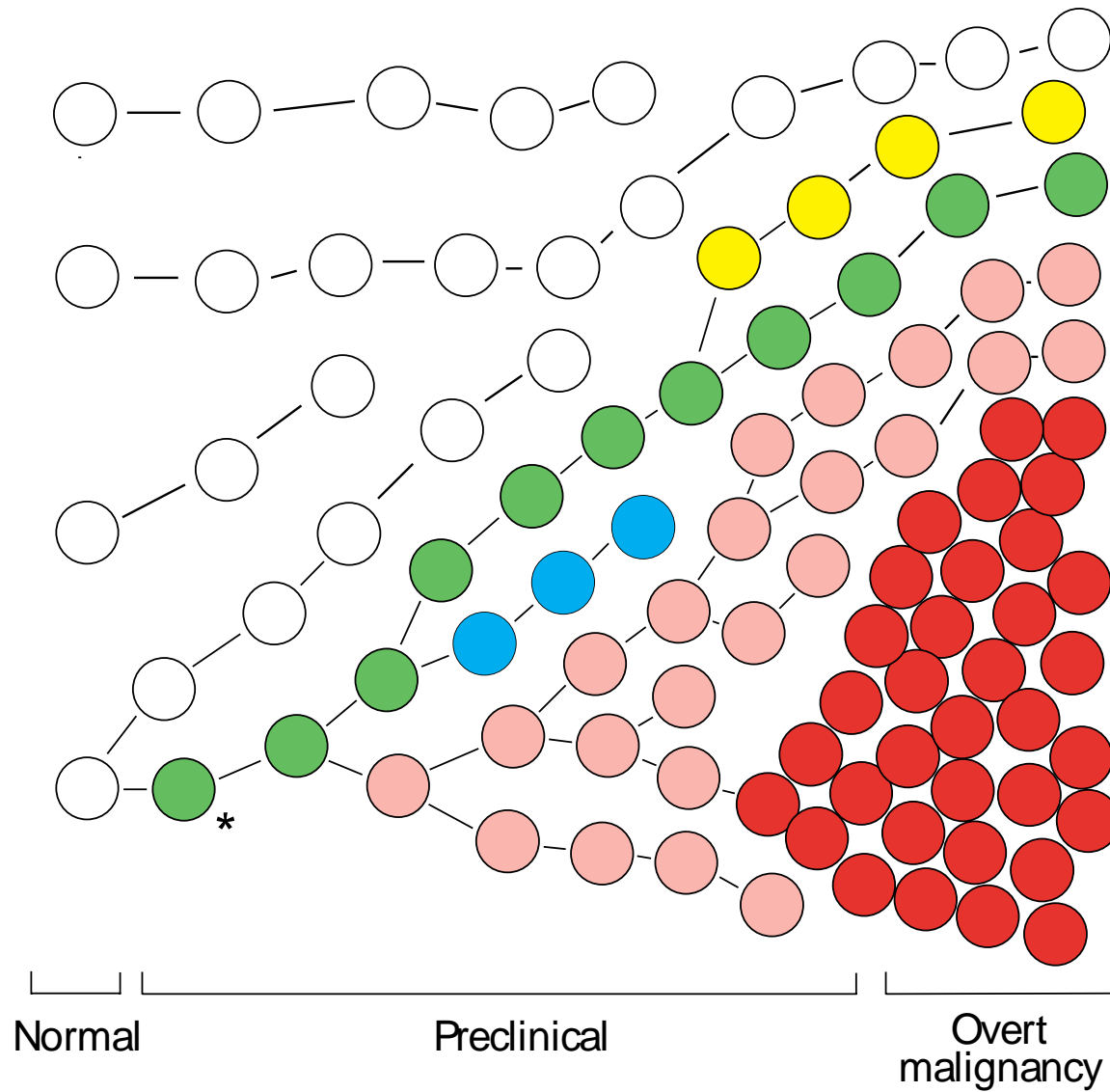


# Interrogating cancer genomes with massively parallel sequencing

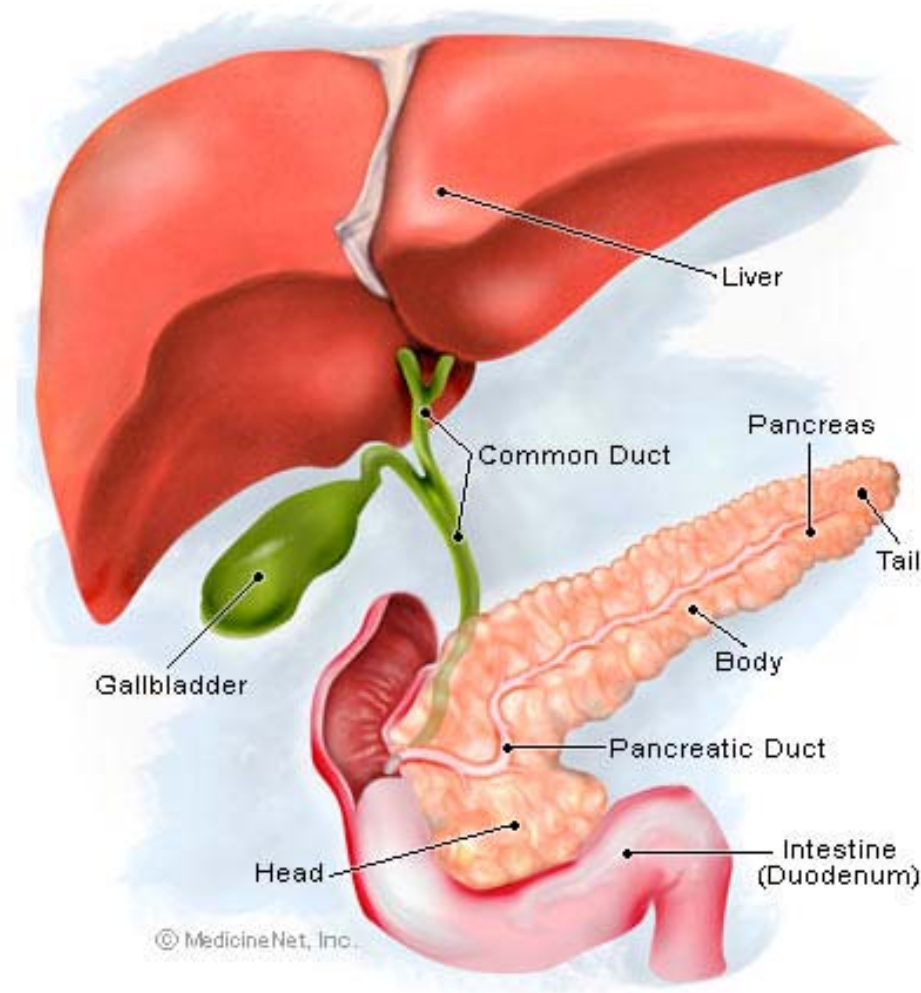
Peter Campbell



# Clonal progression in cancer

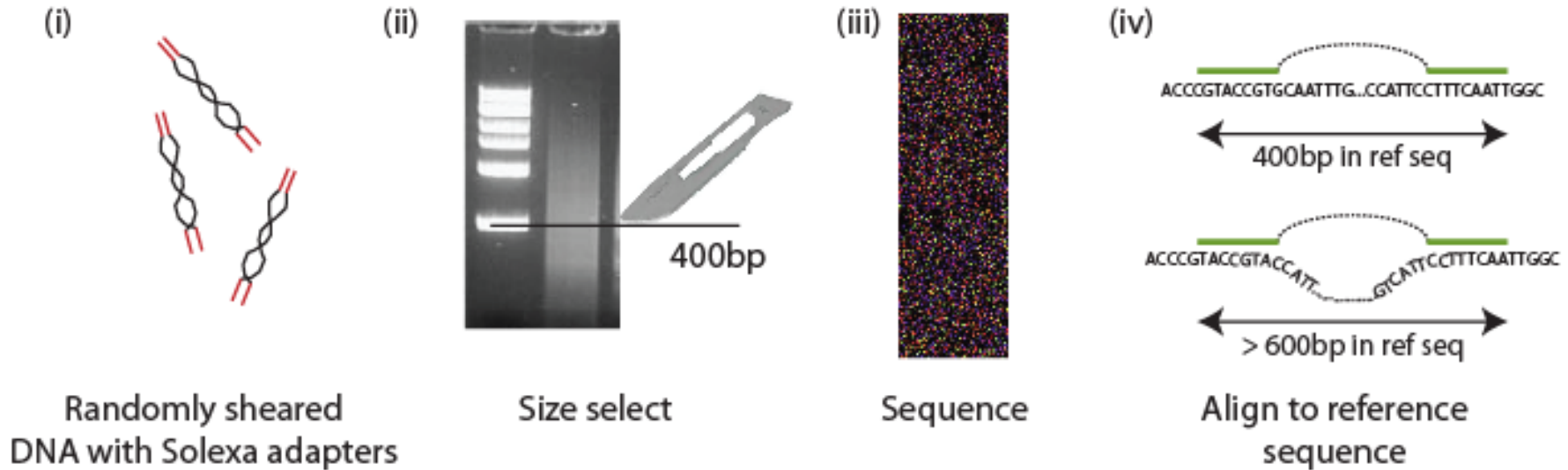


# Spread of pancreatic cancer



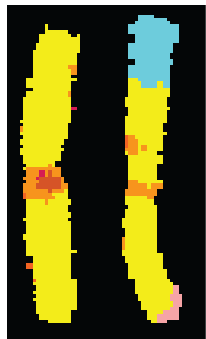
From [www.curepancreaticcancer.com](http://www.curepancreaticcancer.com)

# Protocol



- Correctly mapping reads → Copy number analysis  
Point mutations
- Incorrectly mapping reads → Rearrangement analysis

