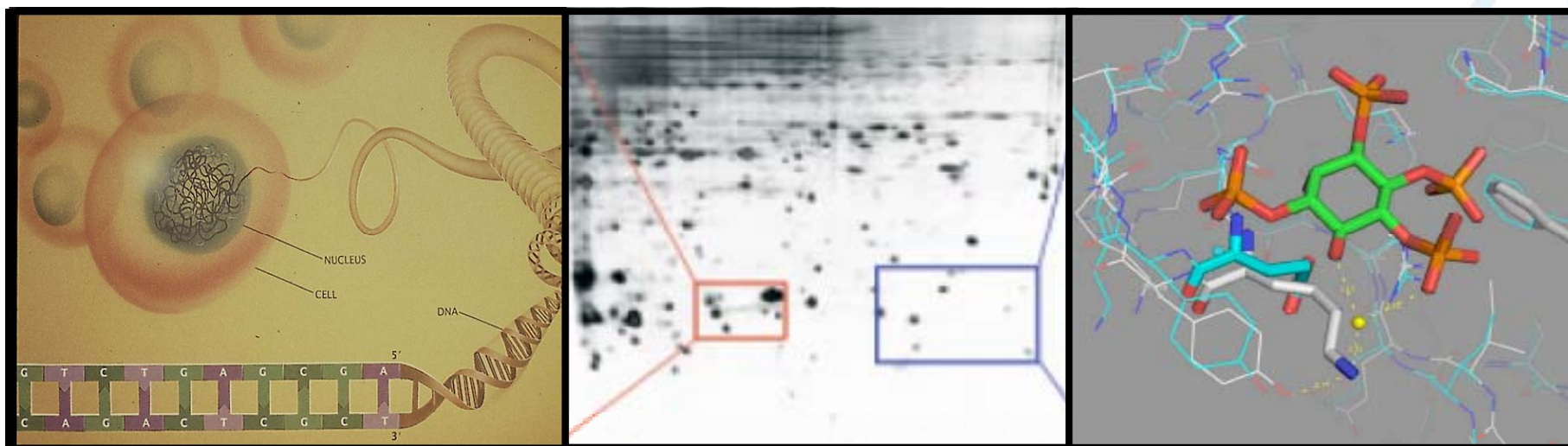


# Genomics-Guided Therapeutic Options for Oncology: Is It Feasible?



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## Introduction

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- Cancer at its most basic essence is a genetic disease.
  - Some intrinsic or extrinsic (carcinogen) factor causes a molecular assault generally leading to some type of DNA damage to lead a cell down the neoplastic pathway.
    - Intrinsic – inherited mutation, aging
    - Extrinsic – cigarettes, UV/radiation exposure, virus, etc
- Discovery of genes altered during tumorigenesis has led to a new and better understanding of the driving forces behind cancer and has provided new ideas for treating cancer.

