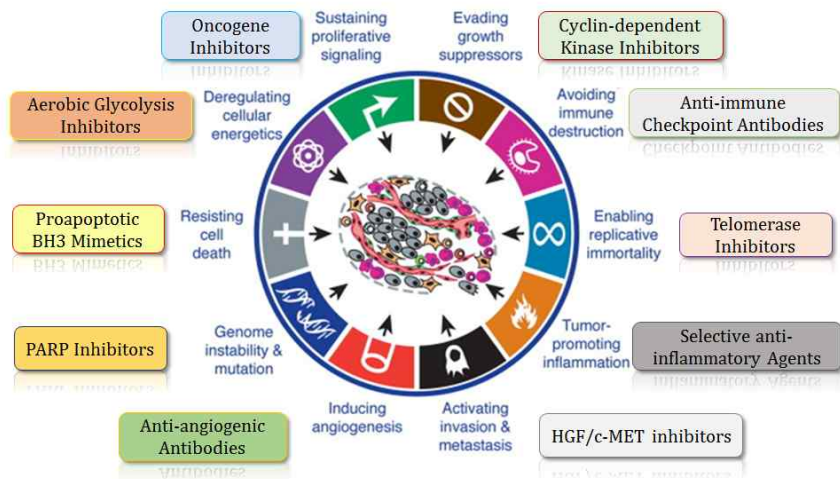


# Future Medicine

*Ageing Society, Personalized Medicine,  
Immunotherapeutics and .....*

## Targeting the Hallmarks of Cancer

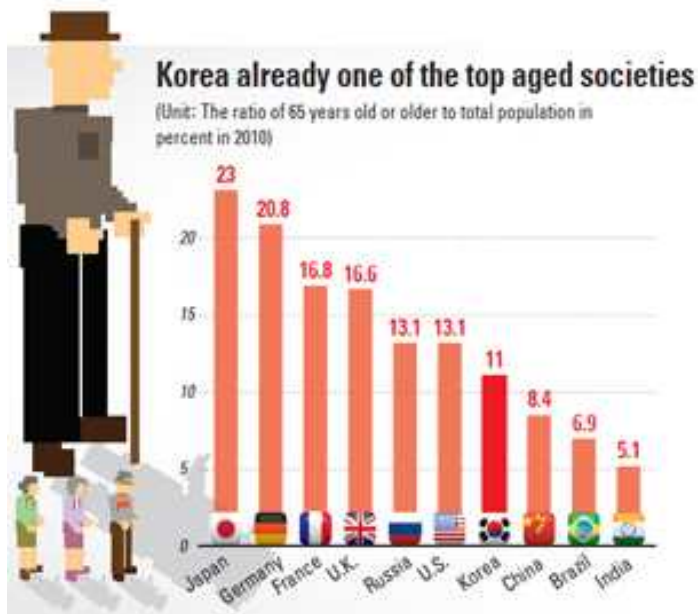


Hanahan and Weinberg. Cell 2011;144:646

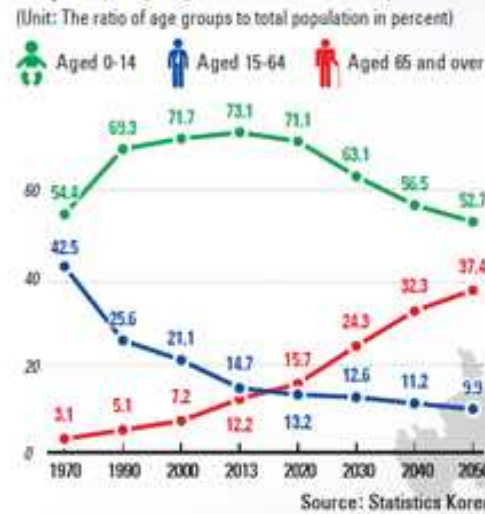
Dae Ho Lee, MD, PhD

Associate Professor, Department of Oncology, University of Ulsan  
College of Medicine, Asan Medical Center, Seoul, Korea

# Not Aging Society But Super Aged Society

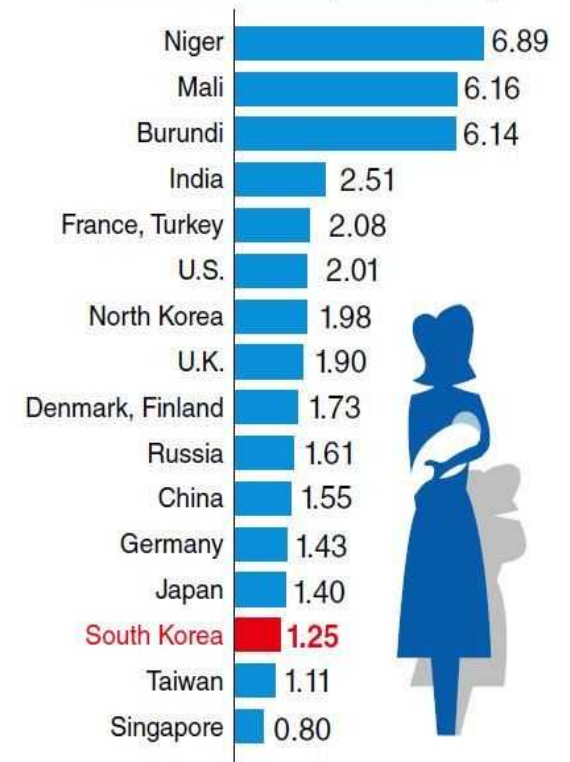


### Rapidly aging Korean society



### National fertility rates

Average number of children a woman will give birth to in her lifetime (2014 estimate)



Source: CIA World Factbook

The rapidly aging population, coupled with the lowest birthrate, is posing a lot of socioeconomic problems for Korea, including a labor shortage, fiscal strains caused by rising welfare costs, chronic economic sluggishness and excessively conservative trends dominating society.

# Not Aging Society But Super Aged Society

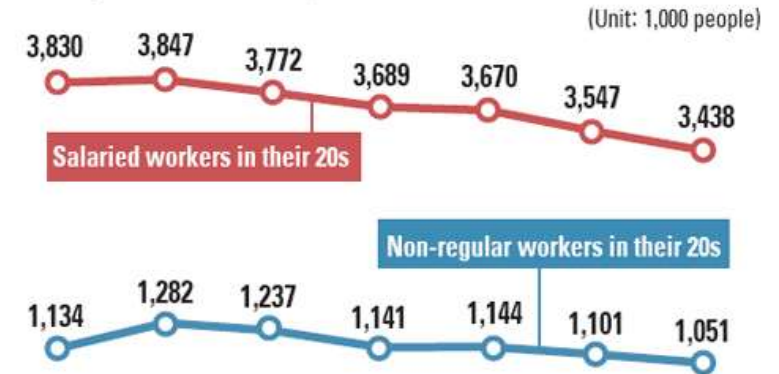
World will have **13 'super-aged' nations** by 2020

By *Financial Times* in London

Country	2015	2030
Japan	26.4	30.7
Germany	21.4	28.2
Italy	21.7	26.8
<b>South Korea</b>	<b>13</b>	<b>23.4</b>
France	18.7	23.2
Switzerland	18.2	21.9
UK	18.1	21.7
US	14.7	20.1
Australia	15	19.2
China	9.5	16.2

## Number of people in their 20s with jobs

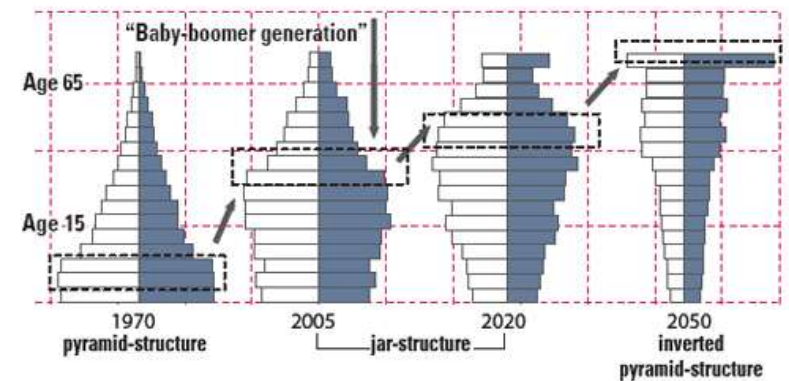
as of August from 2003 to 2008, March for 2009



Source: National Statistical Office

## Korea's population pyramid

(Unit: 1,000 people)



# Health Issues in the Elderly

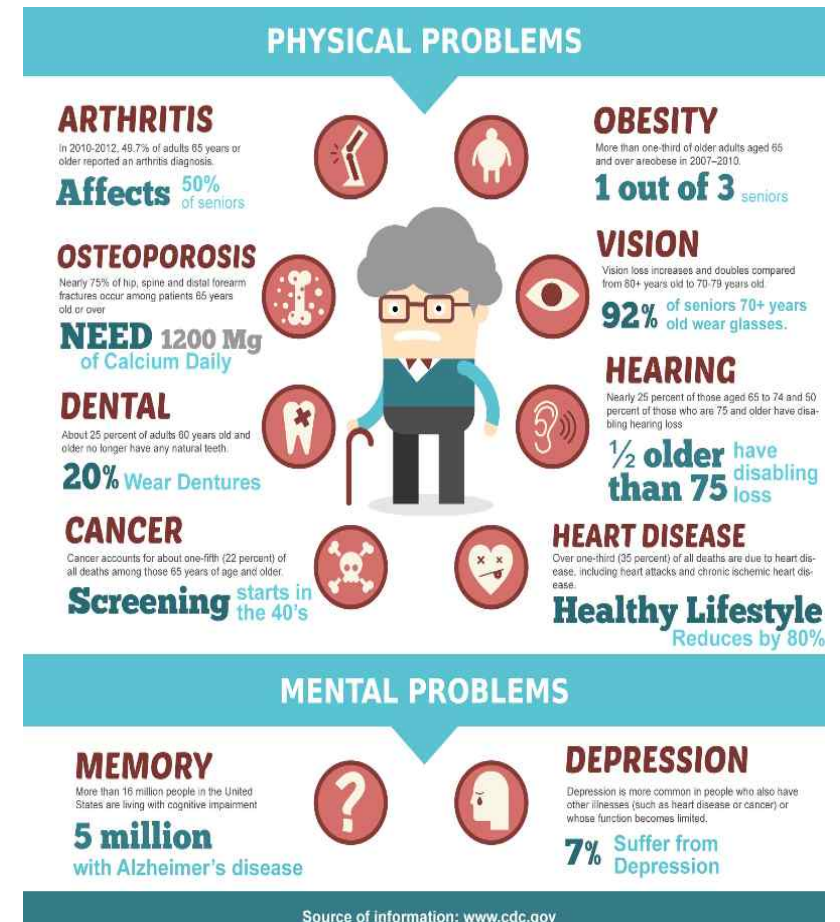
## The Telegraph

Sunday 04 October 2015

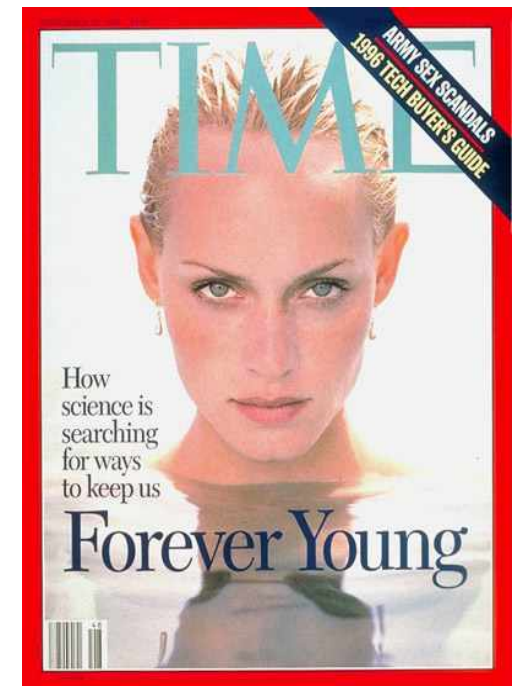
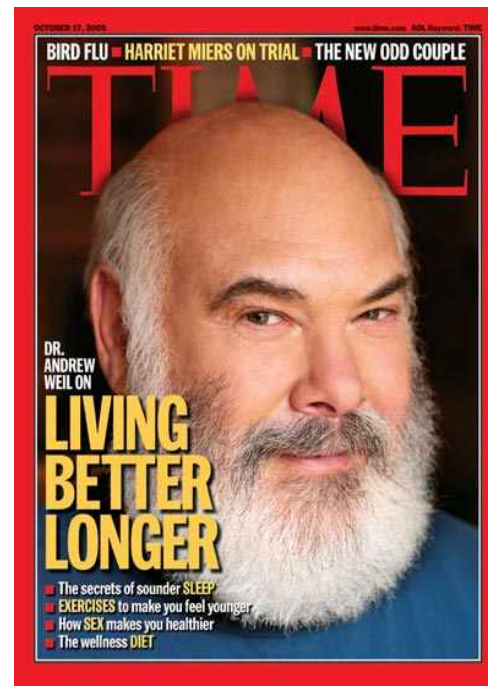
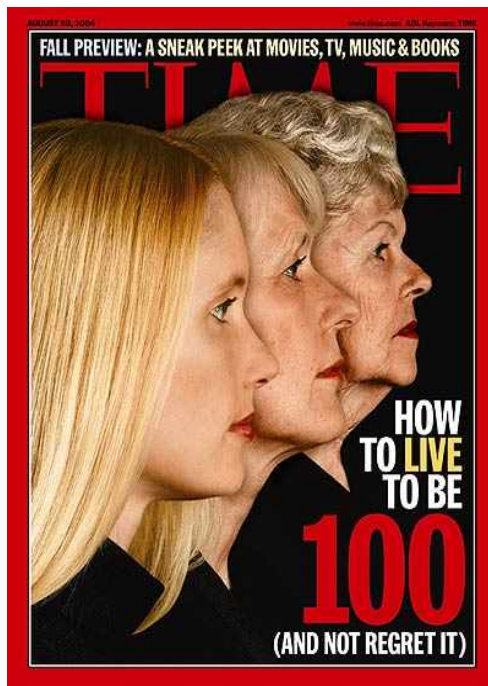
Rising life expectancy means we spend more time being ill

New research reveals that although our life expectancy is rising, we're spending more time living with ill health

- Physiological changes occur in the elderly as a natural part of **Aging**, and can affect their health and lifestyle.
- Most conditions result from **Decreased Function or Degeneration** of the involved organ and some diseases and conditions become more prominent in the elderly.
- Psychosocial issues can also play a role in **physical and mental health** of older adults.



