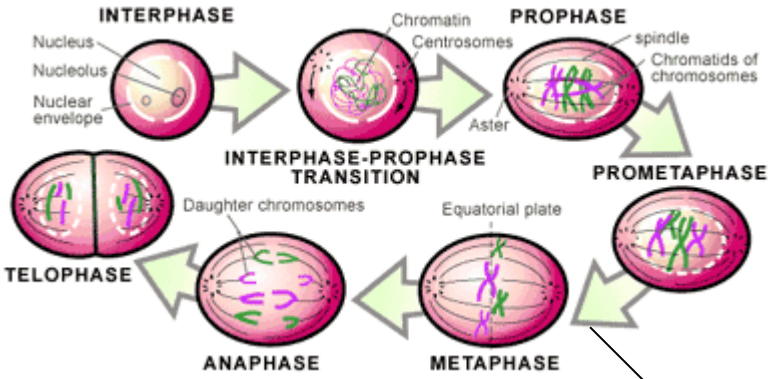
A Personalized Approach to Cancer Therapy

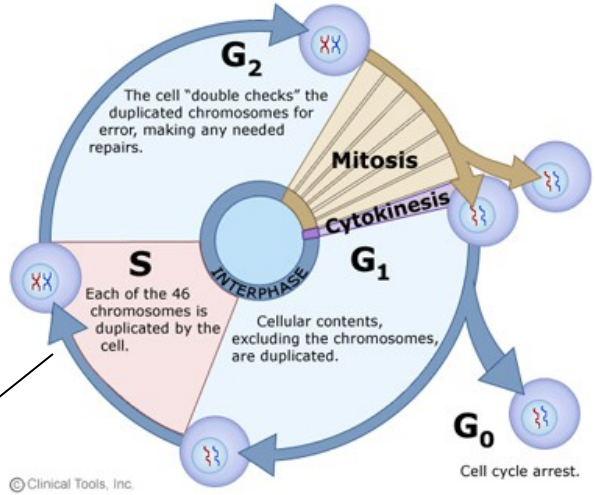
Koraljka Gall Troselj, MD, Ph.D.

Rudjer Boskovic Institute

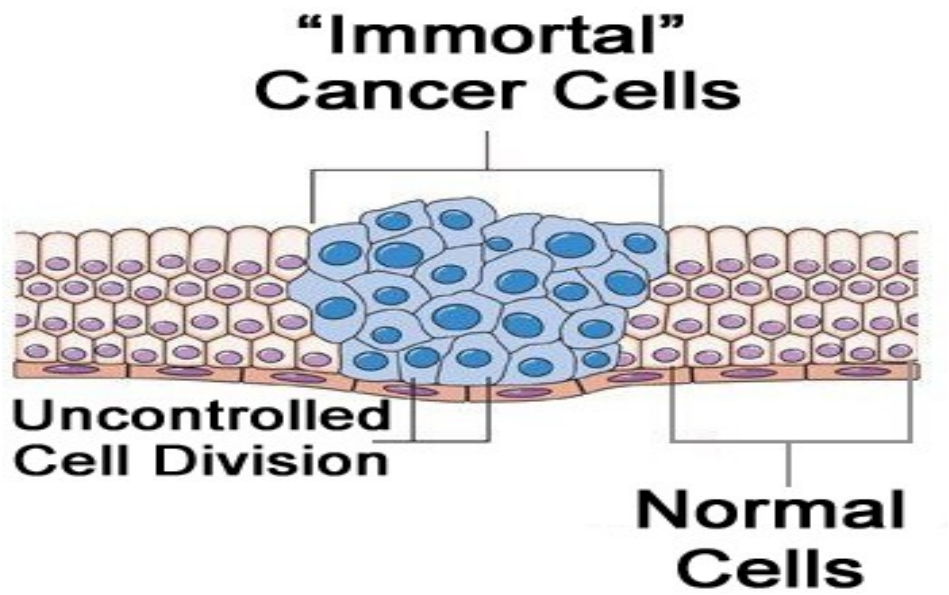
Division of Molecular Medicine
Zagreb
CROATIA

It is all about cellular division…





NORMAL

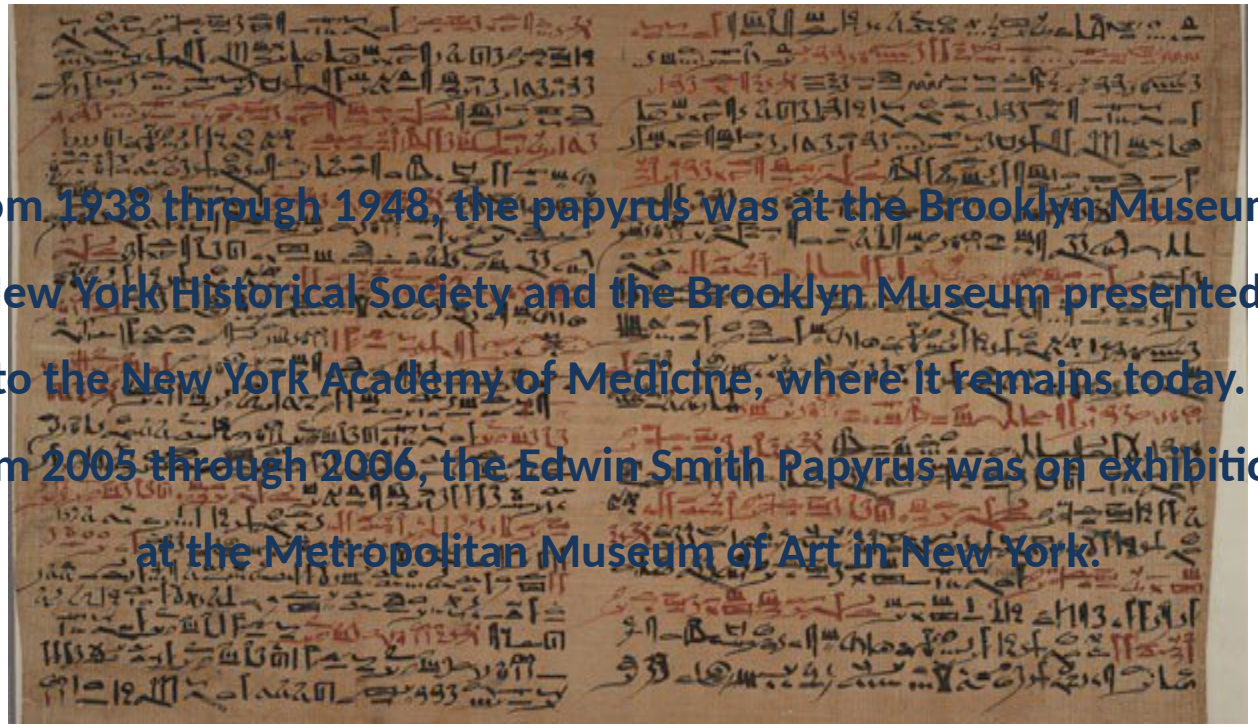


ABNORMAL

The Edwin Smith Papyrus

...describes the earliest known cases of tumors of the breast, that were treated by cauterization with a tool called the "fire drill".

The writing says: "There is no treatment".



From 1938 through 1948, the papyrus was at the Brooklyn Museum.

In 1948, the New York Historical Society and the Brooklyn Museum presented the papyrus to the New York Academy of Medicine, where it remains today.

From 2005 through 2006, the Edwin Smith Papyrus was on exhibition at the Metropolitan Museum of Art in New York.

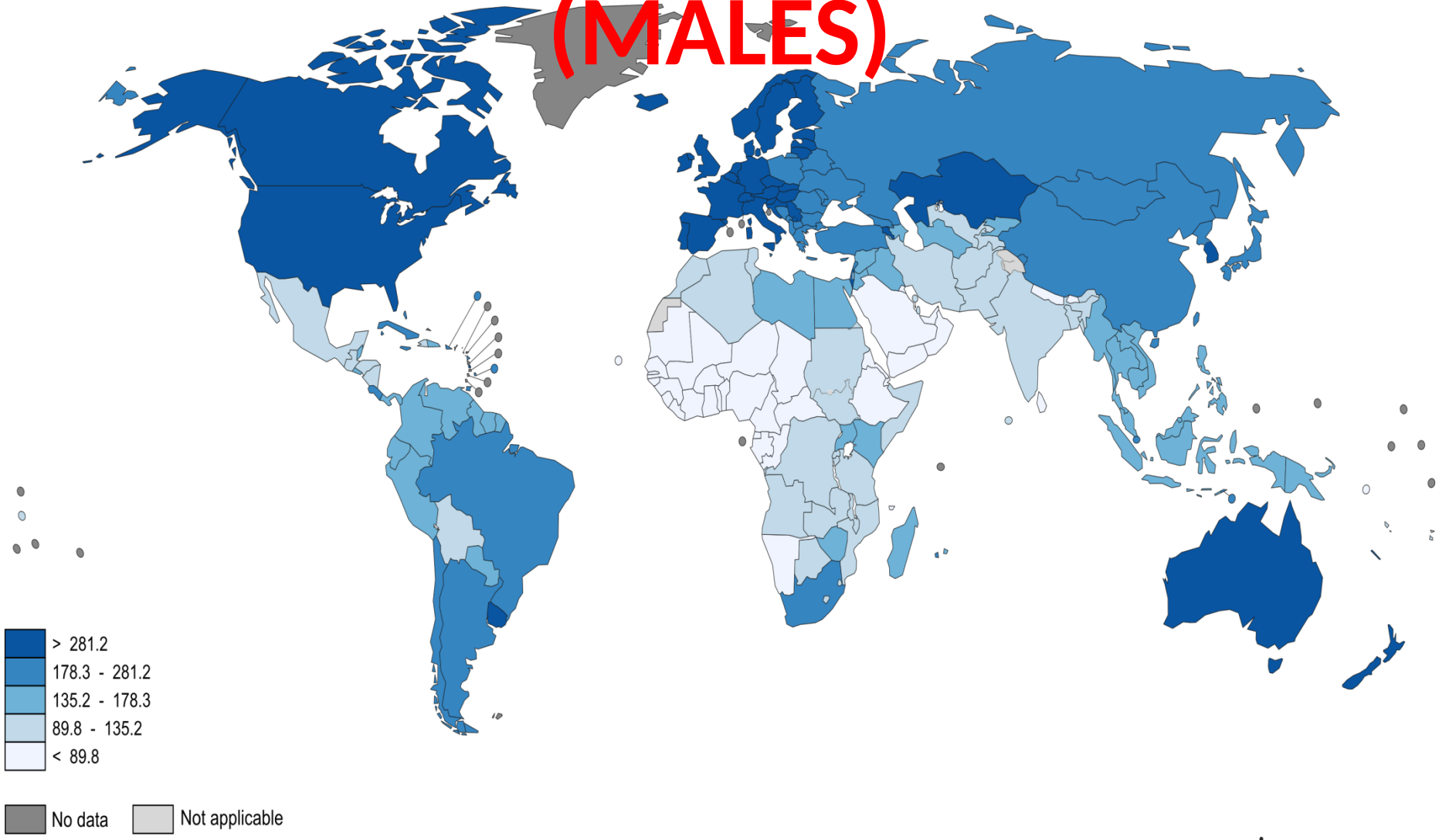
Cancer

According to data released by WHO , in 2015:

- **14.1 million people were diagnosed with cancer**
- **8.7 million people died from cancer**
- **32.6 million people had to live with cancer**

In 2030 12.6 million people will die from cancer

Cancer World Map – 2012 (MALES)

