Genomic ventures to explore tumour development and intra-tumour heterogeneity in breast cancer

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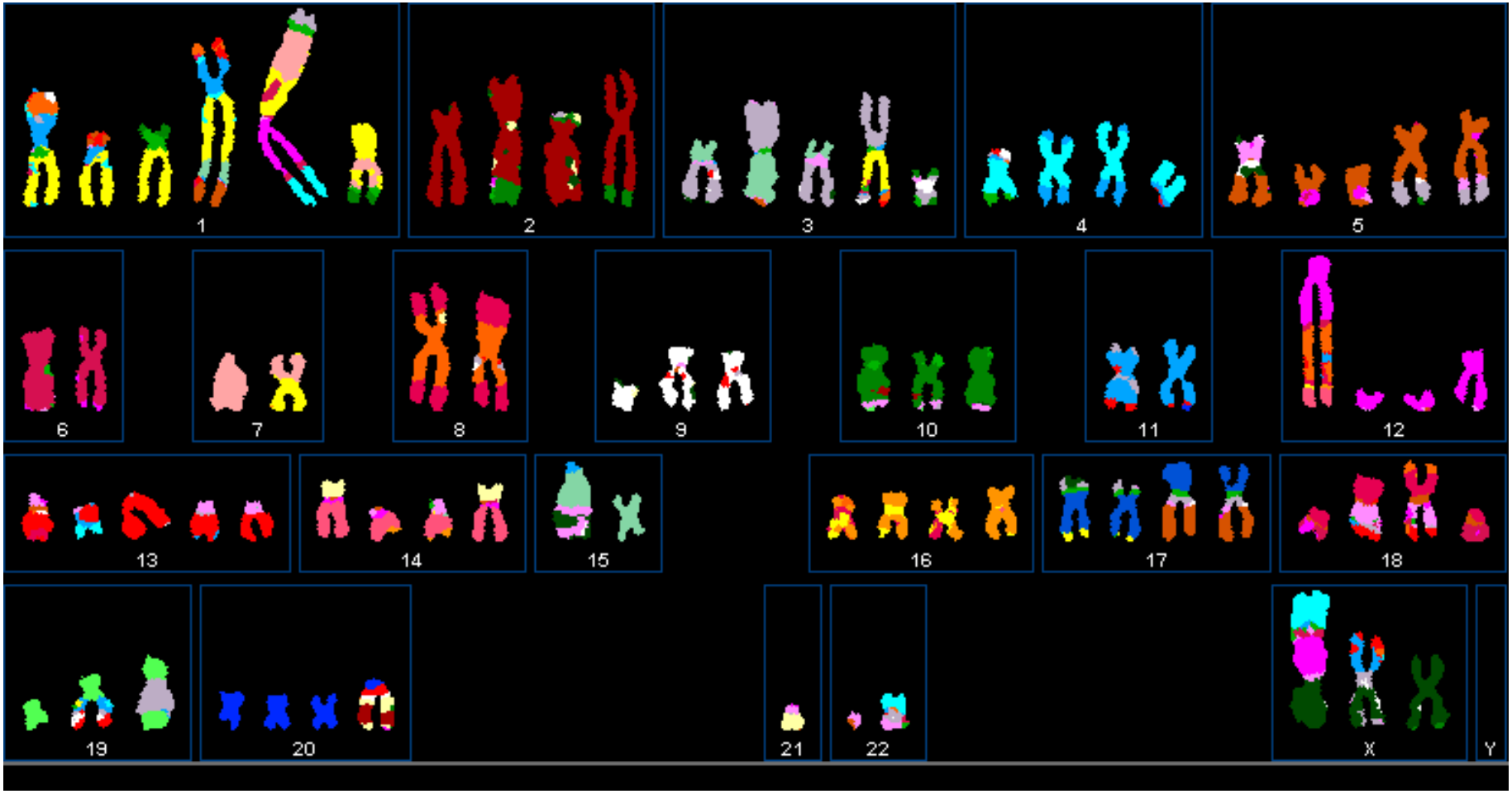
Disclosure information

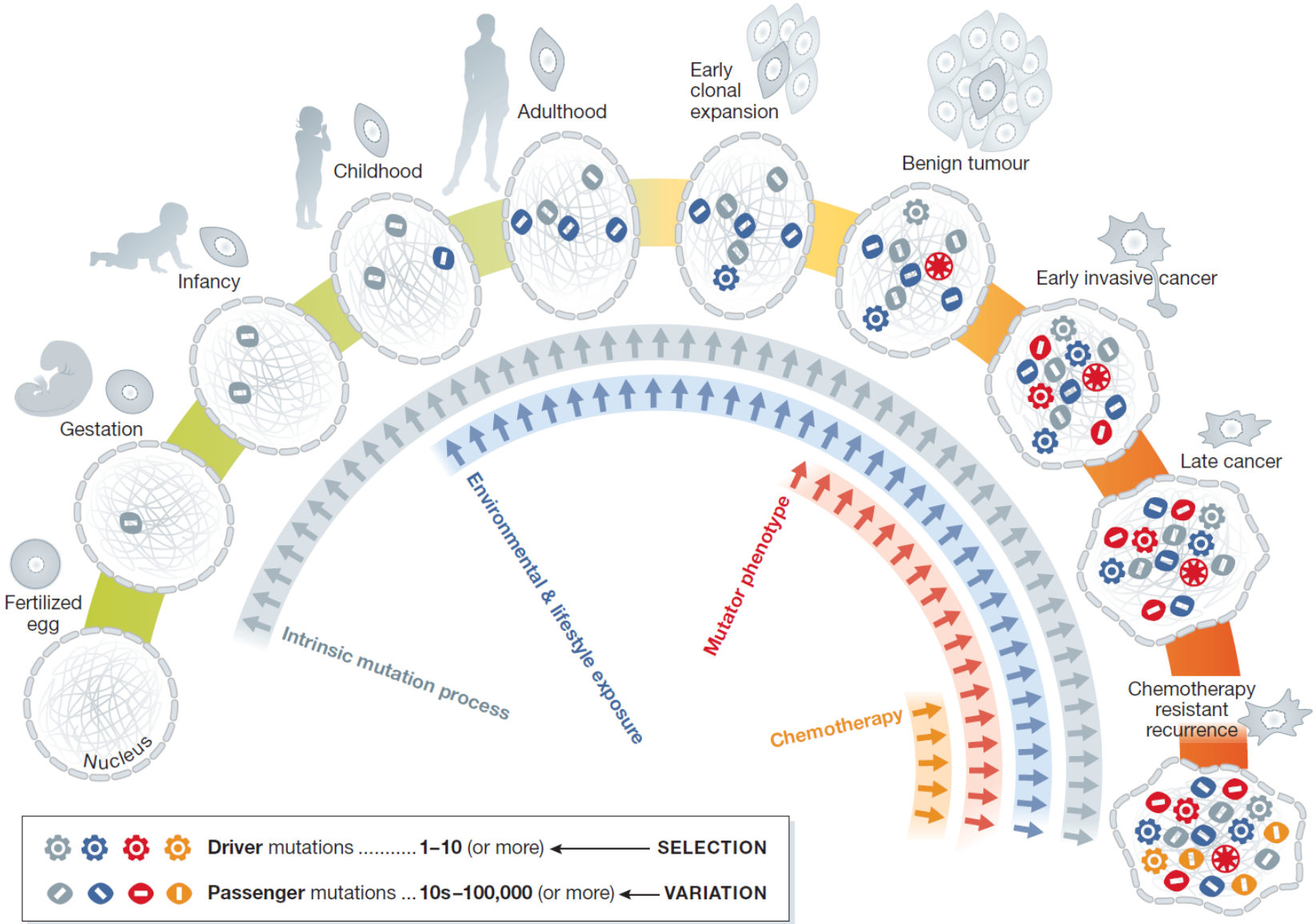
- I have no financial relationships or potential conflicts of interest to disclose

The cancer genome



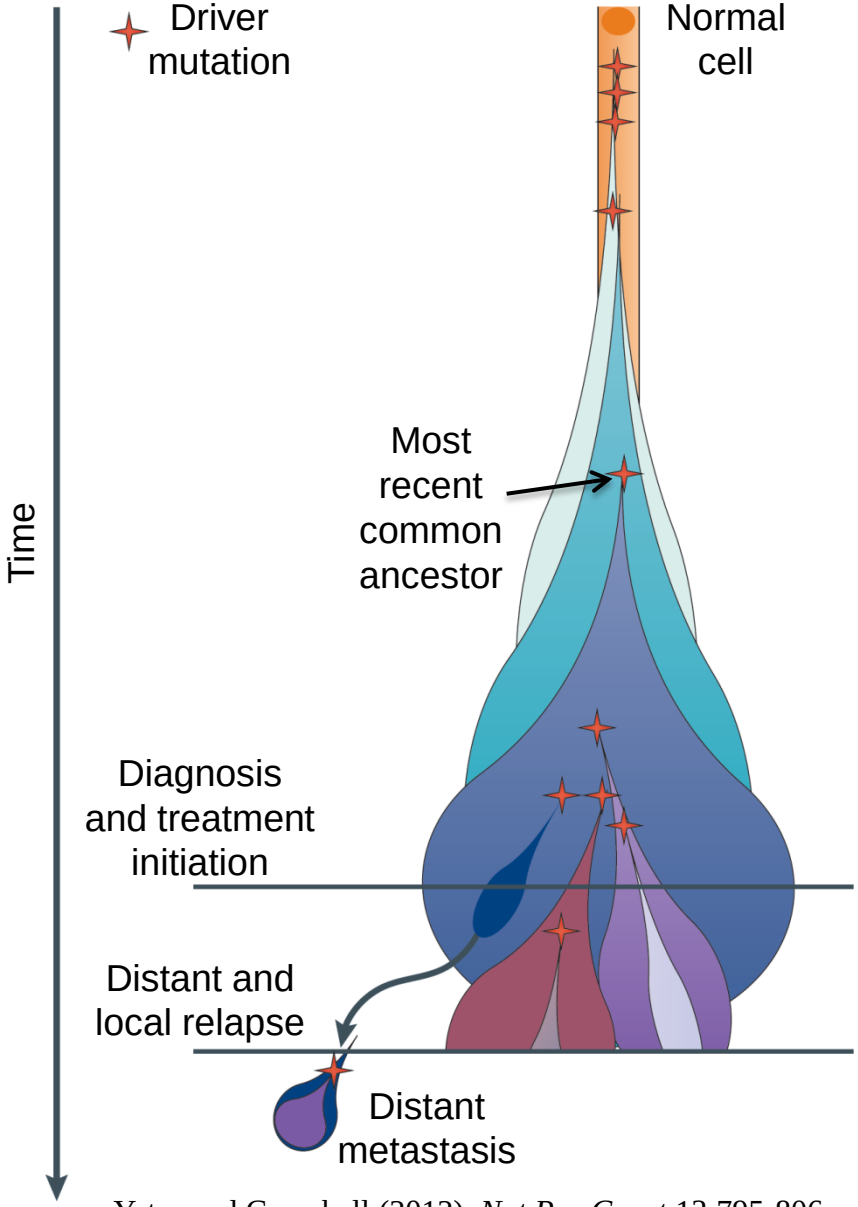
Source: SKY Karyotypes and FISH analysis of Epithelial Cancer Cell Lines,
Cancer Genomics Program, Department of Pathology and Oncology, University of Cambridge,
http://www.path.cam.ac.uk/~pawefish/index.html

