

Real world in cancer? Epistemology of the origin of cancer: new paradigm for the majority of cancers

Background: The somatic mutation theory as the origin of cancer (carcinogenesis) was born some 100 years ago, when Theodor Boveri 1914 suggested that a combination of chromosomal defects may result in cancer. This was followed by Karl-Heinrich Bauer in 1928 suggesting that mutations could cause cancer. Subsequently, in 1953 Carl Nordling proposed that a number of mutated genes could cause cancer. Alfred Knudson in 1971 proposed that one hit (one mutation) would result in a clone of cancerous cells. This was modified to a 2-hit-theory later and it seems that cancer biology has continued to try to bolster the somatic mutation theory by recently suggesting that 'driver' and 'passenger' mutations were necessary and when this proved insufficient, others proposed the hyper-mutation theory in 2014. In the attempt to clothe the Emperor, it was forgotten that mutations found in advanced cancers are either late events or epiphenomena that occur after carcinogenesis (cancer development) and especially after the appearance of a pre-cancerous niche. **Reality:** Fewer than 10% of cancers are proven to be hereditary (i.e., causally related to germline mutations) and this ratio is even lower in cancers of the stomach (<1%), the colorectum (3-8%) and breast (8%). Infection-triggered cancers constitute some 15% of all cancers and the remaining about some 80% cancers are sporadic, meaning their cause is unknown. **New cancer paradigm:** Findings from the plant and animal kingdoms, molecular and clinical data over the last 250 years were critically reviewed and gave rise to a new cancer hypothesis containing a multi-step process of 6 sequences. These include, (1) a pathogenic biological or chemical stimulus is followed by (2) chronic inflammation, from which develops (3) fibrosis with associated changes in the cellular microenvironment. These remodeling changes result in a (4) pre-cancerous niche, which triggers the deployment of (5) a chronic stress escape strategy, and when this fails to resolve, (6) a transition of a normal cell to a cancer cell occurs.

Consequences: This recently proposed cancer model explains the origins of the vast majority of cancers which are until now were referred to as 'sporadic' cancers.

Furthermore, this theory points out the need to establish preventive measures long before a cancer becomes clinically apparent. The epistemology of the origin of cancer is reviewed and presented.



BON SECOURS CANCER INSTITUTE

Bon Secours Richmond Health System

REAL WORLD IN CANCER?

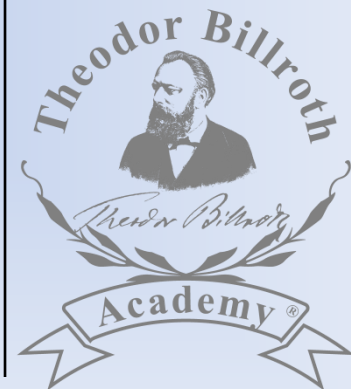
Epistemology of the Origin of Cancer

new paradigm for the majority of cancers

Björn Brücher and Ijaz Jamall

6th March 2015, Munich, Germany

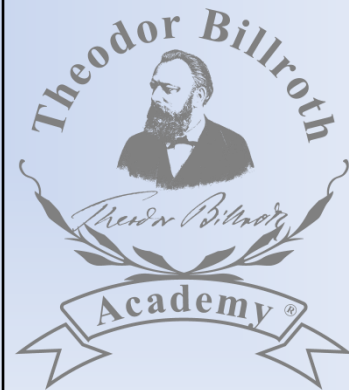
PeerJ PrePrints | <https://dx.doi.org/10.7287/peerj.preprints.1024v1> | CC-BY 4.0 Open Access | rec: 1 May 2015, publ: 1 May 2015



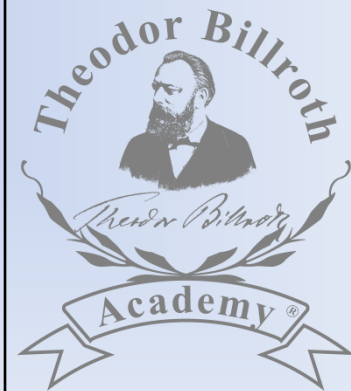
disclosures

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nothing

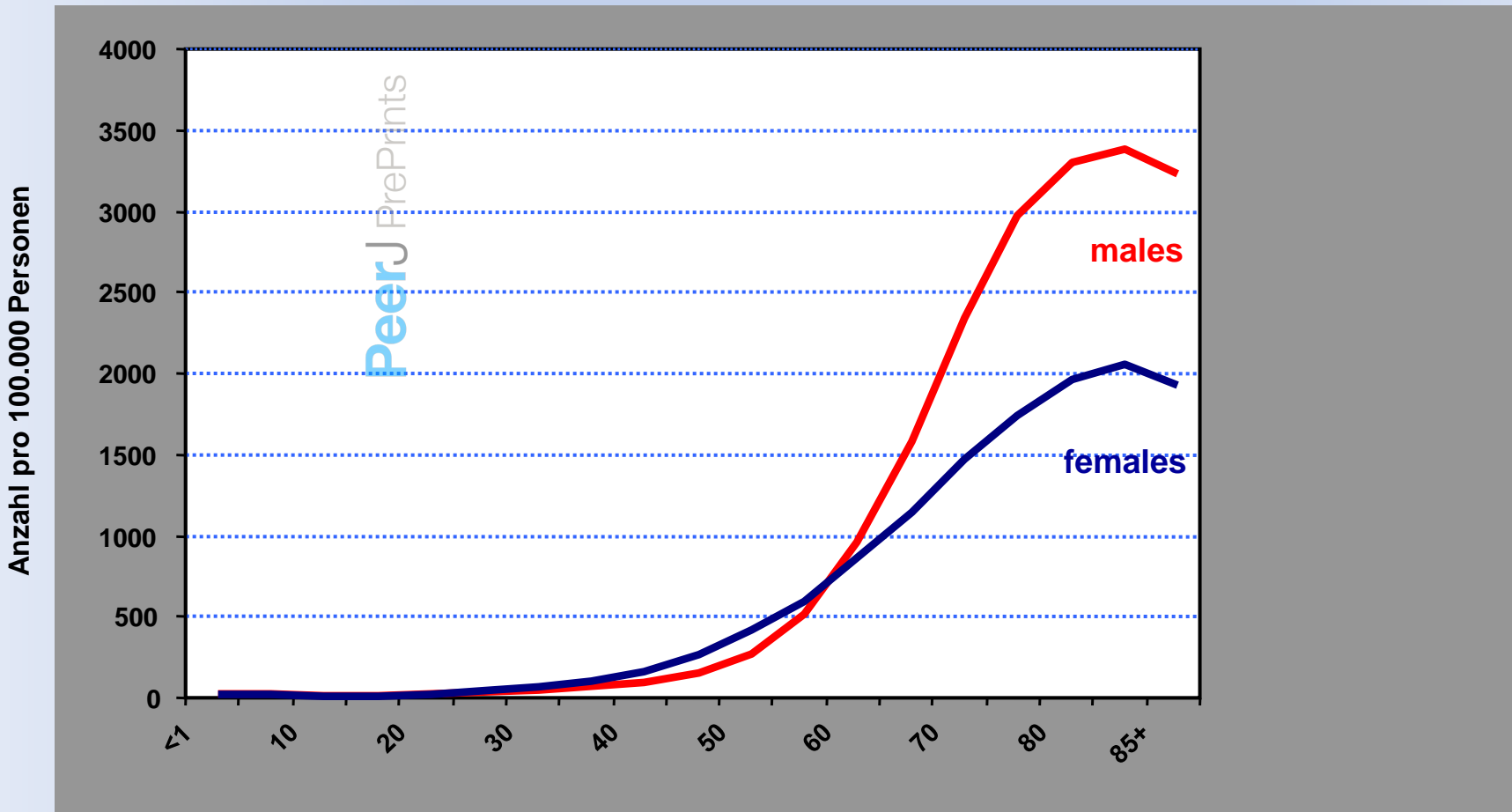


epidemiology and health care



Age distribution and CANCER

age distribution and incidence in cancer



common diseases in the future

prognosis for 2005 until 2020

(Mecklenburg-Vorpommern)

heart attack	+ 28,5%
diabetes mellitus	+ 21,1%
colon carcinoma	+ 30,1%
dementia	+ 91,1%



Diabetes Growth Projections 2012-2030

Diabetes worldwide drug market size \$35 billion
Expected to grow to \$58 billion by 2018



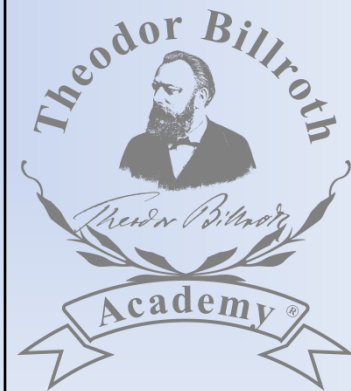
Source: International Diabetes Federation Diabetes Atlas 5th Edition: 2012 Update

Consequences are..

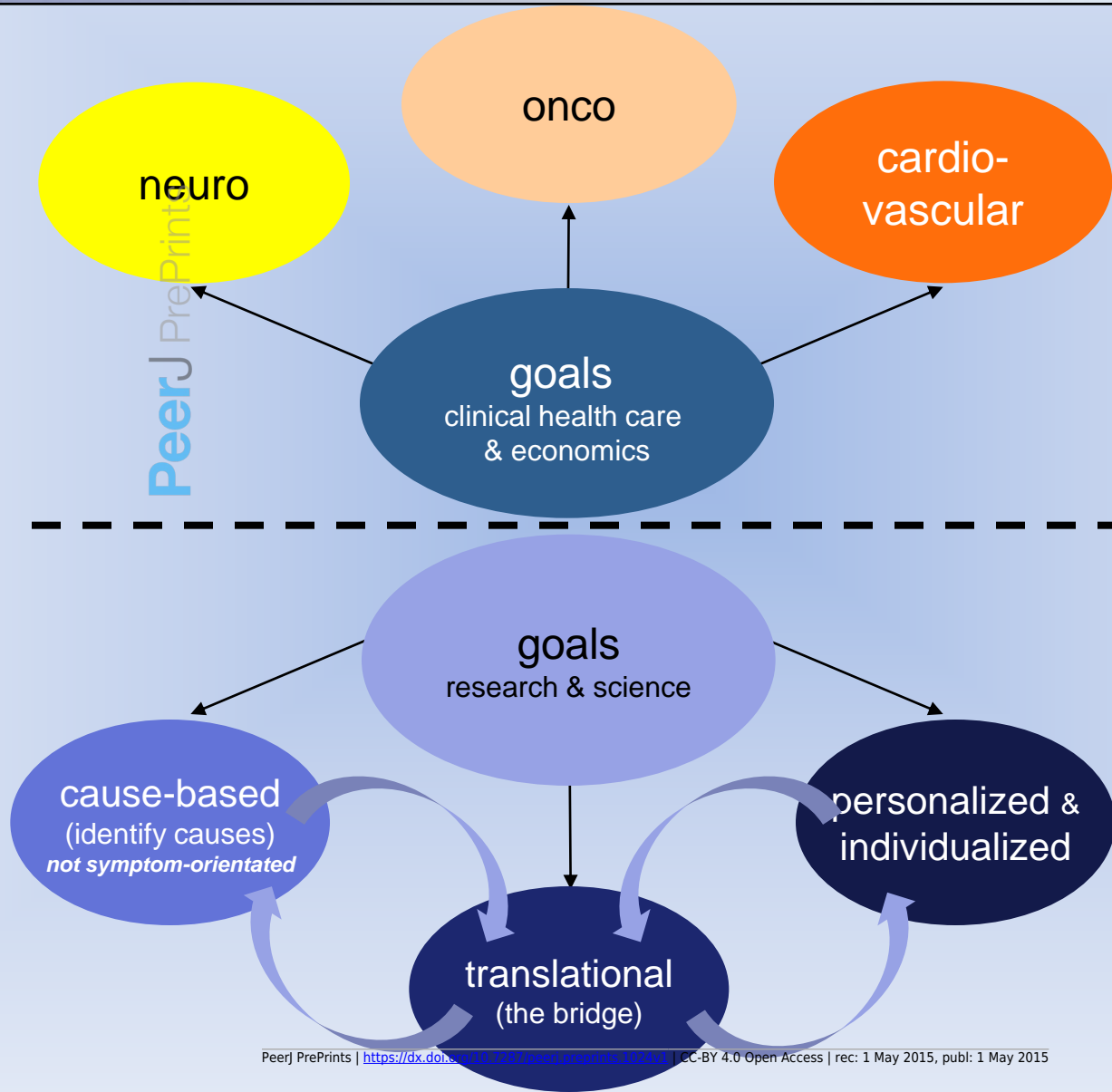
....an enormous
challenge....



