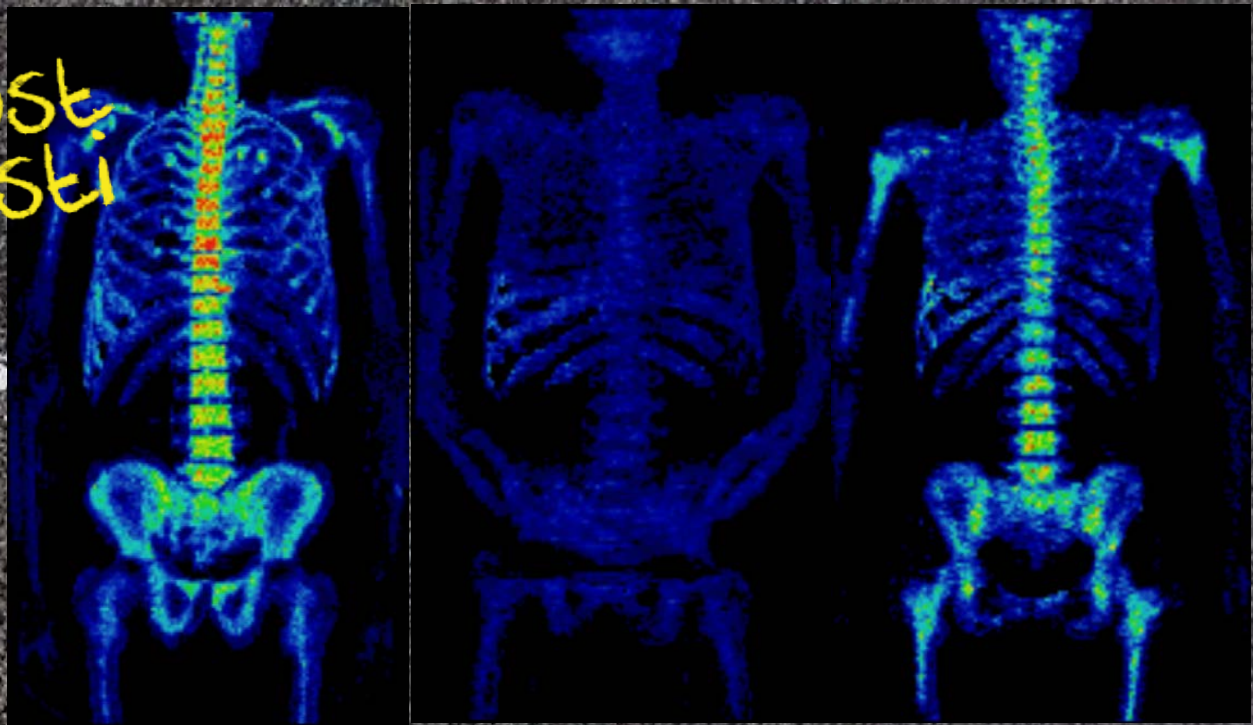


Znanost
na cesti

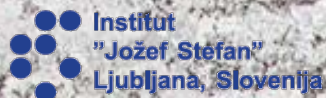


1. april 2015 ob 19h

Prihodnost onkologije z molekularnim slikanjem

Prof. dr. Robert Jeraj, Univerza v Ljubljani, IJS,
in Univerza v Wisconsinu

Maja Ratej, Val 202



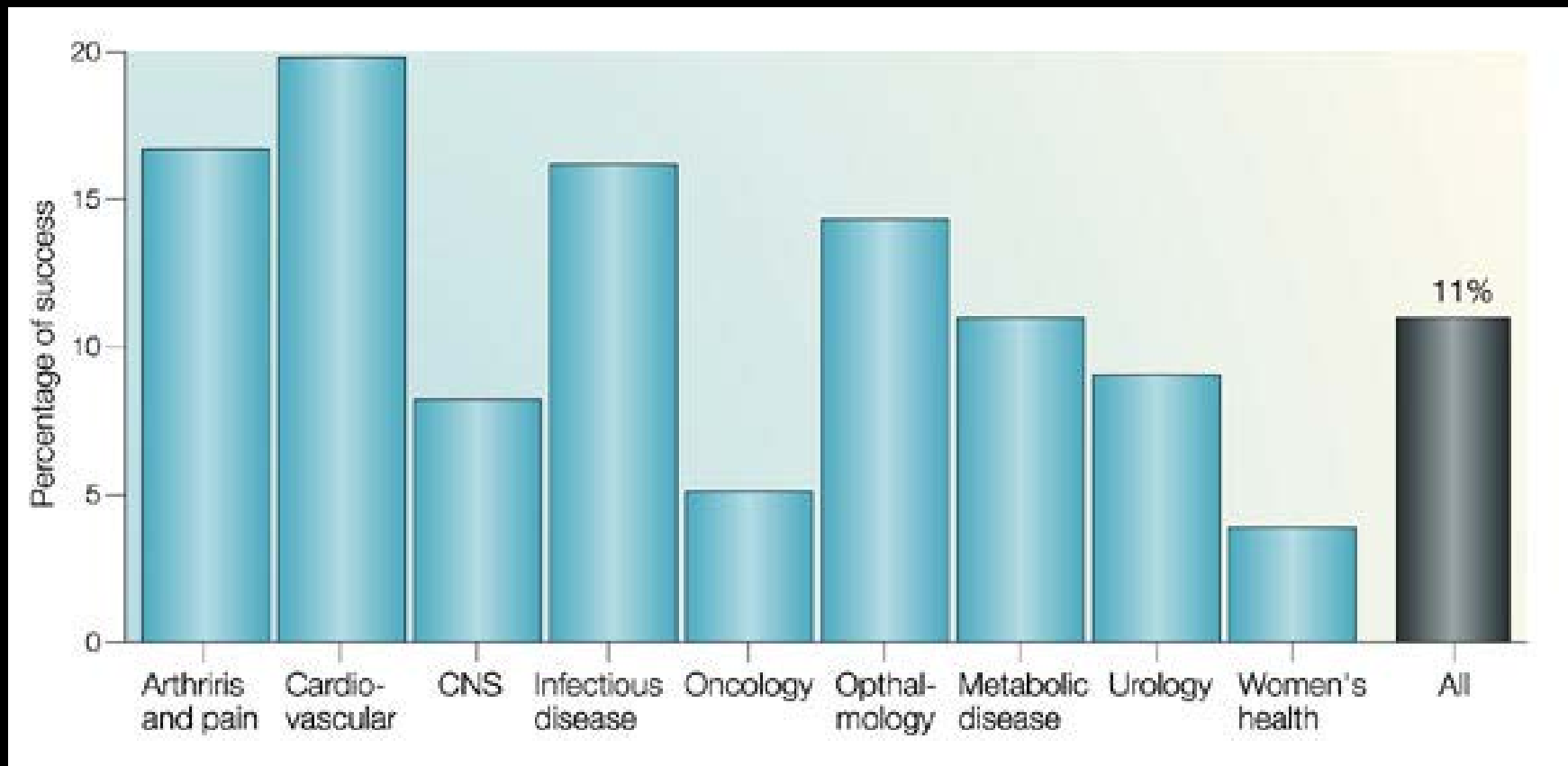
Nastanek raka



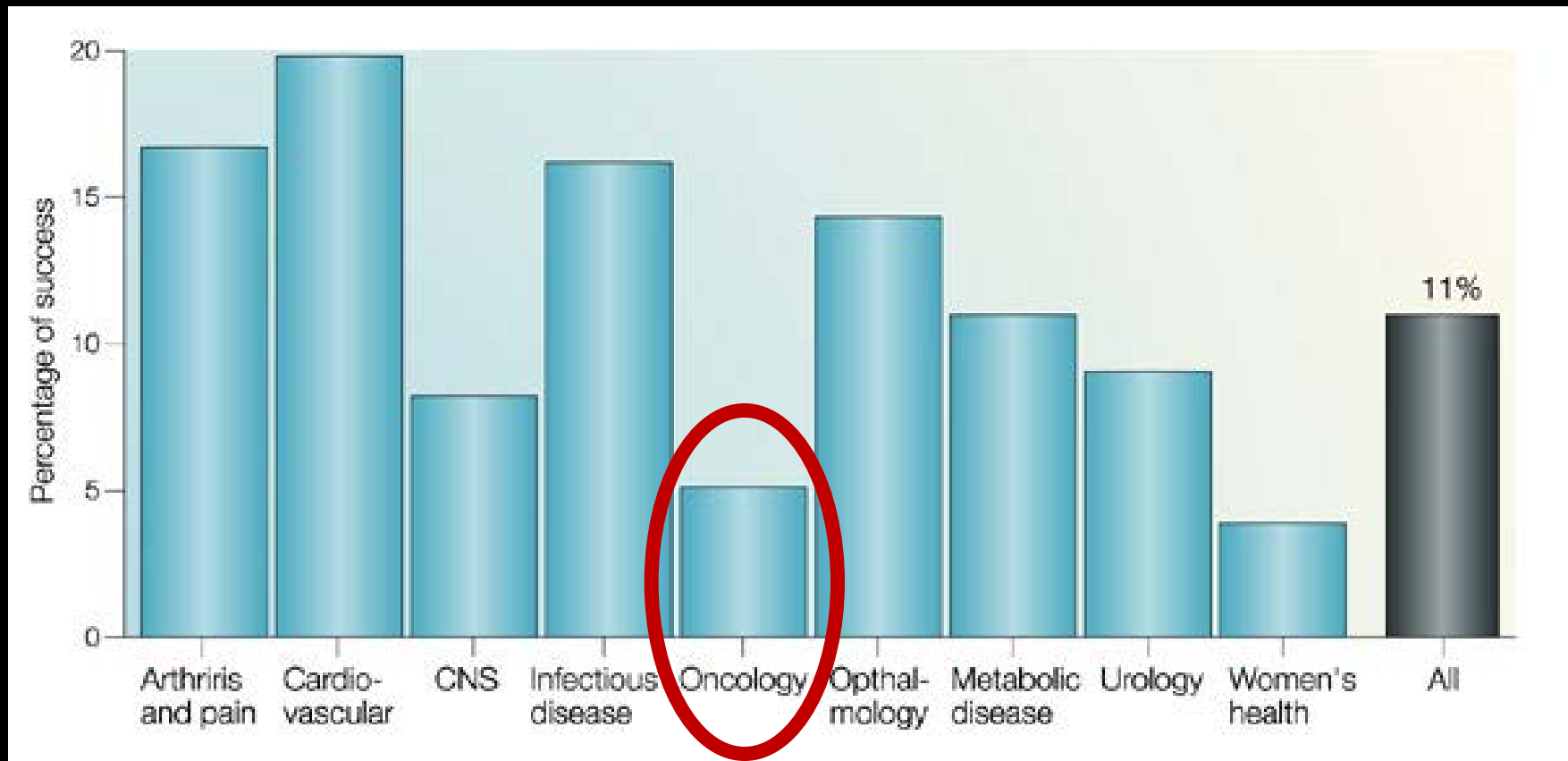
Lastnosti raka



Razvoj zdravil za zdravljenje raka



Razvoj zdravil za zdravljenje raka



Kako izboljšati razvoj zdravil?



- **...ogromne investicije v razvoj novih zdravil**, povezane z visokimi stroški (več kot milijarda dolarjev na uspešno zdravilo), čas razvoja novega zdravila (več kot 15 let!) in **veliko neuspehov**
- ...pomeni da **moramo nekaj spremeniti**
- ...razvoj molekularne biologije, omogoča **molekularno (genetsko) karakterizacijo** tumorjev
- **...tarčne terapije** omogočajo bolj natančno zdravljenje, a le za **malo skupino** pacientov, ki imajo določeno mutacijo
- ...mogoče bomo v prihodnosti lahko **natančno karakterizirali vsak tumor**, in našli ustrezno tarčno zdravilo
- ...a za to potrebujemo **'inteligentno selekcijo biomarkerjev'**, ki bodo „izbirali“ prave paciente za razvoj novih zdravil

Klinične študije včasih in danes



PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

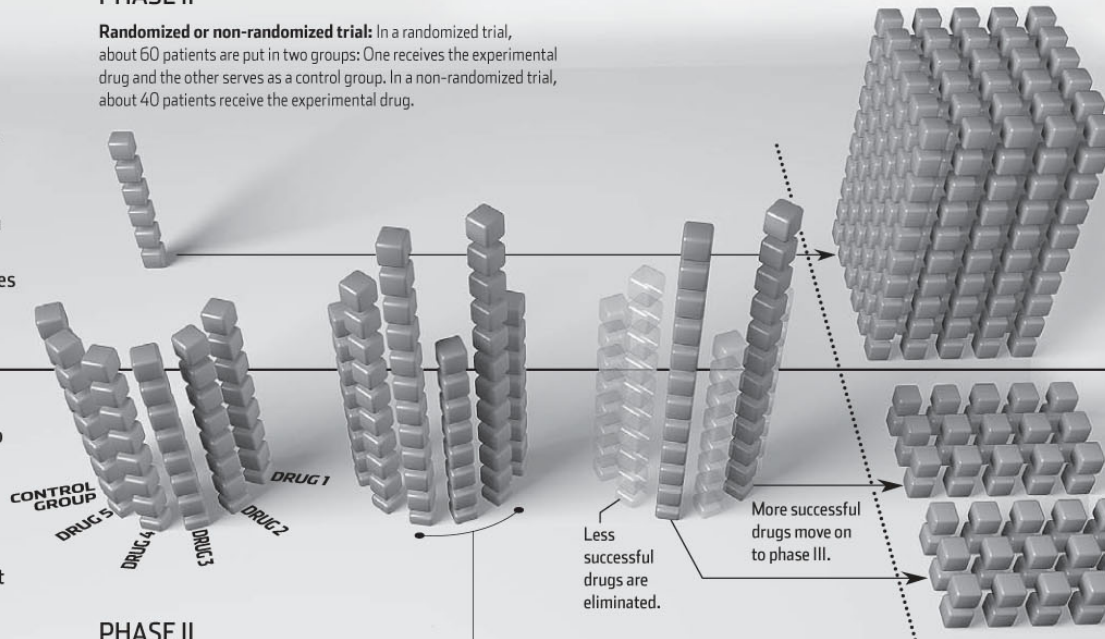
1 cube = 10 patients

Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

PHASE II

Randomized or non-randomized trial: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



PHASE III

If a drug graduates to phase III, it typically takes **3,000 patients** and about three years to determine if it is safe and effective enough for approval.



HISTORIC SUCCESS RATE

30 TO 40%

New trial design

Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either **standard therapy or one of five different drugs** plus standard care.

Early results increase chances that **patients entering the trial later will be assigned to a drug showing benefit** against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine **which ones graduate to phase III studies.**

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with **300 patients** selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



PROBABILITY OF SUCCESS

85%

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

Source: Donald Berry, M.D. Anderson Cancer Center

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A New Rx for Medicine

Fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments.

Winslow 2010, The Wall Street Journal

2016: Natančna medicina



THE PRECISION MEDICINE INITIATIVE

2016: Natančna medicina



\$215M investment



“Tonight, I’m launching a new **Precision Medicine Initiative** to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the **personalized information** we need to keep ourselves and our families healthier.”