Evolution of the cancer genome

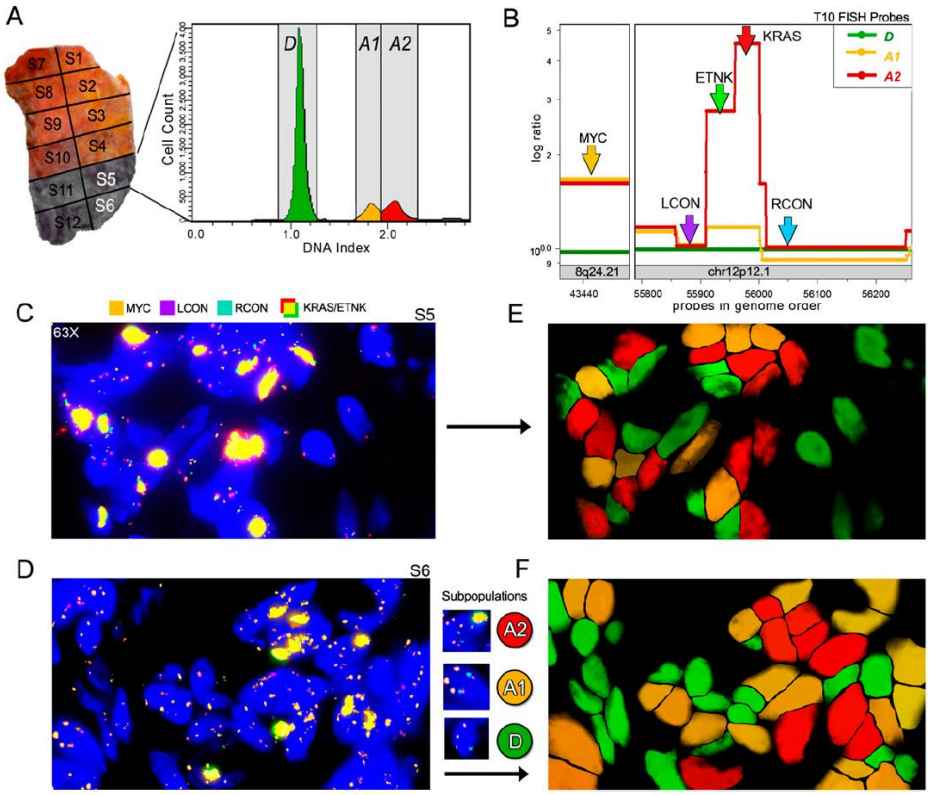


Stratton (2013), EMBO Mol Med 5:169-172

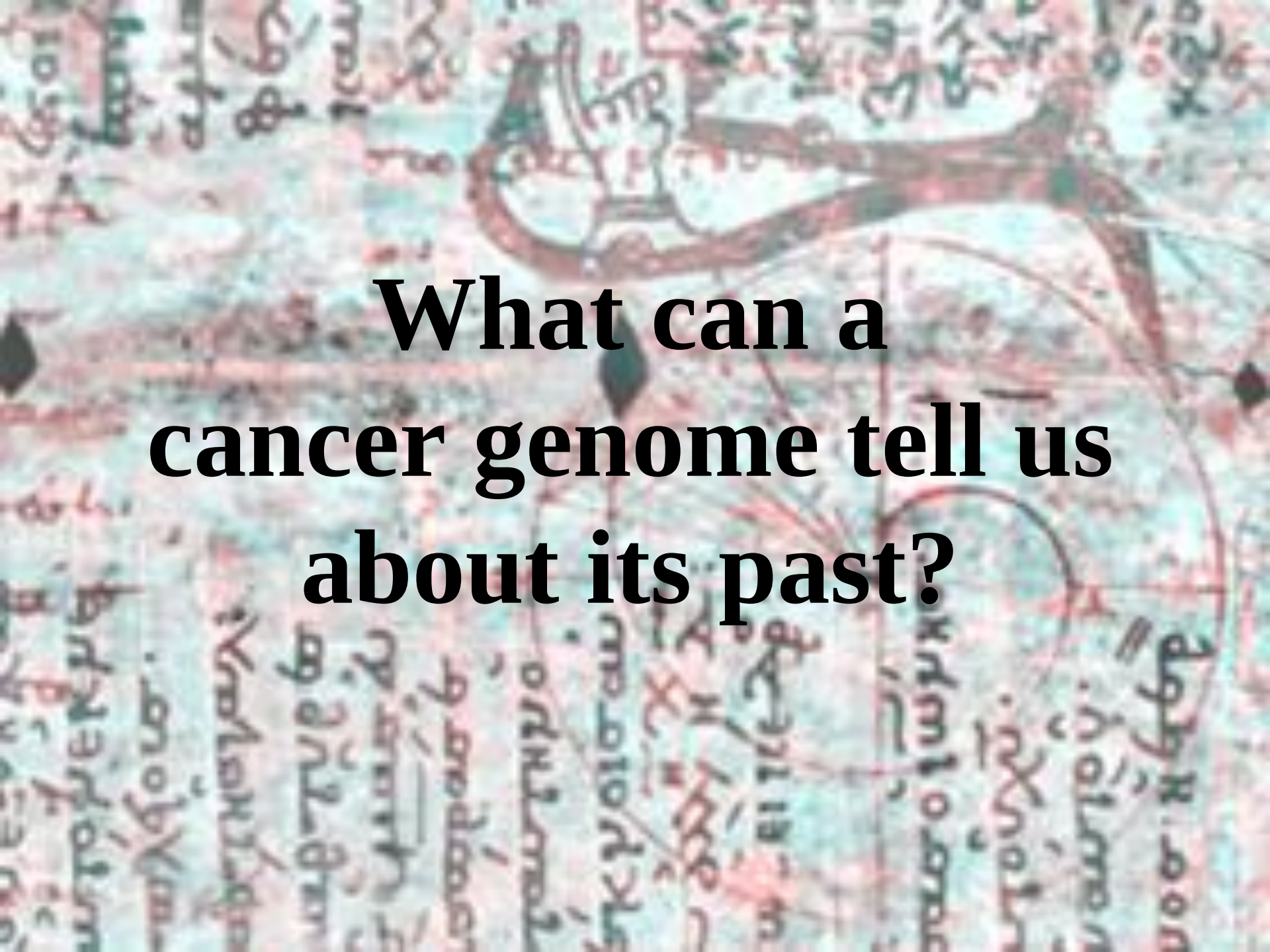
Tumour evolution and intra-tumour heterogeneity



Yates and Campbell (2012), *Nat Rev Genet* 13:795-806

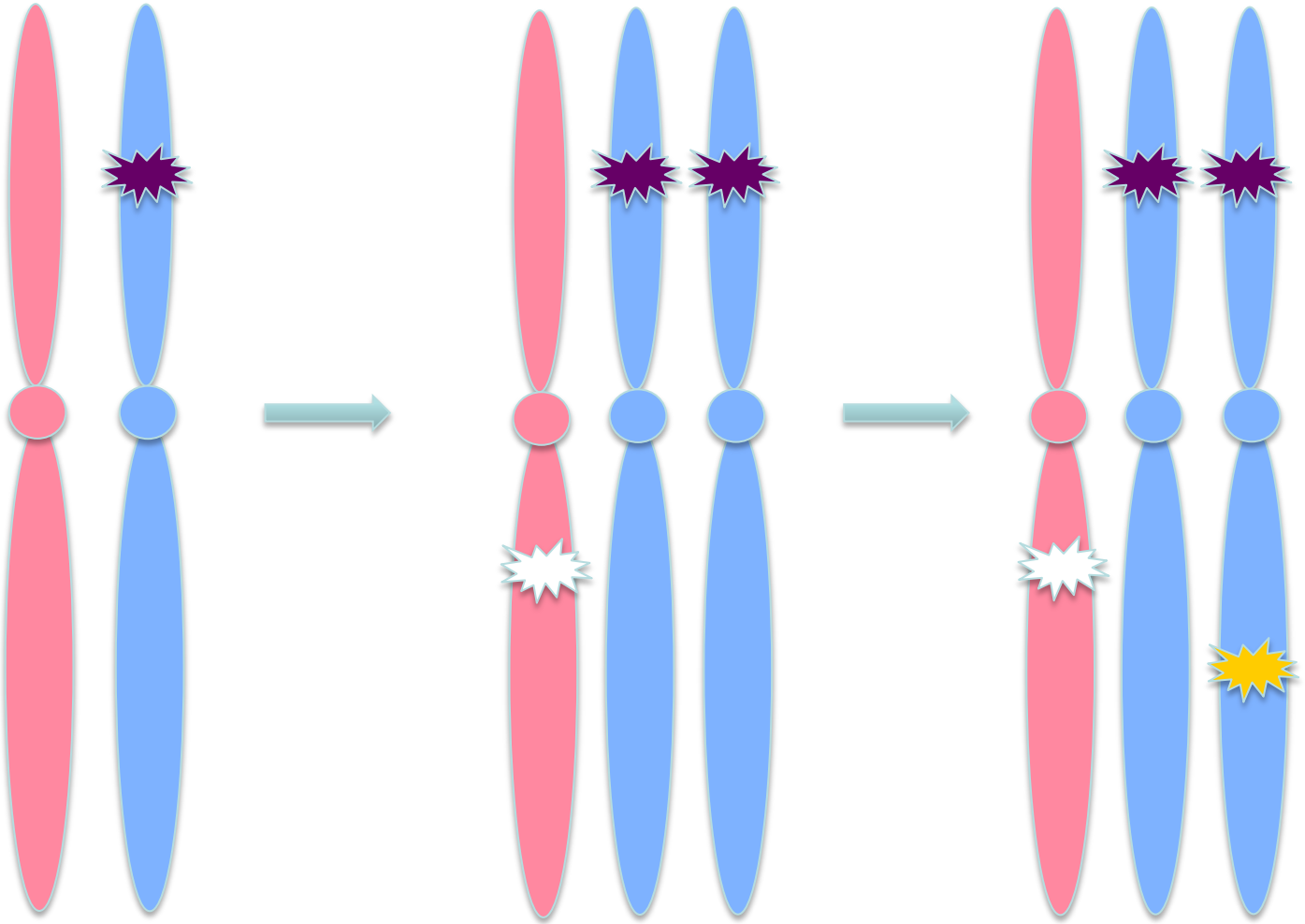


Navin *et al*. (2010). *Genome Res* 20:68-80

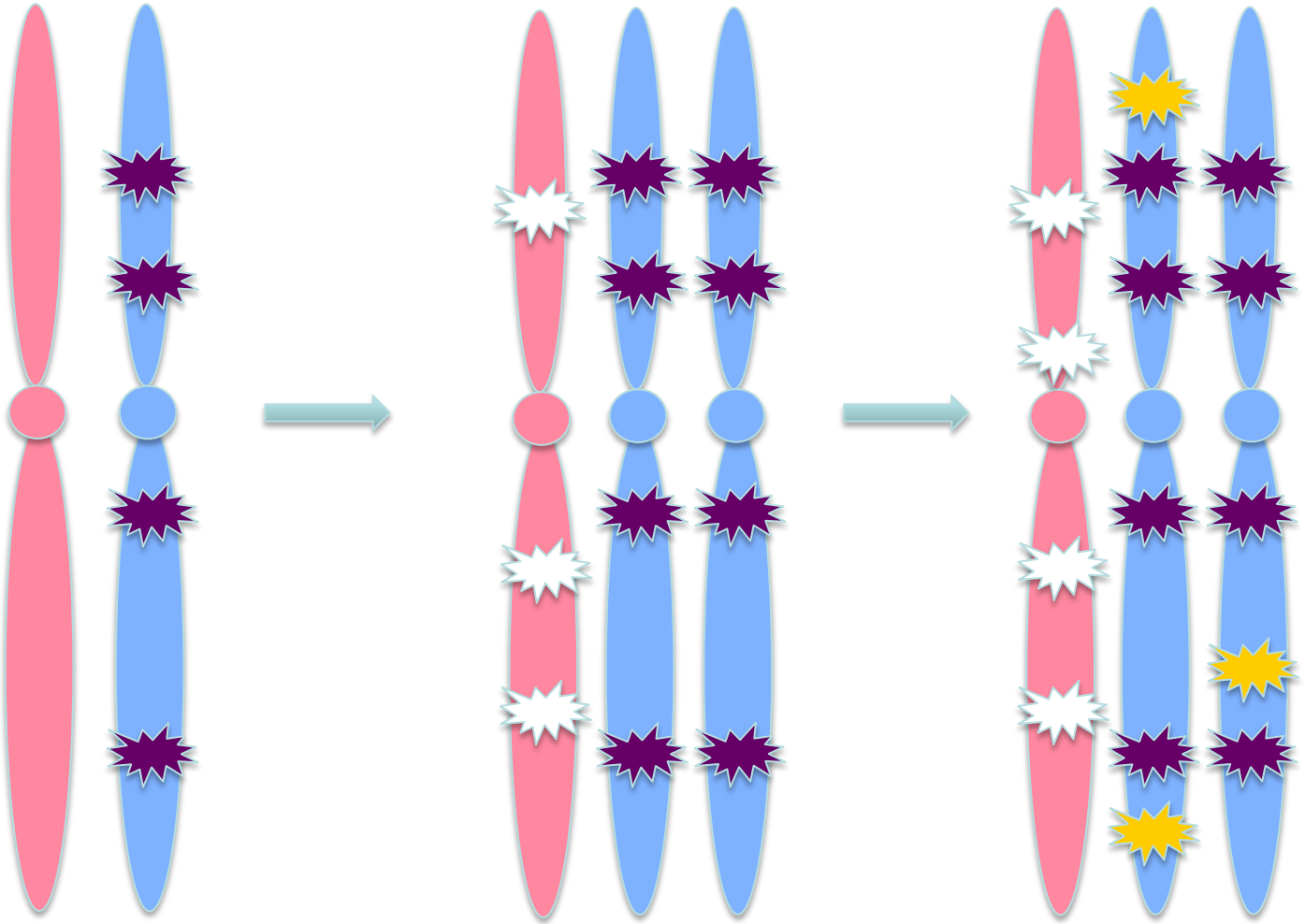


What can a cancer genome tell us about its past?

