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Cancer complexity (!?)

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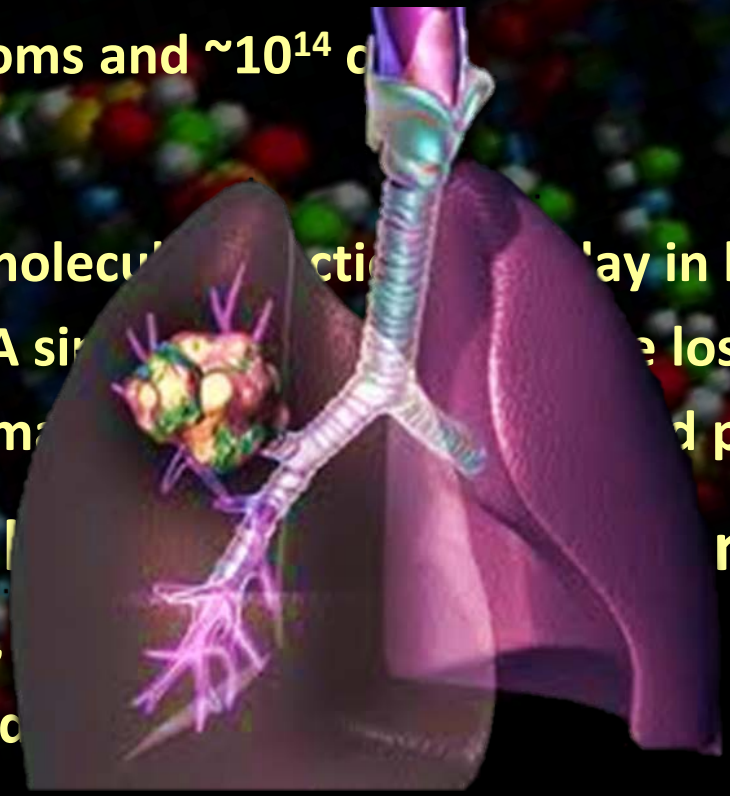
Complexity of human body

- A human body of 70 kg is comprised of:
  - ~$6.7 \cdot 10^{27}$ atoms and ~10^{14} c
- Activity:
  - ~10^{25}–10^{26} molecu cti ay in human body
  - ~10,000 DNA si e loss per cell per day
  - Blood and sm d per day: ~10^{10}–10^{11}
- A human cell nd consists of
  - ~65% water,
  - ~1% RNA and
- No. of genes in the human body: ~20–25,000



for more
information
on lung cancer,
keep smoking.

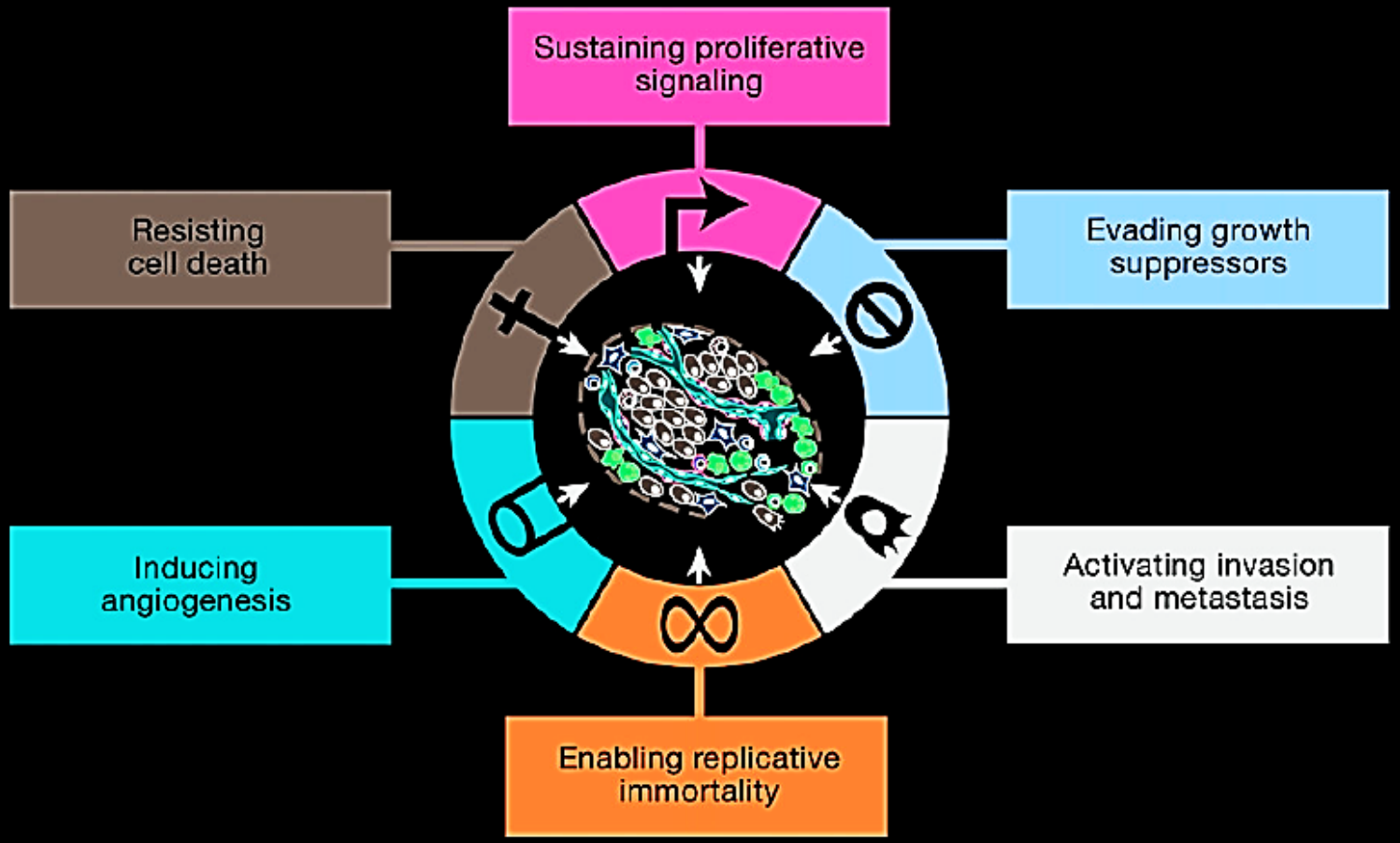
— *the lung association british colombia*

CAUSES OF CANCER

• **Genetic**	**5-10%**	
• **Environmental**	**90-95%**	
• Tobacco		25-30%
• Diet & obesity		30-35%
• Infections		15-20%
• Radiation (ionizing & non-ionizing)		10%
• Pollution		?%

Anand et al. *Pharm Res* 25: 2097 (2008)

The hallmarks of cancer



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Hanahan & Weinberg *Cell* 100: 57 (2000)