# Aging & Anti-Aging vs Disease



Repair, Replacement, Regeneration and Augmentation

# Augmentation Technology

## Hybrid Assisted Limb



## Exoskeletons



## Neuroprosthetics



## Myoelectric Prosthetics



## Optogenetics

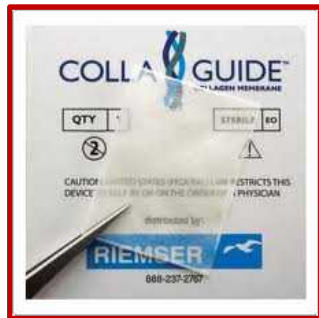


## Augmented Olfaction

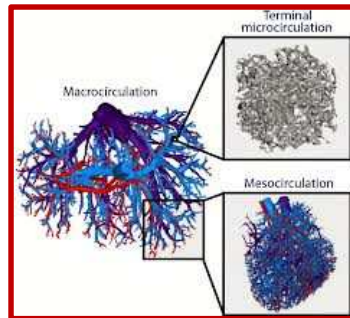


# Regeneration & Replacement Technology

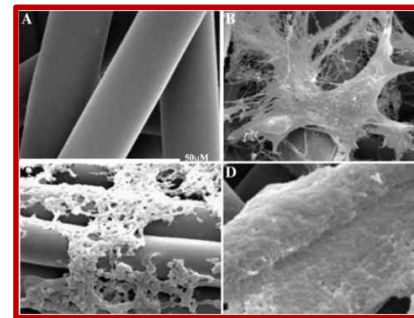
## Tissue Regeneration



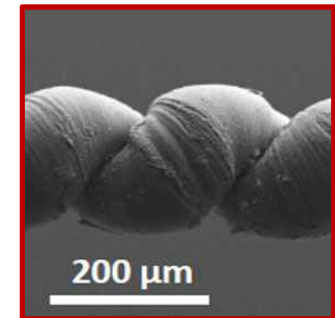
## Artificial Lungs



## Artificial Liver



## Artificial Muscles



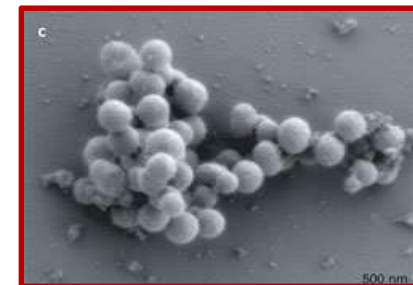
## Artificial Vasculature



## Artificial Organs



## Artificial Cells



# Biogerontology Technology

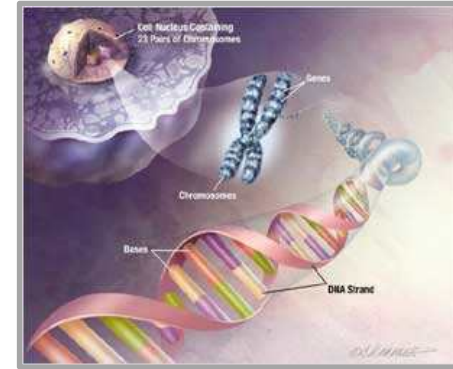
## Anti-aging Drugs



## Anti-aging Cosmetics



## Genetic Engineering



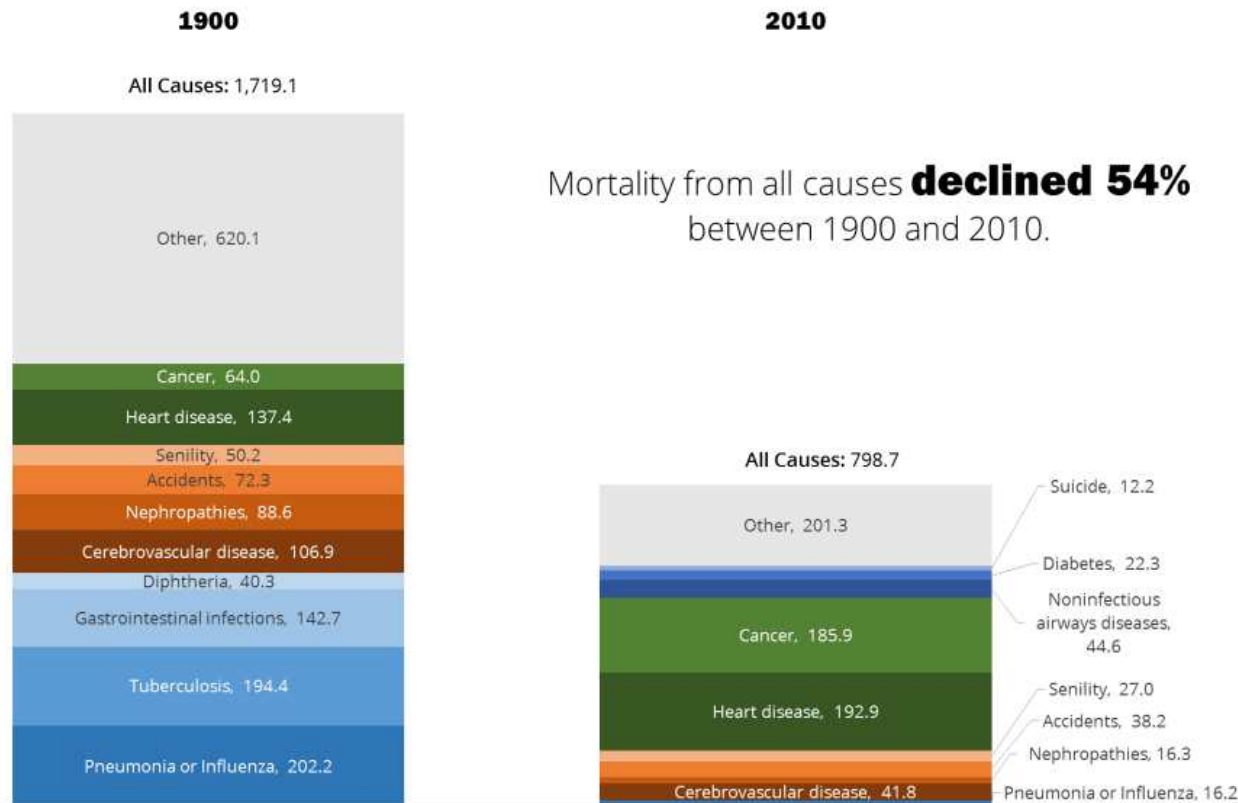
**AGING is a CURABLE DISEASE!**



# Tailoring Treatment for Diseases

## Mortality and Top 10 Causes of Death, USA, 1900 vs. 2010

(Rates per 100,000)



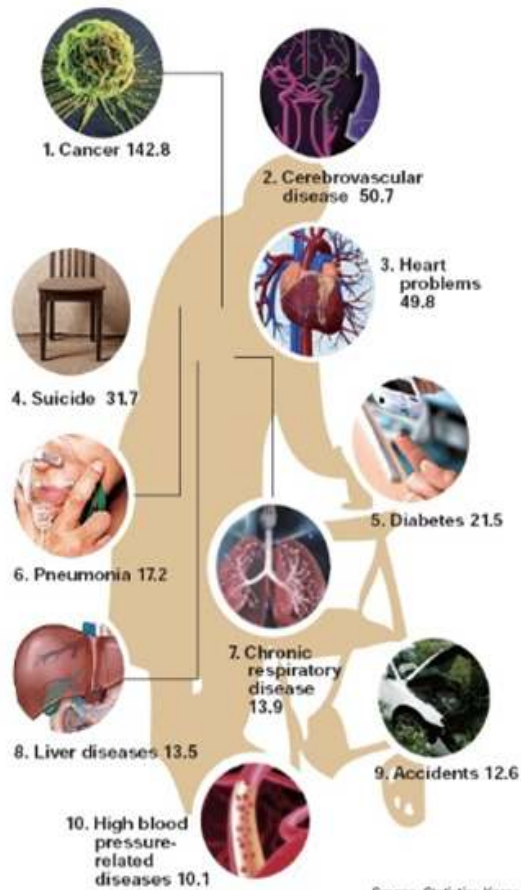
Data Source: Centers for Disease Control



# Change of Disease Pattern to Chronic Disorders

## Top 10 causes of death

Deaths per 100,000 people

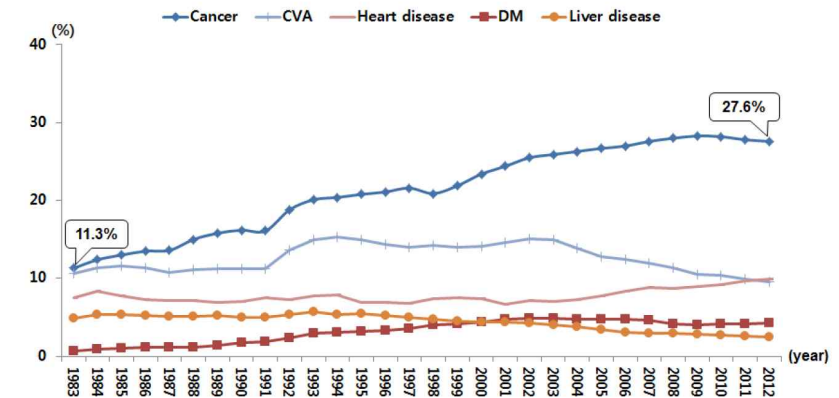


## Cause of death by gender

For every group of 100,000, as of 2008.

Male		Female
27.1	Stomach cancer	14.6
34.4	Liver cancer	11.3
44	Lung cancer	15.8
0.1	Breast cancer	7
6.4	High blood pressure related	12.7
27.8	Heart related	43.6
54.7	Cerebrovascular related	58.3
11.3	Pneumonia	10.8
23.3	Liver disease	5.7
5.9	Tuberculosis	2.7
21.8	Car accidents	7.7
33.4	Suicide	18.7
	Diabetes	20.5

Source: Finance Ministry, Statistics Korea





**DRUGS USED TO BE  
DESIGNED WITH THE  
AVERAGE PATIENT IN MIND**  
NOW, THEY CAN BE TAILORED TO SPECIFIC  
PATIENTS' GENETICS, MICROBES, AND  
CHEMICAL COMPOSITION

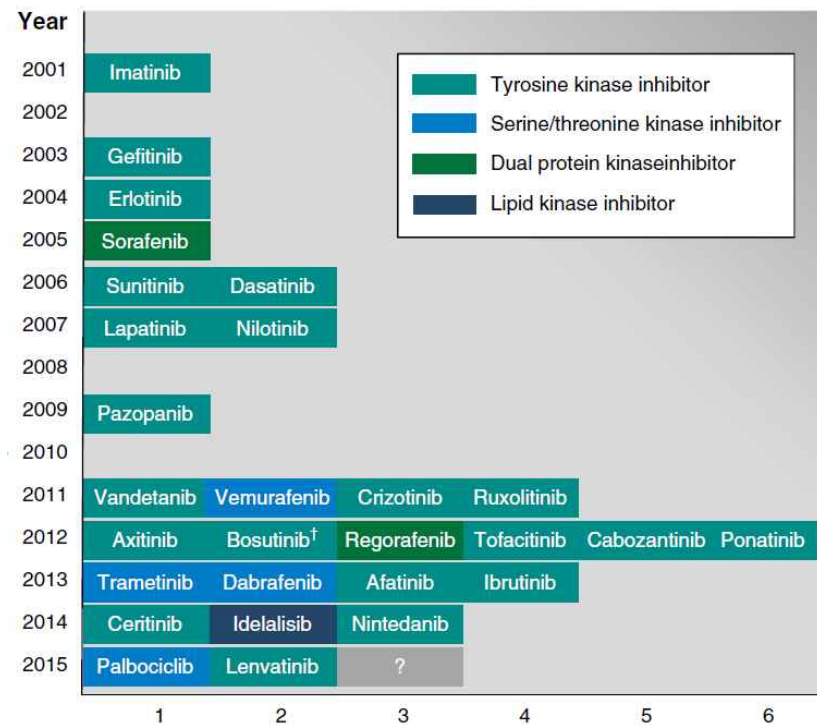
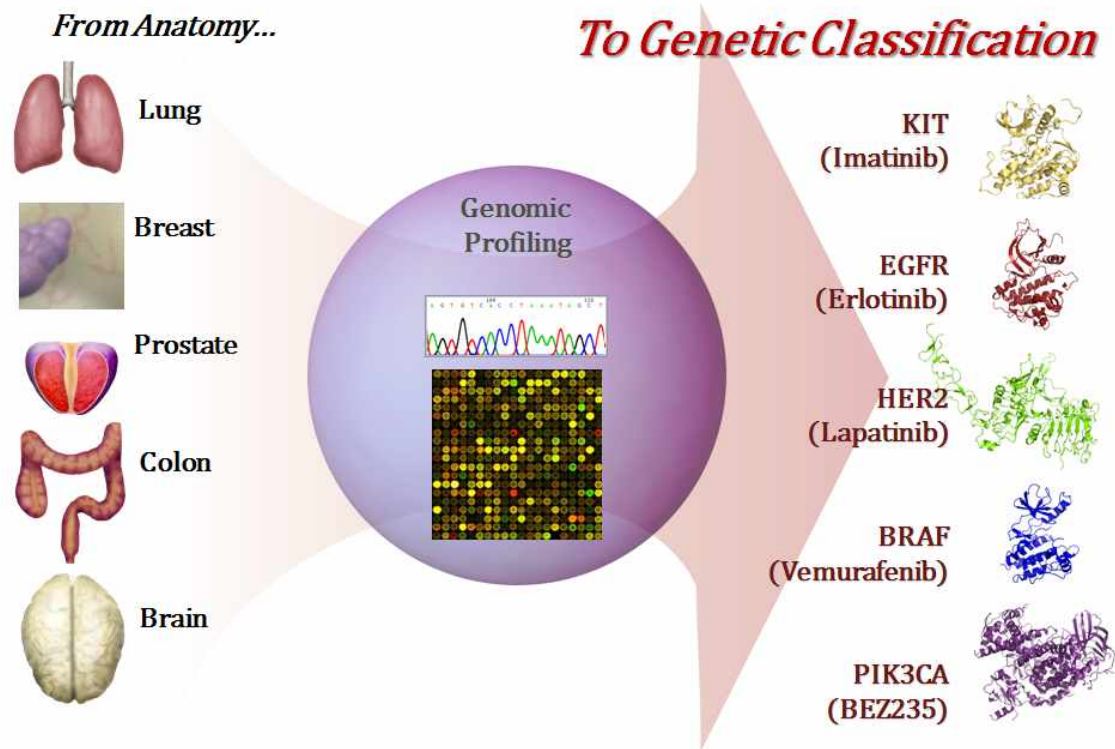


