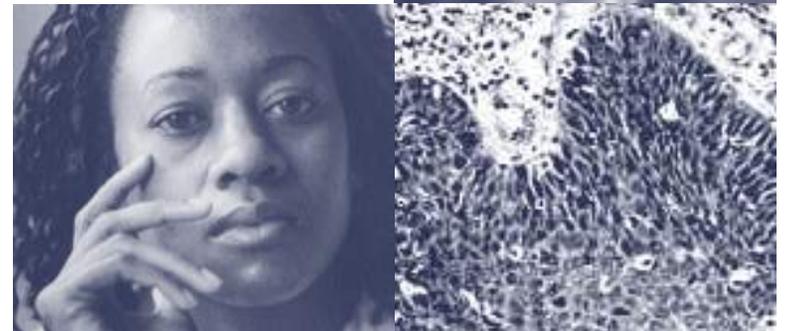




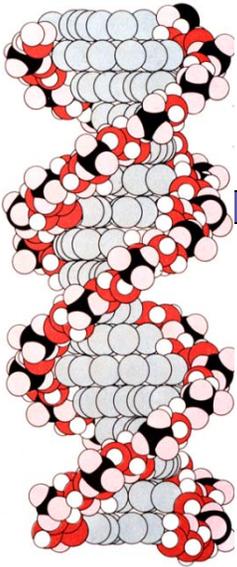
Cancer Genetics and Epigenetics: Growing Impact on Cancer Medicine

William G. Nelson, M.D., Ph.D.
**Director, Johns Hopkins Sidney Kimmel
Comprehensive Cancer Center**

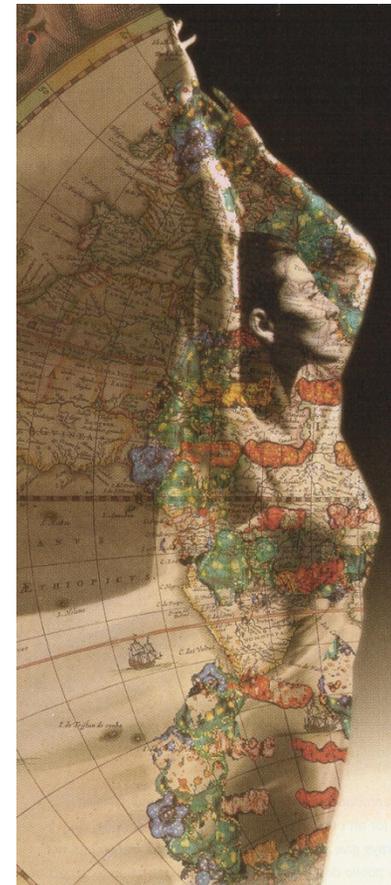
- **Movement toward Personalization of Cancer Care**
- **Genetic/Epigenetic Biomarkers as Resource Allocation Tools**



Mapping/Sequencing of the Human Genome



- Milestone in molecular biology
- Revolutionized cancer genetics and epidemiology
- New technologies for molecular profiling of cancer cells
- Unprecedented opportunities for the discovery of new approaches to cancer treatment and prevention
- Greatly augmented public expectations
- Increased cancer care costs?



Transformation of Medicine by Translational Research*

20th century medicine

treat disease when symptoms arise and normal function is compromised

morphological understanding of disease state

high financial and disability costs

21st century medicine

intervene before symptoms appear and preserve normal function

cellular/molecular understanding of evolving disease process

opportunity for improved efficacy and efficiency

implications

prevention of disease and preservation of health

prediction of disease risk permitting less toxic and more effective intervention

personalization of risks and treatments; greater participation of patients in health care decision-making

*adapted from Hood L, von Eschenbach A, and Zerhouni E (2005-6)