future goals are

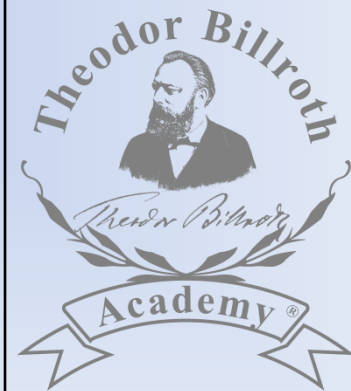
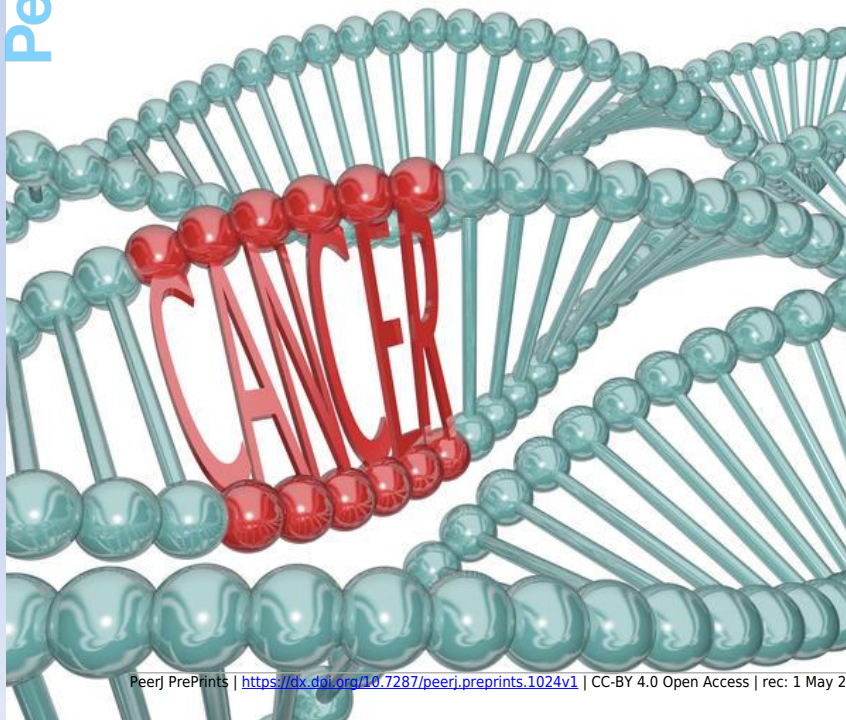


Future goals

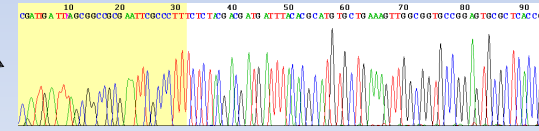
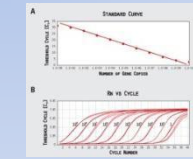
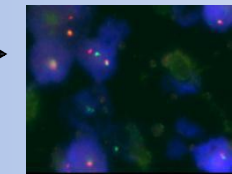
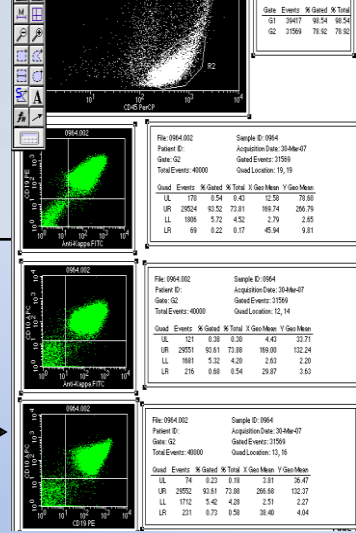
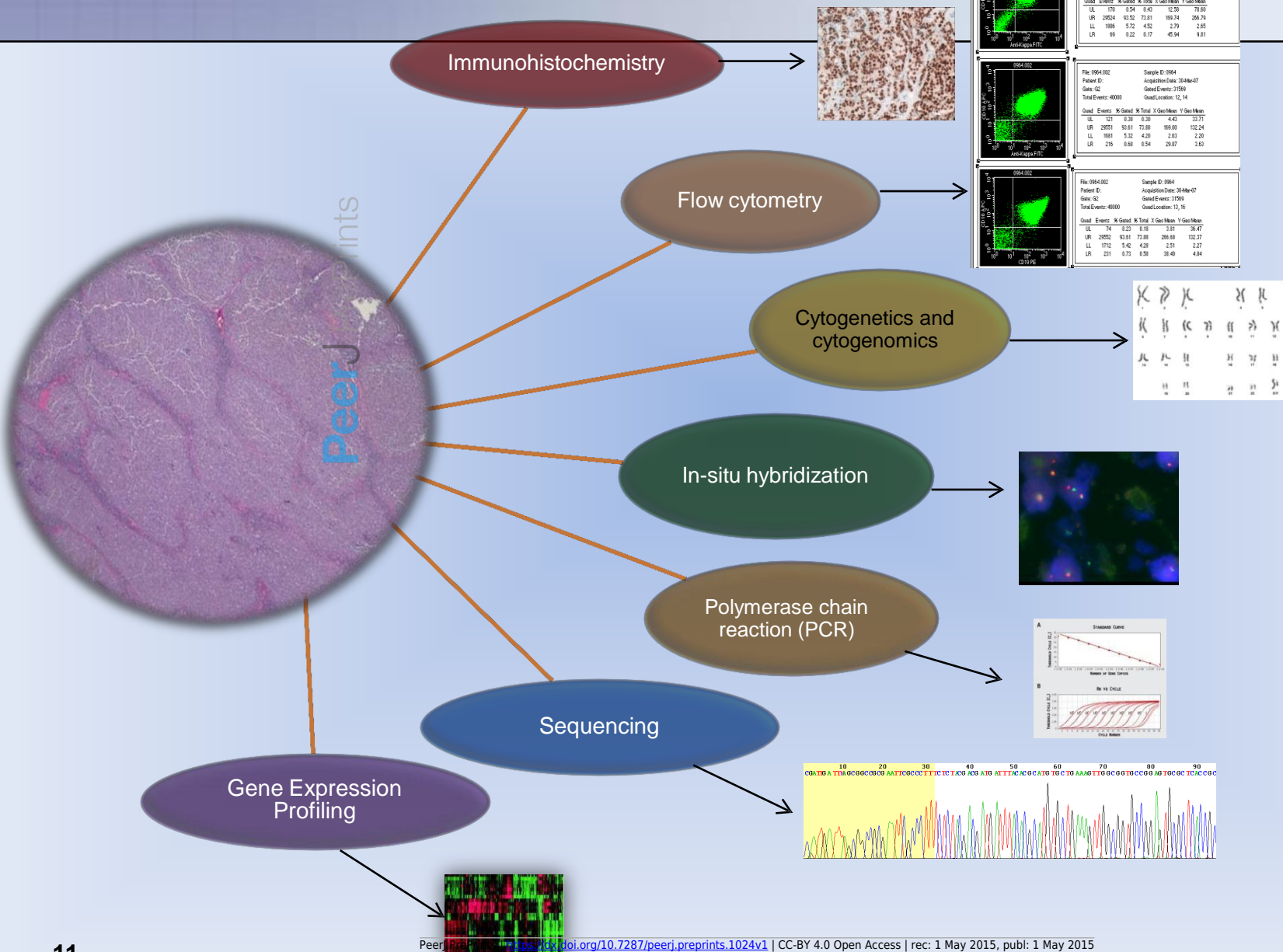


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some demand.....



future comprehensive molecular profiling



EGFR as biomarker

author-year	method	trial	histo	no	samples	preserv	time	treatment	follow-up	resp	surv
Iihara, 1993	IHC	R	ESCC	57	SS	FFPE	post	s.r.	559.2 d	++	n.r
Hickey 1994	IHC	R	ESCC	76 ¹	B	FFPE	pre	s.r., m.s.	16 mo	+++	+
Itakura, 1994	IHC, SB	R*	ESCC	217 ²	SS	FFPE, LN2	post	s.r.	n.r.	n.s.	n.r.
Kitagawa, 1996	SB-hybridization	R	ESCC	107	SS	FFPE	post	m.s., s.r.+post-s.r. RTx.	18 mo	+++	n.r.
Inada, 1999	IHC	R	ESCC	73 ³	SS	FFPE	post*	s.r.	n.r.	+	n.r.
Koyama, 1999	FC	P*	GAC, ESCC	95 ⁴	B, T&NM	RPMI-1640	post	RTx	n.r.	n.r.	++
Shimada, 1999	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	+
Wang, 1999	FC	P*	GAC, ESCC	95 ⁴	B, T&NM	RPMI-1640	post	RTx	n.r.	n.r.	n.r.
Hironaka, 2002	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Miyazono, 2004	qPCR	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.s.
Wilkinson, 2004	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.s.
Chang, 2005	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Fukai, 2005	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Gibault, 2005	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	+	+++
Schneider, 2005	qPCR	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	++	++
Sunpaweravong, 2005	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Hanawa, 2006	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Janmaat, 2006	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	++	++
Langer, 2006	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Vallböhmer, 2006	qPCR	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.r.
Gotoh, 2007	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	+	+
Hoshino, 2007	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	+	n.r.
.....
Lennerz, 2011	FC	P*	GAC, ESCC	95 ⁴	B, T&NM	RPMI-1640	post	RTx	n.r.	n.r.	n.r.
Luber, 2011	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.s.	n.s.
Wainberg, 2011	FC	P*	GAC, ESCC	95 ⁴	B, T&NM	RPMI-1640	post	RTx	n.r.	n.r.	n.r.
Yoon, 2011	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	+++	+++
Chen, 2012	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	+	+
Imamsahan, 2012	IHC	R	ESCC	100	SS	FFPE	post	s.r.	n.r.	n.r.	n.r.
Wang, 2012	SNP	P	EAC,GEJ	65	Blood, SS	FF	pre	s.r.	n.r.	n.r.	n.r.
Wu, 2012	IHC, qRT-PCR	R*	ESCC	126	B, SS	FFPE	pre&post	s.r., m.s.	n.r.	n.s.	n.r.
Yamamoto, 2012	IHC	R	ESCC	100	B, SS	FFPE	pre&post	s.r., m.s. CTx	024 d	+/+ +	+/+ +

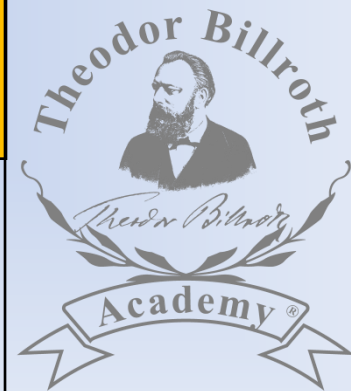
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no standardization of

- preservation
- storage of samples
- use of methods
- which histology for which methodology
- follow-up
- variables to include

but should be already standard?