15 February 2001

# nature

www.nature.com

## the human genome

### Nuclear fission

Five-dimensional  
energy landscapes

### Seafloor spreading

The view from under  
the Arctic icepack

### Career prospects

Sequence creates new  
opportunities

**naturejobs**  
genomics special

# Science

16 February 2001

Vol. 291 No. 5507  
Pages 1145-1434 \$9

## THE HUMAN GENOME

 AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

# Convergence and Emergence of Technologies



Affymetrix GeneChip Systems



Sequenom MassARRAY System



AB SOLiD Next Gen



Illumina Bead Lab



AB DNA Analyzers



Beckman Biomek FX

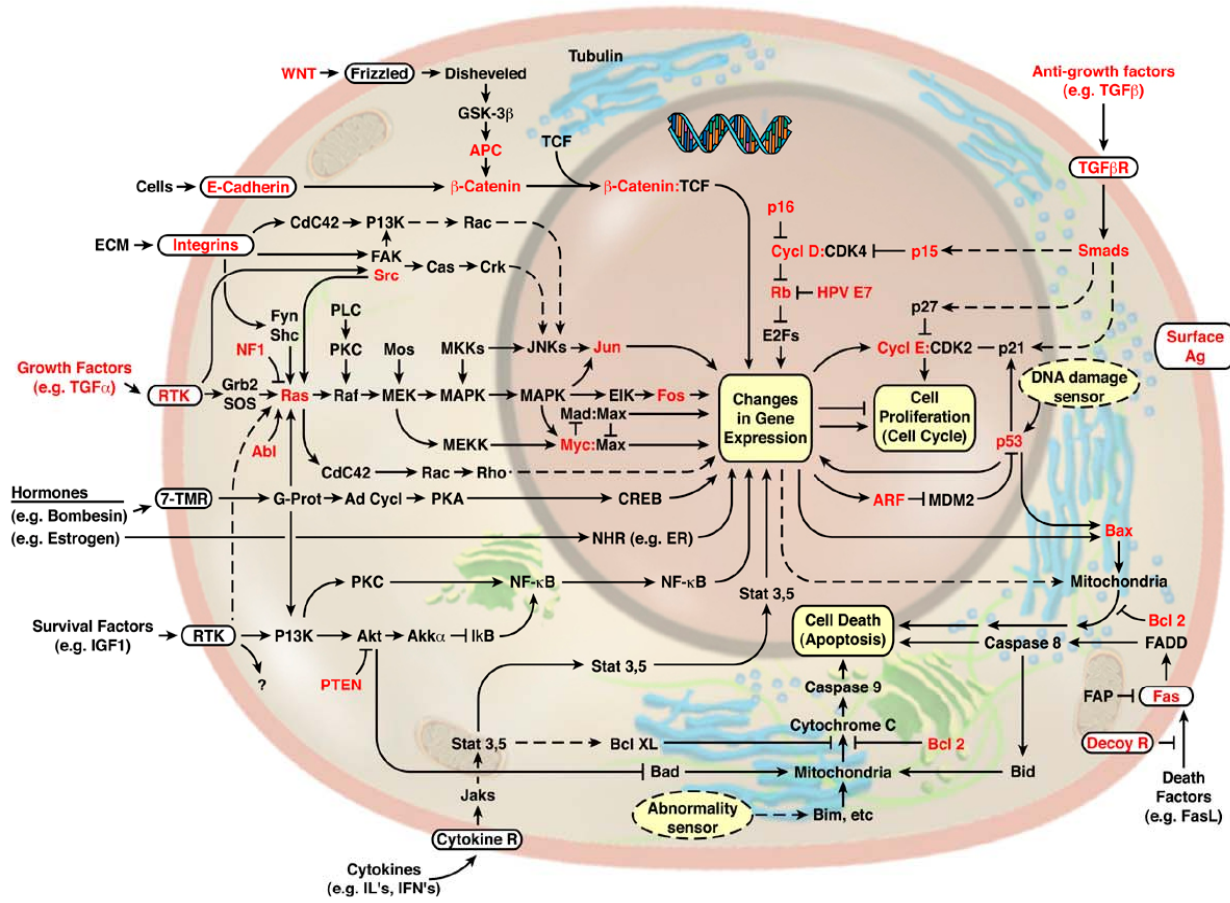


Agilent Array Scanners



Illumina Genome Analyzer

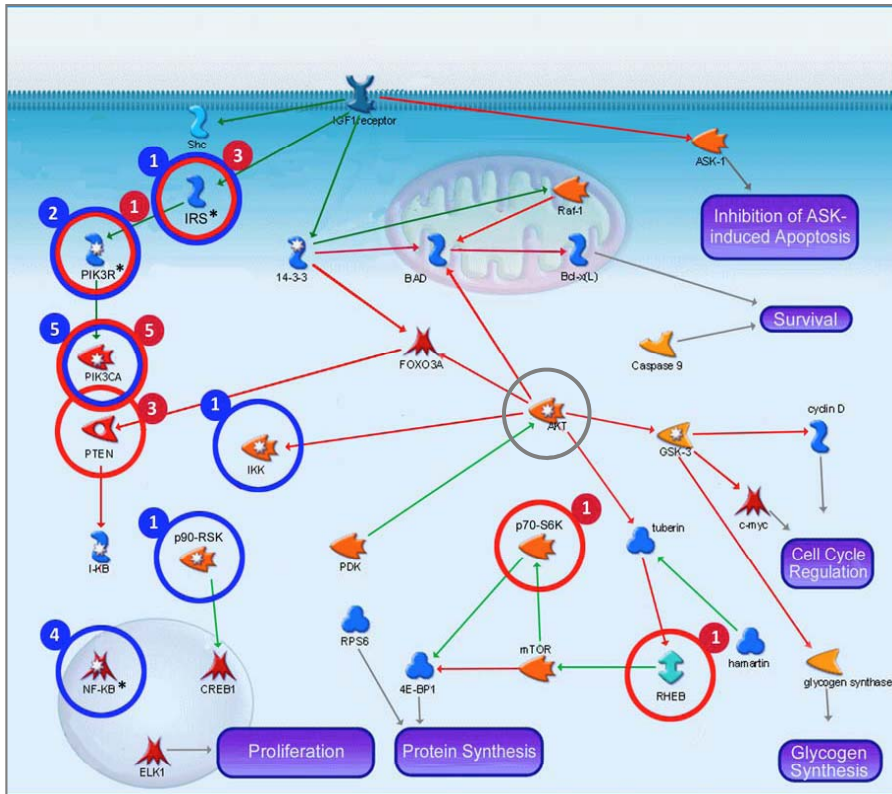
# Biological Pathways and Networks Governing Tumorigenesis



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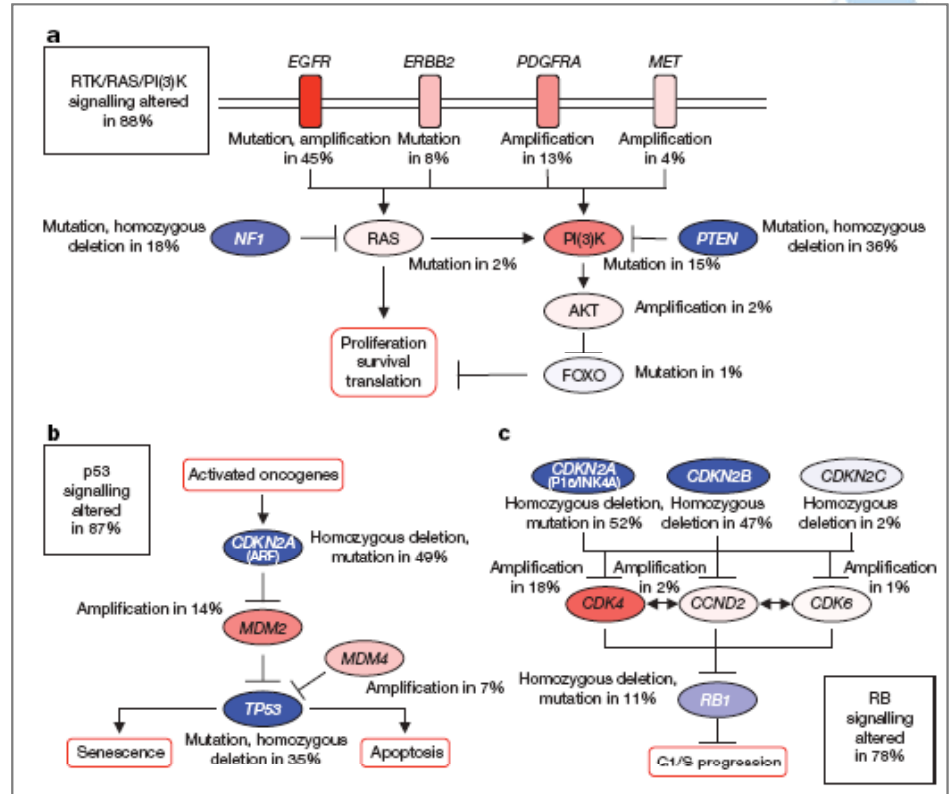
## Commonly Mutated Pathway Model