Current Challenges of Drug Discovery and Development Flow of Approved Products*

Lead Identification

Chemistry
Lead
Optimization

Pharmacologic
Candidate Selection

Production &
Formulation

Safety
Assessment

Phase I
Clinical Trials

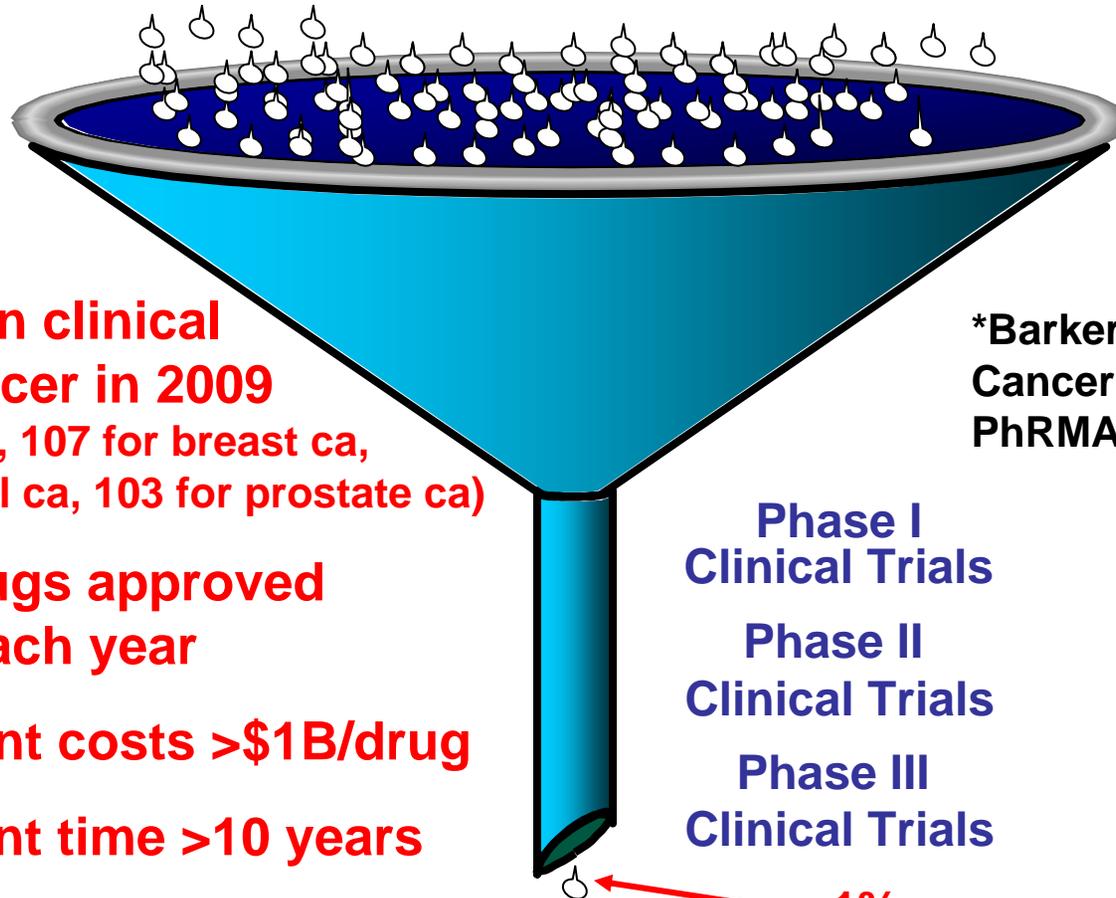
Phase II
Clinical Trials

Phase III
Clinical Trials

approval by U.S.
Food and Drug Administration

*Barker A, National
Cancer Institute;
PhRMA (www.phrma.org)

Current Challenges of Drug Discovery and Development Flow of Approved Products*



- **861 drugs in clinical trials for cancer in 2009**
(122 for lung ca, 107 for breast ca, 70 for colorectal ca, 103 for prostate ca)
- **1-2 new drugs approved for cancer each year**
- **development costs >\$1B/drug**
- **development time >10 years**

*Barker A, National Cancer Institute;
PhRMA (www.phrma.org)

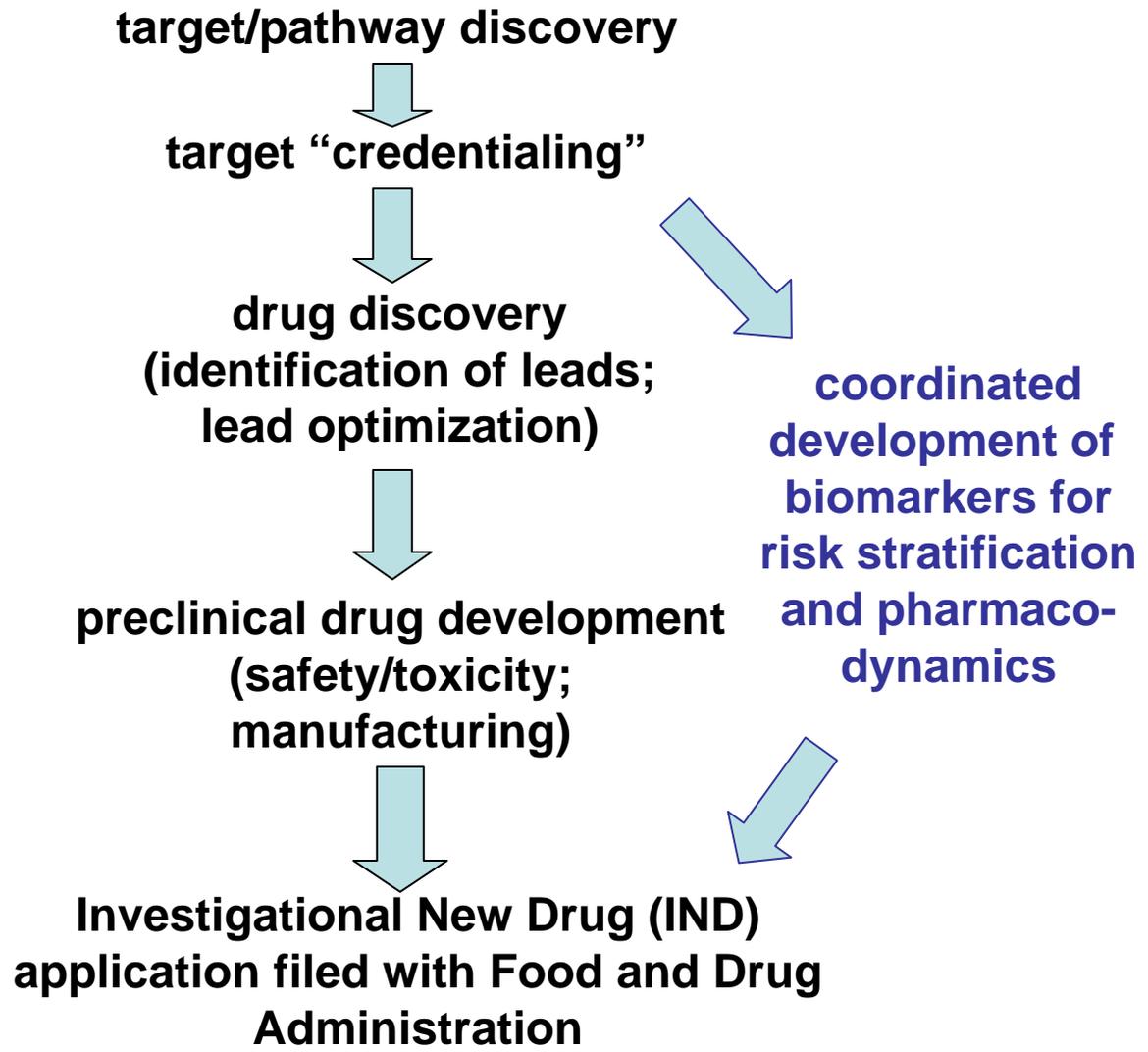
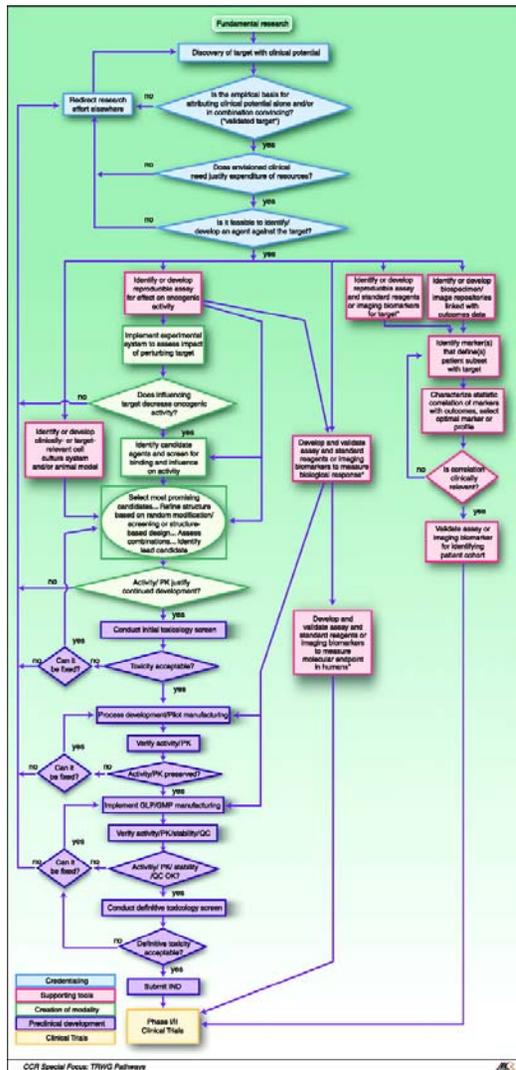
Phase I
Clinical Trials