THE PRECISION MEDICINE INITIATIVE

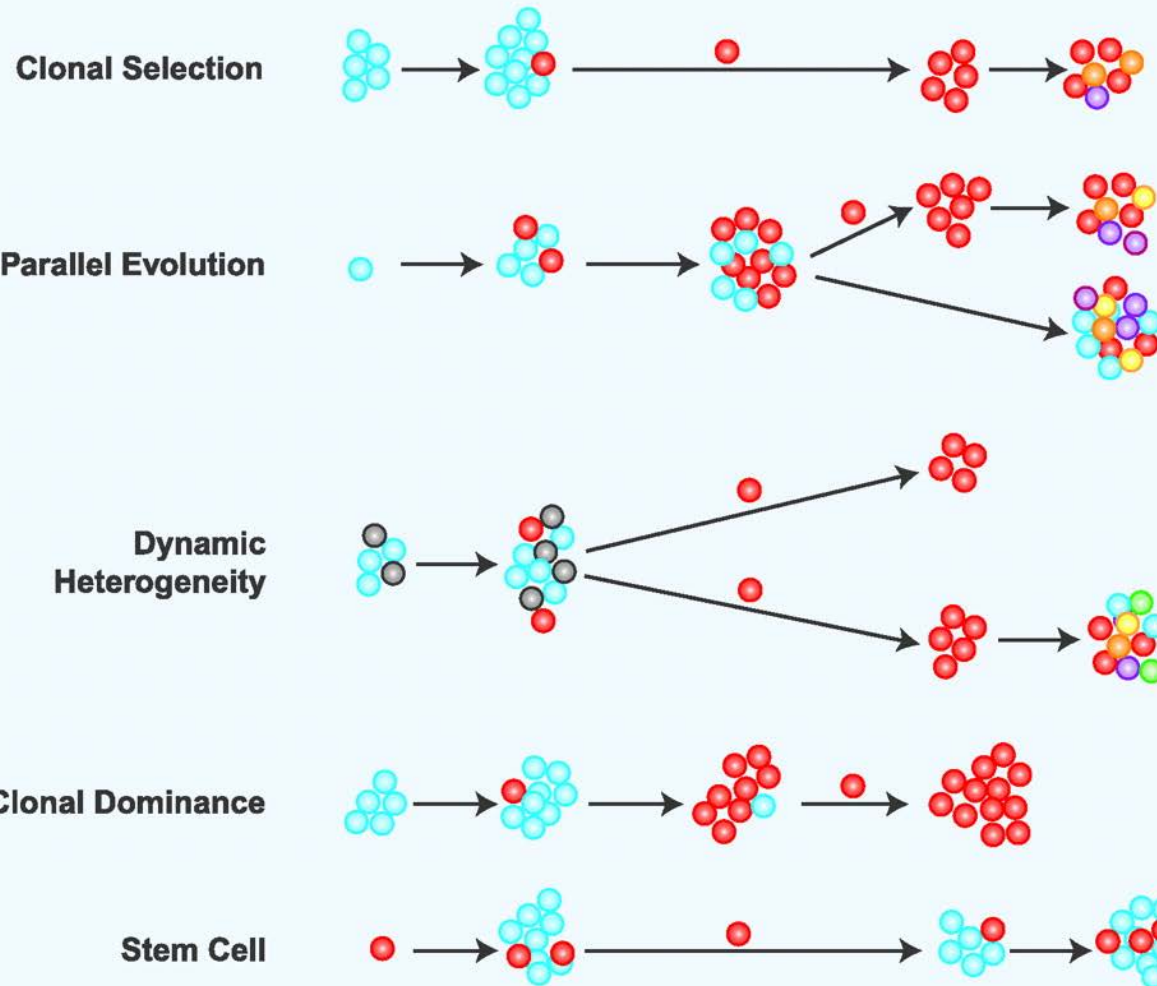
Problem 1: Tumorji so heterogeni...



Clonal Selection



Problem 1: Tumorji so heterogeni...



...in to zelo...



The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 8, 2012

VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed
by Multiregion Sequencing

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...in to zelo...



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Graham Clark, M.D., Szallasi, M.D.,

...tumorji so tako heterogeni, da nam vsaka
biopsija razloži **le 1/3 sestave tumorja**

...in to zelo...



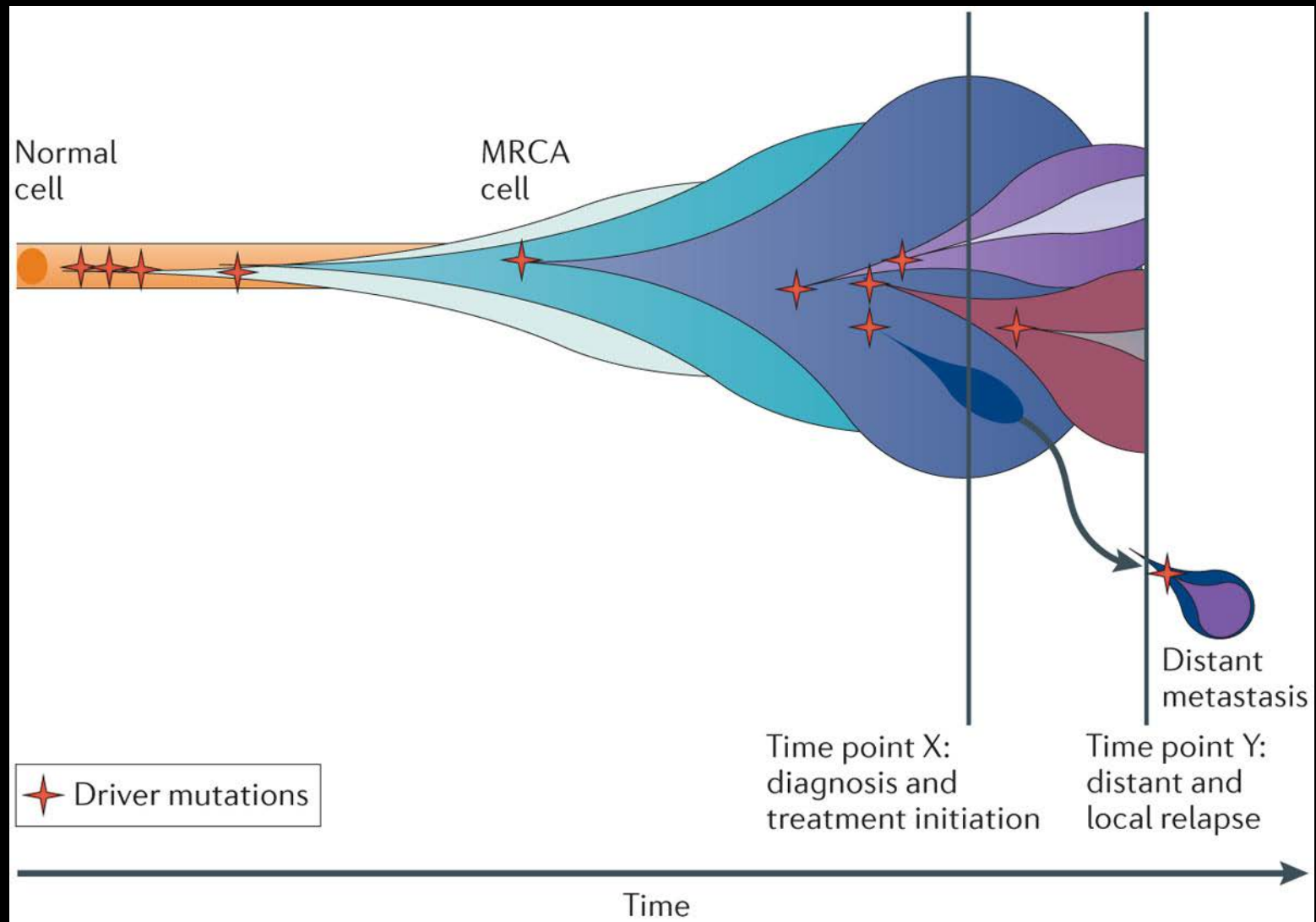
Medicinsko slikanje nam omogoča karakterizacijo tumorske heterogenosti