#AmericaLeads

SOURCE: HHS



# Paradigm Shift to Genomic View of Cancer

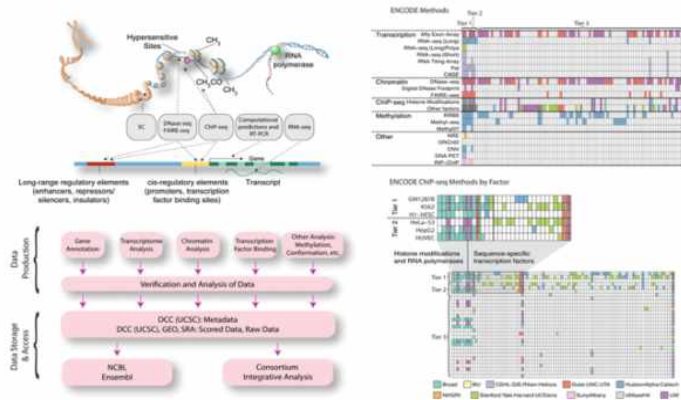


US FDA approved  
28 small molecule kinase inhibitors

Peng W et al. Drug Dis Toda 2015 July

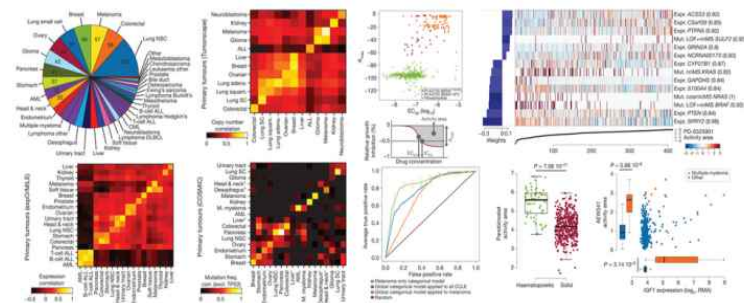
# Genomic Landscape of Cancer

**ENCODE (ENCyclopedia Of DNA Element) Project:**  
 Identification and analysis of functional elements in **1% of the human genome**



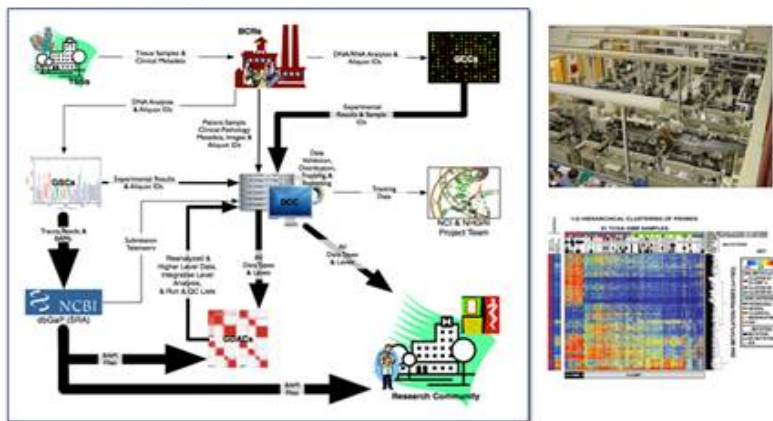
## Cancer Cell Line Encyclopedia (CCLE)

A compilation of gene expression, chromosomal copy number and massively parallel sequencing data from **947 human cancer cell lines**



## The Cancer Genome Atlas (TCGA)

A pilot project developed and tested the research framework needed to systematically explore the entire spectrum of genomic changes involved in more than 20 types of human cancer.

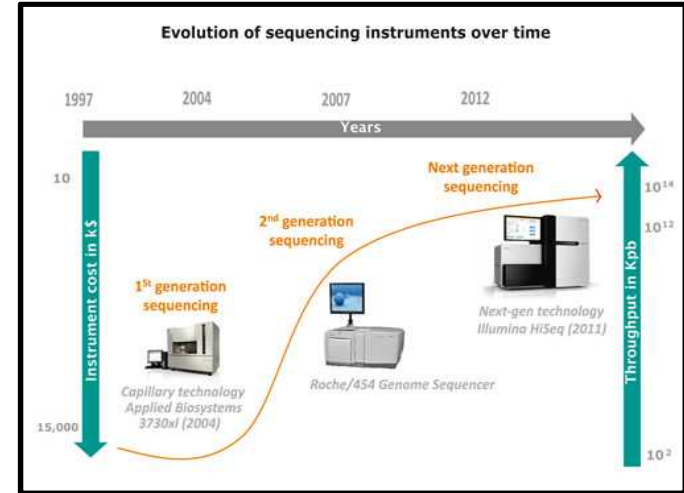
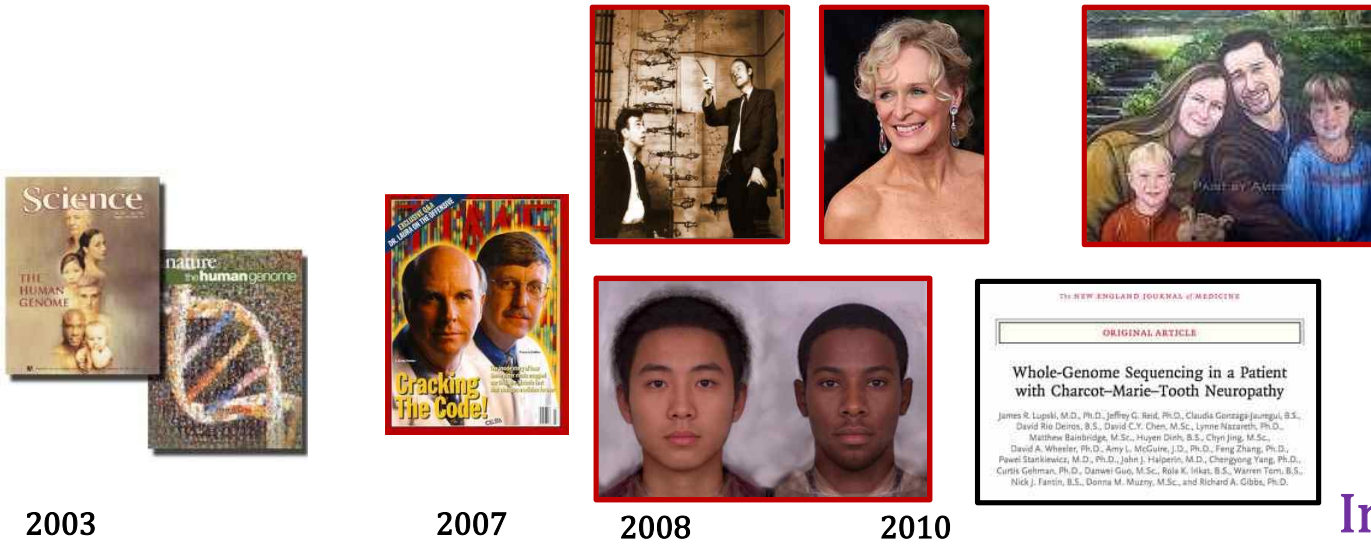


## International Cancer Genome Consortium

To obtain a **comprehensive** description of **genomic, transcriptomic and epigenomic changes** in **50 different tumor types and/or subtypes**



# Genomic Landscape of Cancer



Improvement of Genome Sequencing

**Human genome project**  
13 years, \$2,700,000,000

**Craig Venter genome**  
4 years, \$100,000,000

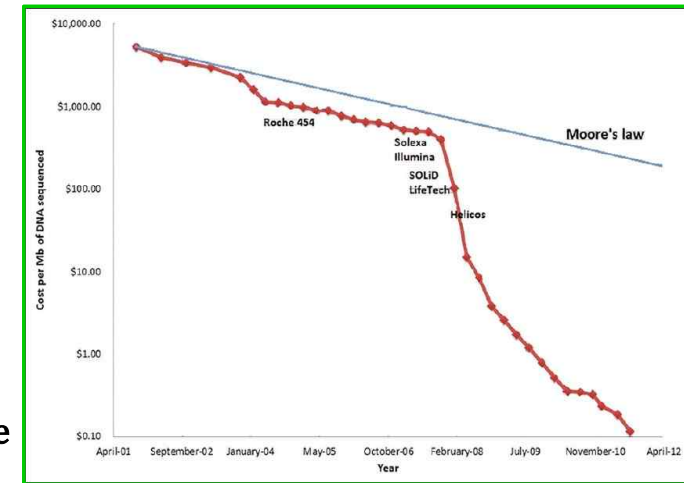
**James Watson genome**  
4 months, \$1,000,000

**1 Asian and 1 African genome**  
1 month, \$ 250,000

**1 Celebrity (Glenn Close)**  
\$ 48,000

**1 Patient c Charcot-Marie-Tooth**  
\$ 50,000

**1 Family (4) c Miller syndrome**  
\$ 25,000



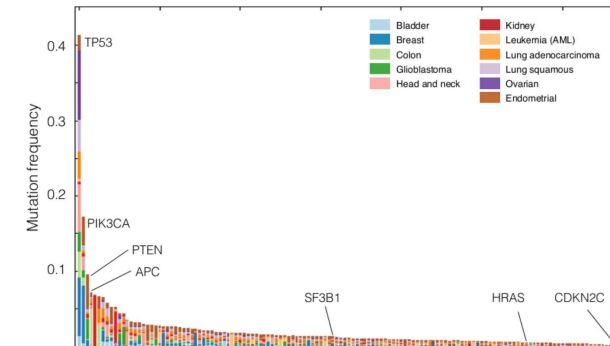
# Genomic Landscape of Cancer



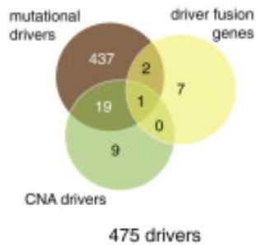
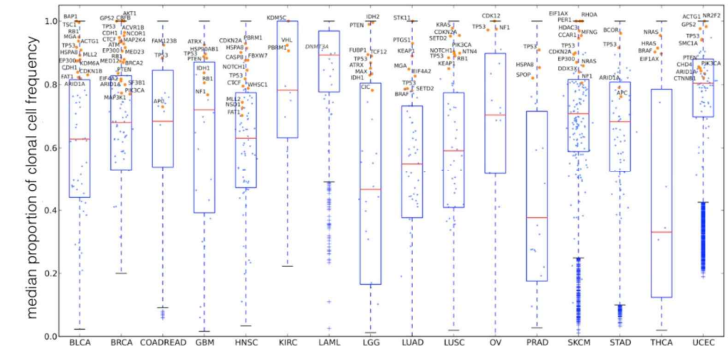
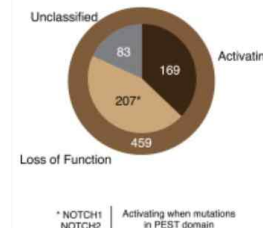
Tumor somatic mutations of 6792 tumor samples from 49 projects from 28 different cancer types



Tumor type	Tumor Type description	Projects	Samples	Mutational driver genes	Tumor type	Tumor Type description	Projects	Samples	Mutational driver genes		
ALL	Acute lymphocytic leukemia	3	122	12	LUSC	Lung squamous cell carcinoma	1	174	147		
AML	Acute myeloid leukemia	1	196	32	MB	Medulloblastoma	2	210	24		
BLCA	Bladder carcinoma	1	98	156	MM	Multiple myeloma	1	69	18		
BRCA	Breast carcinoma	6	1148	184	NB	Neuroblastoma	1	210	27		
CLL	Chronic lymphocytic leukemia	2	290	38	NSCLC	Non small cell lung carcinoma	1	31	11		
CM	Cutaneous melanoma	2	369	250	OV	Serous ovarian adenocarcinoma	1	316	83		
COREAD	Colorectal adenocarcinoma	2	229	95	PA	Piloicytic astrocytoma	2	101	2		
DLBC	Diffuse large B cell lymphoma	1	23	10	PAAD	Pancreas adenocarcinoma	3	214	21		
ESCA	Esophageal carcinoma	1	146	98	PRAD	Prostate adenocarcinoma	1	243	88		
GBM	Glioblastoma multiforme	2	379	75	RCCC	Renal clear cell carcinoma	1	417	105		
HC	Hepatocarcinoma	2	90	30	SCLC	Small cell lung carcinoma	2	69	61		
HNSC	Head and neck squamous cell carcinoma	2	375	167	STAD	Stomach adenocarcinoma	2	161	175		
LGG	Lower grade glioma	1	169	50	THCA	Thyroid carcinoma	1	322	32		
LUAD	Lung adenocarcinoma	2	391	181	UCEC	Uterine corpus endometrioid carcinoma	1	230	149		
				Total					48	6792	459



Most driver genes are lowly frequently mutated.



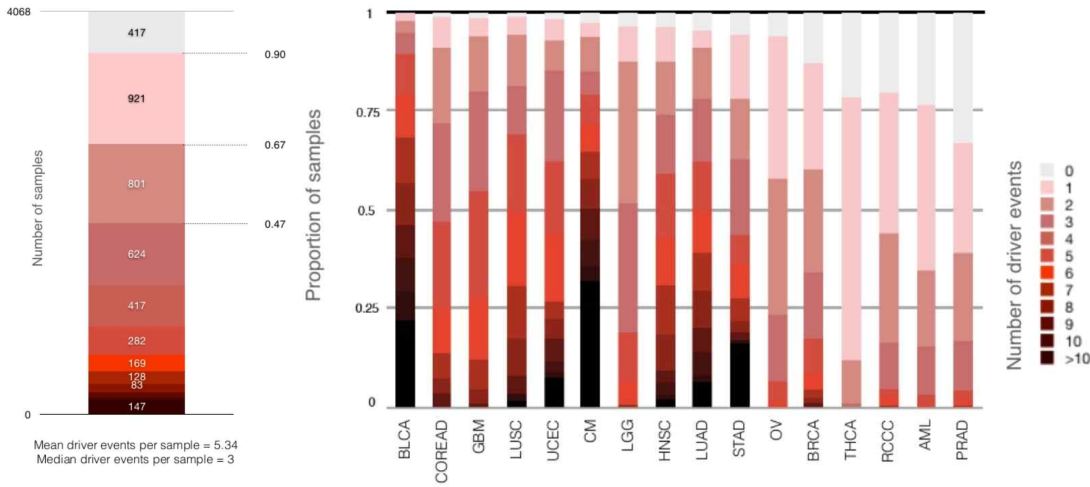
459 Drivers in 28 different cancer types