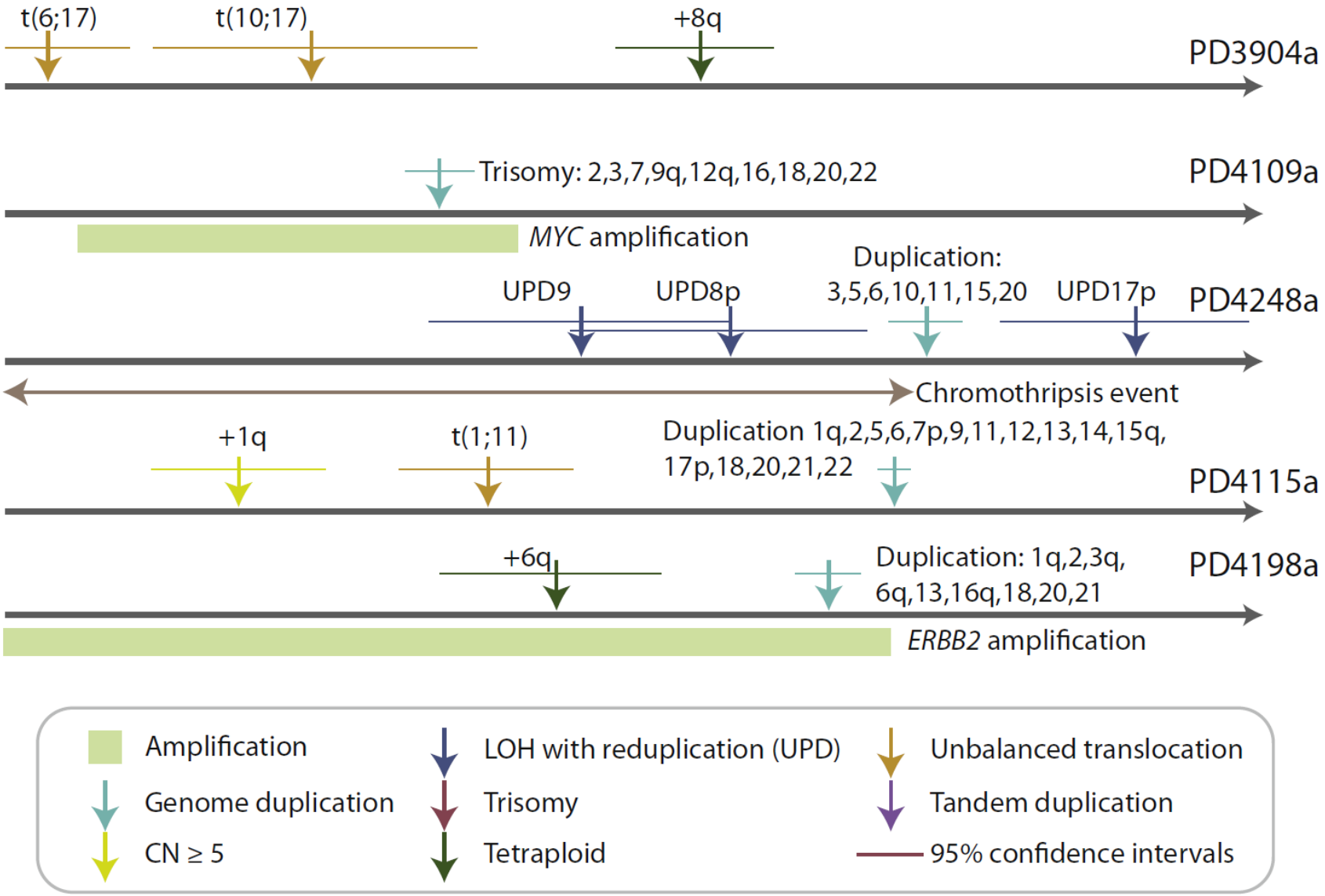
Evolution of cancer genomes in time



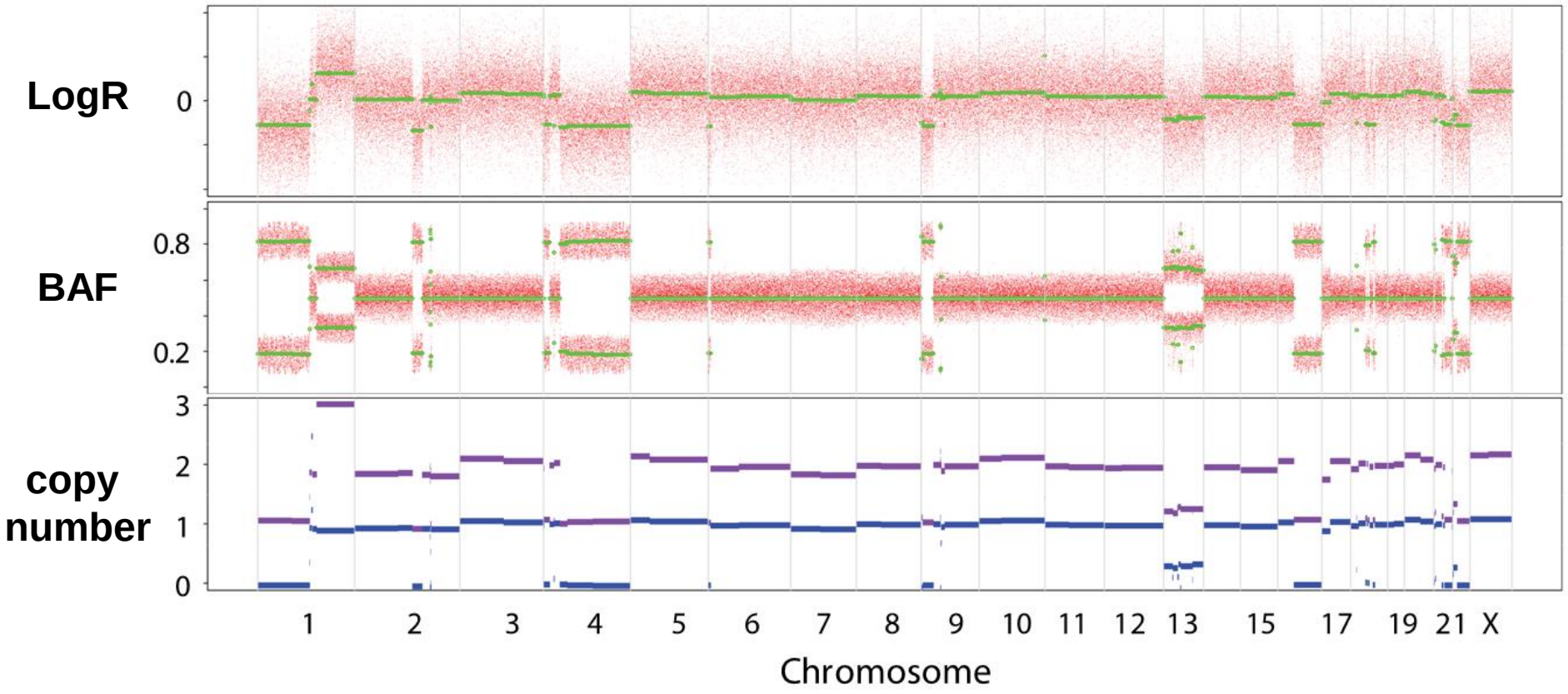
Evolution of cancer genomes in time



Timing copy number gains



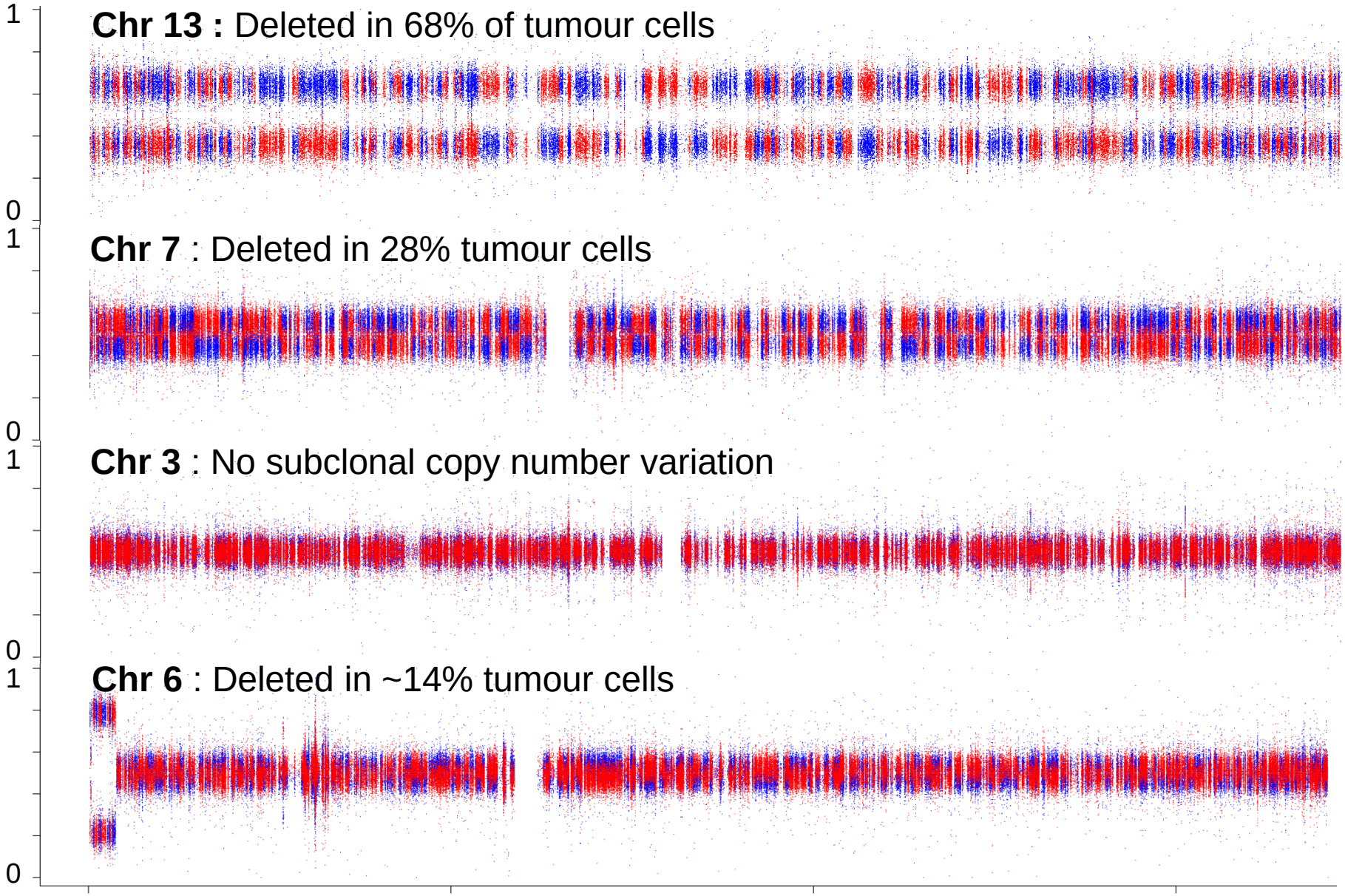
A breast cancer genome sequenced to 188X coverage



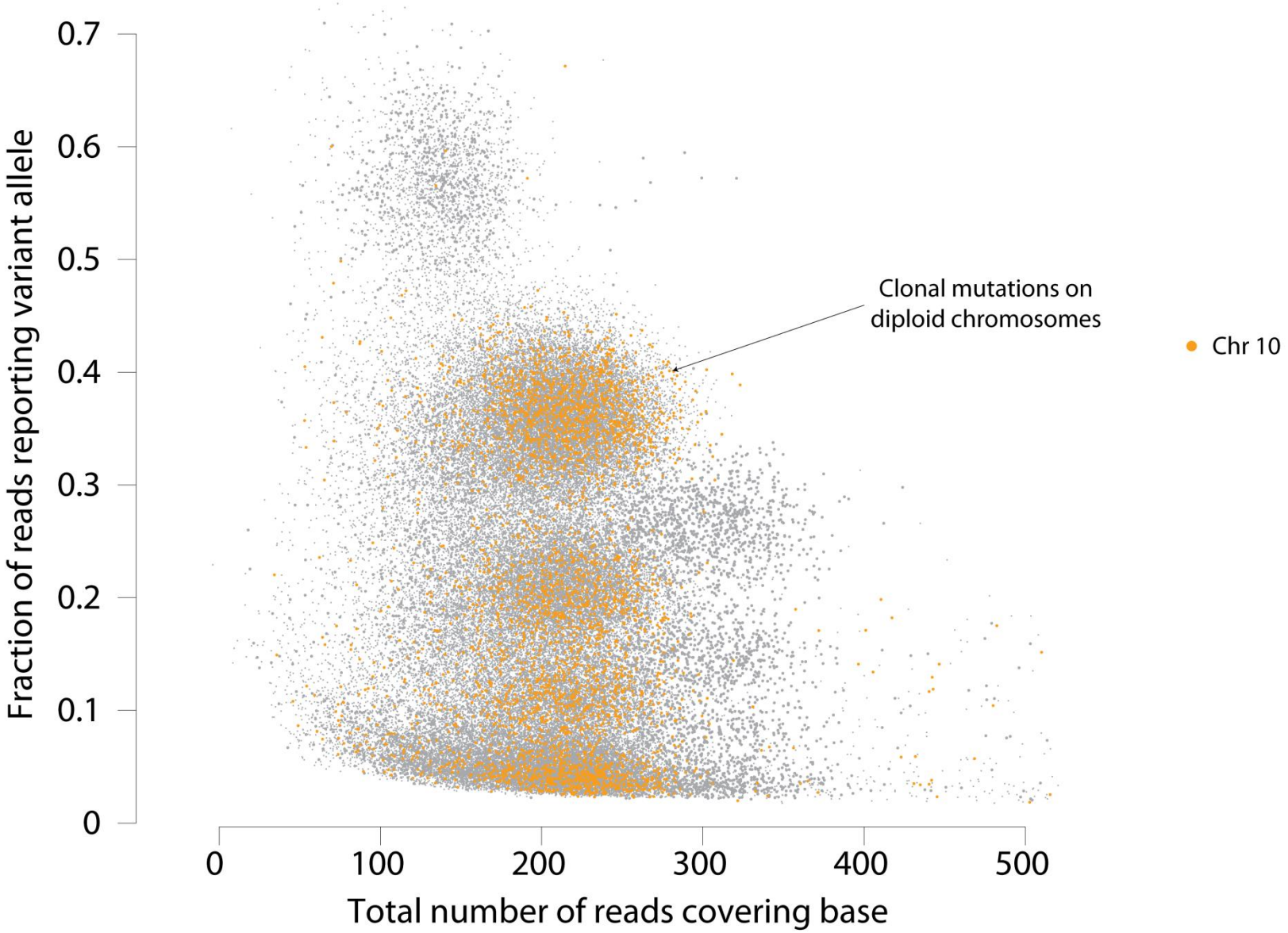
Estimated purity: 70% tumor cells, 30% normal cells

Van Loo*, Nordgard* *et al.* (2010), Allele-specific copy number analysis of tumors. *PNAS* 107:16910-16915.