Cancer diagnosis & therapy in the future needs being outcome orientated



proposed anticancer strategy

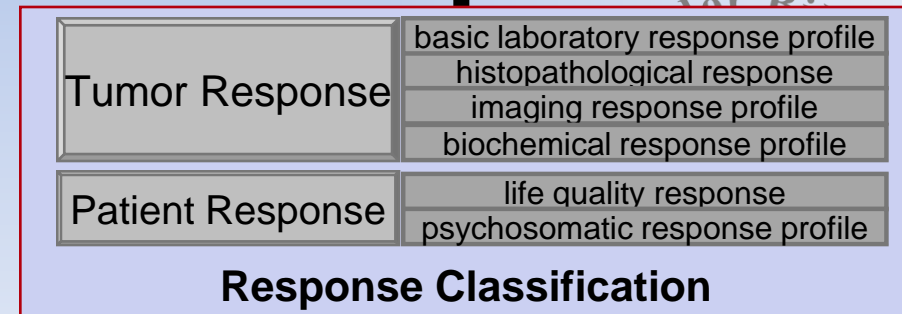
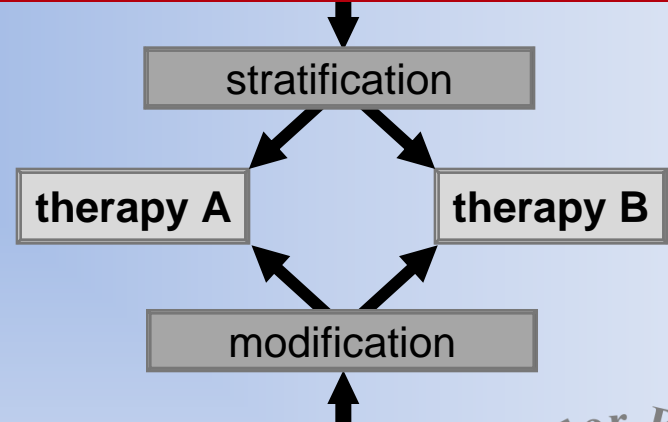
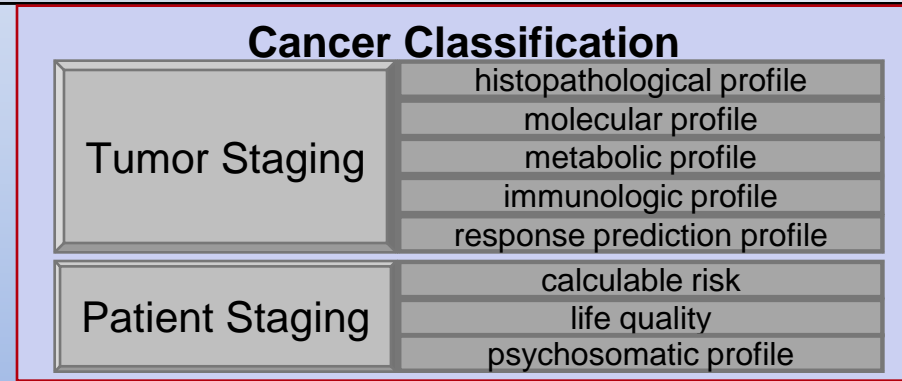
Personalized Strategy
(by Cancer Classification)

Personalized Therapy

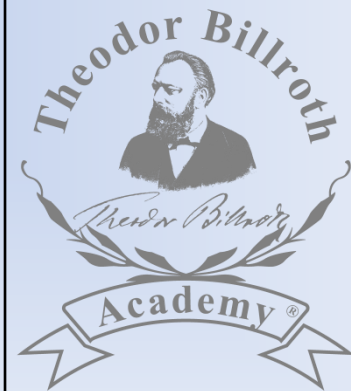
+

Individualized Therapy

Individualized Strategy
(by Response Evaluation)

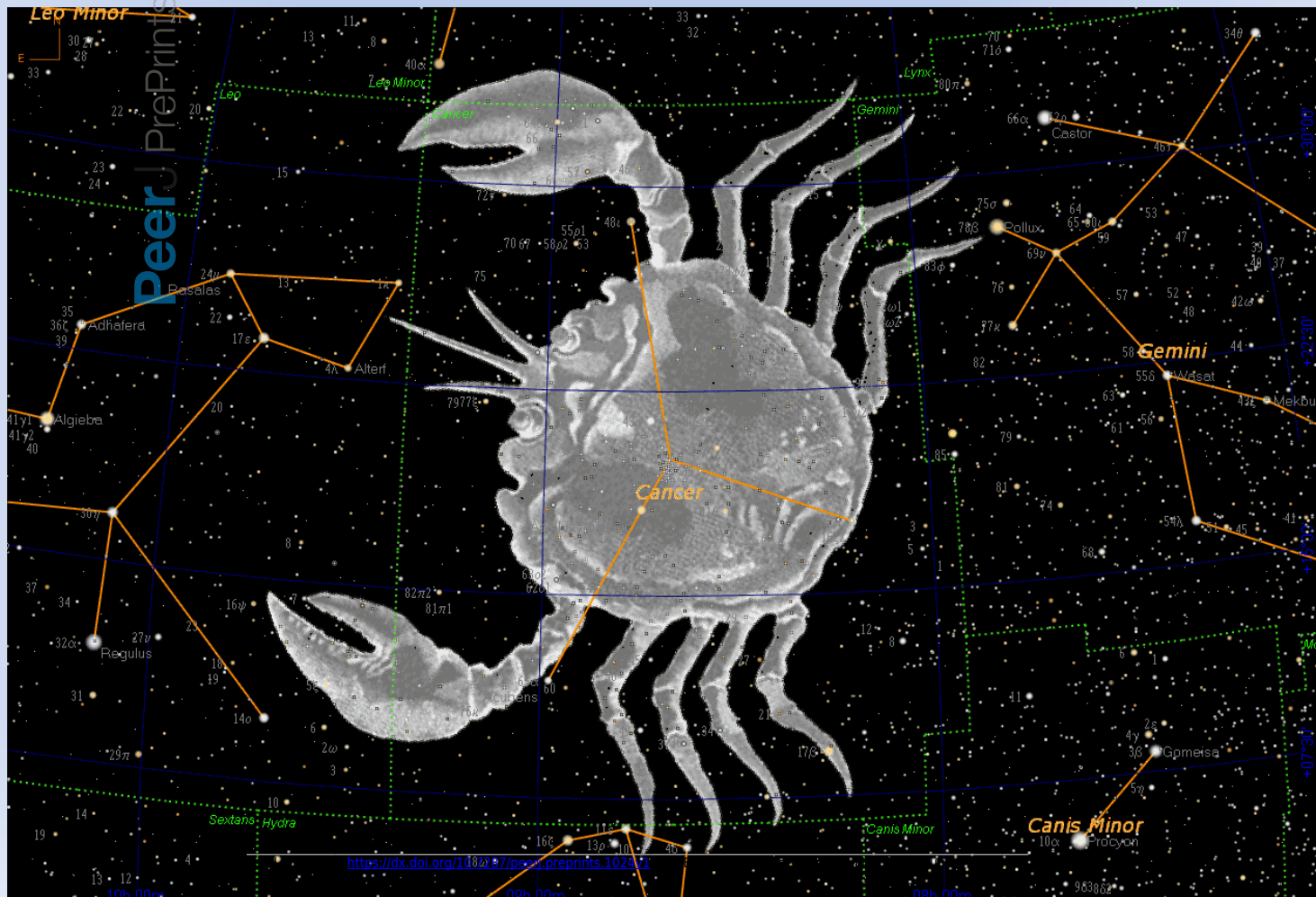


what is cancer



cancer is

is a group of more than 100 diseases that involve the uncontrolled division of the body's cells



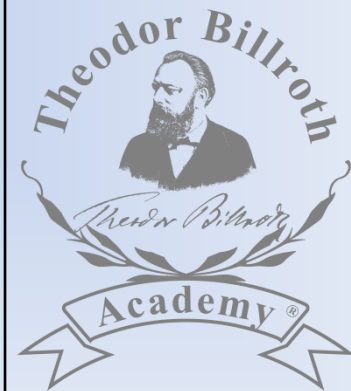


Joseph Joubert
(french moralist)

(* 07.05.1754 - † 04.05.1824)

molecular discoveries

*...understand the past,
to judge the present
if you want to change the future.*





1914

Theodor Boveri

(* 12.10.1862 - † 15.10.1915)

Bamberg - Würzburg

1888

he coined the name
„centrosome“

1914

a combination of
chromosomal defects may
result into cancer

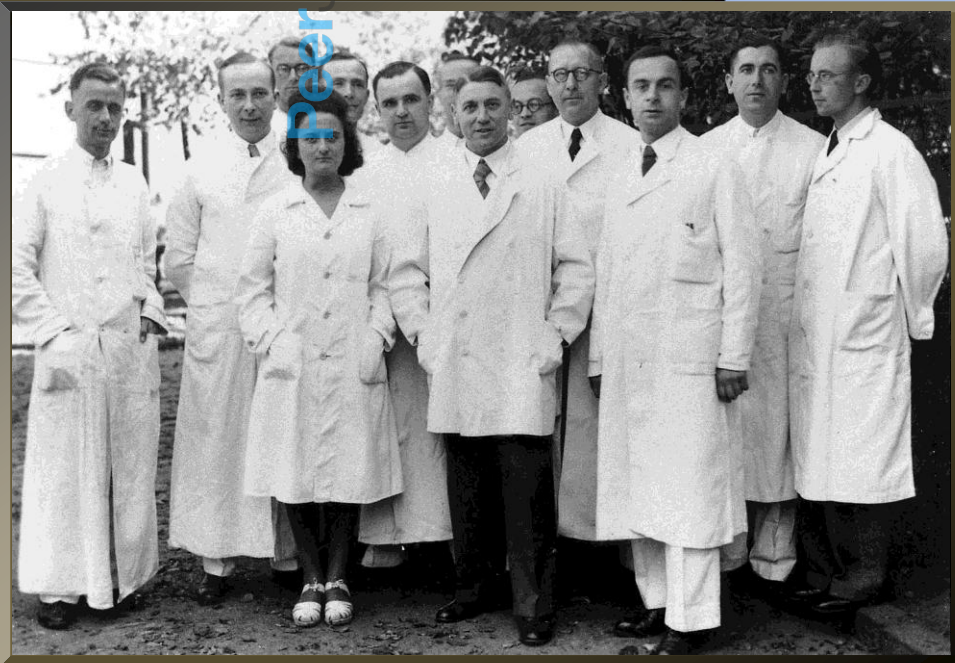


1928

Karl Heinrich Bauer

(* 26.09.1890 - † 07.07.1978)

Breslau (1933-1943)
and
Heidelberg (1943-1962)



1928

suggested
mutations for the origin of
cancer

1940

Erwin Chargaff - 1940 - "Chargaff's rule"

(11th Aug 1905-20th Jun 2002)

- four bases may occur in varying proportions in DNA of different organisms
- # of **A** = # of **T**
(w/ two hydrogen bonds)
- # of **G** and **C** are present
(w/ 3 hydrogen bonds)



1952

Martha Chase and Alfred Hershey

(11th Aug 1905-20th Jun 2002)

- radioactive isotope tracer experiment
- bacterial virus (**bacteriophage T2**) infects a host cell (bacterium *Escherichia coli*)
- found that T2 virus DNA, not its protein coat, enters the host cell
- genetic information for replication of the virus



1950 - 1953

Rosalind Franklin and Maurice Wilkins

(15th Jul 1920-16th Apr 1958 // 15th Dec 1916 – 5th Oct 2004)

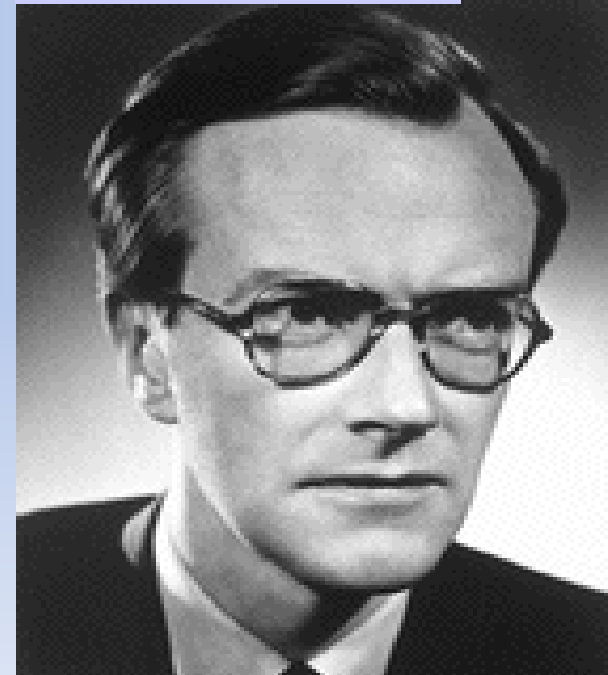
- X-ray diffraction study concluded DNA fibers have two strands.

Franklin R and Gosling RG: Nature 1953. 171: 740-741.

Wilkins MHF et al: Nature 1953. 171: 738-740.