by Multiregion Sequencing

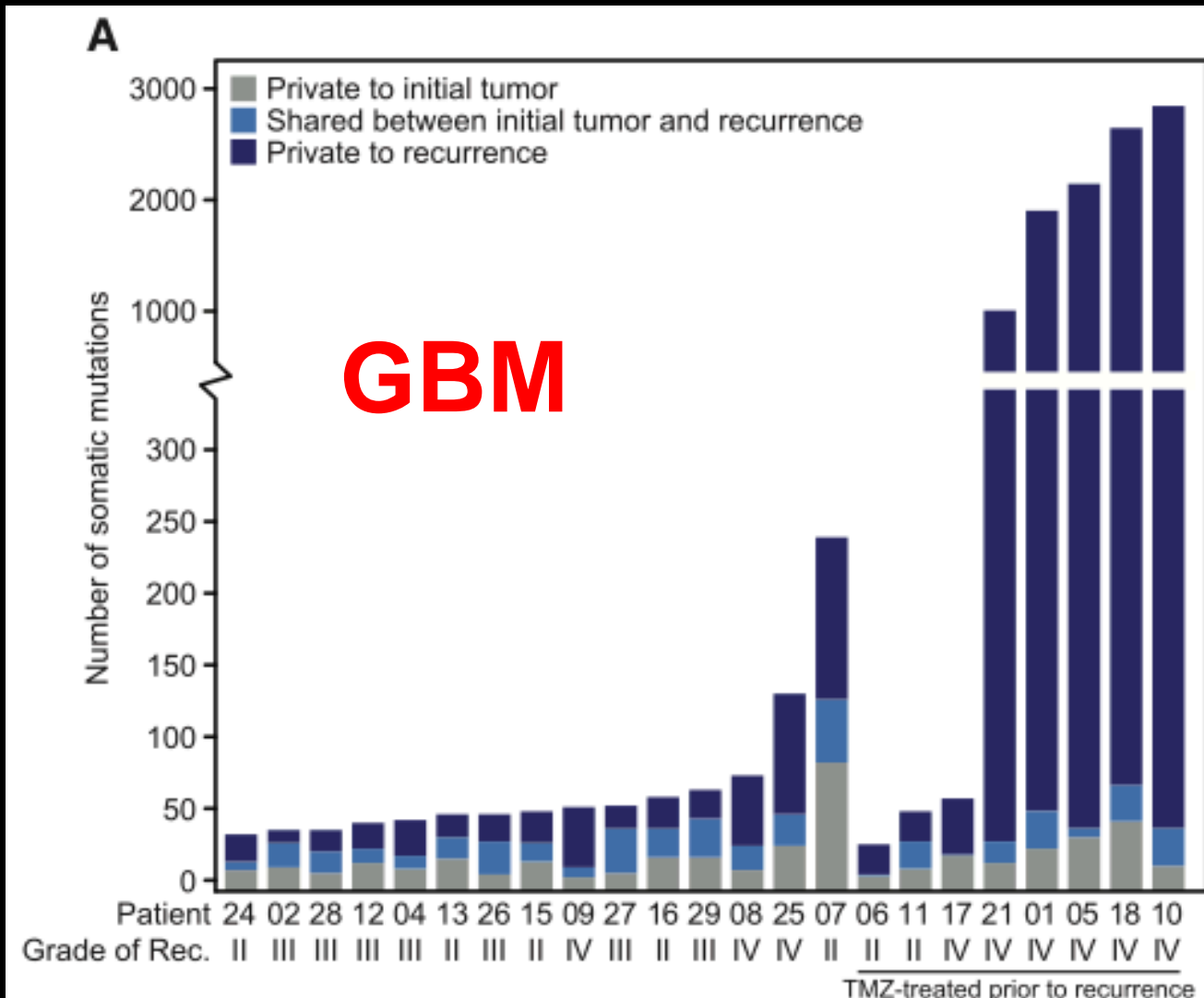
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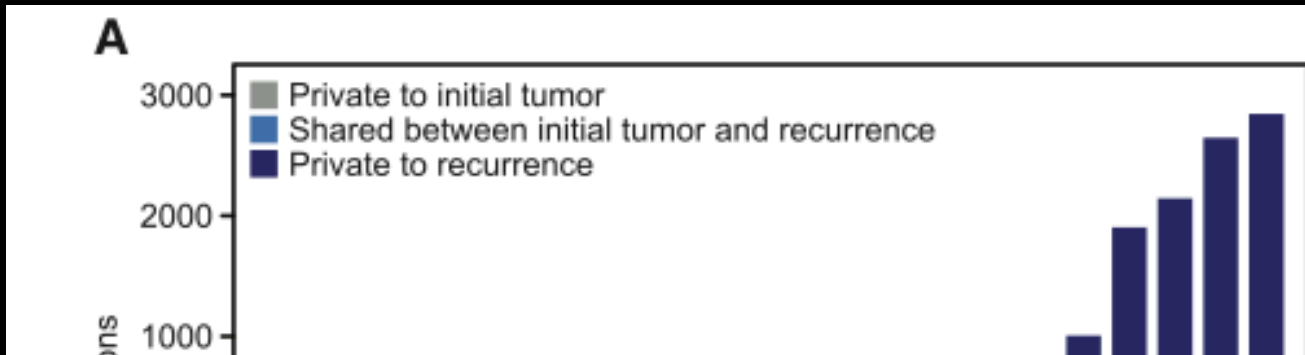
Problem 2: Tumorji se spreminjajo...



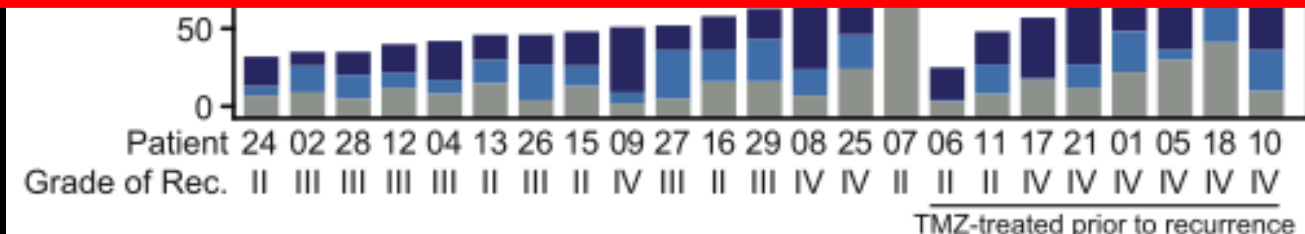
...in to zero...



...in to zelo...