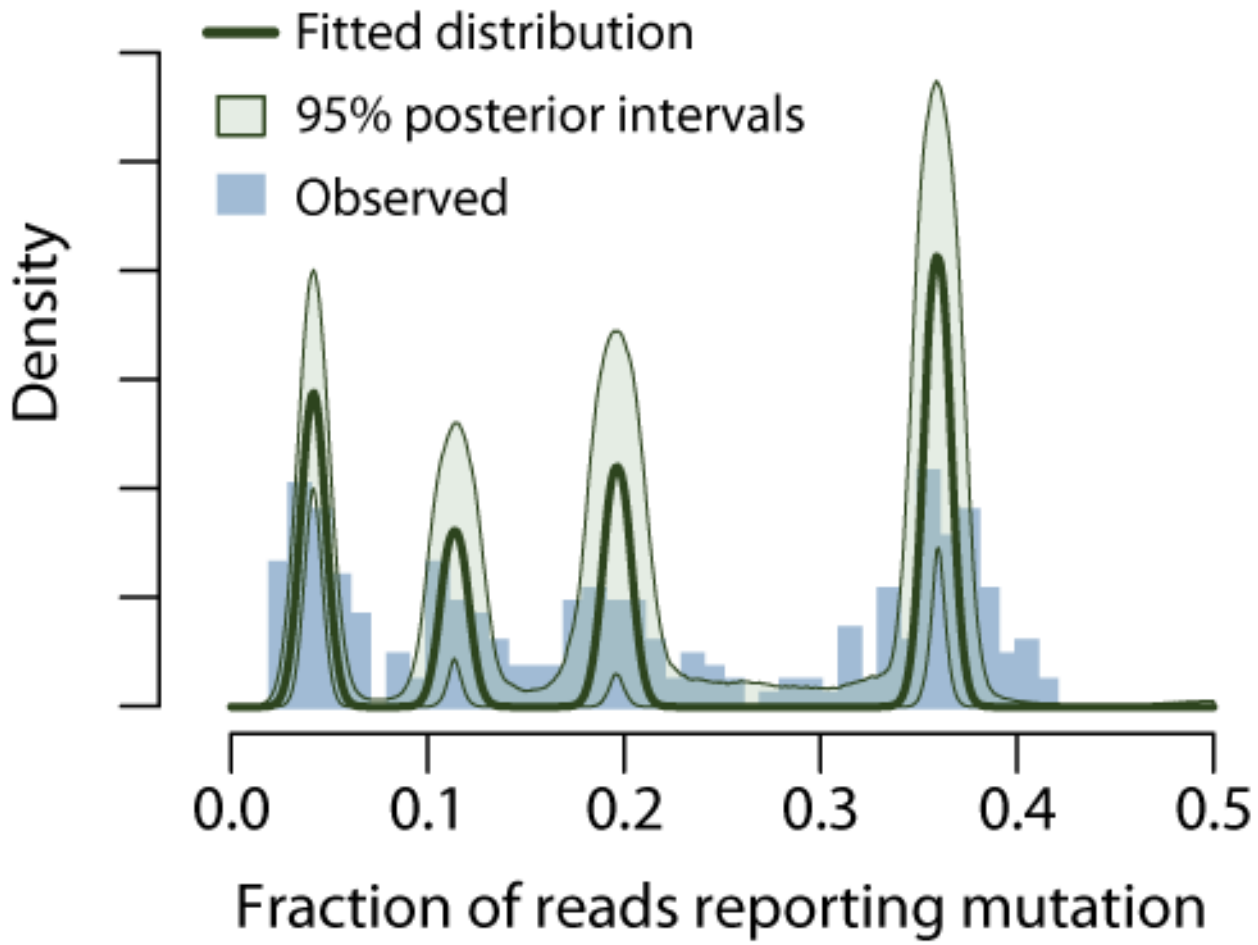
Detecting subclonal copy number changes



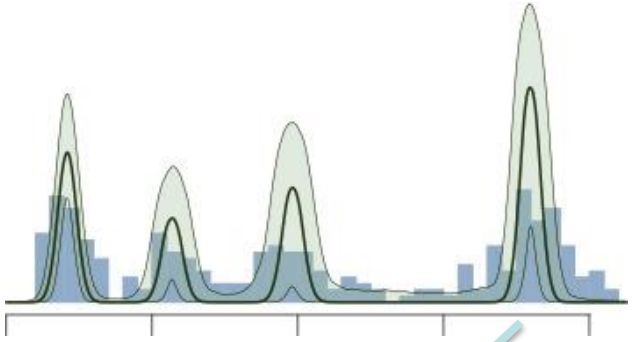
Point mutations



Subclones in mutation data modeled with a Bayesian Dirichlet process



Phylogenetic tree



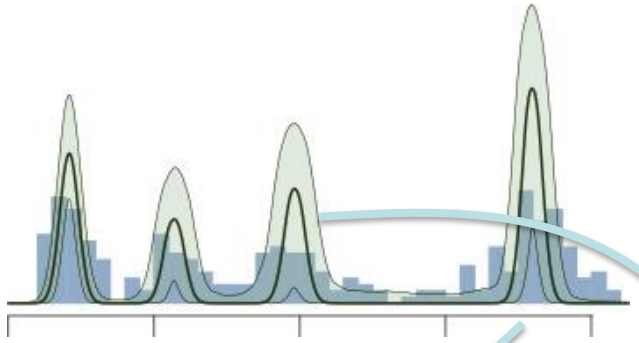
Most recent common ancestor

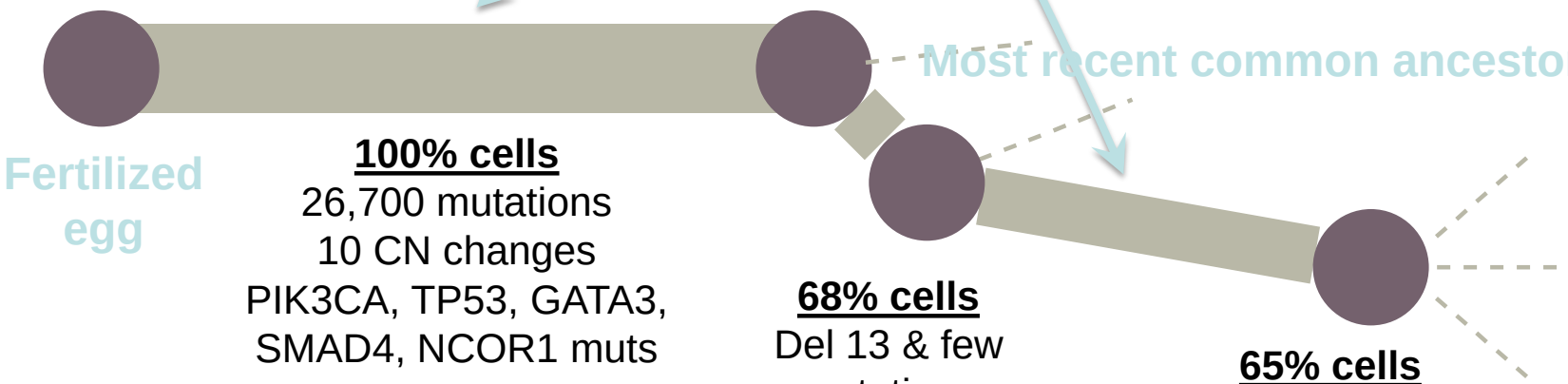
Fertilized egg

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

The pigeonhole principle

Phylogenetic tree





Fertilized egg

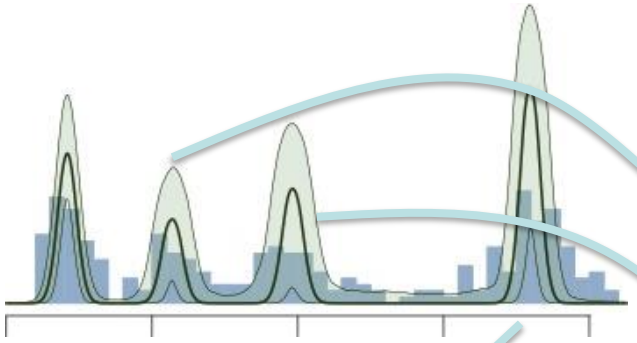
100% cells
26,700 mutations
10 CN changes
PIK3CA, TP53, GATA3, SMAD4, NCOR1 muts

Most recent common ancestor

68% cells
Del 13 & few mutations

65% cells
Del 13 & extra 15,600 muts

Phylogenetic tree



14% cells
Tetraploid with
- Loss of 2 copies of 7^M
- Loss of 2^P and 2^M
- Loss of 6, 8, 9, 11, 12, 14, 15, 18 & 21 (x1 each)

