

암유전체 정보 분석

질병 유전체 분석법

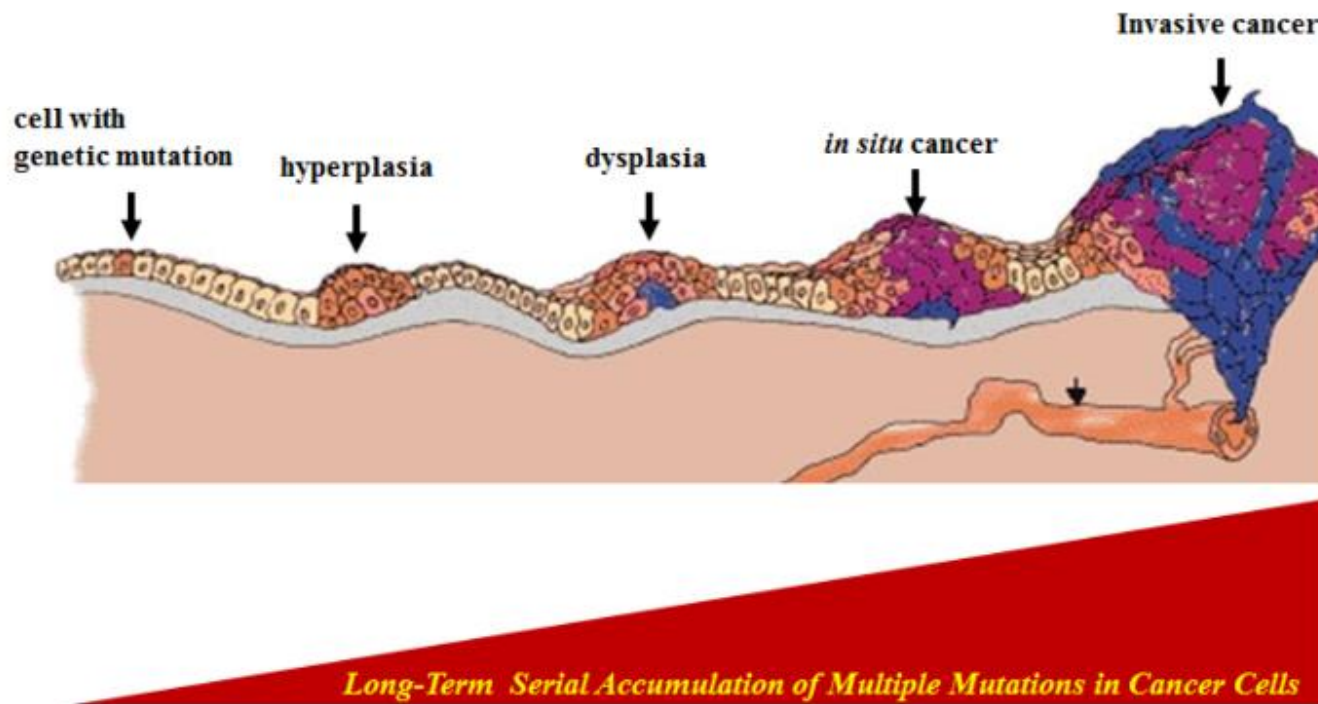
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The stages of tumor development

Stages of Tumor Development: **Cancer is a Disease of the Genome**

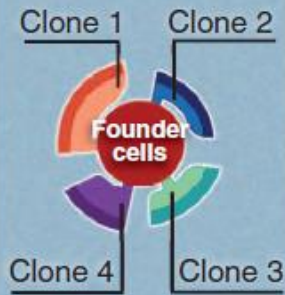


- Clonal heterogeneity in primary tumor
- Clonal evolution after metastasis/treatment