Medicinsko slikanje nam omogoča zasledovanje evolucije tumorjev



Medicinsko slikanje



Anatomsko

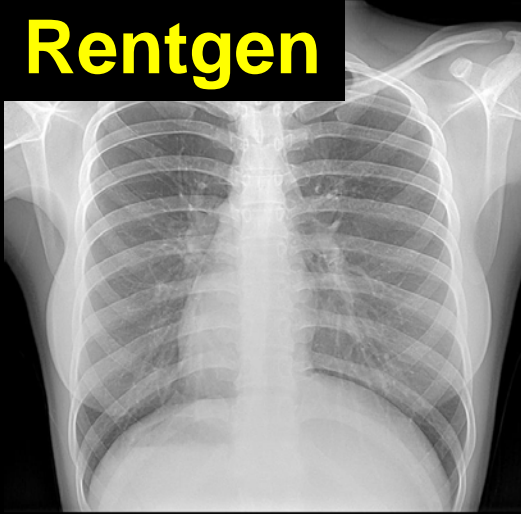
Molekularno

Medicinsko slikanje



Anatomsko

Rentgen



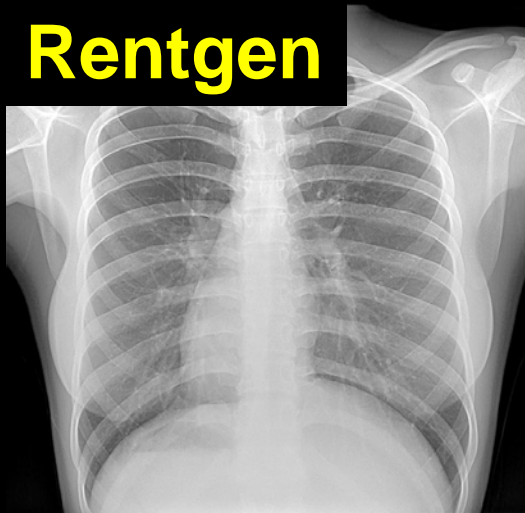
Molekularno

Medicinsko slikanje

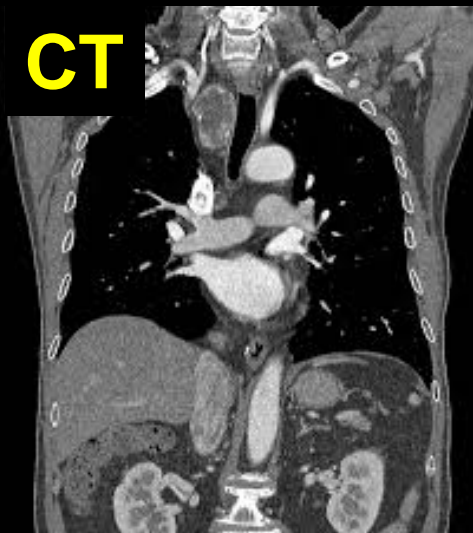


Anatomsko

Rentgen



CT



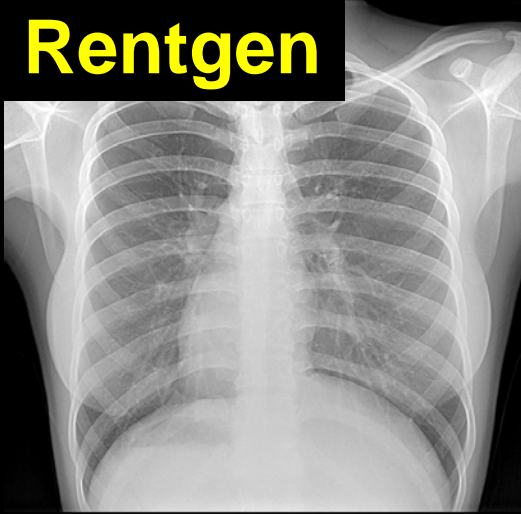
Molekularno

Medicinsko slikanje

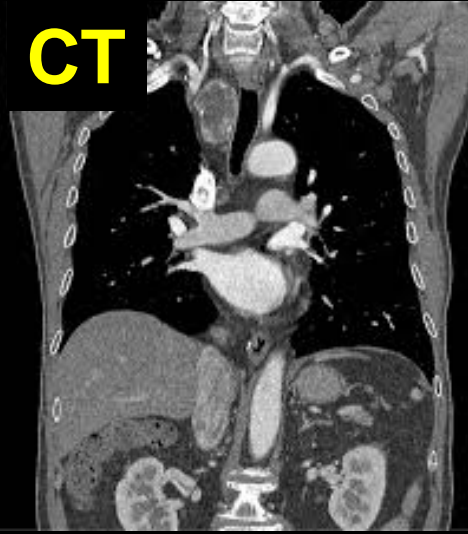


Anatomsko

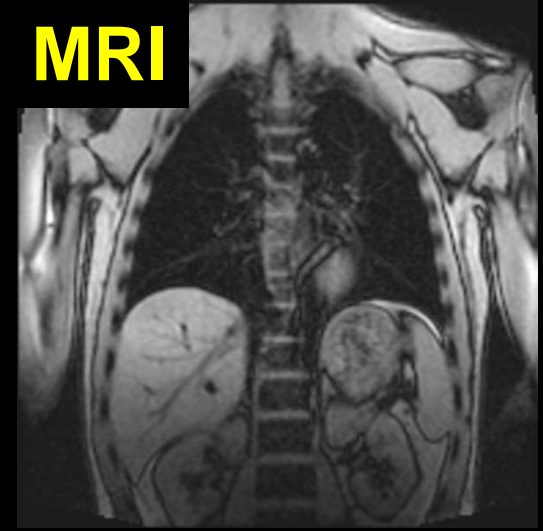
Rentgen



CT



MRI



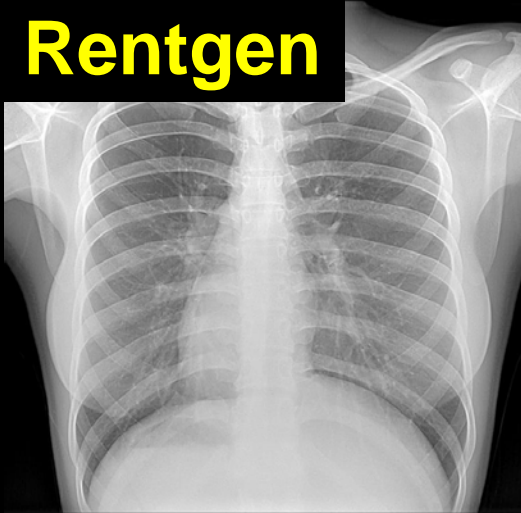
Molekularno

Medicinsko slikanje

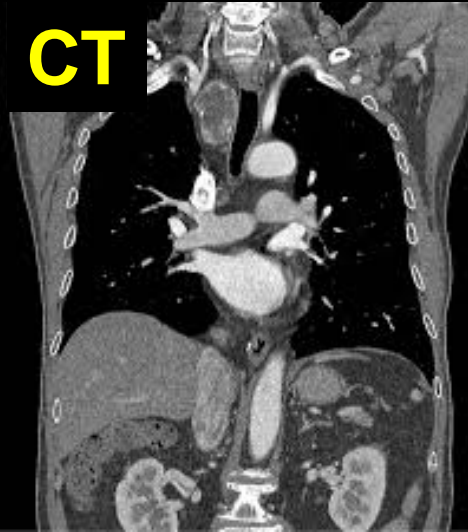


Anatomsko

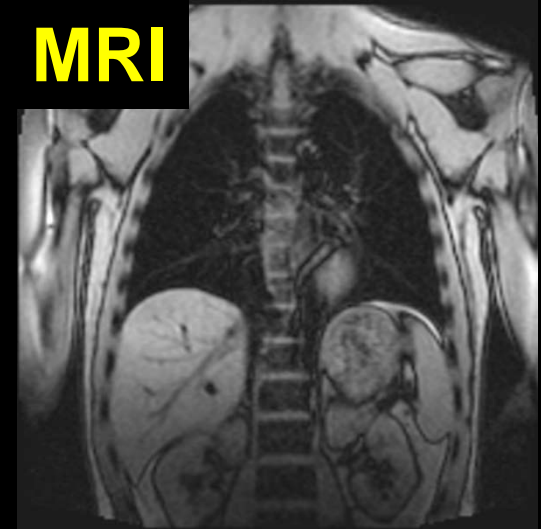
Rentgen



CT



MRI



Molekularno

Scintigrafija

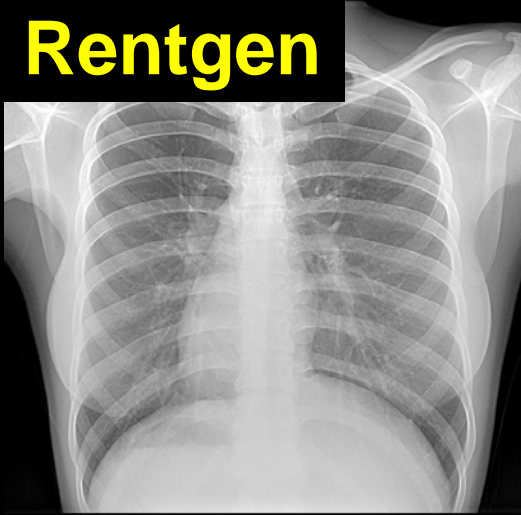


Medicinsko slikanje