18% cells
11,000 muts

Most recent common ancestor

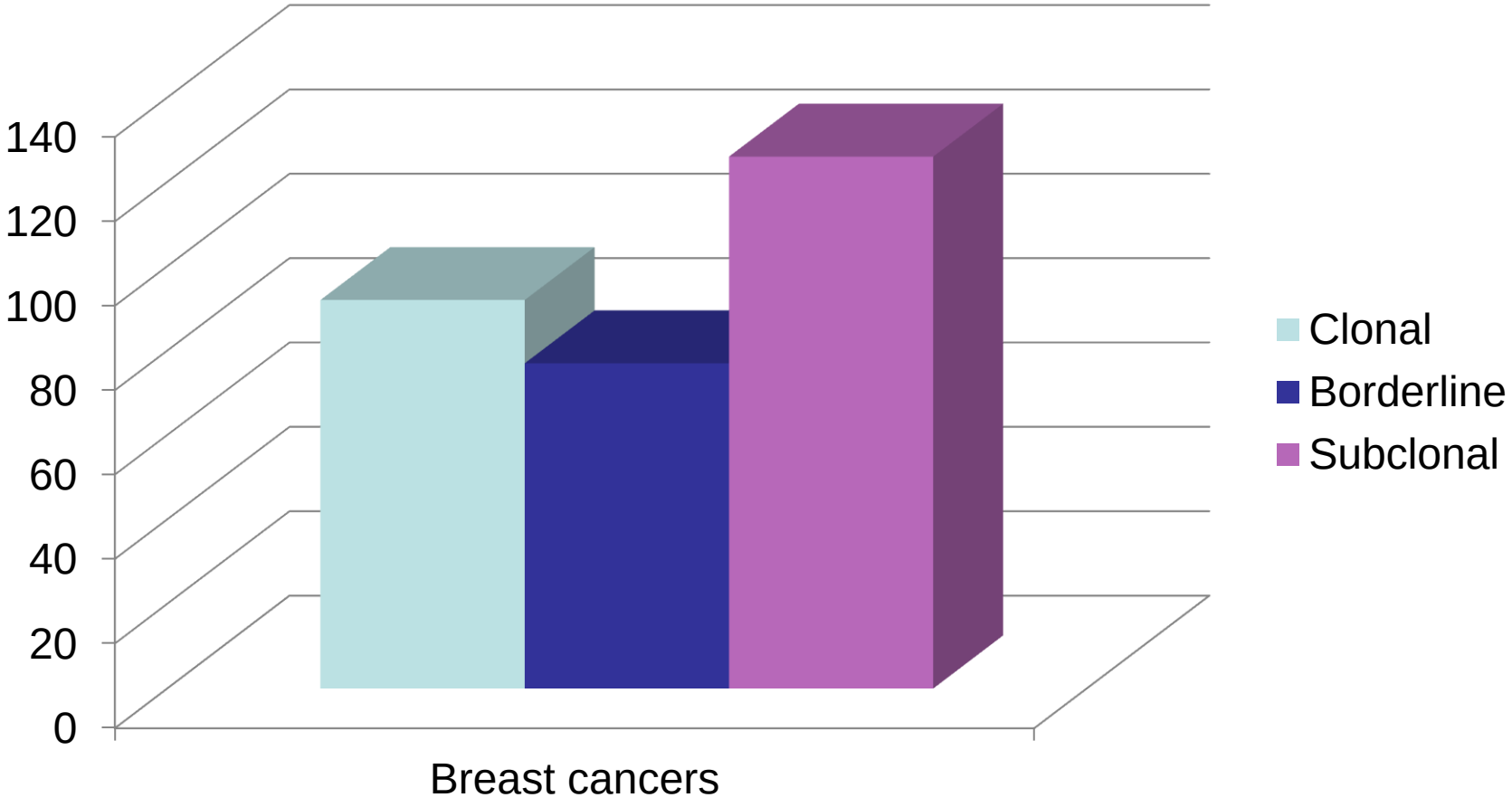
Fertilized egg

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

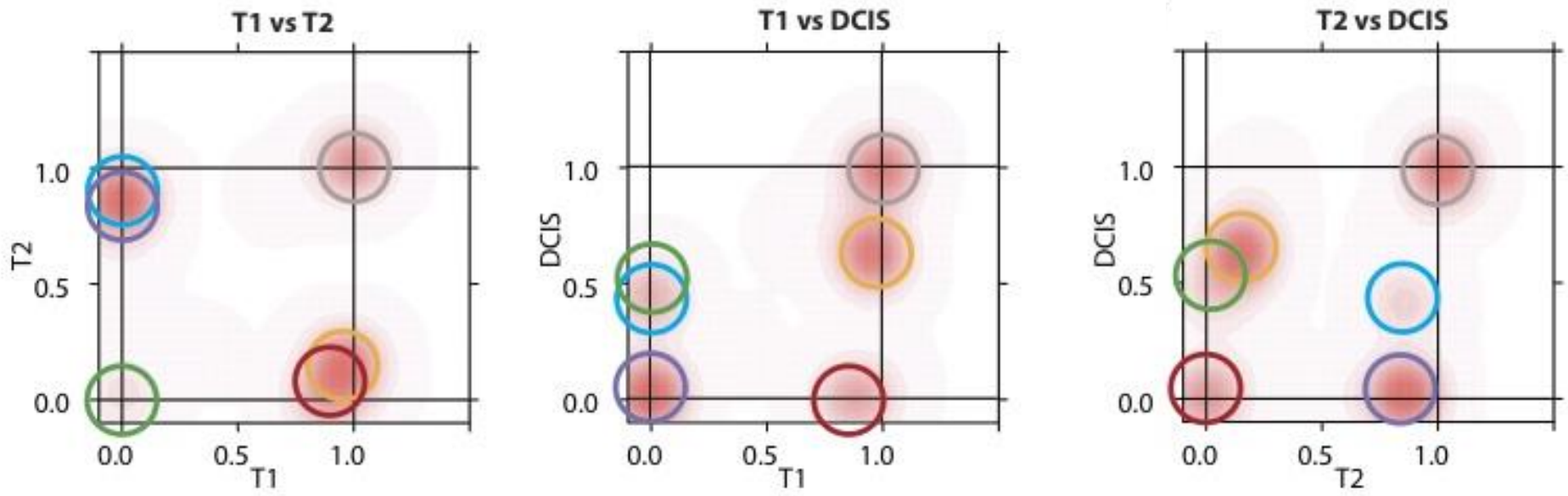
68% cells
Del 13 & few mutations

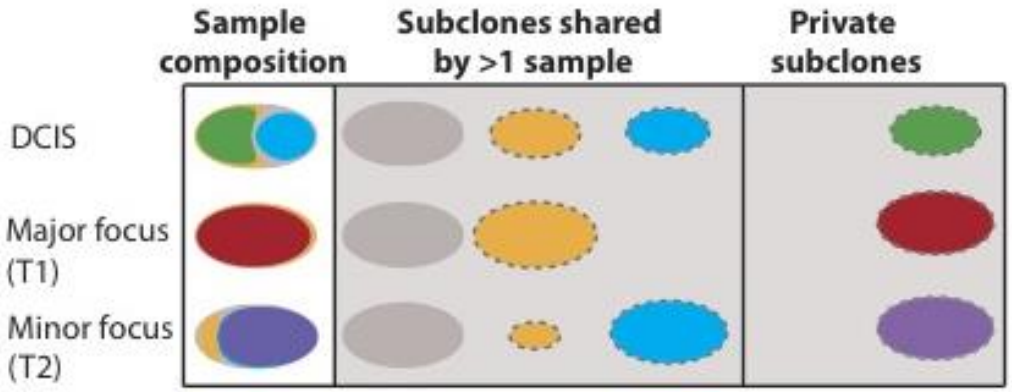
65% cells
Del 13 & extra
15,600 muts

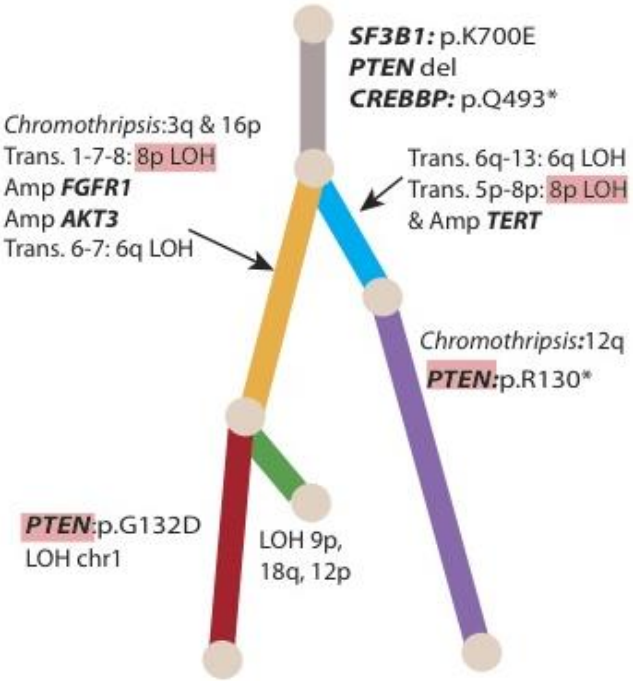
What fraction of breast cancers show subclonal mutations?



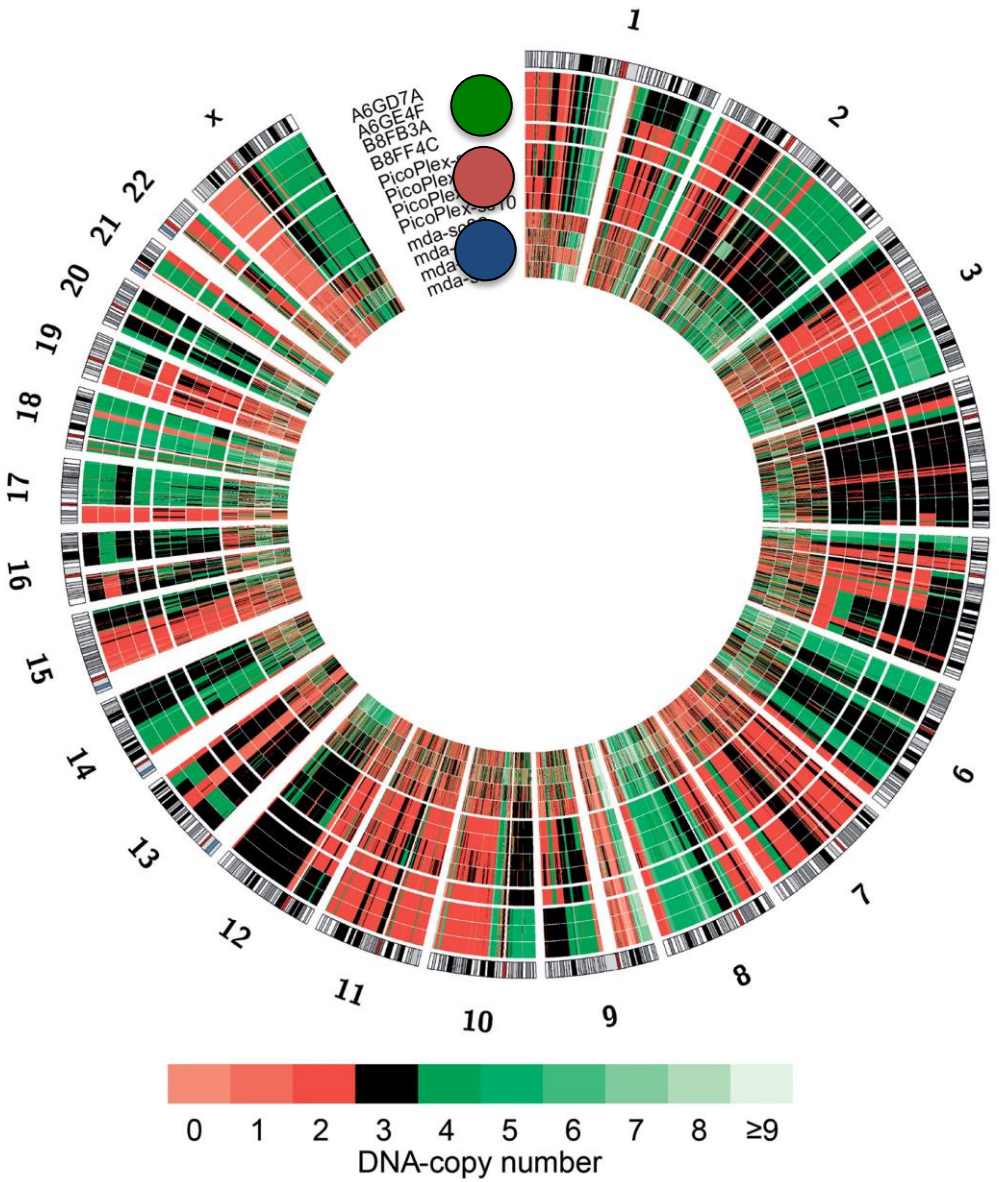
Studying (sub)clonal evolution across samples







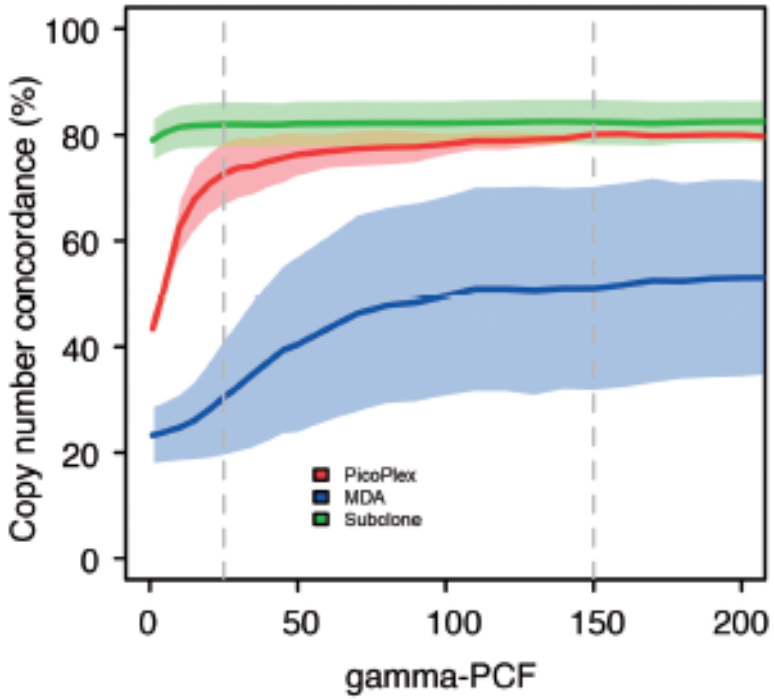
Sequencing single breast cancer cells



4 subclones HCC38 (millions of cells)