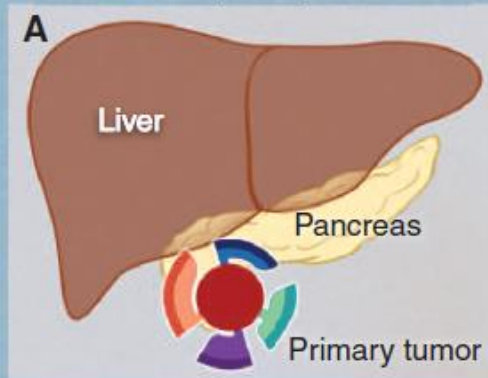
Image from 질병유전체분석법

4 types of genetic heterogeneity in tumors

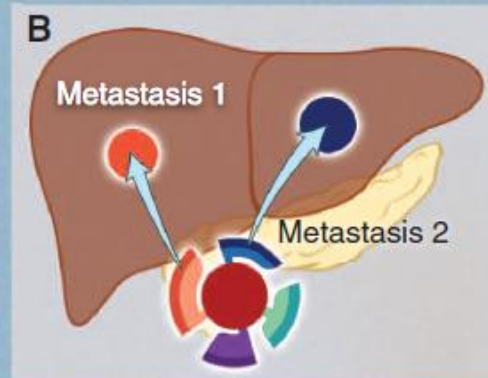
clonal heterogeneity



Intratumoral heterogeneity
within a primary tumor



Intermetastatic heterogeneity
between two metastases



Intrametastatic heterogeneity
within metastatic lesions

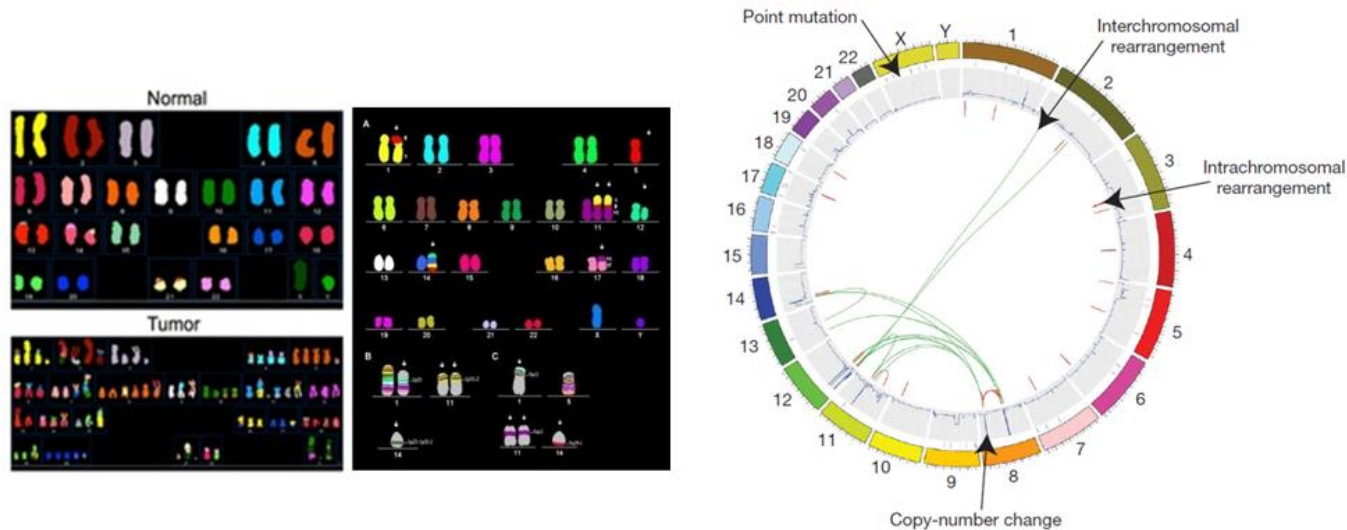


Interpatient heterogeneity



Somatic mutations in tumors

Cancer is a Disease of the Genome: **Somatic Mutations in Cancer Genes**



Group	Mechanism	Detection method	Typical genes	Targeting drug(s)
• Point mutation	Somatic mutation	sequencing	EGFR, BRAF, PIK3CA, AKT1	Gefitinib or Erlotinib (EGFR inhibitors)
• Fusion gene	Chromosomal rearrangement (Inter-/intra-translocation)	FISH, paired-end sequencing	BCR-ABL, TMPRSS2+ETS-family genes (ERG/ETV1/ETV4)	Imatinib mesylate (ABL inhibitor)
• Gene copy number	Gene amplification	arrayCGH	ERBB2=Her2	Trastuzumab (mAb specific to ERBB2)