Rosalind Franklin

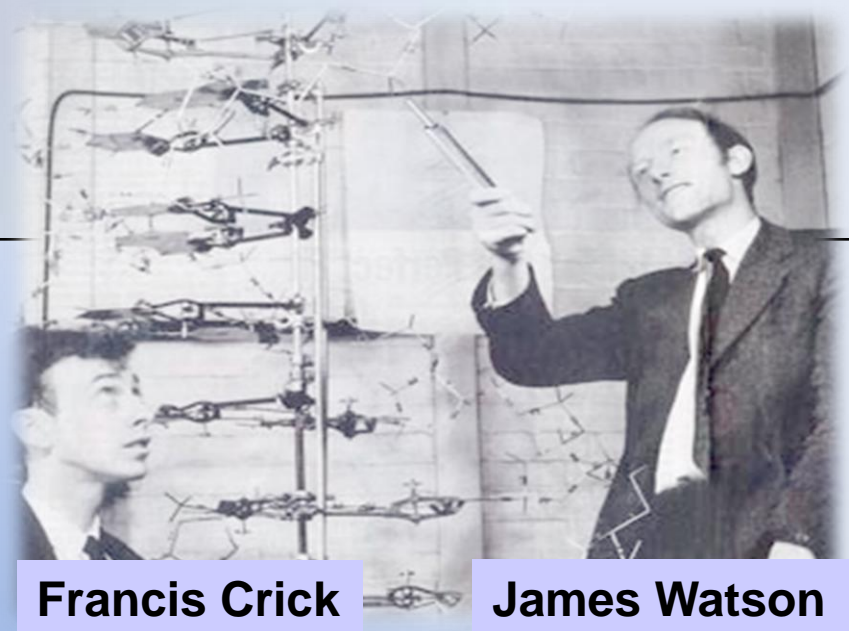


Maurice Wilkins

1953

*James D. Watson and Francis Crick -
University of Cambridge*

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Francis Crick

James Watson

intellectual debate

and worked on problem of making a DNA molecule model that was double stranded but also had the specific A - T and G - C base equivalencies

Solution: double helical structure for DNA

Watson JD and Crick F: Nature 1953. 171: 737-738.



1953

Carl O. Nordling

(* 6th 02.1931 – 15th 02.2007)

Finland

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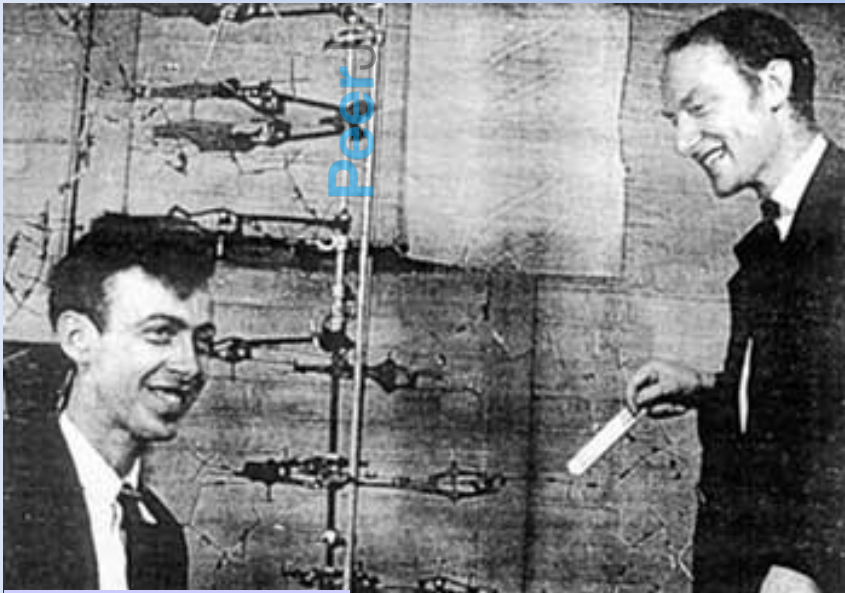


a number of mutated genes cause cancerous cells

1962

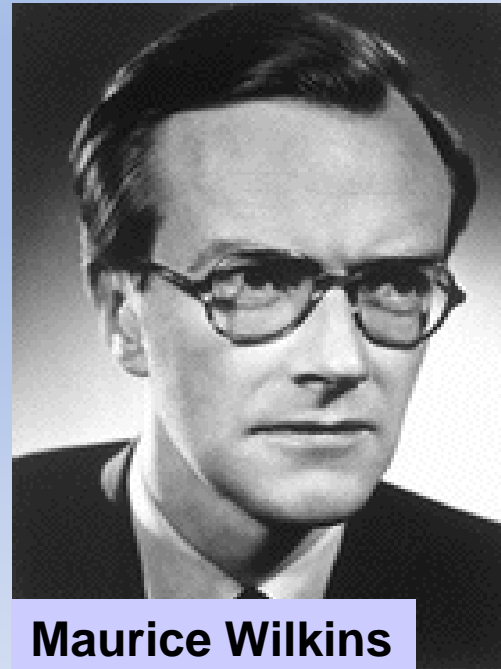
20th Oct 1962

Nobel Prize in Physiology and Medicine



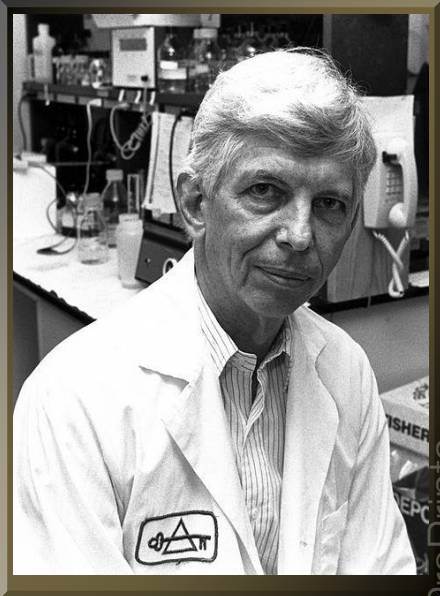
Francis Crick

James Watson



Maurice Wilkins

not-.....Rosalind Franklin (she died earlier)



1971

Alfred G. Knudson

(* 9th 08.1922 –)

Los Angeles

1-hit-theory of carcinogenesis
,Knudson hypothesis‘

→ a cell can initiate a tumor only if it contains 2 mutant alleles

→ a person who inherits a mutant allele must experience a second somatic mutation to initiate carcinogenesis

for the majority of cancer: this is a non-proven theory

Later: 2-hit-theory – ***it takes two to Tango***

Knudson AG: Mutation and cancer: statistical study of retinoblastoma.

PeerJ PrePrints | <https://dx.doi.org/10.7287/peerj.preprint.1924v1> | CC BY 4.0 Open Access | rev 1 May 2015, publ 1 May 2015
Proc Natl Acad Sci USA 1971. 68(4): 820-823.

another theory (carcinogen initiate carcinogenesis)



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Peter Duesberg

(* 2th 12.1936)

[born in Münster, Germany

USA

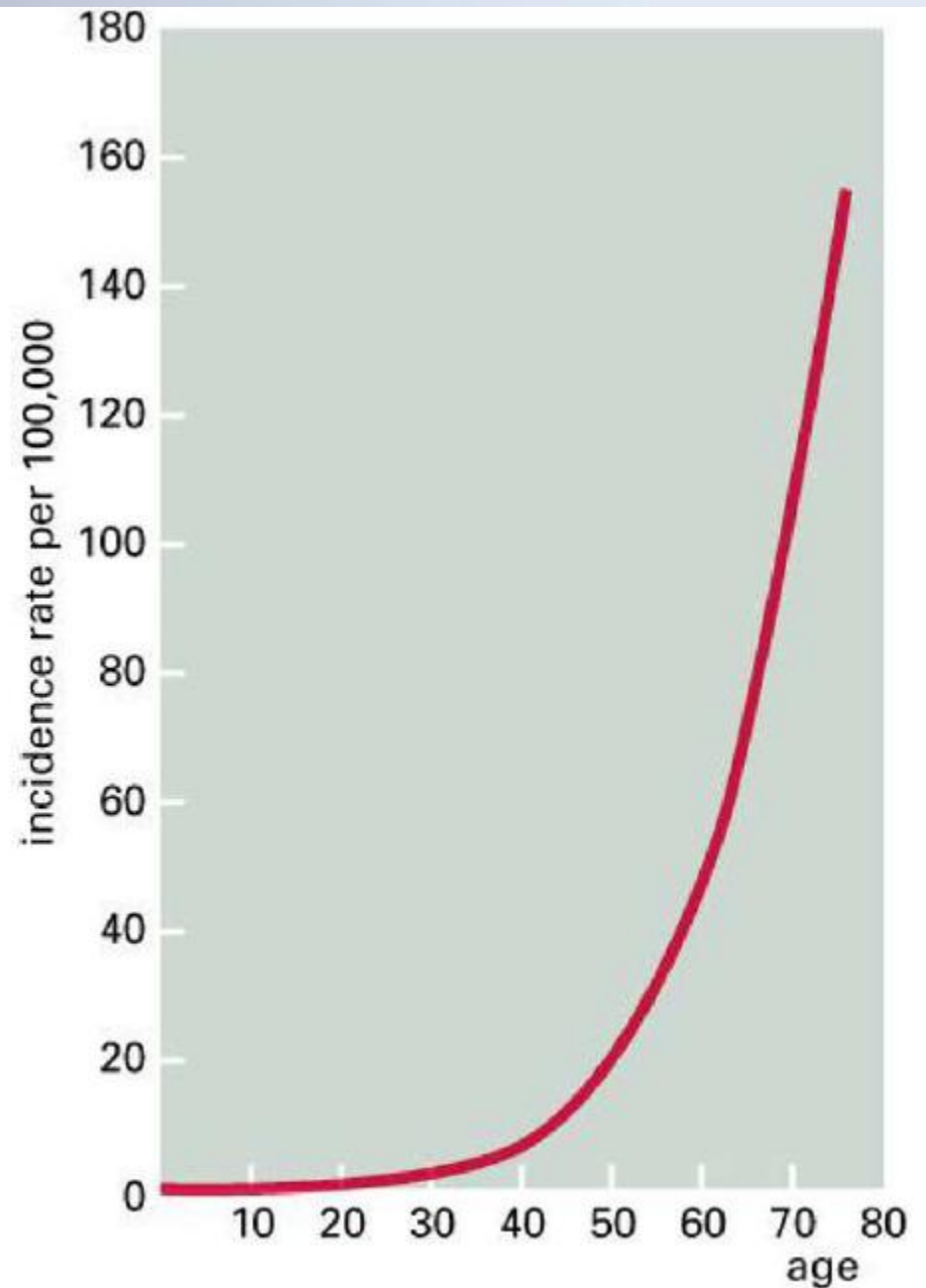
carcinogens initiate carcinogenesis
with a random aneuploidy

- did isolate the first oncogene
- does not believe in HIV virus

Aneuploid cells are error prone

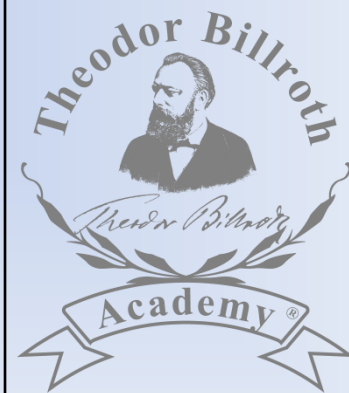
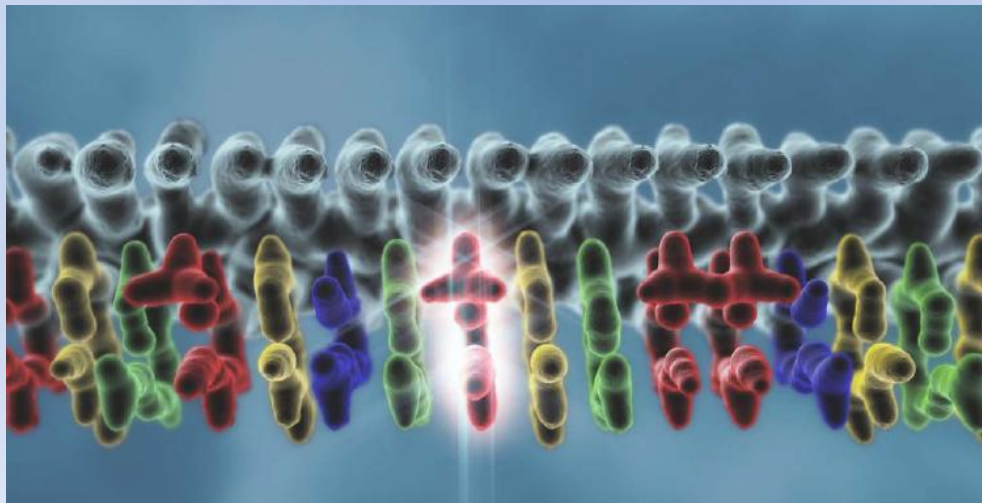
- as chromosome segregation and maintenance systems
- are disbalanced as a result of unbalancing of spindle proteins, repair enzymes, and centrosome numbers.