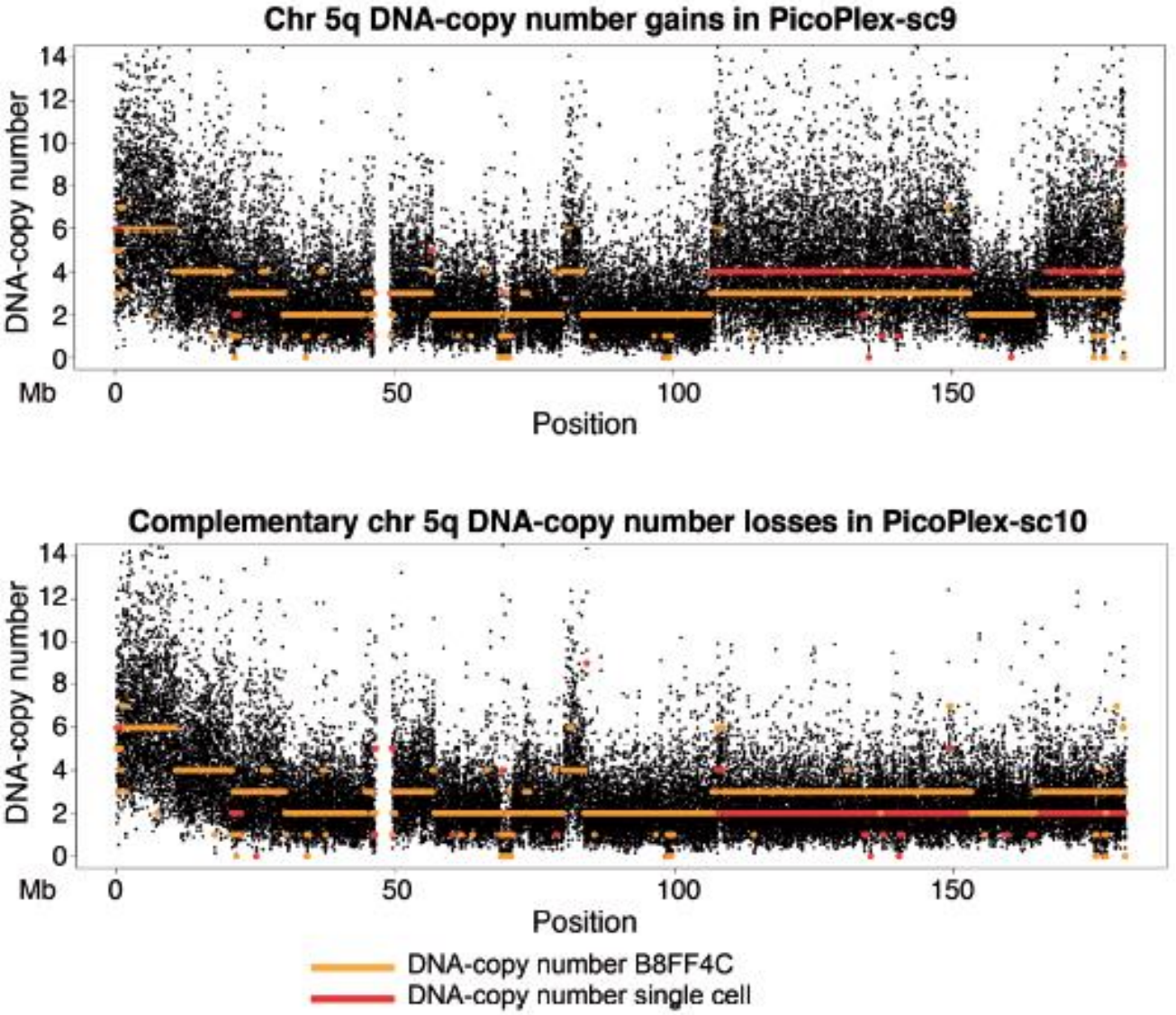
4 single cells PCR-based amplification

4 single cells MDA-based amplification

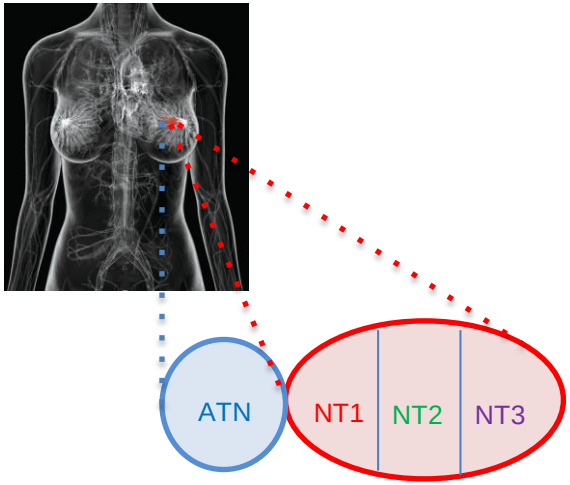


Voet *et al*. (2013), Single-cell paired-end genome sequencing reveals structural variation per cell cycle. *Nucleic Acids Research* 41:6119-6138.

Sister cells show complementary aberrations

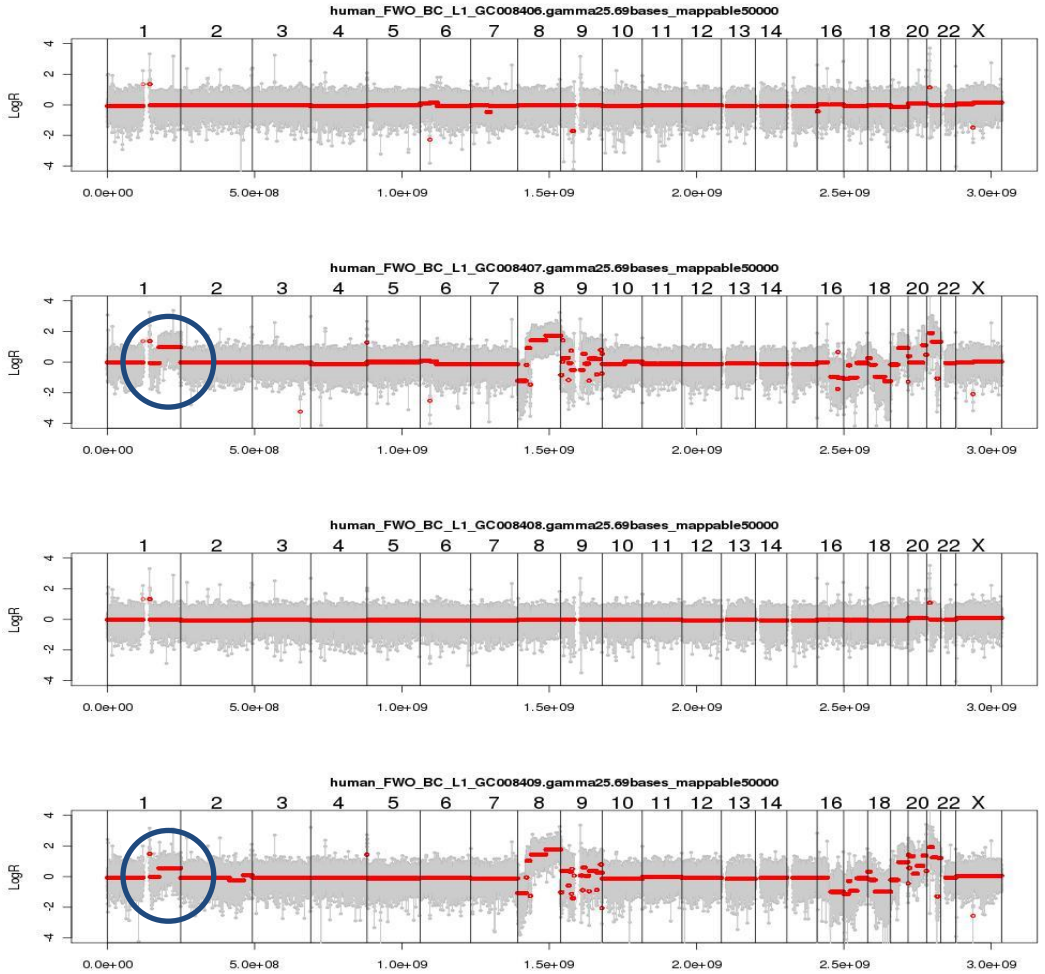


Single cell and bulk tumour sequencing of a primary breast cancer



Breast tumor
3 regions
189 cells

Adjacent normal
(6 cells)



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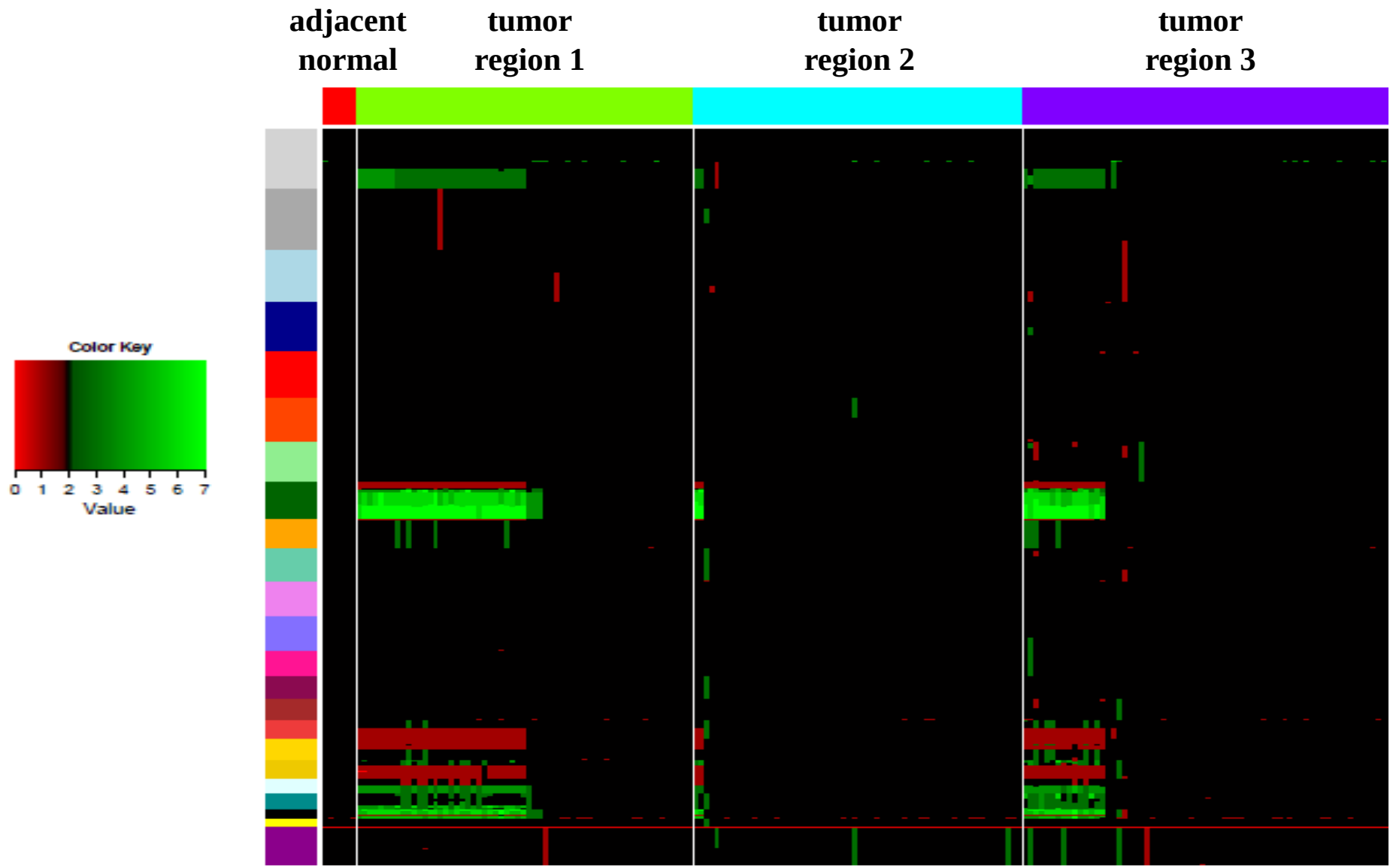
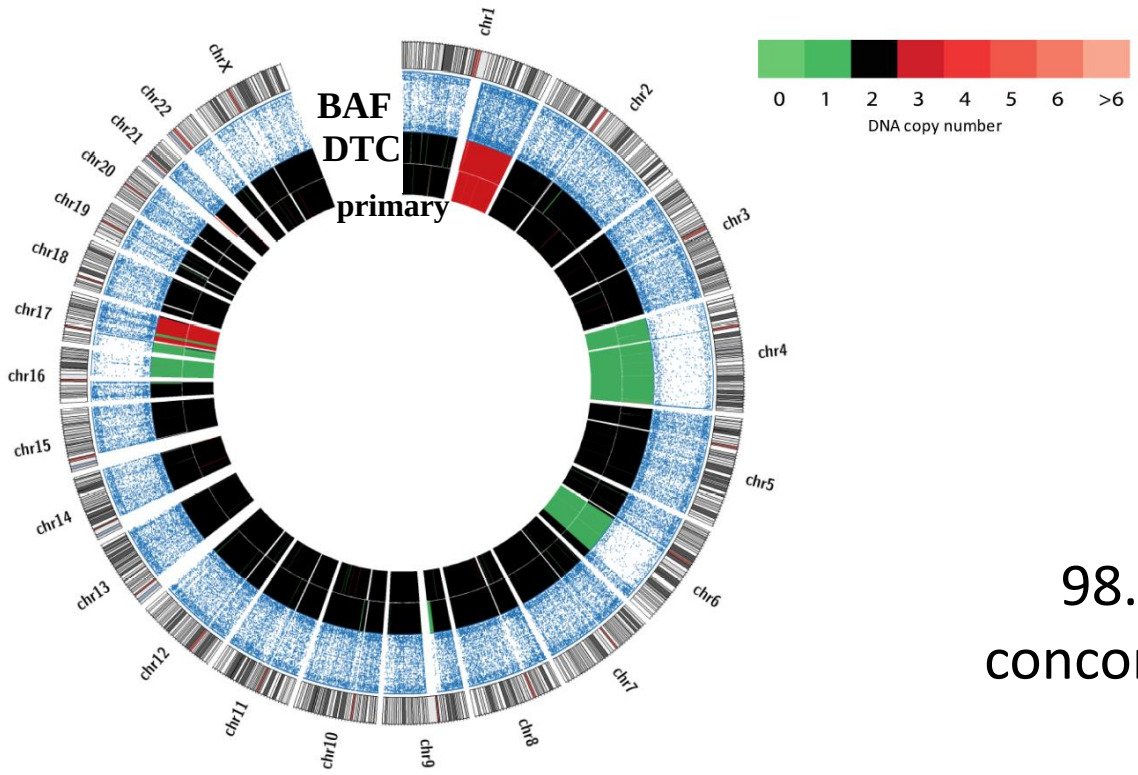
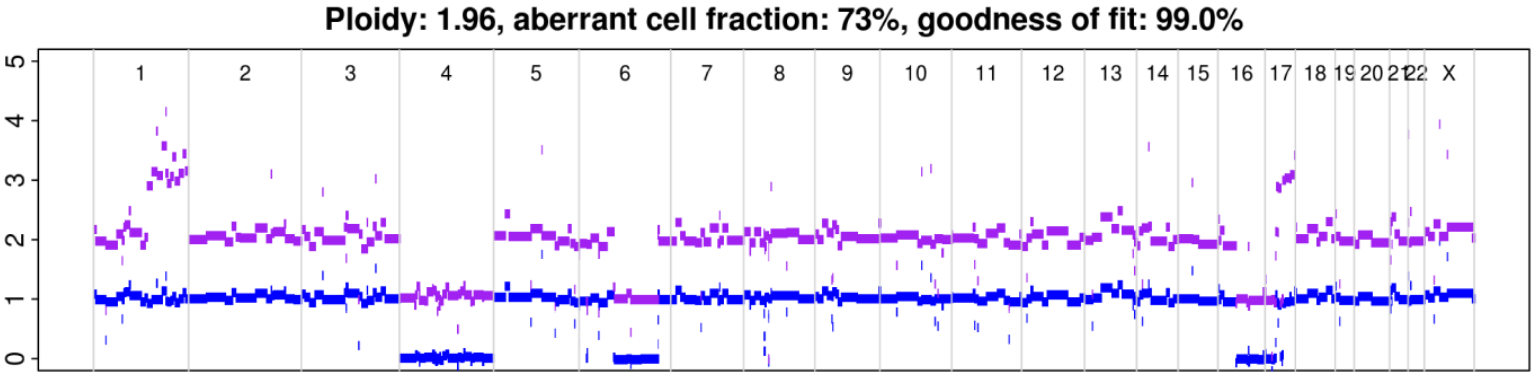