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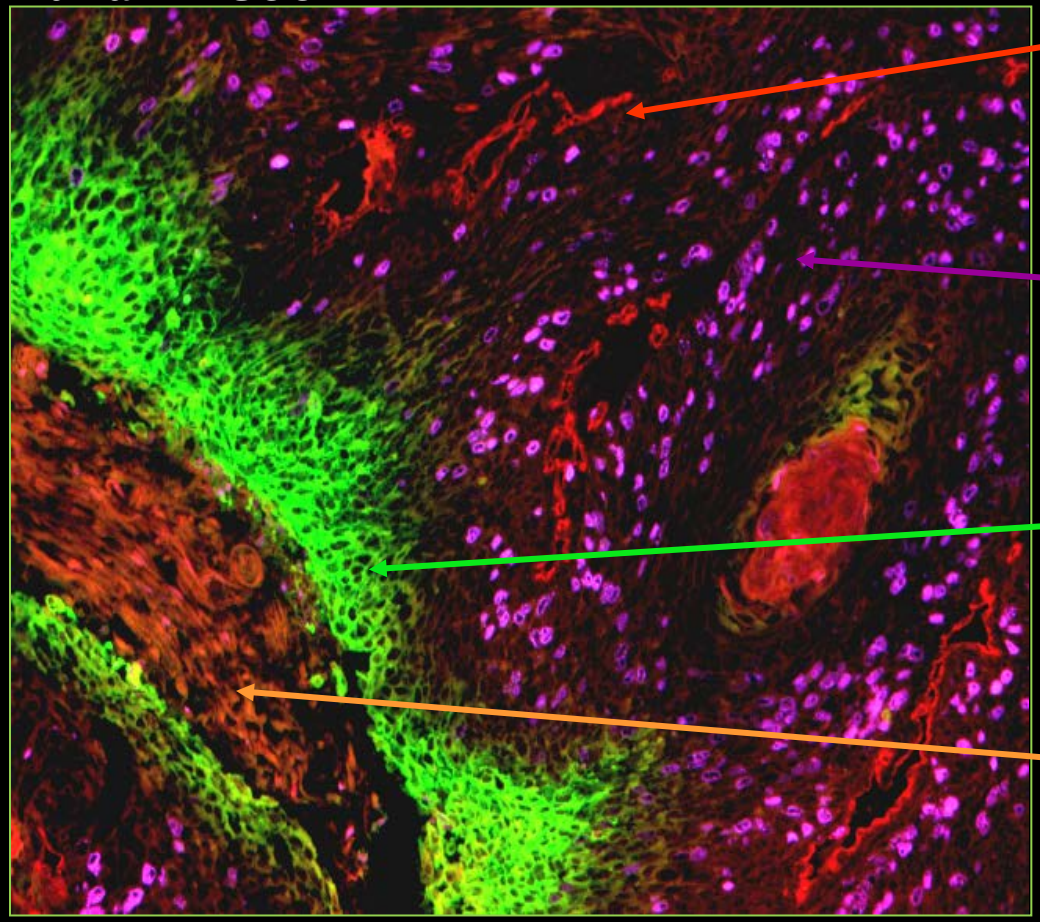
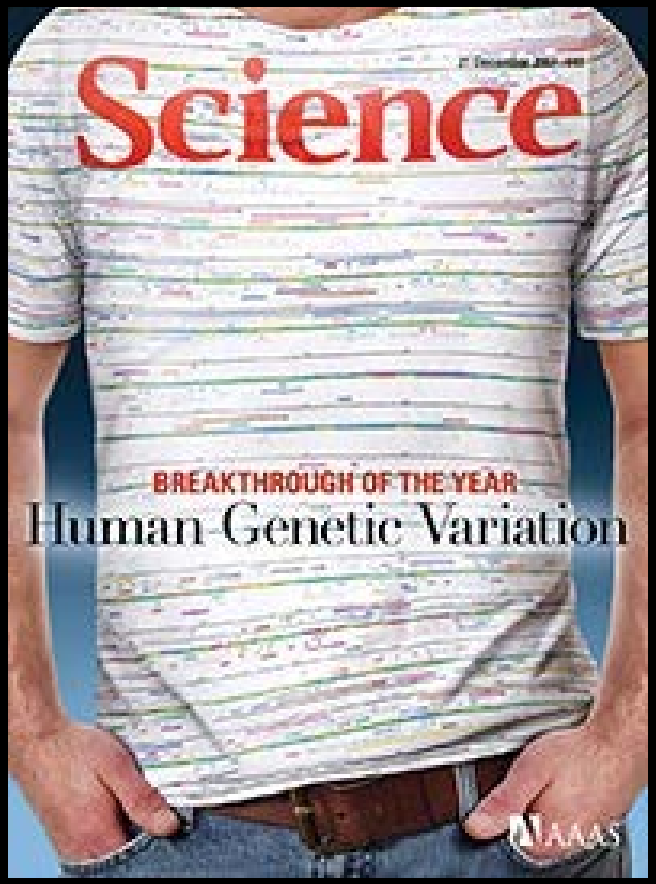
Proliferation and hypoxia at the cellular level