Phase II
Clinical Trials

Phase III
Clinical Trials

<1%
approval by U.S.
Food and Drug Administration

The Discovery and Development of Anti-Cancer Drugs: Role of “Translational Research”*



*Schilsky RL *et al.* Clin Cancer Res. 14: 5685-91 (2008)

Historical Development Pathway for Anti-Cancer Drugs

**Investigational New Drug (IND)
application filed with Food and Drug
Administration**



Phase 1 (Toxicity) Testing
Goal is to determine the dose and
dose-schedule for the drug
(MTD = maximally tolerated dose; DLT = dose-limiting toxicity)



Phase 2 (Efficacy) Testing
Goal is to estimate/define drug benefit
(Response rates: complete responses + partial responses)



Phase 3 (Comparative Efficacy)
Goal is to test patient benefit



FDA Approval/Labeling for Marketing

New Development Pathway for Anti-Cancer Drugs

**Investigational New Drug (IND)
application filed with Food and Drug
Administration**



Phase 1/2 (Toxicity/Efficacy) Testing
Goals are: (i) to determine optimal biological dose
(the dose that maximizes “on-target” effects
while minimizing “off-target” effects, **using molecular
biomarker of pharmacodynamic action**),
and (ii) to estimate drug benefit in setting with
maximal chance of efficacy
(**using molecular biomarker of risk/for indication**)

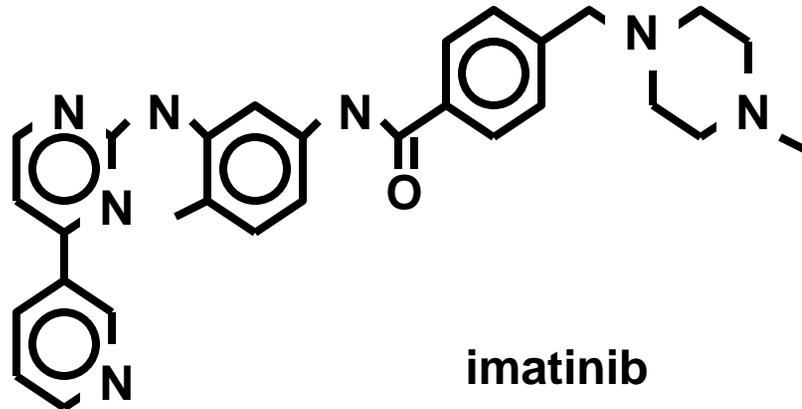


Phase 3 (Comparative Efficacy)
Goal is to test patient benefit



FDA Approval/Labeling for Marketing

Imatinib (Gleevec®): “Targeted” Therapy for Chronic Myelogenous Leukemia (CML) and Gastrointestinal Stromal Tumors (GISTs)