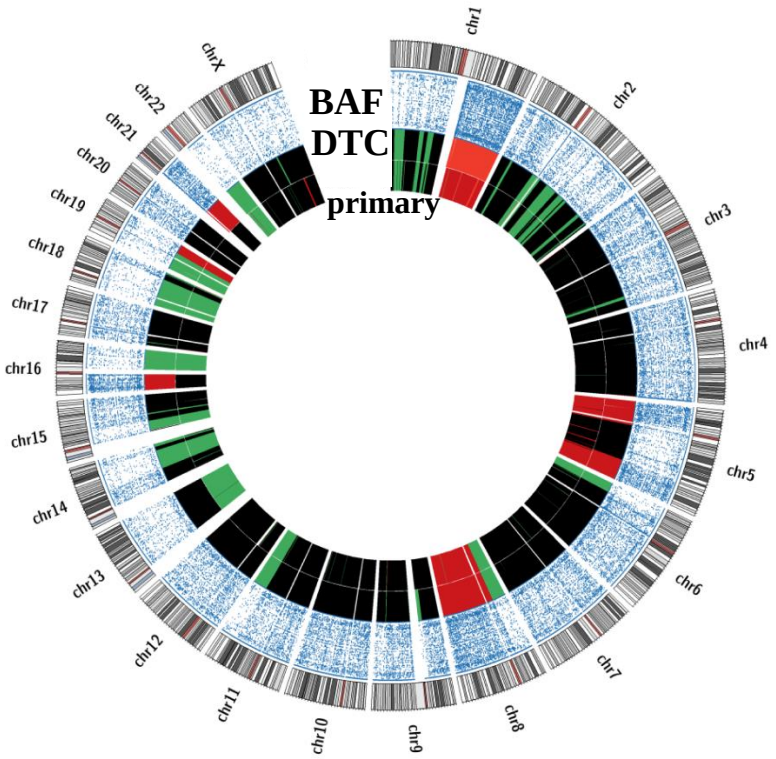
Sequencing disseminated tumour cells

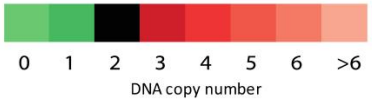


98.6 %
concordance

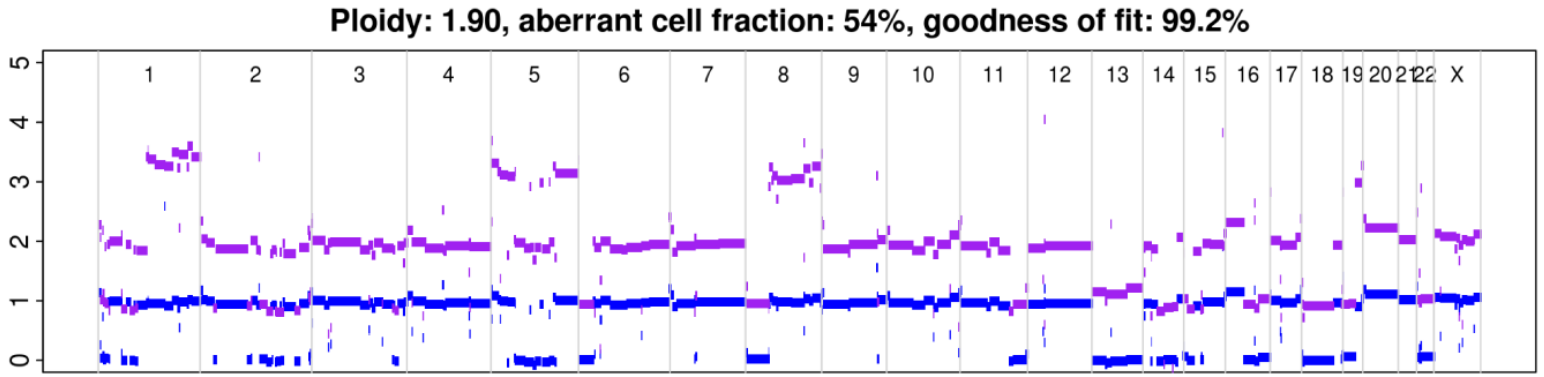


Sequencing disseminated tumour cells





89.4 %
concordance



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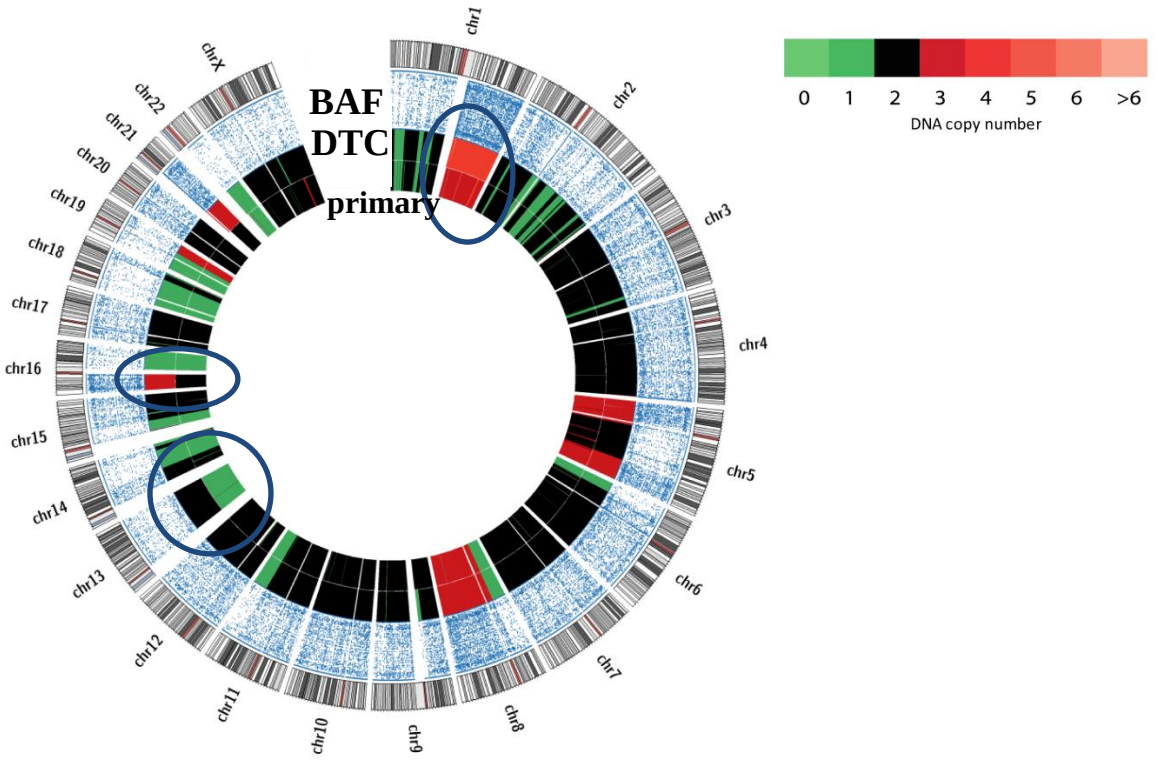

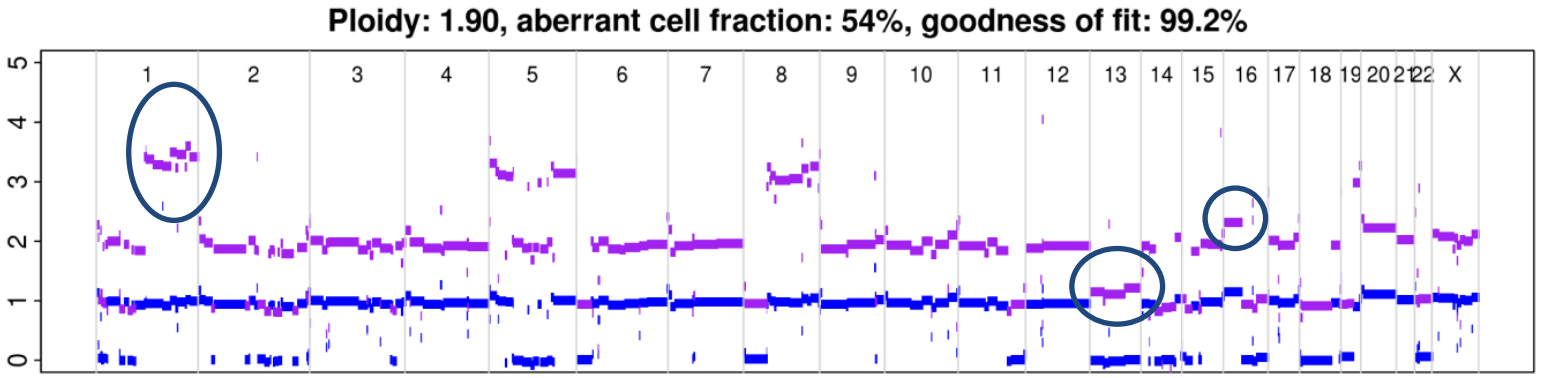

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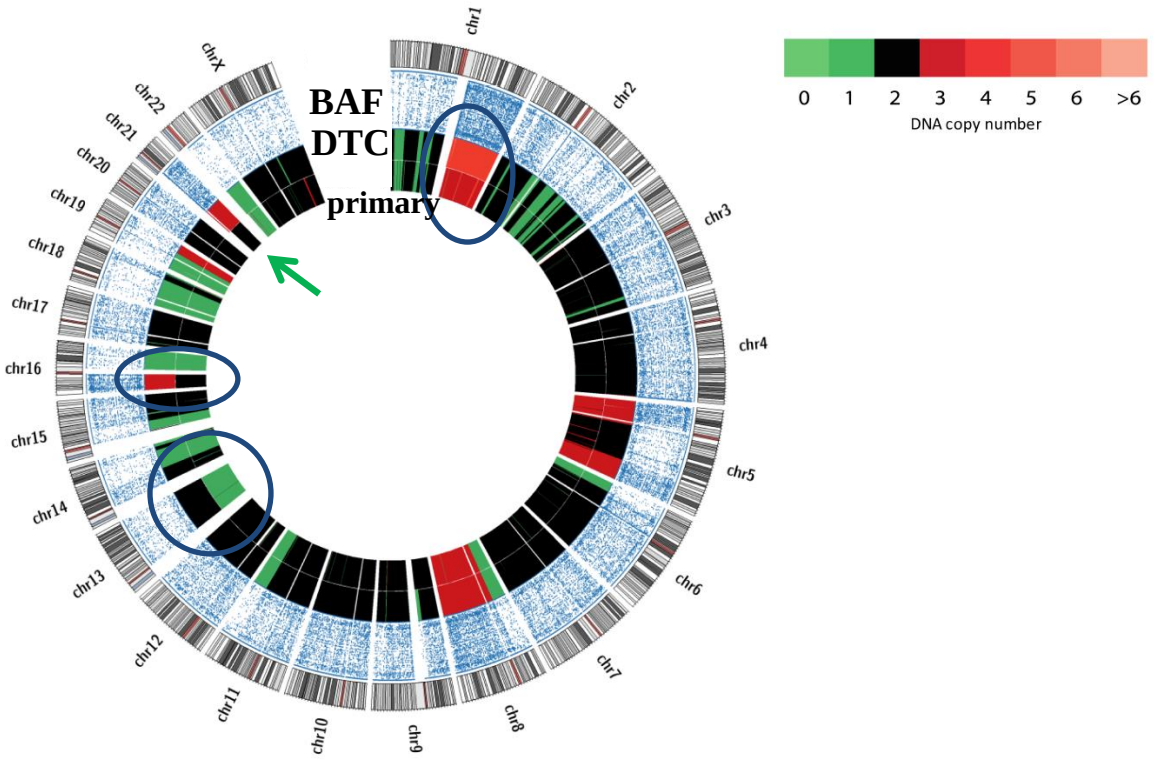