Modified from Stratton MR et al. Nature 2009;458:719-724

Image from 질병유전체분석법

Somatic mutation frequencies across cancers

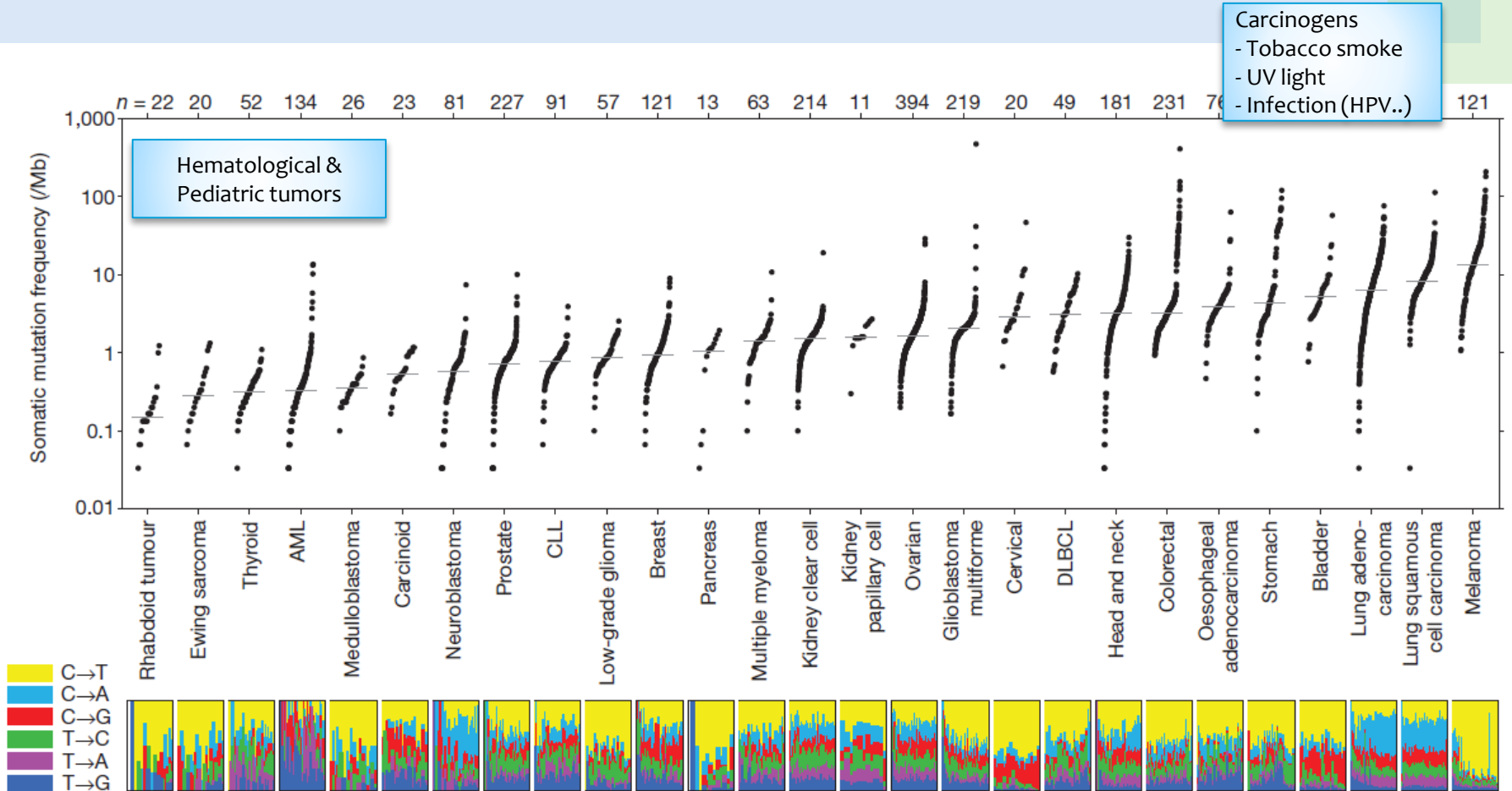
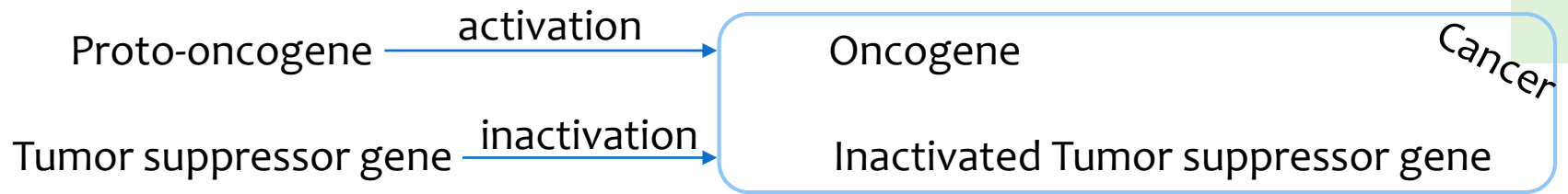