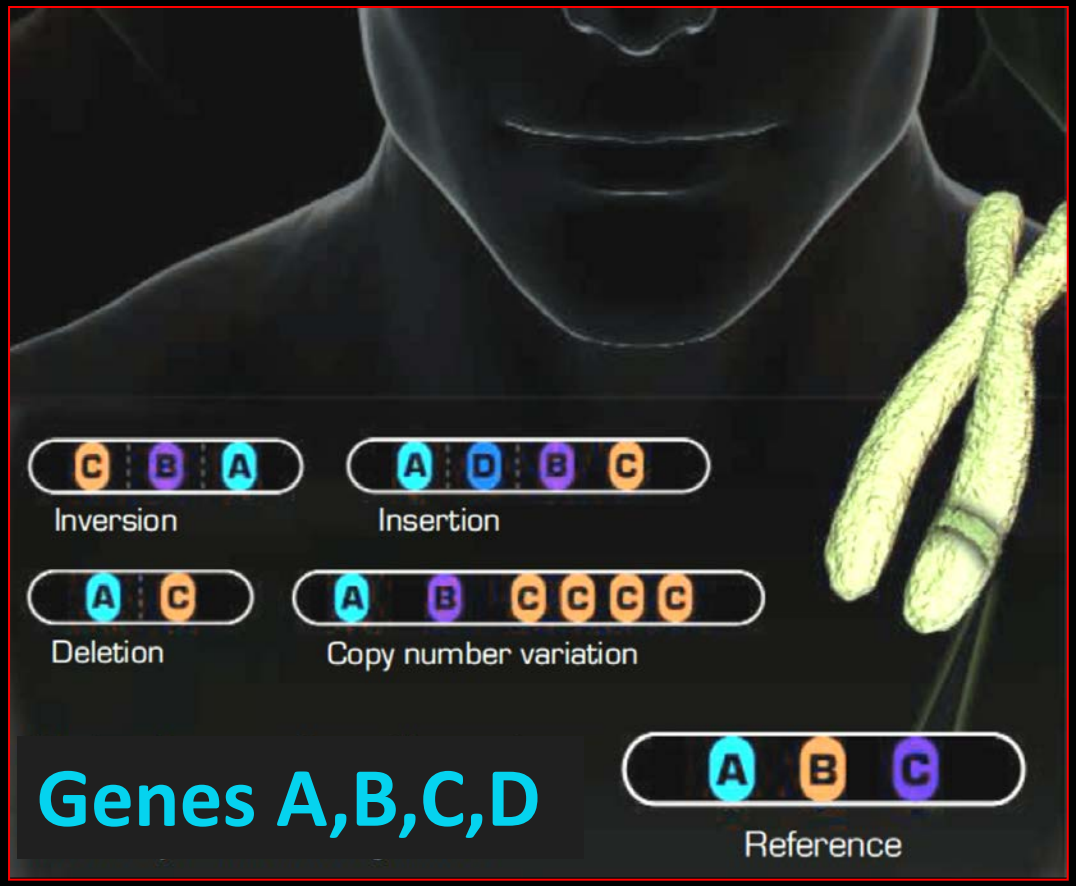
Human HNSCC



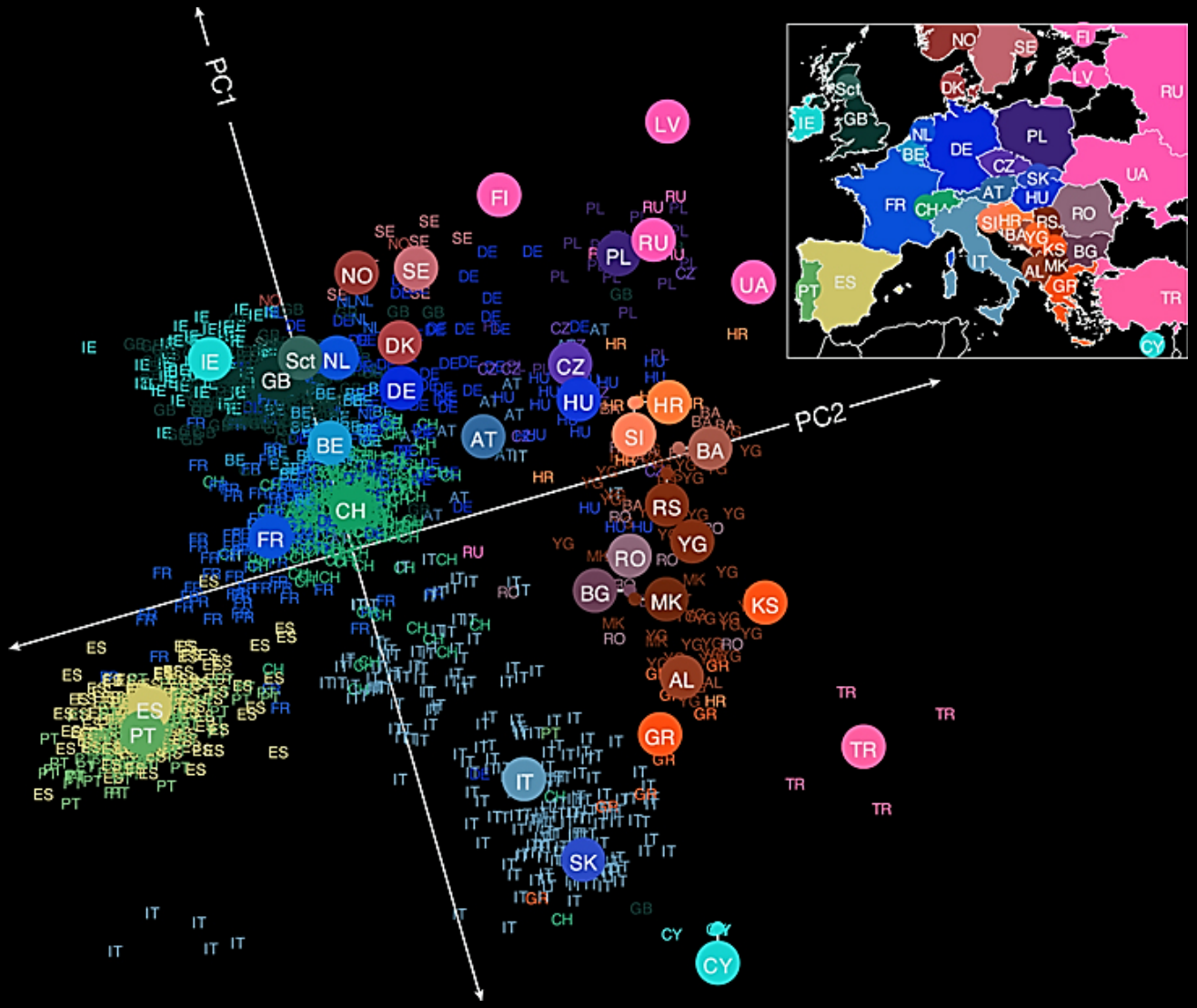
Courtesy of AJ van der Kogel

What makes us unique?



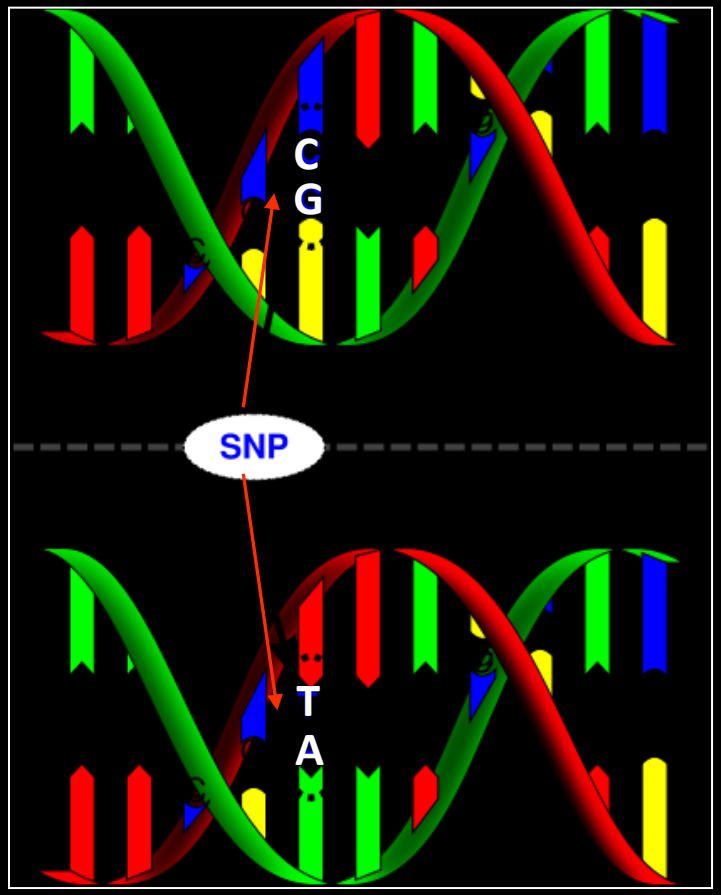


Genes mirror geography



Novembre et al. *Nature* 456: 98 (2008)

Single nucleotide polymorphisms



- Substitution of an alternate base pair at a specific nucleotide location
- Prevalence ≈1:300 nucleotides
- Common SNPs in human genome
  - 7 million SNPs with MAF > 5%
  - 4 million SNPs with 5% > MAF > 1%

RADIOGENOMICS

Linking genomics to patient-to-patient variability in tumor or normal tissue response after radiation therapy alone or combined with drugs

Large studies in progress including 1,000+ patients each

SNP's & late RT toxicity: Validation study

UK RAPPER validation study

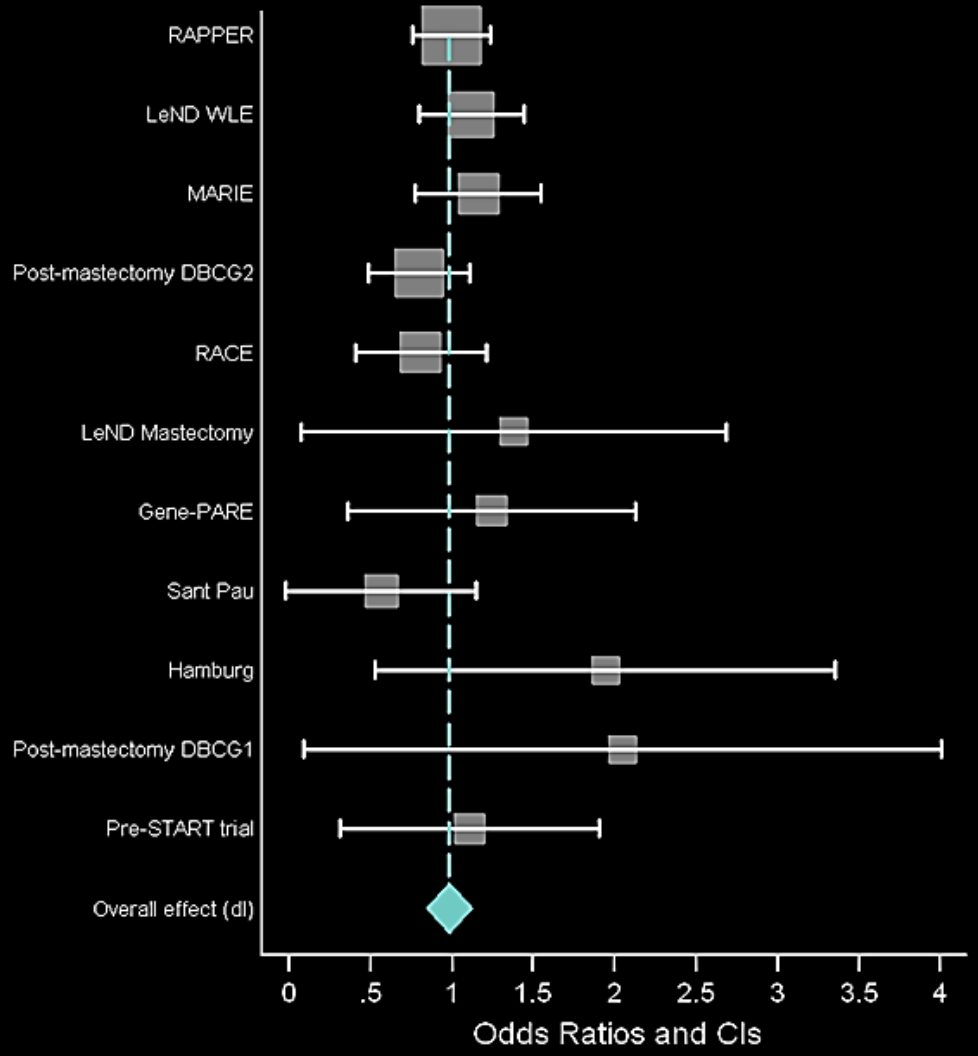
- 92 SNPs in 46 genes previously reported to be associated with RT toxicity
- 1613 patients: 976 post-op breast, 637 radical prostate RT
- Late toxicity assessed two years after RT
- After adjusting for multiple testing, study had 99% power to detect a SNP, with Minor Allele Frequency (MAF) of 0.35, associated with an odds ratio of 2.2.
- **NOT A SINGLE ONE OF THE 92 SNPs WAS SIGNIFICANT !!**