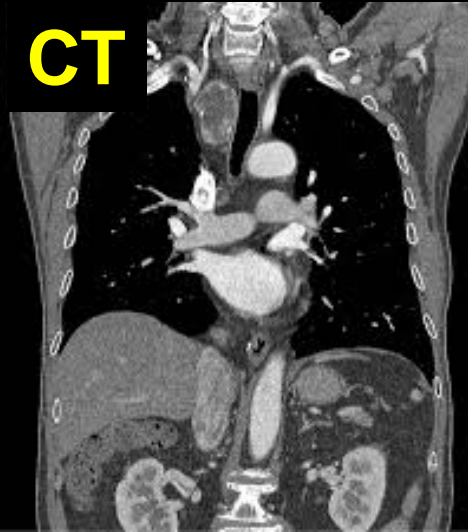


Anatomsko

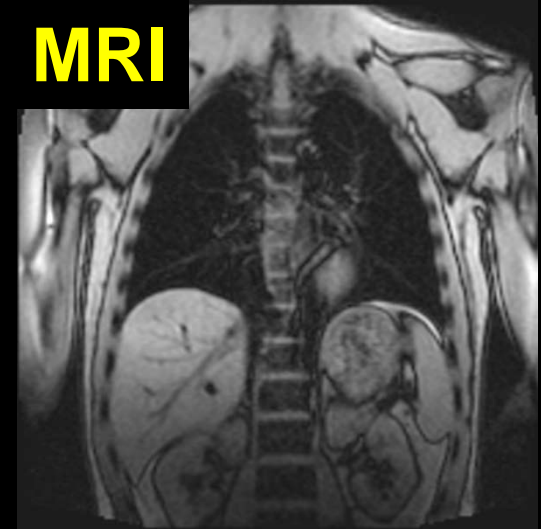
Rentgen



CT



MRI

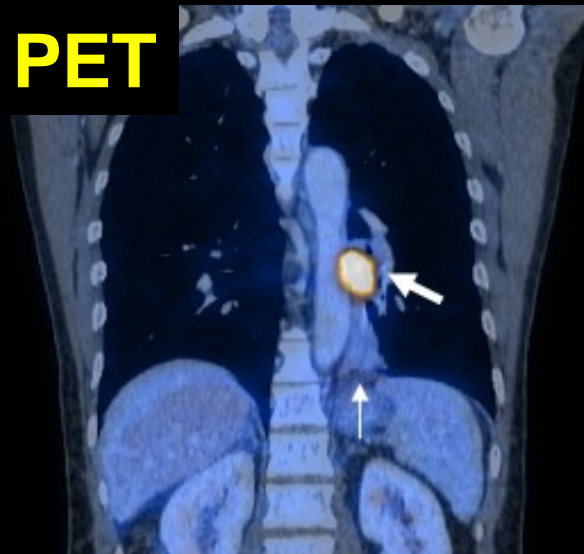


Molekularno

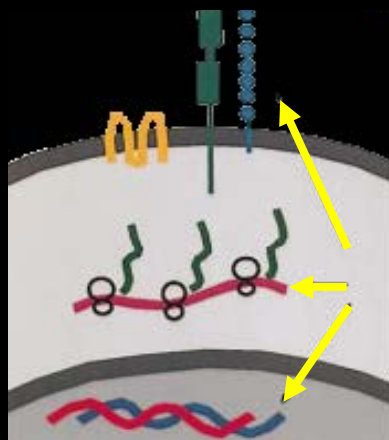
Scintigrafija



PET



Molekularno slikanje

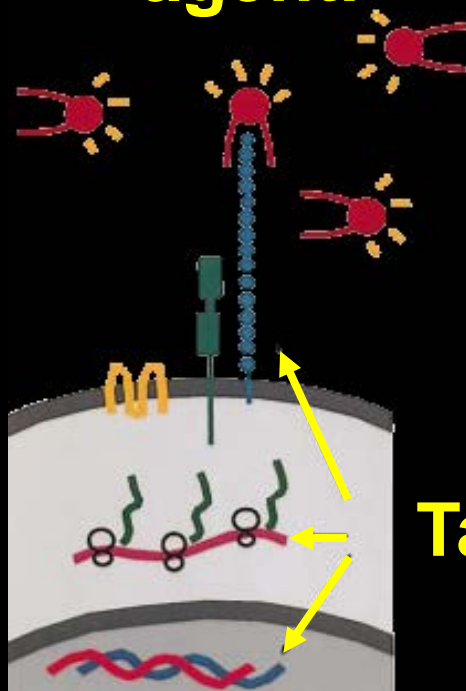


Tarče

Molekularno slikanje

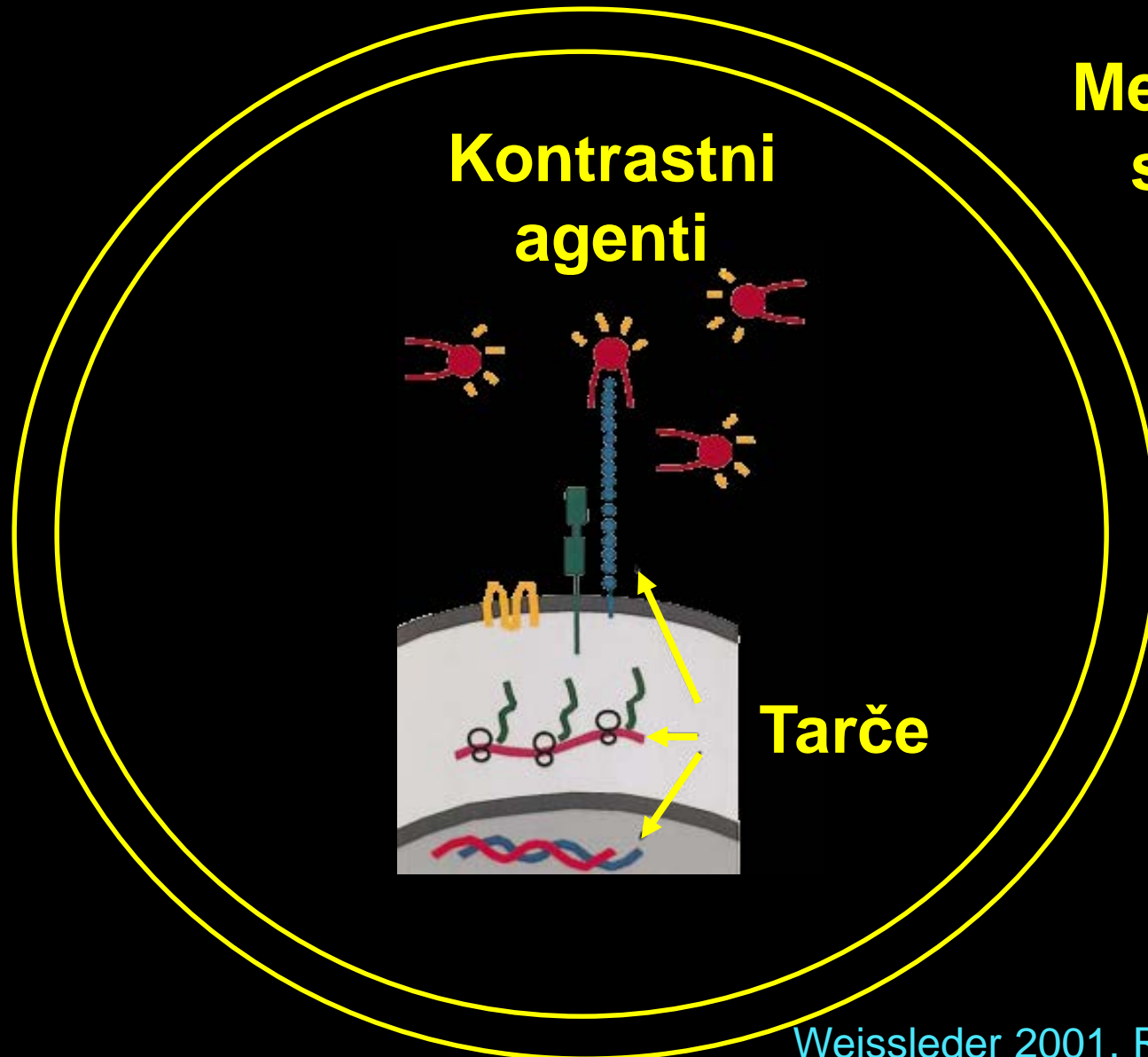


**Kontrastni
agenti**



Tarče

Medicinsko slikanje



Agenti molekularnega slikanja



Optical

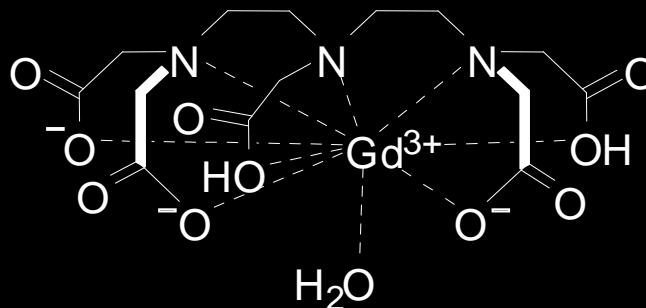


GFP

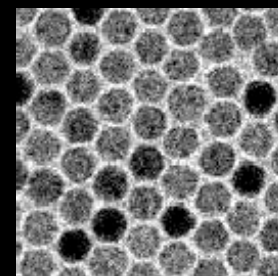


fLUC

MRI

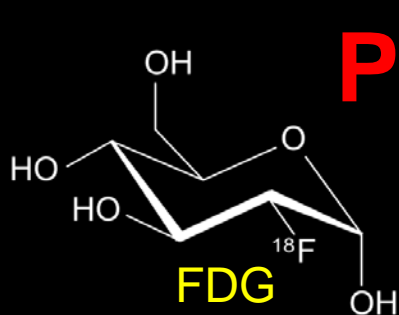


Gd-DTPA

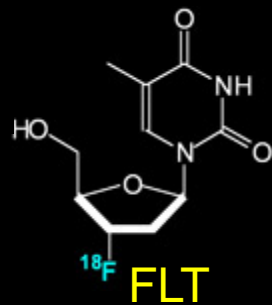


Iron Oxide

PET

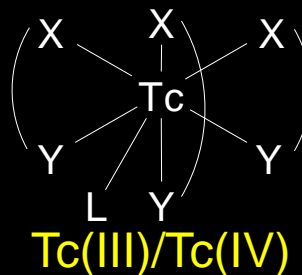


FDG



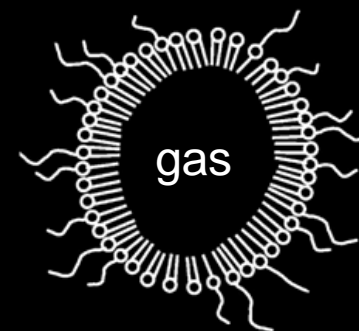
FLT

SPECT

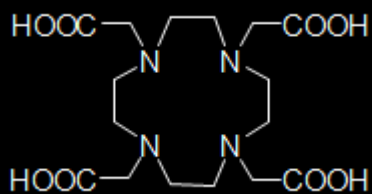


Tc(III)/Tc(IV)