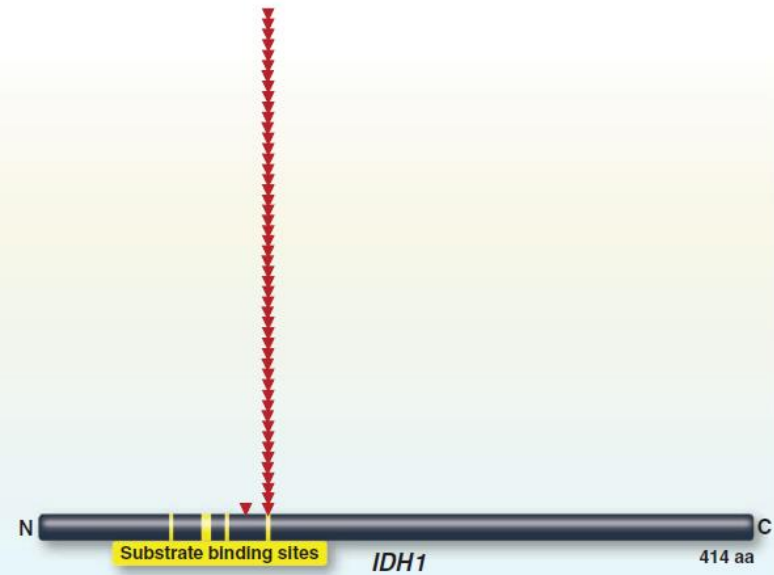
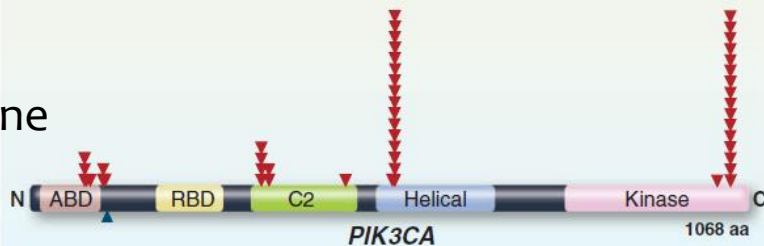
Image from Lawrence MS et al., 2013

Cancer genes



▼ = Missense mutation
▲ = Truncating mutation

Oncogene

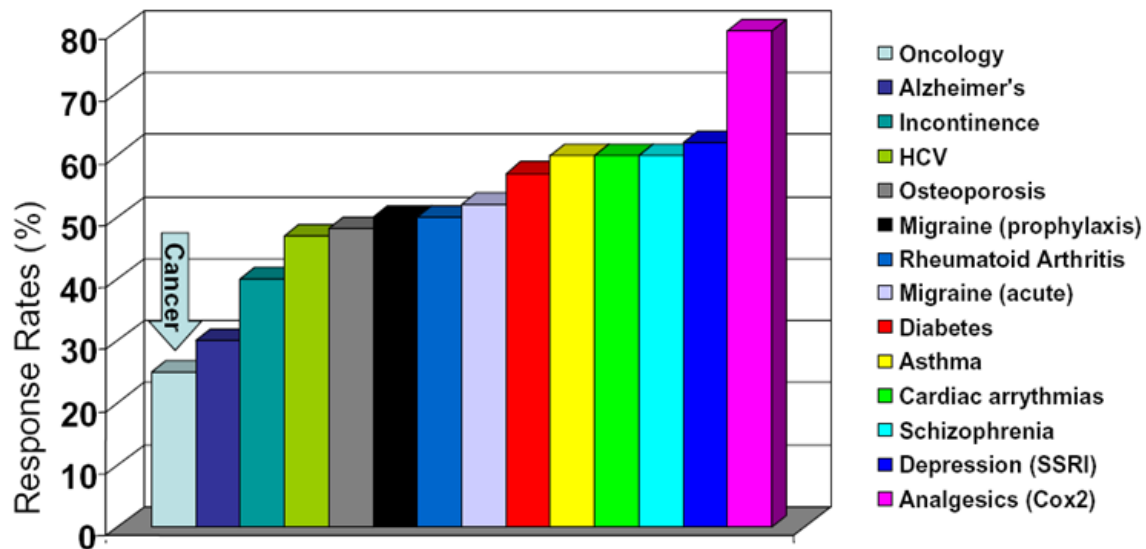


Tumor suppressor gene



Cancer Drugs

Average Response Rate to Drug Treatment:
Most Cancer Drugs Have Low Efficacy & Strong Side-Effects

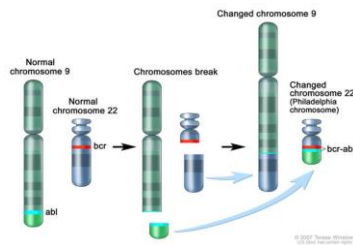


Due to Various mutations
Drug resistance

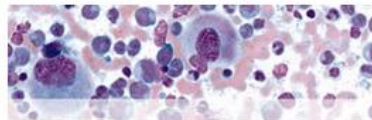
Slide: Paul Waring, Genentech (modified)

Targeted cancer therapy

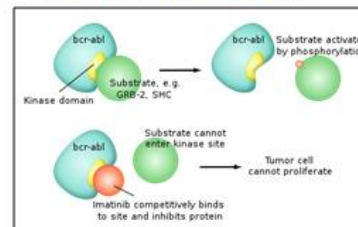
Typical Examples of Targeted Cancer Therapy: **Gleevec** and **Iressa**