Barnett et al. *Lancet Oncol* 13: 65 (2012)

Int'l Radiogenomics Consortium

- 110 members from Europe, North America, Asia
- Steering Committee
  - *C West, B Rosenstein, J Alsner, SM Bentzen, J Chang-Claude, J Deasy, A Dunning, D Seminara, J Yarnold*
- Meetings: Manchester (2009), New York (2010), London (2011)
- Collected clinical outcome and genetic data on 5,603 patients from 20 published and unpublished studies
- Meta-analysis on associations between SNPs in TGFB1 and normal tissue toxicity in progress (*Barnett,…,Bentzen*)

Fibrosis vs. genotype



OR = 0.98 (95% CI 0.85, 1.11)
(99% CI 0.81, 1.16)

Incidence of G2+ fibrosis

Assuming a **25%** incidence with the common variant after adjustment for covariates…
we can exclude an incidence of greater than **27.9%** for carriers of the rare allele of rs1800469 with >99% confidence

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Barnett et al. *R&O* 105: 289 (2012)

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Genome wide association studies

Genome wide association studies (GWAS) take advantage of linkage disequilibrium, typically assessing 200,000–500,000 tag SNPs

Stage I
2,000 patients genotyped for 600,000 tagSNPs covering whole genome

↓

Identify 5% most significant SNPs

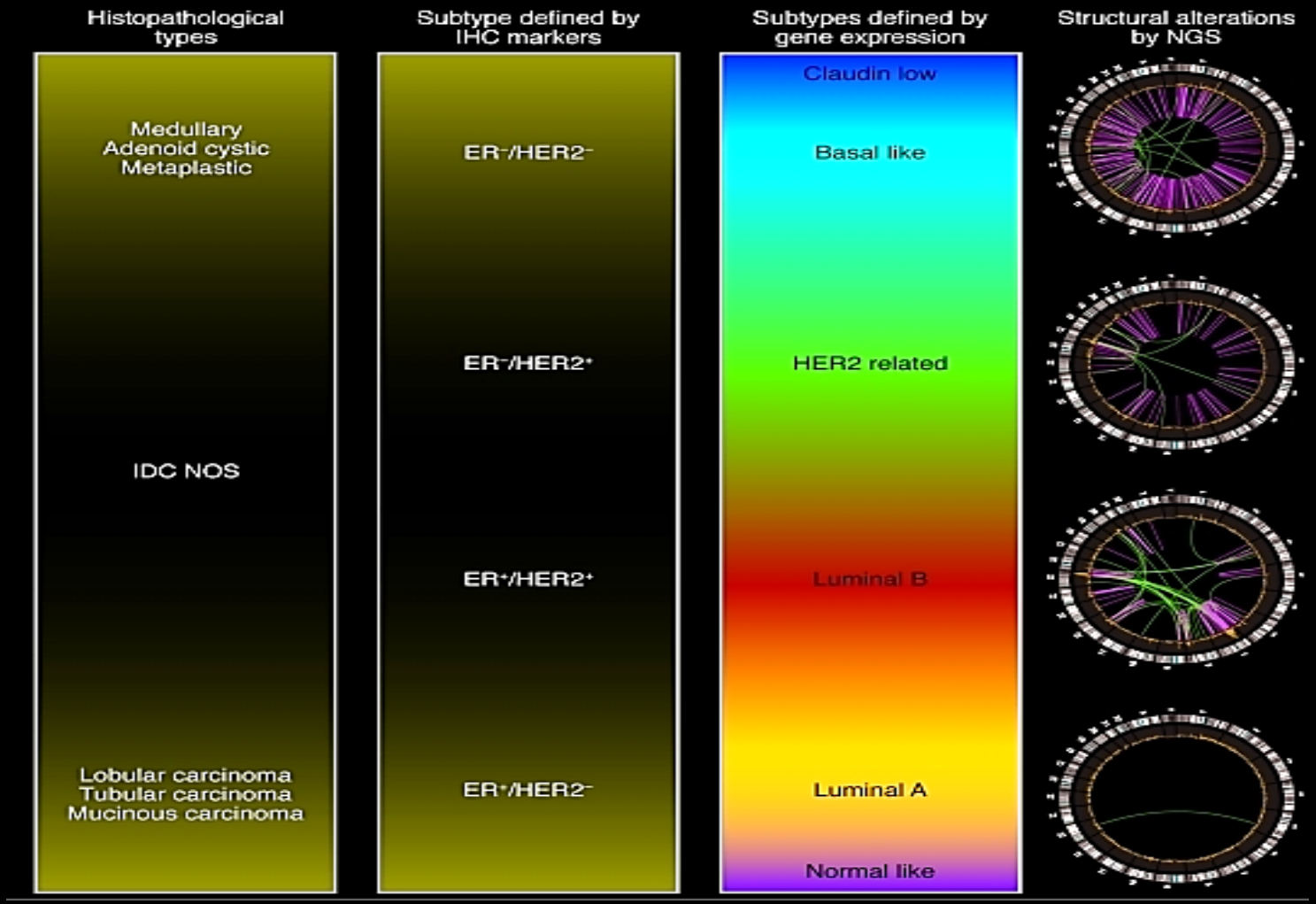
↓

Stage II
8,000 patients genotyped using a custom array containing SNPs identified in stage I