Even with an unstable genome, it takes time to accumulate the multiple mutations that are required for cancerous transformation, so cancer is much more common in older people than in the young



since an opinion changed to the....dogma

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mutation is „the“ cause
for the majority of cancers



mutation theory work for some 5% of cancers

let's create it a bit differently – may this fits in (2007)

1-concept of ,drivers‘ and ,passengers‘

Nature. 2007 March 8; 446(7132): 153–158. doi:10.1038/nature05610.

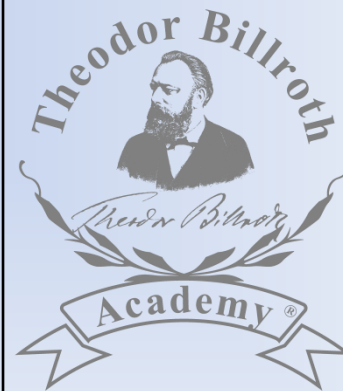
Patterns of somatic mutation in human cancer genomes

Christopher Greenman¹, Philip Stephens¹, Raffaella Smith¹, Gillian L. Dalglish¹, Christopher Hunter¹, Graham Bignell¹, Helen Davies¹, Jon Teague¹, Adam Butler¹, Claire Stevens¹, Sarah Edkins¹, Sarah O'Meara¹, Imre Vastrik², Esther E. Schmidt², Tim Avis¹, Syd Barthorpe¹, Gurpreet Bhamra¹, Gemma Buck¹, Bhudipa Choudhury¹, Jody Clements¹, Jennifer Cole¹, Ed Dicks¹, Simon Forbes¹, Kris Gray¹, Kelly Halliday¹, Rachel Harrison¹, Katy Hills¹, Jon Hinton¹, Andy Jenkinson¹, David Jones¹, Andy Menzies¹, Tatiana Mironenko¹, Janet Perry¹, Keiran Raine¹, Dave Richardson¹, Rebecca Shepherd¹, Alexandra Small¹, Calli Tofts¹, Jennifer Varian¹, Tony Webb¹, Sofie West¹, Sara Widaa¹, Andy Yates¹, Daniel P. Cahill³, David N. Louis³, Peter Goldstraw⁴, Andrew G. Nicholson⁴, Francis Brasseur⁵, Leendert Looijenga⁶, Barbara L. Weber⁷, Yoke-Eng Chiew⁸, Anna deFazio⁸, Mel F. Greaves⁹, Anthony R. Green¹⁰, Peter Campbell¹, Ewan Birney², Douglas F. Easton¹¹, Georgia Chenevix-Trench¹², Min-Han Tan¹³, Sok Kean Khoo¹³, Bin Tean Teh¹³, Siu Tsan Yuen¹⁴, Suet Yi Leung¹⁴, Richard Wooster¹, P. Andrew Futreal¹, and Michael R. Stratton^{1,9}

CANCER

Drivers and passengers

Daniel A. Haber and Jeff Settleman



mutation theory work for some 5% of cancers

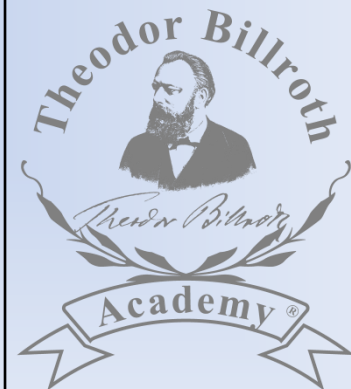
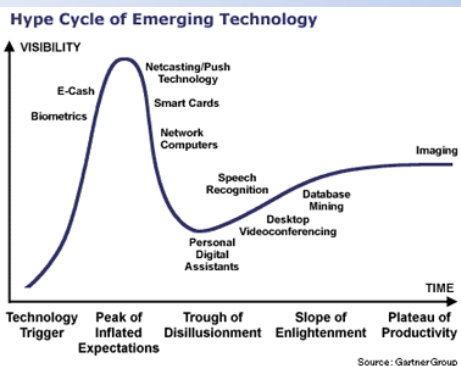
*..creating it even more different..... (2014)
– maybe this fits in*

2-concept of ,hypermutation theory‘

Nat Rev Cancer, 2014 December ; 14(12): 786–800.

Hypermutation in human cancer genomes: footprints and mechanisms

Steven A. Roberts and Dmitry A. Gordenin*



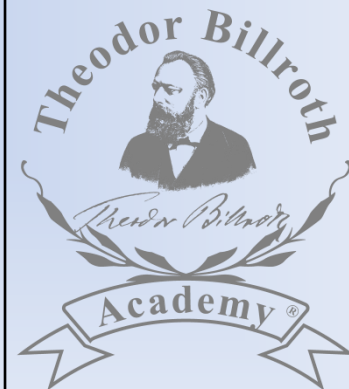
or maybe we should create in the future the....

(2030?)

ultra-hyper-super-mutation-theory



or maybe we just re-think.....



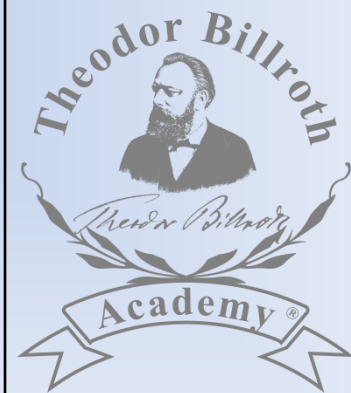
one would expect.....

scientists rest,pause and

re-think

instead trying fitting in (or better:
pressing in) a theory, which did
work for a minority *but not for a
majority of cancers.*

didnt we have that behavior with cholesterol, salt dietary intake and hypertonus, the climatic change, etc.?



An apple found in a car.....

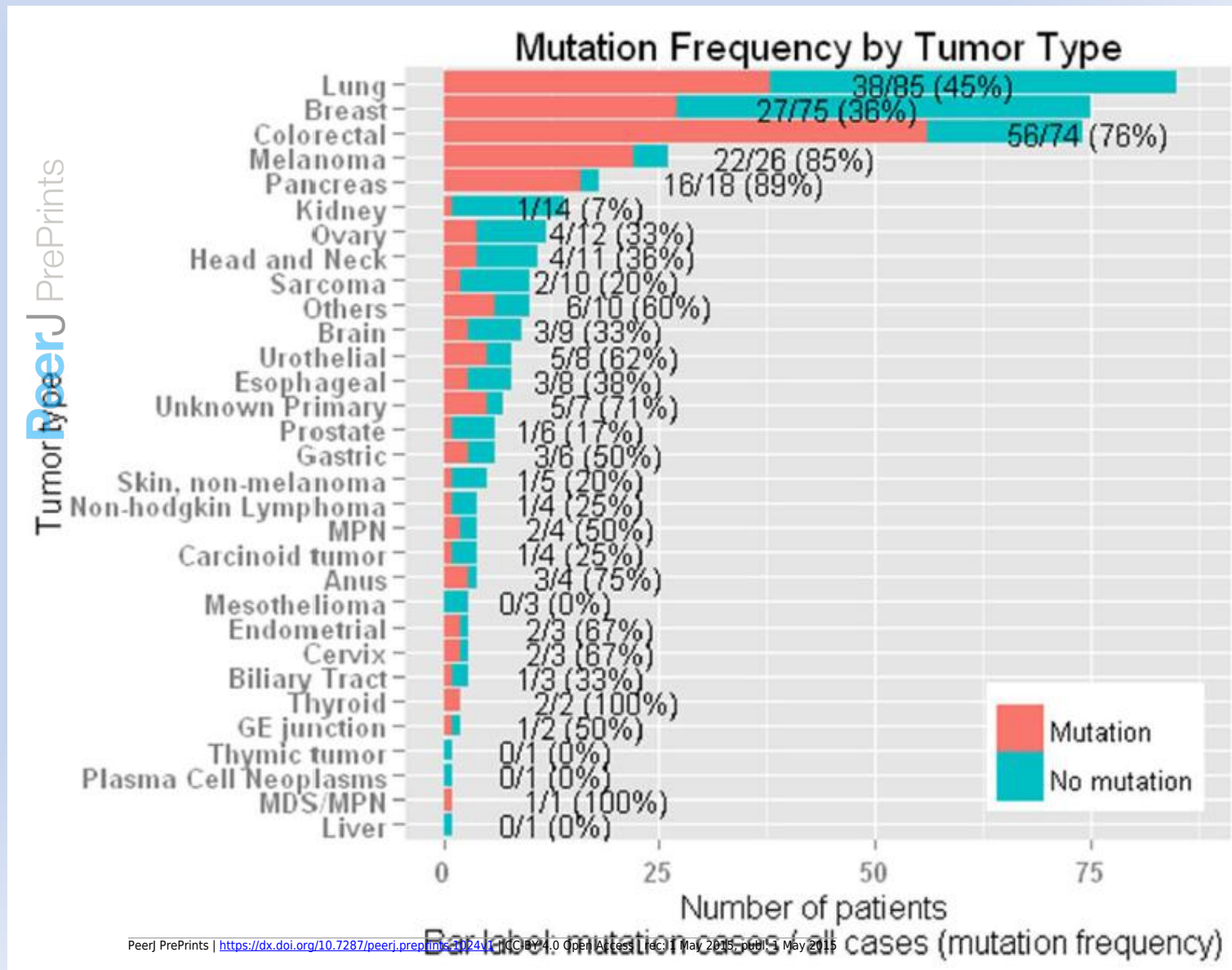
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is **not** synonym of prove apples grow in car's.

a correct observation (mutation in advanced cancers) is not synonym of prove being the cause for carcinogenesis (= cancer development)

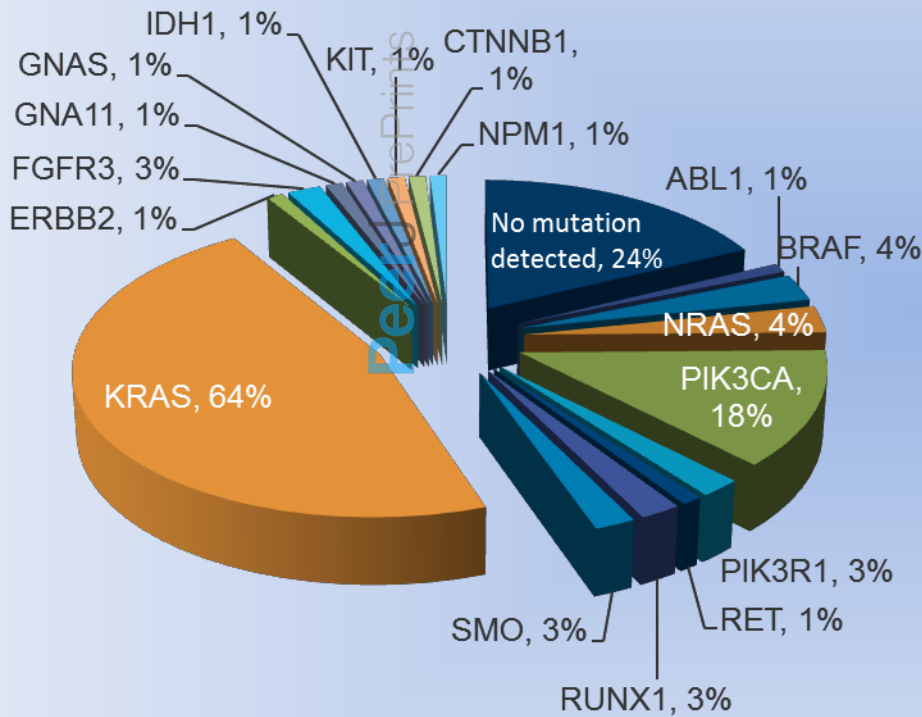
frequency of mutations by disease state



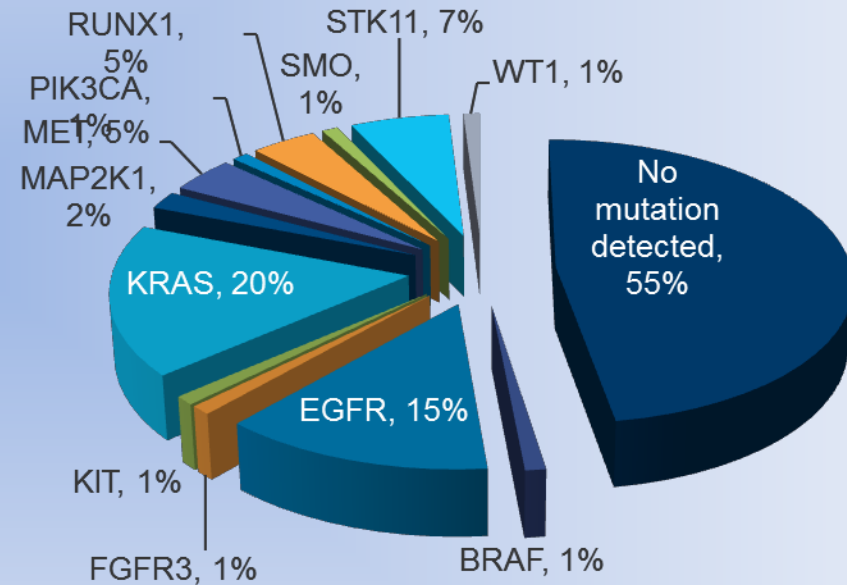
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mutations status of selected tumors

