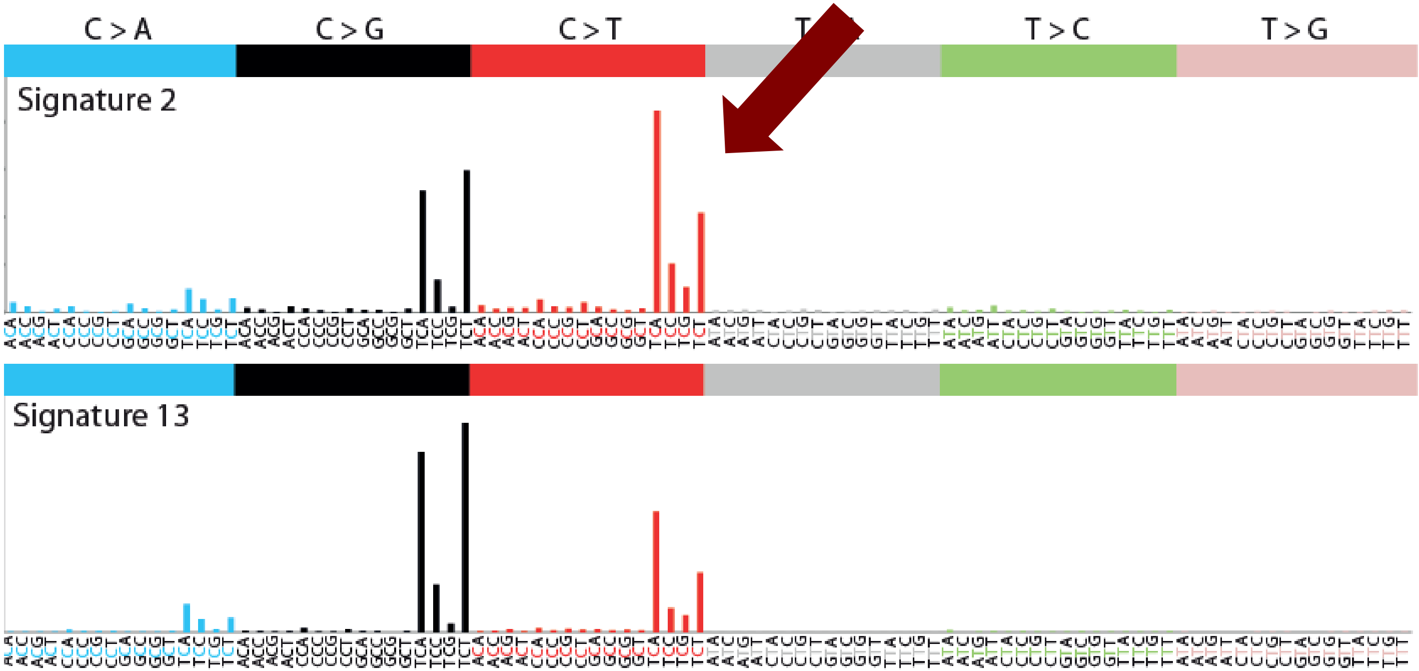
TpCpC

TpCpG

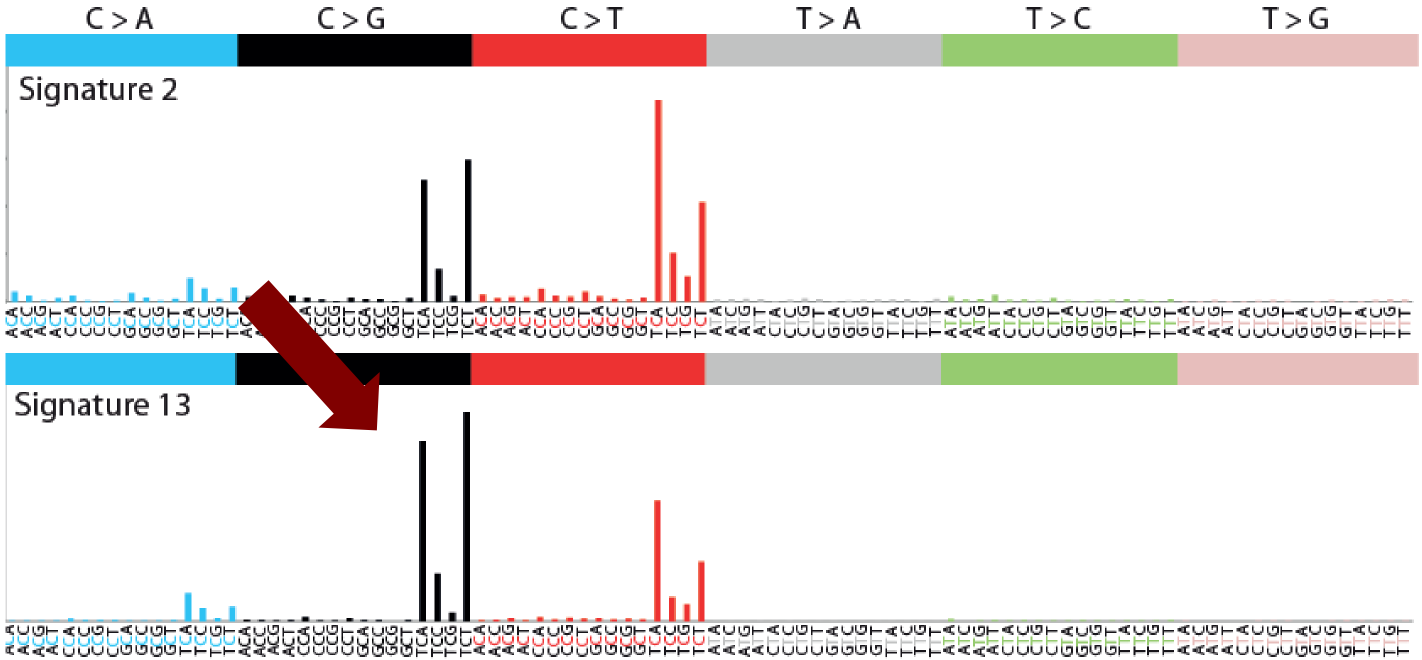
TpCpA

TpCpT

Mutation signatures present in many cancer types



Mutation signatures present in many cancer types



What is the biological explanation for the mutagenic process underlying Signature 2/13?

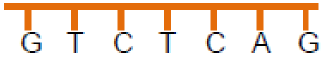
What is the biological explanation for the mutagenic process underlying Signature 2/13?

- Deamination of cytosine by one of the family of AID/APOBEC enzymes?

- The family includes

  AID
  APOBEC1
  APOBEC2
  APOBEC3A-H
  APOBEC4

What is the biological explanation for the mutagenic process underlying Signature 2/13?



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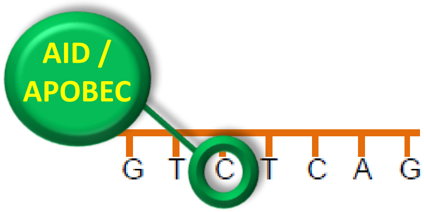

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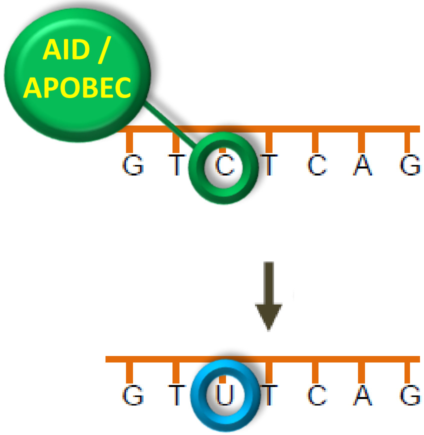

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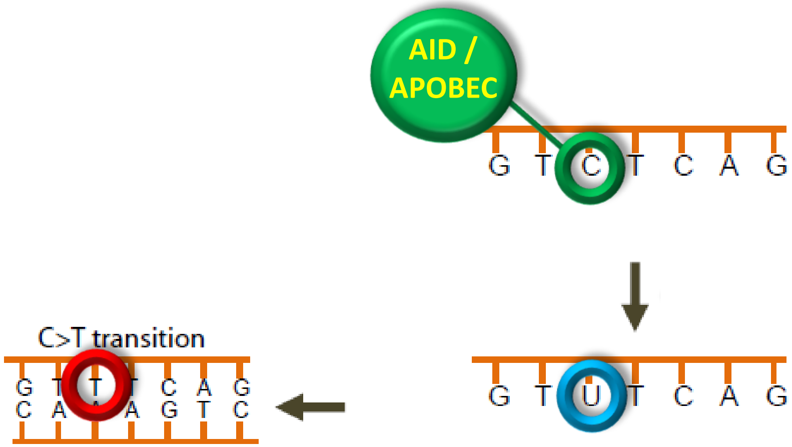

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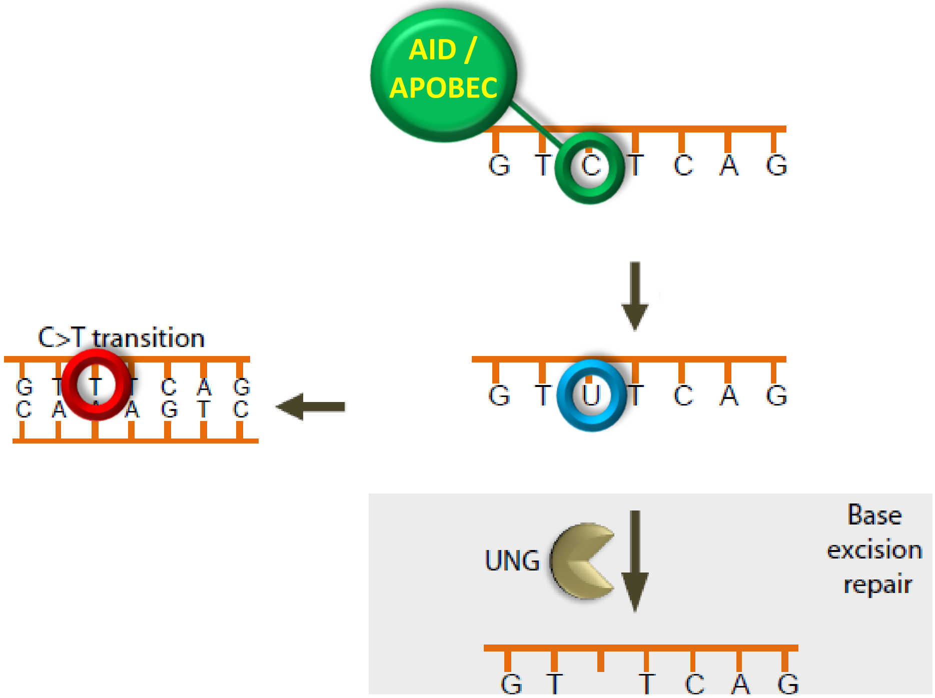

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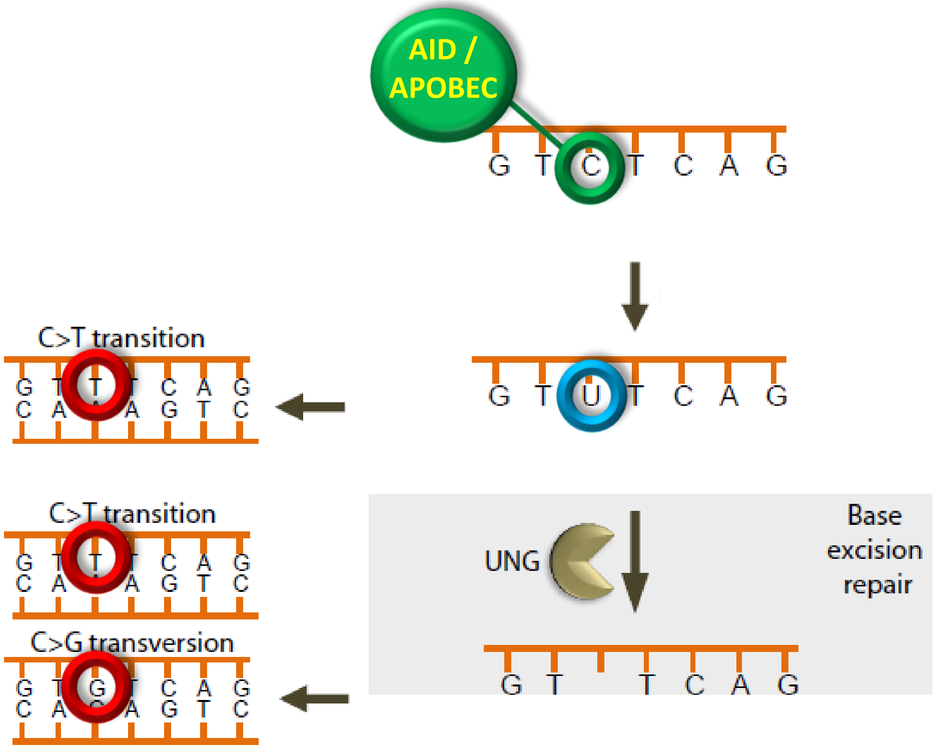
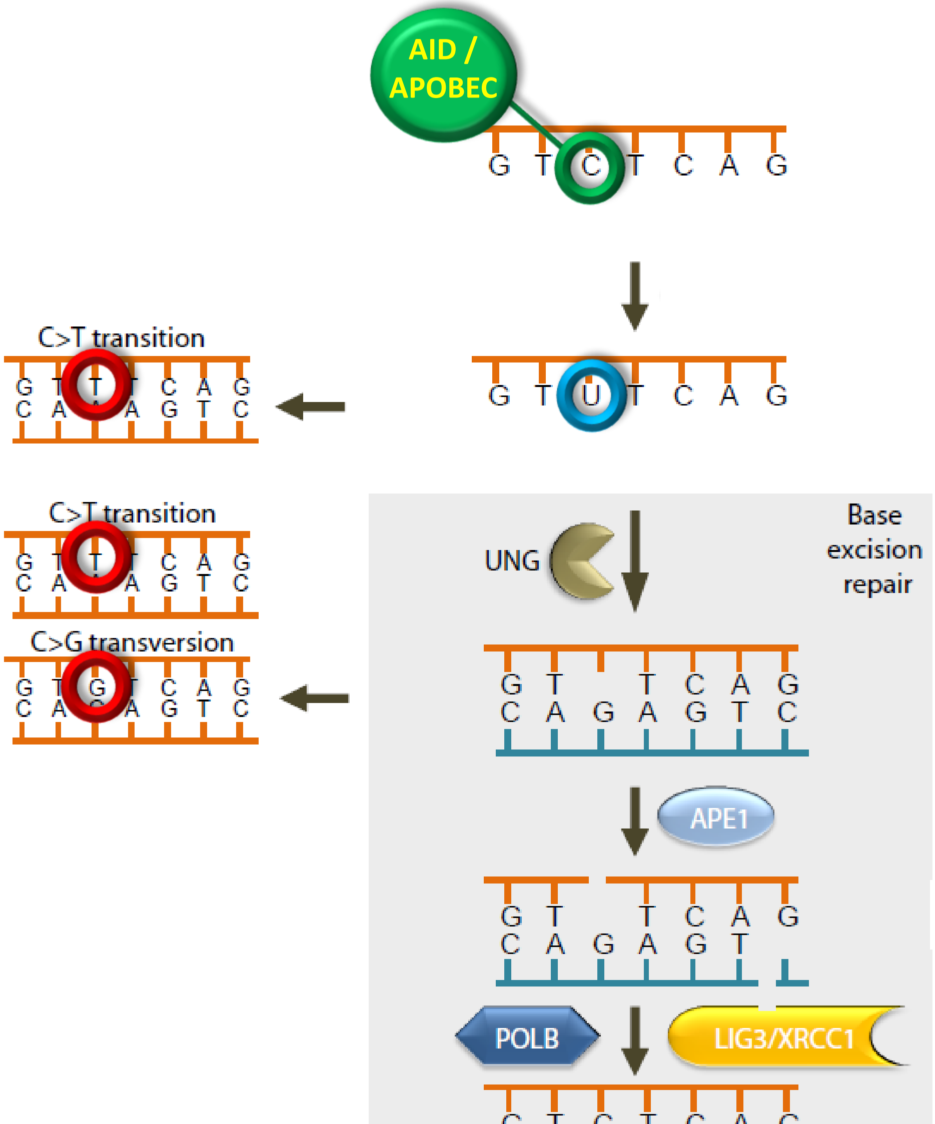