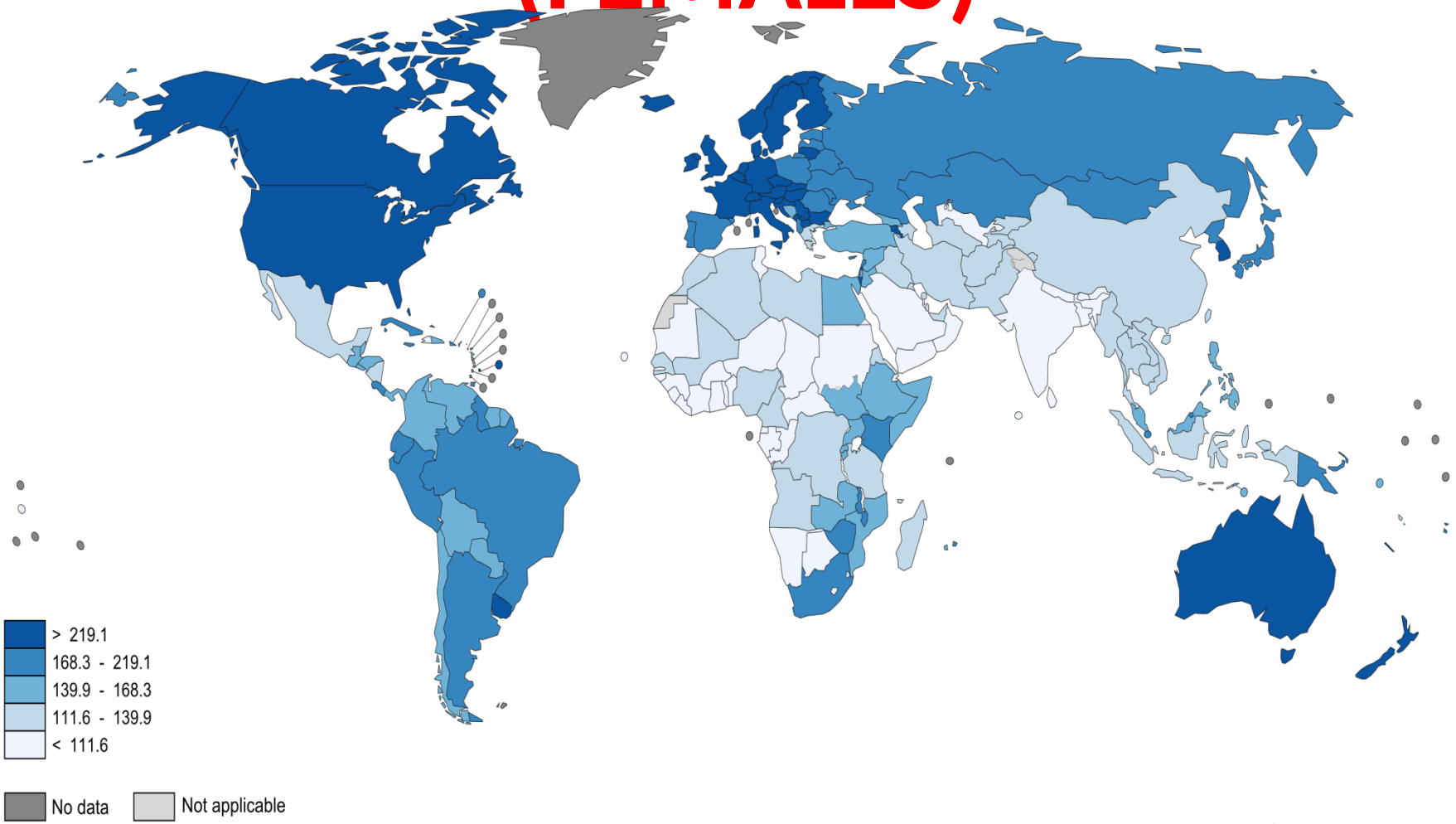


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Cancer World Map – 2012 (FEMALES)

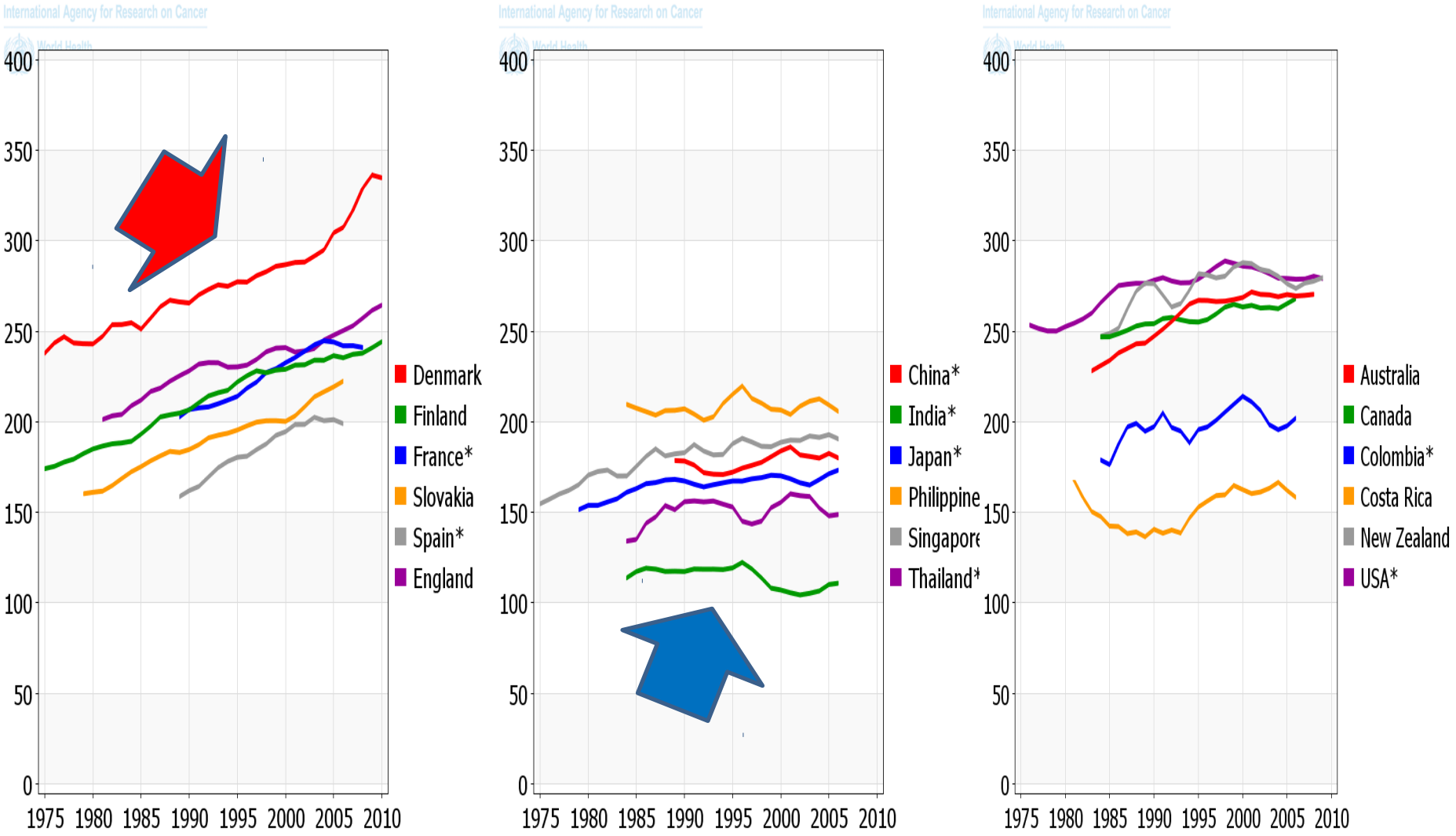


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

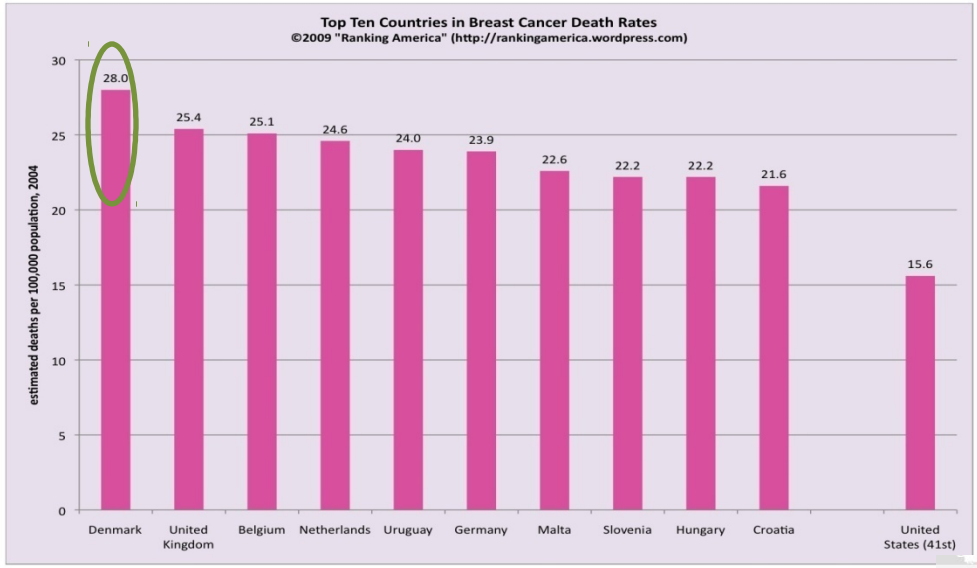
Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Age-standardised rate per 100,000; women

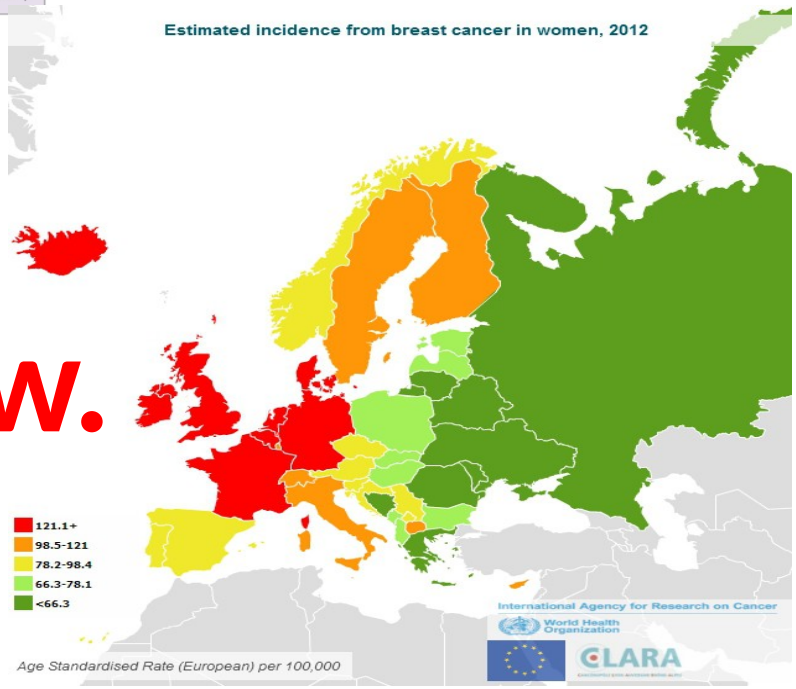


Why Dennmark?



Data from World Health Organization
http://www.who.int/whosis/whostat/2008/en/index.html

We do NOT know.



The Cancer Genome Atlas (TCGA)

a collaboration between the **National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI)**, has generated comprehensive, multi-dimensional maps of the key genomic changes in **33 types of cancer**. The TCGA dataset, **2.5 petabytes** of data describing tumor tissue and matched normal tissues from more than 11,000 patients.