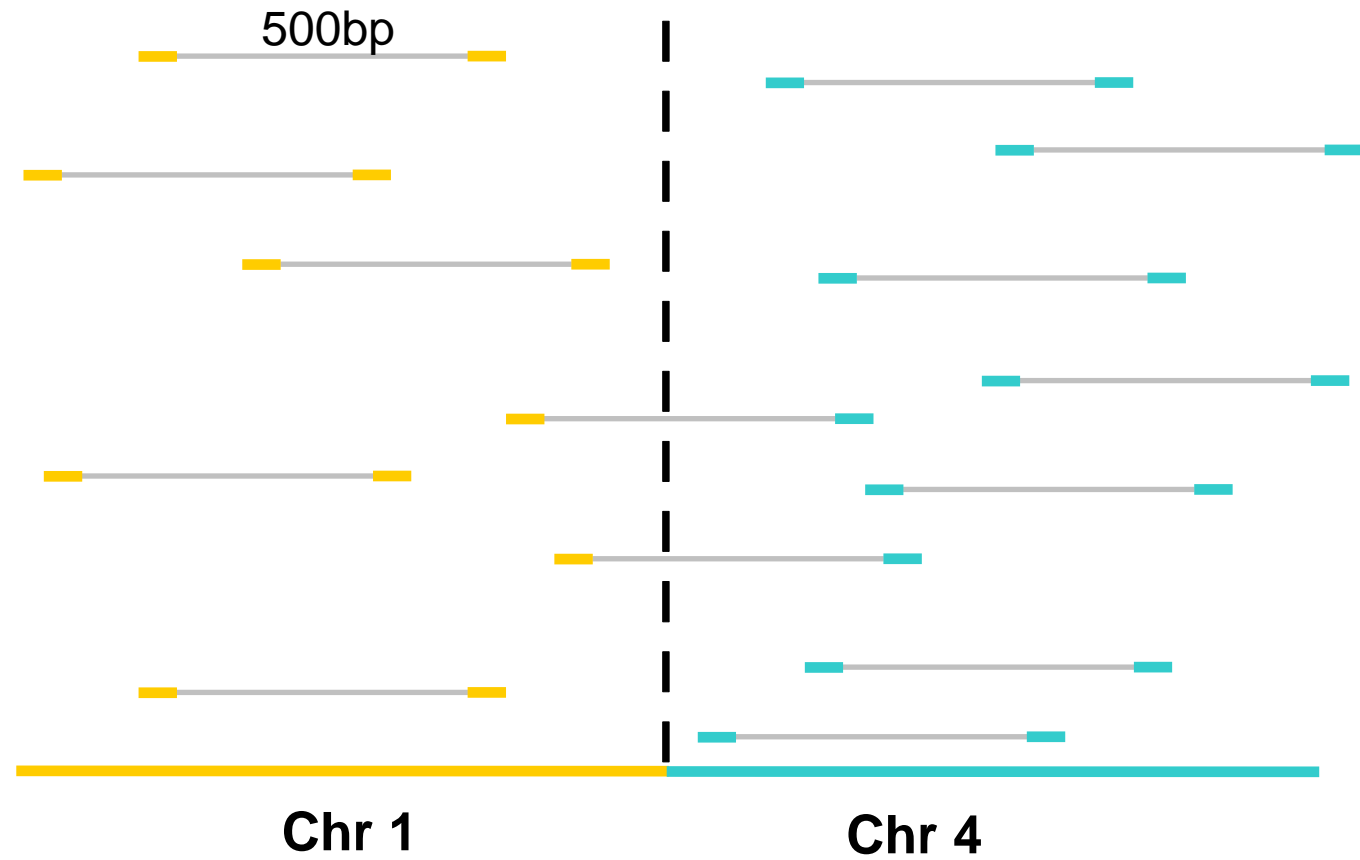
# Paired-end sequencing



Chr 1



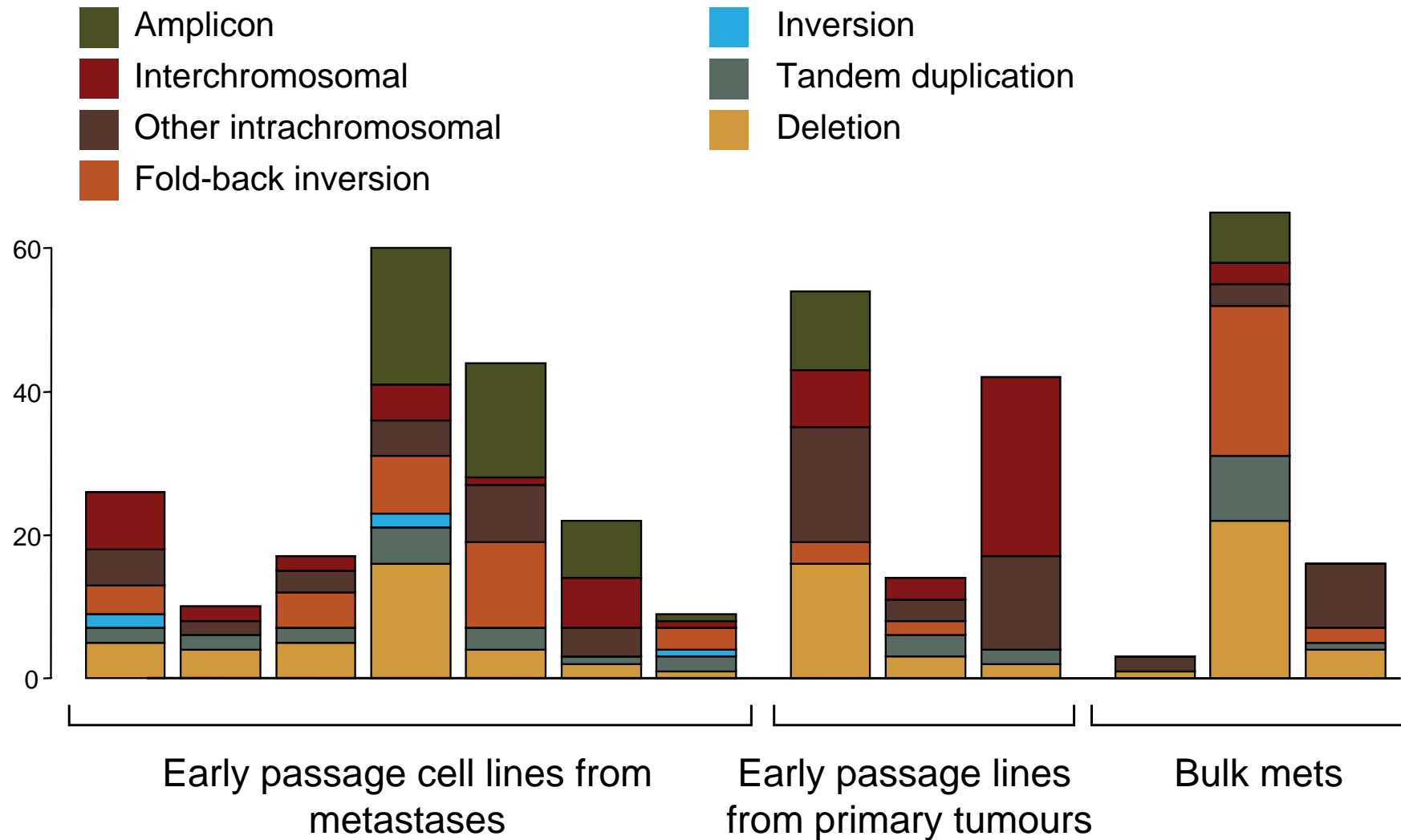
Chr 4



# Outline

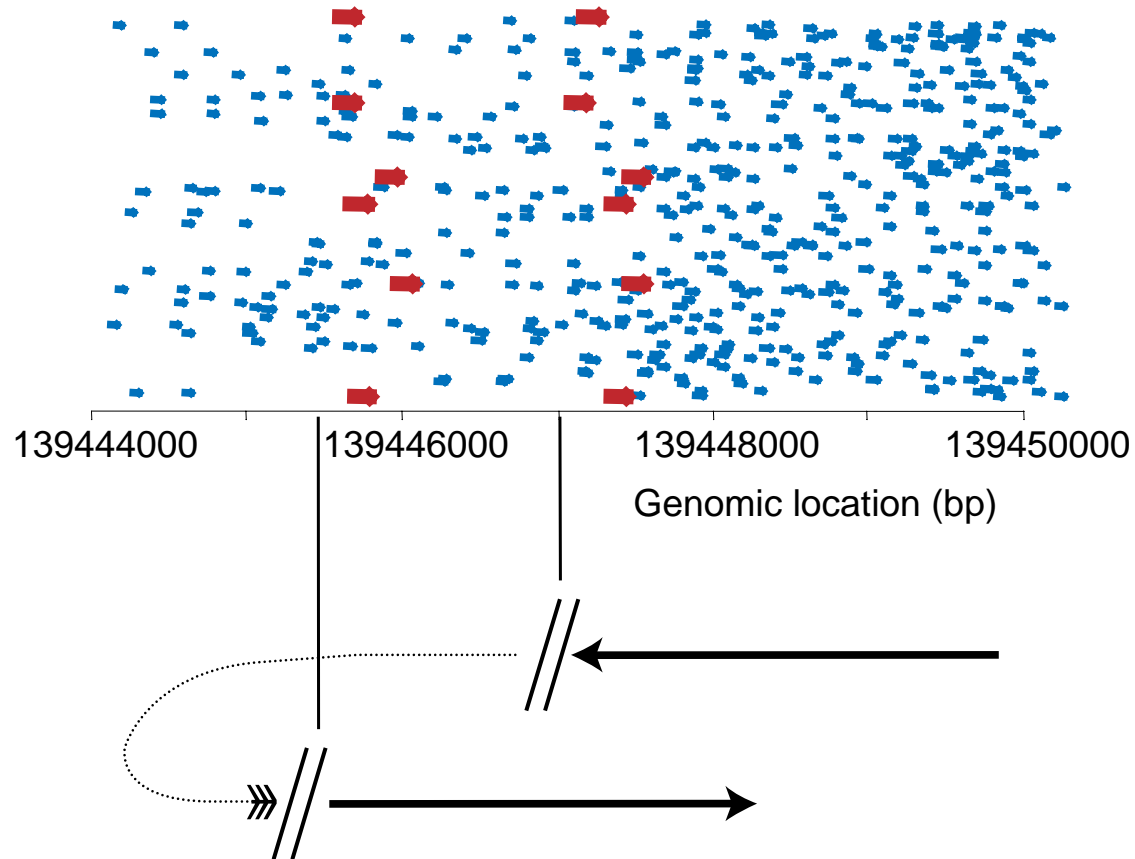
- Patterns of rearrangement in pancreatic cancer
- Phylogenetic studies
- Translational applications