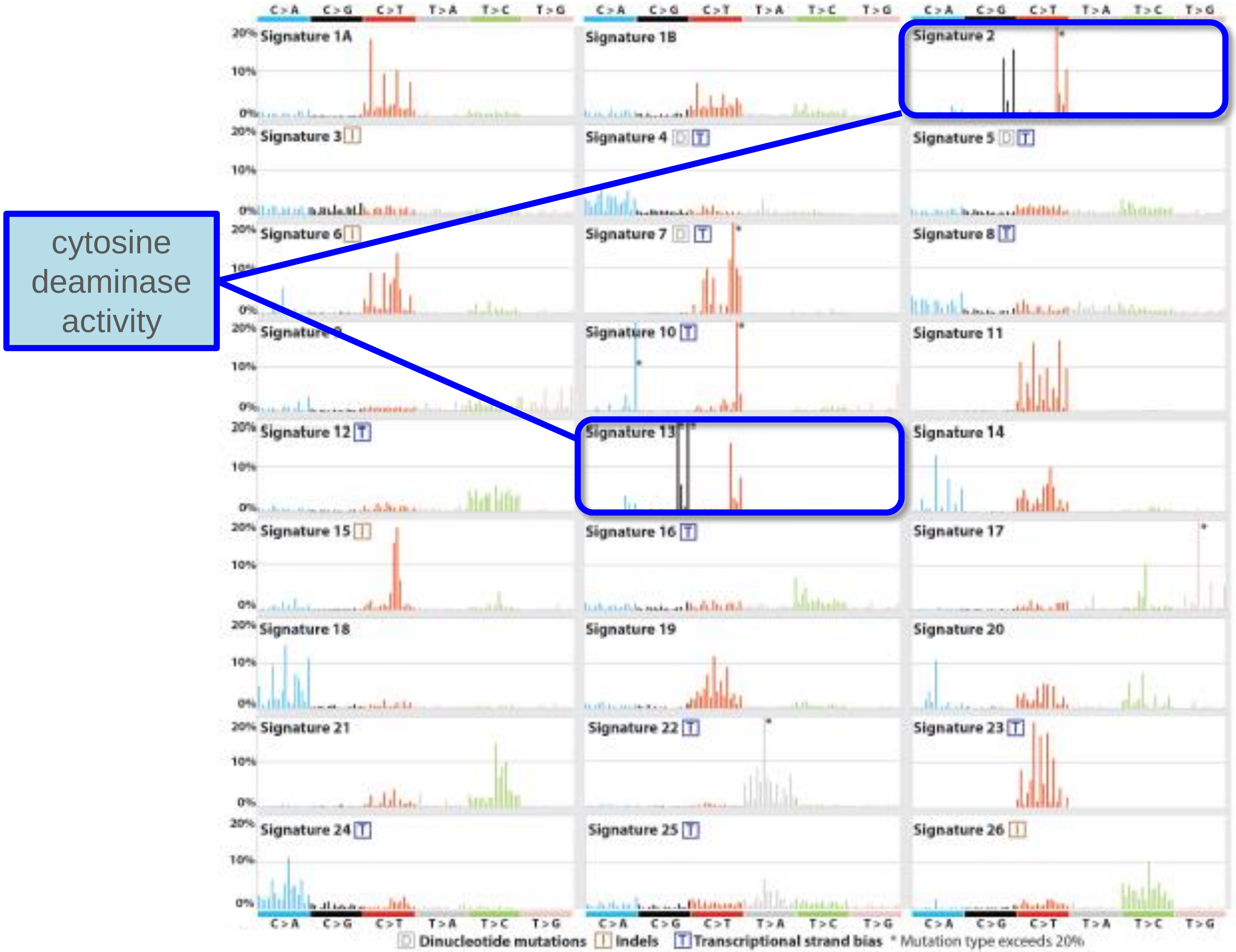
What is the biological explanation for the mutagenic process underlying Signature 2/13?



Which member(s) of the family is responsible for Signature 2/13?

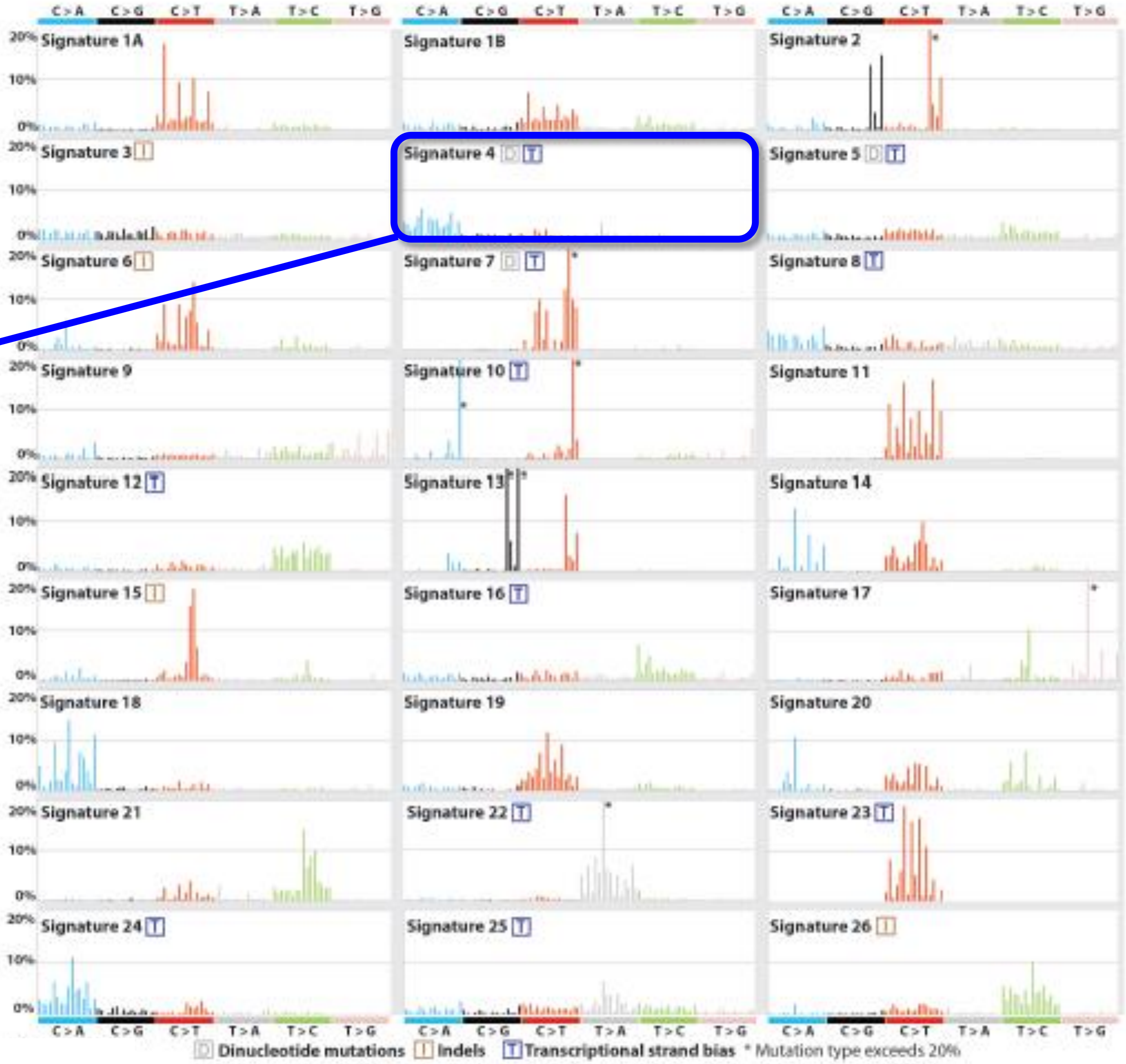
~~AID~~
[✓ APOBEC1]
APOBEC2
[✓ APOBEC3A]
[✓ APOBEC3B]
APOBEC3C
APOBEC3DE
APOBEC3F
APOBEC3G
APOBEC3G
APOBEC3H
APOBEC4