PI3K/AKT pathway mutations in breast and colon cancer



Woods et al, *Science*, 2007

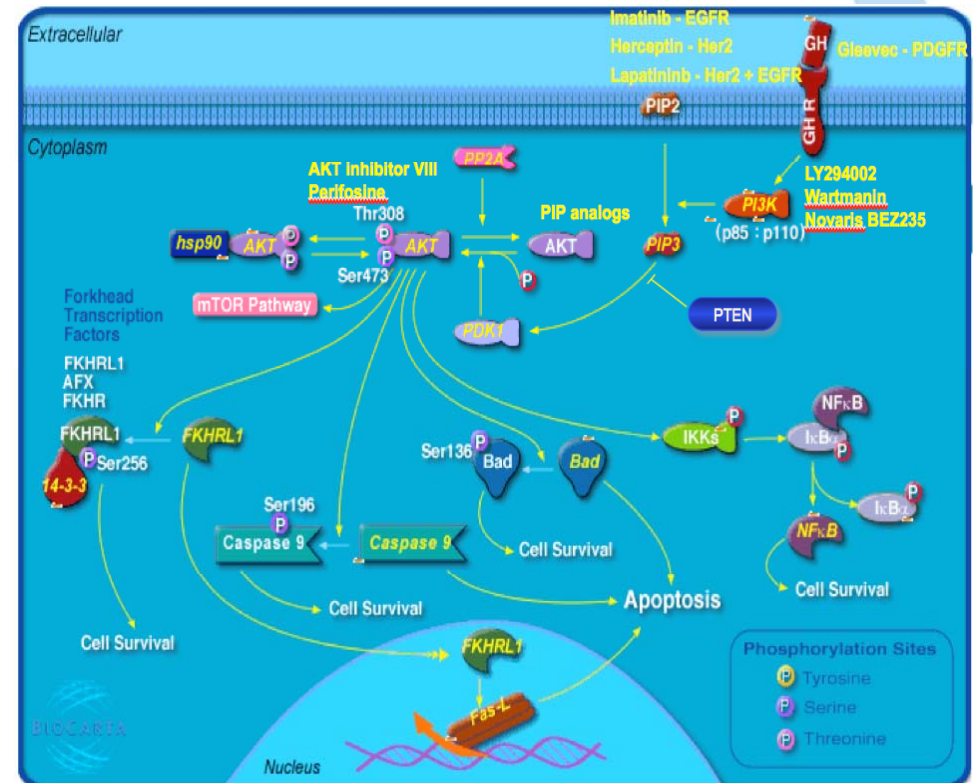
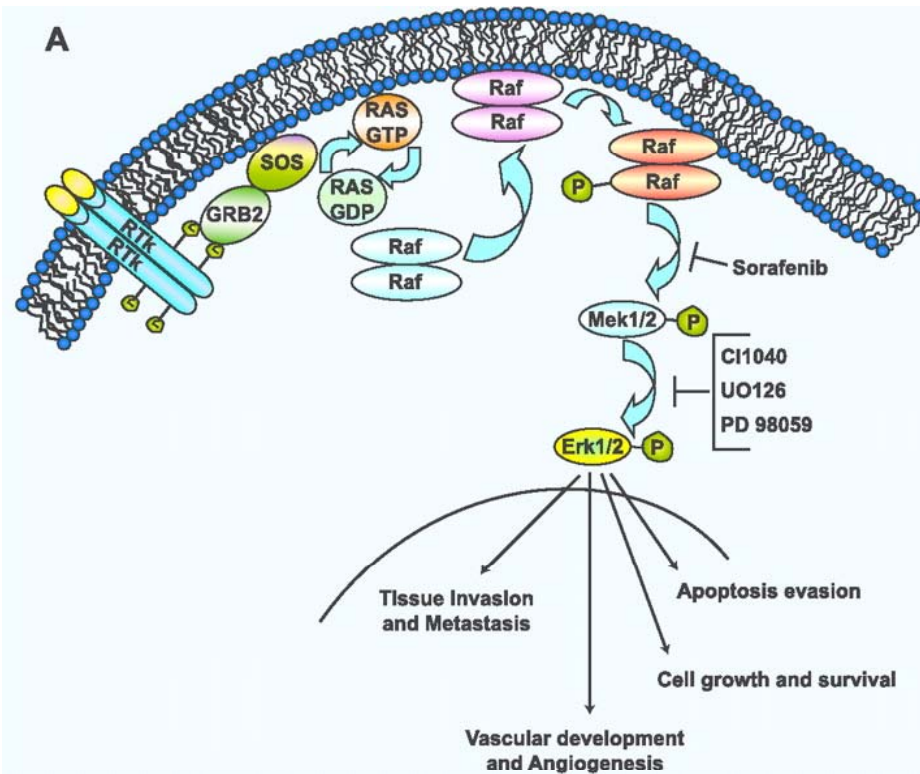
Ras/PI3K/AKT/p53 pathway mutations in glioblastoma