# Comparison across samples



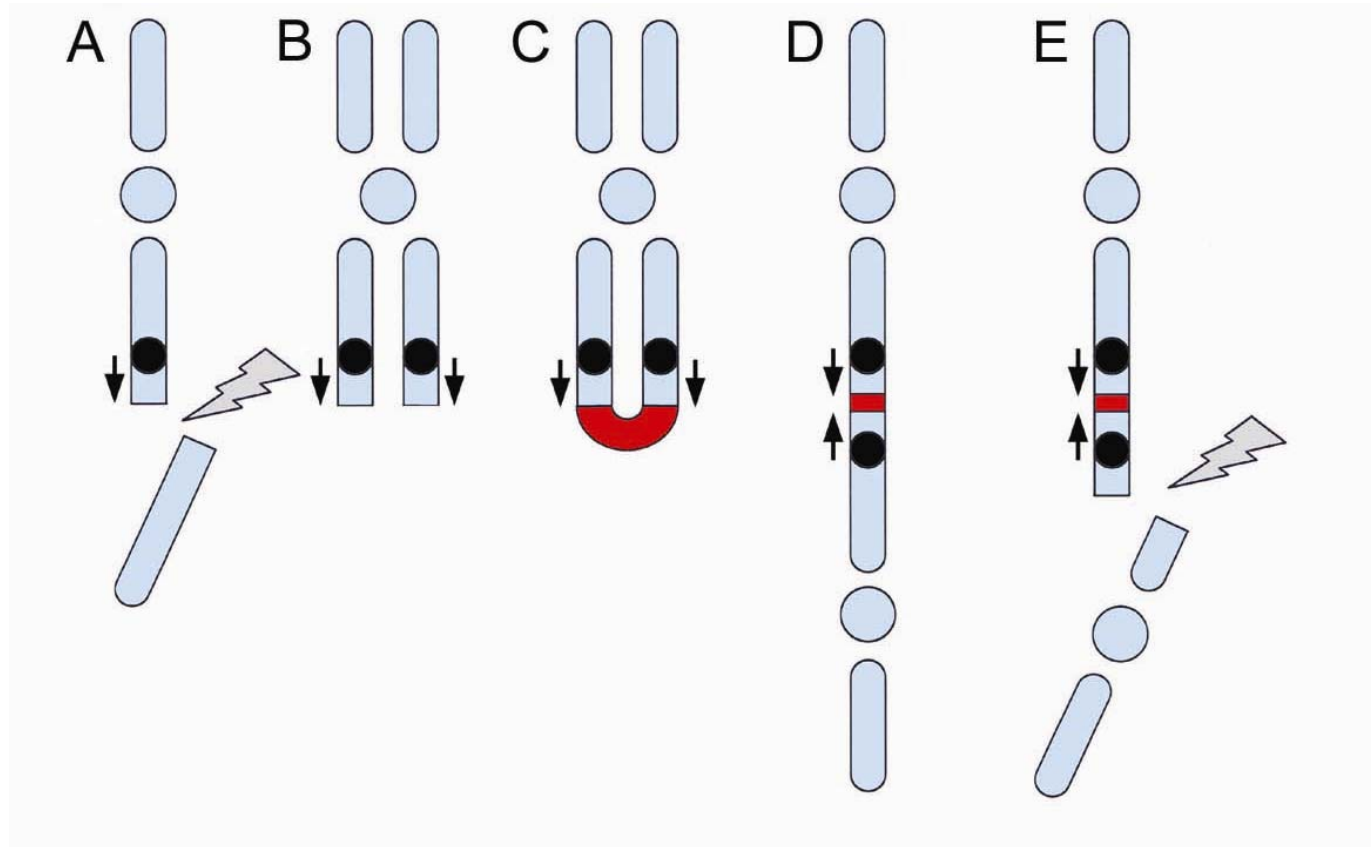
# Fold-back inversions

- Reads mapped correctly
- Ends mapped in inverted orientation

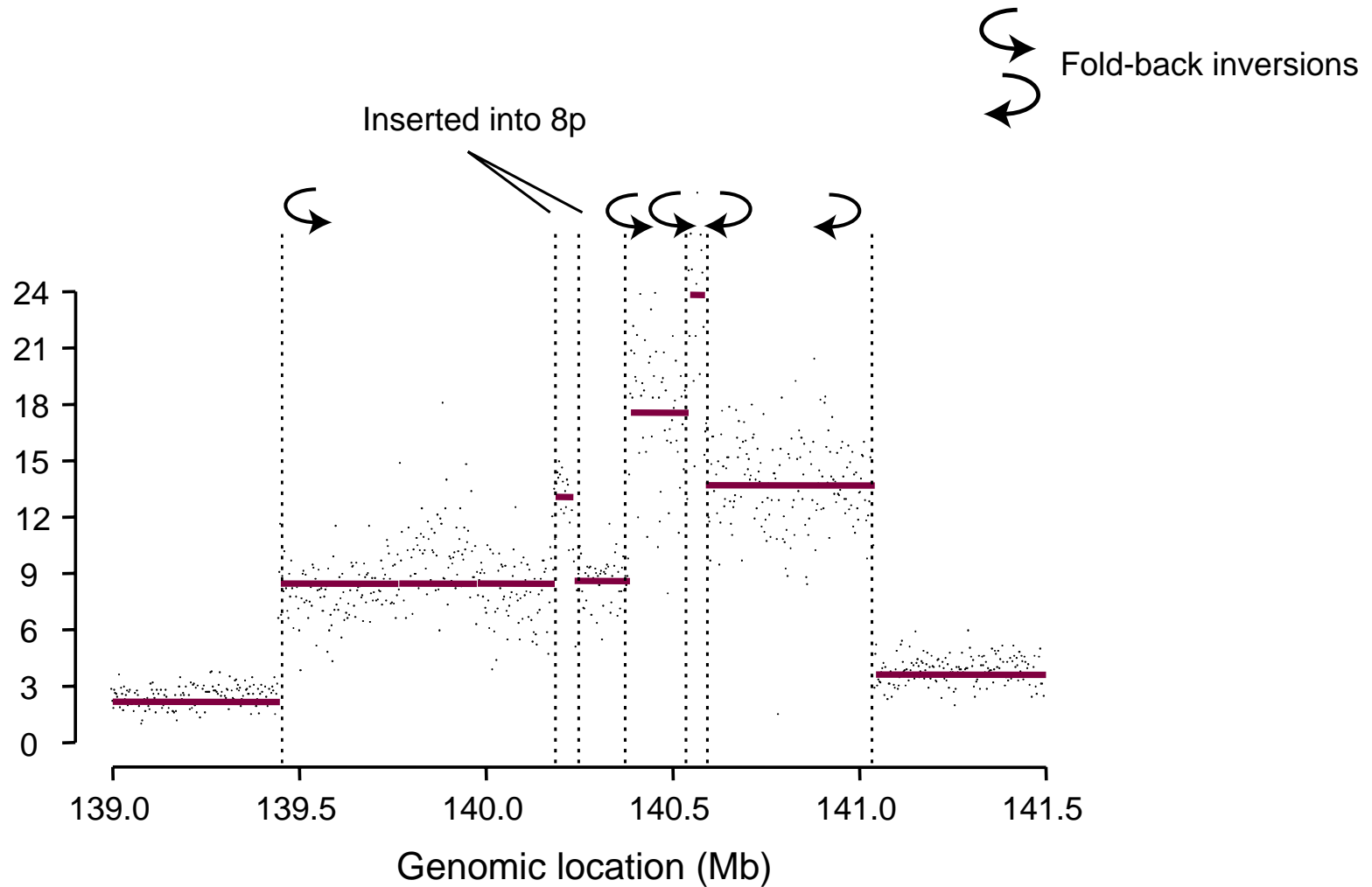




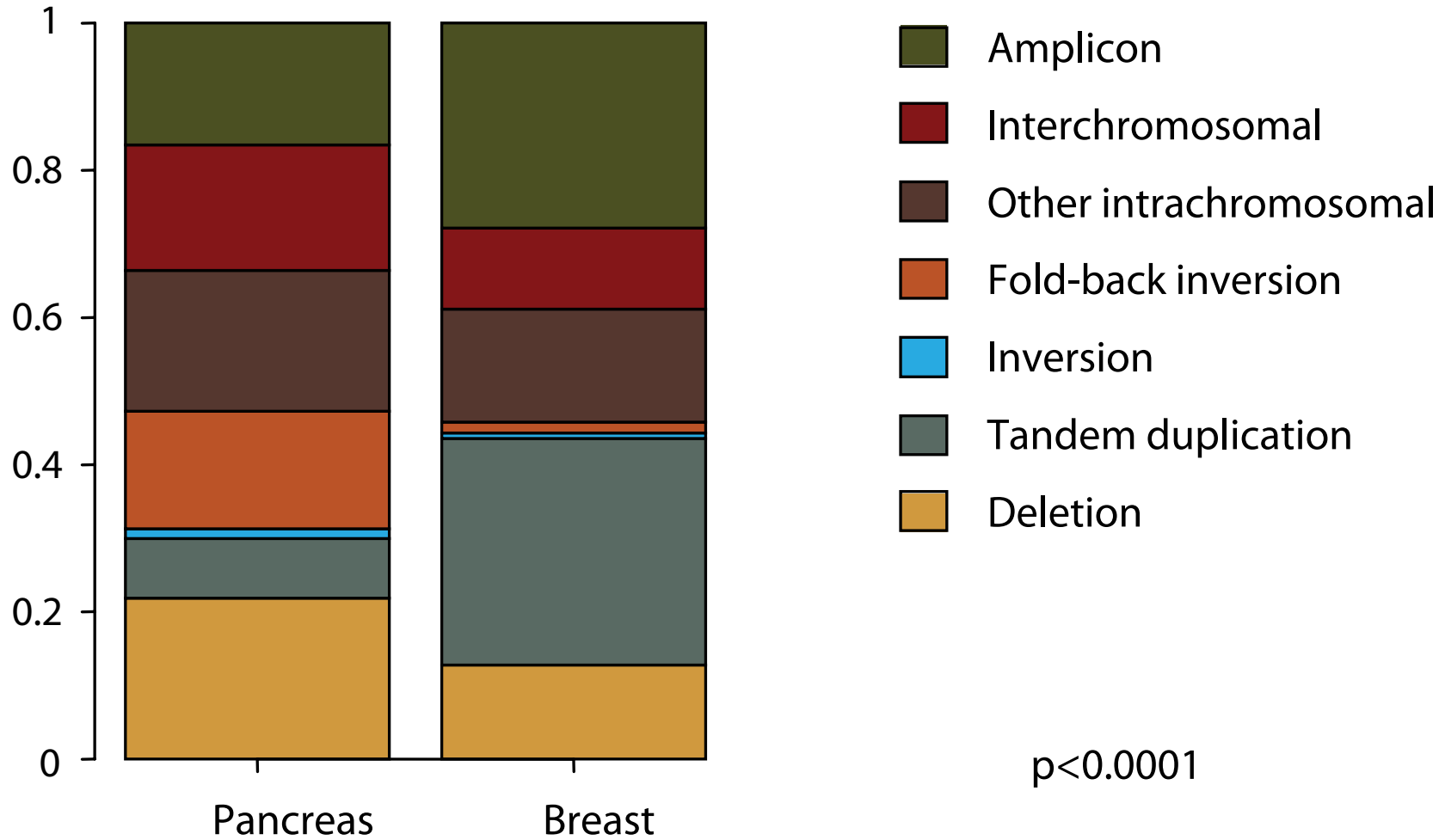
# Breakage-Fusion-Bridge



# Repeated breakage-fusion-bridge



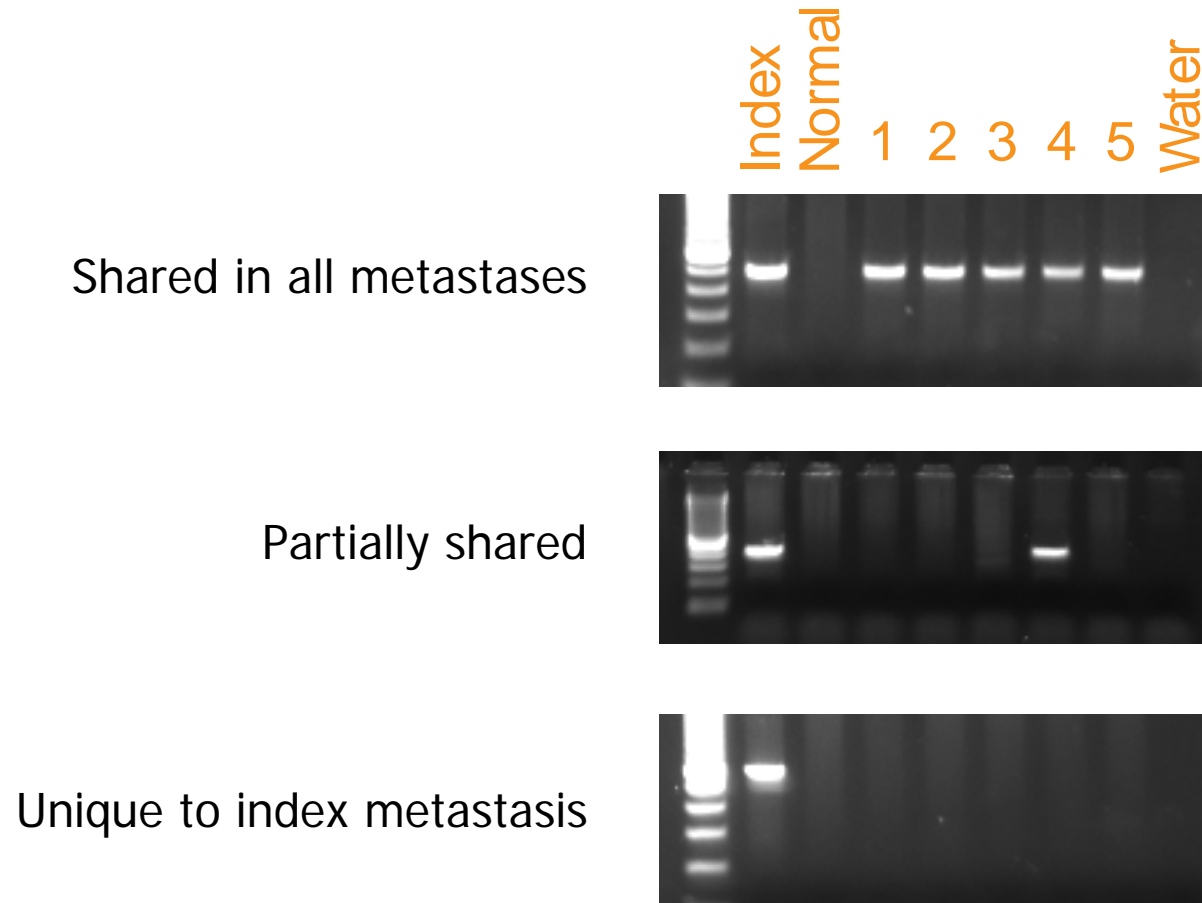
# Comparison with breast cancer



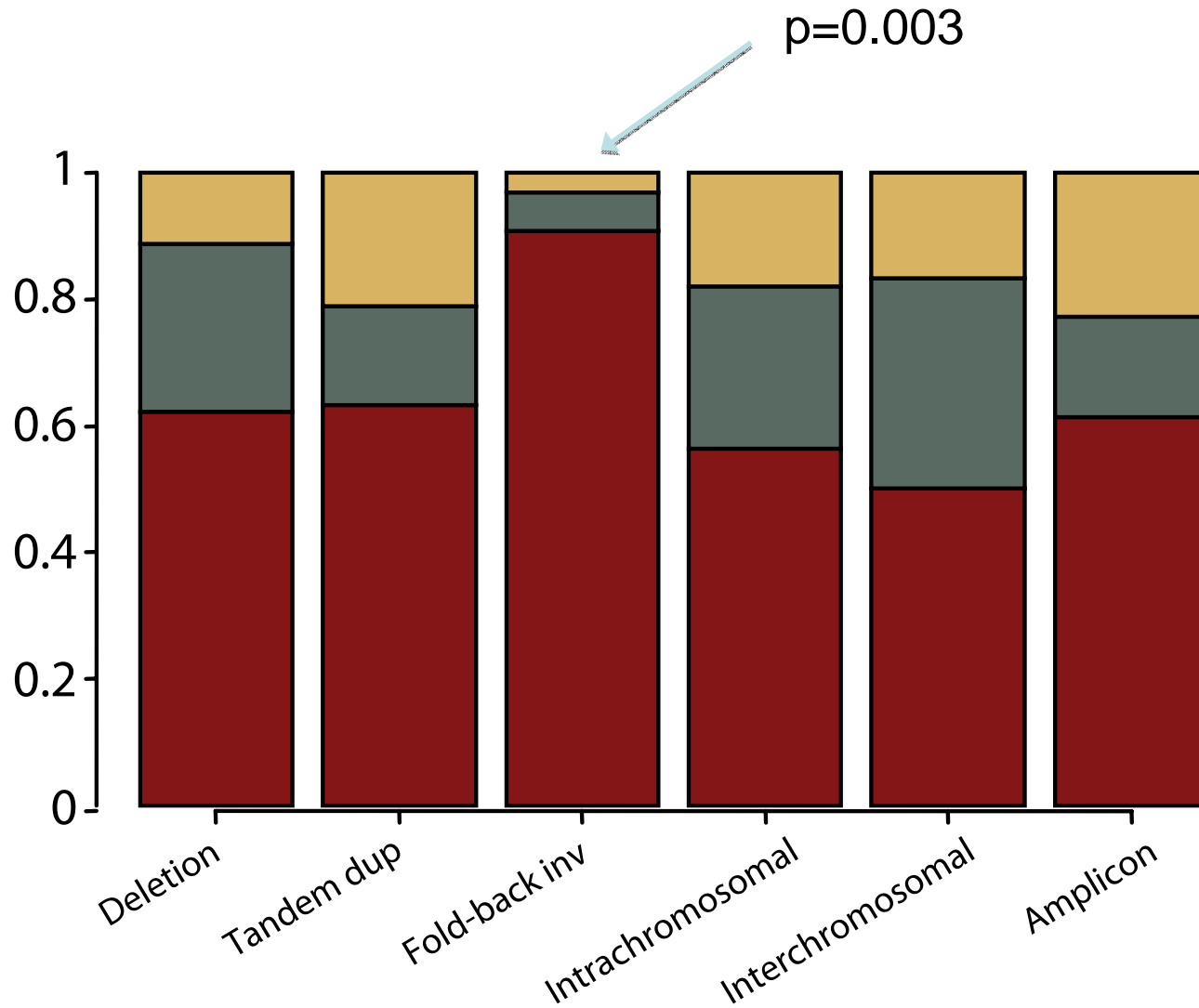