Mutation signatures present in many human cancers



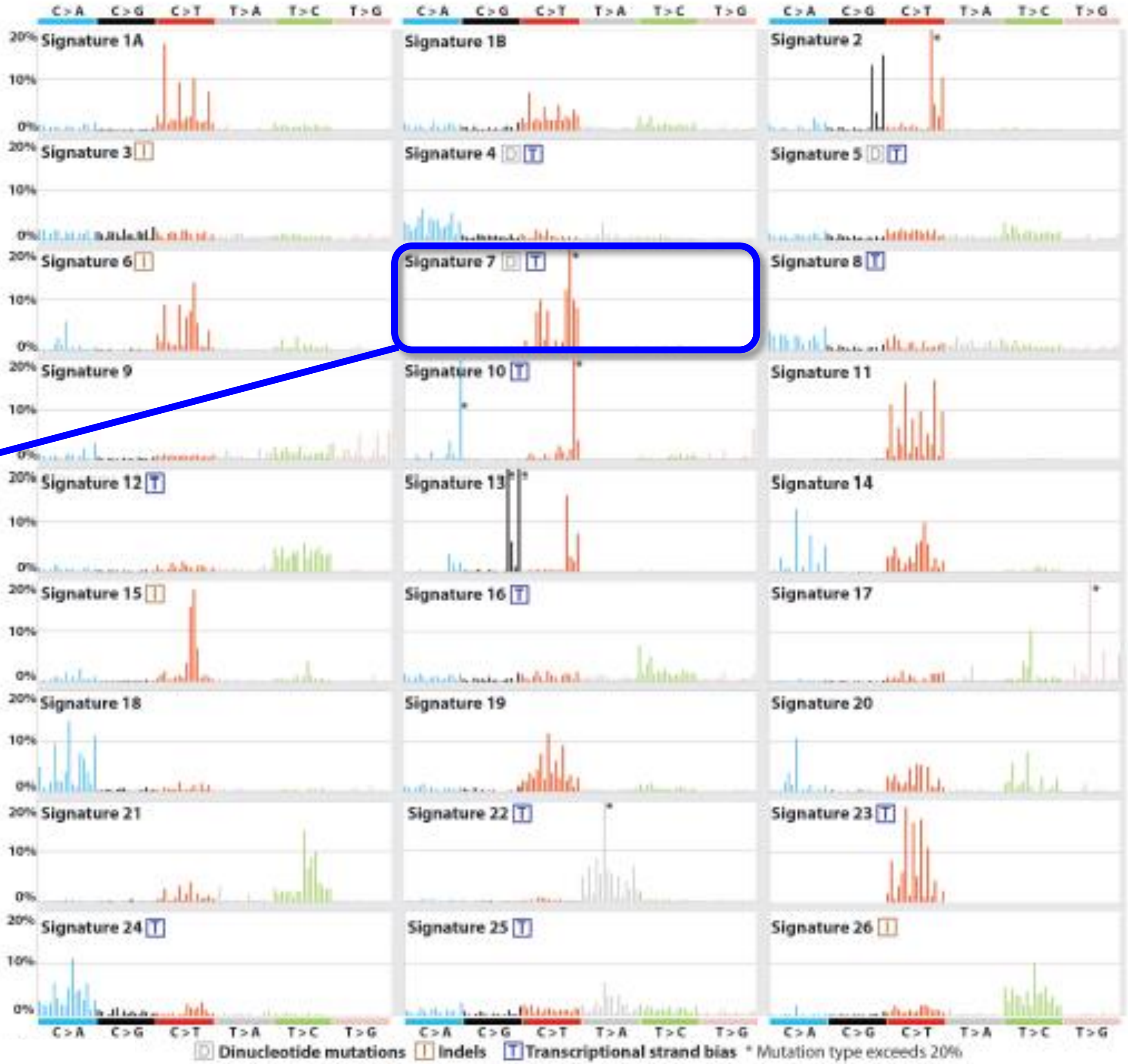
cytosine deaminase activity

Mutation signatures due to environmental exposures



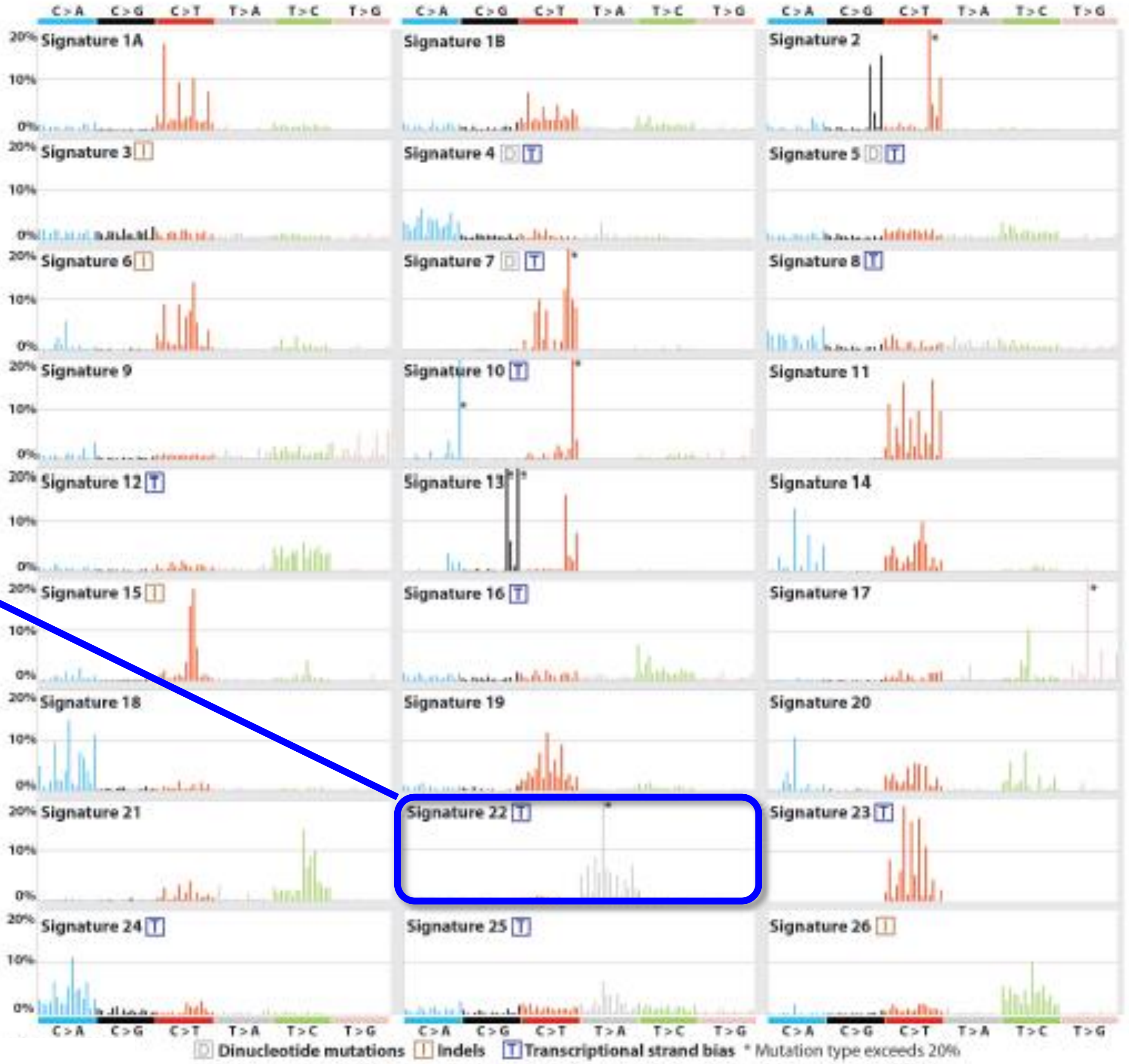
tobacco

Mutation signatures due to environmental exposures



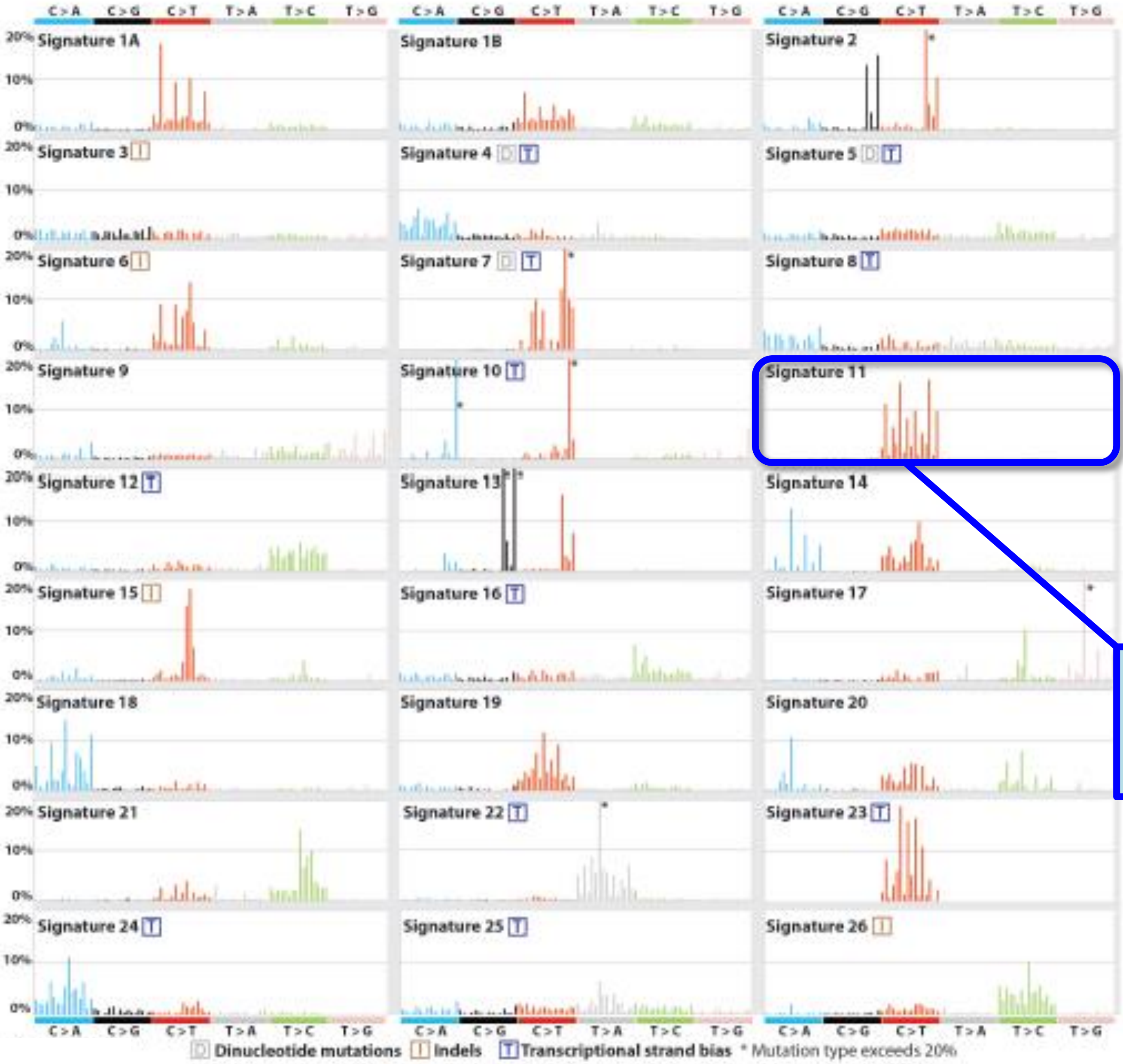
ultraviolet radiation

Mutation signatures due to environmental exposures



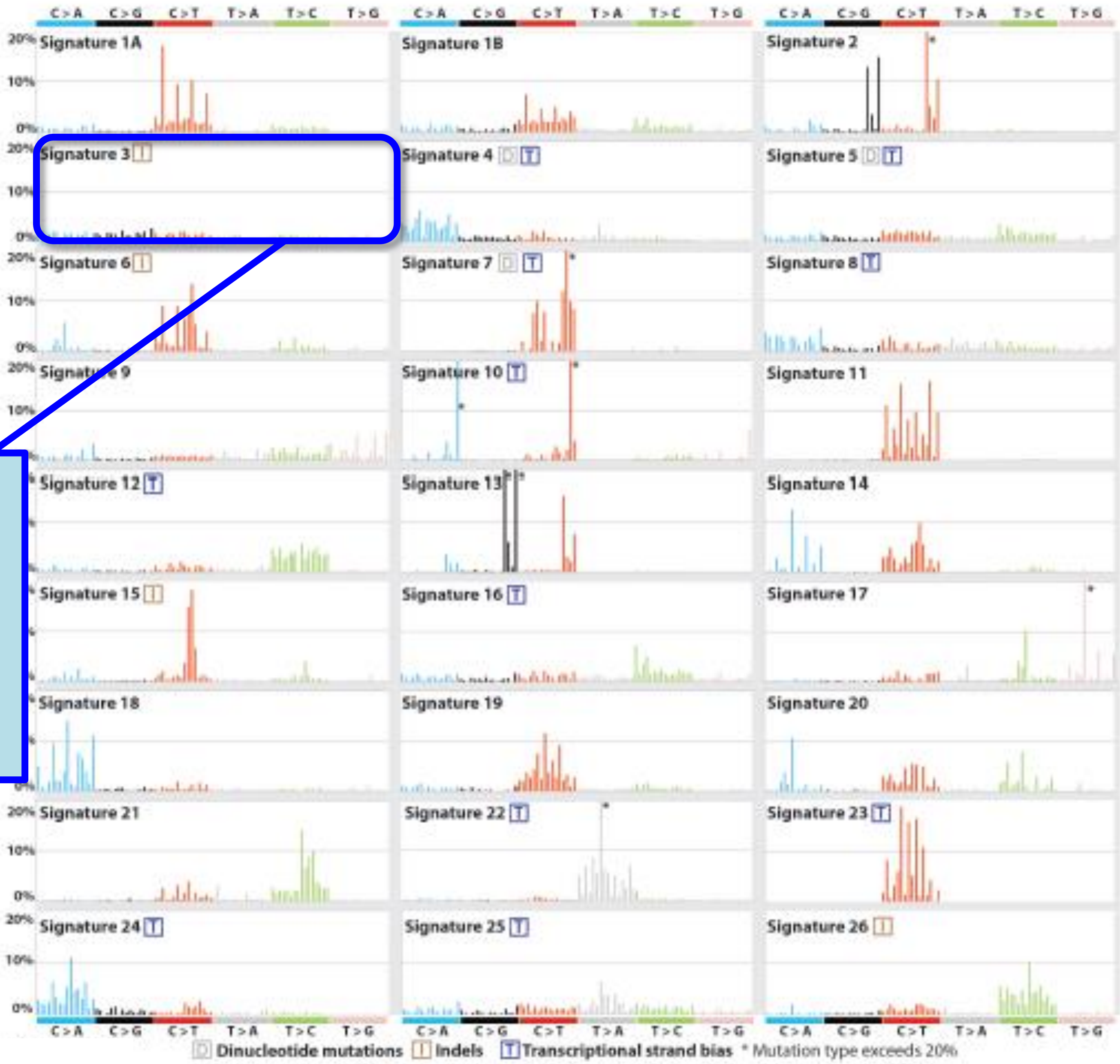
aristolochic acid

Mutation signatures due to environmental exposures



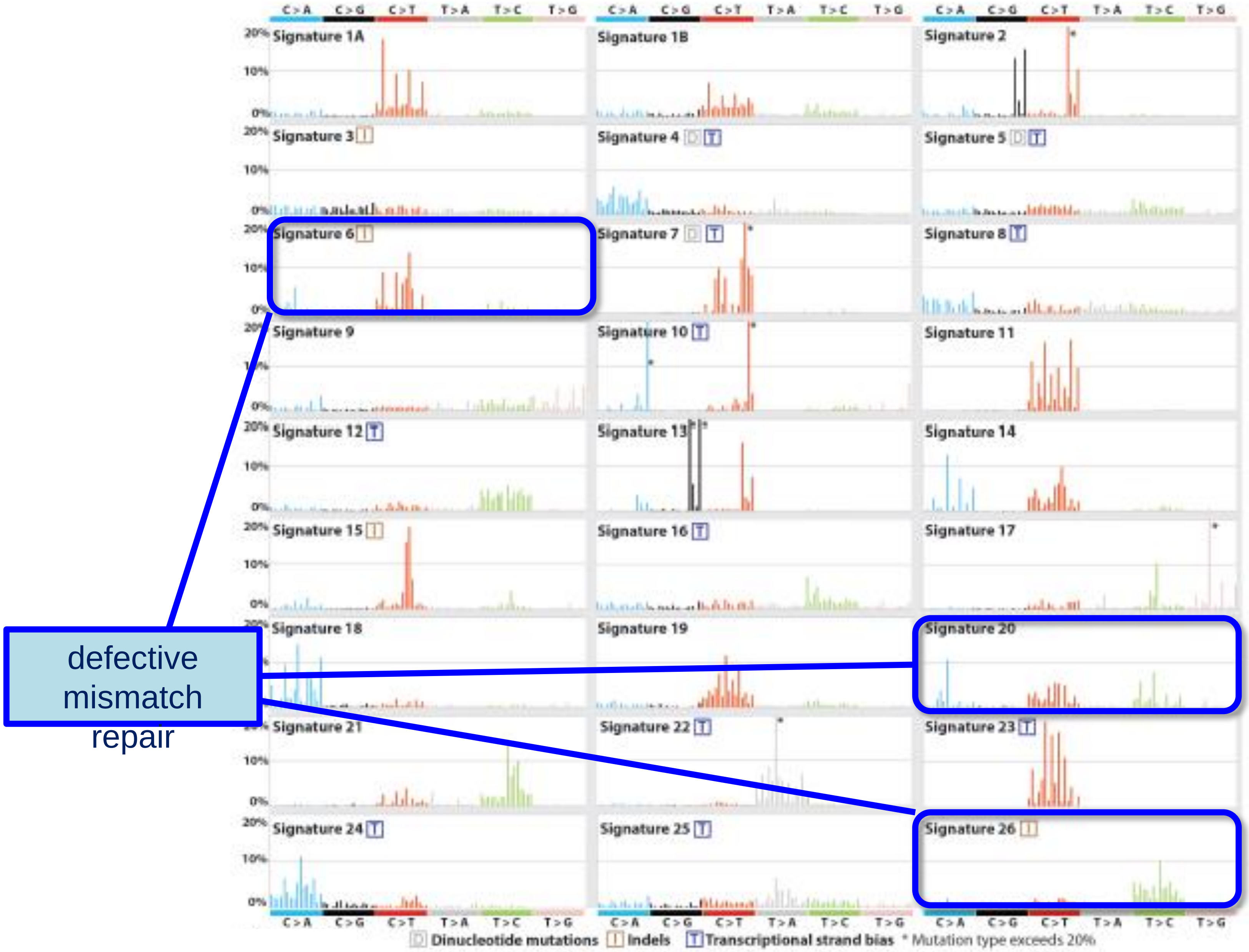
chemo-therapeutic agent

Mutation signatures due to defective DNA repair



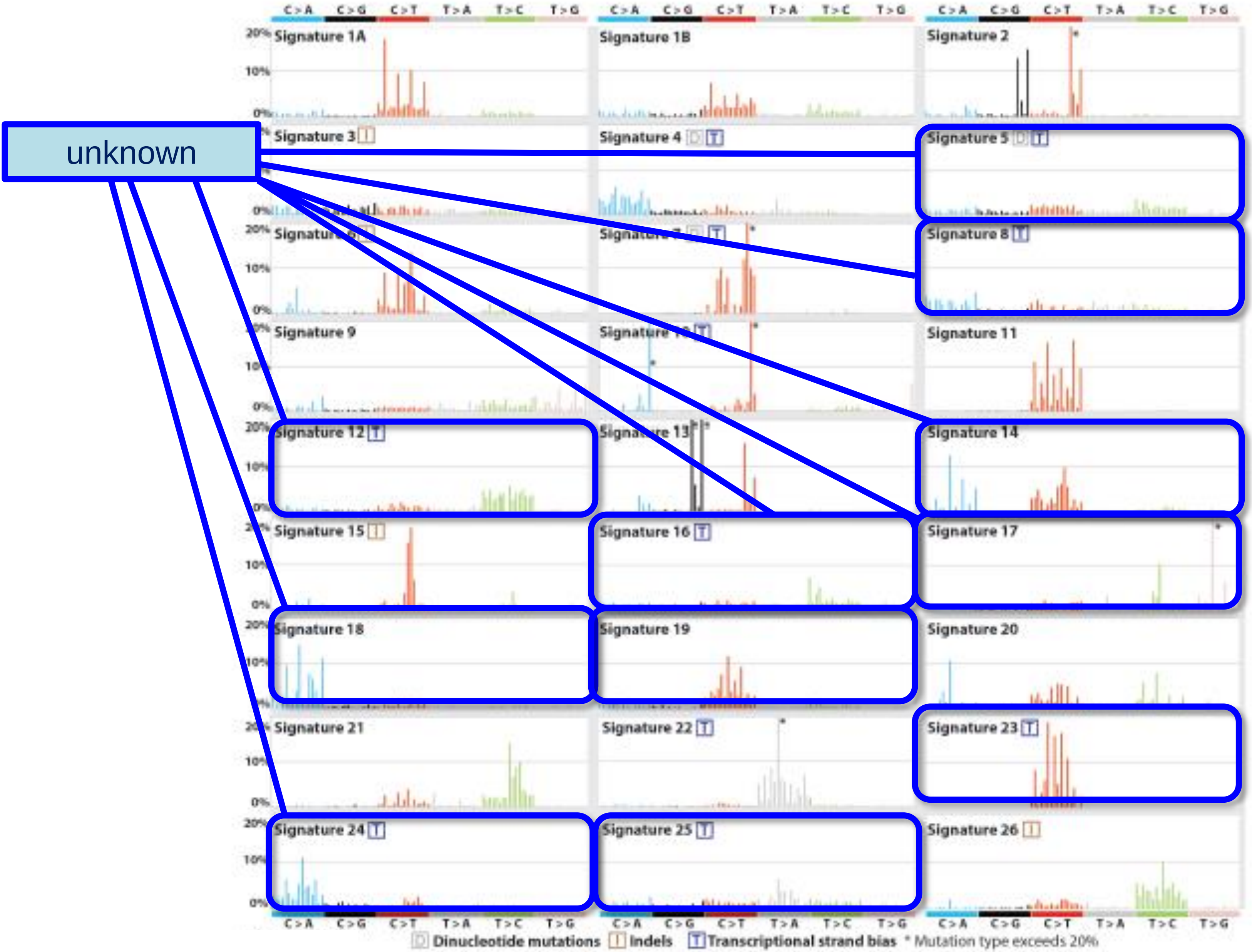
BRCA1 and *BRCA2* mutations : defective homologous recombination based DSBR