TCGA, *Nature*, 2007

# Biological Pathways and Networks Governing Tumorigenesis

## Targeted Chemotherapy



## Targeted Therapeutics

- Many targeted therapeutics are aimed at molecules associated with genomic alterations including somatic mutations

Tumor type	Genomic Alteration	Proposed Mechanism	Drug
CML	BCR-ABL (mutation)	Activating fusion oncogene	Imatinib (dasatinib)
GIST	cKIT, PDGFR mutation	Activating mutations	Imatinib
Breast	Her2-neu	Kinase Activation	Trastuzumab
Breast	Her2-neu/EGFR	Kinase Activation	Lapatinib
NSCLC	EGFR (mutation)	Kinase Activation	Gefitinin/Cituximab
NSCLC	ELM4-ALK	Activating fusion oncogene	PF-02341066
Myeloma	NF $\kappa$ B/proteasome (mutation)	Aberrant degradation/NF $\kappa$ B pathway activation	Bortezomib
BCC	PTCH2 mutation	Hedgehog pathway activation	GDC-0449
Melanoma/RCC	BRAF mutation/VEGFR-2/PDGFR	Kinase Activation	Sunitinib
AI Prostate	PI3K/AKT/PTEN	PI3K/AKT pathway activation	Temsirolimus
TNBC/Basal	BRCA1/BRCA2 mutation	Defects in double strand break repair	PARP inhibitors

## Rationale

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- Can we improve clinical management through increasing discovery and knowledge of the alterations driving tumorigenesis.
  - Discovery of new drug targets
  - Clinical trial design through patient stratification
  - Knowledge based-therapeutic decision making
- Is molecular profiling using new technologies a rationale approach to increase the “options” available to oncologists for treating cancer patients, namely those who fail standard of care or those patients with otherwise chemo-resistant metastatic cancer?

## Cancer Alterations Are Uncovered With Different Technologies

Point Mutation

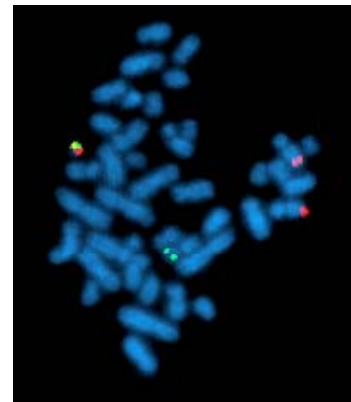
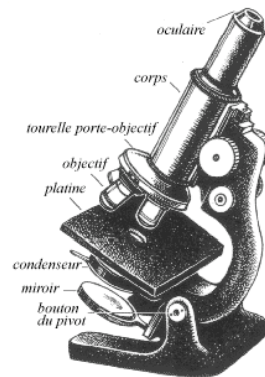