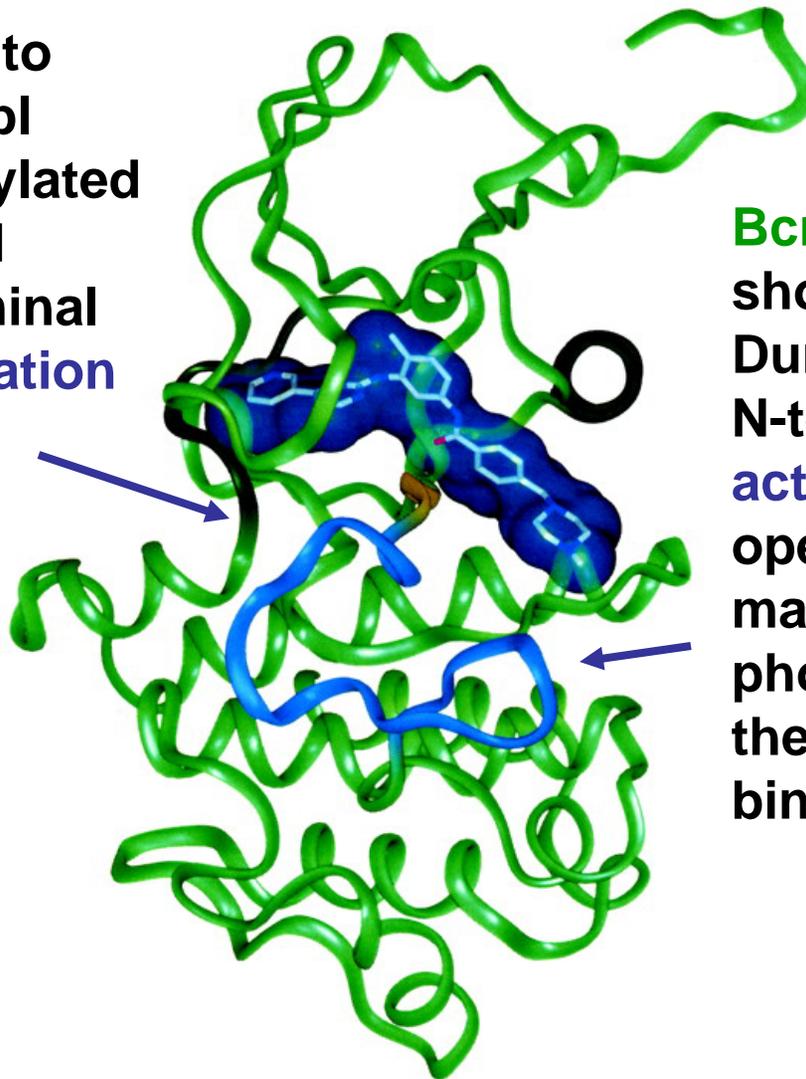


imatinib



Imatinib Binding to Bcr-Abl Kinase Domain

Imatinib binds to inactive Bcr-Abl (not phosphorylated at Tyr-393) and distorts N-terminal region of **activation loop**, freezing enzyme into an inactive conformation.



Bcr-Abl kinase domain showing **activation loop**. During catalysis, the N-terminal region of the **activation loop** adopts an open conformation to bind magnesium and coordinate phosphate groups of ATP; the C-terminal region binds substrates.

Nagar B *et al.*
Cancer Res
62: 4236-4243 (2002)

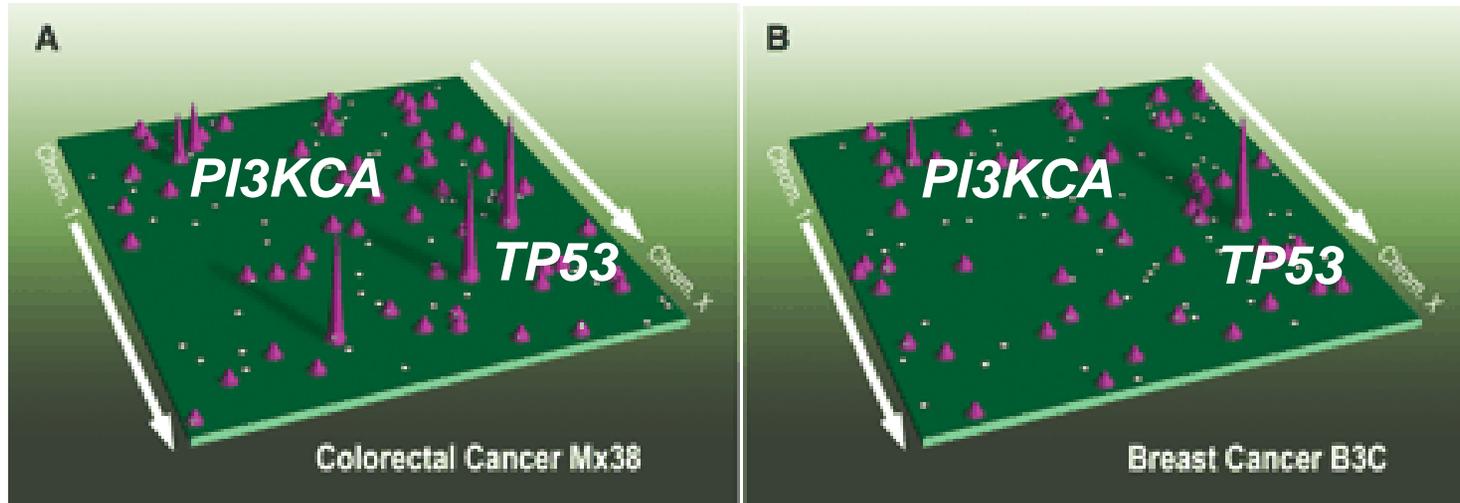
Imatinib Efficacy in Chronic Myelogenous Leukemia (CML)*

Hematologic response to imatinib in *Bcr-Abl* chronic myelogenous leukemia (CML)

DOSE (mg/DAY)	ALL	PATIENTS WITH	PATIENTS WITH
	PATIENTS	RESPONSES	COMPLETE RESPONSES
	no.	no. (%)	
25 or 50	6	2 (33)	0
85	4	2 (50)	1 (25)
140	3	3 (100)	1 (33)
200 or 250	16	16 (100)	9 (56)
300–1000	54	54 (100)	53 (98)
Total	83	77 (93)	64 (77)

*Druker BJ et al. *New Engl J Med* 344:1031-1037 (2001)

High Dimensional Sequencing of Cancer Genomes Reveals Both Common and Rare Gene Defects in Human Cancers*