Peta = 10^{15}

Human Genome Project Goals:

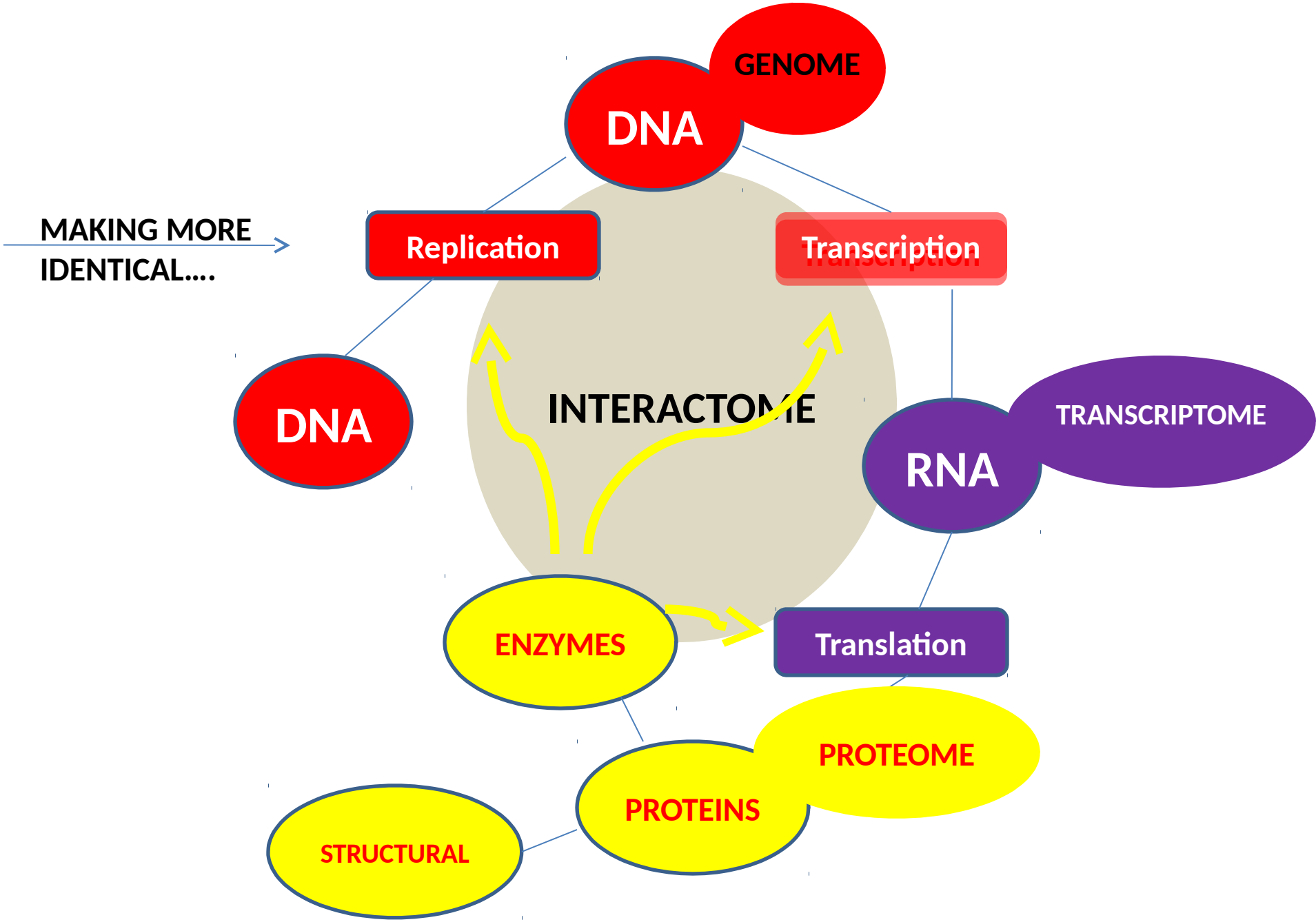
- ***identify*** **all the approximately 20,000-25,000 genes in human DNA,**
- ***determine*** **the sequences of the 3 billion chemical base pairs that make up human DNA,**
- ***store*** **this information in databases,**
- ***improve*** **tools for data analysis,**
- ***transfer*** **related technologies to the private sector, and**
- ***address*** **the ethical, legal, and social issues (ELSI) that may arise from the project.**

Manel Esteller:

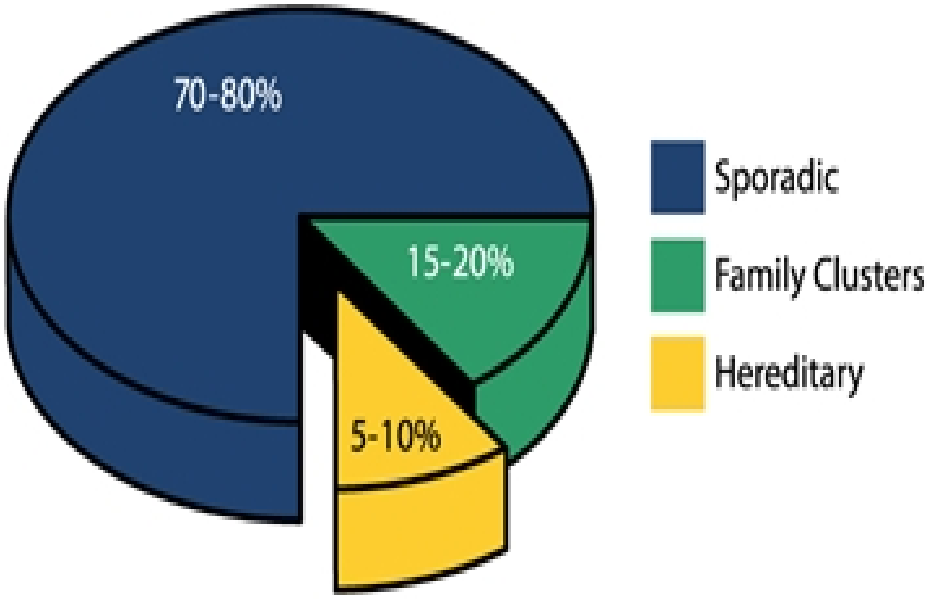
"We have this huge phone book, but it is the time to organize it and make

some calls

to be sure that the names and addresses correspond to those numbers" .


GENOME
DNA
MAKING MORE IDENTICAL….
Replication
Transcription
DNA
INTERACTOME
RNA
TRANSCRIPTOME
ENZYMES
Translation
PROTEOME
PROTEINS
STRUCTURAL

GENOME AND CANCER



In hereditary cancer, one damaged gene is inherited.

Some Inherited Cancer Syndromes

Familial retinoblastoma	Rb1
Li-Fraumeni Syndrome	TP53
Familial Adenomatous Polyposis	APC
Hereditary Nonpolyposis Colorectal Cancer	MLH1, MSH2, MSH6, PMS1, PMS2
Wilms's Tumor	WT1
Breast and Ovarian Cancer	BRCA1-1 and BRCA-2
Von Hippel-Lindau	VHL
Cowden Disease	PTEN

BRCA-1 AND BRCA-2

When mutated, these genes significantly increase the risk of breast and ovarian cancer

and

Myriad

and

Association for Molecular Pathology

v.

Myriad Genetics

Importance of legal action

The case put in question **the validity of gene patents** in the US.

Questionable claims related to the ownership of:

a) **DNA SEQUENCE;**

b) **DIAGNOSTIC METHOD(S) BASED ON TESTING ALREADY "OWNED" DNA SEQUENCE;**

c) **METHODS TO IDENTIFY DRUGS USING "OWNED" DNA SEQUENCES.**

June 13th, 2013:

Naturally occurring DNA sequences, even when isolated from the body,

CANNOT BE PATENTED,

but artificially created DNA is patent eligible because it is not naturally occurring.

Describing Personalized Medicine

"Providing the right treatment to the right patient, at the right dose at the right time"

European Union

"A form of medicine that uses information about a person's

GENES,
PROTEINS,
AND ENVIRONMENT
to
prevent, diagnose, and treat disease."

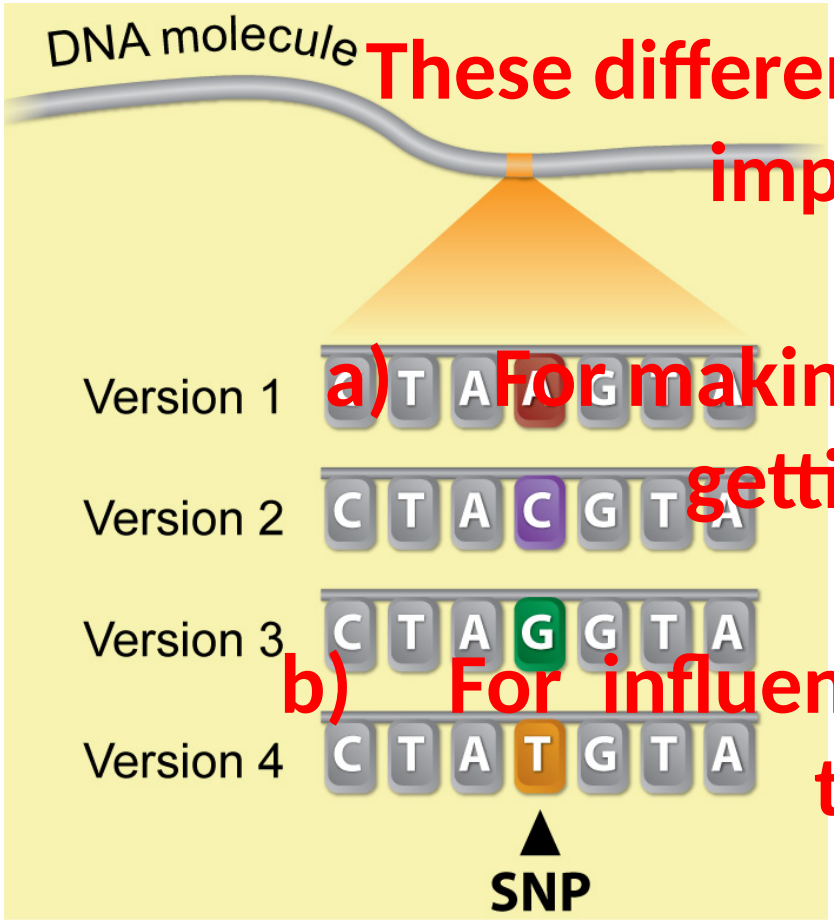
National Cancer Institute, NIH

How different are we at the level of DNA?

As of 16 October 2014, dbSNP listed 112,736,879 SNPs in humans

As of 8 June 2015, dbSNP listed 149,735,377 SNPs in humans

As of June 26th 2017, dbSNP lists 336,838,138 SNPs, in humans



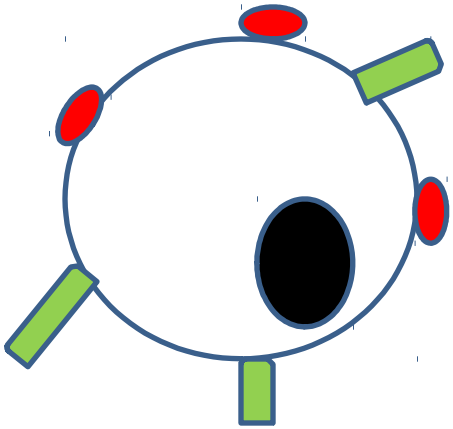
These differences are of utmost importance:

a) For making us susceptible for getting disease,

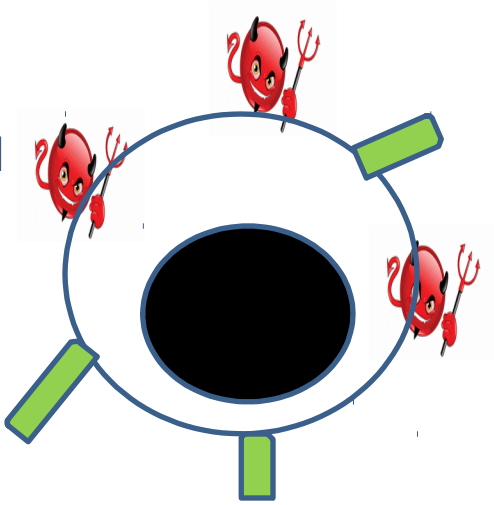
b) For influencing our response to therapy.