Chronic Myeloid Leukemia (CML)



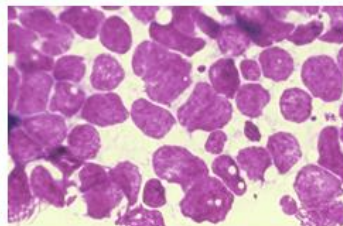
Bcr-Abl fusion mutation



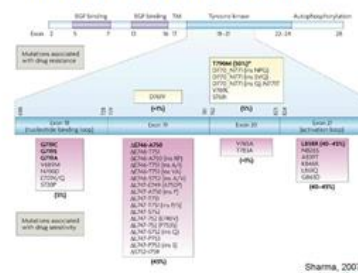
Gleevec



Non-Small Cell Lung Cancers (NSCLC)

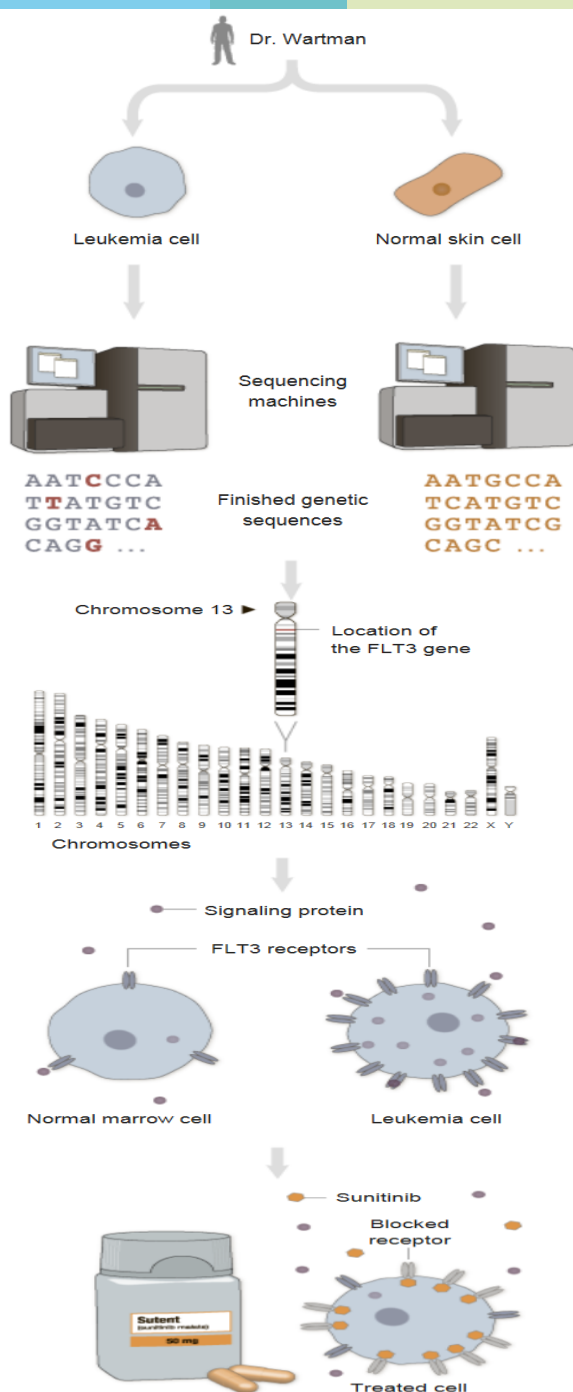


Somatic EGFR mutations



Iressa





SAMPLE

The sequencing process began with two small tissue samples taken from Dr. Wartman, abnormal leukemia cells removed from his bone marrow and normal skin cells.

SEQUENCE

The team extracted both DNA and RNA from his cells, giving it two types of genetic material to test. After a month of work to sequence the material, the team had a large set of results to feed to a supercomputer for analysis.

COMPARE

Dr. Wartman's DNA sequences showed some genetic mutations possibly related to his leukemia, but none seemed treatable. But RNA sequencing revealed that a normal gene, FLT3, was overactive in his leukemia cells.

TARGET

The FLT3 gene helps create new white blood cells in the marrow. The cells in Dr. Wartman's marrow were covered with an extremely high number of FLT3 receptors, which appeared to be driving the growth of his leukemia.

TREAT

An expensive drug called sunitinib, typically used to treat kidney cancer, was known to block FLT3 receptors. Two weeks after Dr. Wartman began taking the drug, tests revealed that his leukemia was in remission.