N = 10,000
$P < 10^{-7}$

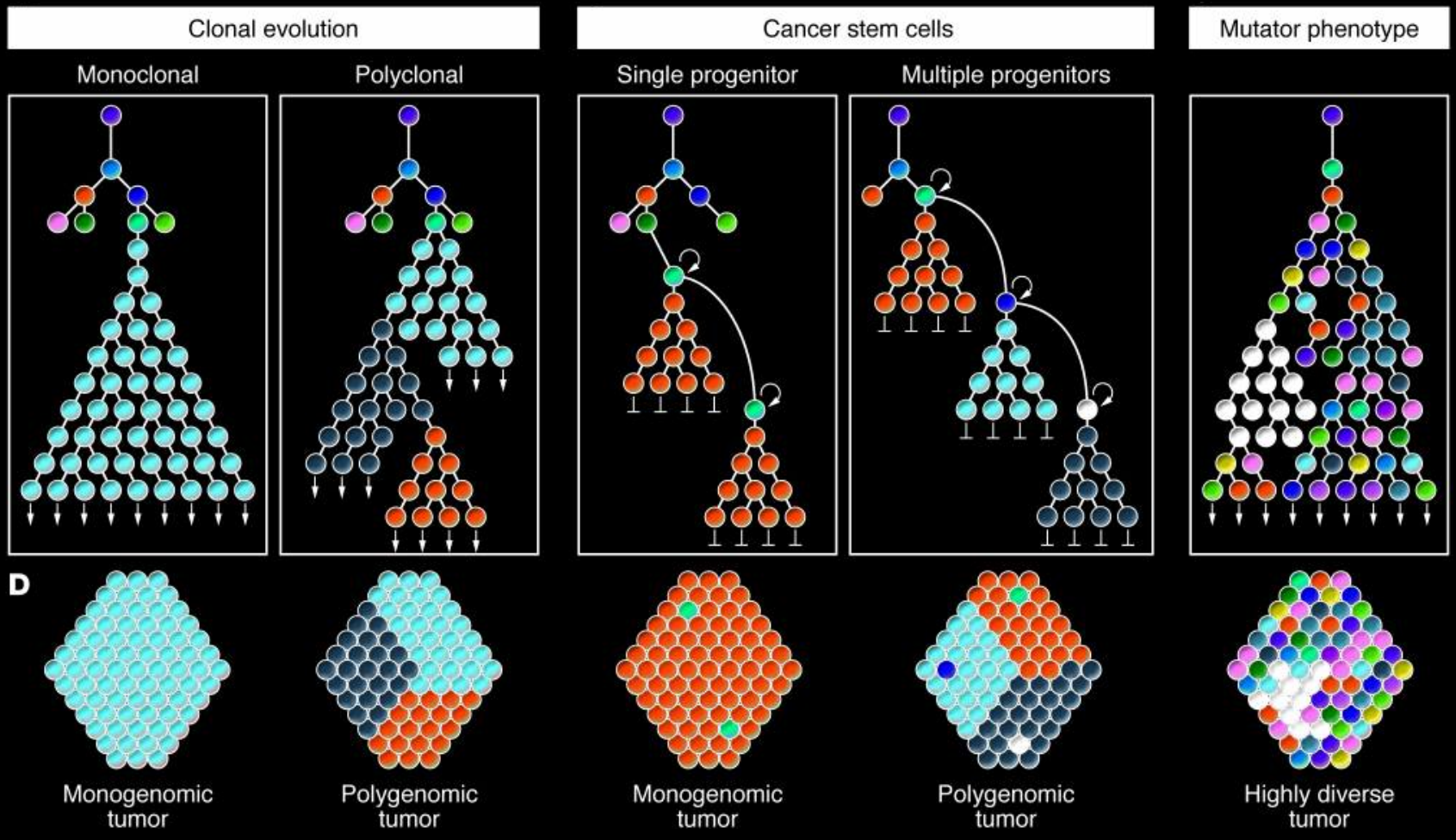
Barnett et al 2009, Nat Rev Cancer

Breast cancer subtypes



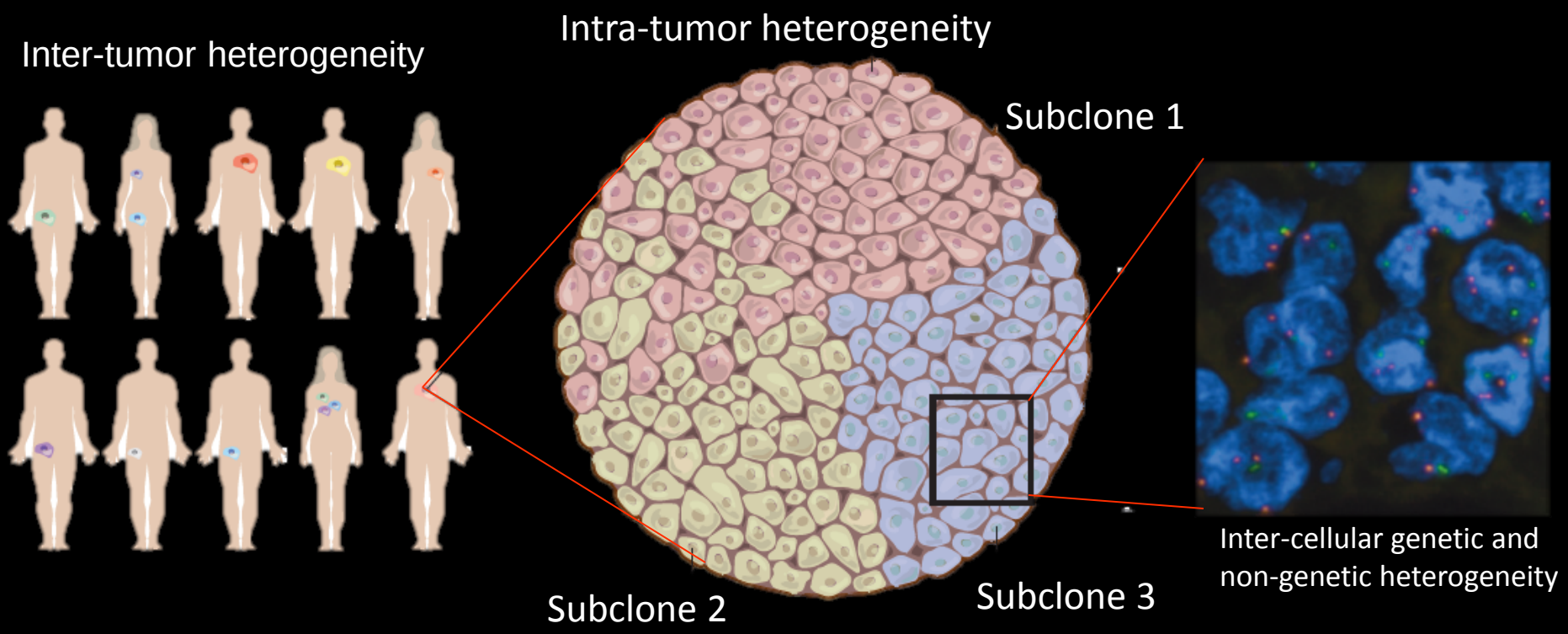
Russnes et al. *J Clin Invest*. 121: 3810 (2011)

Genetic heterogeneity



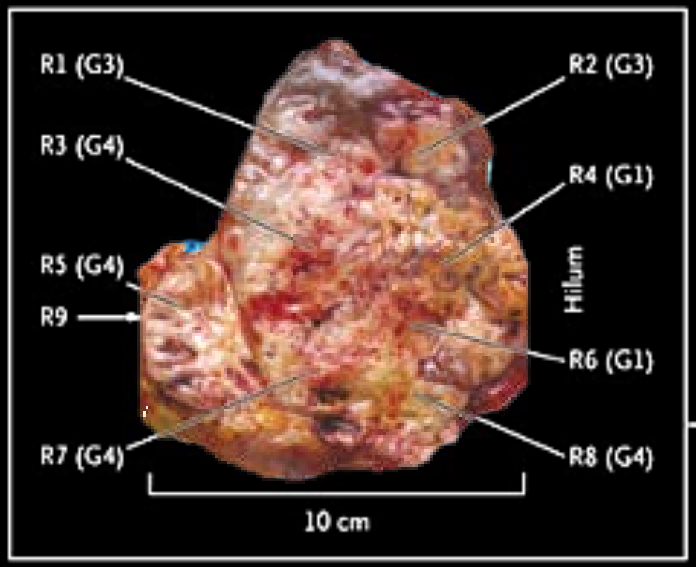
Russnes et al. *J Clin Invest*. 121: 3810 (2011)

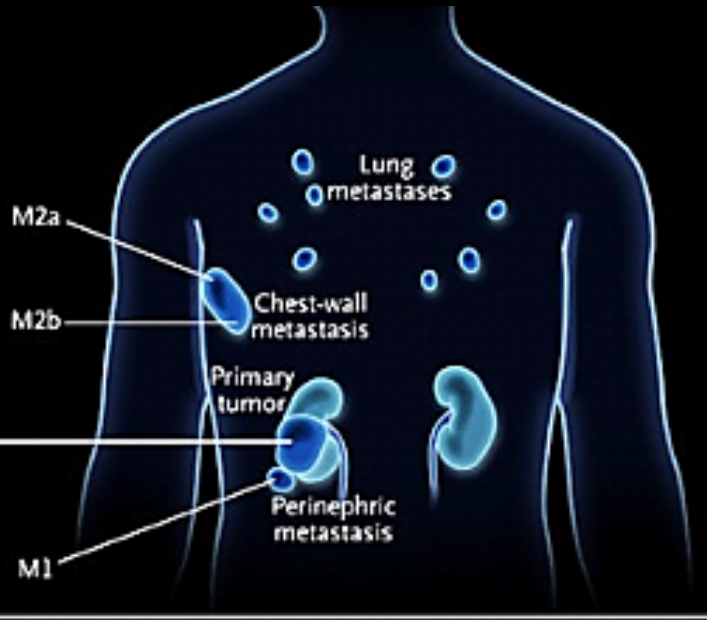
Tumor heterogeneity



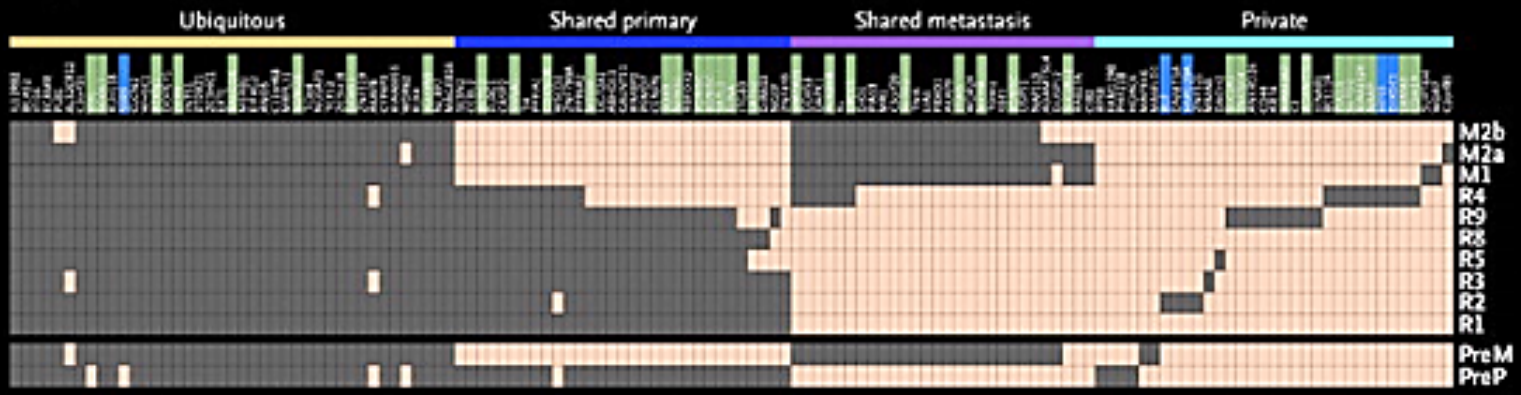
Burrell et al. *Nature* 501: 338 (2013)

