Visualising the true spectrum of cancer by molecular sequencing

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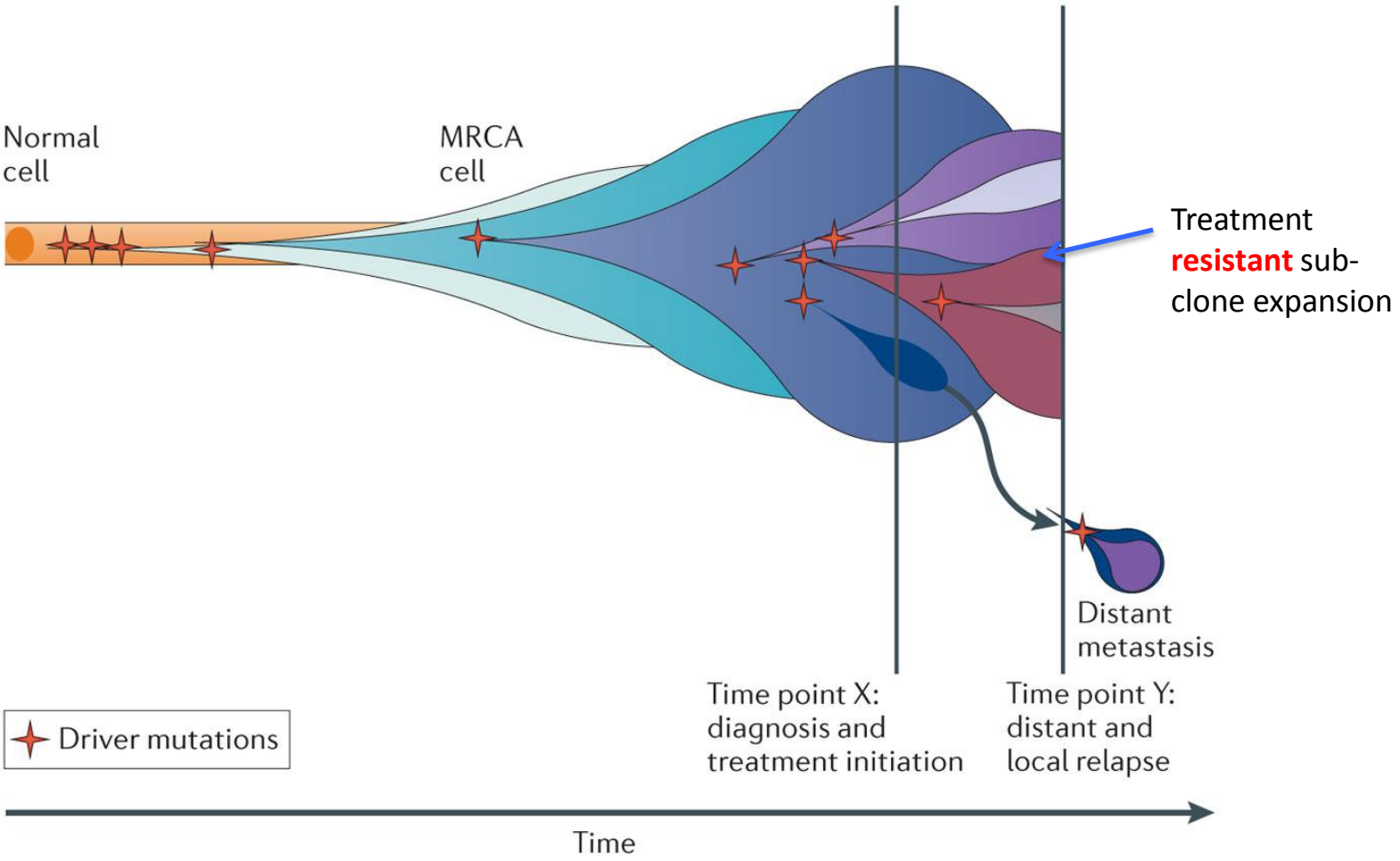
Cancer Evolution & Genomic Heterogeneity

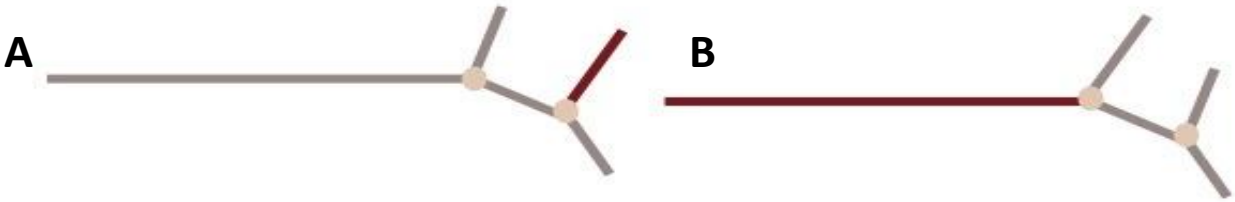


Nature Reviews | Genetics

Yates & Campbell, 2013

Three Questions

1. **How do aggressive hallmarks of cancer relate to the sub-clonal composition of breast cancers?**