Few drivers dominate the clonal landscapes

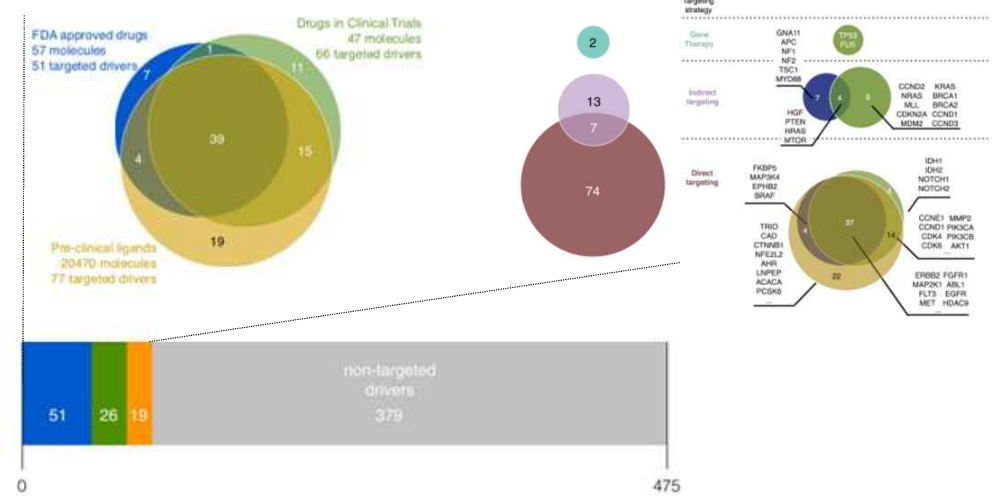
Rubio-Perez C et al. Cancer Cell 2015;27:382



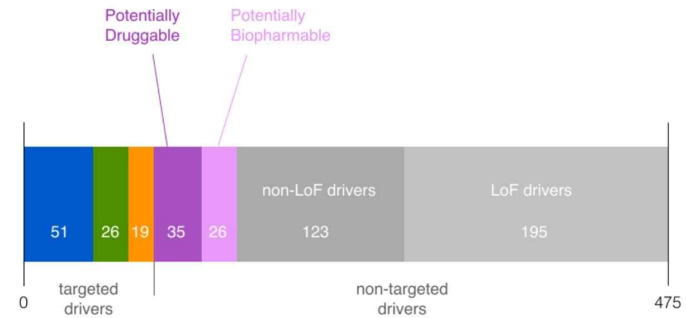
# Genomic Landscape of Cancer



90% of tumors show at least one driver alteration



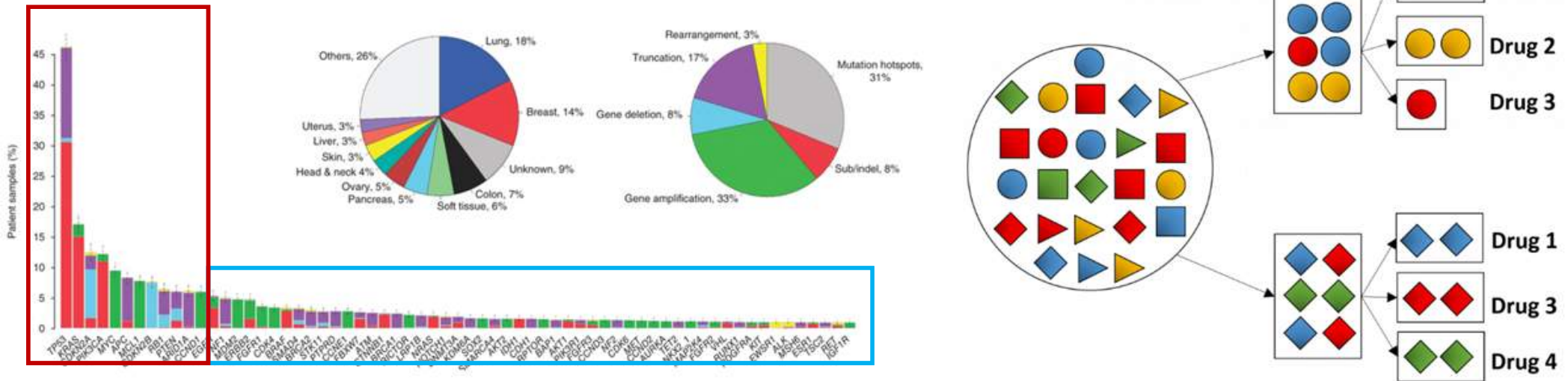
Drugs targeting cancer drivers are limited so far.



Rubio-Perez C et al. Cancer Cell 2015;27:382

# Knowledge of Genomic Landscape Changes Clinical Practice!

## Clinically actionable alterations in patient samples



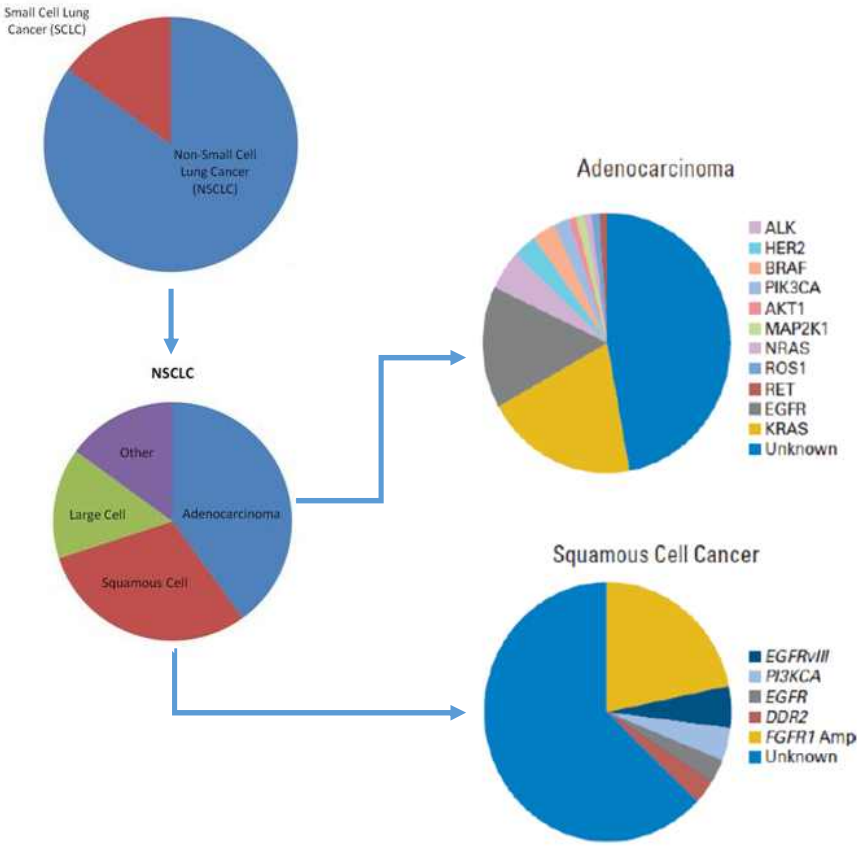
Frampton GM et al. Nature Biotech 2013;31: 1023

November 22, 2015

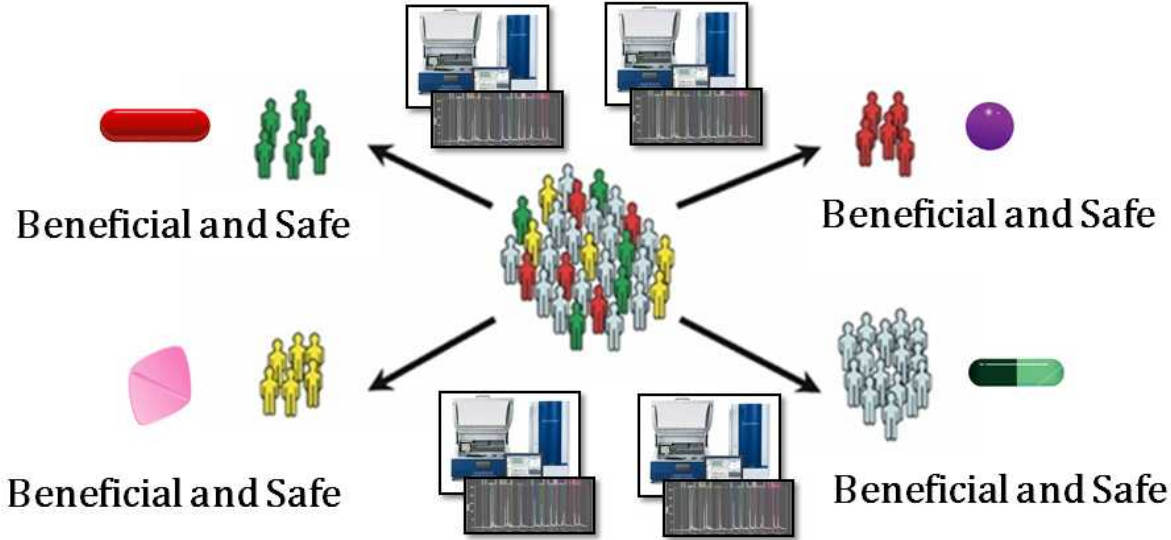
HUFF POST SCIENCE

## Genomics Moves From the Lab to the Doctor's Office

# Increasing Knowledge of Genomic Landscape Changes Oncology Trial and Clinical Practice!

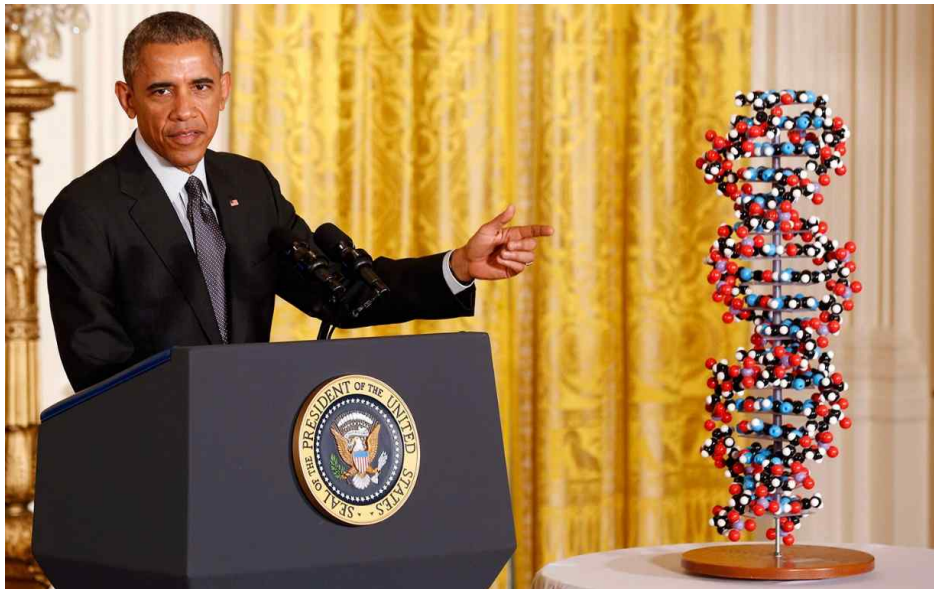


Evolution of lung cancer from Histologic subsets to Genomic subsets



Simultaneous and Multiplex Testing Platform

## Obama calls on Congress to fund 'precision medicine'



## Precision Medicine Initiative Obama Announces \$215 Million Precision-Medicine Genetic Plan

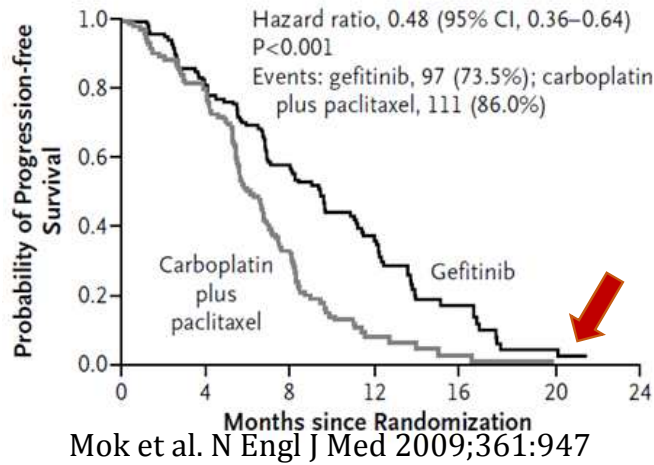
On Jan 30, 2015



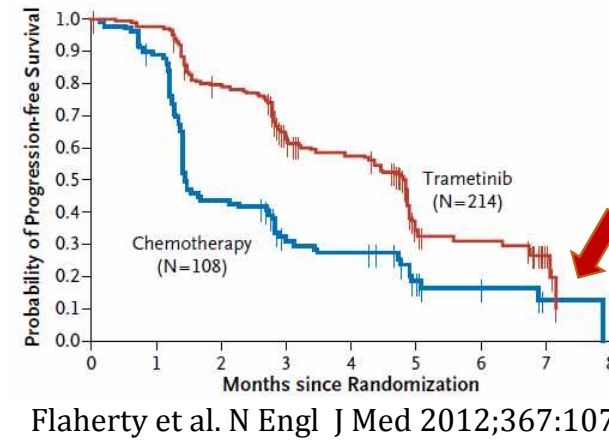
The National Cancer Institute would get \$70 million to study genetic causes of cancer; the FDA would get \$10 million to evaluate new diagnostic devices and drugs; and \$5 million would be devoted to building the computing and privacy components of the genetic-data network.