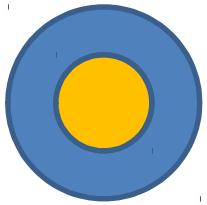
What is the basic idea (I)?

Normal Cell



Malignant Cell



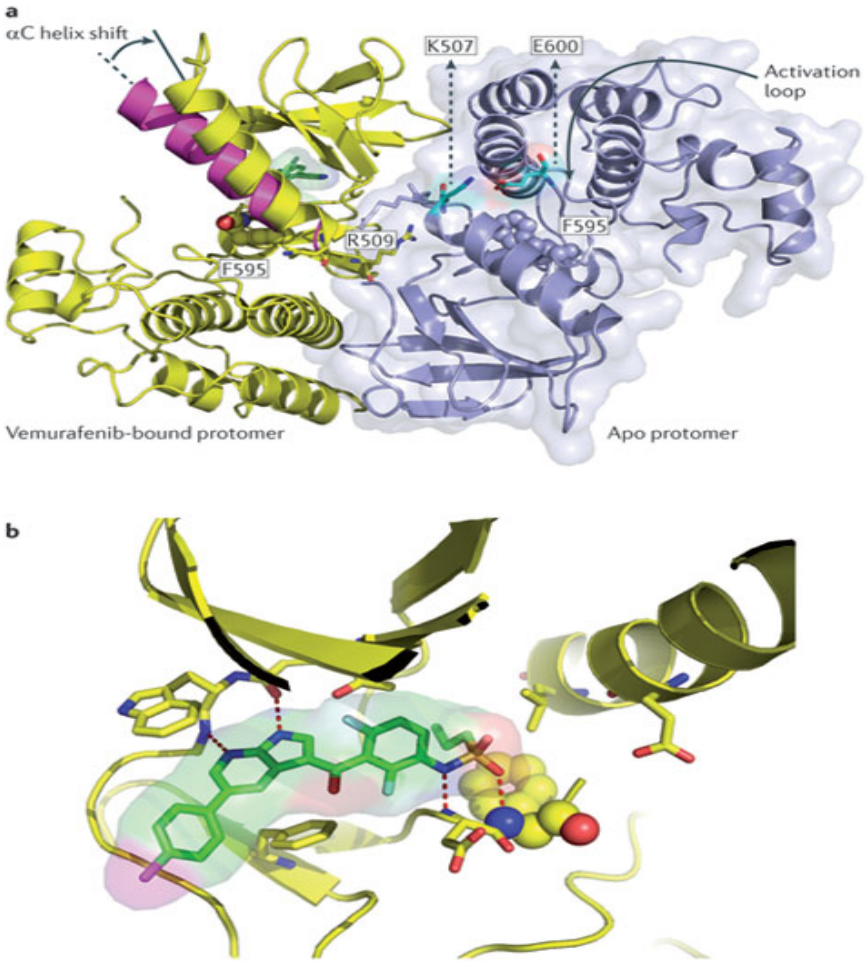


About half of all melanomas have changes (mutations) in the *BRAF* gene. These changes cause the gene to make an altered BRAF protein that signals the melanoma cells

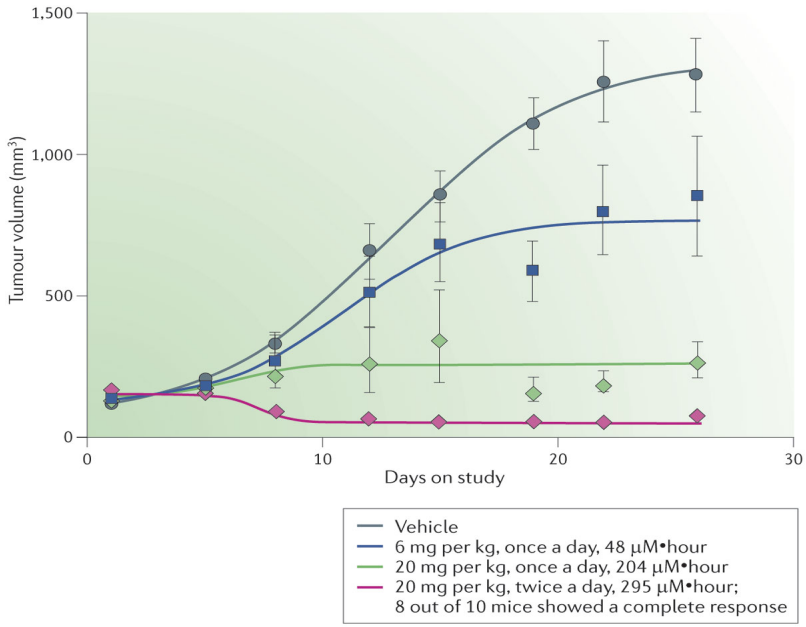
to grow and divide quickly.

What is the basic idea (II)?

Vemurafenib – V600E mutated BRAF (Zelboraf)



Nature Reviews | Drug Discovery

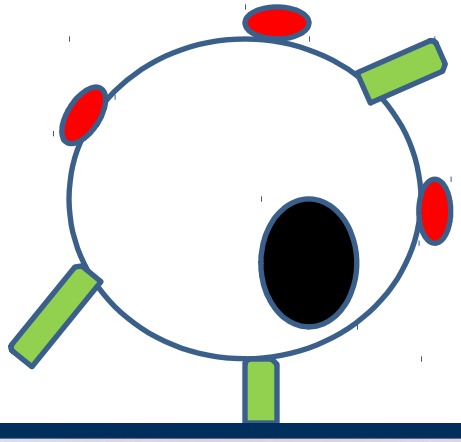


Nature Reviews | Drug Discovery

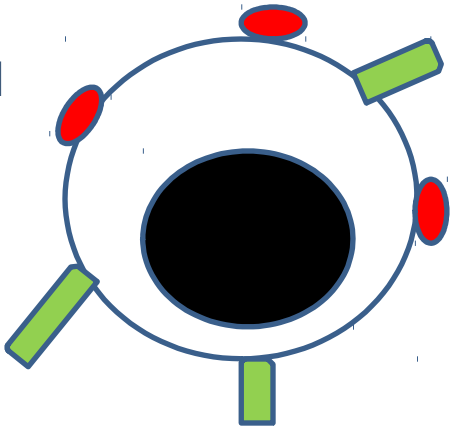
Bollag et al., November 2012

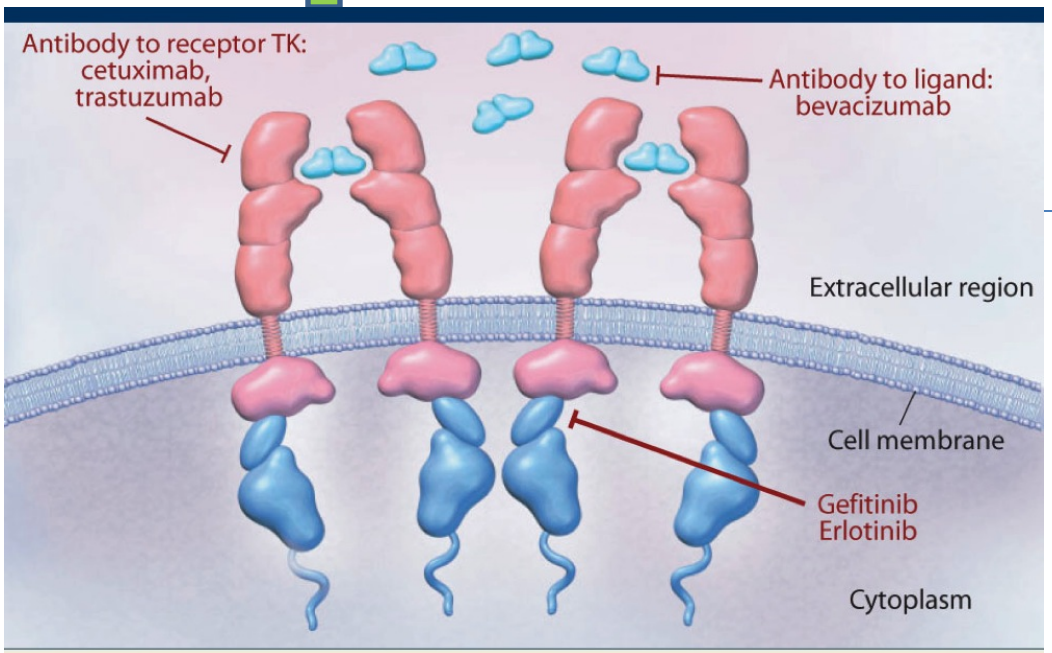
What is the basic idea (III)?

Normal Cell



Malignant Cell





Small Molecule Inhibitors of Receptor TKs

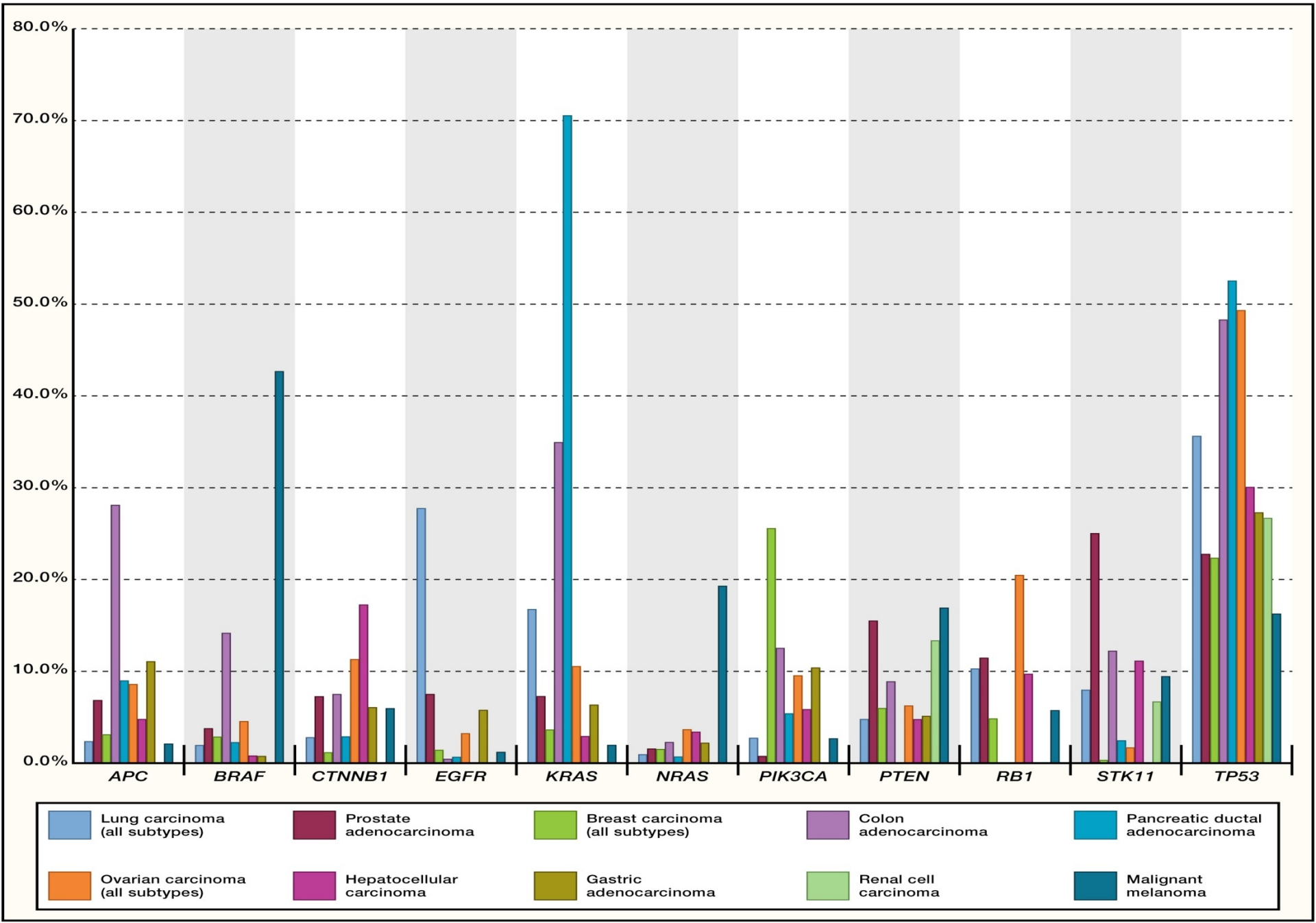
Krause DS, Van Etten RA. *New Engl J Med* 2005;353(2):172-187. © 2005 Massachusetts Medical Society. All rights reserved.