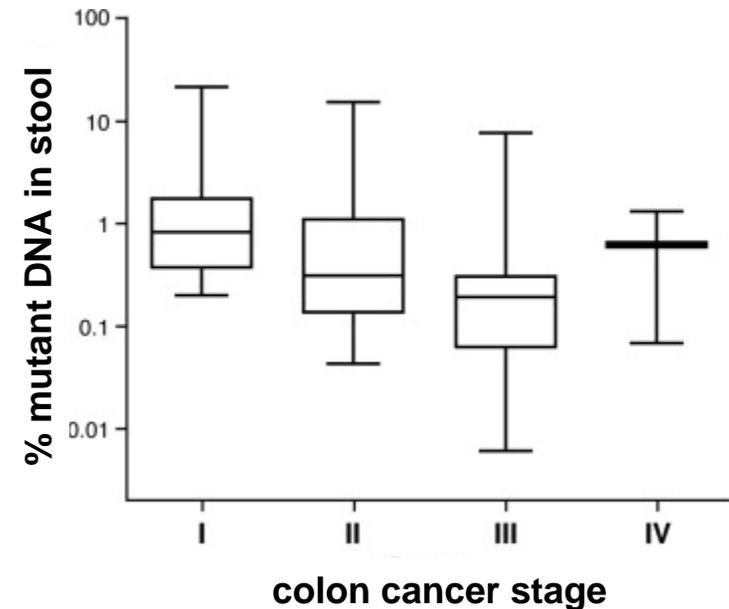
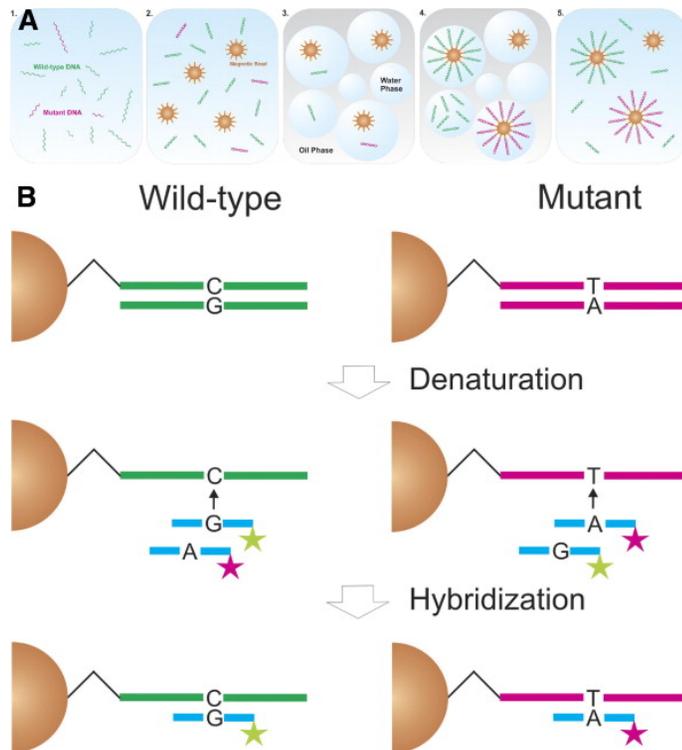


*Wood LD *et al.* Science 318: 1108 – 13 (2007)

New Technologies Detect Cancer-Specific Gene Mutations in Blood and Body Fluids

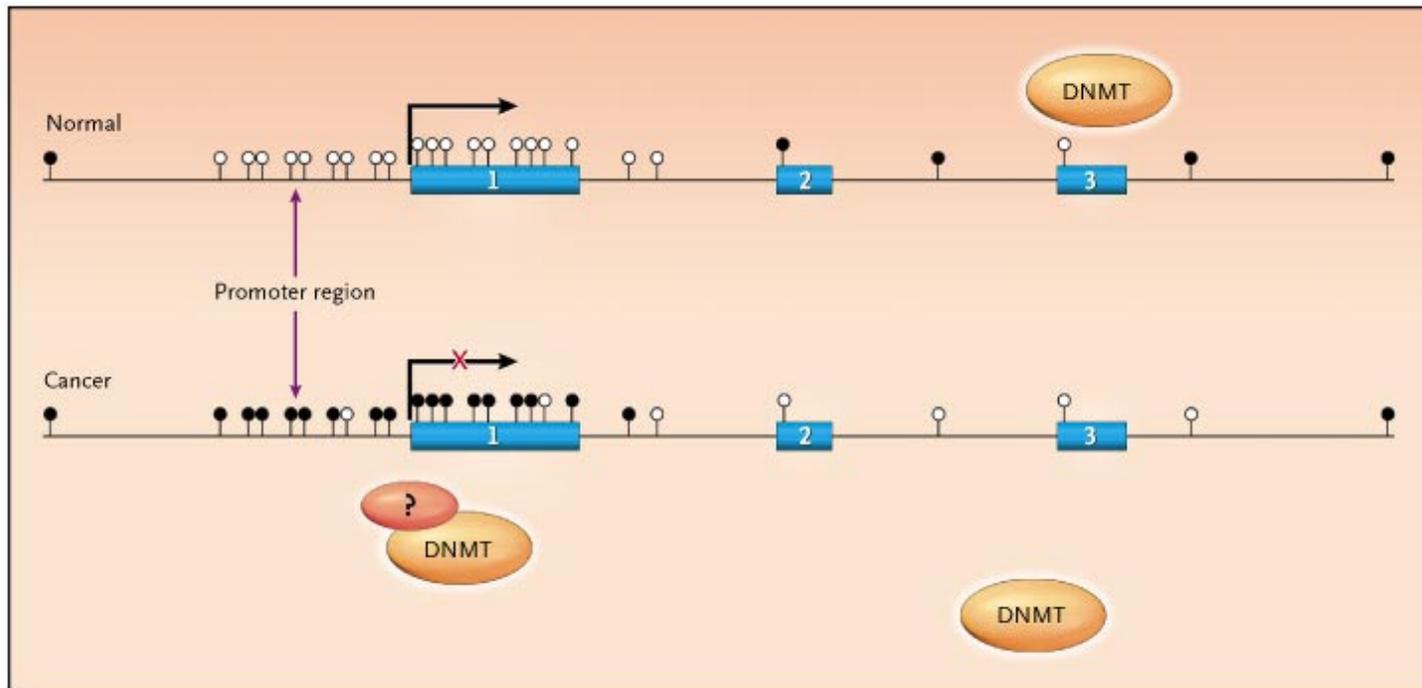
Opportunity for Screening and Early Detection*