# Is there Hope for Cures?

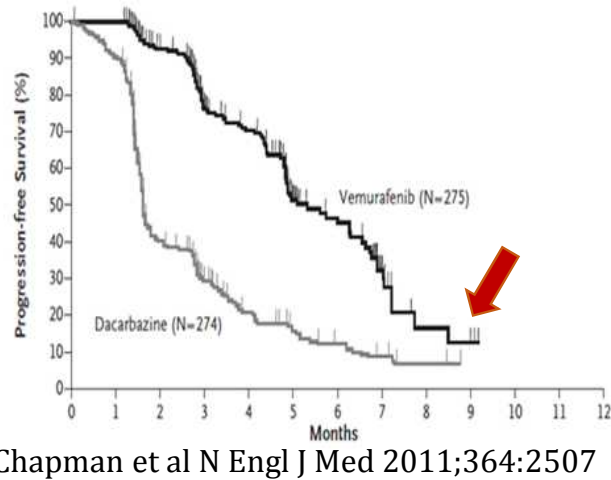
## Gefitinib



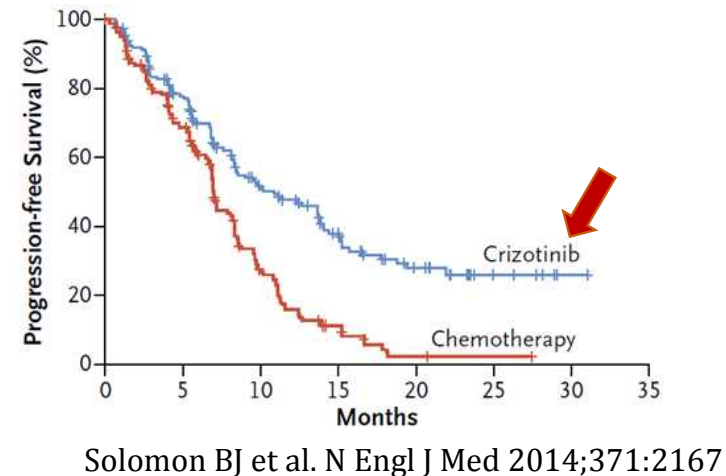
## Trametinib



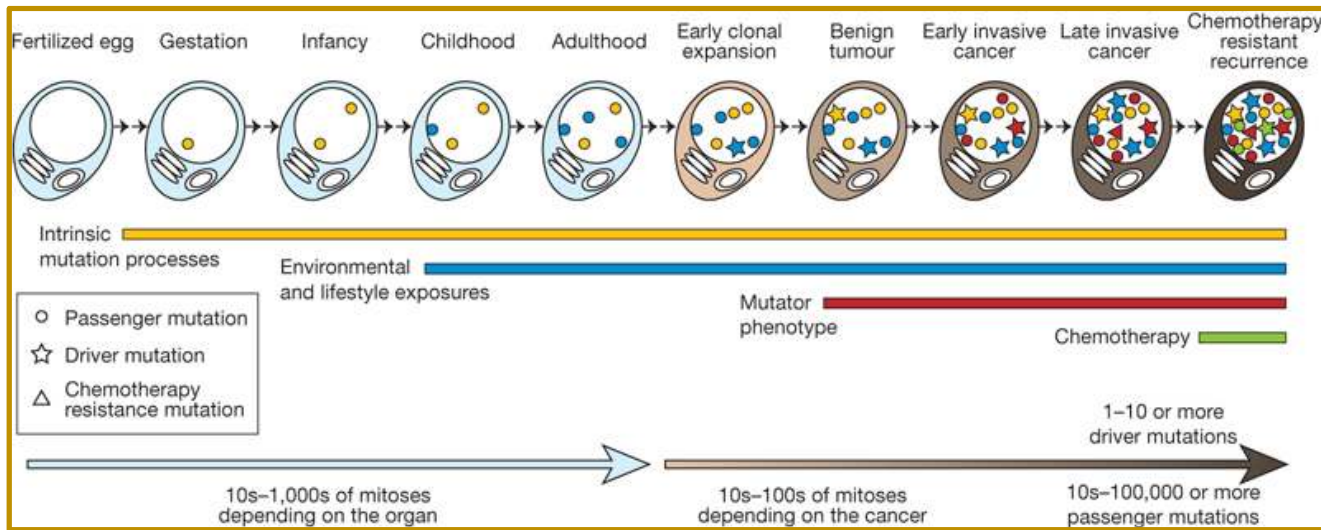
## Vemurafenib



## Crizotinib



# Knowledge of Genomic Landscape is Enough?

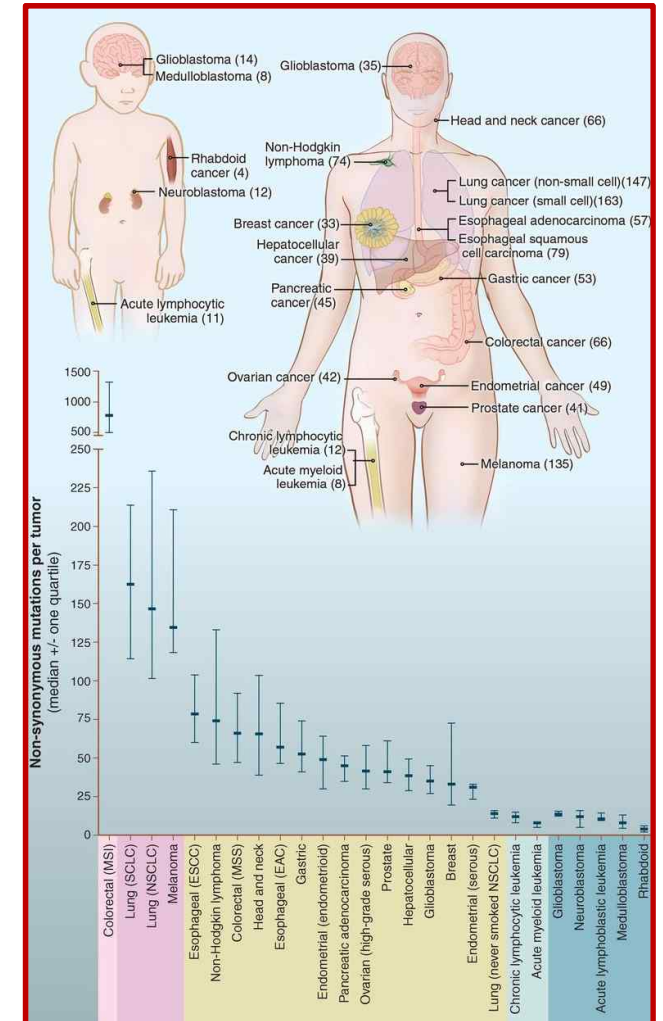


**Passenger mutations** do not have any effect on the cancer cell, but **driver mutations** will cause a clonal expansion. Relapse after chemotherapy can be associated with **resistance mutations** that often predate the initiation of treatment.

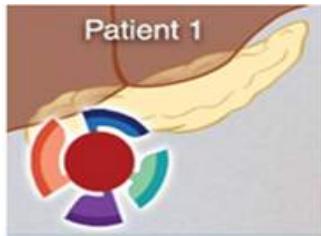
Stratton MR et al. *Nature* 2009;458:719

Typical solid tumors contain **30 to 70 mutations** that alter the amino acid sequences of the proteins encoded by the affected genes.

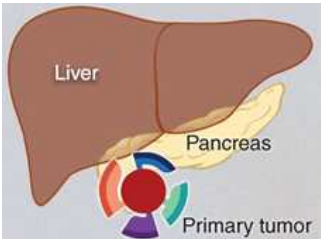
Vogelstein B et al. *Science* 2013;339:1546



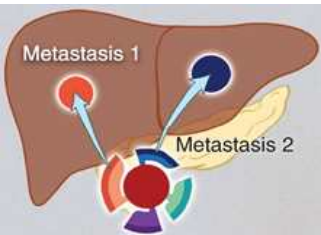
# Tumor Heterogeneity



- **Interpatient** heterogeneity among the tumors of **different patients**



- **Intratumoral** heterogeneity among **the cells of the primary tumor**



- **Intermetastatic** heterogeneity among **different metastatic lesions** in the same patient

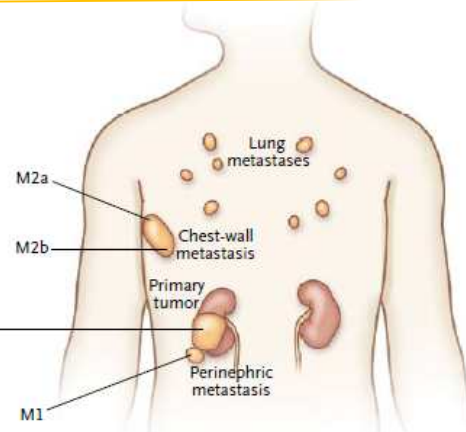
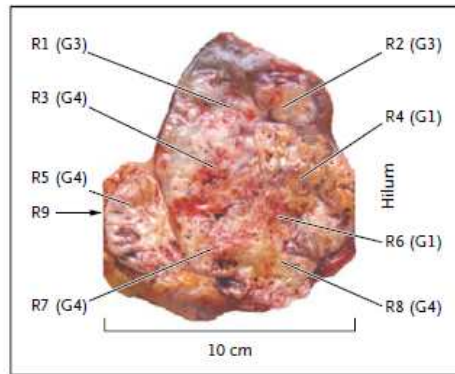


- **Intrametastatic** heterogeneity among **the cells of each metastasis**

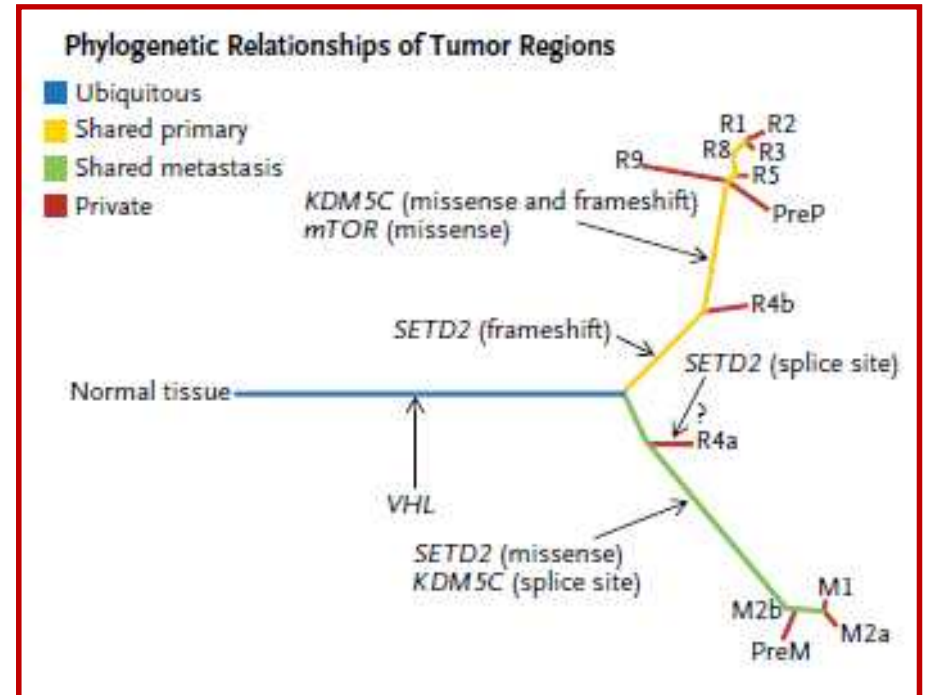
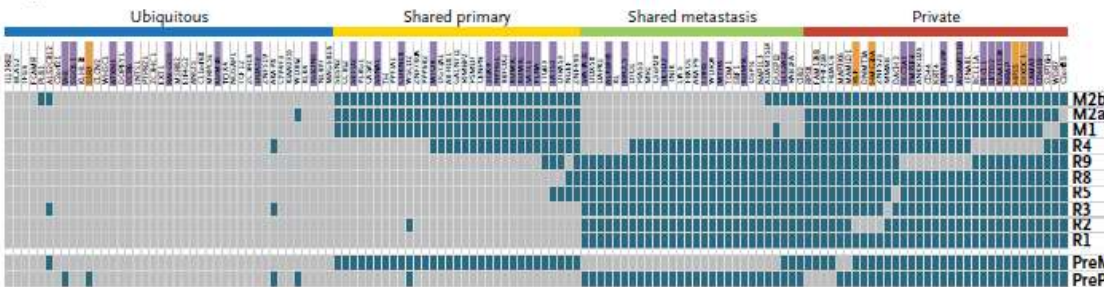
*Vogelstein B et al. Science 2013;339:1546*

# Tumor Heterogeneity

Biopsy Sites



Regional Distribution of Mutations

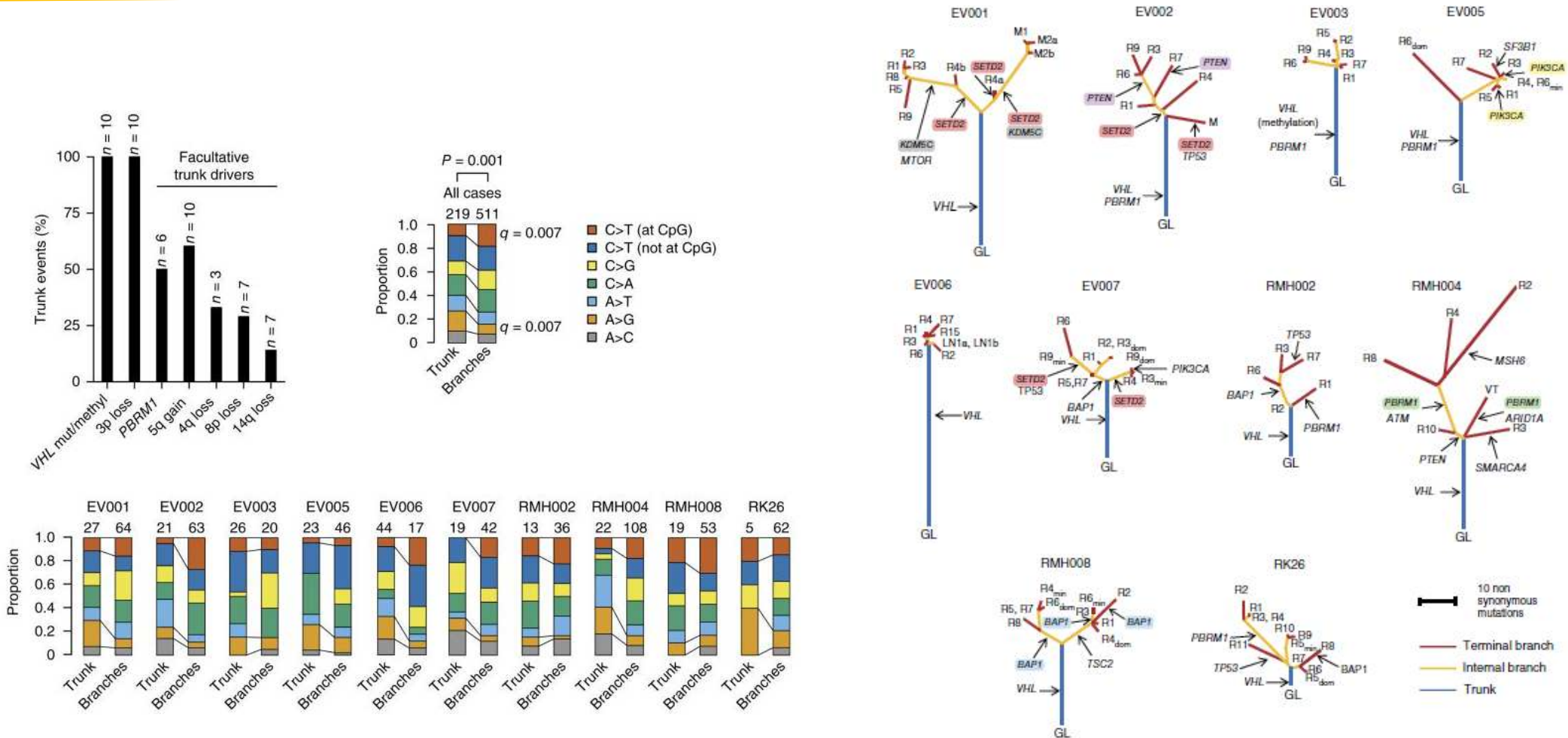


**Intra- and Inter-tumor heterogeneity** can lead underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present **major challenges to personalized medicine and biomarker development.**