Personalized medicine



Wartman

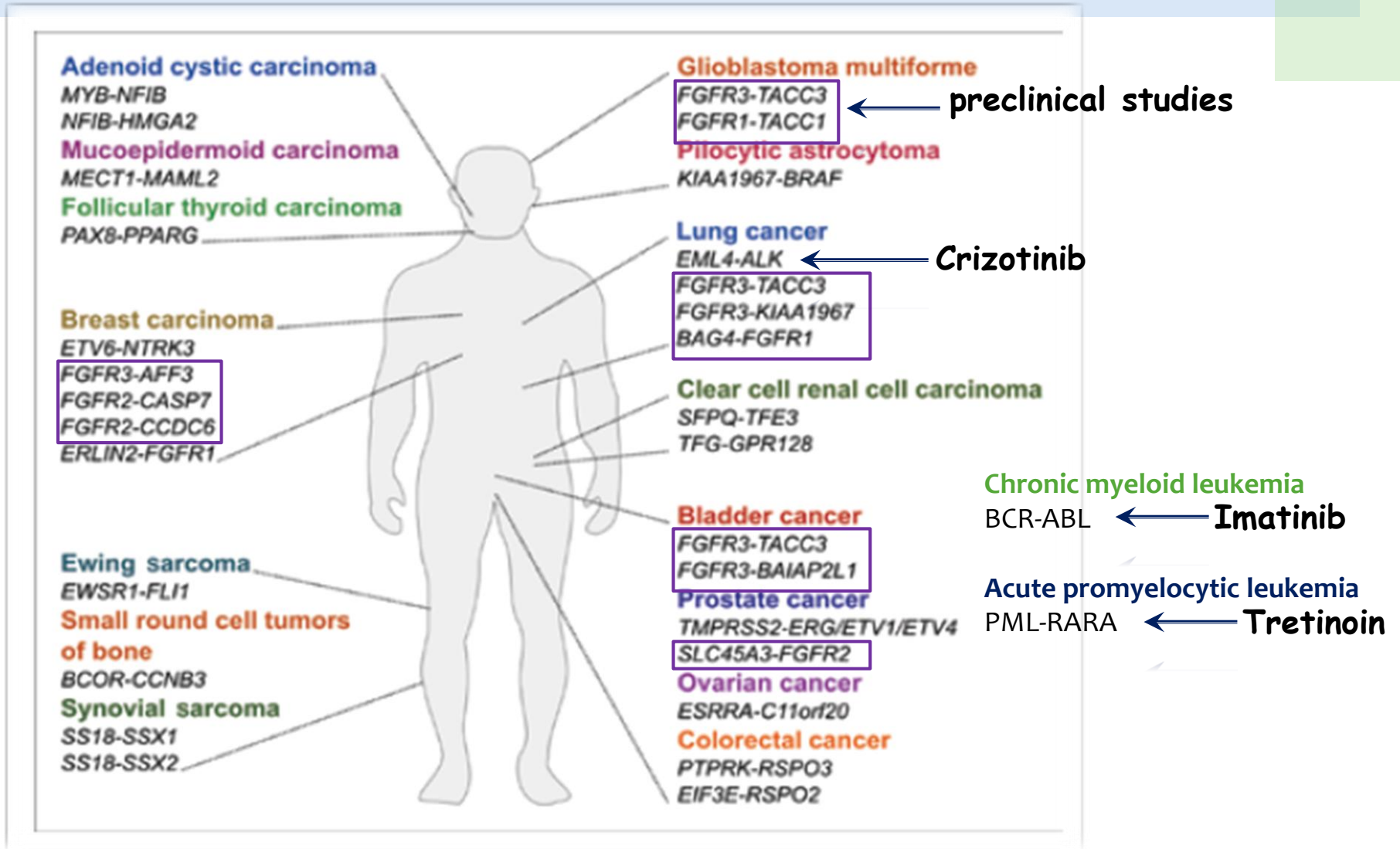


Steve Jobs
Pancreatic cancer



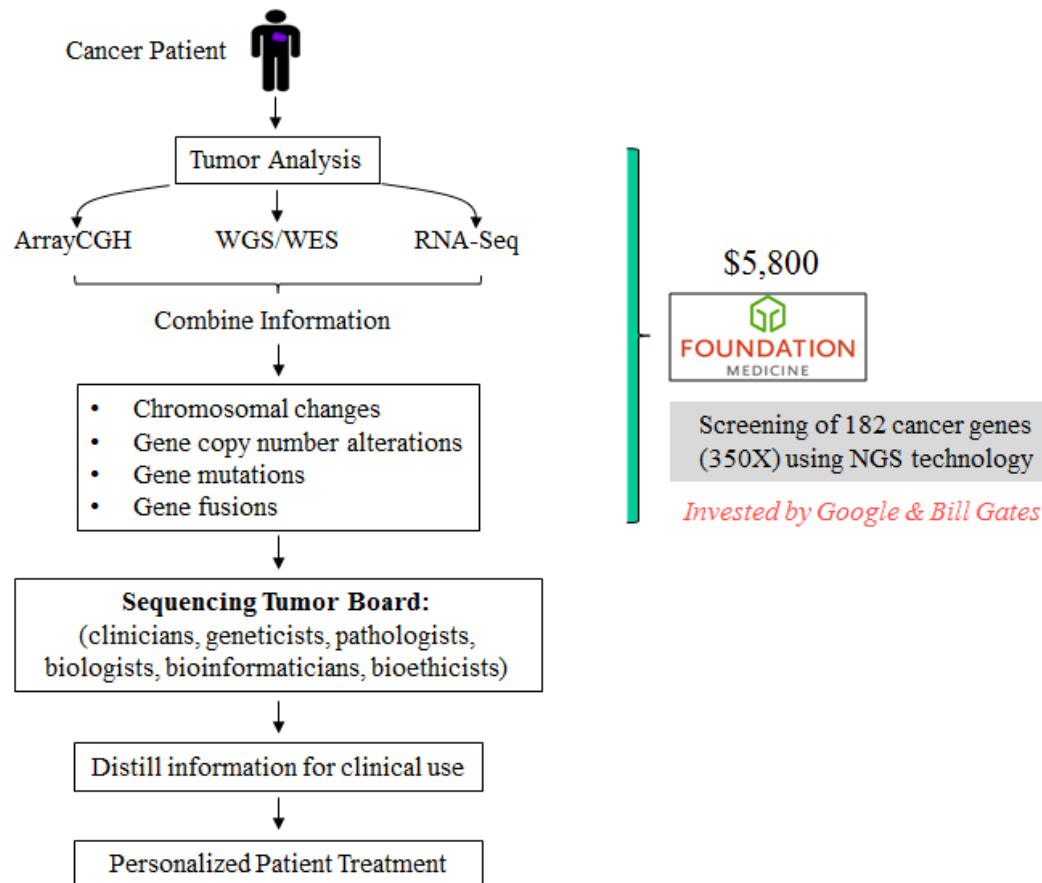
Christopher Hitchens
Esophageal cancer