“BEAMing” for mutant DNA



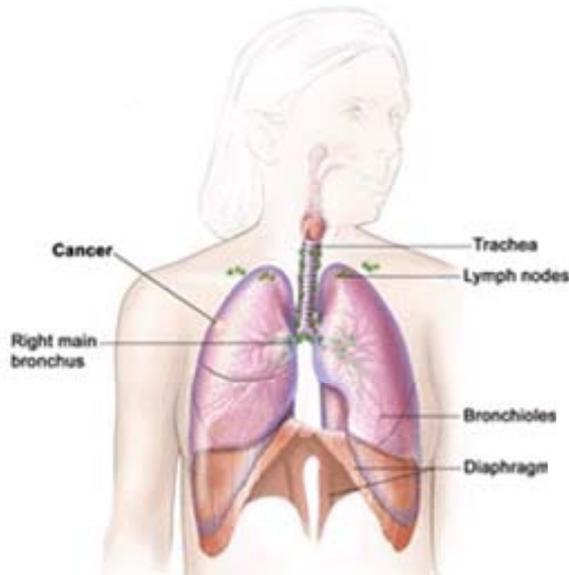
*Diehl F *et al.* *Gastroenterology* 135: 489-98 (2008)

DNA Methylation Patterns in Normal Cells Versus Cancer Cells*

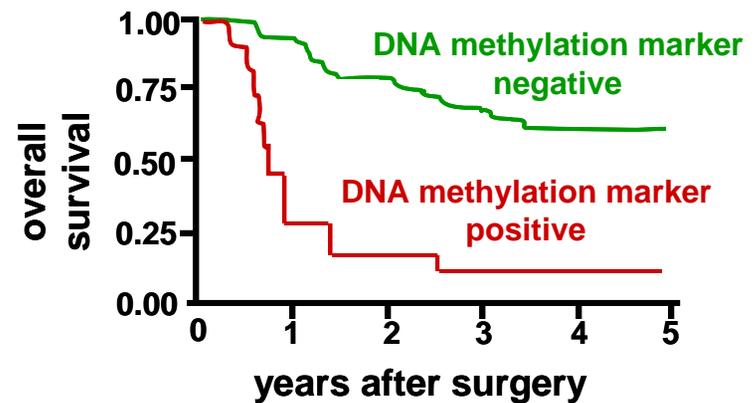
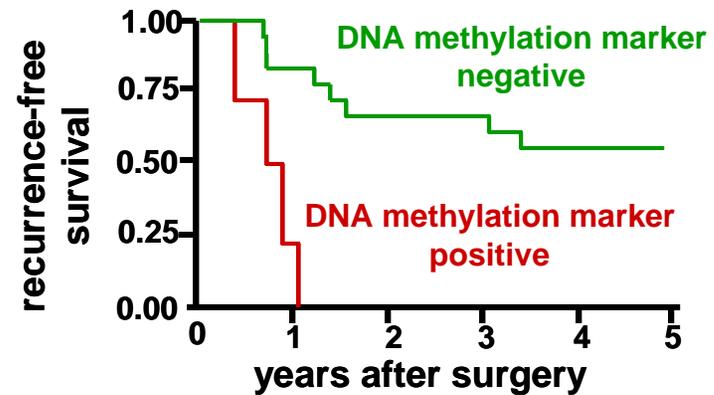


*Herman JG and Baylin SB. *New Engl J Med*
349: 2042-54 (2003)

DNA Methylation Biomarkers Improve Lung Cancer Staging*

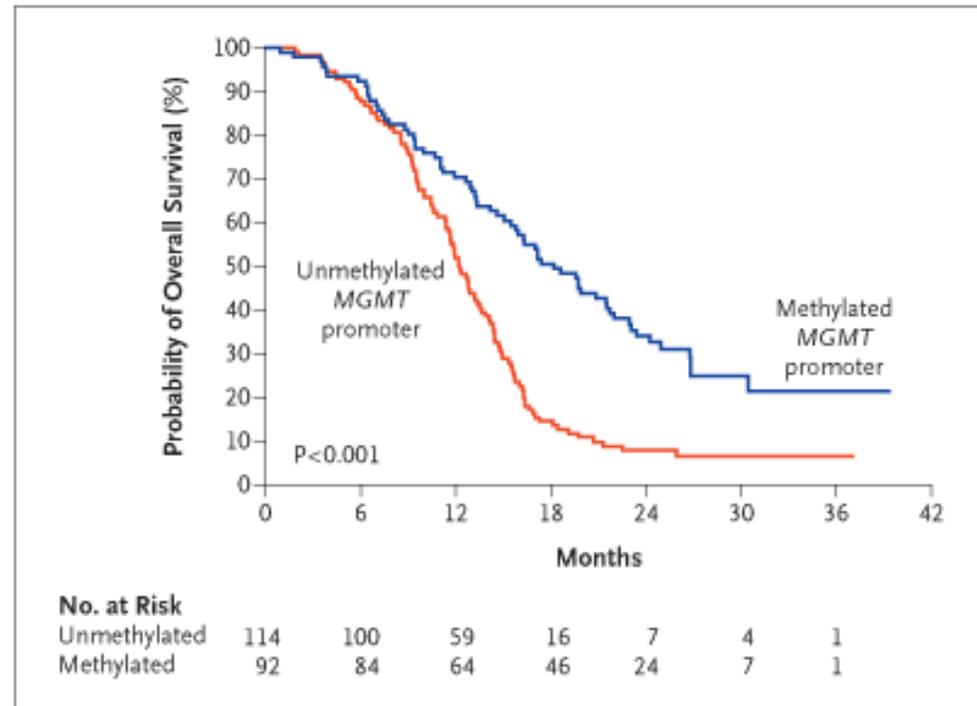
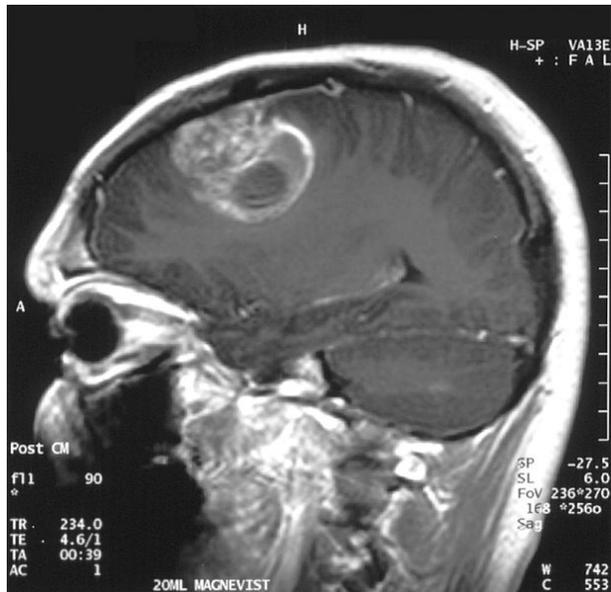