Gerlinger M et al. N Engl J Med 2012;366:10

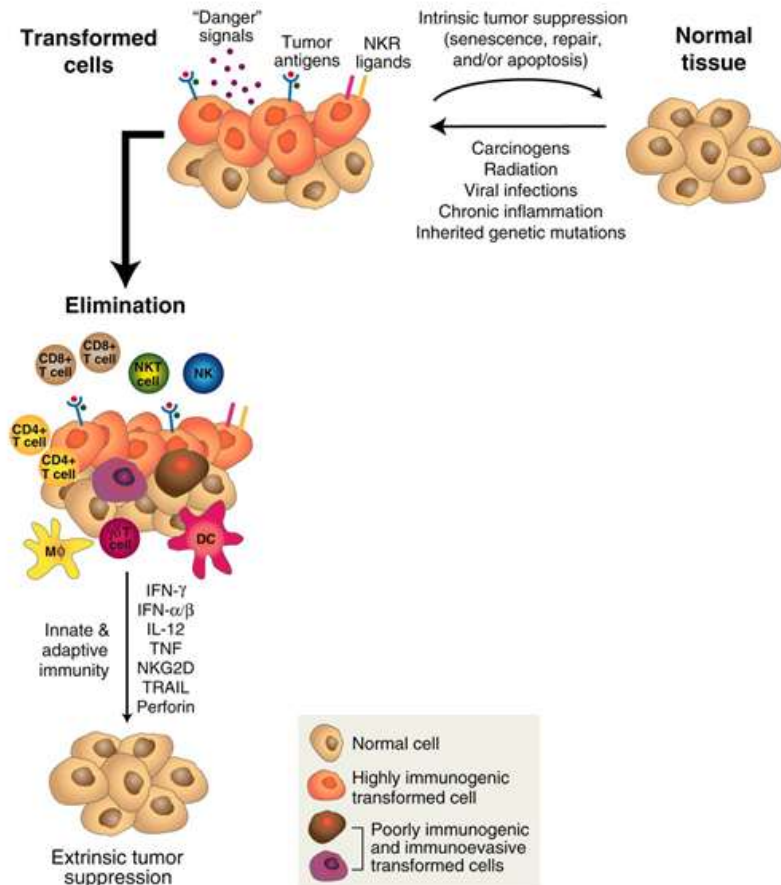


# Clonal Evolution, not Random Process!



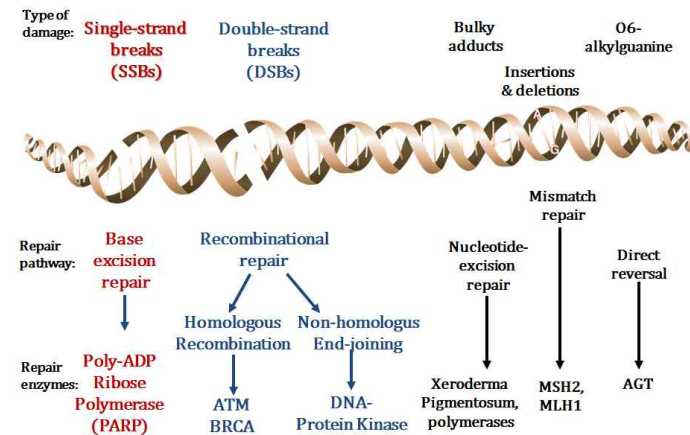
Gerlinger et al. Nature Genetics 2014;46:225

# Why Cancer Cells Survive in **Someone, not Everyone** ?



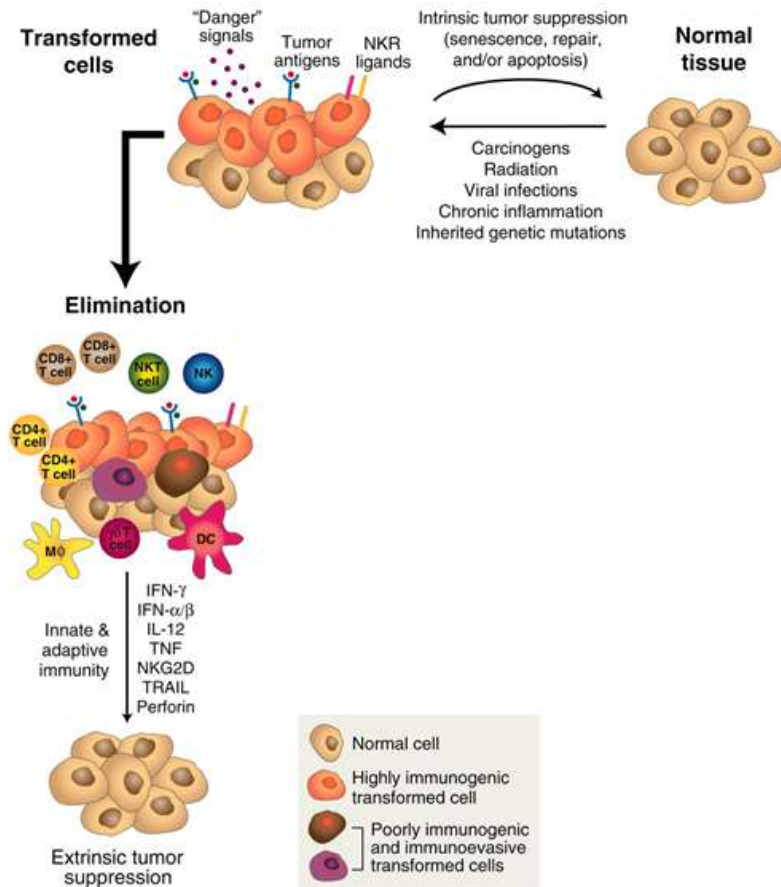
- **Intrinsic Tumor Suppression: DNA Repair or Apoptosis**

## Genomic Instability & Apoptosis

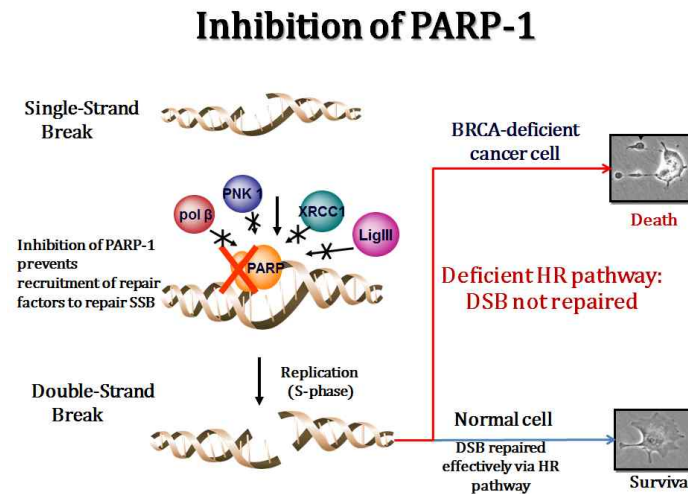


- **Extrinsic Tumor Suppression: Innate & Adaptive Immunity**

# Why Cancer Cells Survive in **Someone, not Everyone** ?

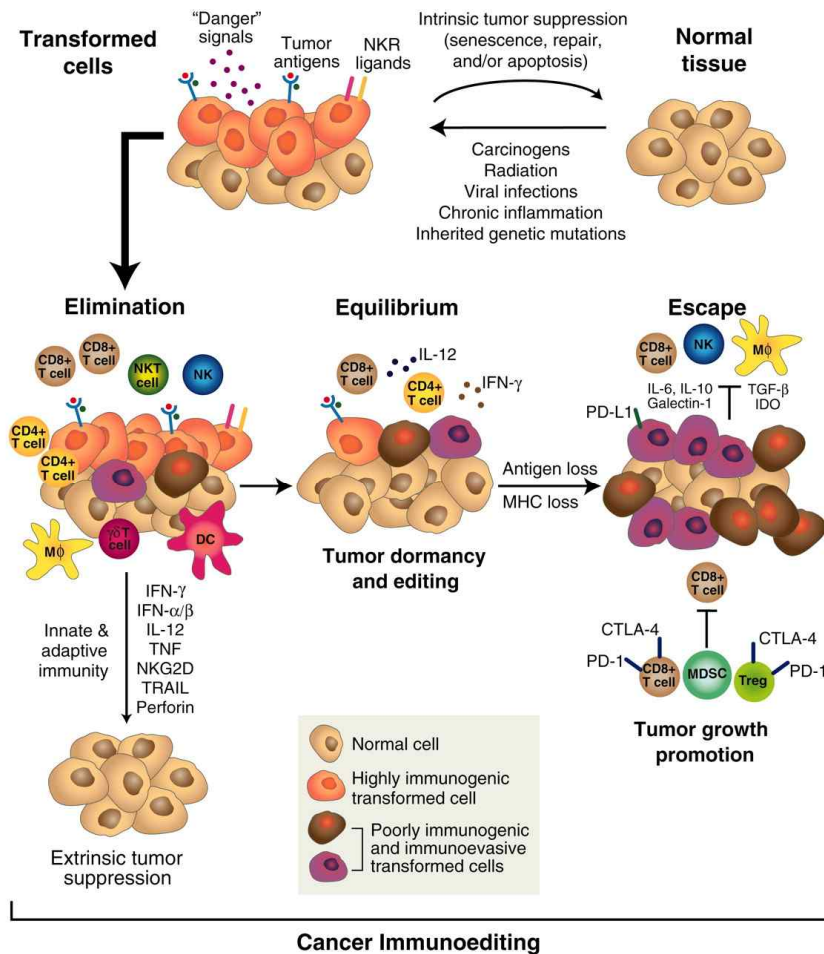


- **Intrinsic Tumor Suppression: DNA Repair or Apoptosis**

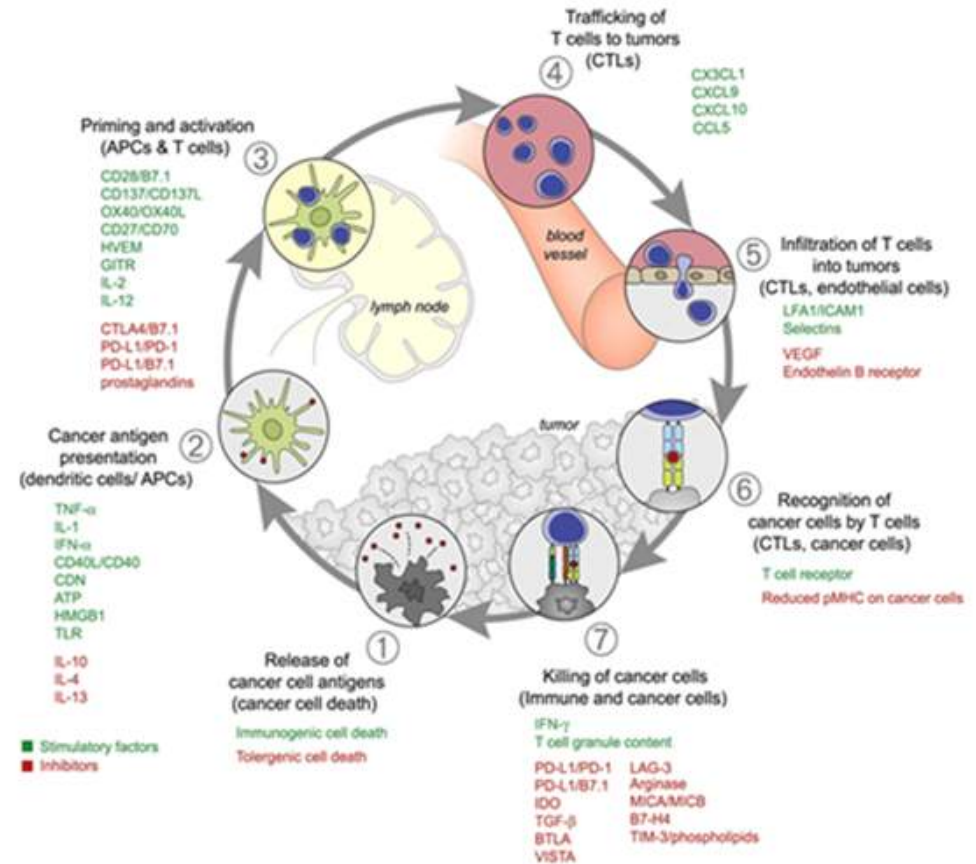


- **Extrinsic Tumor Suppression: Innate & Adaptive Immunity**

# Why Cancer Cells Survive in **Someone**, not **Everyone** ?

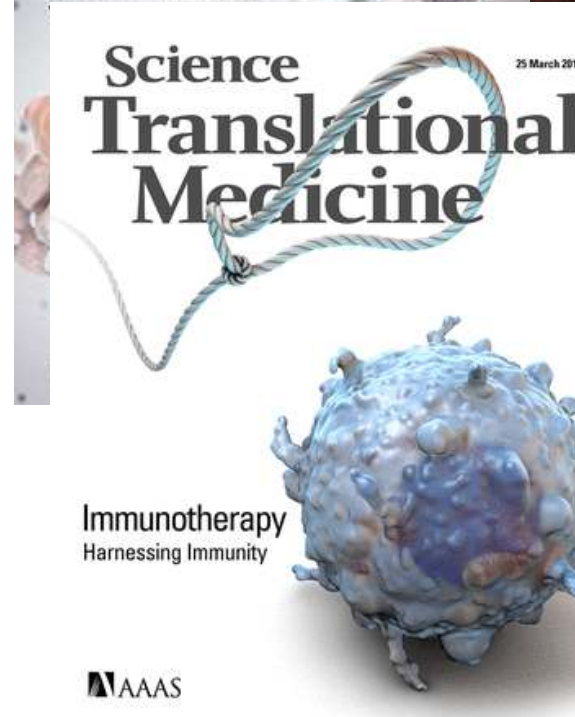
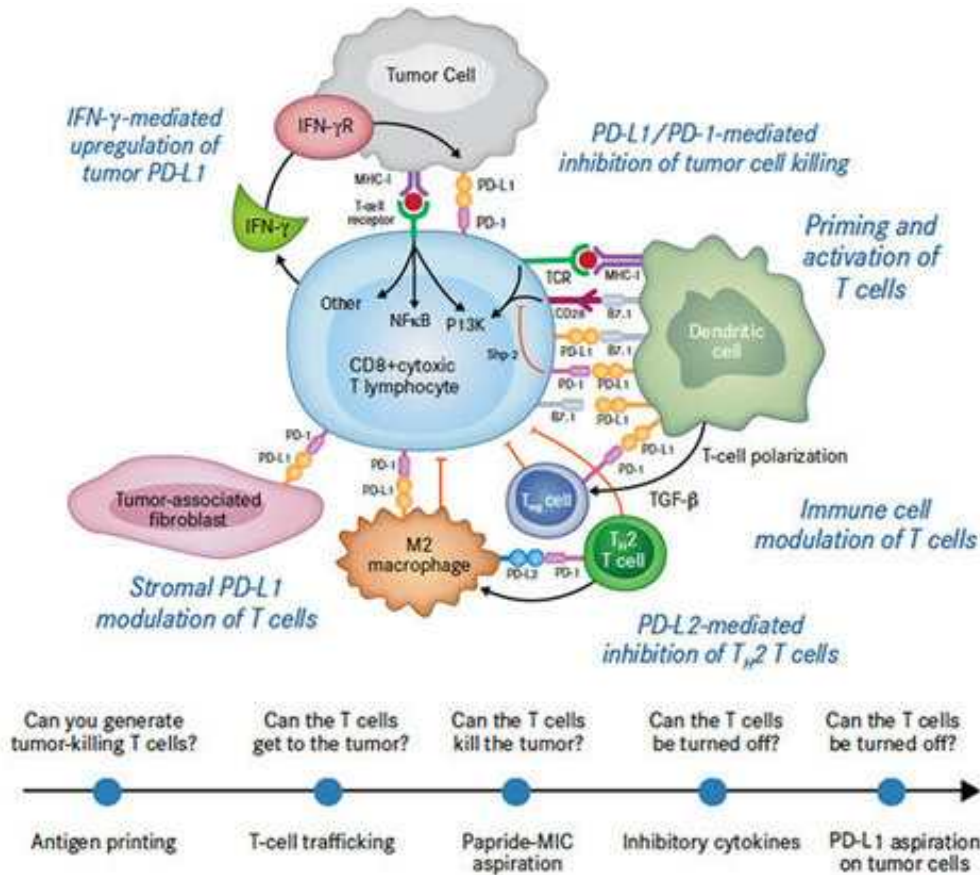