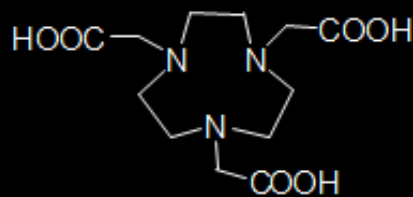
US



Microbubbles



DOTA



NOTA

Adapted from W. Cai, UW

Agenti molekularnega slikanja



Optical

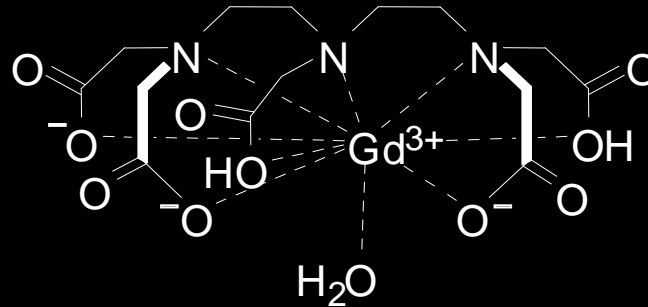


GFP

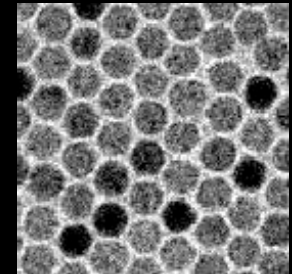


fLUC

MRI

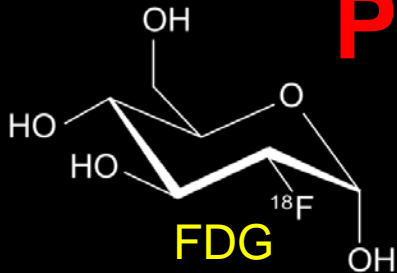


Gd-DTPA

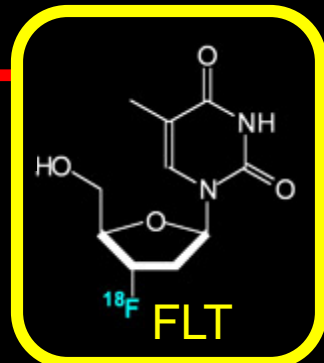


Iron Oxide

PET

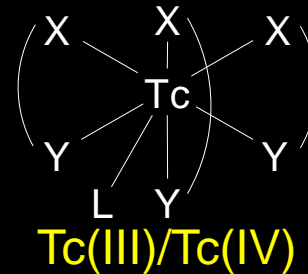


FDG



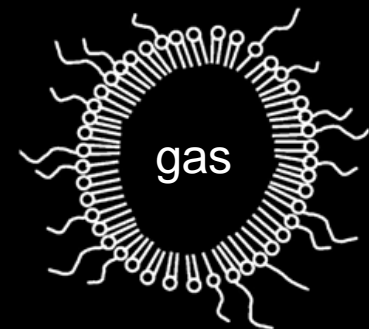
FLT

SPECT

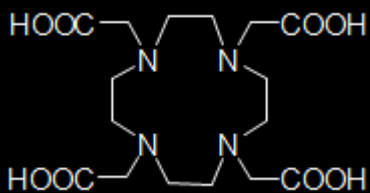


Tc(III)/Tc(IV)

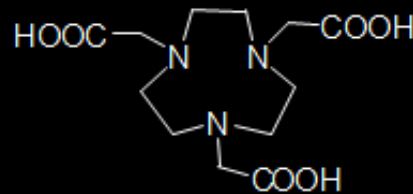
US



Microbubbles



DOTA



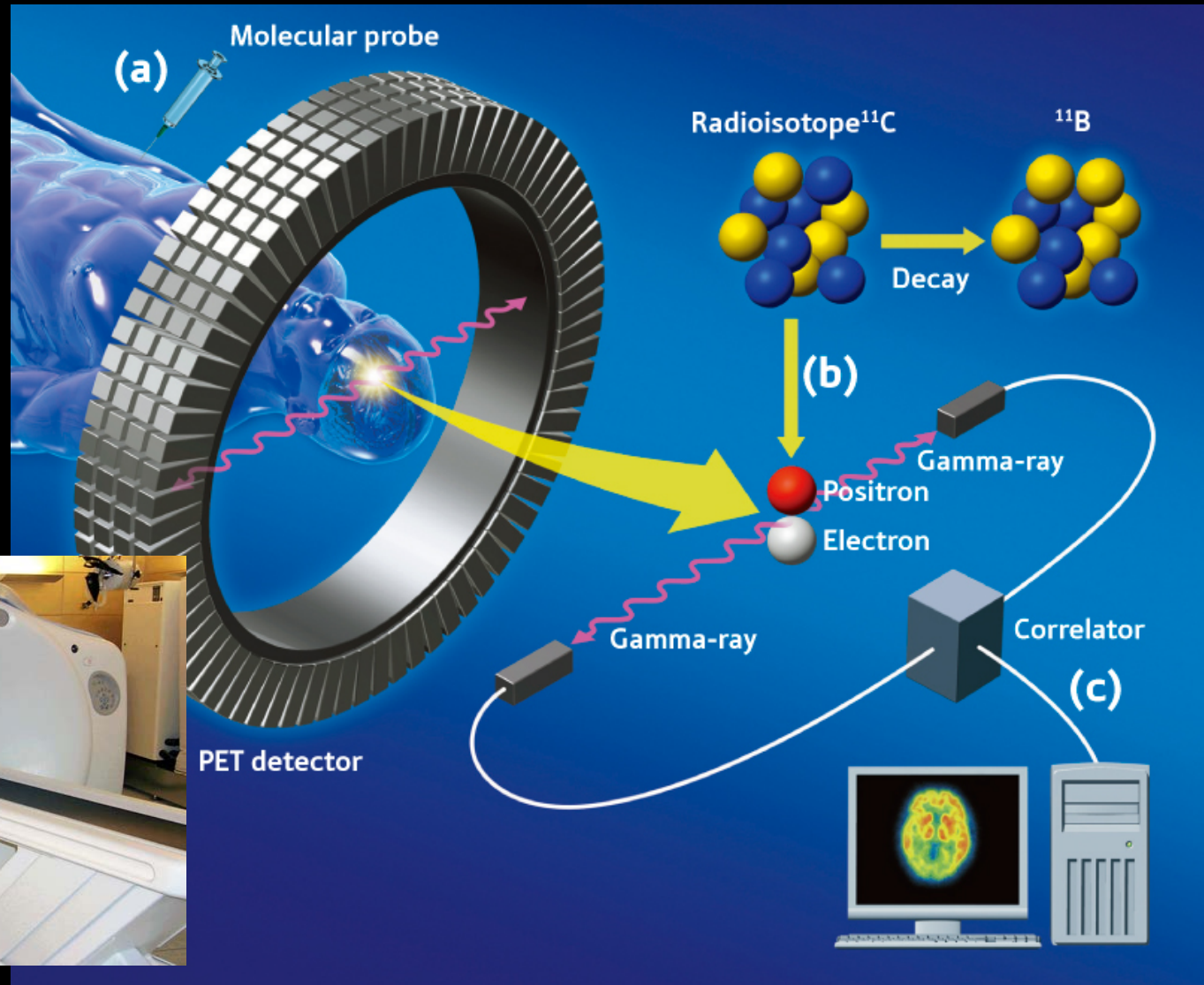
NOTA

Adapted from W. Cai, UW

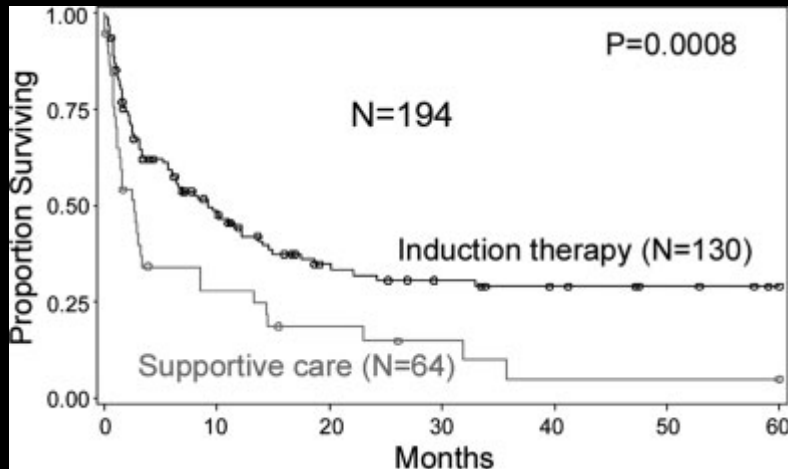
Znanstvena fantastika...