Genetic intra-tumor heterogeneity





Regional distribution of mutations



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Gerlinger et al. *NEJM* 366: 883 (2012)

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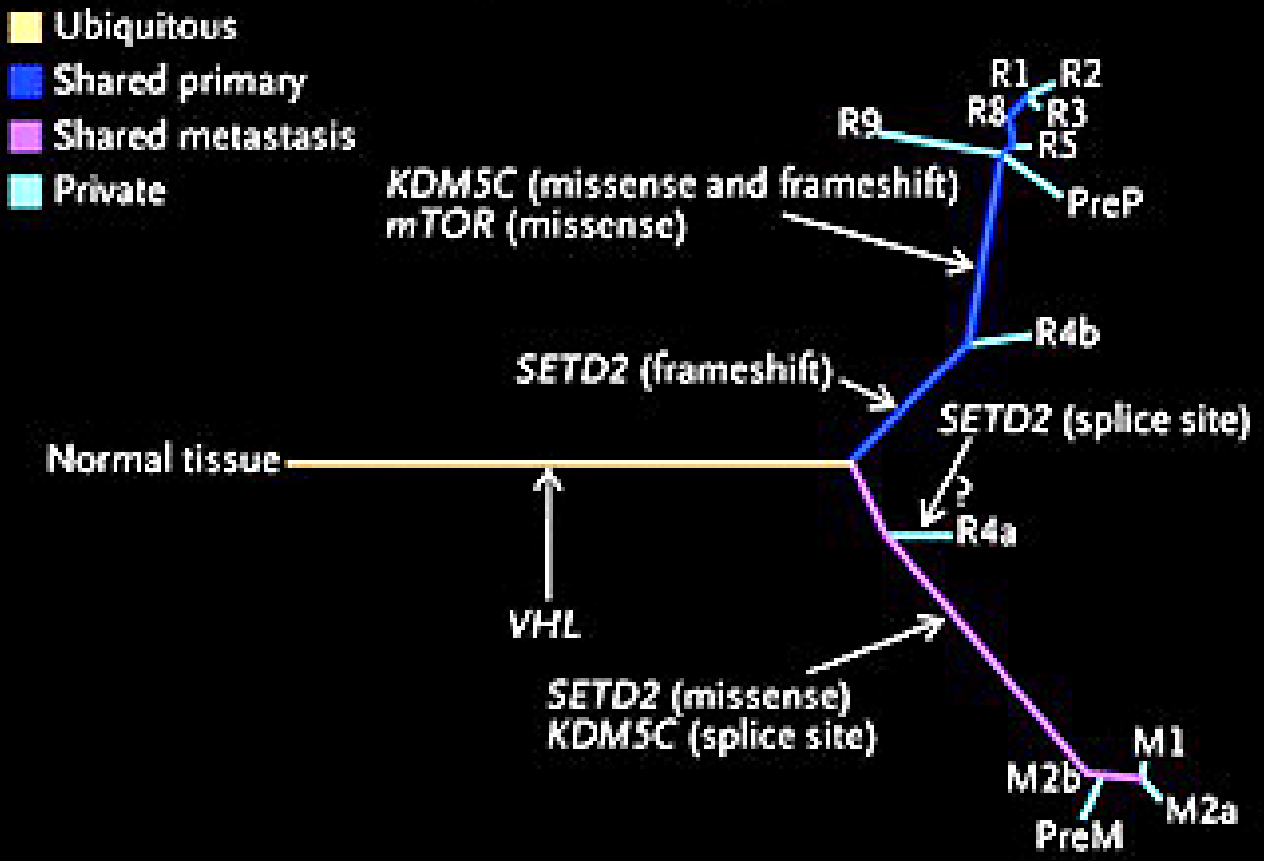
Phylogenetic relationship of tumor regions



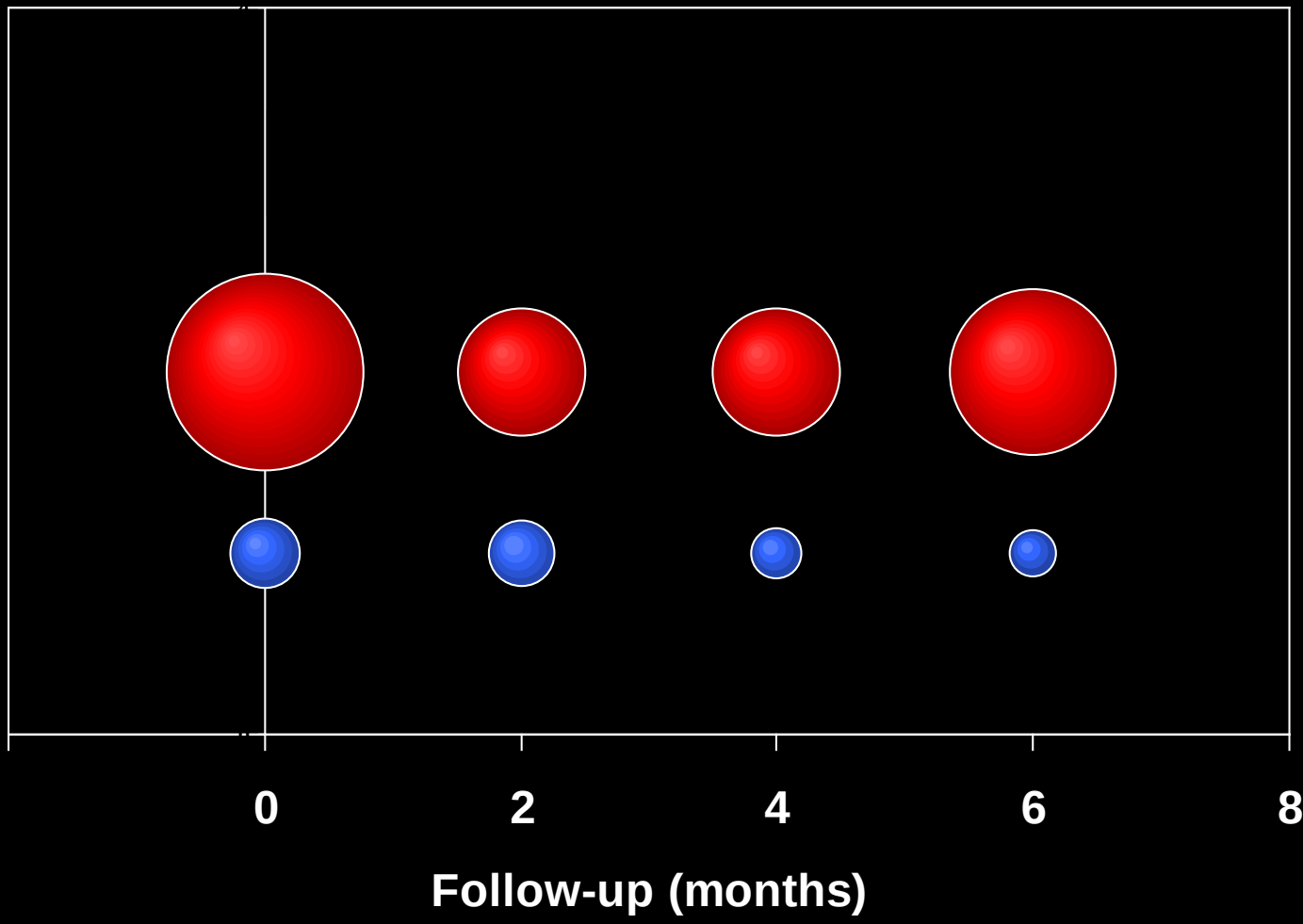
Gerlinger et al. *NEJM* 366: 883 (2012)