Agilent Array Scanner

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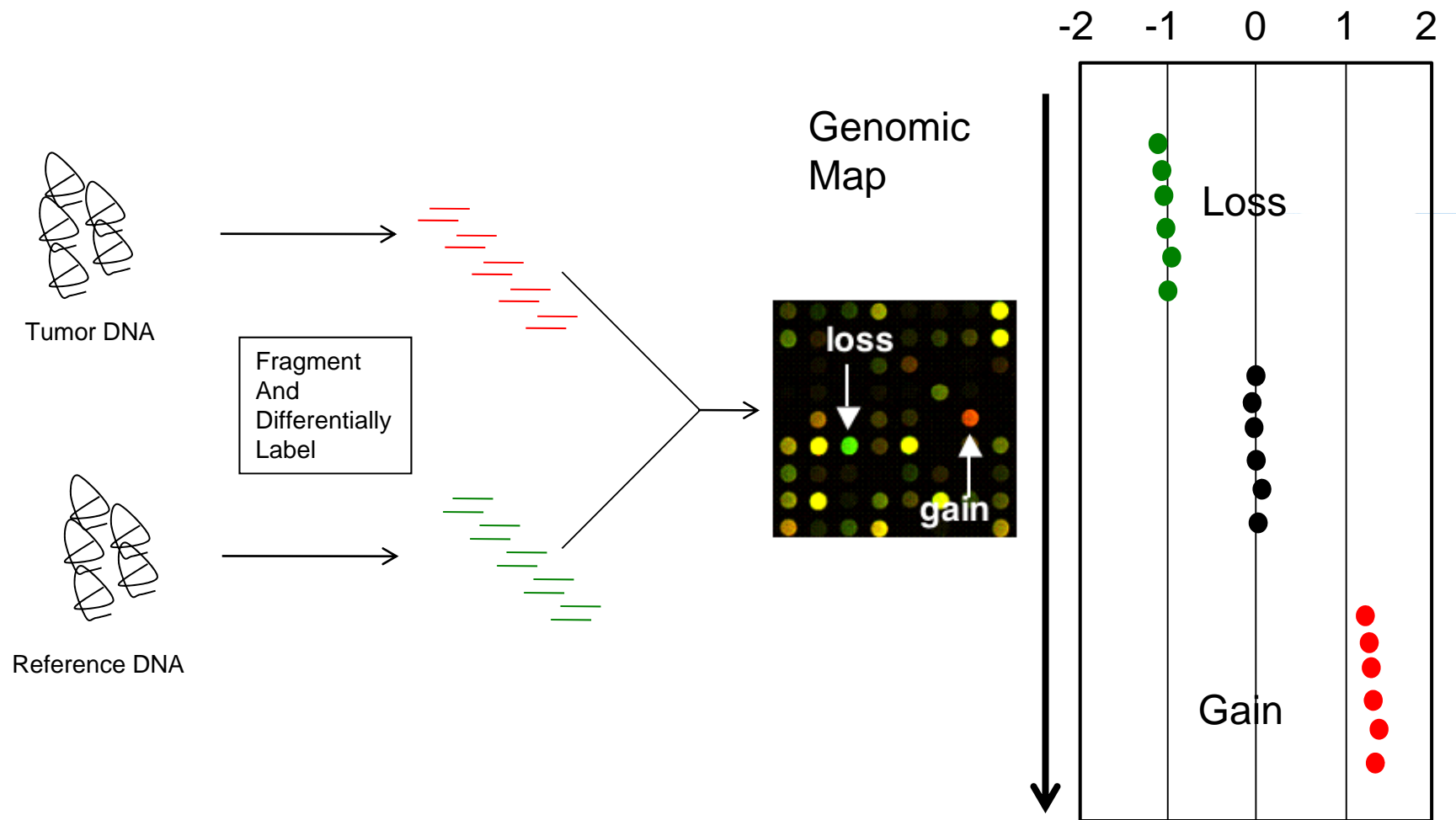