Mutation signatures due to defective DNA repair

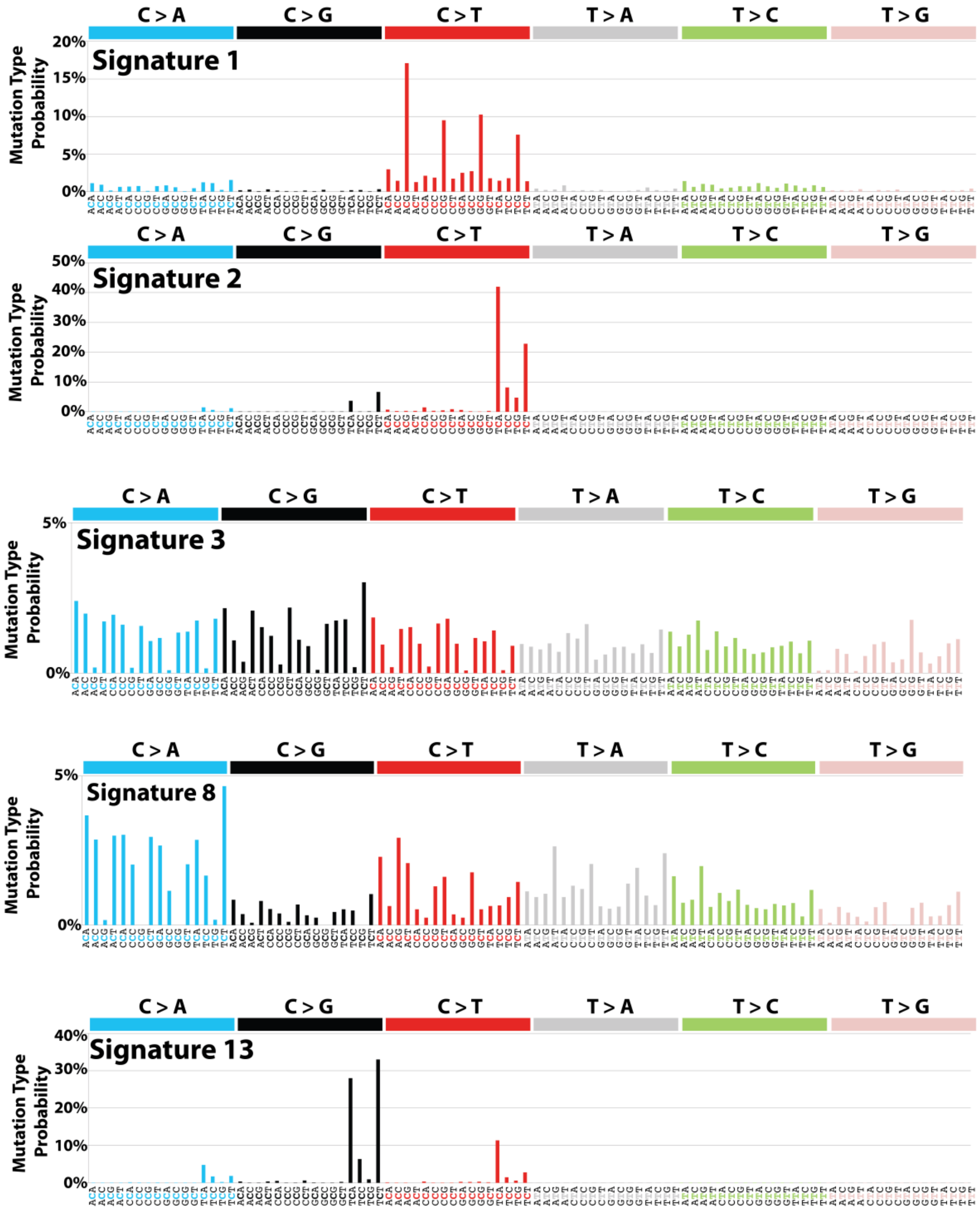


defective mismatch repair

Mutation signatures of unknown aetiology



Mutation signatures in breast cancer



Summary II

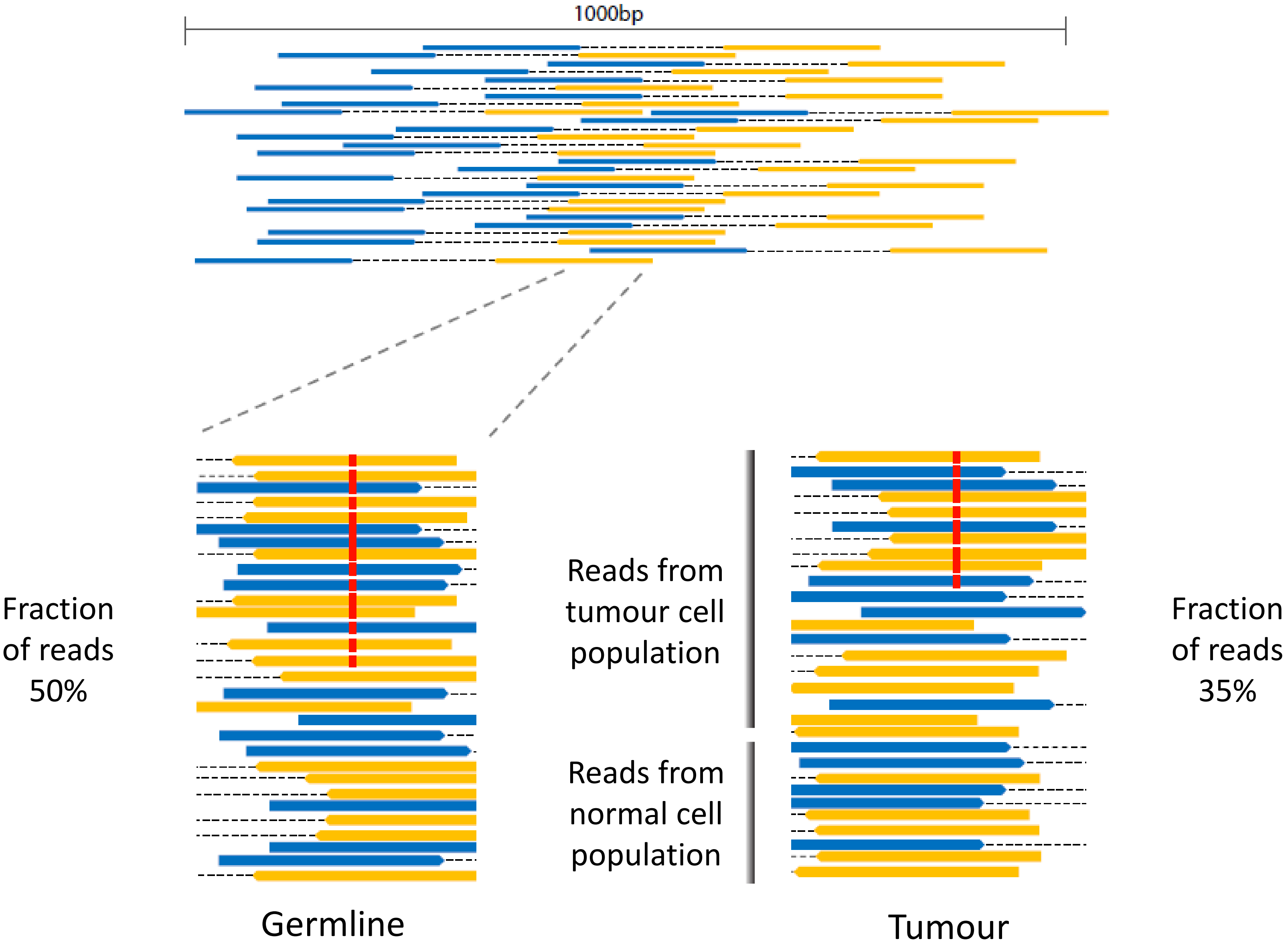
- Modern sequencing technology permits unprecedented access to all parts of the human genome

- The enormous datasets that we can now glean through these new approaches contain a vast amount of information

- We need to ask questions of these datasets in order to extract maximum information from them
  - Ascertain all the “drivers” in a cancer
  - Use all the “passengers” to inform us about cancer biology through mutation signatures