stage 1 non-small cell lung cancer
(no spread to mediastinal lymph nodes)



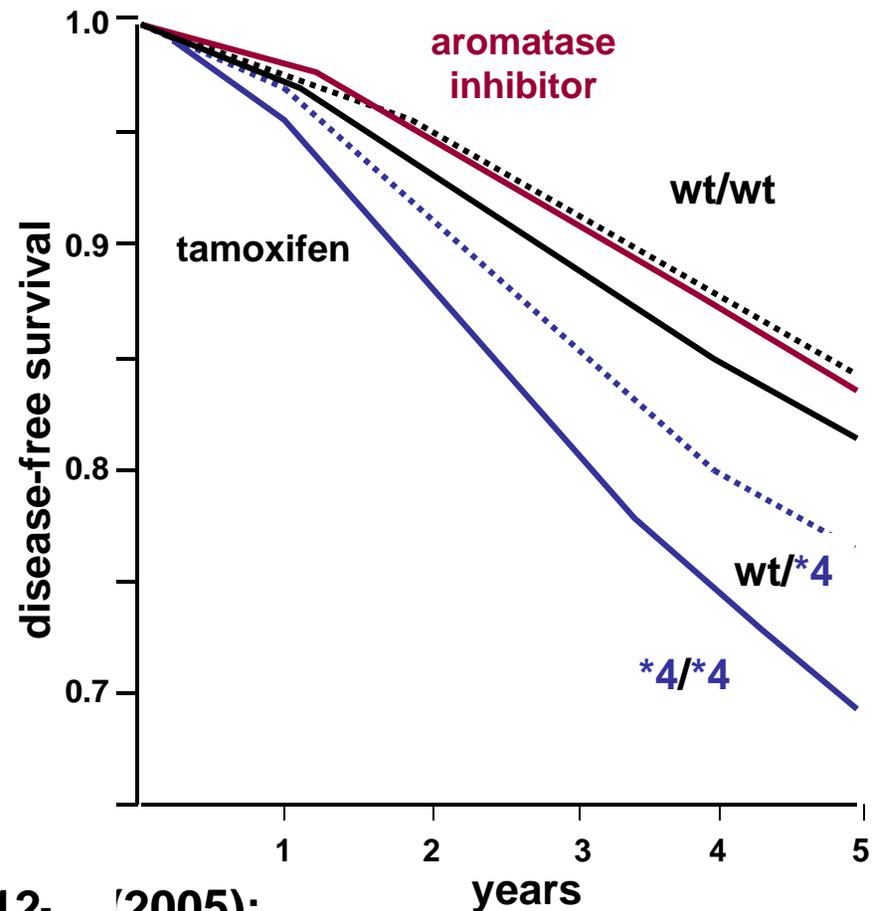
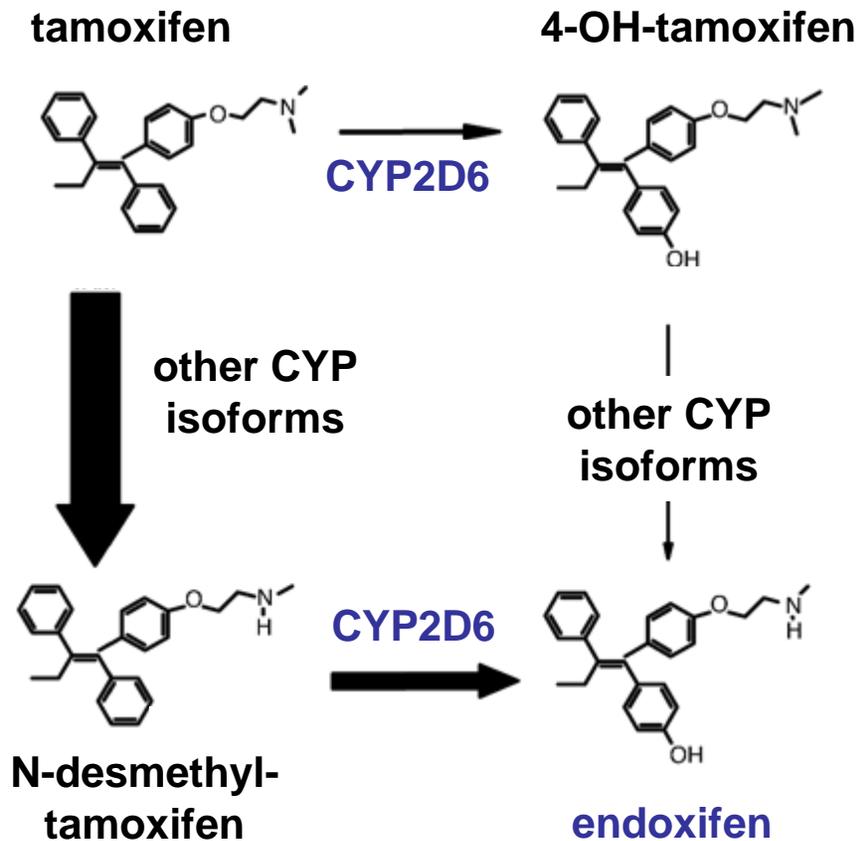
*Brock MV *et al.* New Engl J Med 358: 1118-28 (2008)