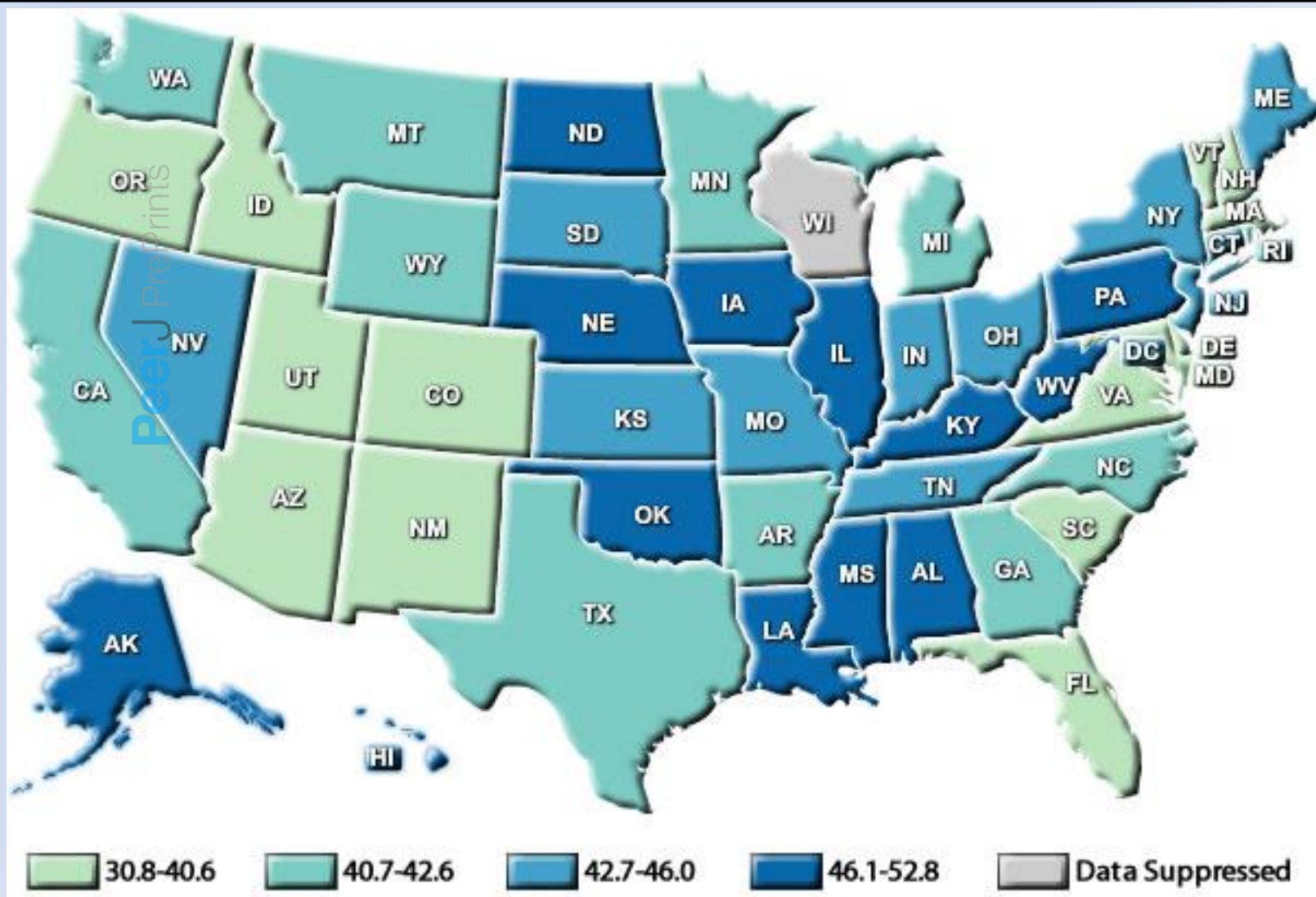
Colorectal (N = 74)



Lung (N = 85)

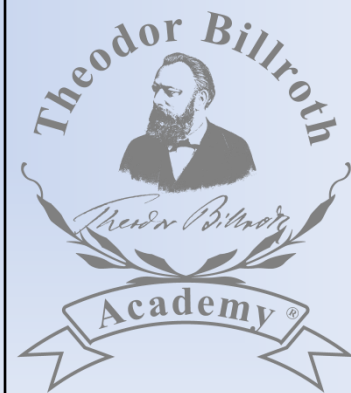


but it also seems being different where....



mutations and genetics are.....

of significant importance,
for understanding biology
or even (partially) nature
but don't explain anything!



reality (1): cancer is triggered in

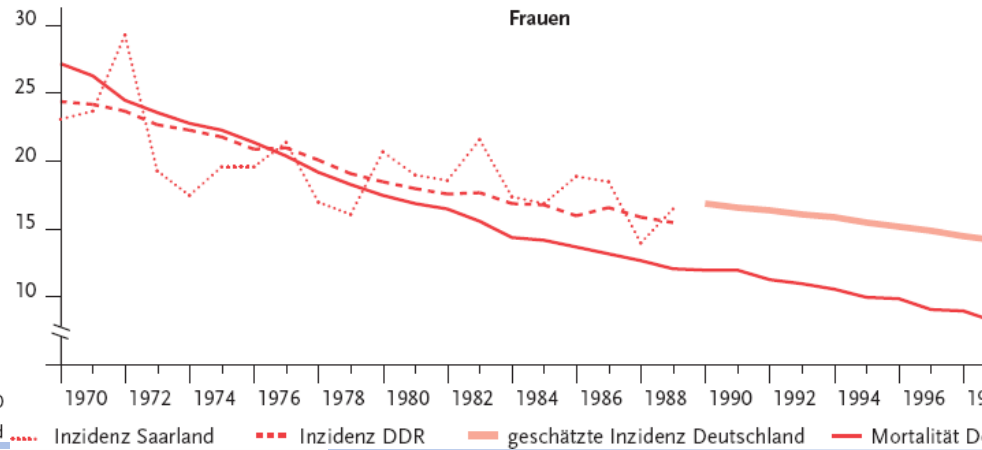
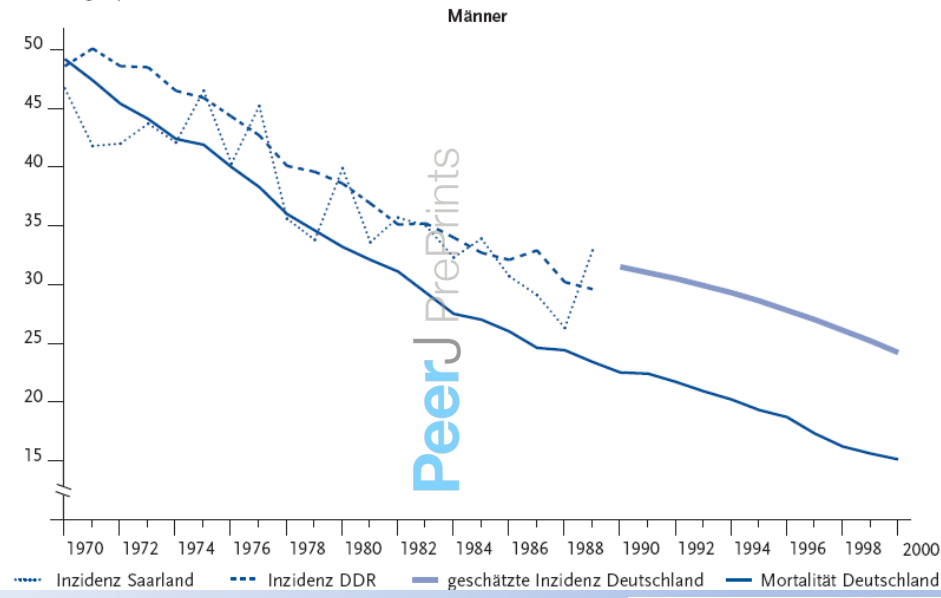
5-10% hereditary

15% inflammation

80% sporadic (=unknown!!)

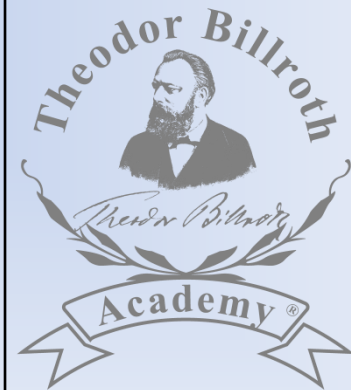
gastric carcinoma

Altersstandardisierte Inzidenz und Mortalität in Deutschland 1970–2000
Erkrankungen pro 100.000

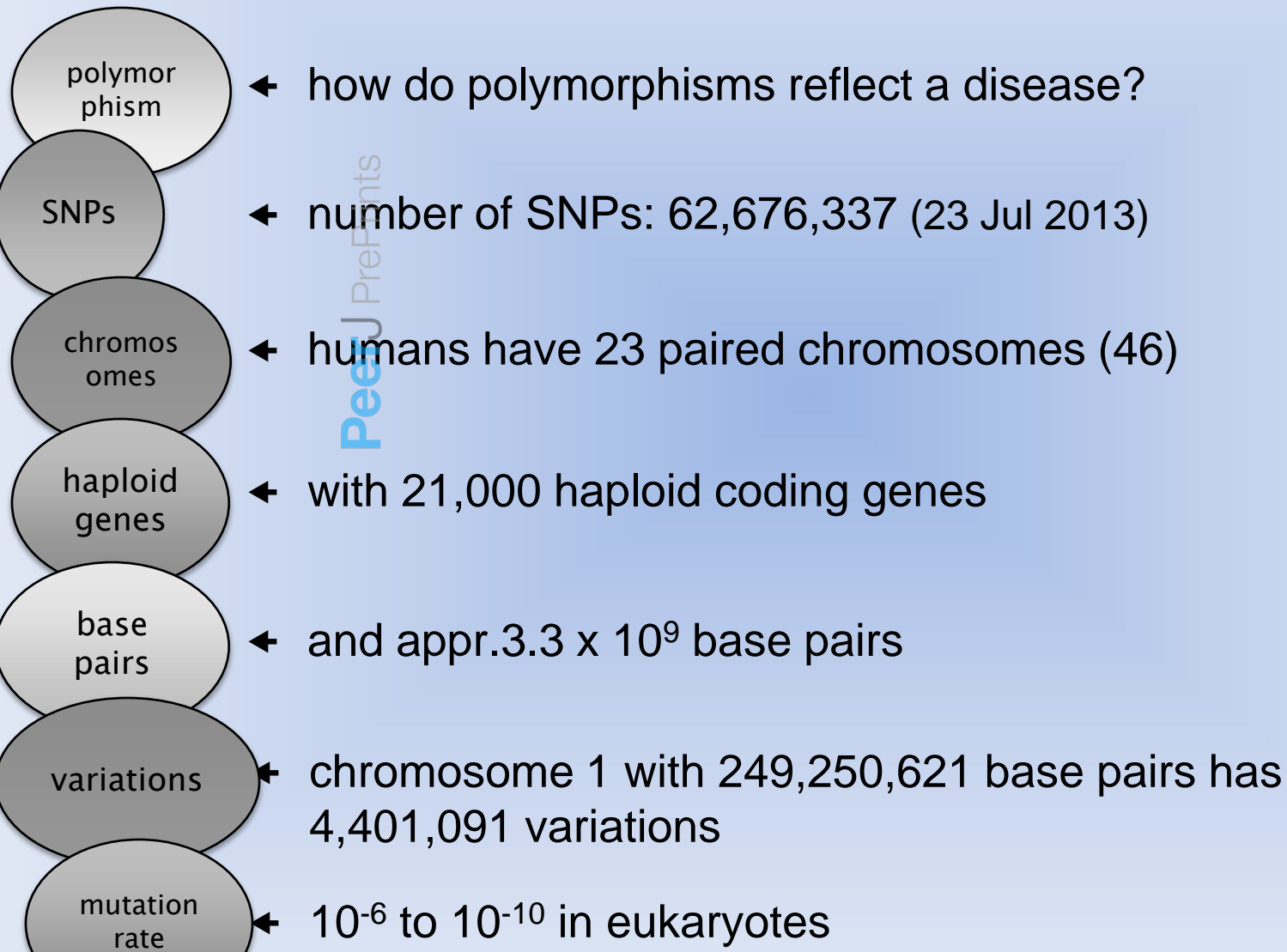


Reality (2)