THINK ABOUT TREATING CANCER AS PUTTING A KEY IN A LOCK.

"A CANCER-CAUSING GENETIC MUTATION IS LIKE A LOCK. THEN FOR EACH LOCK, THERE'S THE SPECIFIC KEY OF A DRUG. YOU PUT THE RIGHT KEY IN THE RIGHT LOCK AND YOU'VE UNLOCKED OR SOLVED A TYPE OF CANCER."

–ROBERT C. DOEBELE, MD, PHD

Different cancer types and different frequencies of mutated genes

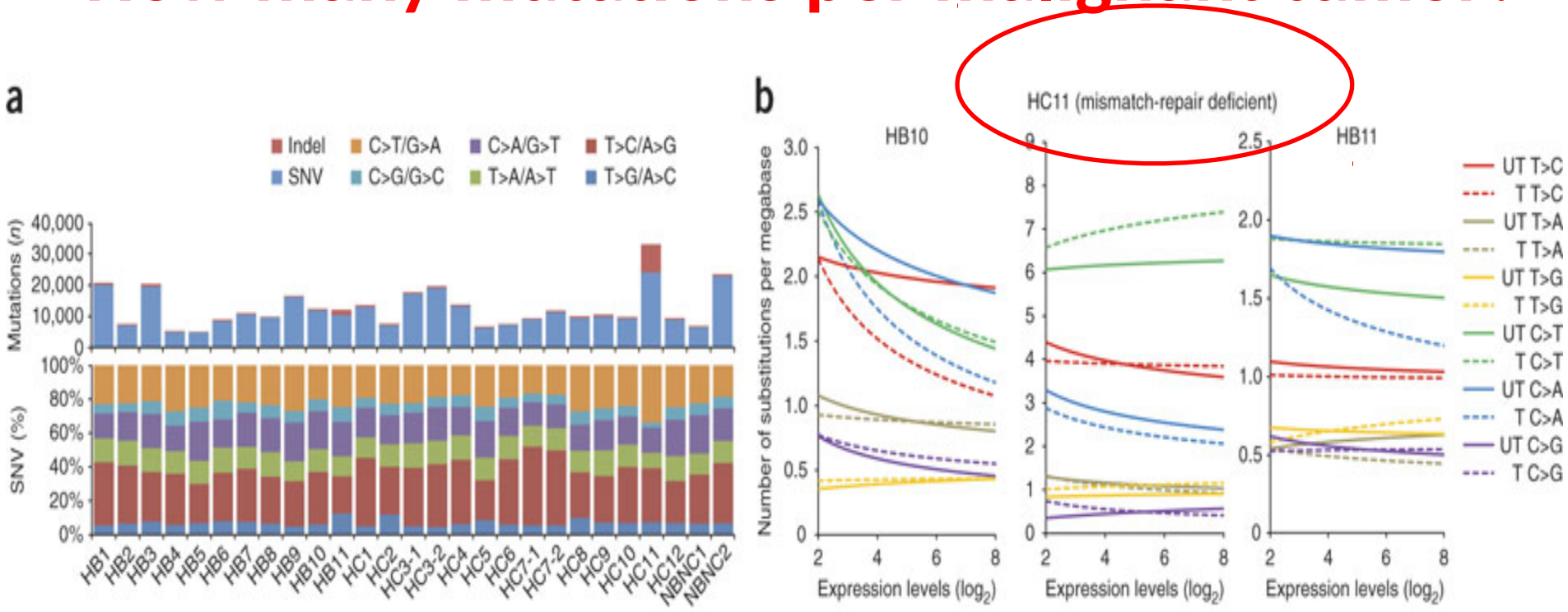


FDA approves first cancer treatment for any solid tumor with a specific genetic feature

May 23, 2017

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with **unresectable or metastatic solid tumors** that have been **identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).**

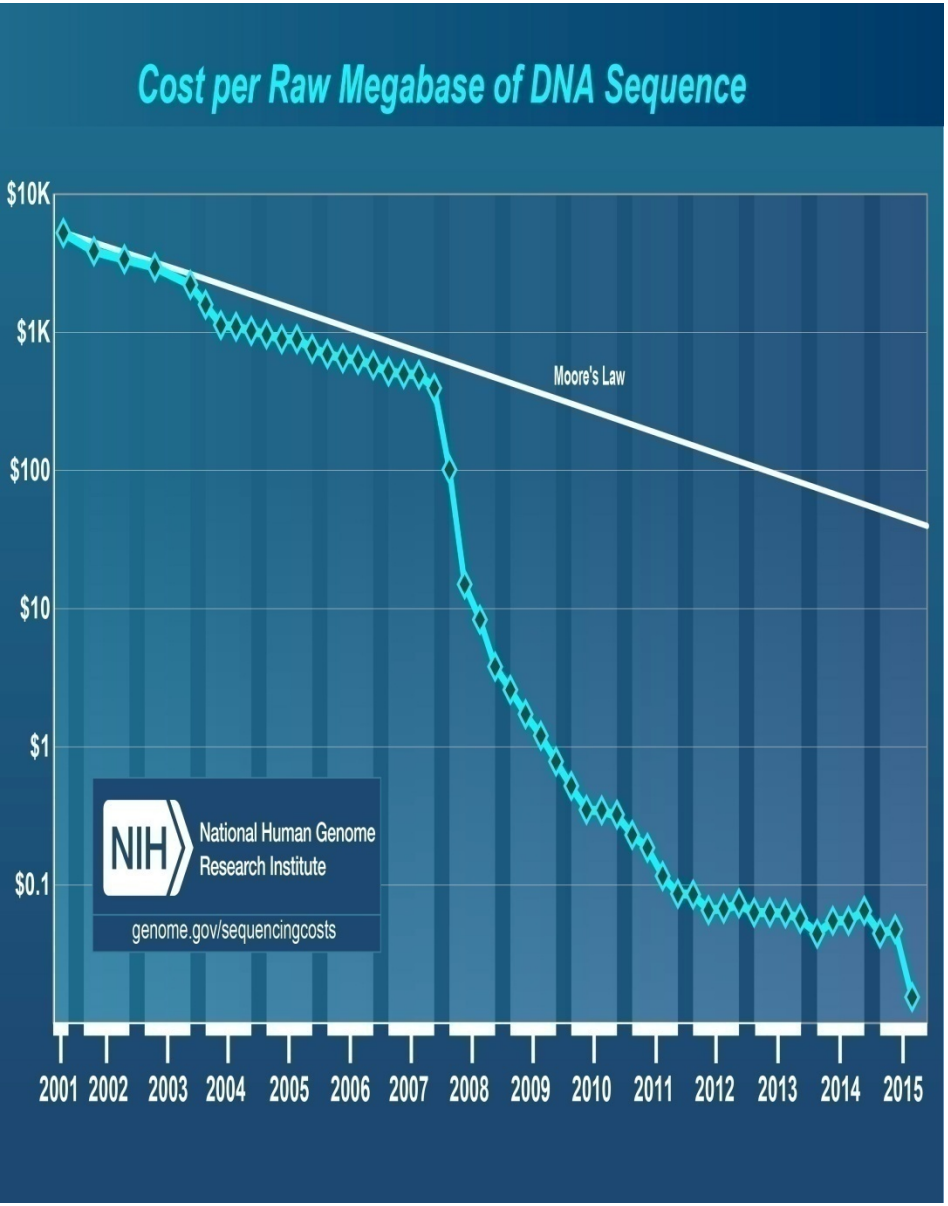
How many mutations per malignant tumor?

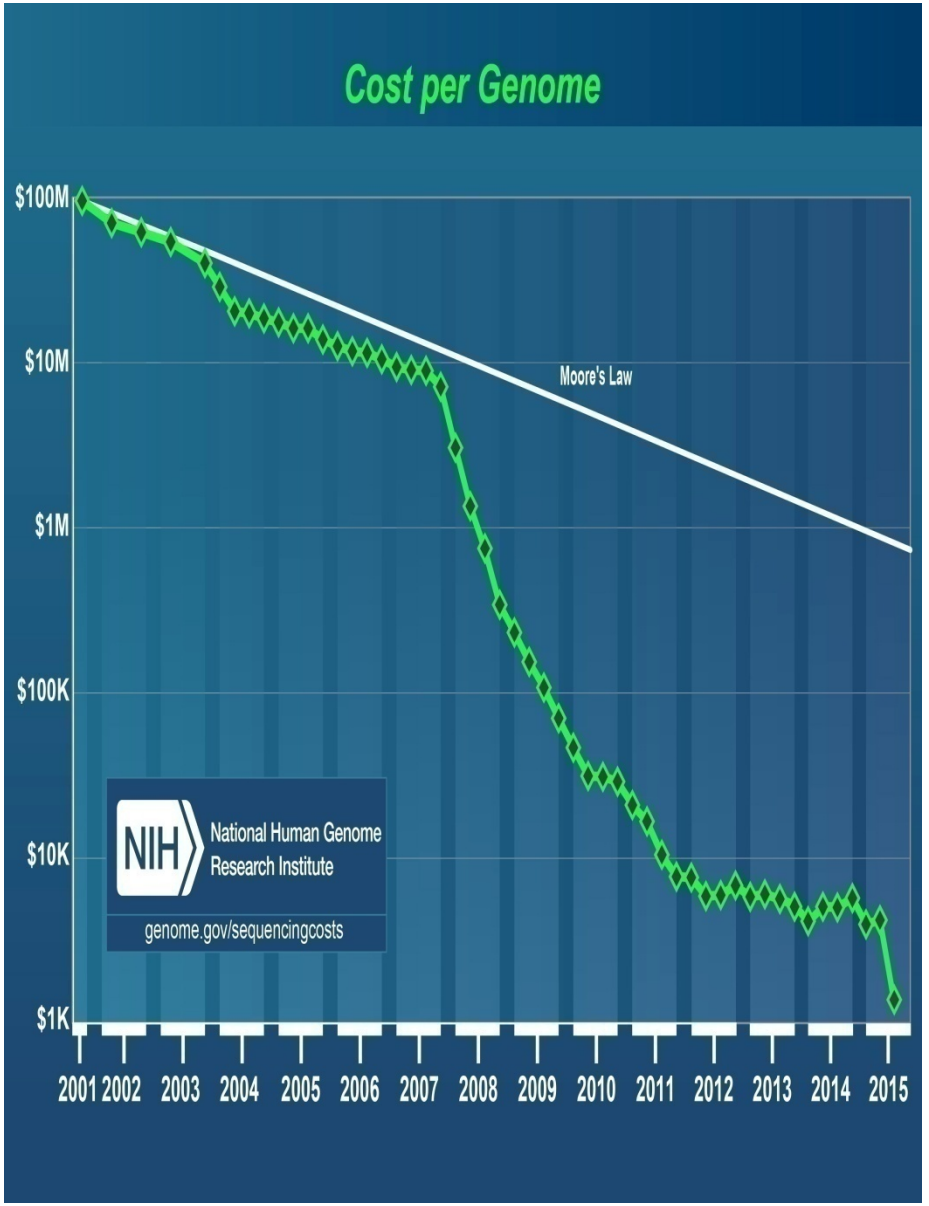


Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators.