MGMT CpG Island/Promoter Methylation and Glioblastoma Response to Temozolomide*



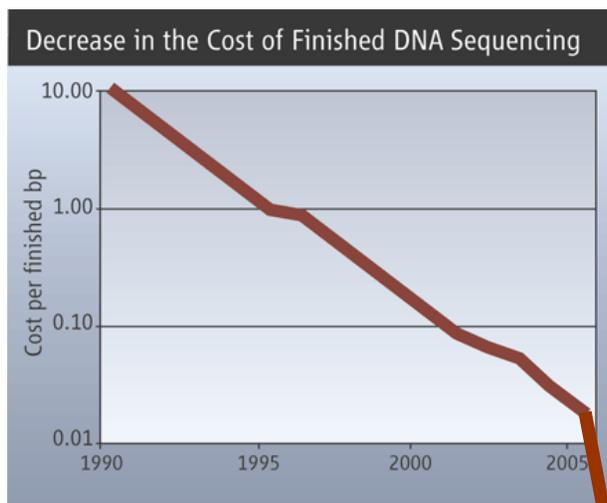
*Hegi ME et al. New Engl J Med 352: 997-1003 (2005)

Pharmacogenetics of Tamoxifen for Breast Cancer Improved Efficacy, Improved Safety, Cost Savings*



*Goetz MP *et al.* J Clin Oncol 23: 9312- (2005);
 Punglia RS *et al.* J Natl Cancer Inst 100: 642-8 (2008)

Trends in DNA sequencing... Impact of New Technologies*

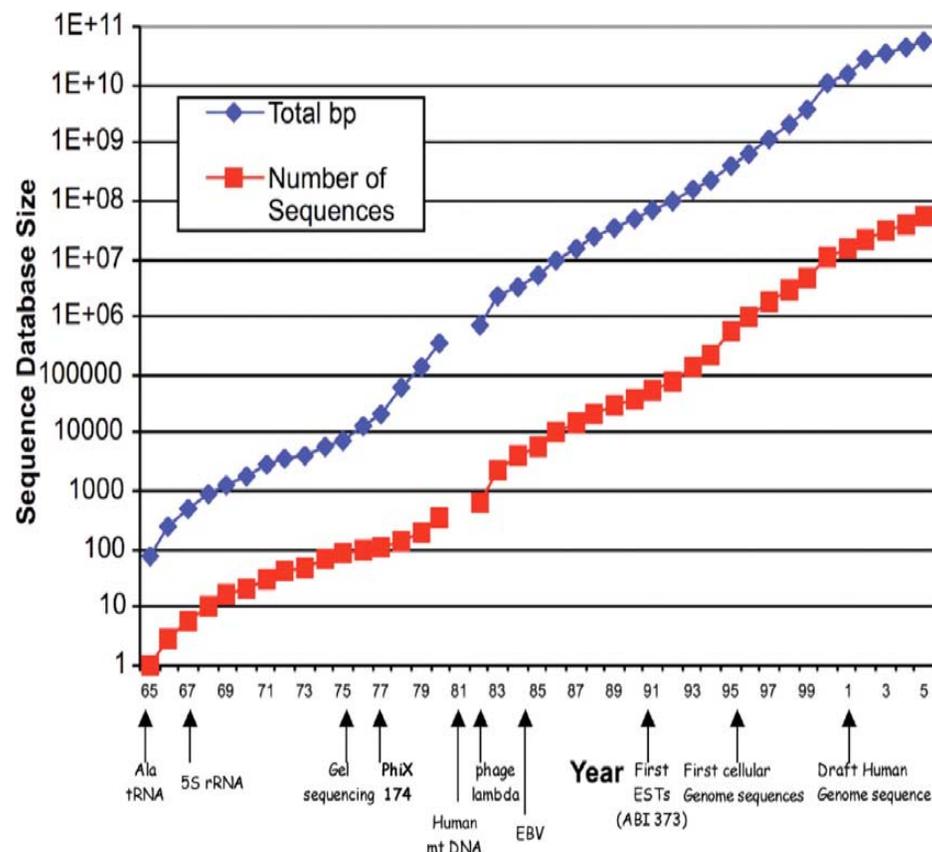


*Service RF Science
311: 1544-6 (2006)

2007: $\$10^{-4}/\text{bp}$

2008: $\$10^{-5}/\text{bp}$

2009: $\$10^{-6}/\text{bp}$



*Hutchison CA Nucl Acids Res
35: 6227-37 (2007)

... and still going ...

Cancer Genetics and Epigenetics: Personalization of Cancer Medicine

Key Points

- **Both Germline and Somatic Genetic and Epigenetic Information will Impact Cancer Risk Stratification, Screening, Early Detection, Diagnosis, Prevention, and Treatment**
- **Genetic/Epigenetic Biomarkers as New Tests that Improve Efficacy, Safety, and Cost-Effectiveness of Cancer Care**