2. **Is sub-clonal heterogeneity geographically defined?**

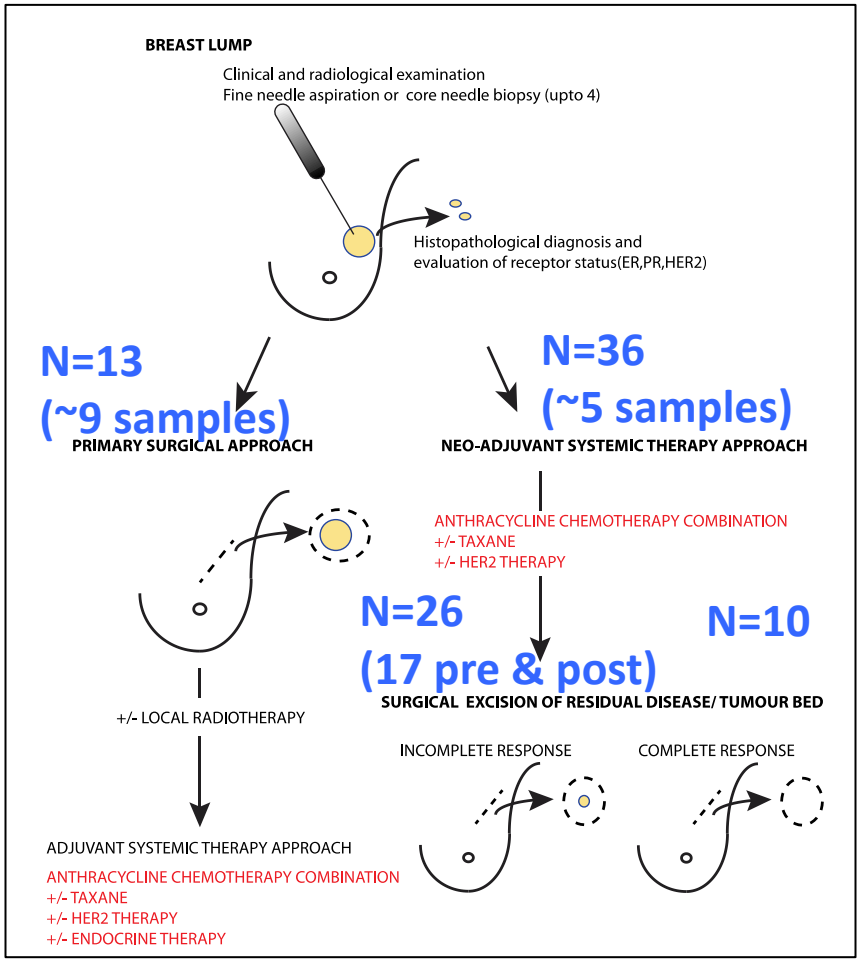
1. **How does heterogeneity relate to clinical features of disease?**

Sampling & Sequencing

- **49 patients** with >1 sample from the primary tumor and a matched normal
- **295 tumor samples**

- **Whole genome sequencing**: 29 samples, 13 patients (40-60X)

- **Targeted gene capture**: 282 samples, 48 patients (165X)
  - Bait design targets ~400 cancer related genes & SNPs for copy number analysis



Extent of Spatial Heterogeneity

- Two thirds of patients have heterogeneity of any mutation/ copy number
- 11/49 patients have heterogeneity of driver mutations or copy number changes
- Affected cancer genes: **TP53, PIK3CA,PTEN, BRCA2, CDKN2A**
- Affected copy number changes:
  - Arm level 1q, 8q gain, 17p loss
  - Focal amplifications: MYC, FGFR1, CDK6

Conclusions

1. Understanding **sub-clonal diversification** is clearly important for understanding the origins of aggressive characteristics of cancer in some breast cancers

2. The degree of sub-clonal diversification **varies from cancer to cancer**:
   - In 11/49 patients we identified geographically defined heterogeneity of driver point mutations/ copy number changes
   - This is enriched in the systematically sampled 12 patients (50%) which may reflect limitations of blindly attained samples

1. **Clinically**
   - Heterogeneity is associated with a trend for increasing grade & ductal sub-type but not response
   - Number of mutations may be important

With Thanks!

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