# Outline

- Patterns of rearrangement
- Phylogenetic studies
- Translational applications

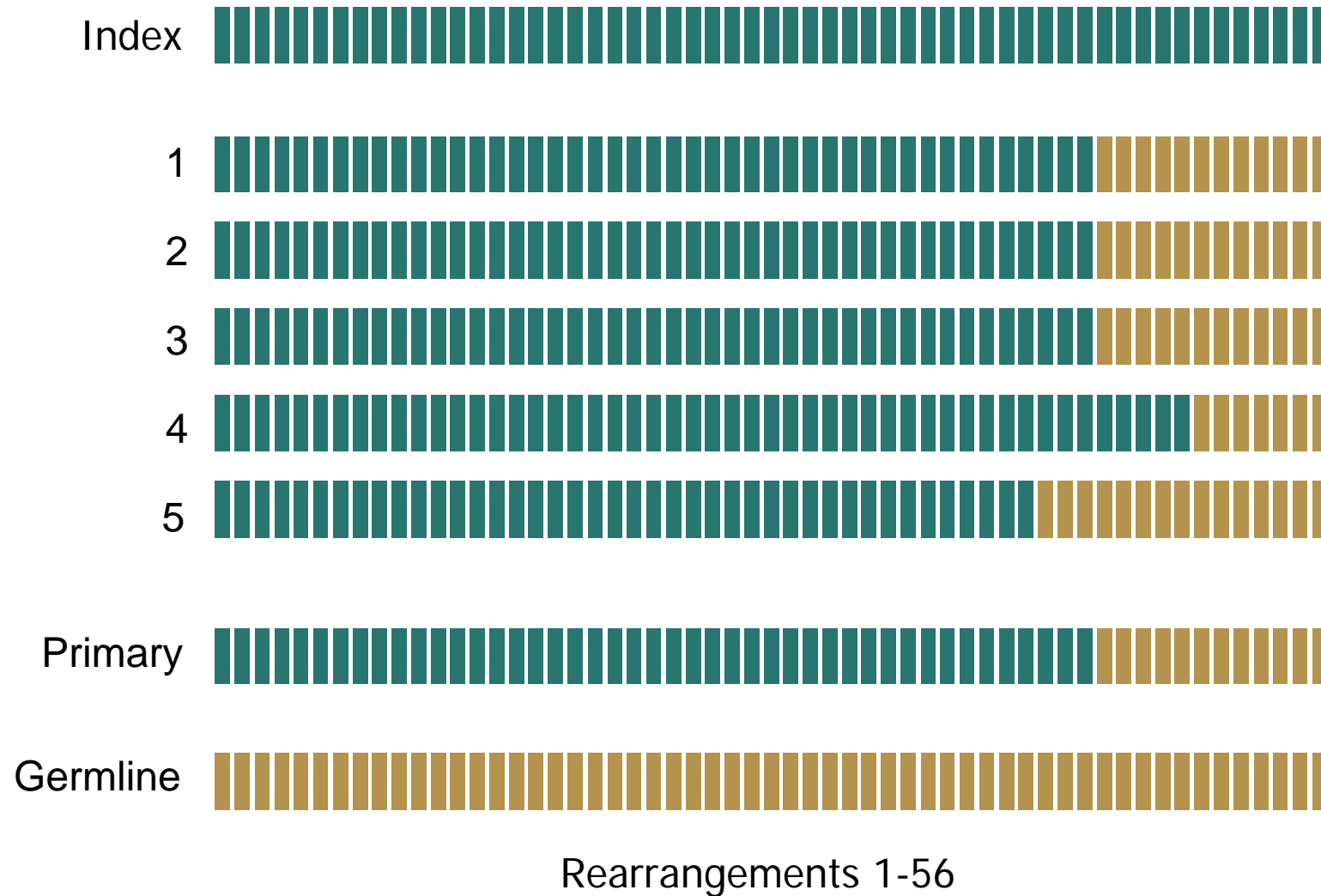
# Dynamics of genomic instability



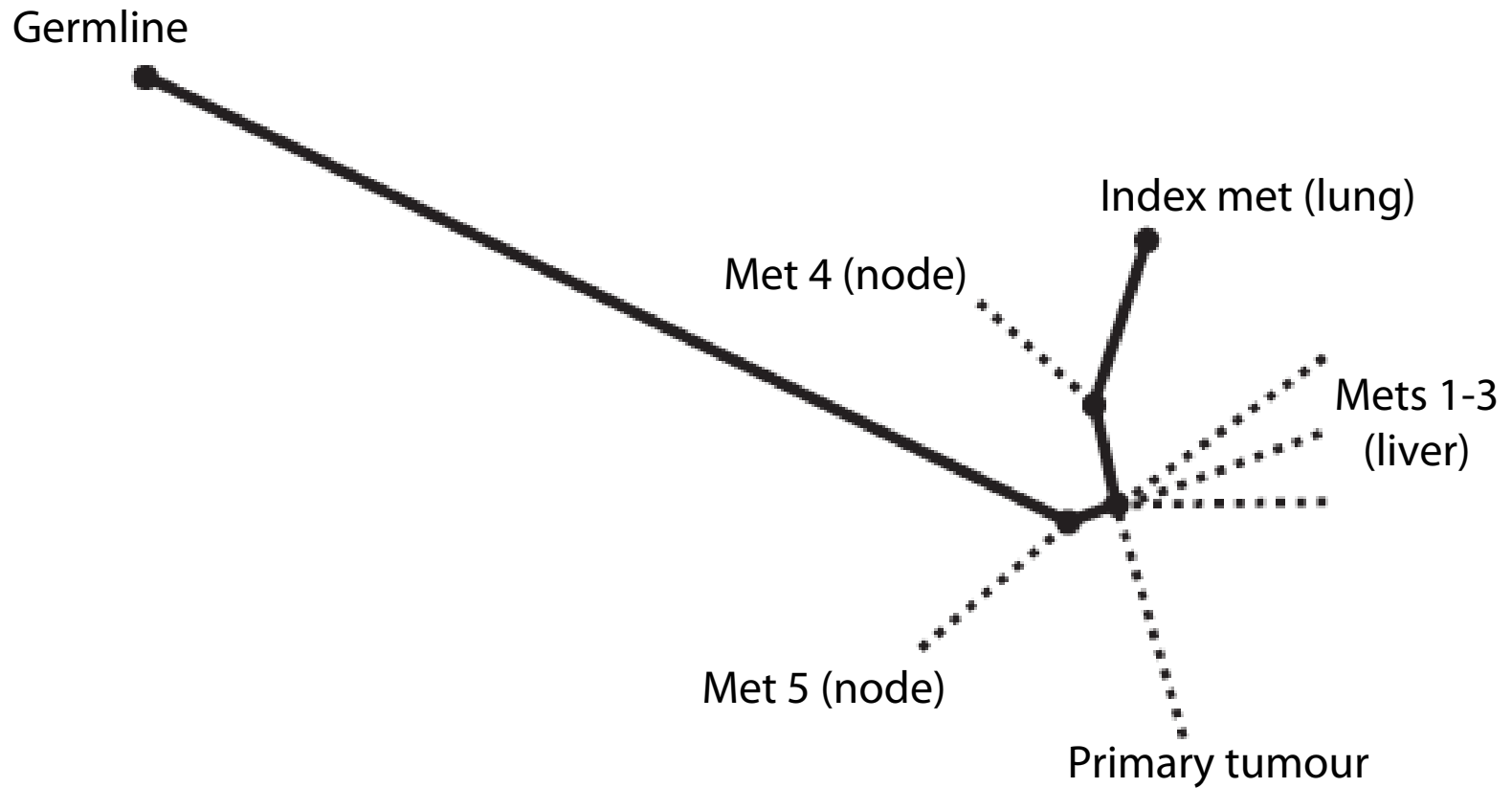
# Types of rearrangement



# Phylogenetic relationships

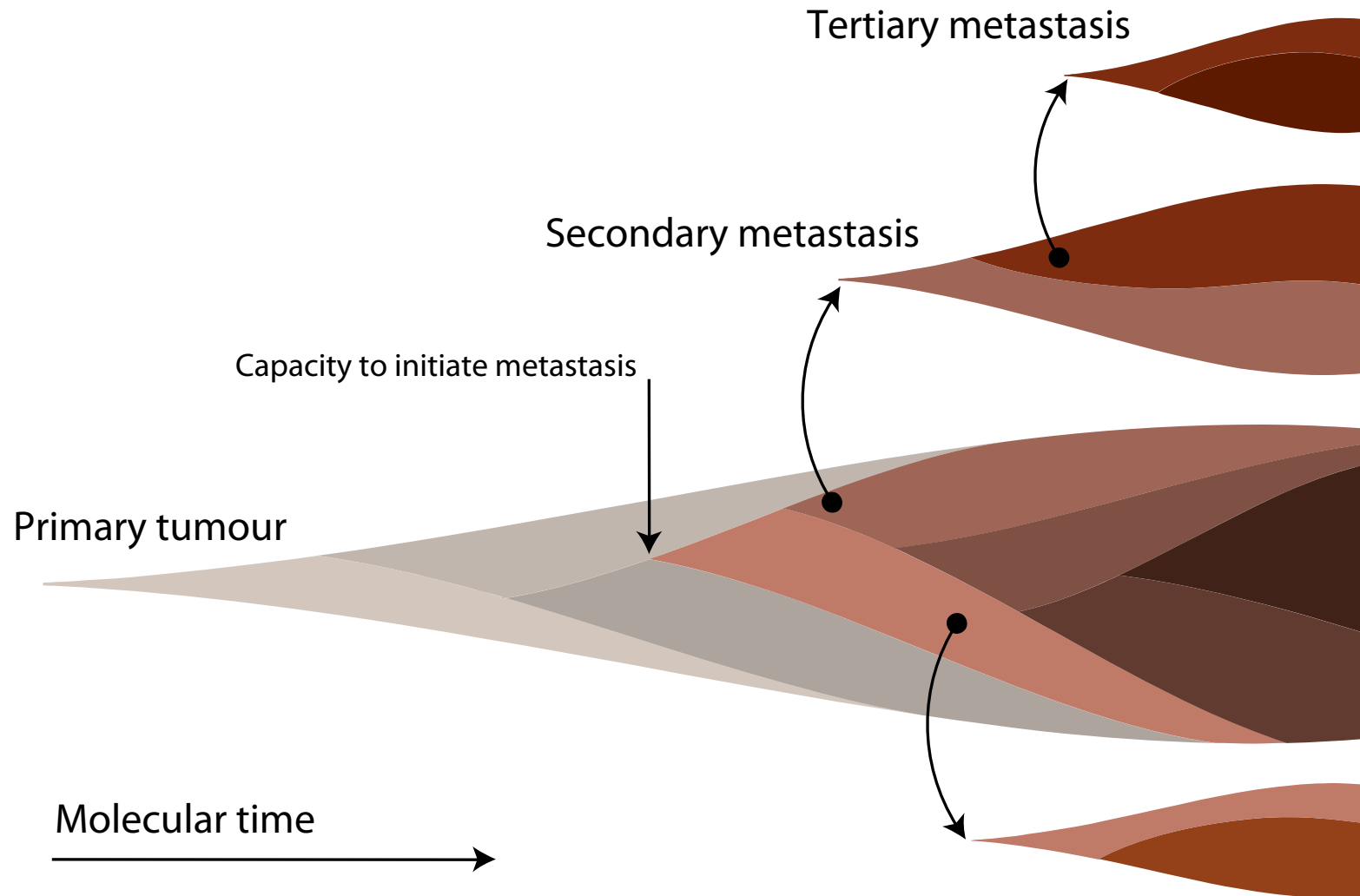


# Phylogenetic tree

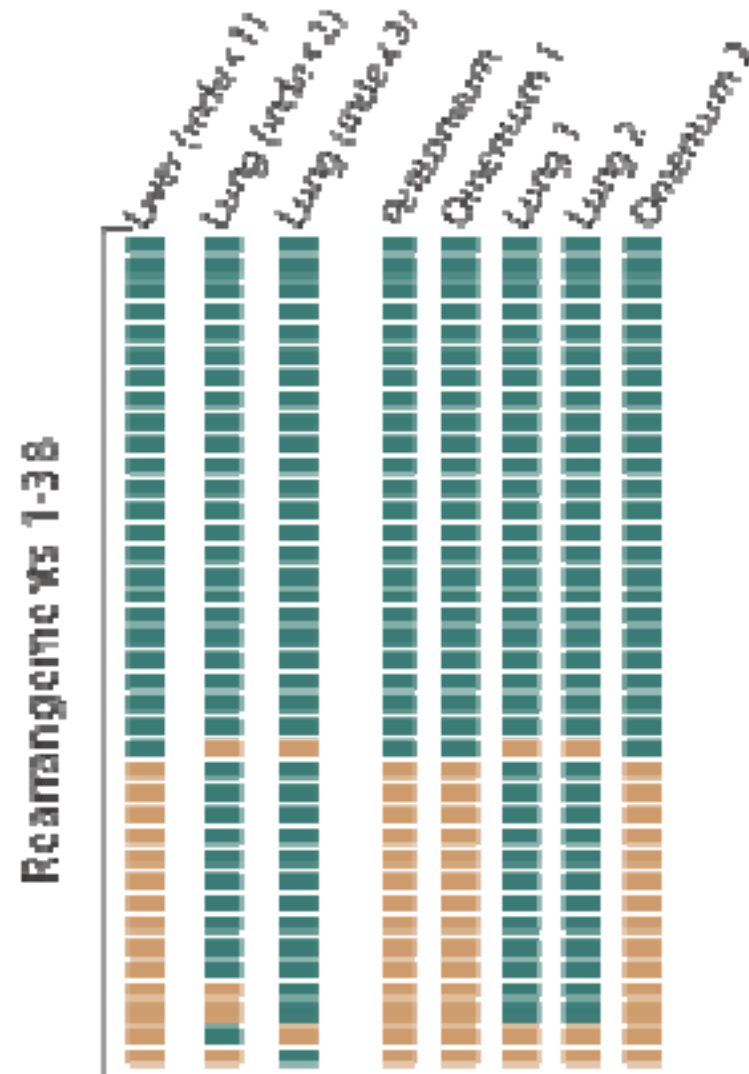