DNA alterations are not the sole criterion for phenotypical changes

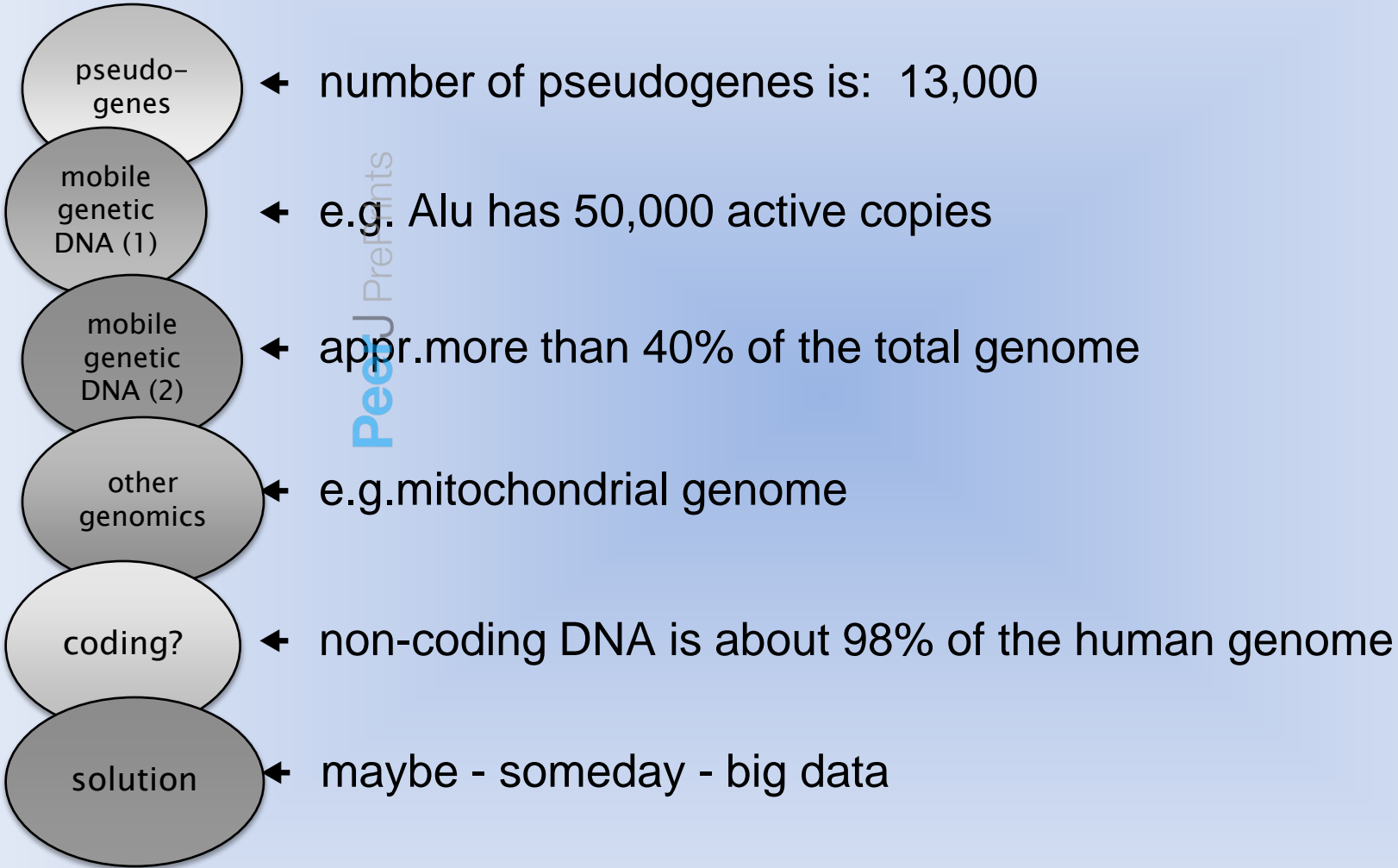


genes and important numbers



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.....and

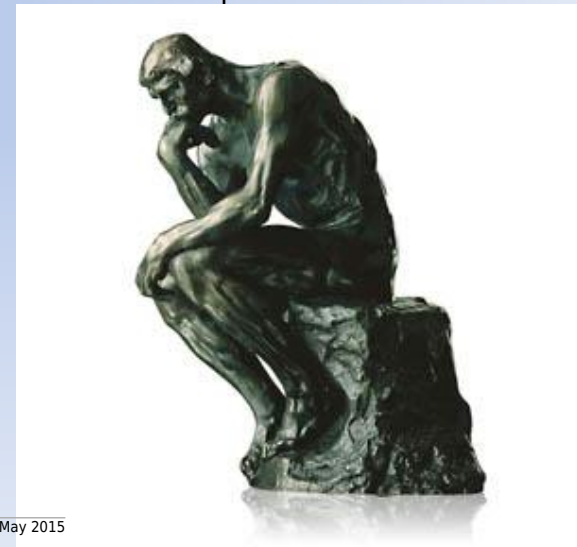


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Billrothstraße

Wrong way

real world?



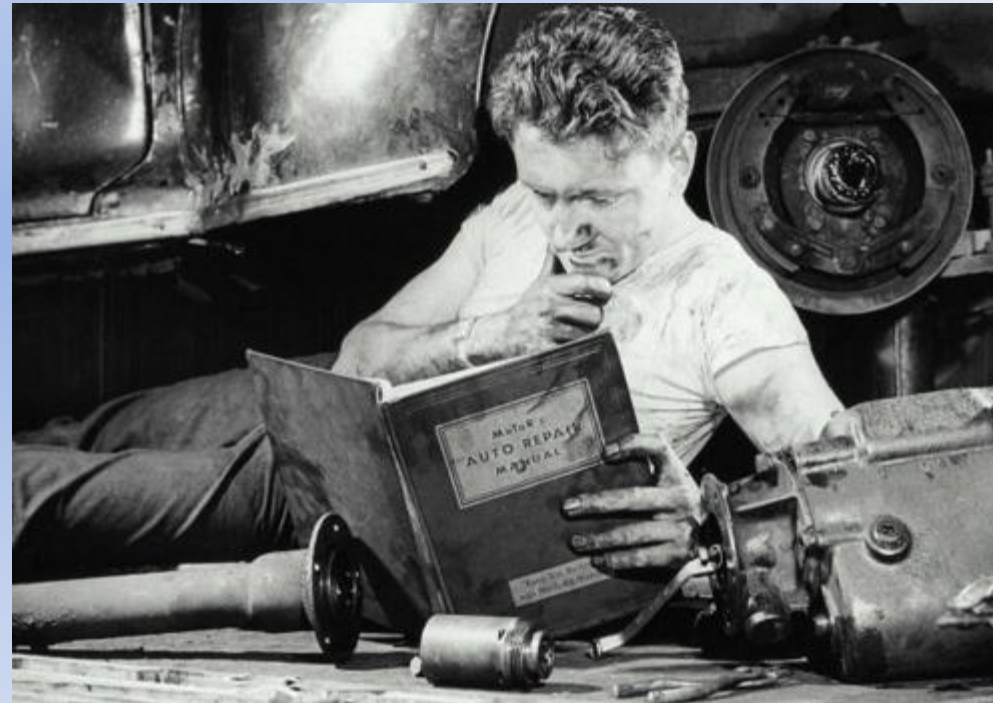
.....if you have a smoky engine.....



you may take the car to....



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or someone tells.....

detecting particles in the smoke....

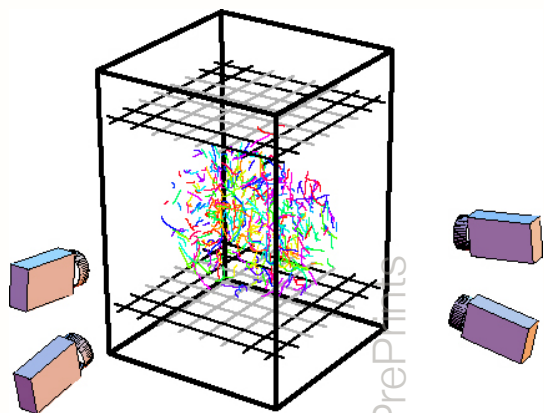
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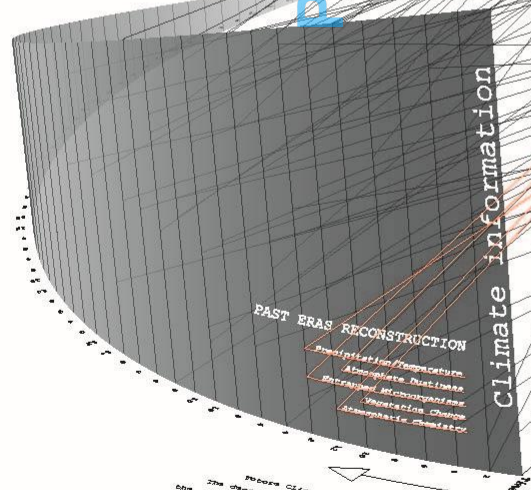
....making nice pictures and to....



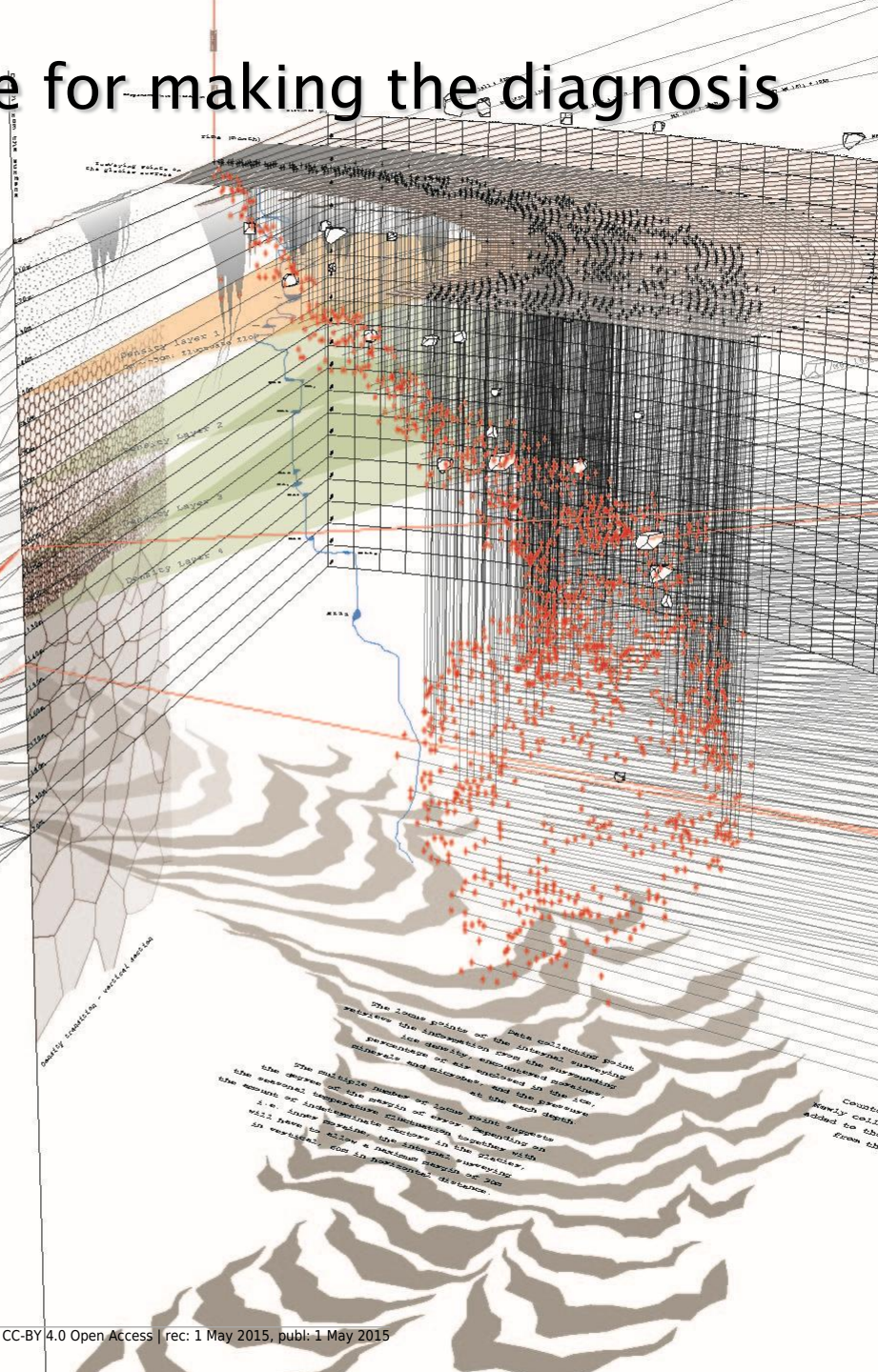
..measure particles in the smoke for making the diagnosis