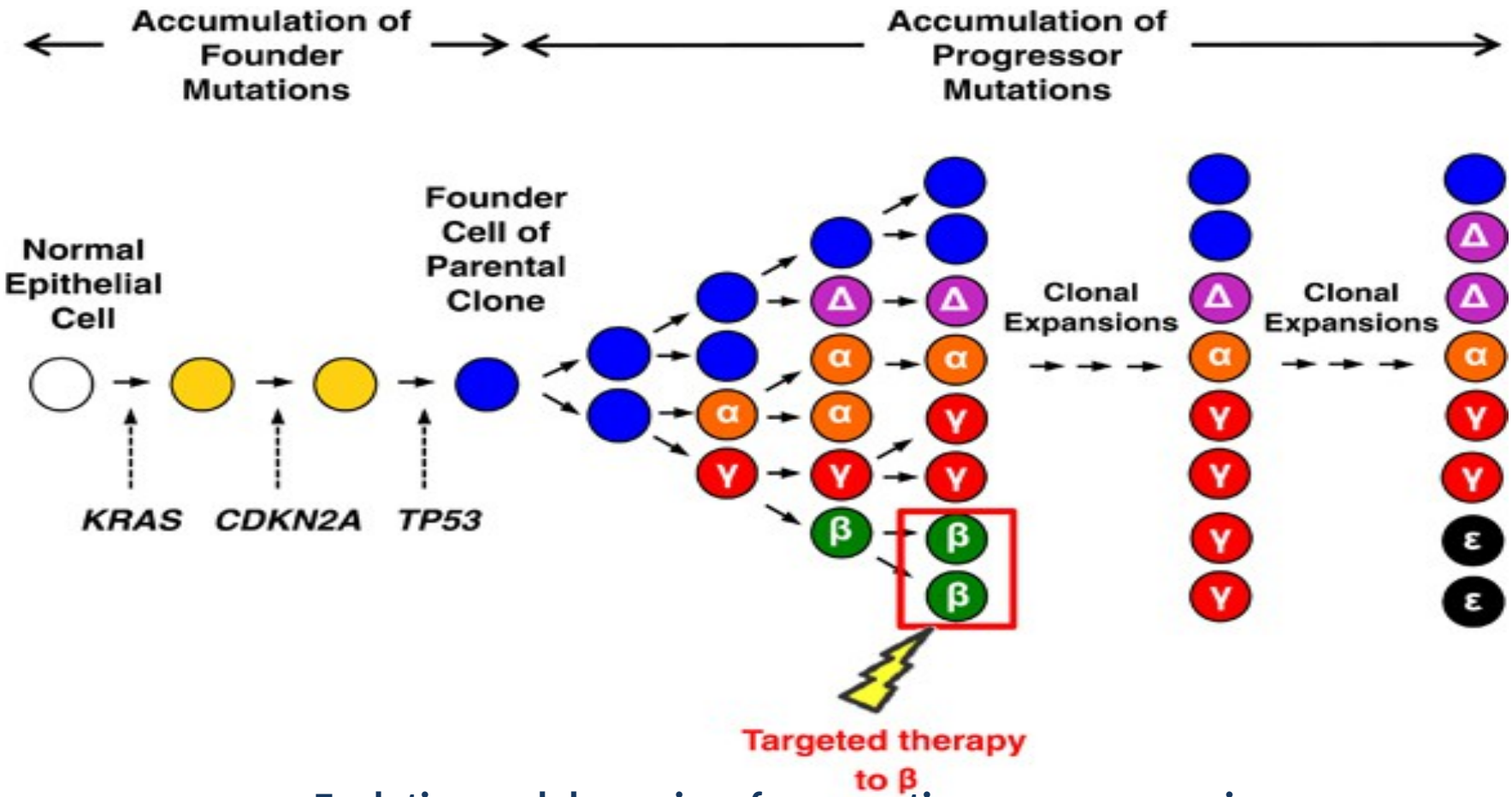
Fujimoto A et al. *Nature Genetics 44, 760–764 (2012)*
Citations: 492

How much should we pay for performing the test?





Are these mutations equally strong?



Evolution and dynamics of pancreatic cancer progression
Yachida S, Iacobuzio-Donahue CA. Oncogene, November 2013

Successful story of HER-2 and Herceptin (1)

1979: *HER-2 identification in breast cancer – Dr. Robert Weinberg;*

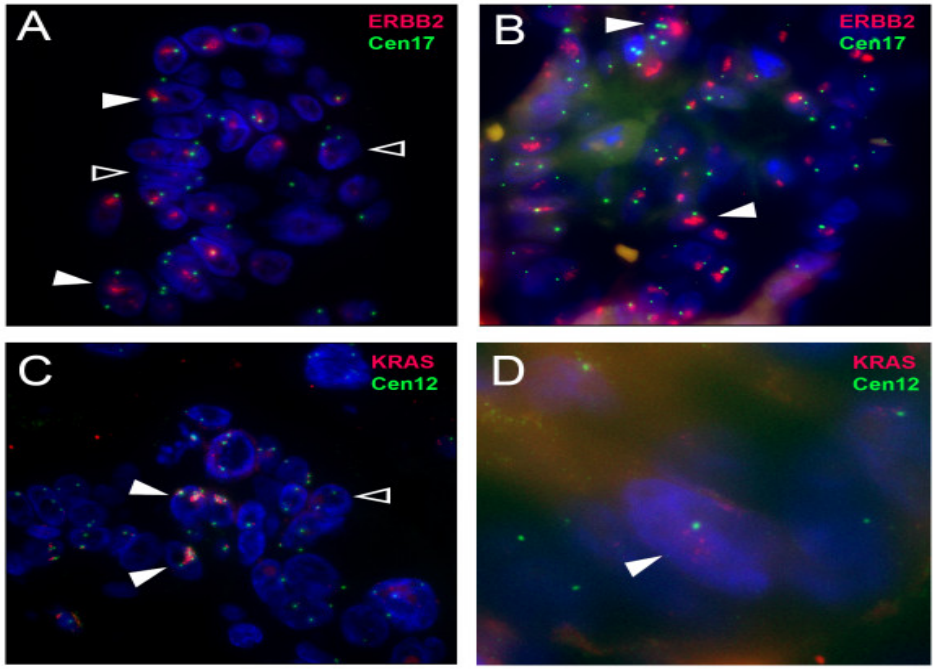
Association with aggressive forms of breast cancer (up to 30%) – Dr. Dennis Slamon

MAY:

1998: *TRASTUZUMAB - Herceptin was presented in front of 18000 attendees of the annual meeting of the American Society for Clinical Oncology (ASCO)*

SEPTEMBER:

FDA approved Herceptin for the treatment of HER2 positive metastatic breast cancers.



Successful story of HER-2 and Herceptin (2)

… AND NOT ONLY THAT……

On that same day, the FDA granted approval to DAKO Corp for

HercepTest, an in vitro assay

to detect HER2 protein overexpression in breast cancer cells.

The Essence of Personalized Medicine

Simultaneous approval of the gene-targeting drug and assay of the drug's potential effectiveness marked the beginning of what many hoped would be an exciting trend toward

co-development of

A) GENE-BASED THERAPIES

with

B) TESTS TO DETECT THE DRUG'S TARGETS,

in order to identify…

… THE RIGHT THERAPIES FOR THE RIGHT PATIENTS.

In 2012, Genentech was awarded approval by FDA for pertuzumab ***Perjeta®*** *.*

Perjeta targets a different part of the HER-protein than Herceptin, resulting in further reduction in growth and survival of HER2-positive breast cancer cells.

Approved Indication:

a) in combination with Herceptin (chemical name: trastuzumab) and

b) Taxotere (chemical name: docetaxel)

c) to treat HER2-positive, metastatic breast cancer

d) that hasn't been treated with either Herceptin or chemotherapy.

The Guardian, September 2014:

Data released by the pharmaceutical company Roche suggests Perjeta could, in combination with other drugs, **increase the survival** of women with advanced breast cancer **by 15 months.**

Affordability question:

The treatment costs around £43,000 a year.

"Breast cancer patients and their families are paying the price for the failures of the pharmaceutical industry and of government to find a long-term solution.

It's impossible to put a price on life's precious moments.

But it's not impossible to put a fair price on drugs which could stop more of these moments being missed."

IRESSA – gefitinib

locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK

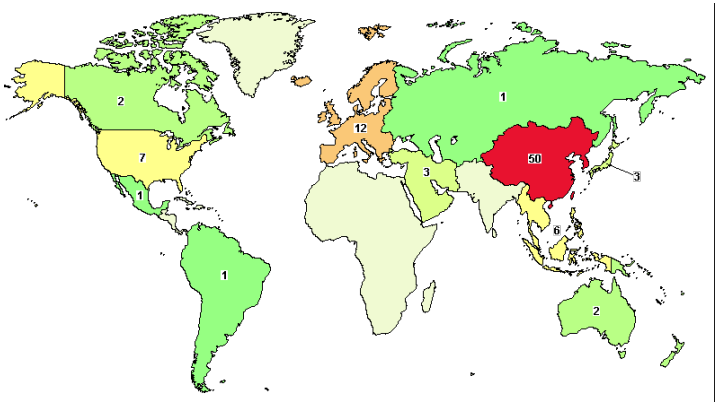
IPASS study - IRESSA versus carboplatin/paclitaxel; 1217 patients

Population	N	Objective response rates	Progression free survival	Overall survival
Overall	1217	43.0% vs 32.2%	5.7 m vs 5.8 m p	18.8 m vs 17. 4m
EGFR mutation-positive	261	71.2% vs 47.3%	9.5 m vs 6.3 m	21.6 m vs 21.9 m
EGFR mutation-negative	176	1.1% vs 23.5%	1.5 m vs 5.5 m	11.2 m vs 12.7 m
EGFR mutation unknown	780	43.3% vs 29.2%	6.6 m vs 5.8 m	18.9 m vs. 17.2 m

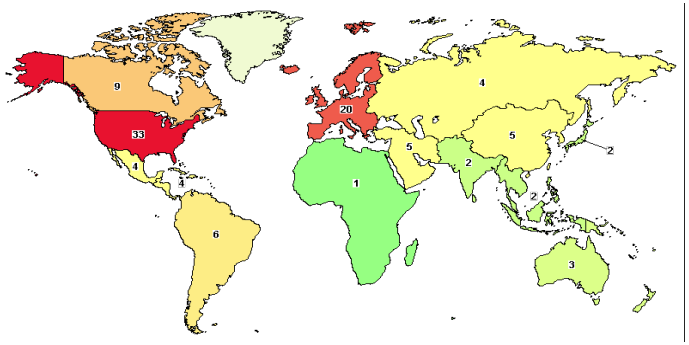
***ClinicalTrials.gov** is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.*

Key word: IRESSA
80 studies

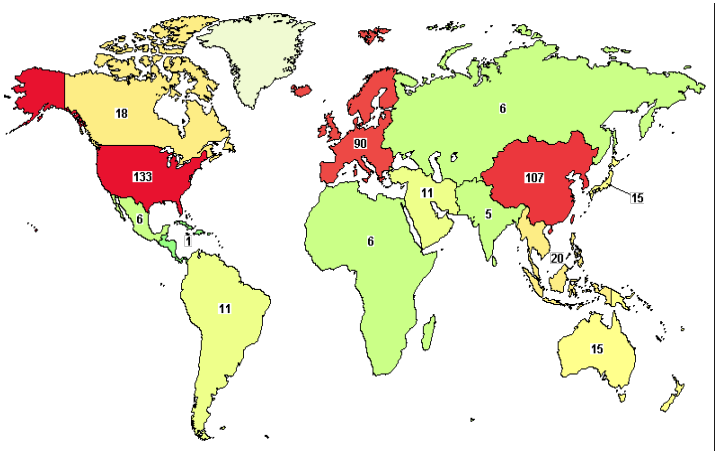
Accesed on July 5th, 2015.