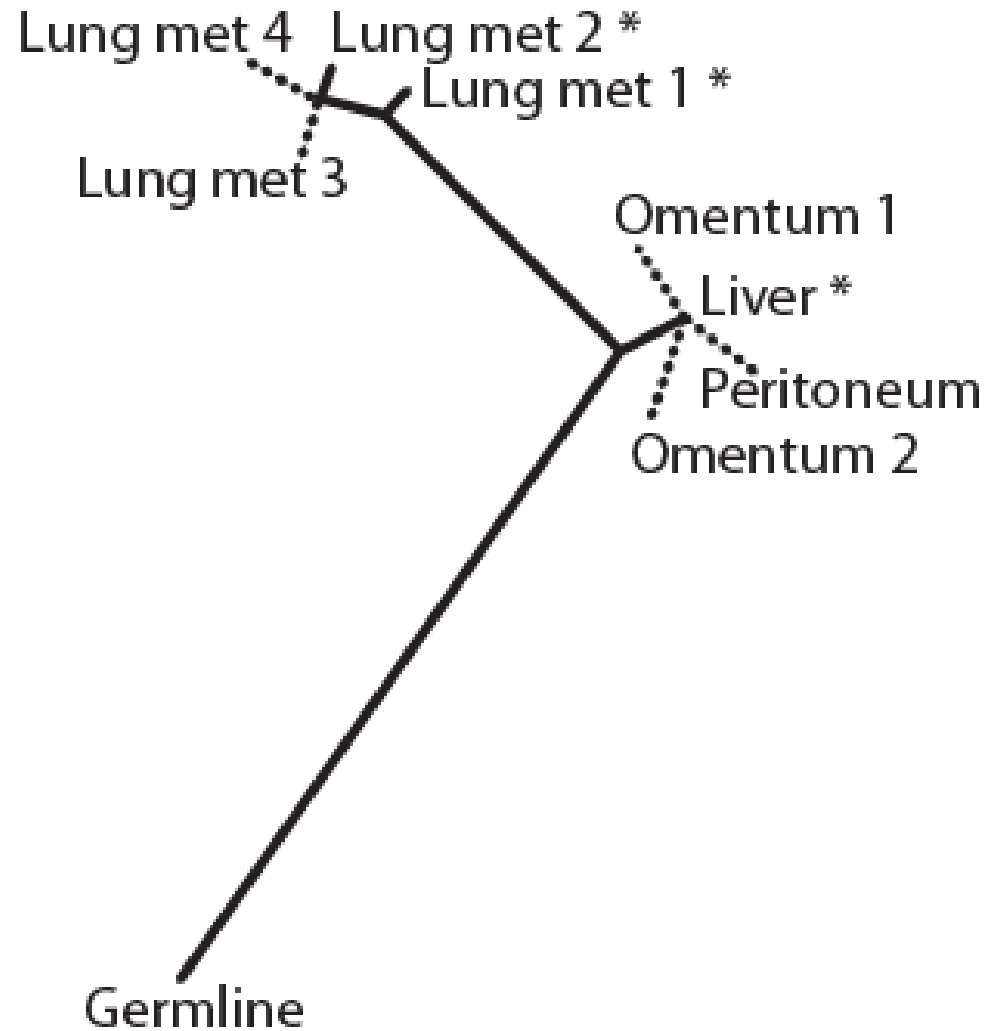
# Dynamics of genomic instability



# Clonal relationships across organs

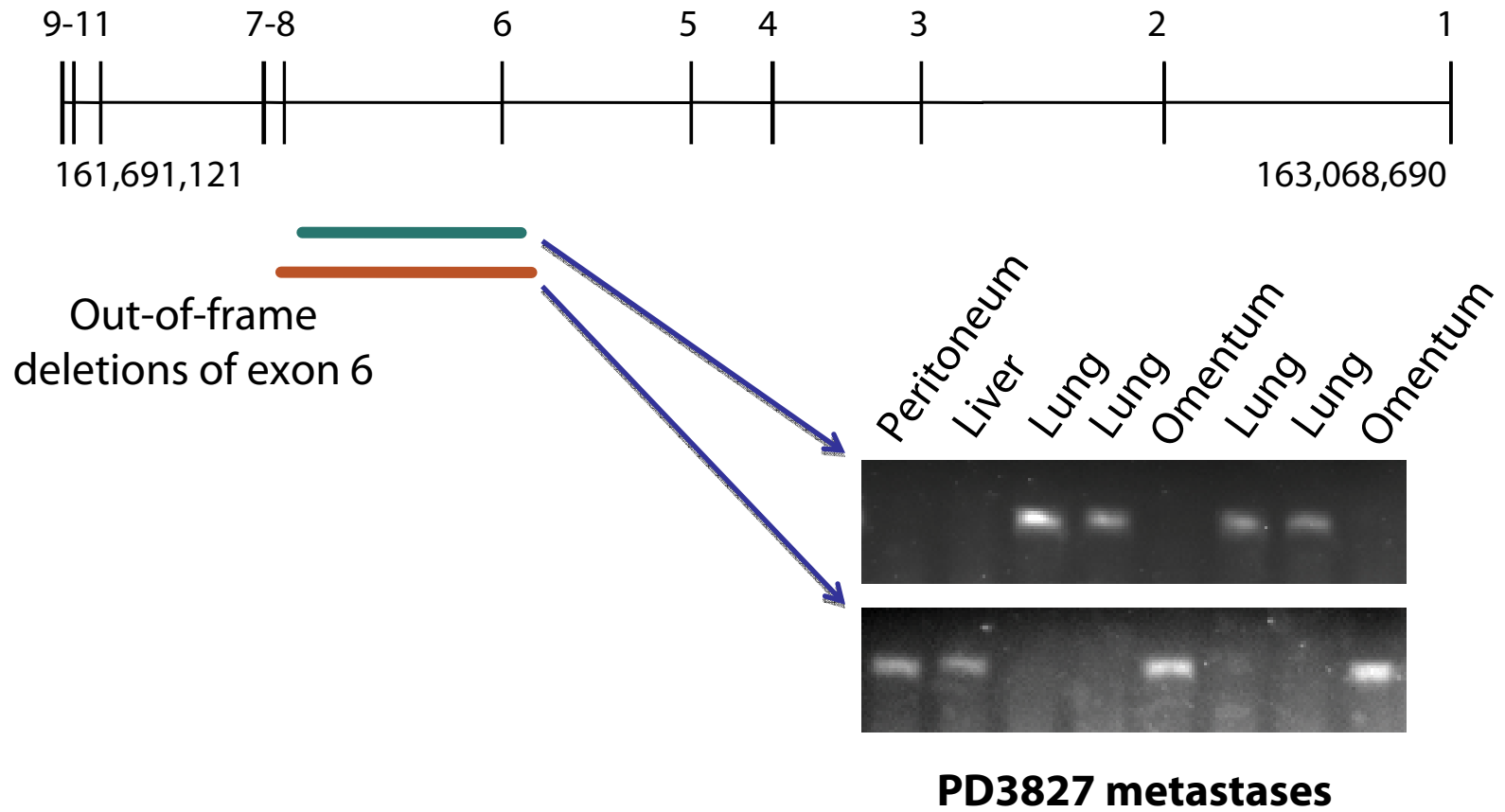


# Organ-specific branches

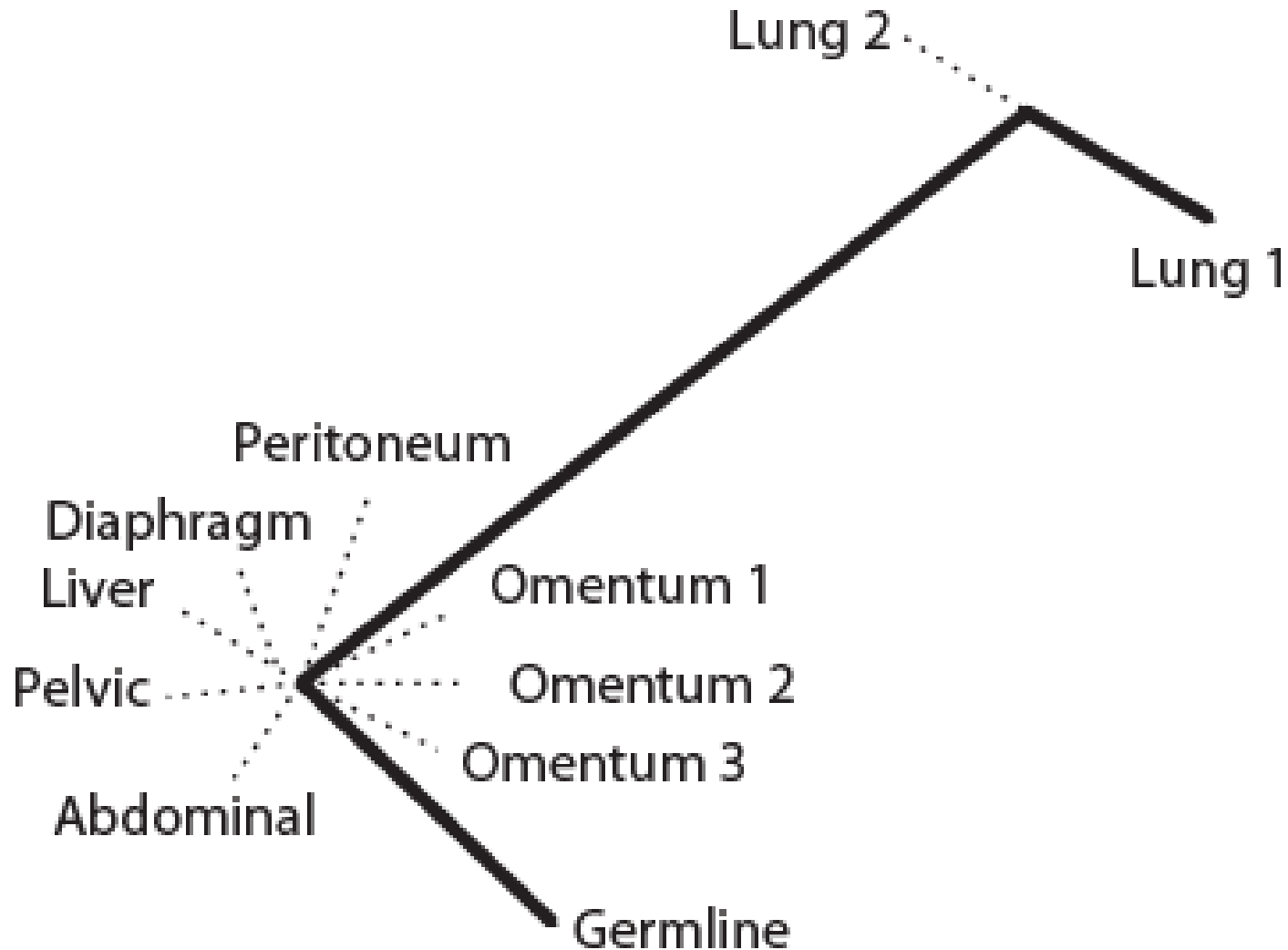


# Convergent evolution

*PARK2*

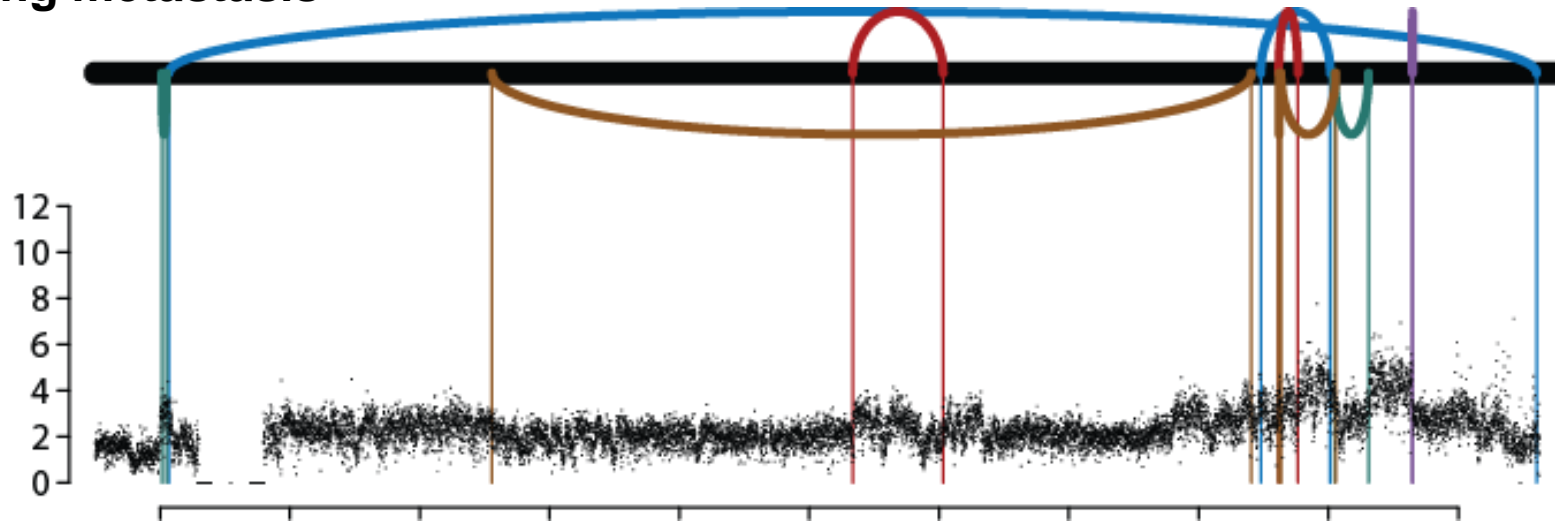


# Organ-specific signature

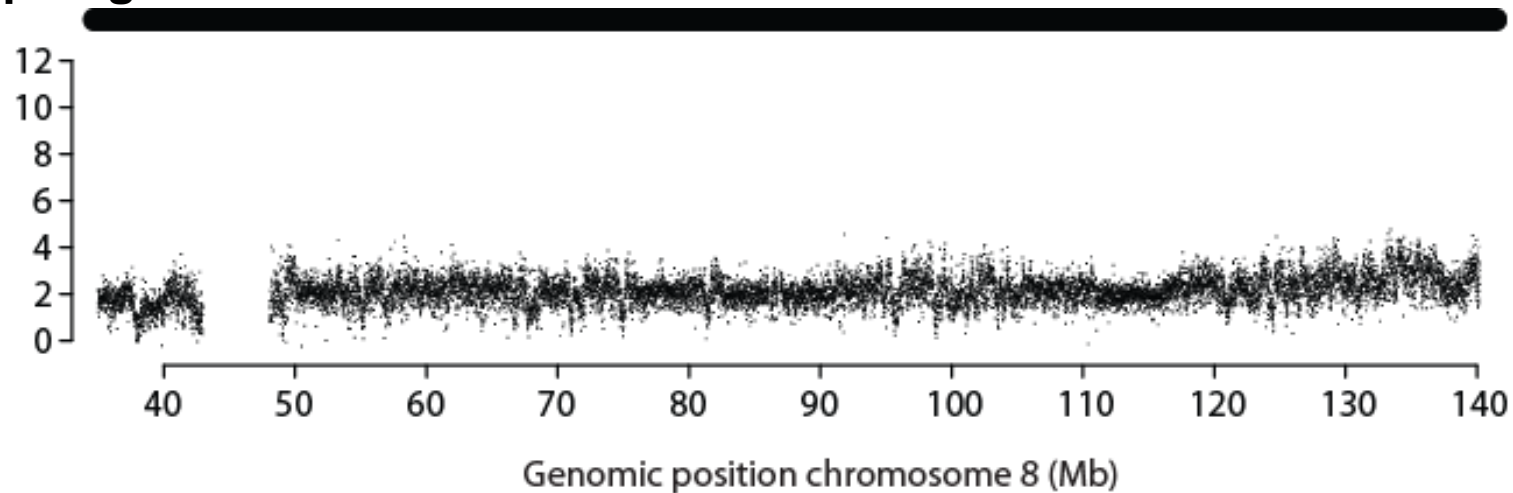