Drug and Fusion location in the human body



Personalized cancer treatment

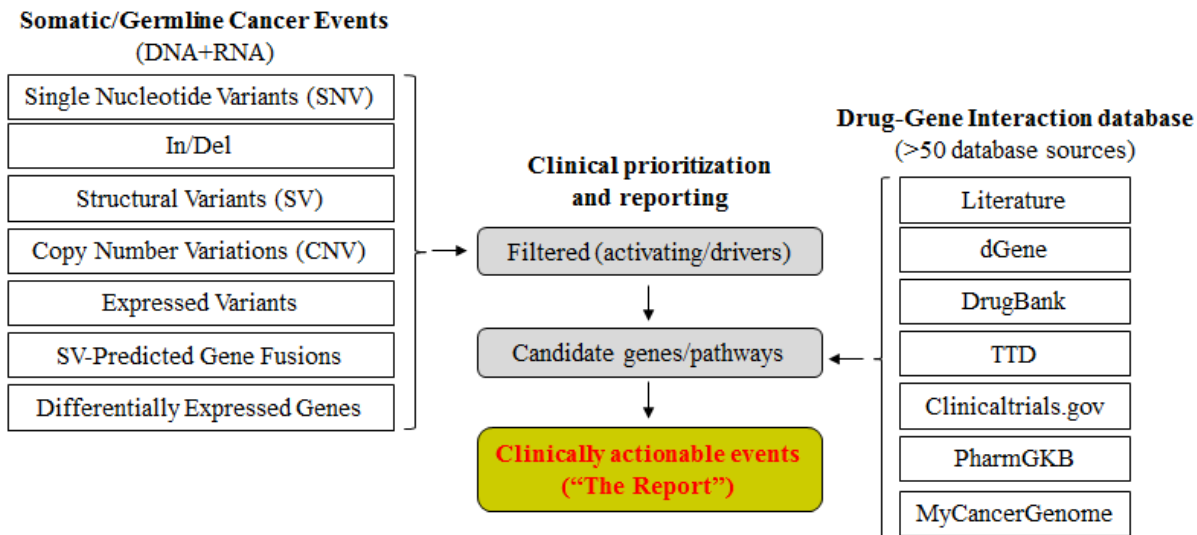
Personalized Cancer Diagnosis and Targeted Therapy