Biomarker concordance primary v. met

Tumour type	Biomarker	Prognostic or predictive	Evidence of discordance
Oligodendroglioma	1p and 19q co-deletion	Prognostic/predictive	Not applicable
	MGMT promoter methylation	Prognostic/predictive	
Medullary thyroid	*RET* mutation	Prognostic[102]	Unknown
Breast	ER expression	Prognostic/predictive	7–25%
	PR expression	Prognostic	16–49%
	HER2 amplification	Prognostic/predictive	3–24%
Lung	*EGFR* mutation	Prognostic/predictive	0–38%
	EML4-ALK translocation	Prognostic/predictive	1–2%
Gastric	*HER2* amplification	Prognostic[106]/predictive	1–3%
Colorectal	*KRAS* mutation	Predictive	0–10%
Melanoma	*BRAF* mutation	Prognostic/predictive	4–25%
Gastrointestinal stromal	*KIT* mutation	Predictive	Acquired mutations evolve inhibitor treatment
	PDGFRA mutation	Predictive	

Bedard et al. *Nature* 501: 355 (2013)

Brain met volume versus time



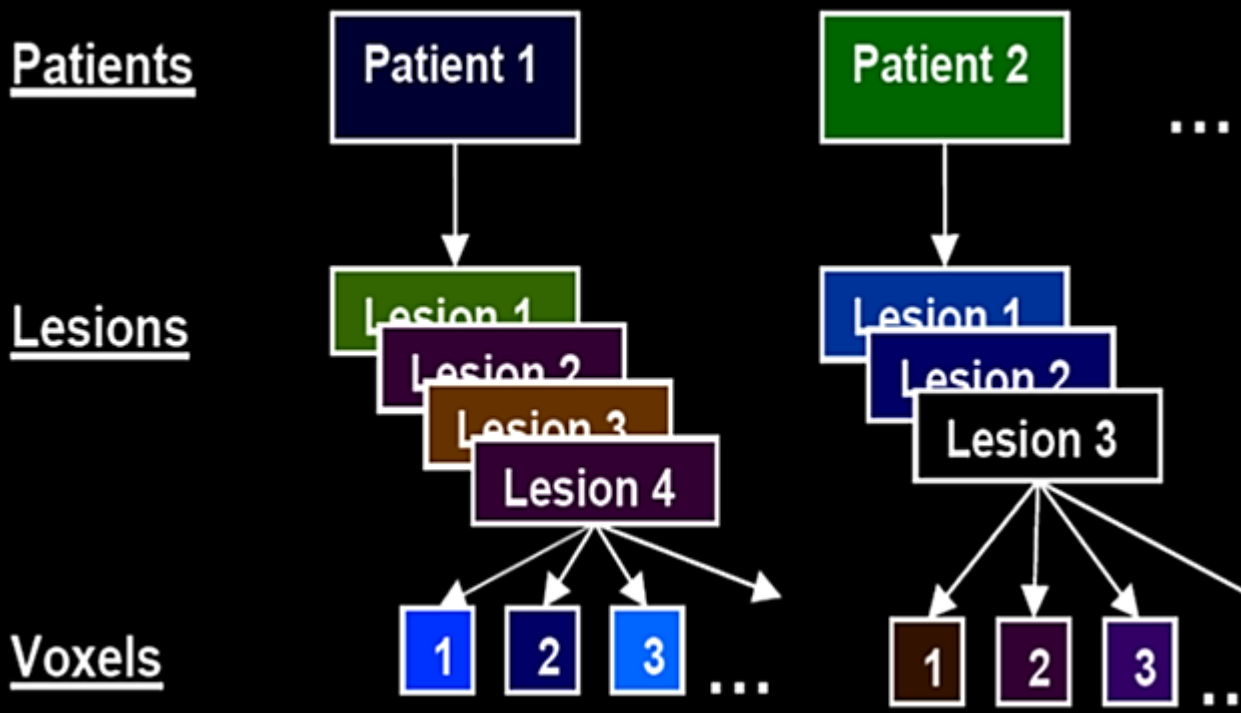
Bentzen et al. (in preparation)

Variance components

- Material: 247 independent brain mets in 86 evaluable patients from the WBRT alone arm of the phase III Metoxafin Gadolinium trial
- Endpoint: Relative tumor volume @ 4 months assessed from standardized Gd contrast MRI
- Maximum likelihood variance component analysis
- Variance components:
  - between subjects 57%
  - between lesions 43±5%

Bentzen et al. (in preparation)