# Organ-specific signature

## Lung metastasis



## Diaphragm metastasis



# Summary

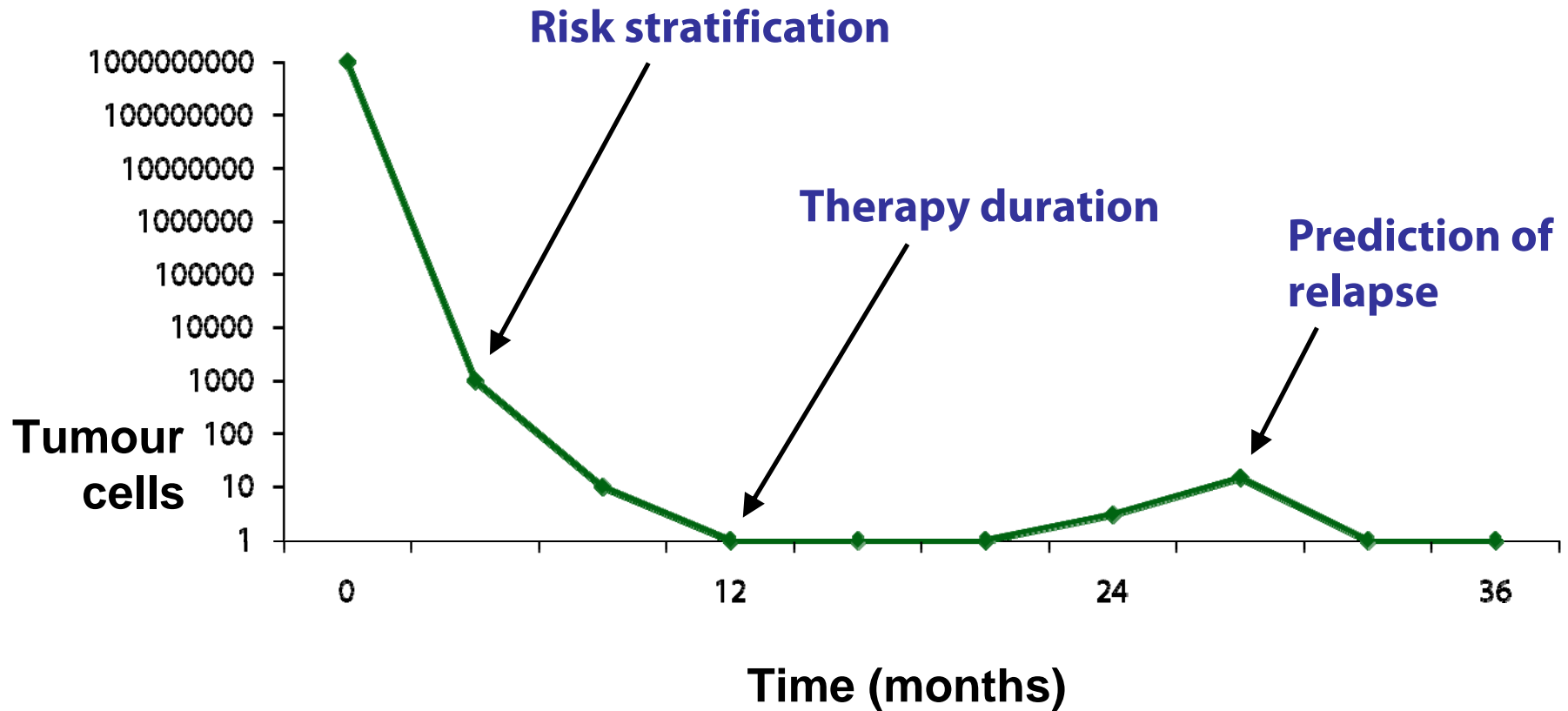
- Genomic instability changes through cancer 'life cycle'
- Metastases show on-going, parallel and even convergent evolution
- Signatures of selection among metastases
- Organ-specific genomic signatures

# Outline

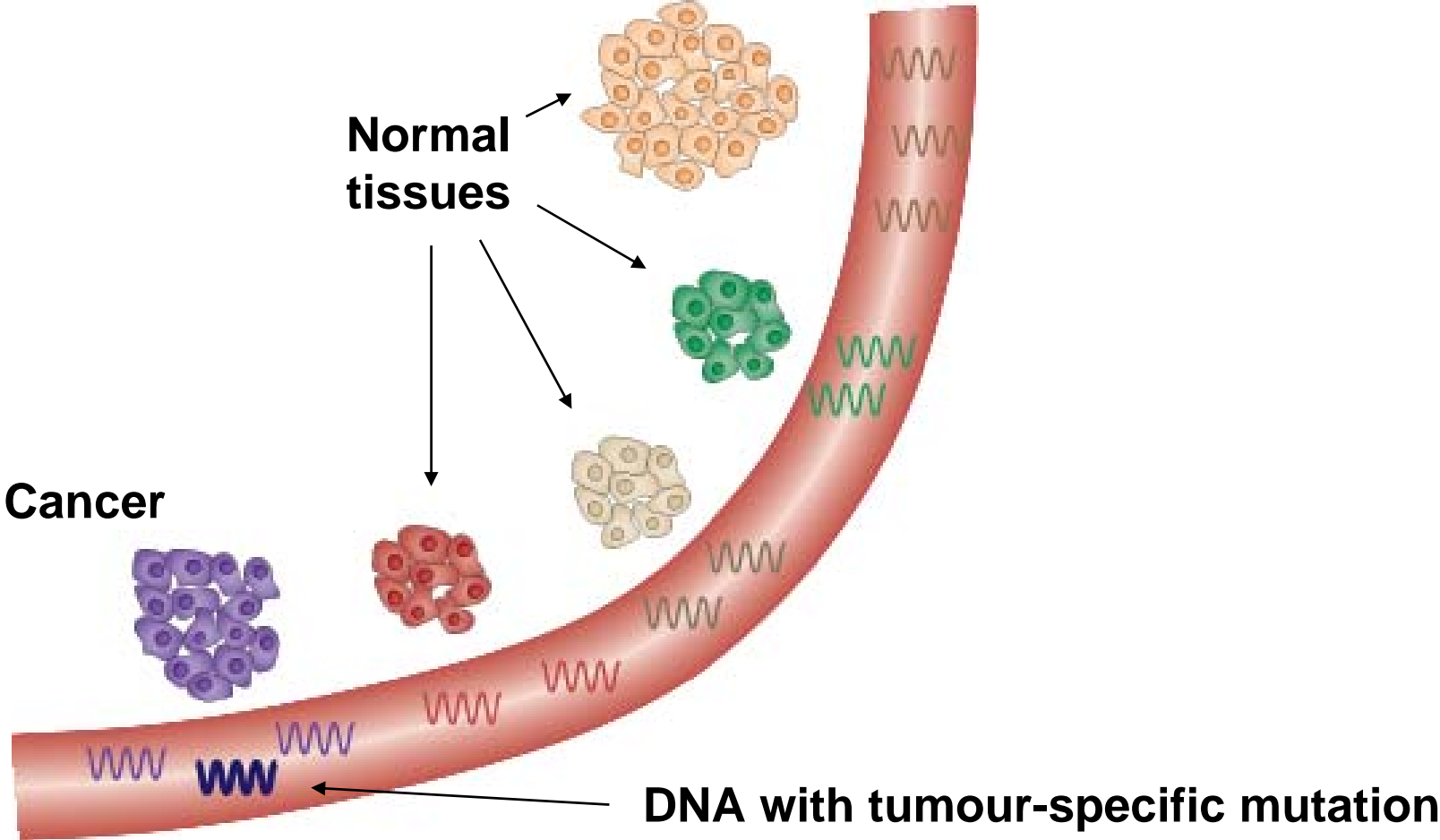
- Patterns of rearrangement
- Phylogenetic studies
- Translational applications