Modified from Corless CL. Science 2011;334(6060):1217-8

Actionable mutations

Linking Somatic Variants to Therapies: **Therapeutic Interpretation of Variants**

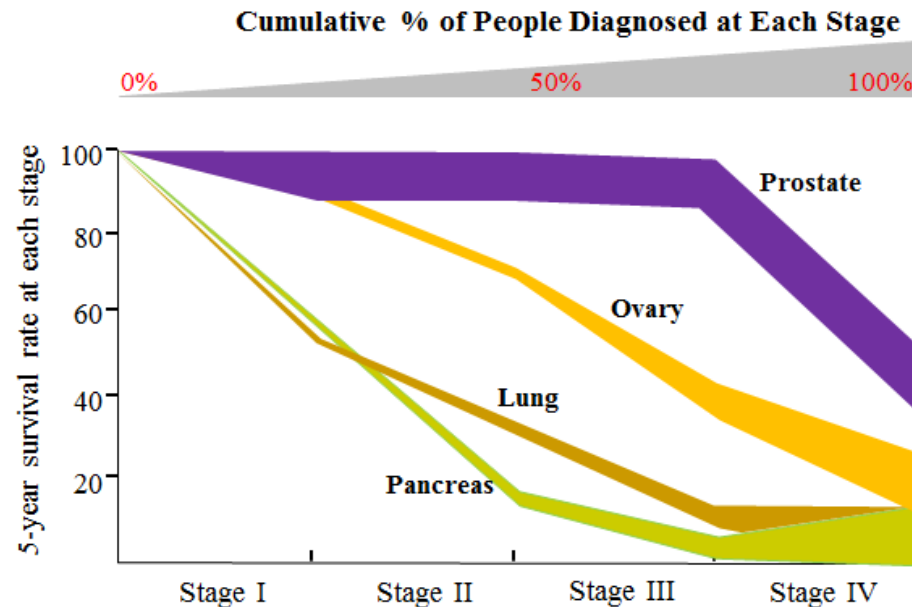


Modified from Malachi & Obi Frifflth

dGene: collection of Druggable Genes
TTD: therapeutic targets drug

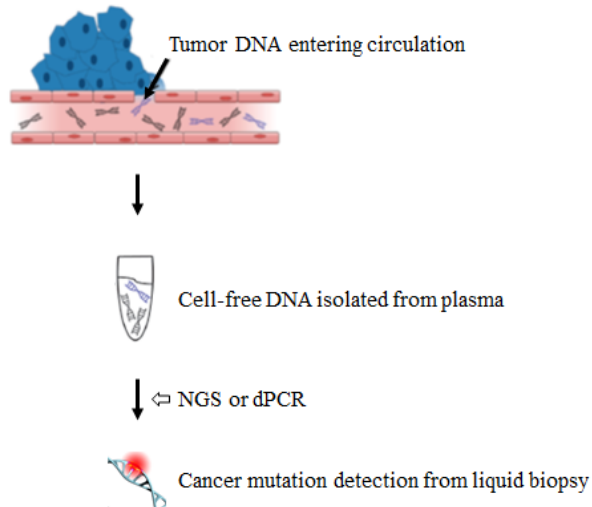
The importance of Early diagnosis

Why **Early Detection** Is the Best Way to Beat Cancer



ctDNA sequencing

Cancer Genome Analysis from Cancer Patient's Blood (Plasma)



Applications of Circulating Tumor DNA (ctDNA)

1. Detection or screening of early cancers
2. Monitoring of disease progression
3. Determination of patient prognosis
4. Prediction of treatment response
5. Early detection of recurrence or resistance

ctDNA sequencing

Tumor-Associated Genetic Aberrations in Circulating Free DNA

Tumor type	Tumor-specific aberration	Source	Technique
Colorectal cancer	APC, KRAS, PIK3CA, TP53	Plasma and/or serum	BEAMing, PCR-SSCP, ME-PCR
Breast cancer	PIK3CA, TP53	Plasma and/or serum	ARMS-Scorpion PCR, BEAMing, TAm-Seq and digital PCR
Ovarian cancer	TP53, PTEN, EGFR, BRAF, KRAS, PIK3CA	Plasma or serum	Tam-seq, Digital PCR, Fluorescent-PCR
Hepatocellular carcinoma	SNV	Plasma	WGS
Pancreatic cancer	KRAS	Plasma	MASA PCR, RFLP-PCR
Oral squamous-cell carcinoma	Microsatellite loci	Serum	PCR
Non-small-cell lung cancer	KRAS	Plasma	ARMS-qPCR
Breast and osteosarcoma	Genomic alterations	Plasma and serum	Nested-real time PCR
Colorectal and breast cancer	Chromosomal alterations	Plasma	WGS

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Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84

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