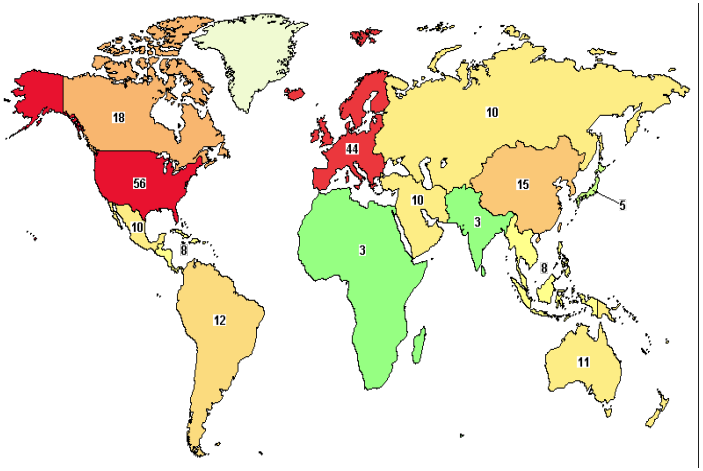
Key word: Perjeta
52 studies



345 studies Accesed on November 10th, 2015.

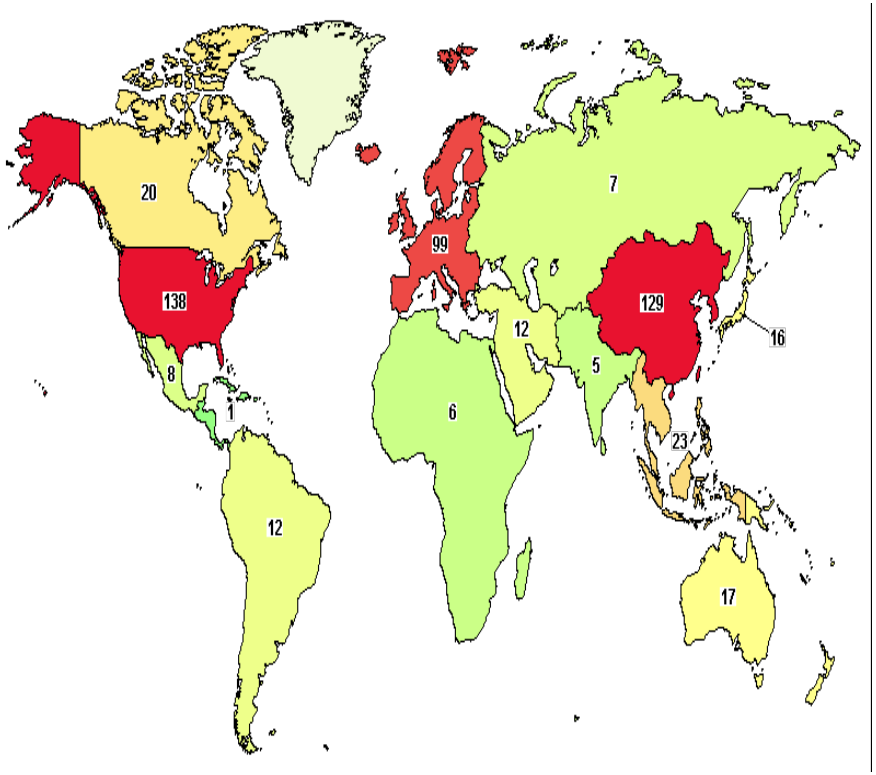


101 studies

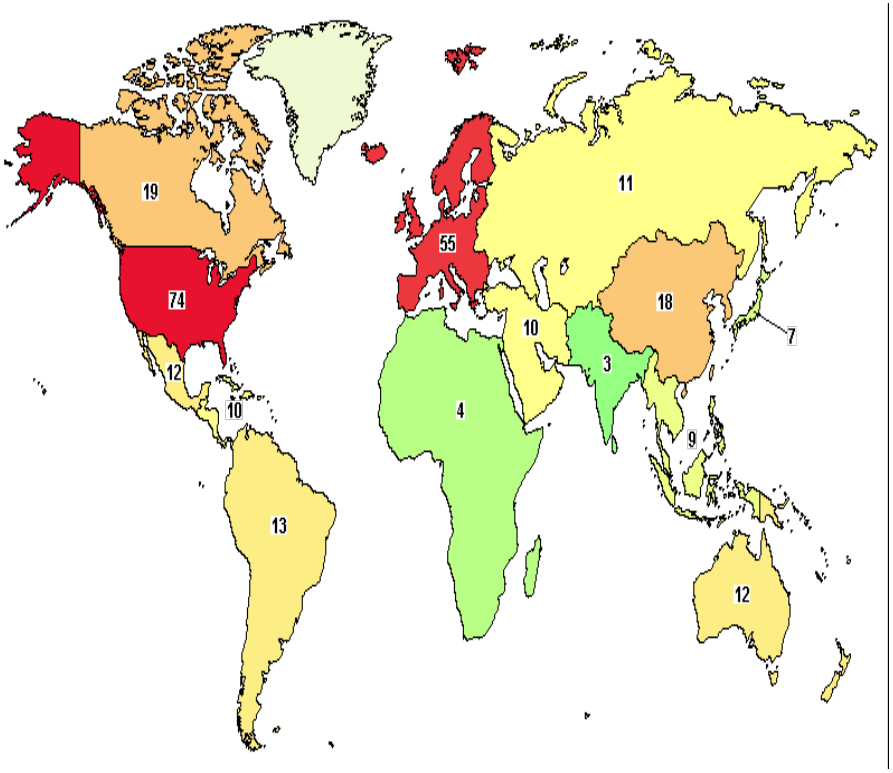


Accesed on June 27th, 2017.

IRESSA 394 studies



PERJETA 130 studies



	N	*EGFR* Mutation-Positive		*EGFR* Mutation-Negative		*p*
		n (%)	95% CI	n (%)	95% CI	
Country/region						<0.001
China	741	372 (50.2)	46.6–53.8	369 (49.8)	46.2–53.4	
Hong Kong	161	76 (47.2)	39.6–54.9	85 (52.8)	45.1–60.4	
India	72	16 (22.2)	14.2–33.1	56 (77.8)	66.9–85.8	
Philippines	65	34 (52.3)	40.4–64.0	31 (47.7)	36.0–59.6	
Taiwan	174	108 (62.1)	54.7–68.9	66 (37.9)	31.1–45.3	
Thailand	117	63 (53.8)	44.8–62.6	54 (46.2)	37.4–55.2	
Vietnam	120	77 (64.2)	55.3–72.2	43 (35.8)	27.8–44.7	
Sex						<0.001
Female	628	384 (61.1)	57.3–64.9	244 (38.9)	35.1–42.7	
Male	822	362 (44.0)	40.7–47.5	460 (56.0)	52.5–59.3	
Smoking history[a]						<0.001
Never-smoker	761	462 (60.7)	57.2–64.1	299 (39.3)	35.9–42.8	
Ex-smoker	301	130 (43.2)	37.7–48.8	171 (56.8)	51.2–62.3	
Occasional smoker	64	33 (51.6)	39.6–63.4	31 (48.4)	36.6–60.4	
Regular smoker	324	121 (37.3)	32.3–42.7	203 (62.7)	57.3–67.7	

Source: Yunakai S et al. A Prospective, Molecular Epidemiology Study of EGFR Mutations in Asian Patients with Advanced Non–Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER). February 2014.

SOME MORE DIFFERENCES:

Variable	*#positive/# tested*	*Percentage*	*Fisher's Exact* p value
Gender			0.002
Male	16/201	8.00%	
Female	53/296	17.90%	
Race			<0.001
African American	3/63	4.80%	
Caucasian	53/388	13.70%	
Asian American	10/16	65.20%	
Hispanic	0/3	0.00%	
Other	2/19	10.50%	
Smoking status			<0.001
Never Smoker	42/100	42%	
Ever Smoker	26/393	6%	

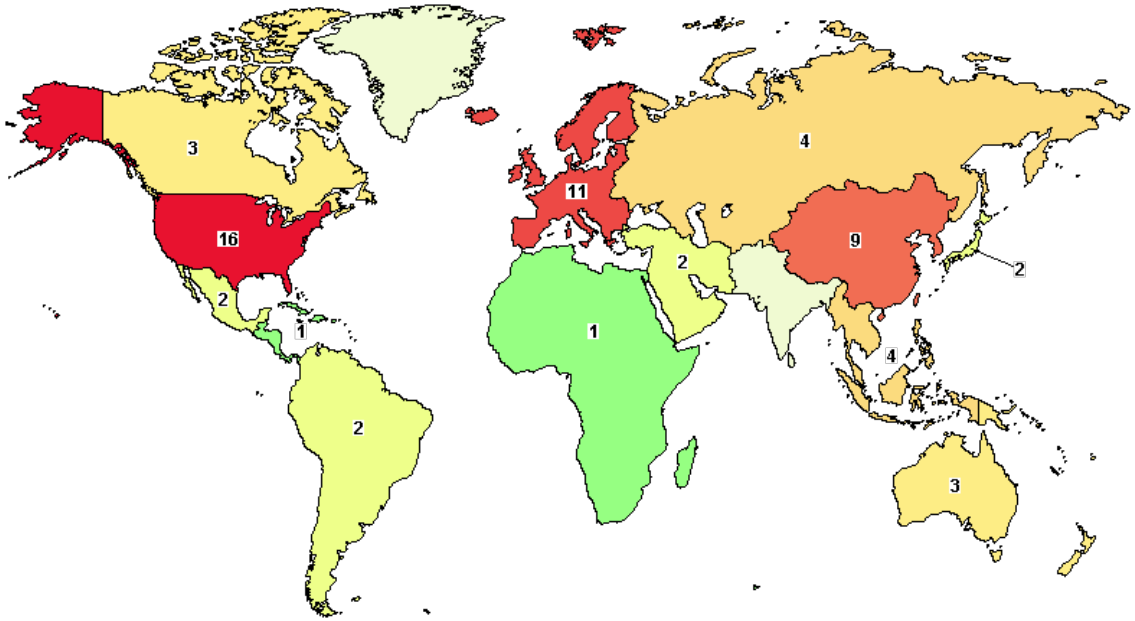
Source: Bauml J et al. **Frequency of *EGFR* and *KRAS* Mutations in Patients with Non Small Cell Lung Cancer by Racial Background: Do Disparities exist?** Lung Cancer 2013; 81: 347–53.