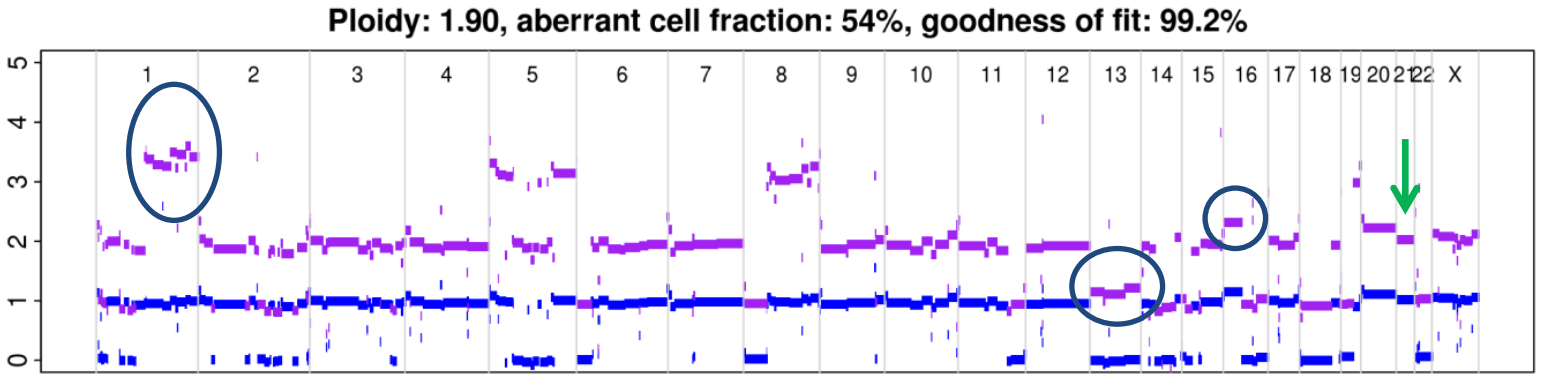

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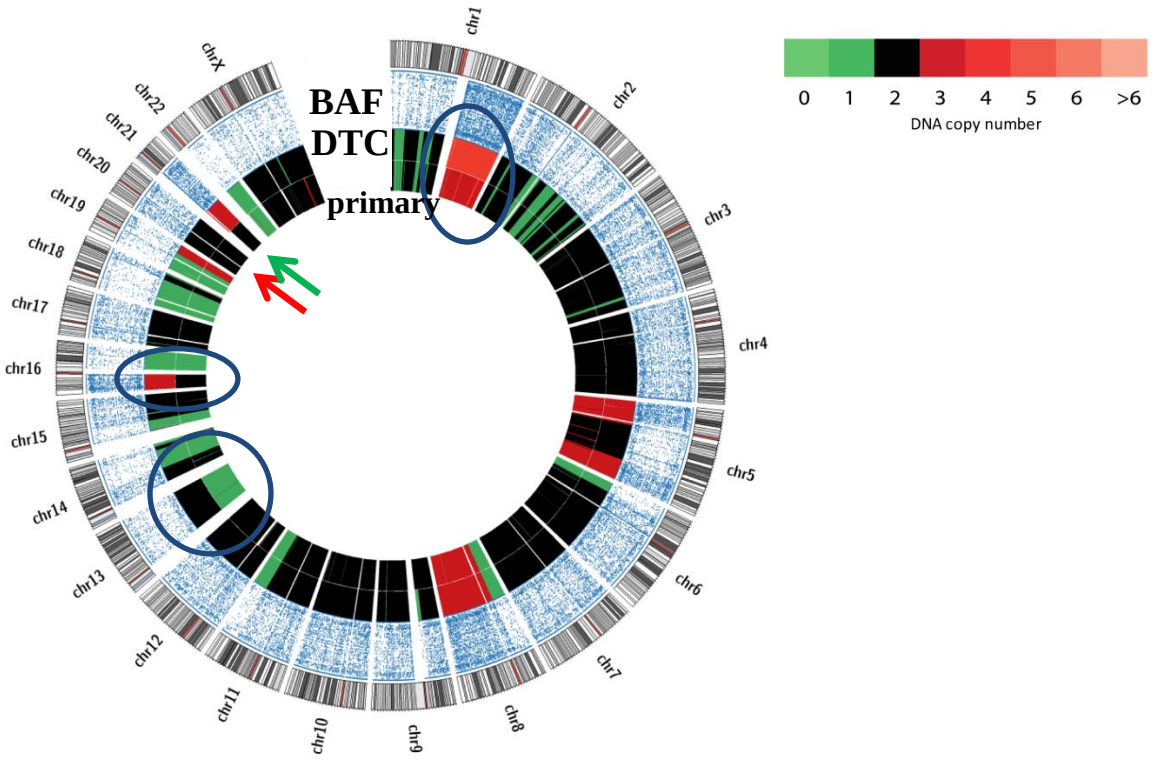
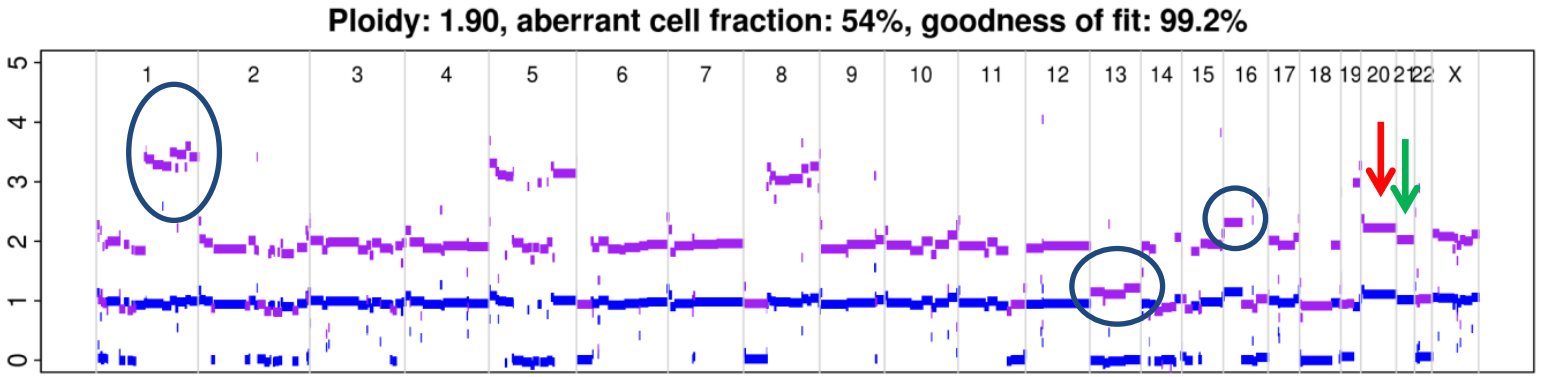




Phylogeny inference

MRCA primary tumour

+1q, +13, +16p

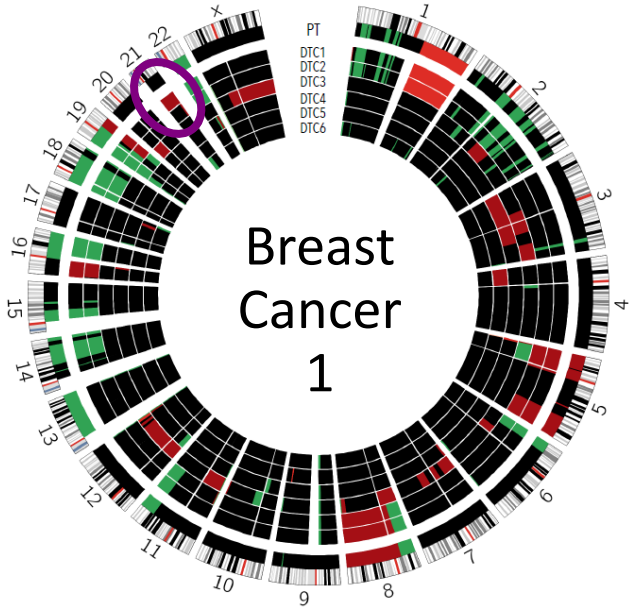
+20

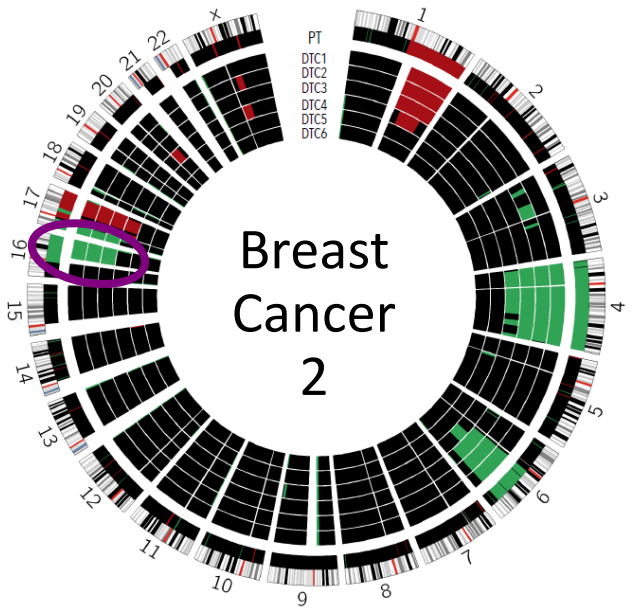
Subclones primary tumour

+21

DTC

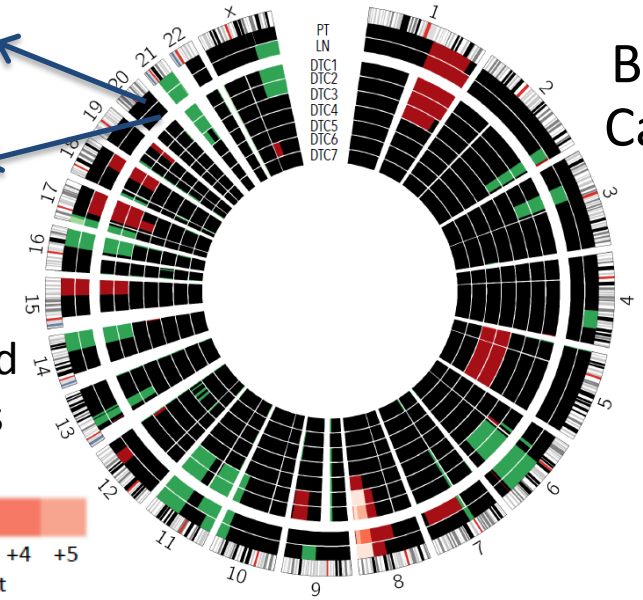
Similarities and differences between DTCs





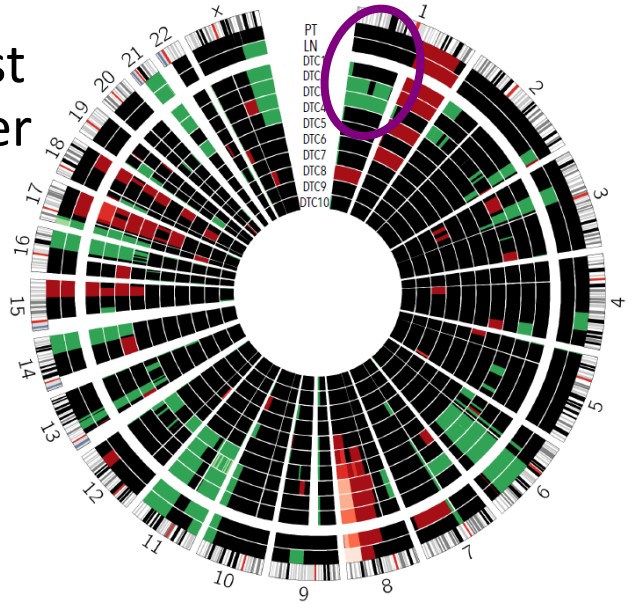
primary

lymph node metastasis



DTCs isolated at diagnosis

Breast Cancer 3



DTCs isolated three years after diagnosis

Conclusions

- **Molecular archeology of cancer**:
  - **Disentangle the subclonal architecture and life history of tumours** from one cancer sample
  - **Track evolution** of clones and subclones over time and space
- Single cell sequencing:
  - Obtain **accurate copy number profiles**
  - **Infer phylogeny** of single tumour cells and DTCs
  - Allows to see **changes over one cell cycle**

Thank you!

Cancer Genome Project,
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Andy Futreal

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Serena Nik-Zainal
Lucy Yates
Gunes Gundem
Helen Davies

And many others!

The Breast Cancer Working Group of the International Cancer Genome Consortium

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Christos Sotiriou

Genomic ventures to explore tumour development and intra-tumour heterogeneity in breast cancer

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We are recruiting!

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