Schreiber RD et al. Science 2011;331:1565



Chen DS et al. Immunity 2013;39:1

# Immuno-oncology Therapeutics is Coming of Age

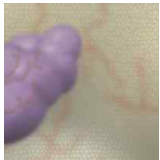


# Paradigm Shift in View of Cancer

*From Anatomy...*



Lung



Breast



Prostate

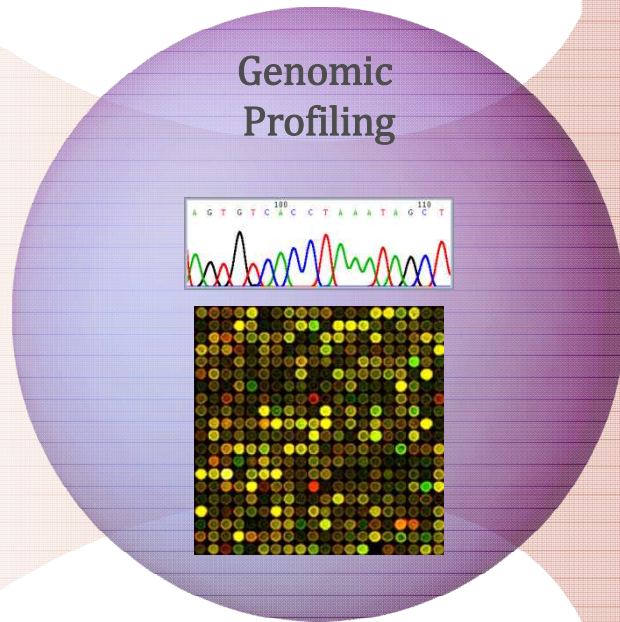


Colon

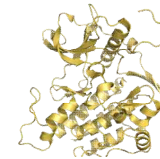


Brain

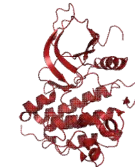
*To Genetic Classification*



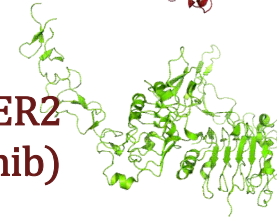
KIT  
(Imatinib)



EGFR  
(Erlotinib)



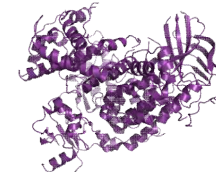
HER2  
(Lapatinib)



BRAF  
(Vemurafenib)



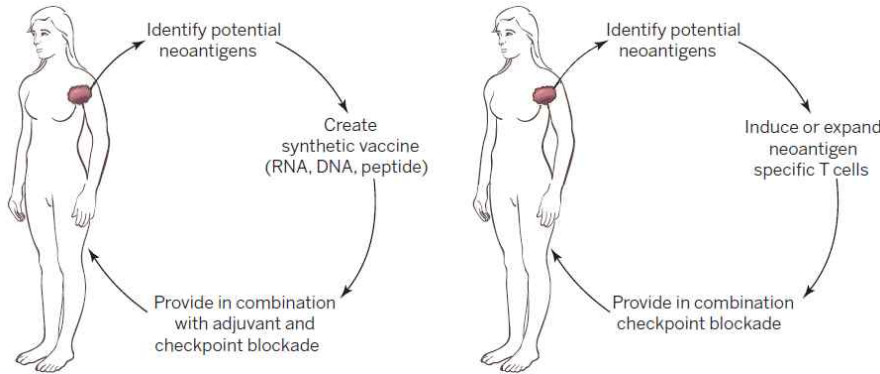
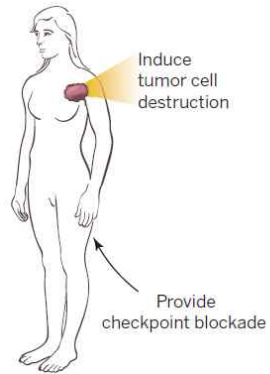
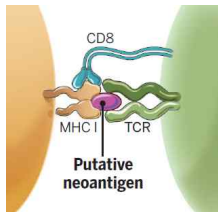
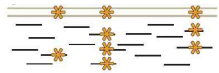
PIK3CA  
(BEZ235)



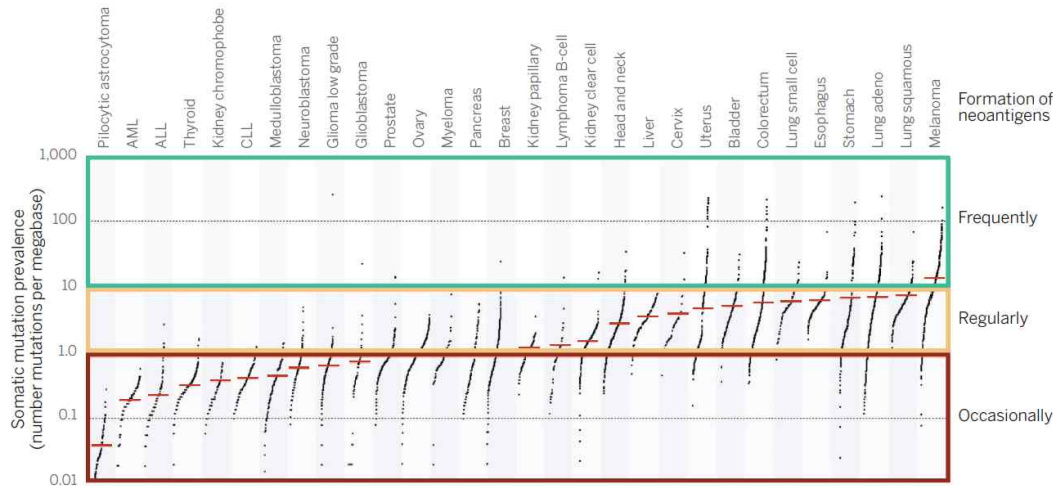


# Neoantigen & Immunotherapy

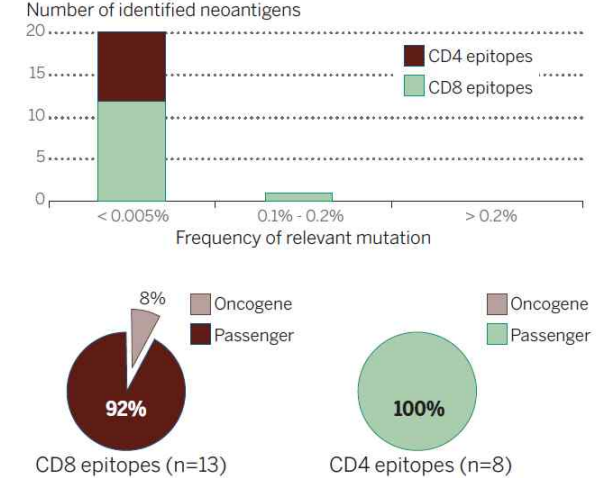
## Neoantigen



## Estimate of the neoantigen repertoire in human cancer



## Mutation-derived neoantigens in human cancer



- Interventions enhancing exposure to autologous neoantigen
- Patient-specific cancer vaccine to identified potential neoantigens
- Induction or expansion in vitro of T cells specific for potential neoantigens.

Schmacher TN et al. Science 2015;348:69



## Jimmy Carter, Melanoma And The Promise Of Immunotherapy In The Elderly



Jimmy Carter's cancer treatment includes a **'breakthrough' drug fast-tracked for FDA approval.**

FDA News Release

### FDA approves Keytruda for advanced melanoma

*First PD-1 blocking drug to receive agency approval*

For Immediate  
Release

September 4, 2014

FDA News Release

### FDA approves Opdivo for advanced melanoma

For Immediate  
Release

December 22, 2014

FDA News Release

### FDA expands approved use of Opdivo to treat lung cancer

For Immediate  
Release

March 4, 2015

FDA News Release

### FDA approves Keytruda for advanced non-small cell lung cancer

*First drug approved in lung cancer for patients whose tumors express PD-L1*

For Immediate  
Release

October 2, 2015

FDA News Release

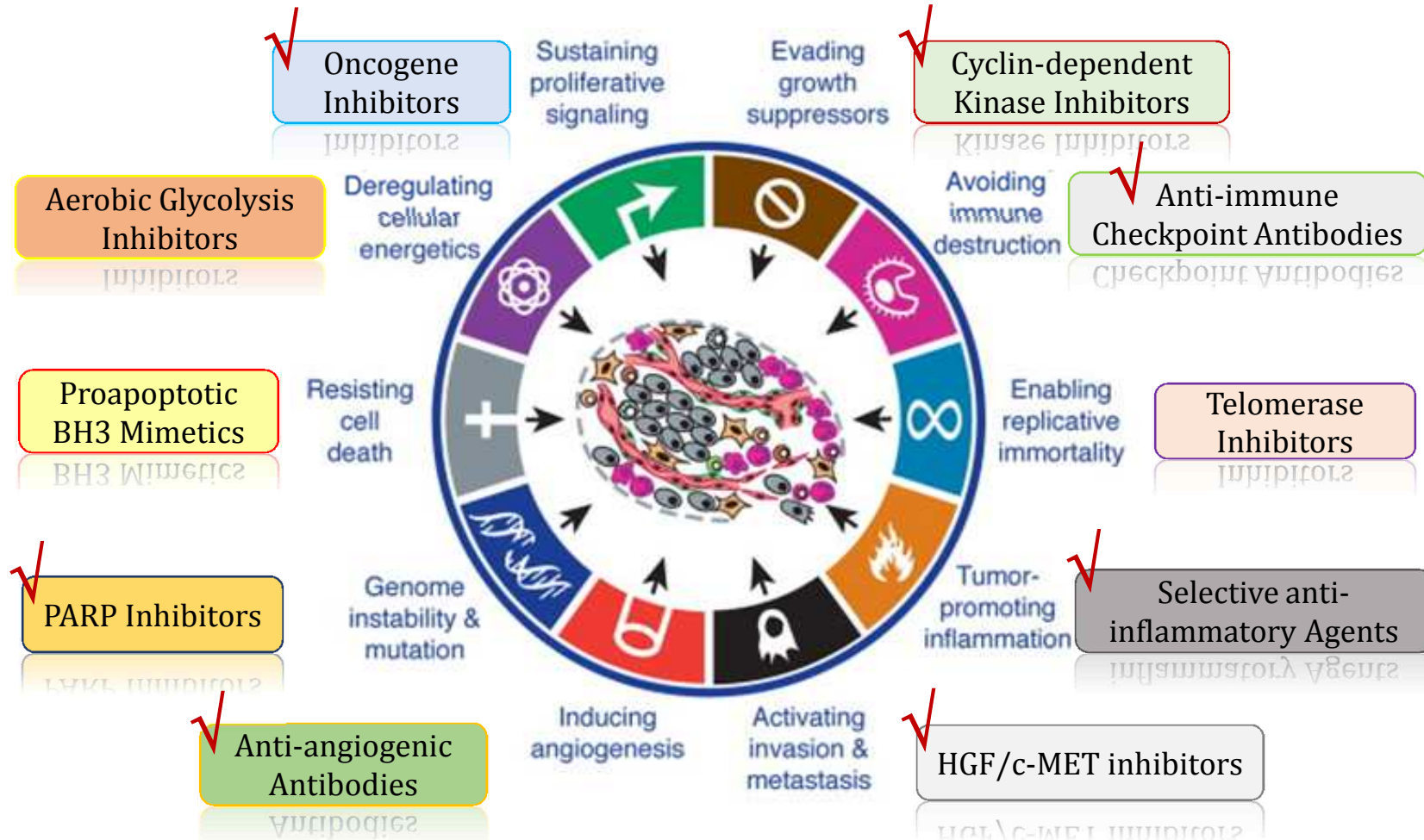
### FDA expands approved use of Opdivo in advanced lung cancer

*Opdivo demonstrates survival benefit in squamous and non-squamous non-small cell lung cancer*