# Personalised Haematology



# Plasma DNA



# 2 patients with breast cancer

**Identify tumour-specific rearrangements  
from cancer DNA**  
(>20 per patient)



**Design quantitative assay for rearrangement**  
(3 per patient)

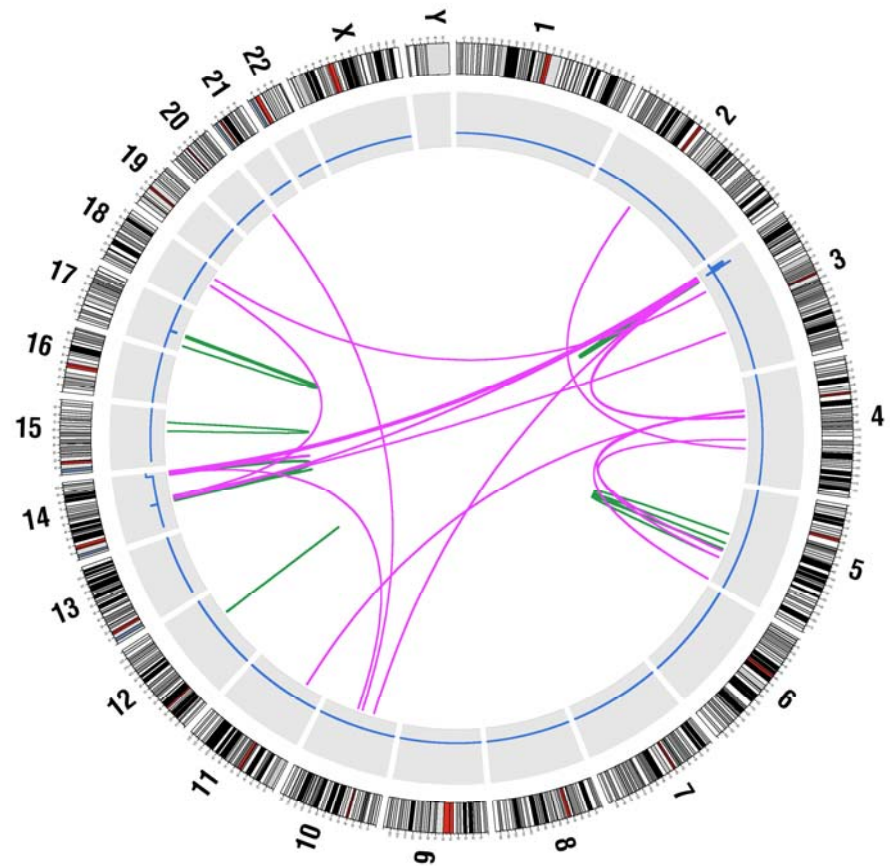
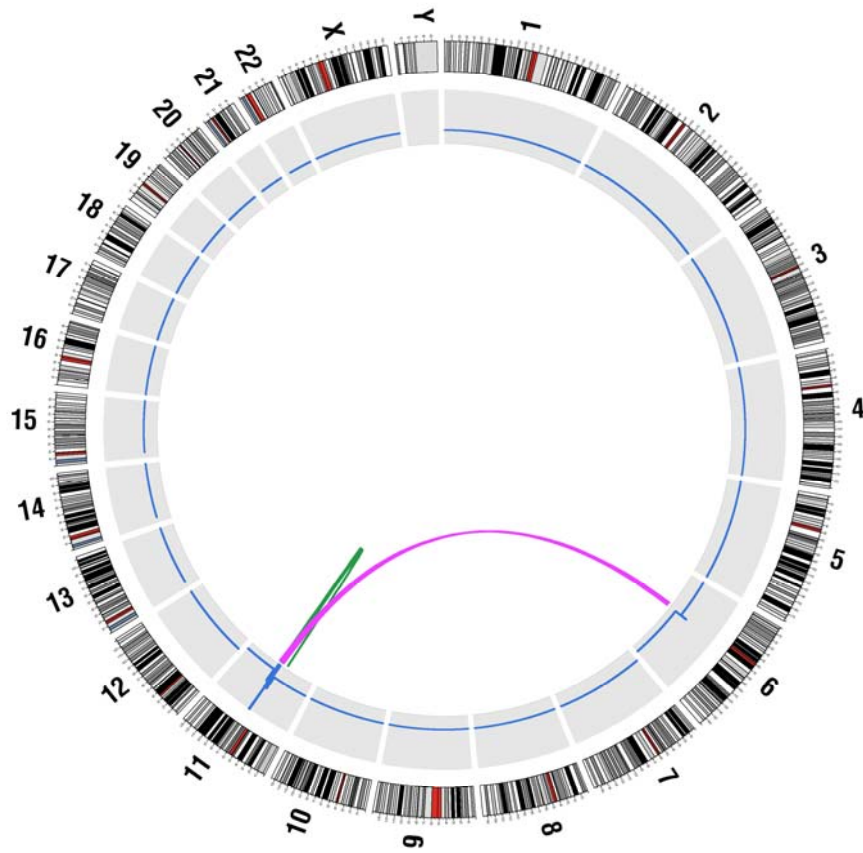


**Extract DNA from plasma**  
(5-10ml blood sample)

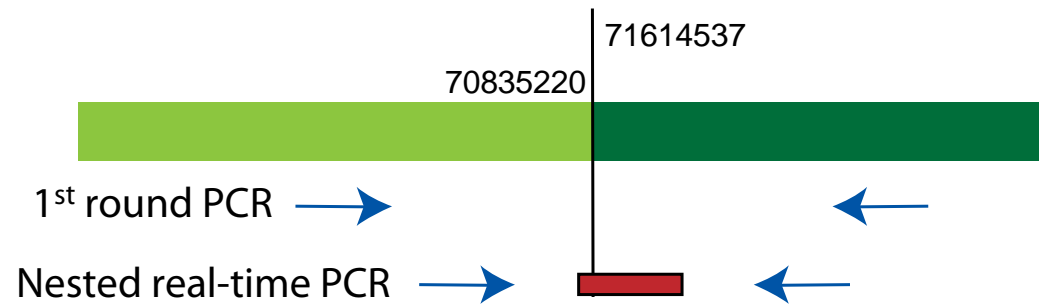
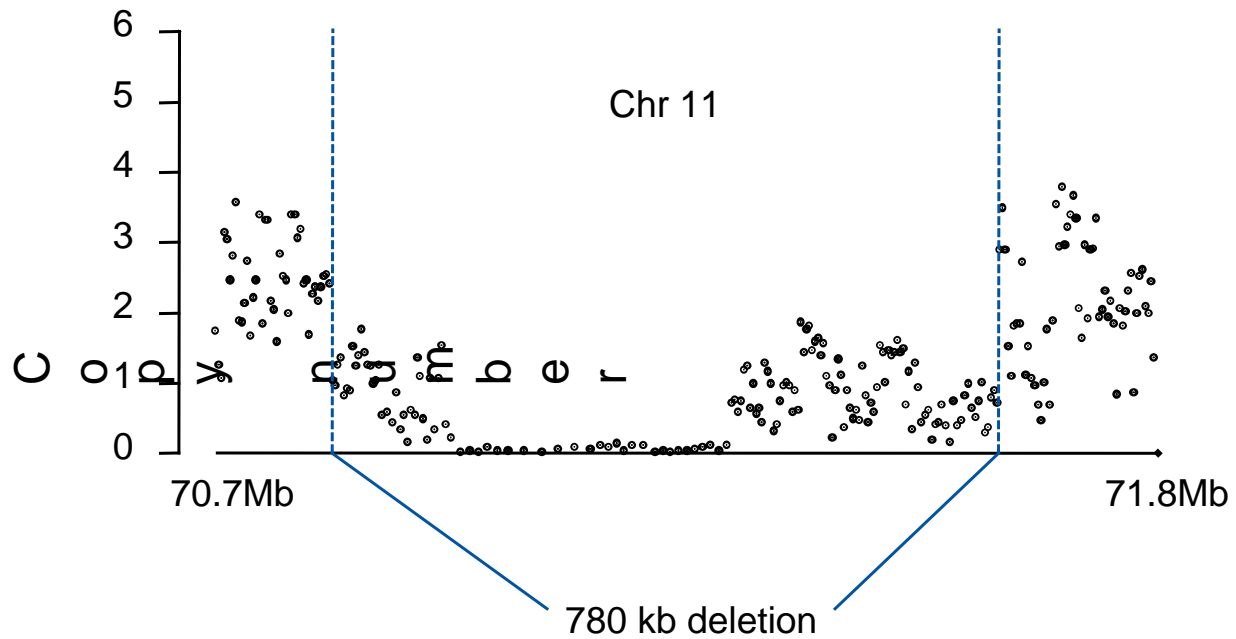