PART III

CONSTRUCTING EVOLUTIONARY TREES IN HUMAN BREAST CANCER



Fraction of reads 50%

Reads from tumour cell population

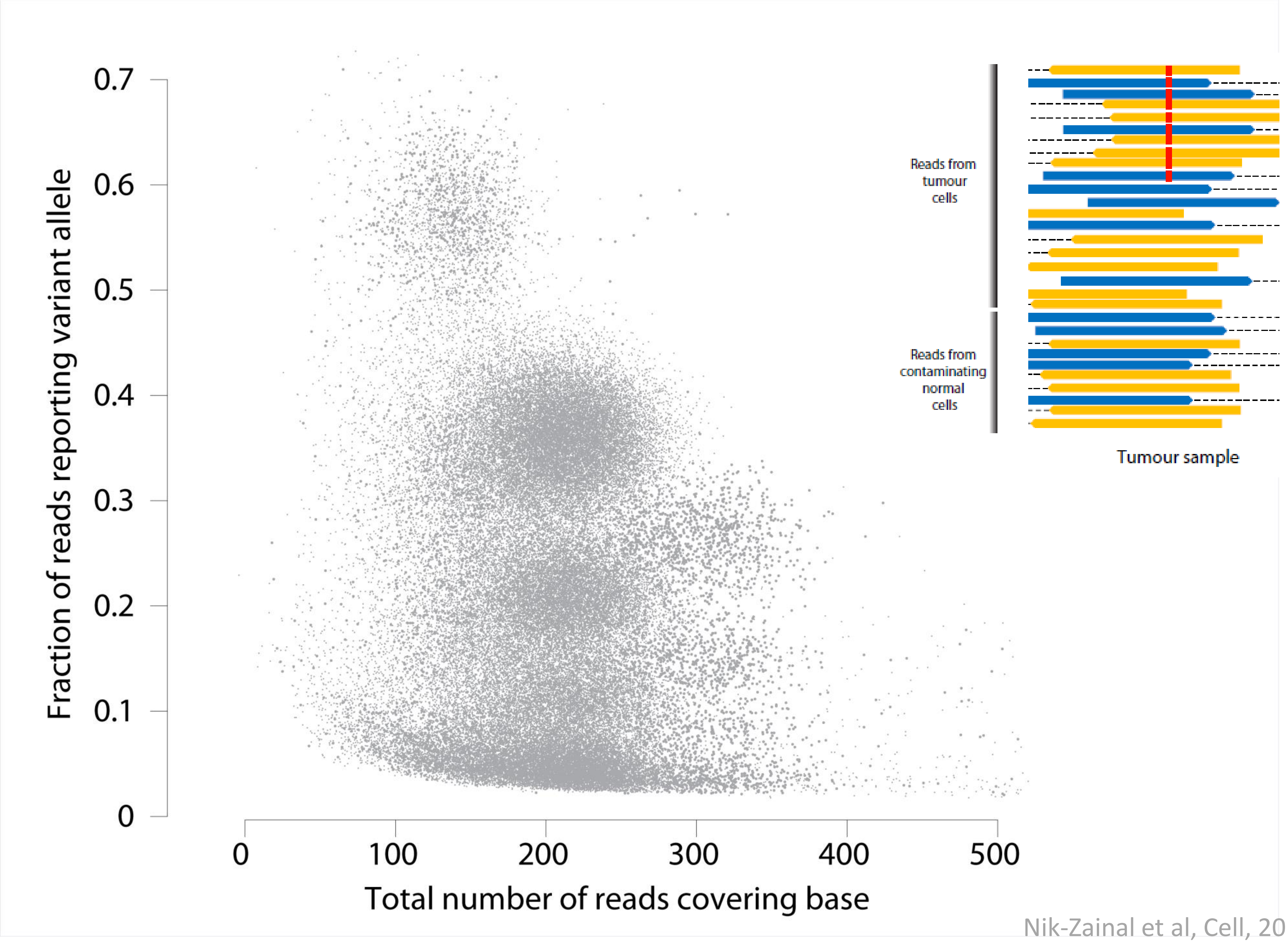
Reads from normal cell population

Fraction of reads 35%

Germline

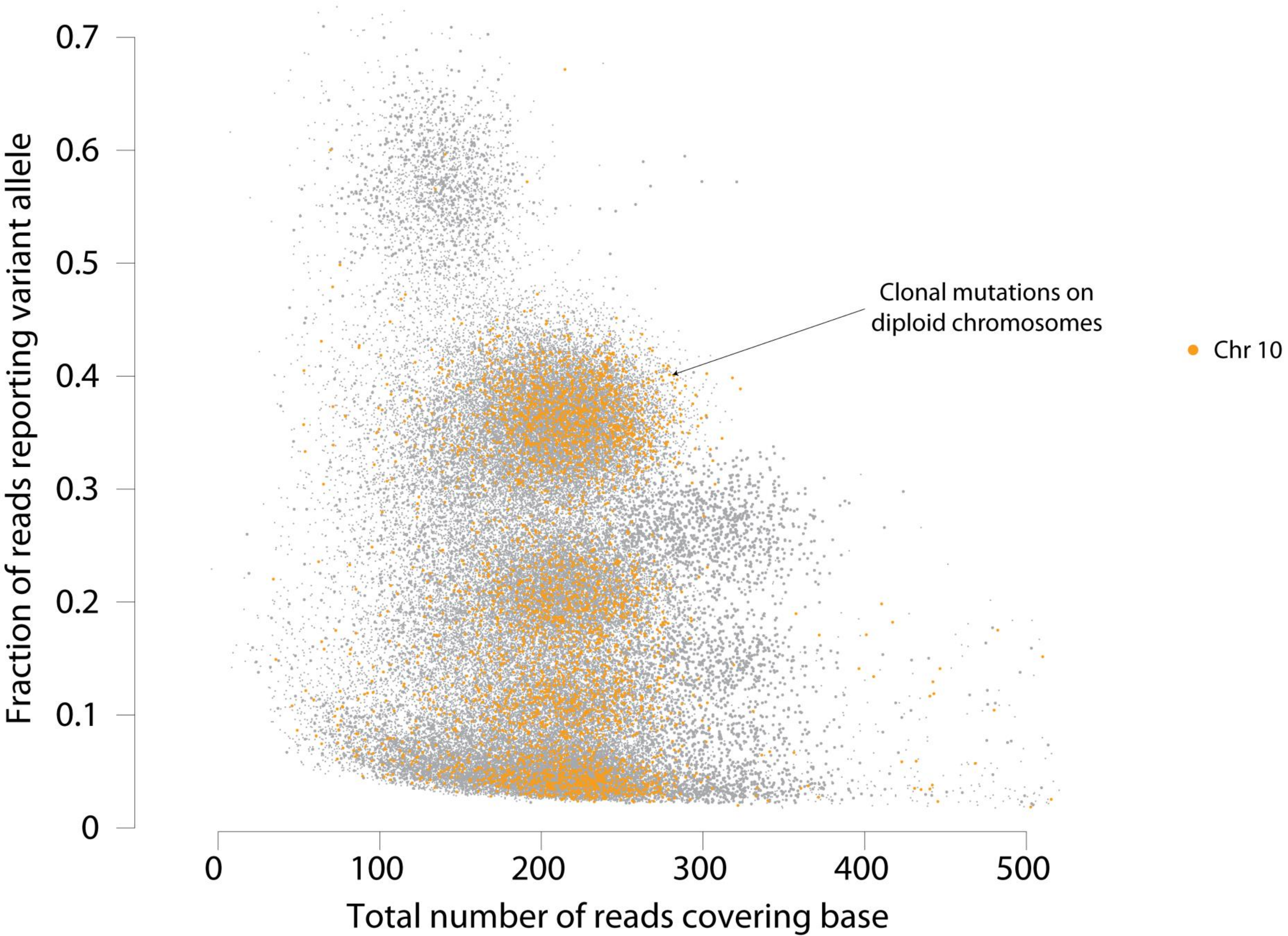
Tumour

Downstream analyses III: Cancer evolution



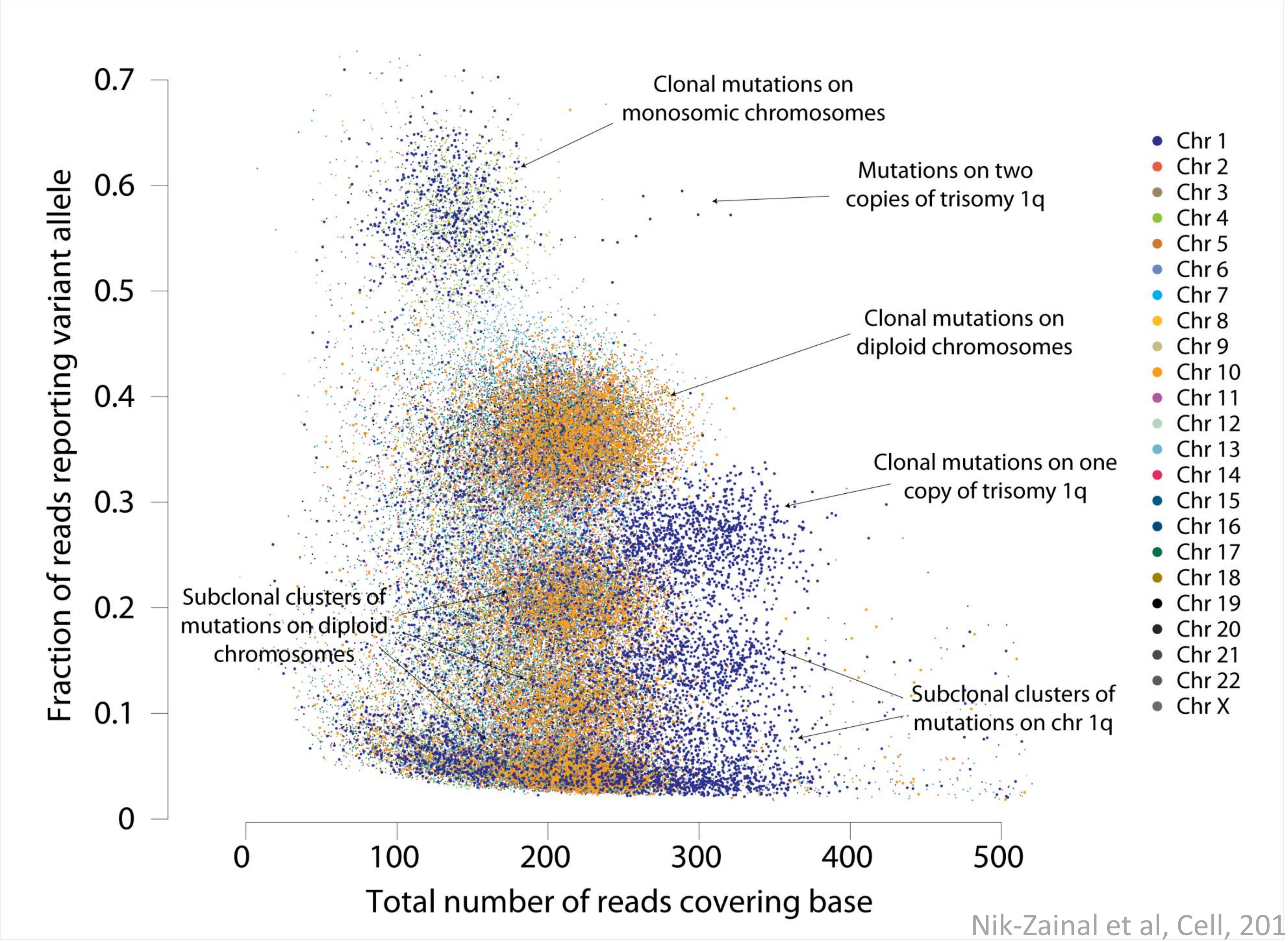
Nik-Zainal et al, Cell, 2012b

Downstream analyses III: Cancer evolution



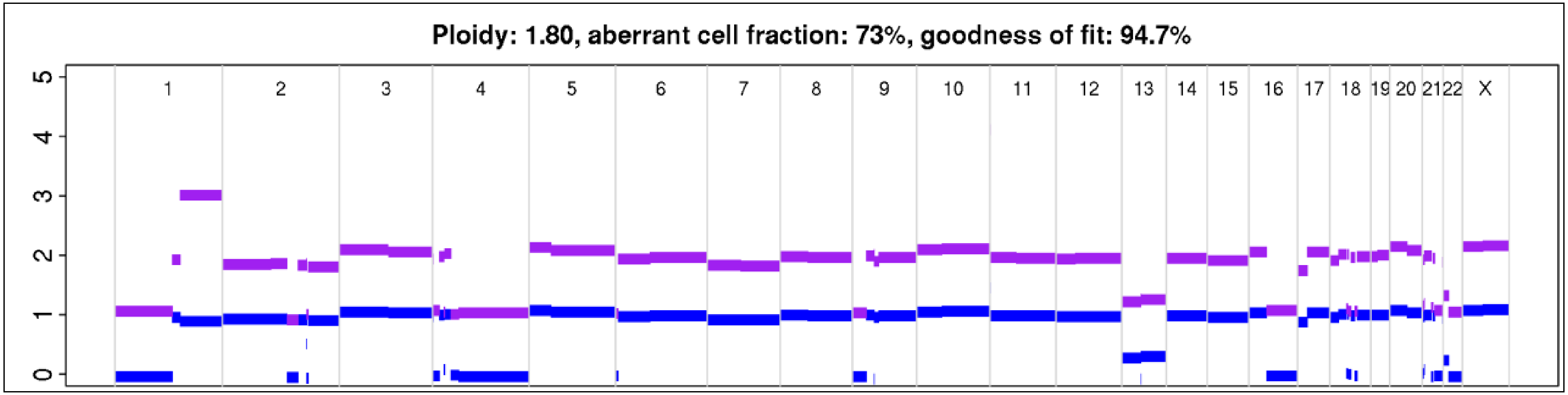
Nik-Zainal et al, Cell, 2012b

Downstream analyses III: Cancer evolution



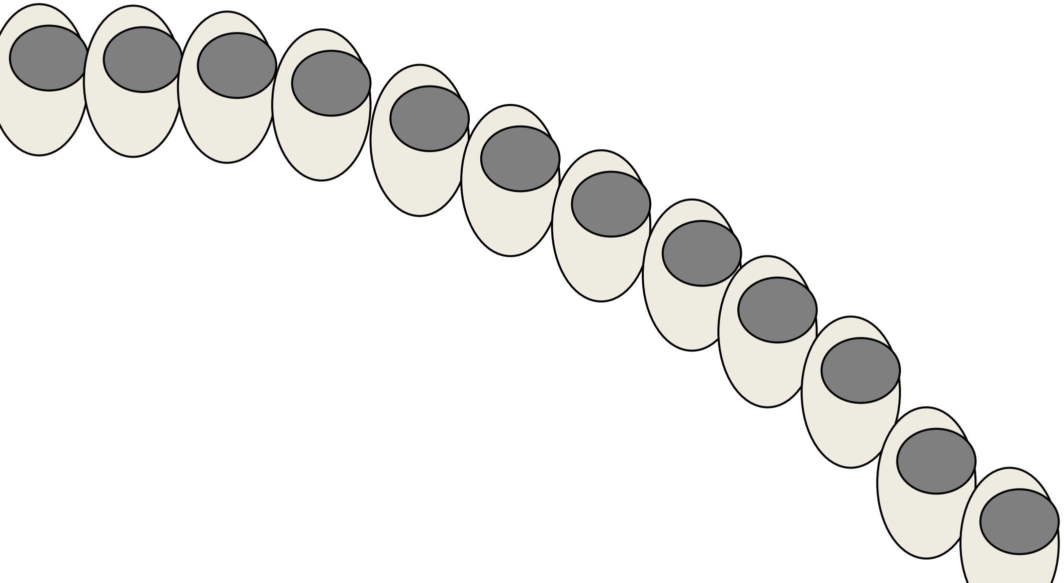
Nik-Zainal et al, Cell, 2012b

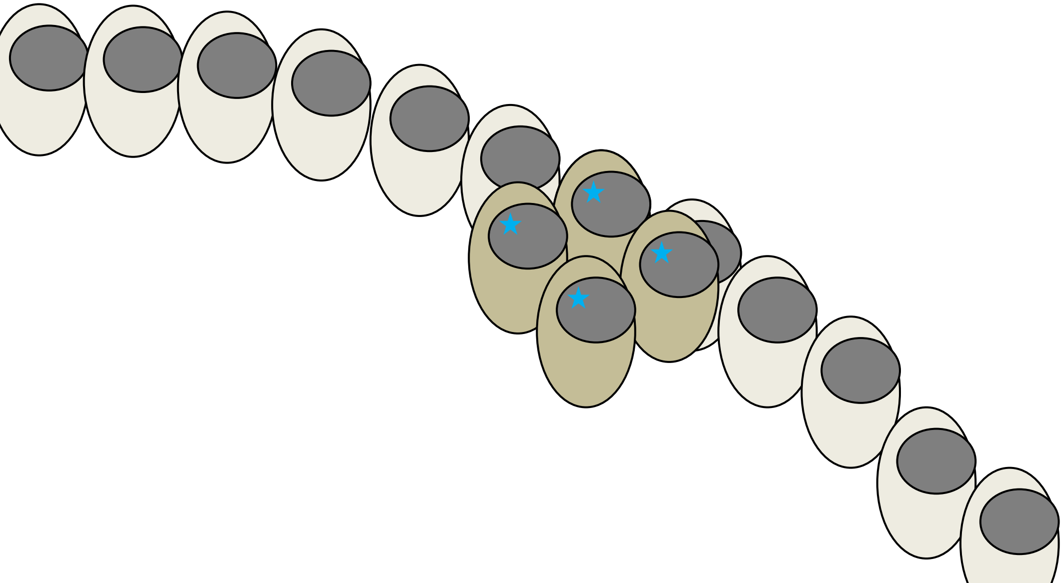
Downstream analyses III: Cancer evolution

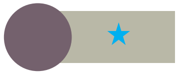


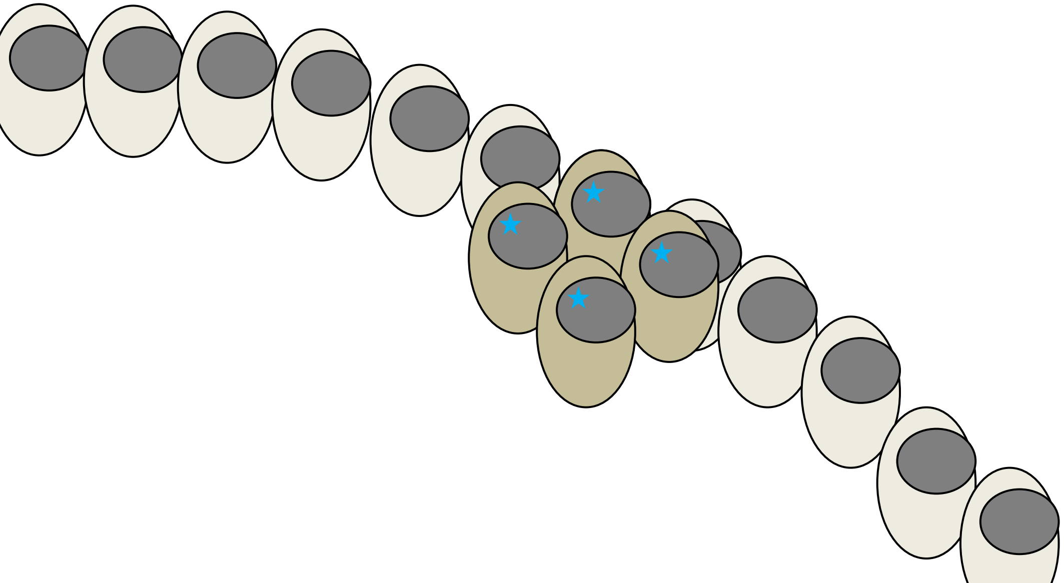
Ploidy: 1.80, aberrant cell fraction: 73%, goodness of fit: 94.7%