Levels of variance



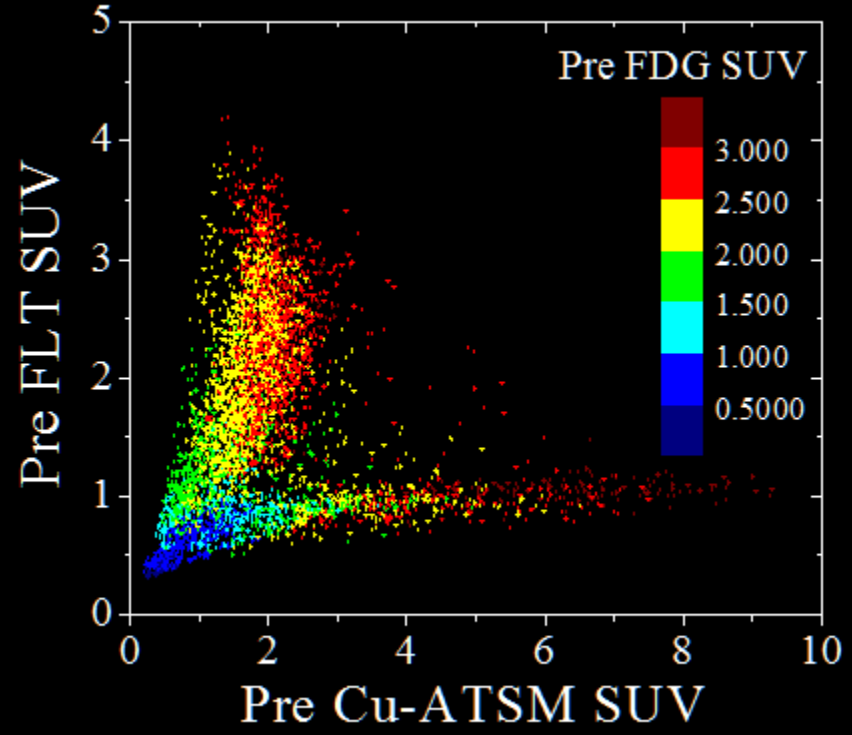
Individualized dose prescription

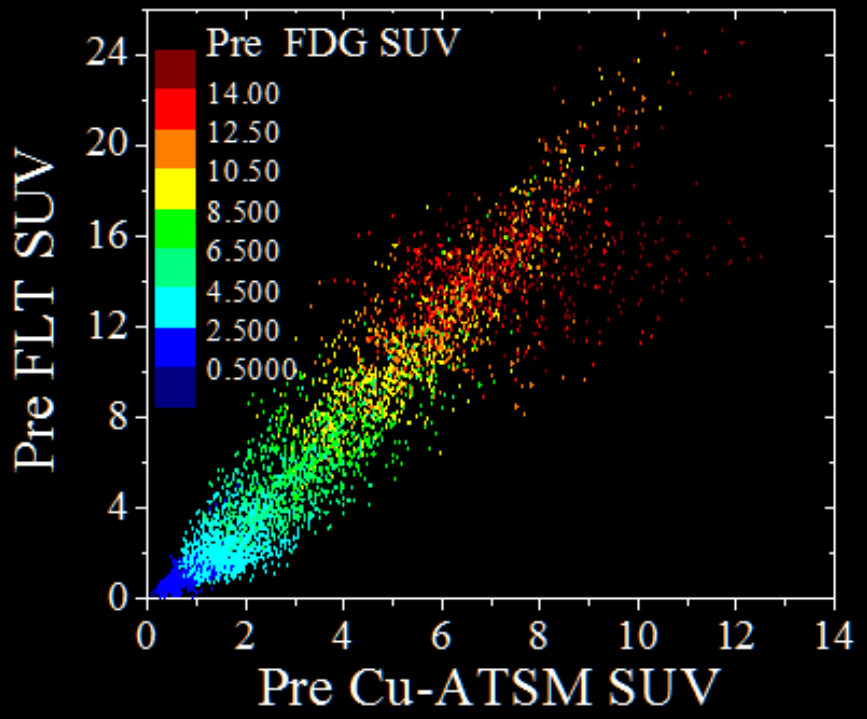
***Inter*-lesion theragnostics**

***Intra*-lesion theragnostics**

Voxel-level correlation between tracers

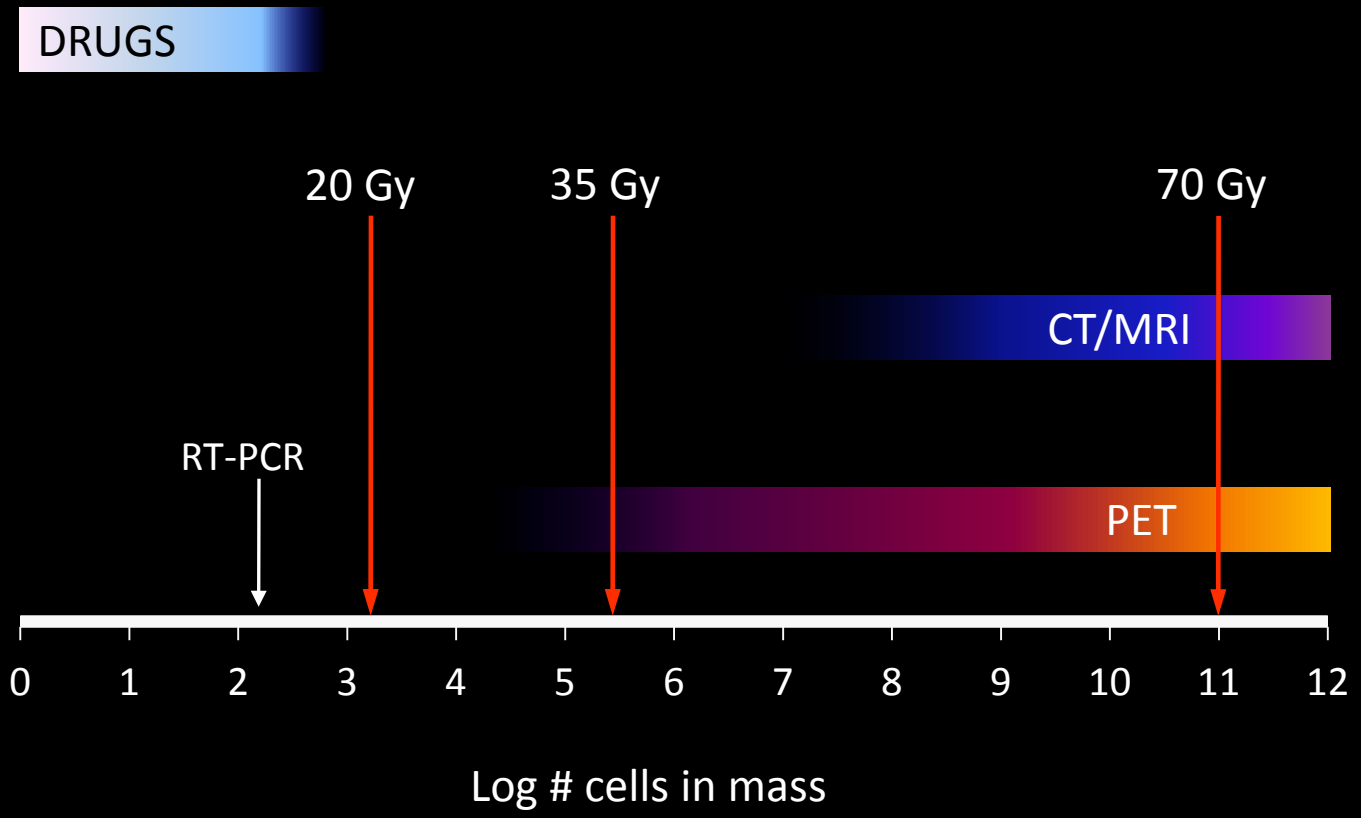
Two canine patients with sino-nasal malignancy



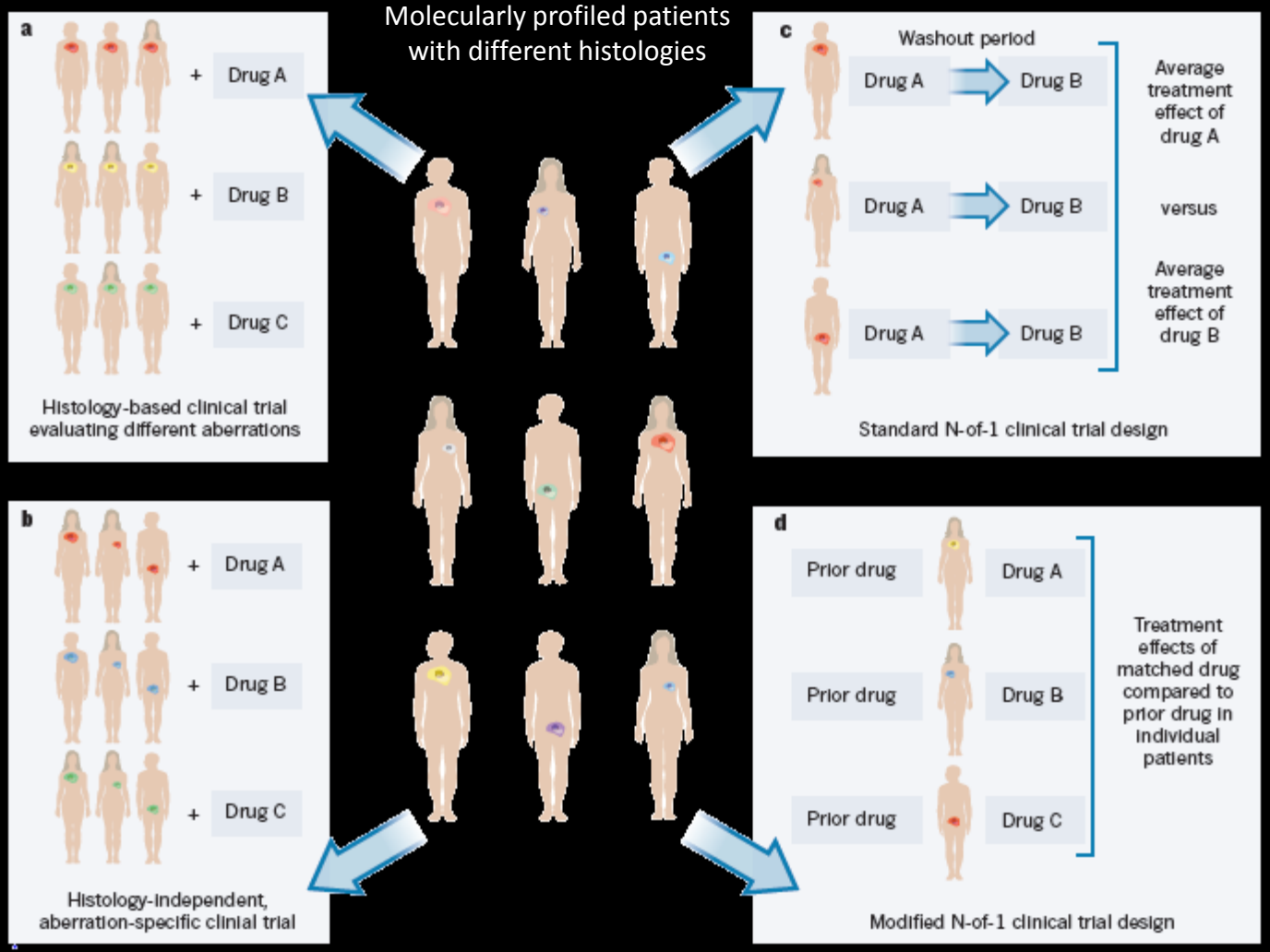


Bowen et al. *R&O* 105: 41 (2012)

The theragnostic imaging blind spot



Clinical trials and molecular profiling



Bedard et al. *Nature* 501: 355 (2013)