**Quantify tumour DNA**

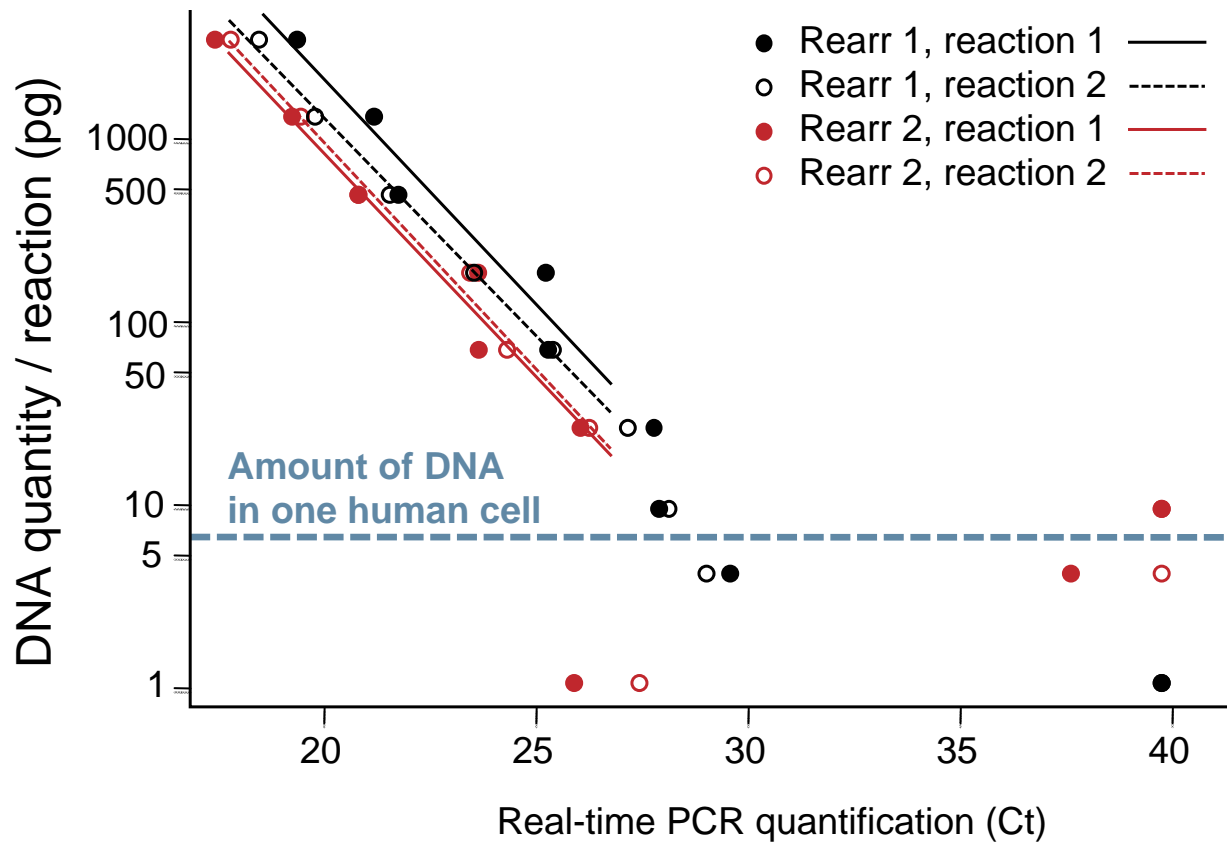
# Tumour-specific rearrangements



# Assay design

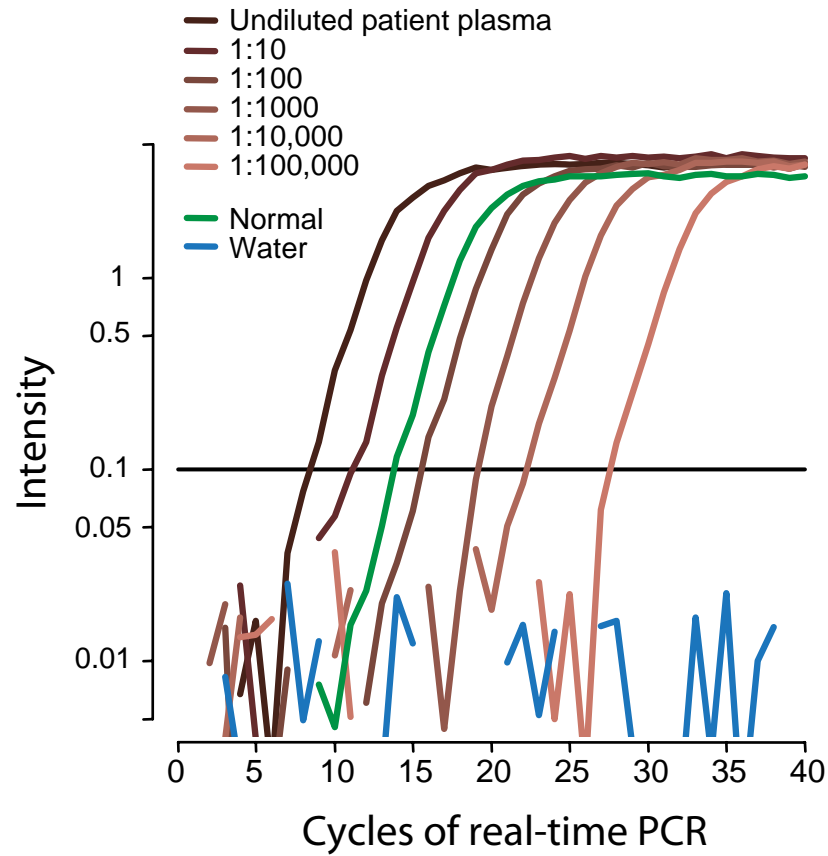


# Detecting 1 copy of tumour genome

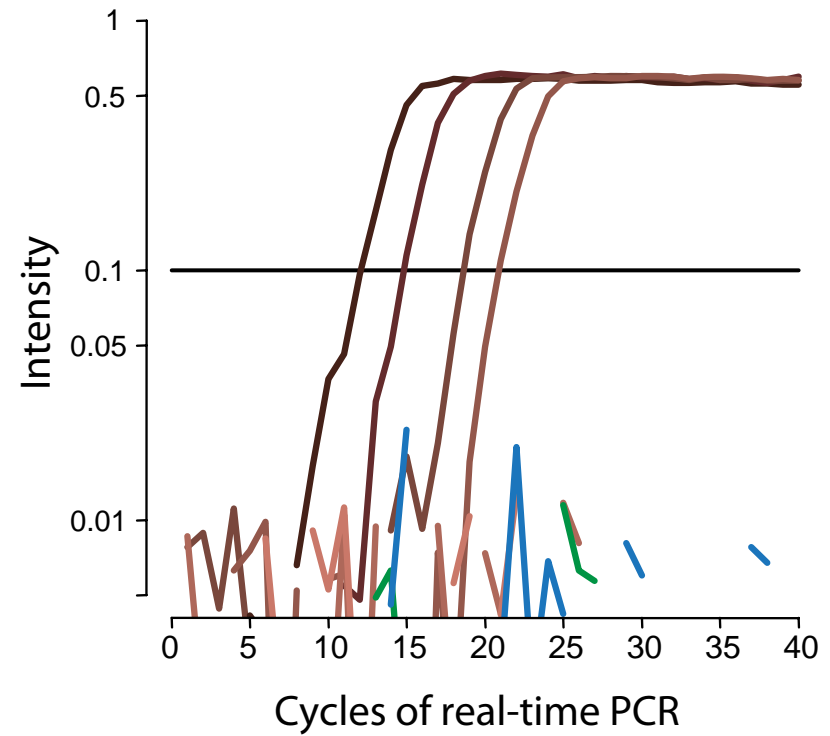


# Relapsing breast cancer

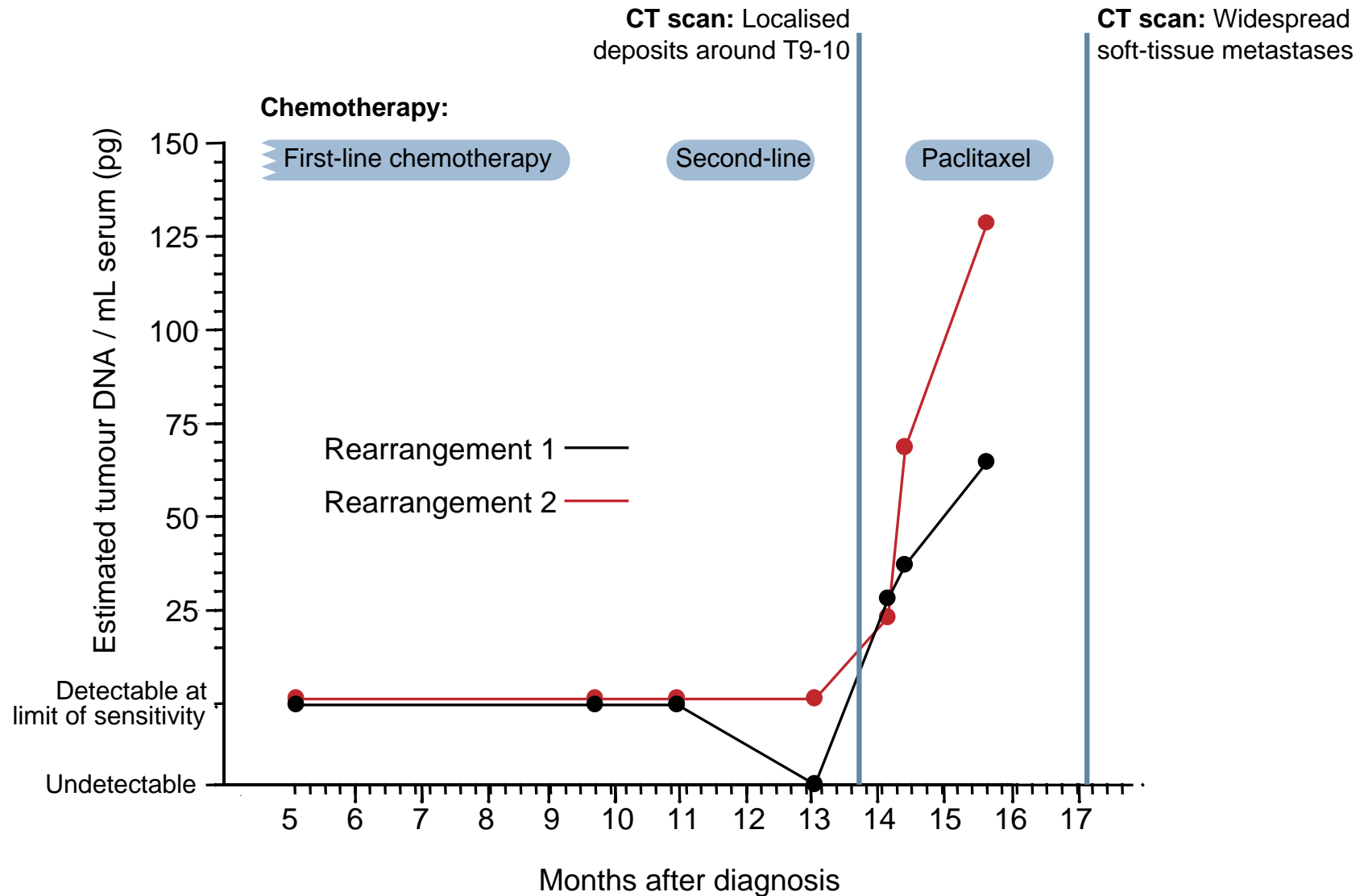
Non-rearranged genomic region



Tumour-specific rearrangement



# Serial measurements

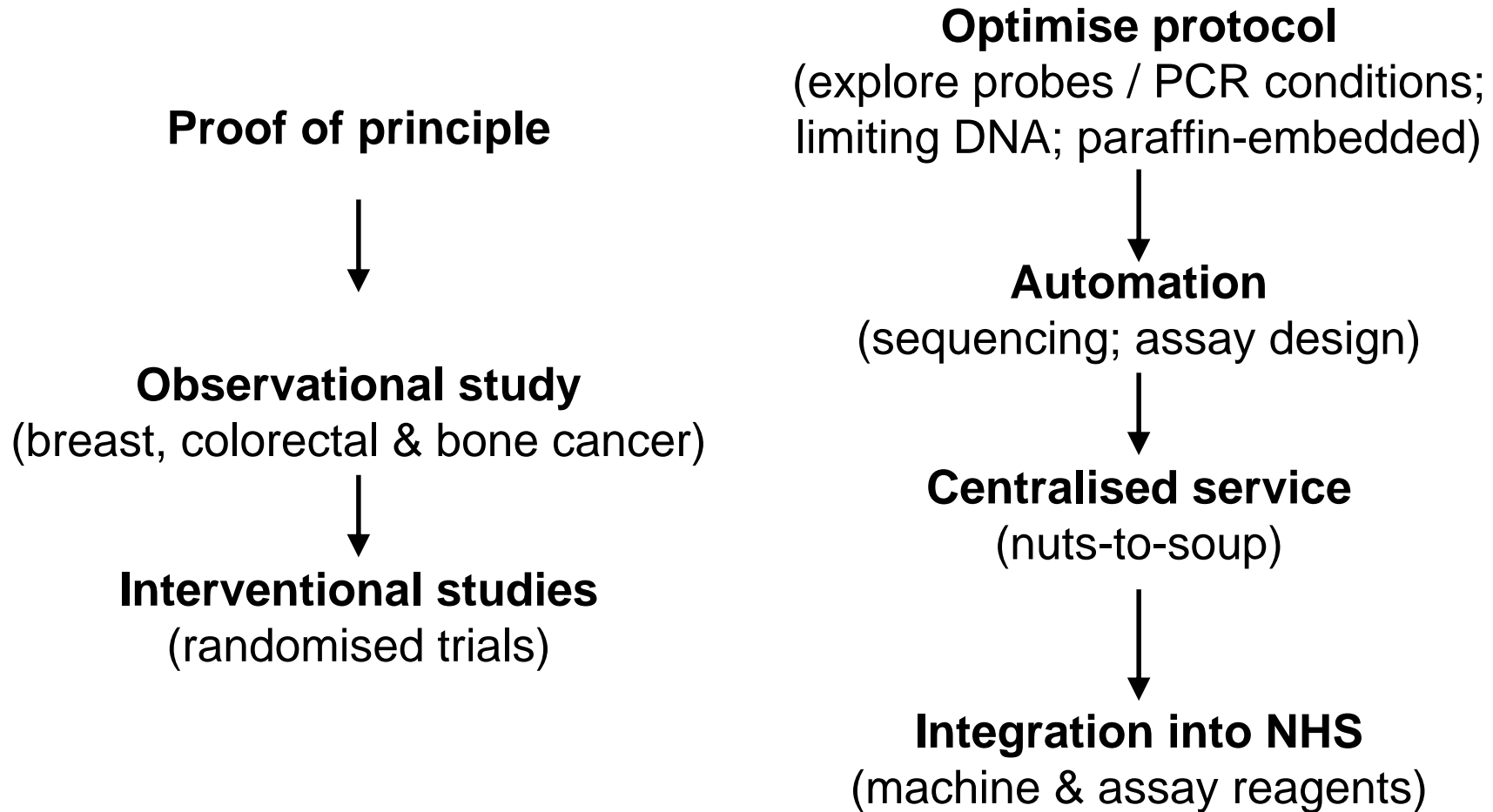




# Potential healthcare applications

- Monitoring tumour response to therapy in real-time
  - Reduce toxicity, prevent drug wastage
- Identifying disease relapse before clinically evident
  - Pre-emptive therapy
- Choosing intensity of adjuvant therapy based on risk stratification
- Surrogate marker of cell kill in early phase clinical trials

# Translation strategy



# Acknowledgements

## Cancer Genome Project

- David McBride
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- Christos Sotiriou

## Helsinki

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**welcome**trust

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