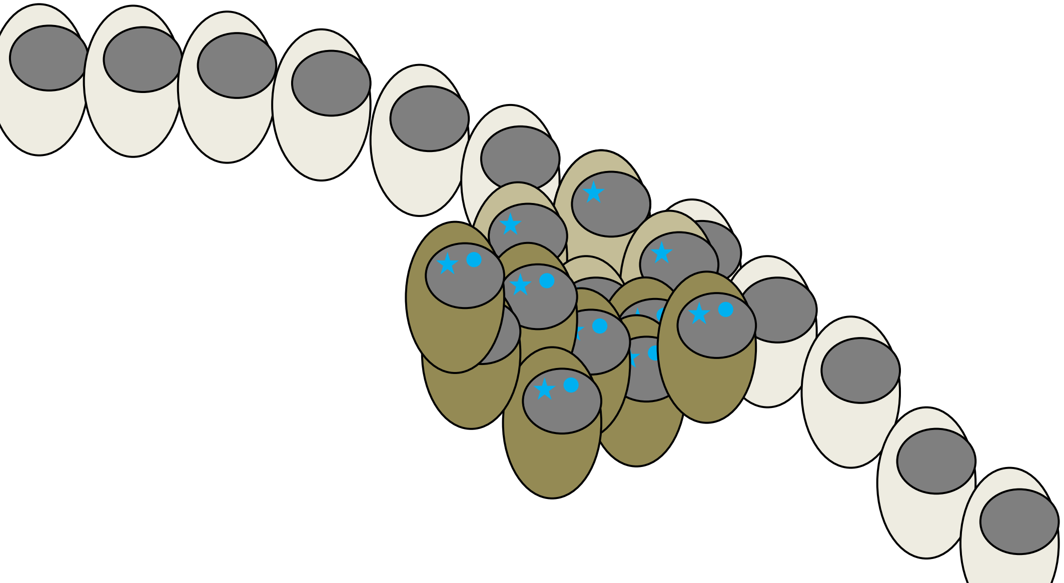
Nik-Zainal et al, Cell, 2012b

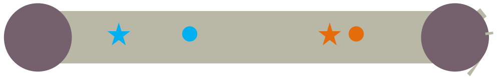


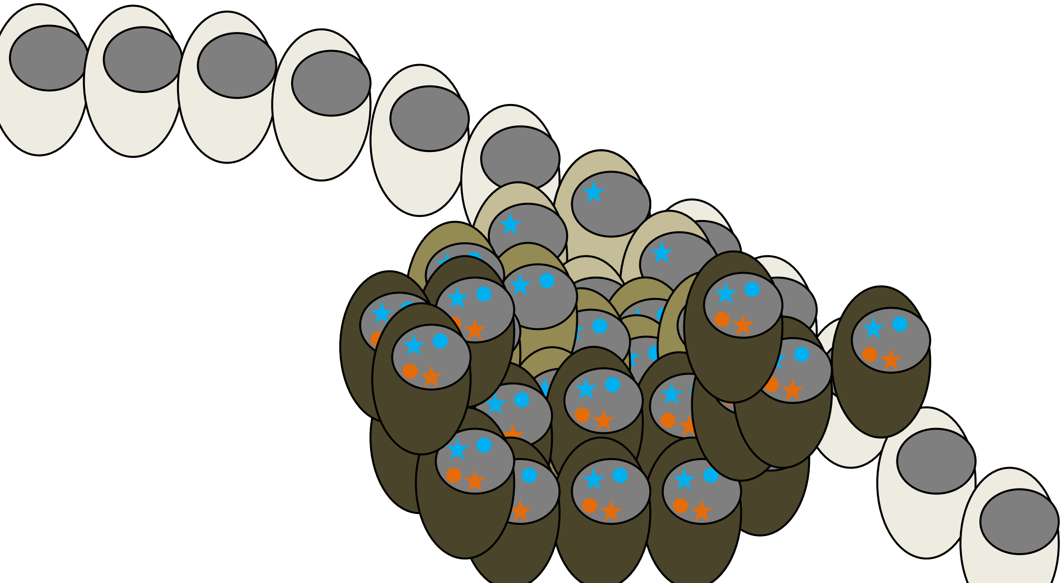


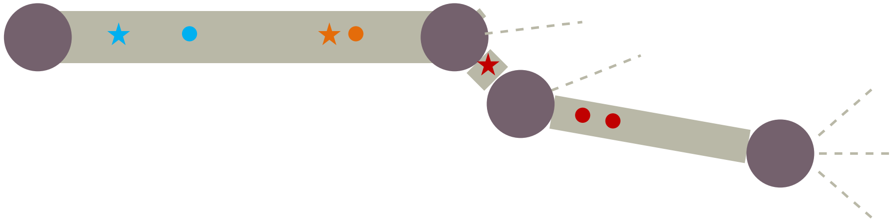


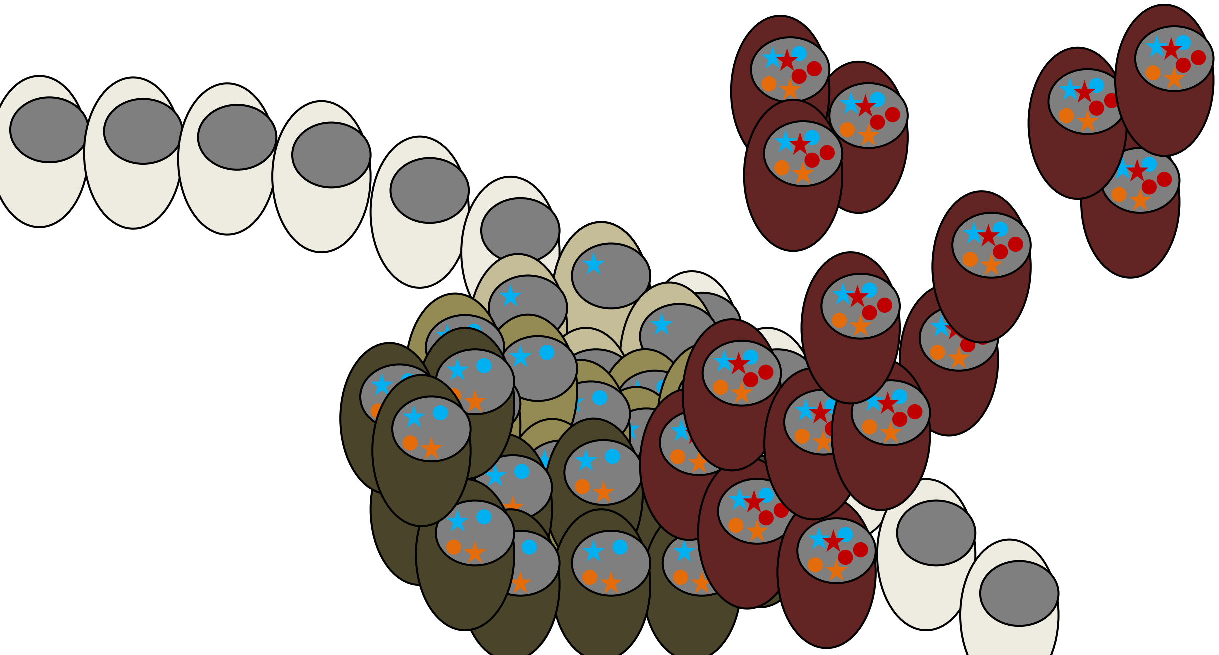


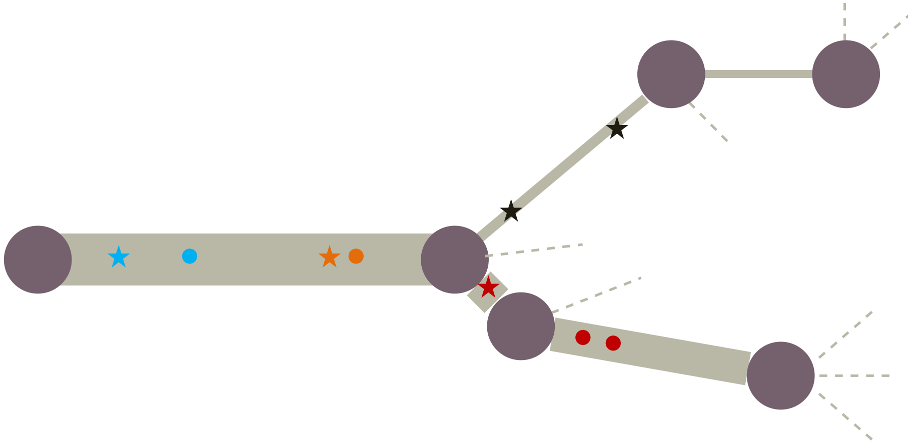


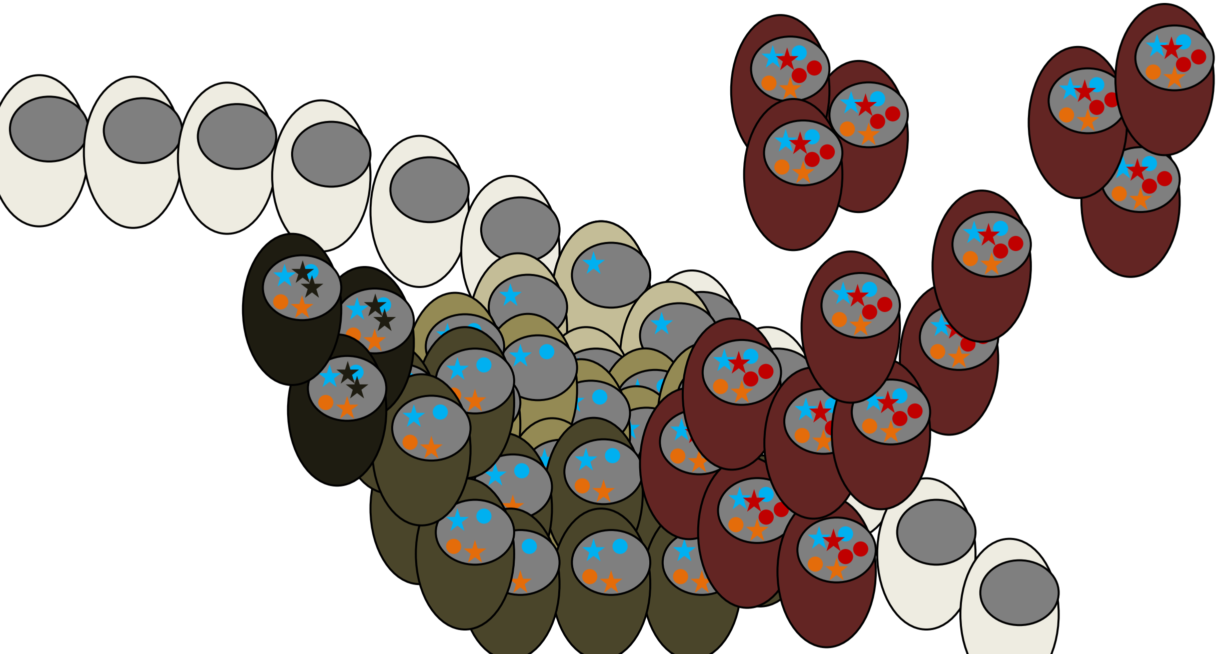


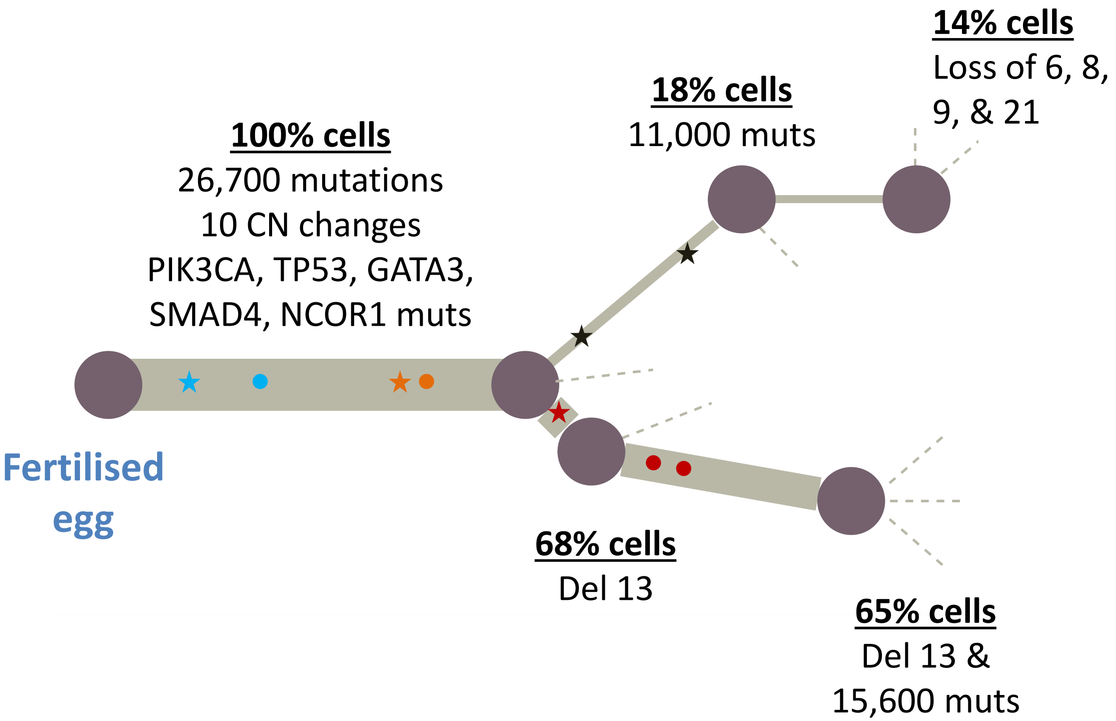












100% cells
26,700 mutations
10 CN changes
PIK3CA, TP53, GATA3,
SMAD4, NCOR1 muts

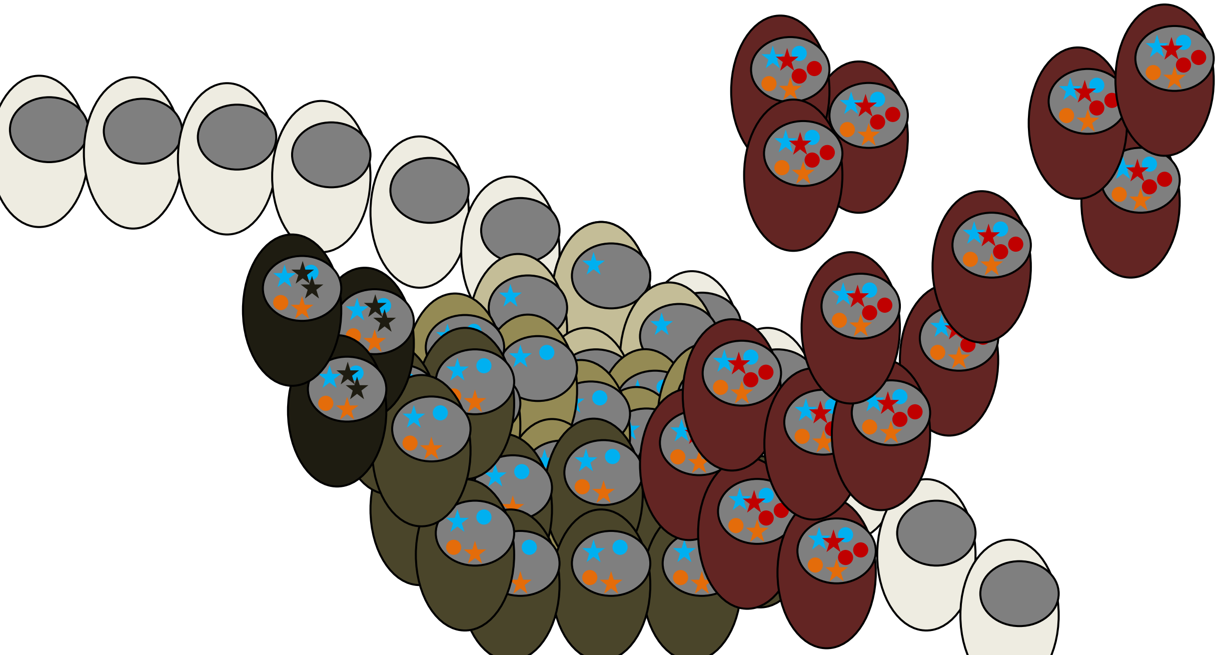
18% cells
11,000 muts

14% cells
Loss of 6, 8,
9, & 21

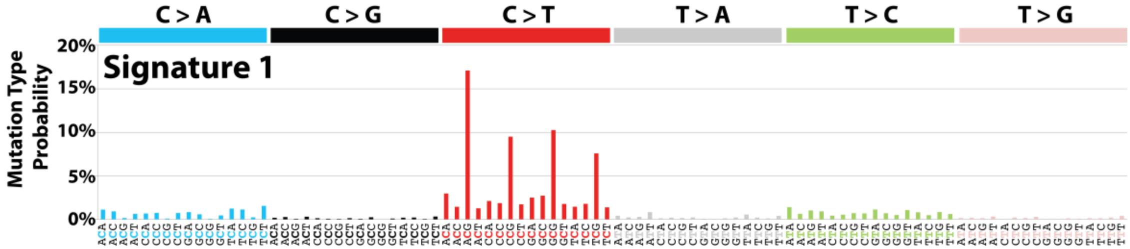
Fertilised
egg

68% cells
Del 13

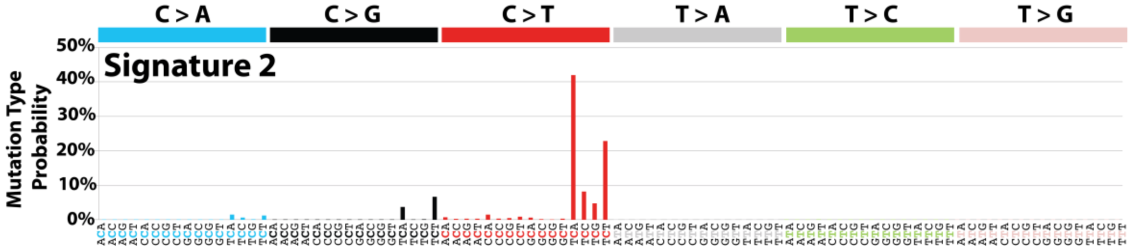
65% cells
Del 13 &
15,600 muts



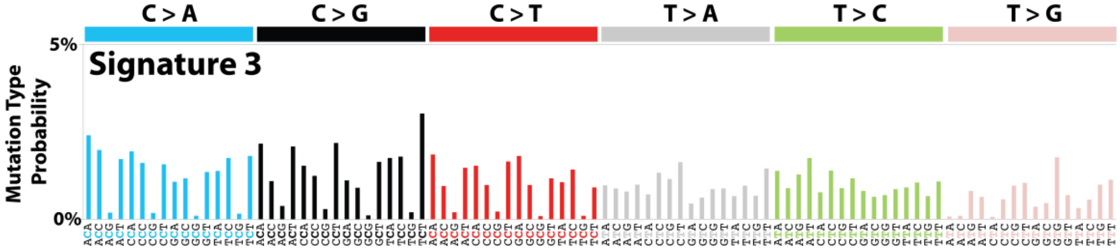
Nik-Zainal et al, Cell, 2012b


C > A
C > G
C > T
T > A
T > C
T > G
Signature 1
Mutation Type Probability
20%
15%
10%
5%
0%