Gross Rearrangement



# Cancer Genome Interrogation

## Comparative Genomic Hybridization

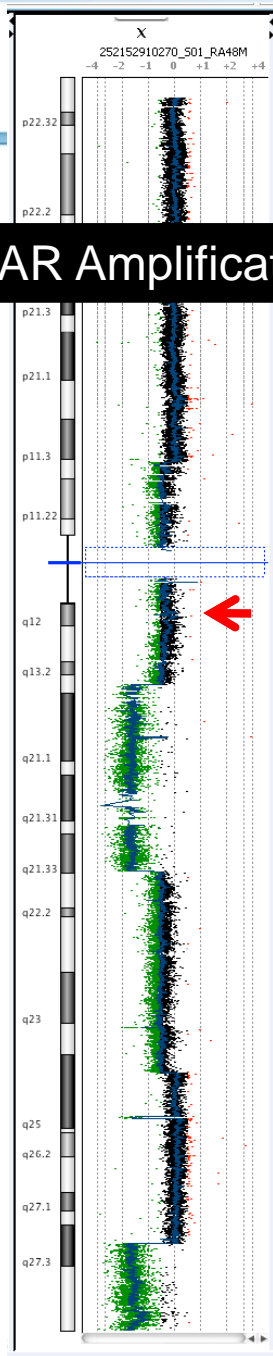


## Case Study 1

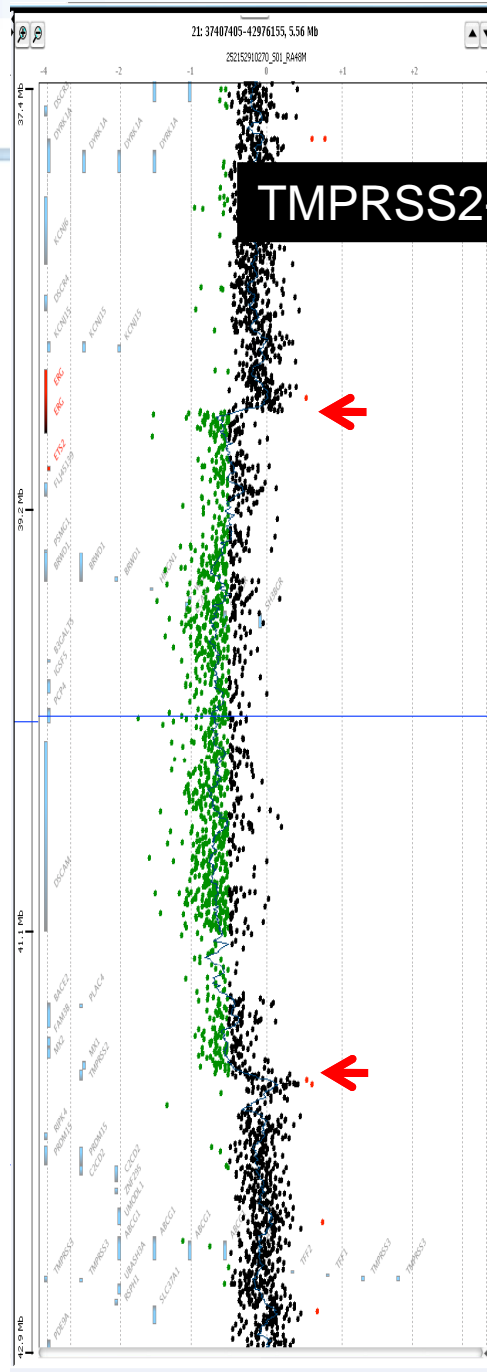
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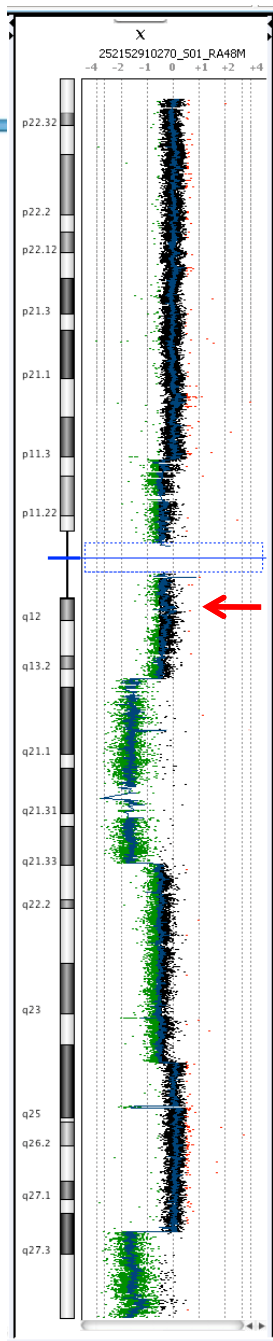
- 70 year old patient with Androgen Independent metastatic prostate cancer
- Frozen bone biopsy available
- Genomic analysis of metastatic tumor (CGH and Sanger Sequencing)

No AR Amplification



TMPRSS2-ERG breakpoint event





AR H874Y ligand binding domain activating mutation