For Immediate  
Release

October 9, 2015

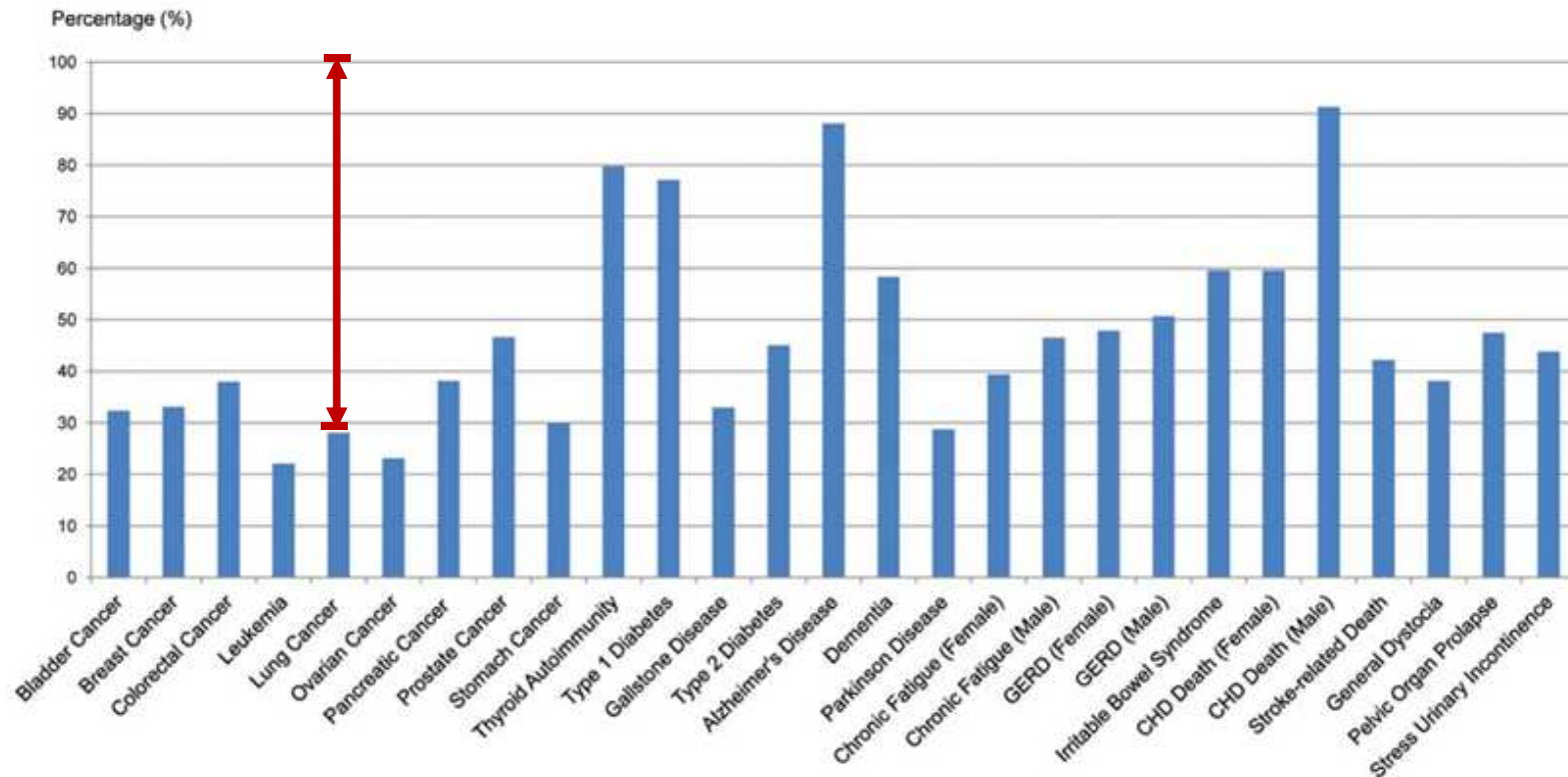
# Targeting the Hallmarks of Cancer



Hanahan and Weinberg. Cell 2011;144:646



# Personalized Medicine: Genomics Plus .....

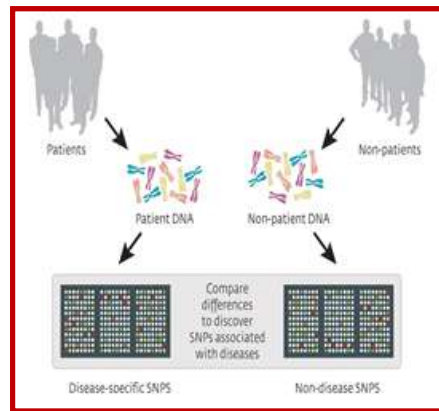


## Risk Assessment and Stratification by Genomics: Not Sufficient

The portion of people with a disease who would have tested positive for a genetic risk varied by illness.

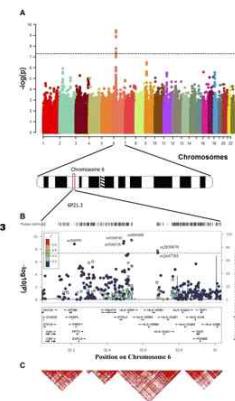
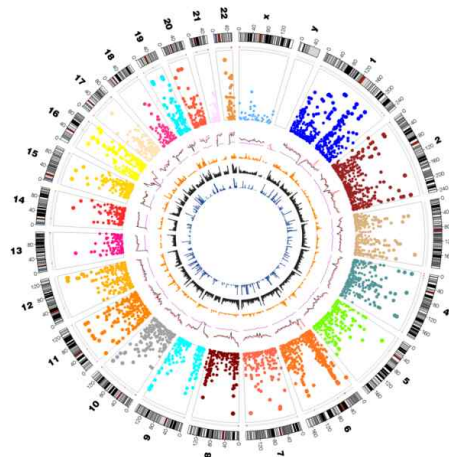
# From Genome Medicine to Personalized Medicine

## Genome-wide Association Study



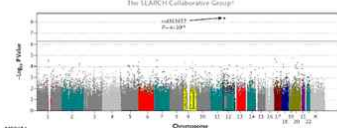
## 18 traits SNP-trait associations

- Digestive system disease
- Cardiovascular disease
- Metabolic disease
- Immune system disease
- Nervous system disease
- Liver enzyme measurement
- Lipid or lipoprotein measurement
- Inflammatory marker measurement
- Hematological measurement
- Body measurement
- Cardiovascular measurement
- Other measurement
- Response to drug
- Biological process
- Cancer
- Other disease
- Other trait

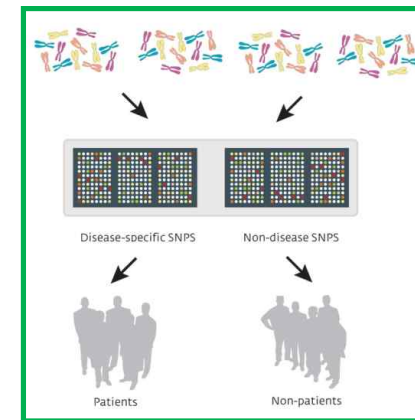
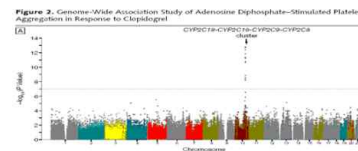


The NEW ENGLAND JOURNAL of MEDICINE

ARTICLE 23, 2009  
**SLCO1B1 Variants and Statin-Induced Myopathy — A Genome-wide Study**  
 The SEARCH Collaborative Group\*

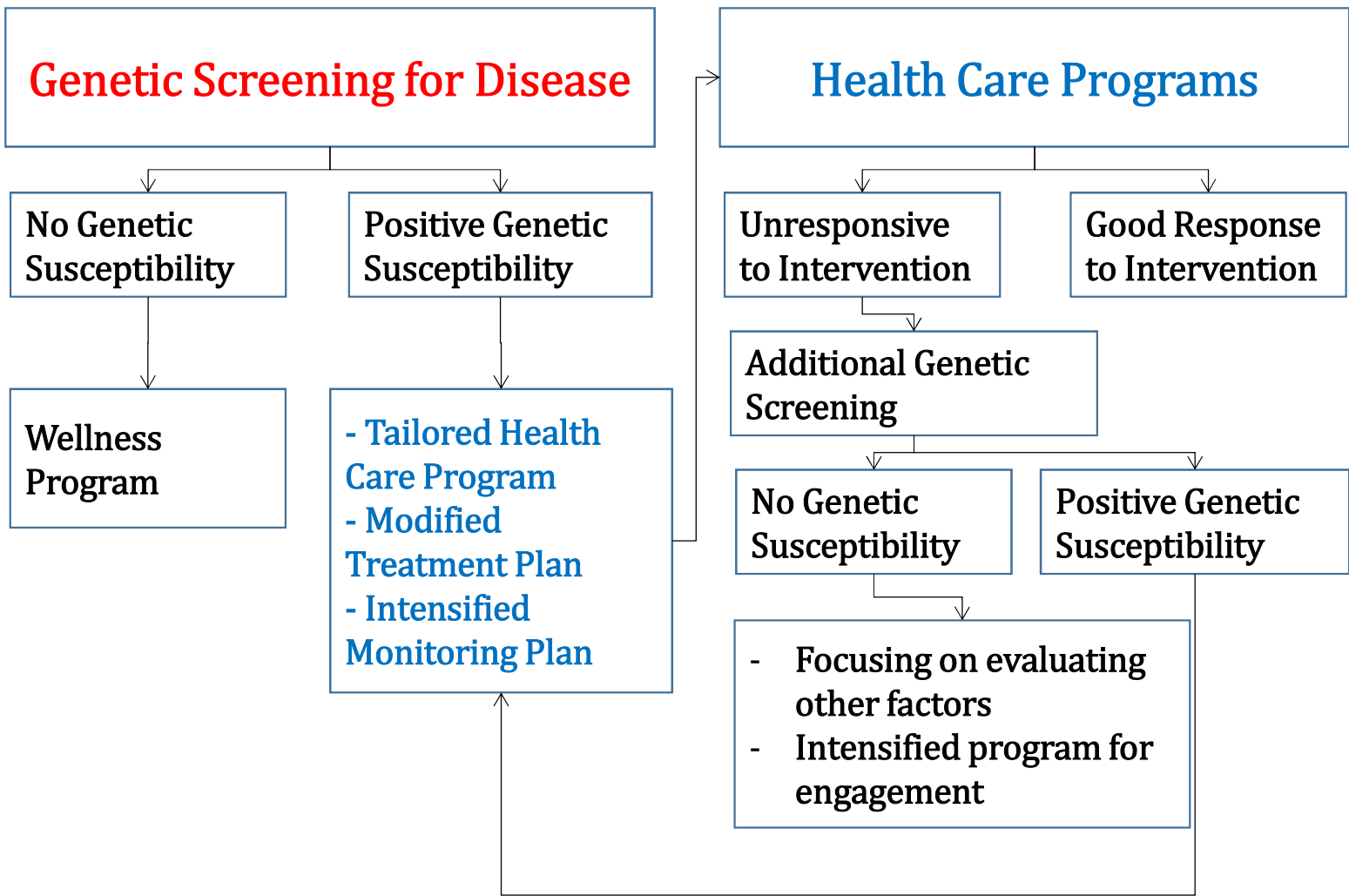


**JAMA** Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy  
 Alan R. Shuldiner, Jeffrey R. O'Connell, Kevin P. Bliden, et al.  
 JAMA. 2009;302(8):849-857 (doi:10.1001/jama.2009.1232)





# Personalized Predictive Medicine



# Active Participatory Medicine

Women's Health Panel Risk Assessment  
Genetic Report CIN:01432101

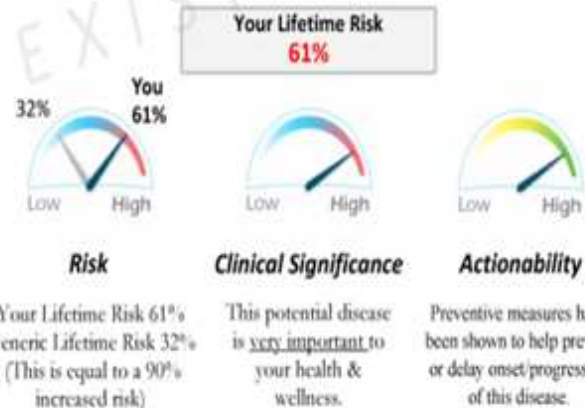


## Heart Attack

A heart attack occurs when the blood supply to the heart is interrupted, causing some heart tissue to die. A heart attack is an emergency because it may cause sudden death or, following a heart attack, the heart may not function correctly. The most common cause is a build-up of plaque in one of the blood vessels feeding the heart, a condition referred to as coronary artery disease, which is related to high cholesterol levels.

Over one million people suffer a heart attack each year in the United States and about 40% of these people will die from the heart attack. Heart disease, including heart attacks, is the leading cause of death in the world but numerous preventive measures exist.

### Your Predictive Medicine Assessment



### Onset & Symptoms

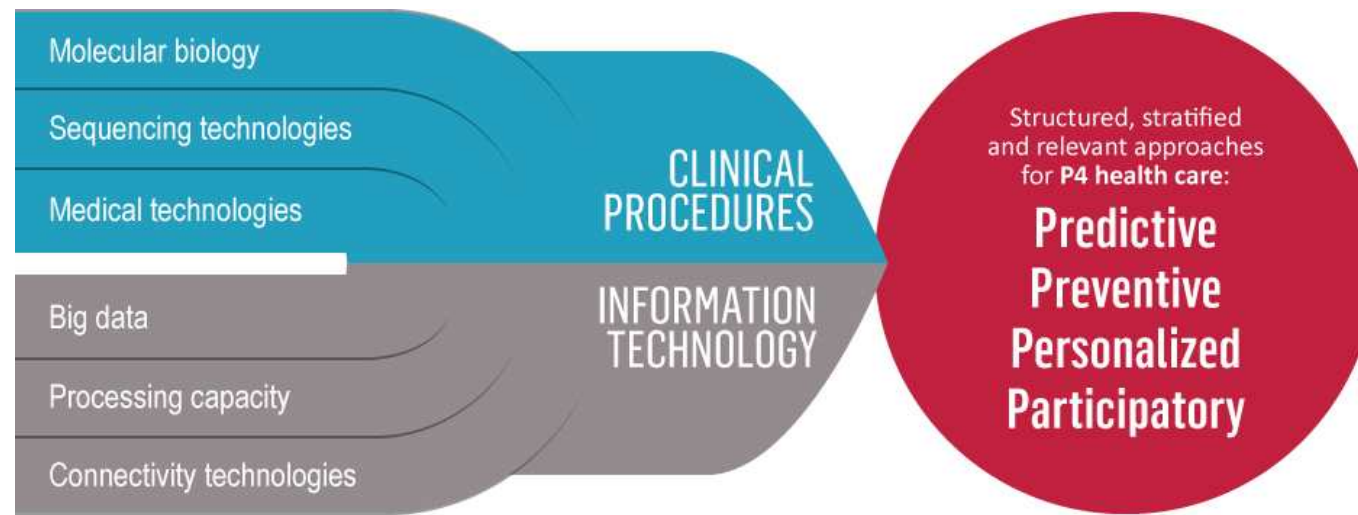
You are at greatest risk of a heart attack after the age of 40. Symptoms of a heart attack include chest pain that may radiate down the left arm or up to the jaw as well as shortness of breath, fatigue, sweating and nausea and/or vomiting.

A heart attack is an emergency situation and if it is suspected, you should be brought to an emergency room immediately or call 911.





# Health Care Platform for P4 Health Care



- **Molecular Biology & Sequencing Technologies:**  
Cracking the Code of Human Life
- **Medical Technologies & Companion Decision Tools:**  
Guiding and Evaluating Health Care
- **Information & Communication Technologies:**  
Capturing and Interpreting Health Information

# P4 Medicine Transforms Healthcare

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- **Personalize Medicine** reduces variability and delivers evidence medicine.
- **Predictive, Preventive and Personalized Medicine** is based stratification of patients to create smaller and precise groups by analyzing data, vice versa creating knowledge
- Patient's active **Participation** is the most important

**4P's Medicine to 1P's Medicine,  
“Perfect Medicine”**