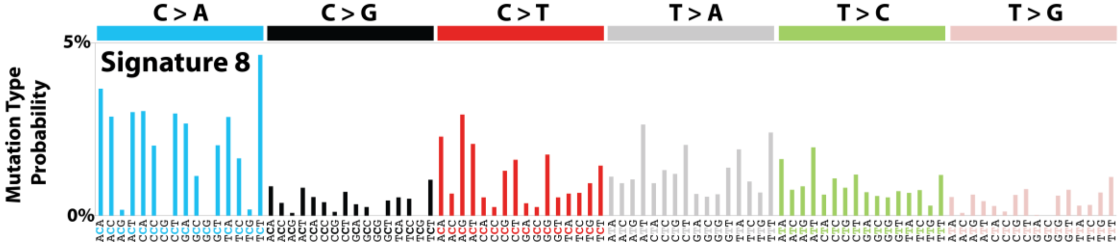
🟩


C > A
C > G
C > T
T > A
T > C
T > G
Signature 2
Mutation Type Probability
50%
40%
30%
20%
10%
0%

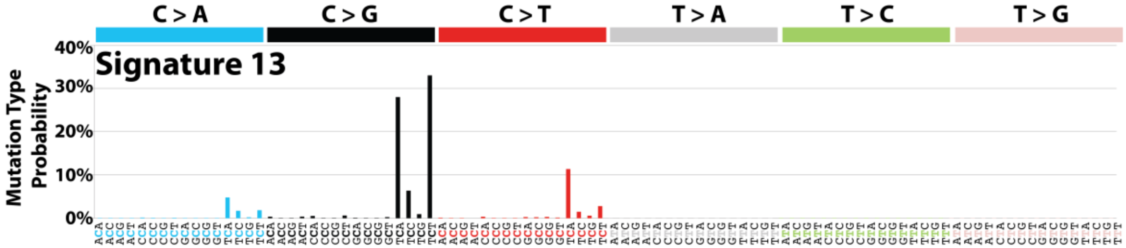
🟧


C > A
C > G
C > T
T > A
T > C
T > G
Signature 3
Mutation Type Probability
5%
0%

🟪

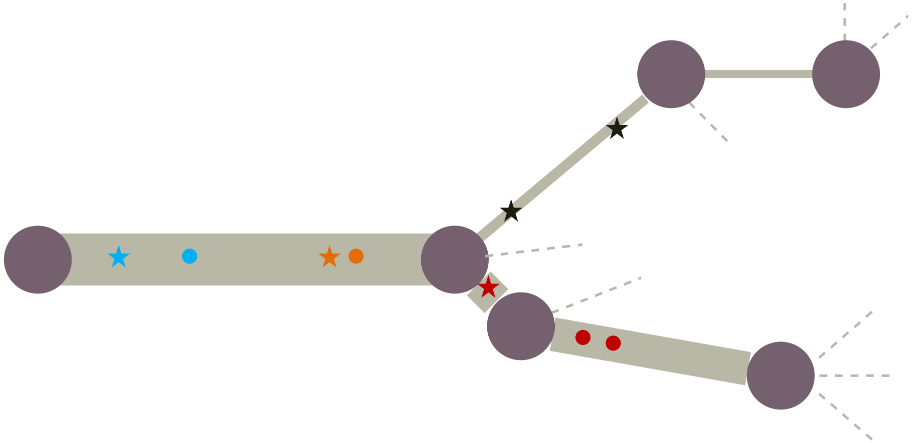

C > A
C > G
C > T
T > A
T > C
T > G
Signature 8
Mutation Type Probability
5%
0%

🟨

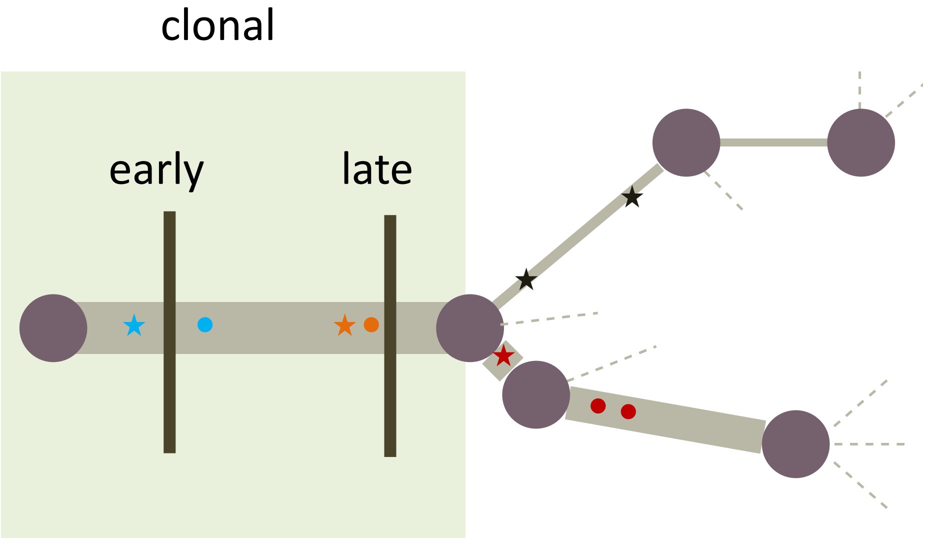

C > A
C > G
C > T
T > A
T > C
T > G
Signature 13
Mutation Type Probability
40%
30%
20%
10%
0%

🟧

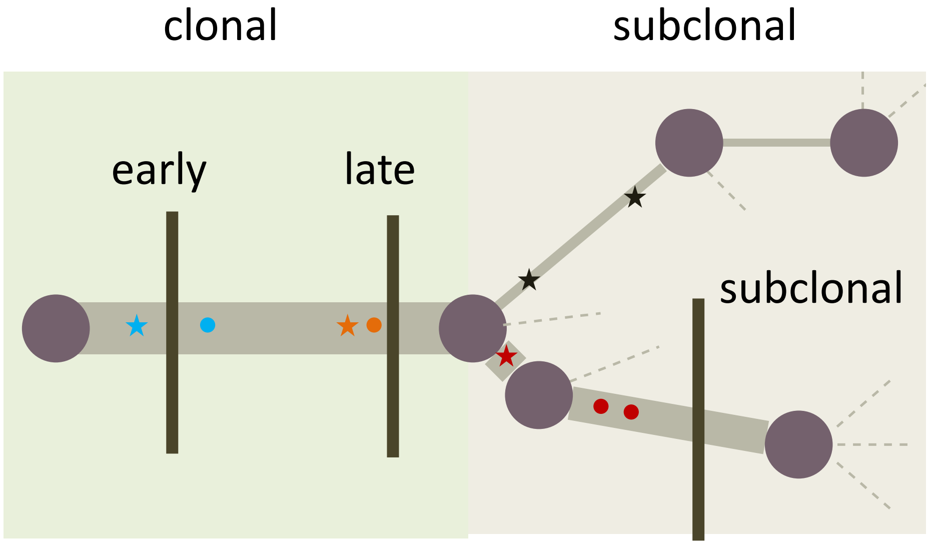
PD4120a



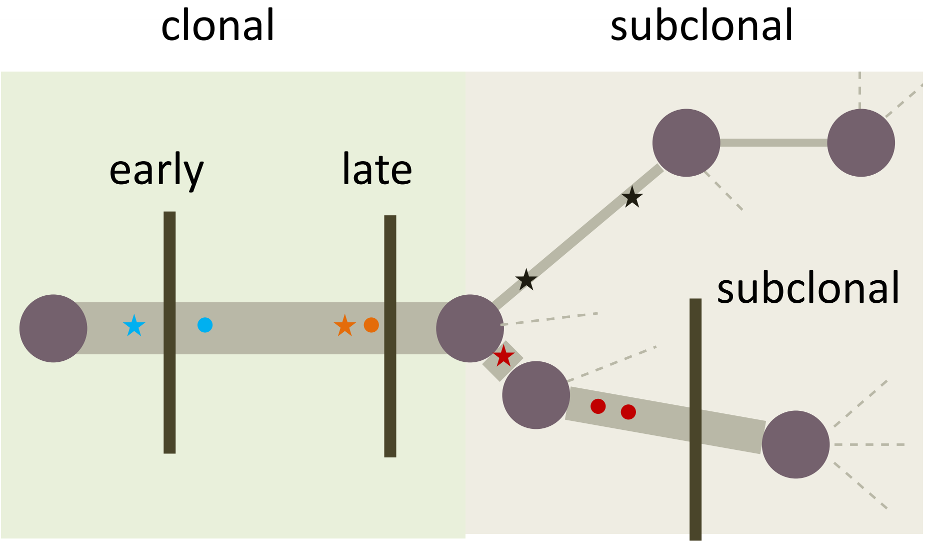
PD4120a



PD4120a



PD4120a



PD4005a

PD4107a

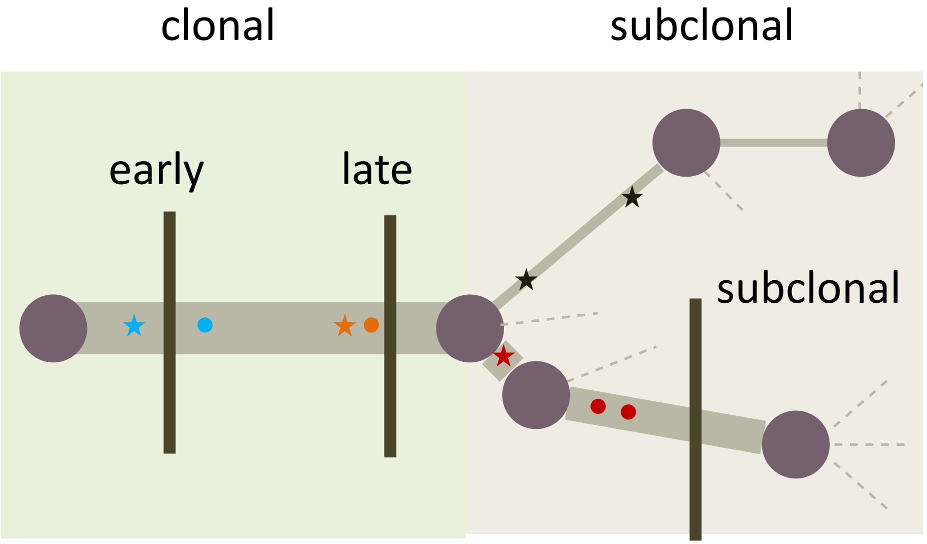
PD4116a

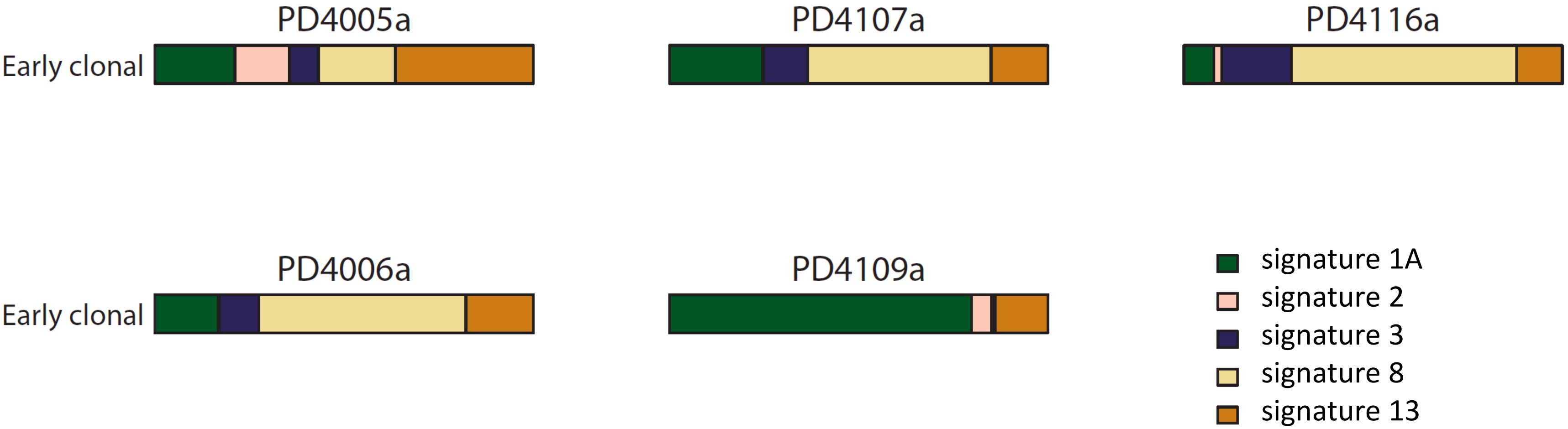
PD4006a

PD4109a

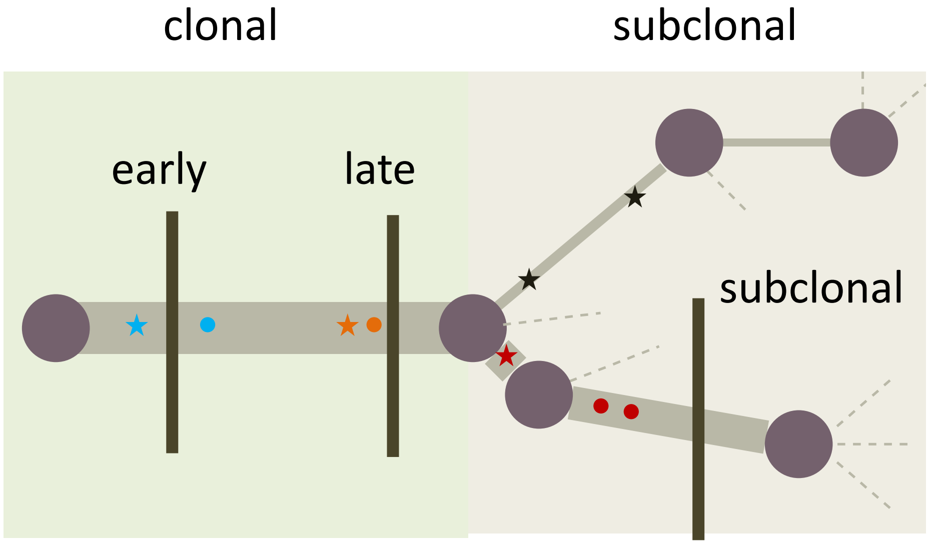
🟩 signature 1A
🟥 signature 2
🟦 signature 3
🟨 signature 8
🟧 signature 13