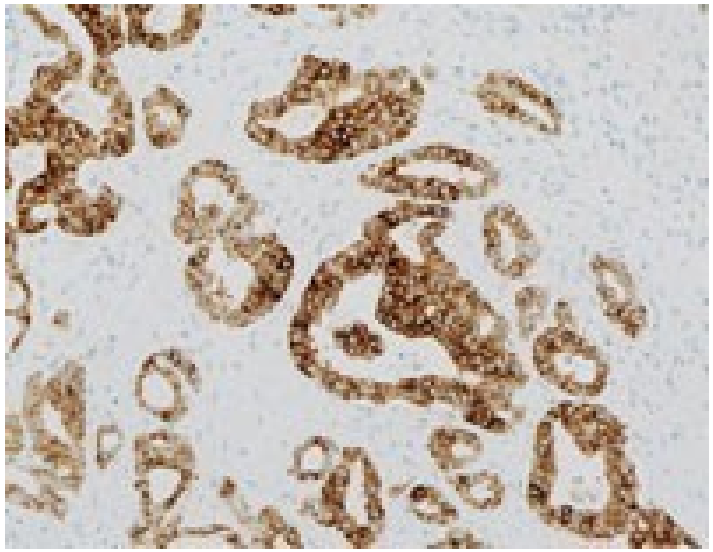
Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

The New England Journal of Medicine, June 2017

…" Eligible patients had histologically or cytologically confirmed advanced NSCLC that was

***ALK*-positive by VENTANA ALK (D5F3) immunohistochemical assay…"**





April 2015:

A real-world study has suggested diagnostic testing for targeted therapy of lung cancer patients is not being performed effectively, which could impact patient survival…

(2015 European Lung Cancer Conference in Geneva)

More than half of the 562 oncologists surveyed said that…

… their treatment selection was NOT guided by a patient's EGFR mutation status…

… 92% of newly diagnosed patients in Asia being tested compared to

77% in Europe and

76% in North America.

Professor Silvia Novello, Department of Oncology at the University of Turin, Italy:

“The results suggest "incomplete integration of multidisciplinary oncology teams" and "an imperfect knowledge of data regarding the use of EGFR inhibitors”.

Development of companion diagnostics together with therapeutics should in theory allow for more efficient studies with smaller patient populations while also leading to more focused therapies that offer better outcomes, less toxicity, and fewer treatment delays.

1. Rosenberg L at al.
A hypothesis: **nonsteroidal anti-inflammatory drugs** reduce the incidence of large-bowel cancer **(1326 patients)**. *J Natl Cancer Inst* 1991;83: 355-8.
"*The present data **suggest** that the sustained use of NSAIDs reduces the incidence of human large-bowel cancer*".

2. Thun MJ at al.
Aspirin use and reduced risk of fatal colon cancer. (**662424 patients**)
N Engl J Med 1991; 325: 1593-6.

3. Clinical trials for **blockbuster drugs** typically enroll somewhere on the order of **7000 patients**

4. August 2011:
FDA approved crizotinib (Xalkori),
+
an ALK FISH probe companion diagnostic

255 patients, 4.9 months approval process

POST-MARKET SURVEILLANCE IS CRITICAL TO THE SUCCESS OF PERSONALIZED MEDICINE

Adverse events must be traced for multiple products that are used together, *e.g., a diagnostic and a therapeutic product.*

WHY?

Because….

Adverse event associated with the use of a therapeutic product may have arisen as
a result of failure of the test to identify the optimal subset of patients due to:

a) design deficiencies;

b) manufacturing deficiencies, or

c) operator error.

Top 10 Best-Selling Biotech Drugs 2014 (WORLD)

		INDICATION	DRUG REVENUE
1.	**Humira**	Rheumatoid arthritis (RA)	**$12.5 billion**
2.	**Remicade**	RA	**$9.2 billion**
3.	**Rituxan**	RA	**$8.7 billion**
4.	**Enbrel**	RA	**$8.5 billion**
5.	**Lantus**	Diabetes mellitus	**$7.3 billion**
6.	**Avastin**	Various malignant tumors	**$7.0 billion**
7.	**Herceptin**	Breast cancer	**$6.8 billion**
8.	**Neulasta**	Chemotherapy related infections	**$5.9 billion**
9.	**Prevnar**	Pneumococcal pneumonia	**$4.5 billion**
10.	**Avonex**	Multiple sclerosis	**$3 billion**

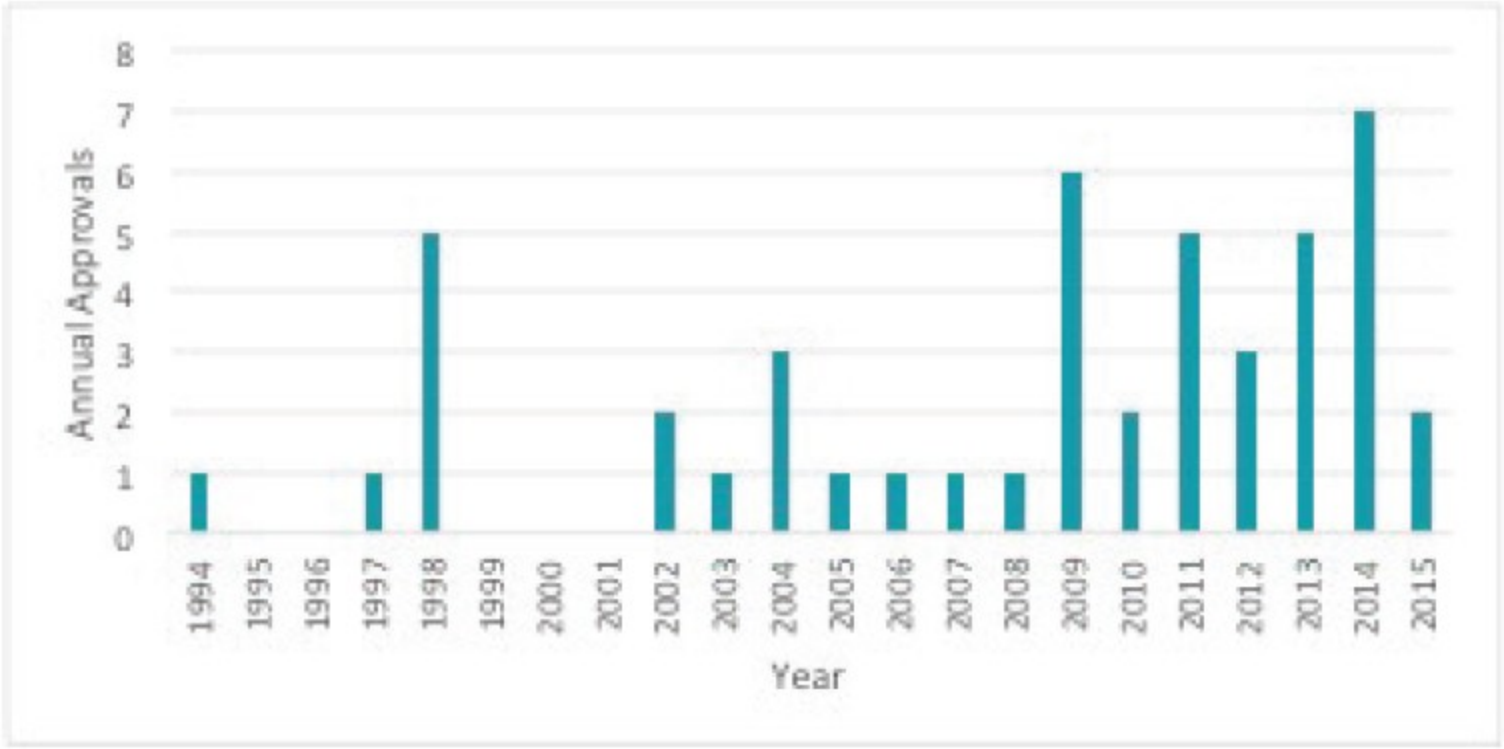


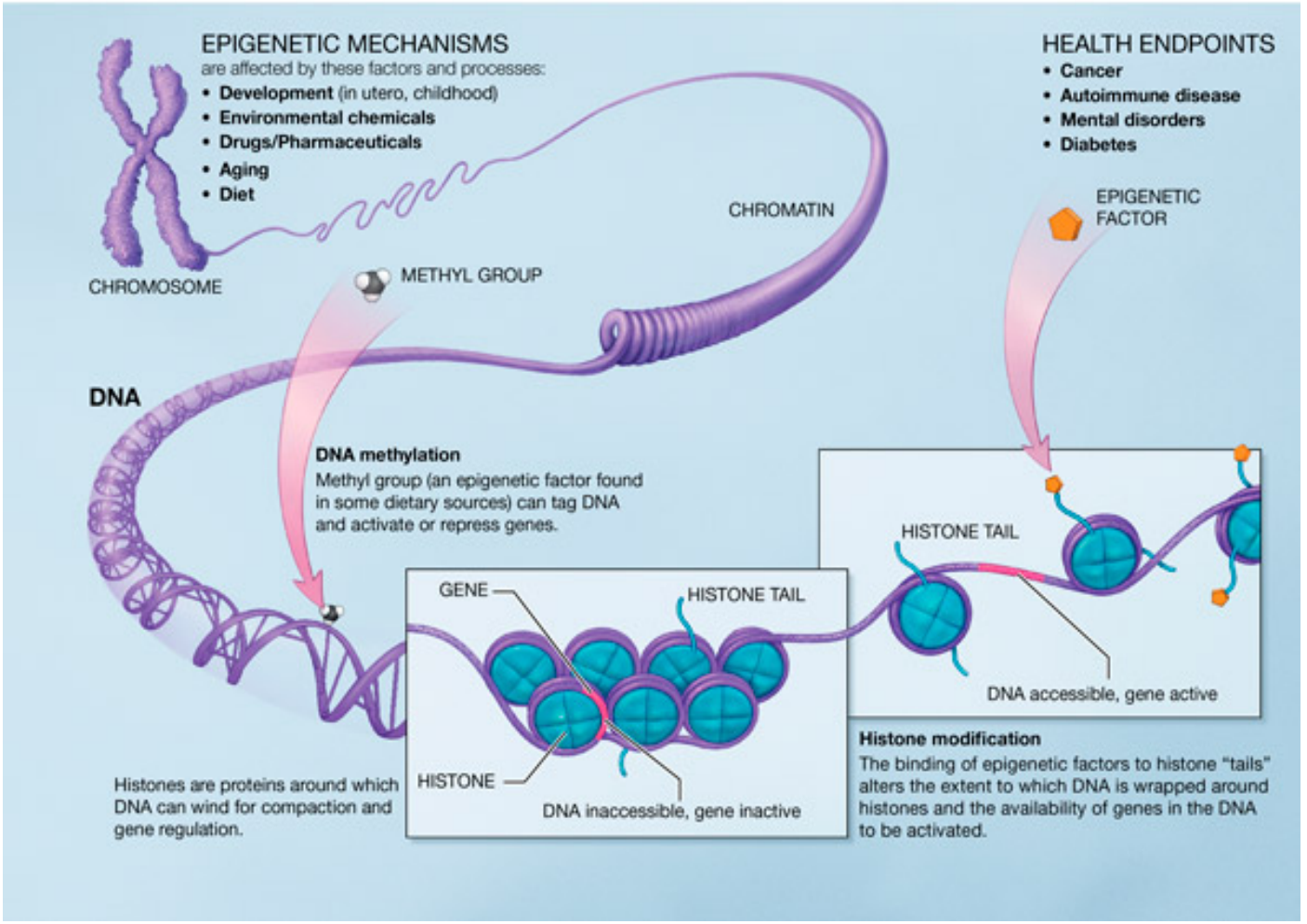
Figure 1. Annual Approvals for MAb Products Currently Marketed in US/EU.

Present (and future) challenges:

1. Limited understanding of the intrinsic biology of disease
2. Common conditions involving multiple genes/biomarkers
3. An outdated disease classification system
4. Lack of infrastructure
5. Clinical implementation of new diagnostics
6. Investment uncertainties
7. Access to personalized therapeutics

"**DISEASE IS ABOUT MORE THAN GENETICS**. It's about **how genes are regulated** — how and when they work in both health and disease," said NIH Director Elias A. Zerhouni, M.D. , in 2008.

"Epigenomics will build upon our new knowledge of the human genome and help us better understand the role of the environment in regulating genes that protect our health or make us more susceptible to disease." (http://www.nih.gov/news/health/jan2008/od-22.htm)



LEGACY FOR THE FUTURE