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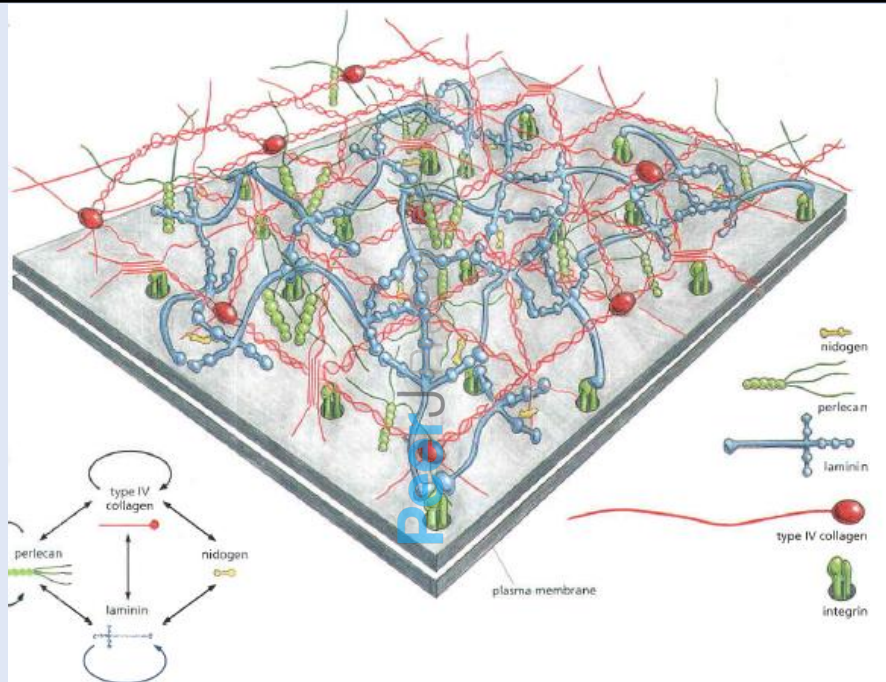
The degree of reconstruction is based on the number of parameters known from the past. The more parameters are known, the more accurate the reconstruction is. From the degree of reconstruction, the degree of reconstruction is able to be determined.





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basal membrane and extracellular matrix



Yurchenco PD and Schittny JC,
FASEB J 1990. 4: 1577-1590.

Strength – Triple helix provides tensile strength

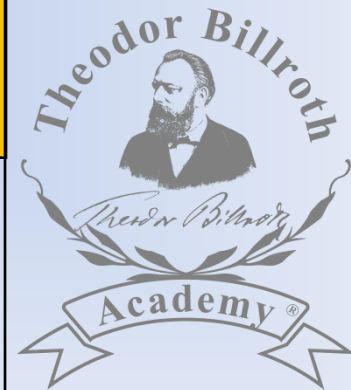
Scaffold – Provides organization and structure for the ECM

Without it, what would happen?

- Loss of cell-cell communication
- Cell migration
- Loss of cell shape

Epistemology of the origin of cancer: a new paradigm

Epistemology of the origin of cancer a new paradigm. BMC Cancer **2014**, *14*: 331:1-15



Sequence

Unsuccessful

Successful

1. Pathogenic stimulus

Acute Inflammation

2. Chronic Inflammation

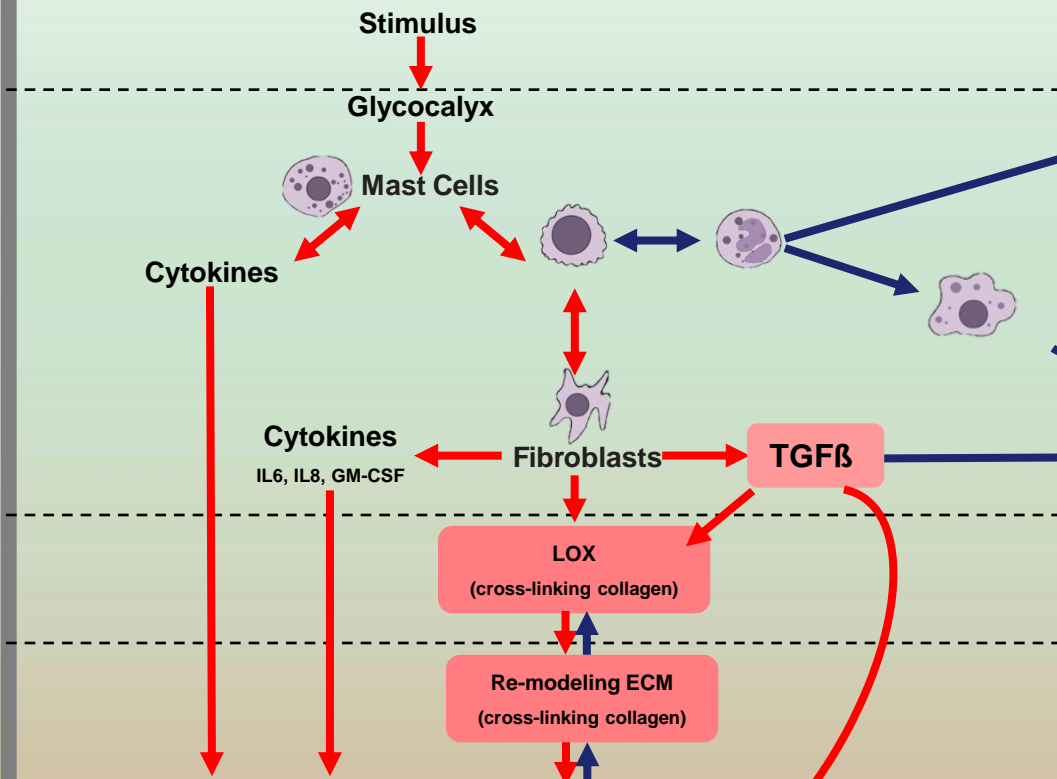
3. Fibrosis

4. Pre-cancerous niche

5. CSES

6. NCCCT

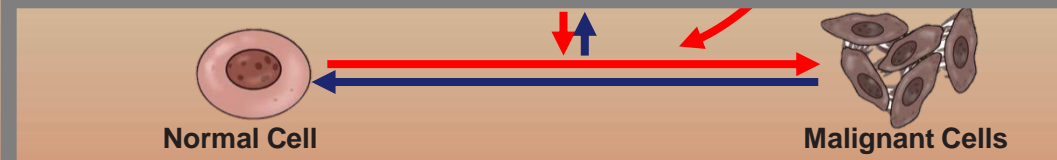
Later Events



Normal Wound Healing

Apoptosis

Chronic-Stress-Escape-Strategy

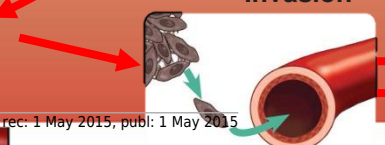
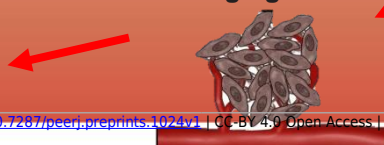
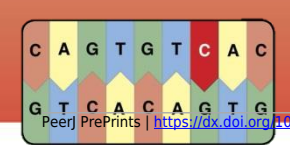


Normal-Cell-Cancer-Cell-Transition

Mutagenesis / Genomic Instability

Proliferation & Angiogenesis

Detachment / Invasion



Metastasis

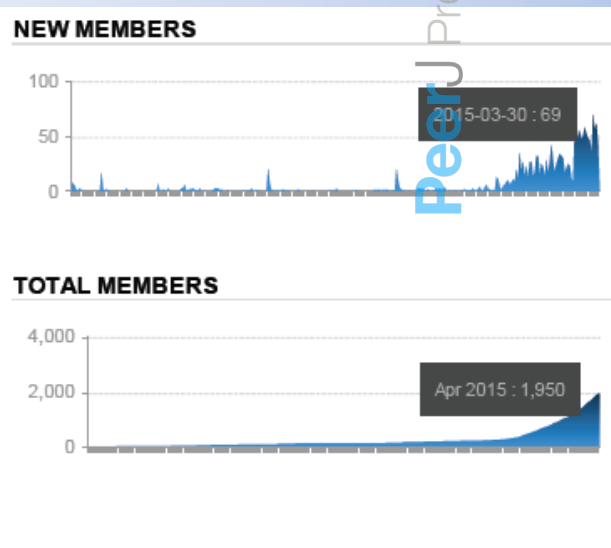
further reading.....

→ Epistemology of the origin of cancer: a new paradigm.
BMC Cancer 2014;14(331):1-15.

→ Cell-cell communication in the tumor microenvironment,
carcinogenesis, and anticancer treatment.
Cell Physiol Biochem 2014;34(2):213-243.

critical blinker-free open-minded discussions

Join the web group



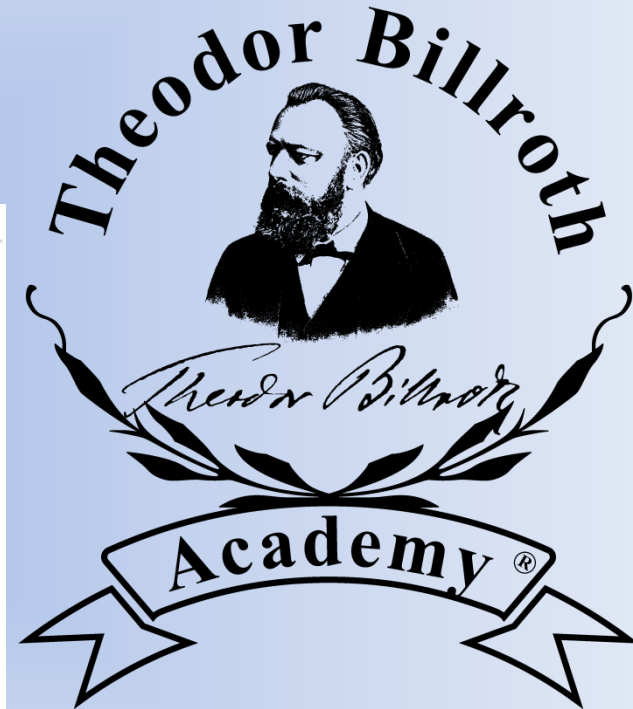
MEMBERS

1,957

Like any community, a LinkedIn group might be close-knit or vast, brand new or already thriving. Explore this group to see if it's right for you.

NEW MEMBERS LAST WEEK

43



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Thank you very much
for your
kind attention !