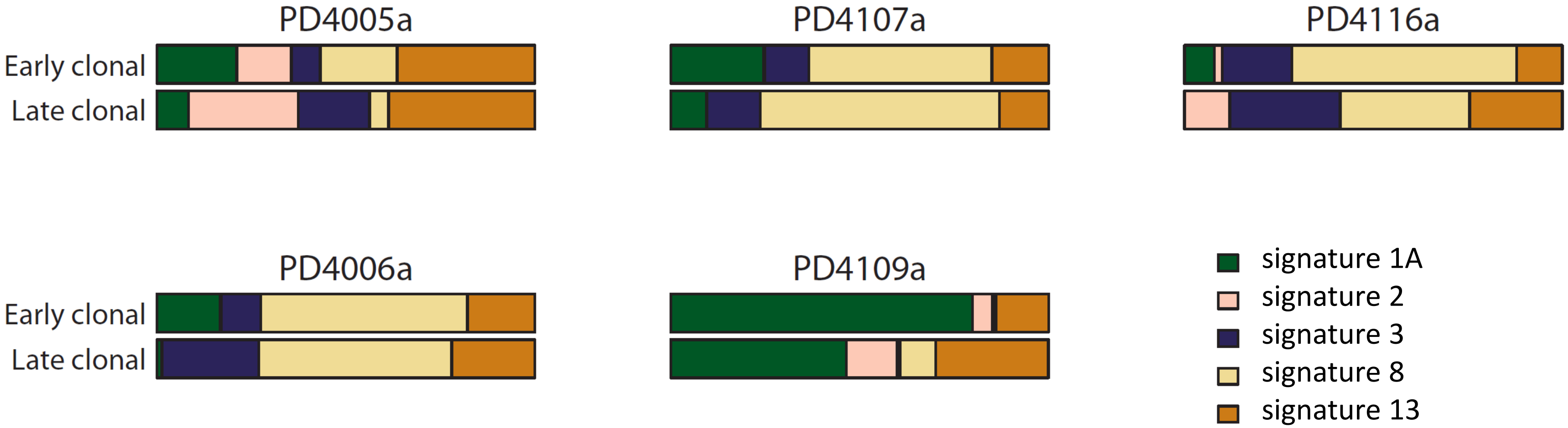
PD4120a


clonal
subclonal
early
late
subclonal

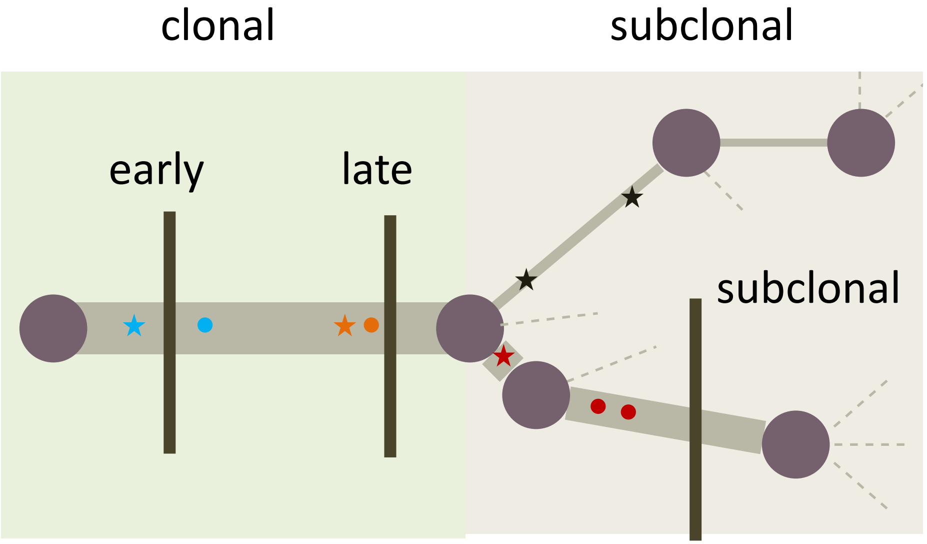

PD4005a
Early clonal
PD4107a
PD4116a
PD4006a
Early clonal
PD4109a
signature 1A
signature 2
signature 3
signature 8
signature 13

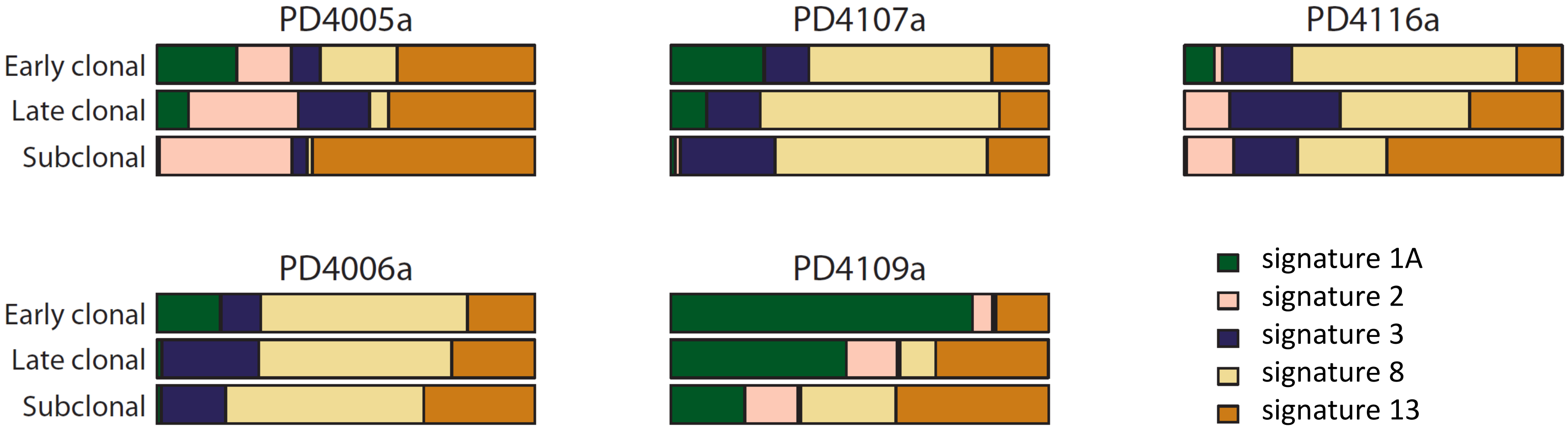
PD4120a


clonal
subclonal
early
late
subclonal


PD4005a
Early clonal
Late clonal
PD4107a
PD4116a
PD4006a
Early clonal
Late clonal
PD4109a
signature 1A
signature 2
signature 3
signature 8
signature 13

PD4120a


clonal
subclonal
early
late
subclonal


PD4005a
Early clonal
Late clonal
Subclonal
PD4107a
PD4116a
PD4006a
Early clonal
Late clonal
Subclonal
PD4109a
signature 1A
signature 2
signature 3
signature 8
signature 13

Summary III

- Exploiting the digital features of NGS technology, we can delve deep into the biology of tumours to gain insights into cancer evolution

- Using the totality of base subsitution mutations as well as copy number information, we can integrate this data in order to draw up phylogenetic structures of each patient's cancer

- We can identify the main cancer clone as well as subclonal populations in cancers.

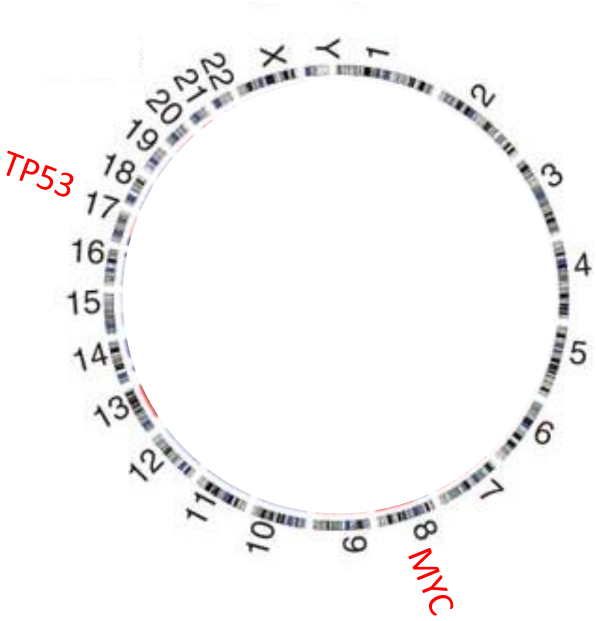
- Not only can we place cancer genes within the phylogenetic tree of individual cancers, we can identify the signatures within different parts of a tree structure and examine how those signatures change in time

PART IV

WHAT DOES THE FUTURE HOLD?

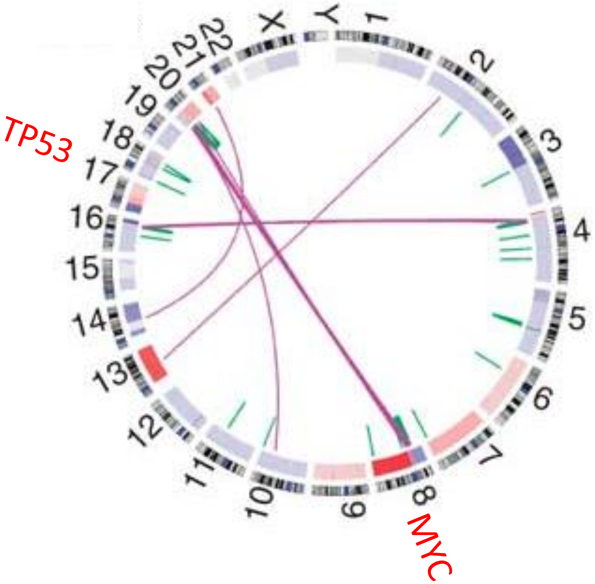
Improving genomic profiling

- Cancer genes



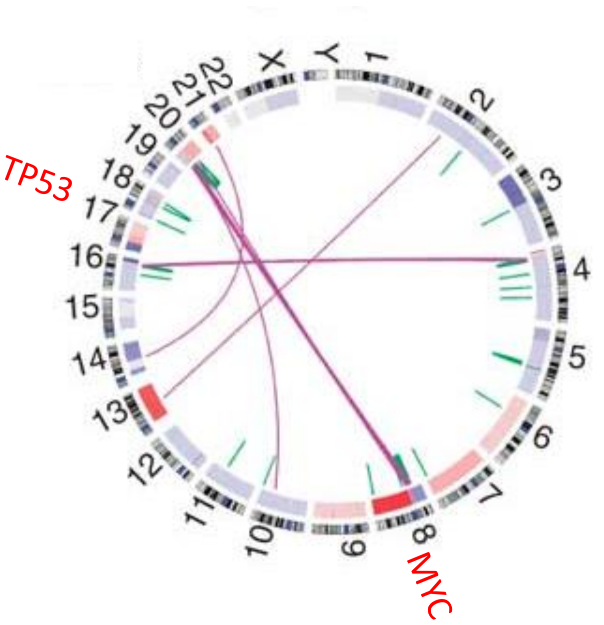
Improving genomic profiling

- Cancer genes
- Comprehensive genomic characterisation



Improving genomic profiling

- Cancer genes
- Comprehensive genomic characterisation
- Signatures



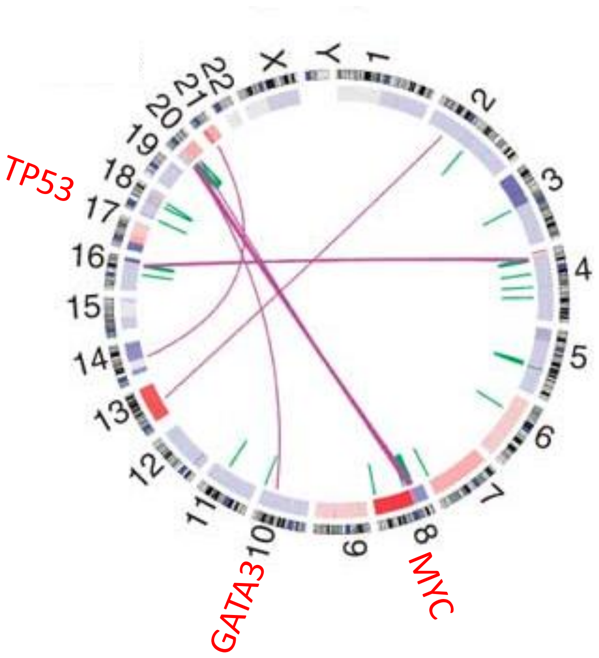
Signature 1

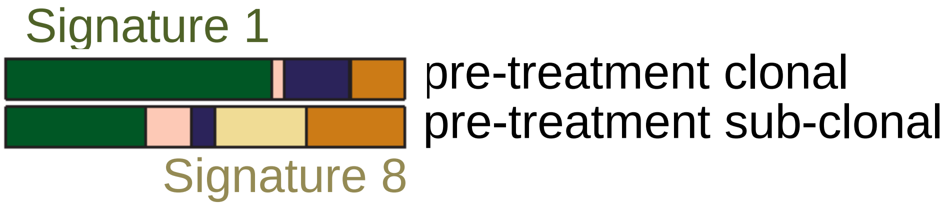
pre-treatment clonal

Drug sensitivities:
drug A

Improving genomic profiling

- Cancer genes
- Comprehensive genomic characterisation
- Signatures
- Subclonal populations




Signature 1

pre-treatment clonal

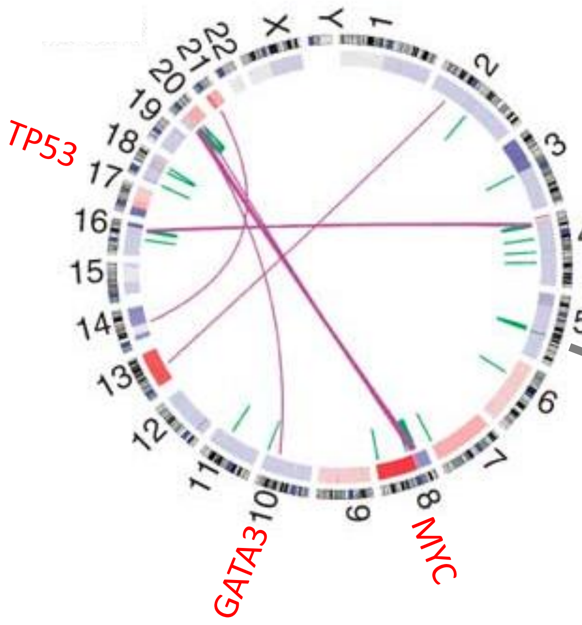
pre-treatment sub-clonal

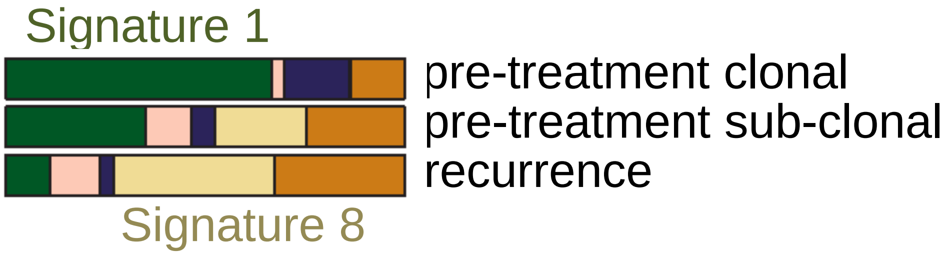
Signature 8

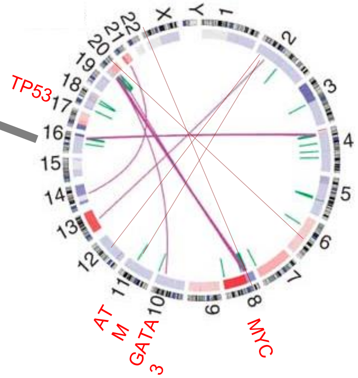
Drug sensitivities:
drug A
drug B

Improving genomic profiling

- Cancer genes
- Comprehensive genomic characterisation
- Signatures
- Subclonal populations







Drug sensitivities:

drug A
drug B

drug A
drug C

Final Summary

- The increased speed and scale of NGS technology allows the collection of vast amounts of genomic information about each person’s cancer genome

- Crosstalk between clinicians, biologists and mathematicians/statisticians is required in order to extract the value-added information that is buried in cancer genomic data

- We need to have an awareness that there are still difficulties in processing and analysis data (reproducibility).

- The challenge is to design trials that best use the improved ability to stratify patients using genomic information

- Notwithstanding, there is a future to look forward to which is altogether more individual to each patient

International Cancer Genome Consortium

wellcome trust sanger institute

BREAST CANCER WORKING GROUP

The Cancer Genome Atlas

Breast Cancer Working Group
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Jorge Reis-Filho
Sunil Lakhani
Mike Lee
Larry Norton
Angelo Paradiso
Martine Piccart
Jorge Reis-Filho
Andrea Richardson
Anne Salomon
Christos Sotiriou
Paul Spellman
Henk Stunnenberg
Fred Sweep
Benita Tan
Gilles Thomas
Andy Tutt
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Marc Van de Vijver

Sanger Institute
Ludmil Alexandrov
Peter van Loo
David Wedge
Patrick Tarpey
Keiran Raine
Helen Davies
Manasa Ramakrishna
Dominik Glodzik
Xueqing Zou
Sancha Martin
Andy Futreal
Ultan McDermott
Peter Campbell
Michael R Stratton

Harold Swerdlow (some NGS slides

wellcome trust

WELLCOME-BEIT MEMORIAL

BREAST CANCER BREAKTHROUGH

SEVENTH FRAMEWORK PROGRAMME