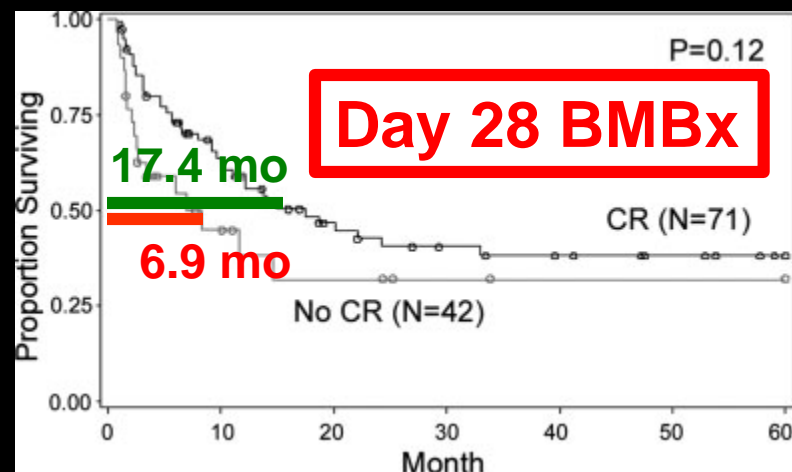
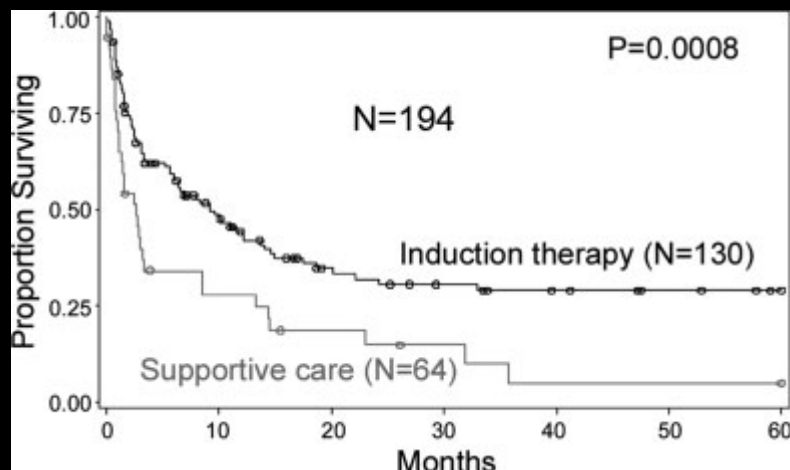
Pozitronska emisijska tomografija (PET)



Akutna milenoidna levkemija (AML)



Akutna milenoidna levkemija (AML)



Akutna milenoidna levkemija (AML)

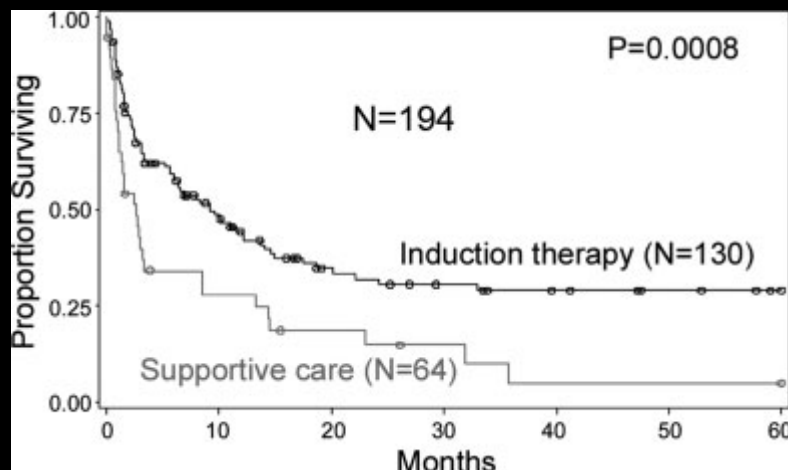
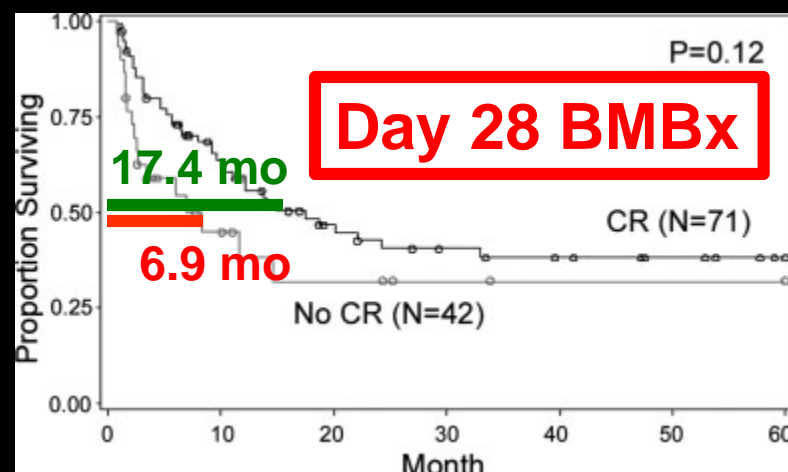


TABLE II. Predictive Utility of Day 14 BM on Day 28 Complete Remission Rate

	Day 14 BMBx	Day 28 BMBx		
		≤5%	>5%	
Day 14 BMBx	≤5%	46	12	58
	>5%	5	9	14
		51	21	72 ^a



NPV = 64%

Molekularno slikanje z FLT PET



Kemoterapija



Teden 0

1

2



Molekularno slikanje z FLT PET



Kemoterapija



Teden 0

1

2



FLT₁



FLT₂



FLT₂

Molekularno slikanje z FLT PET



Kemoterapija



Teden 0

1

2



FLT₁



FLT₂



FLT₂



FLT₂

Molekularno slikanje z FLT PET



Kemoterapija



Teden 0

1

2



FLT₁



FLT₂



FLT₂



FLT₂



FLT₂

Molekularno slikanje z FLT PET



Kemoterapija



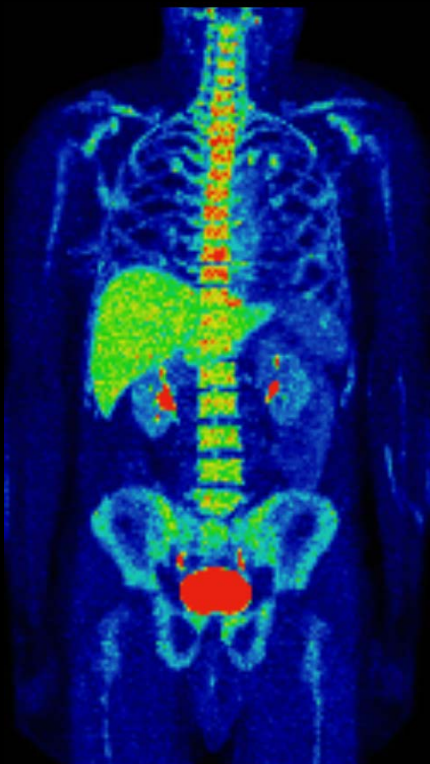
Teden 0

1

2



FLT PET/CT

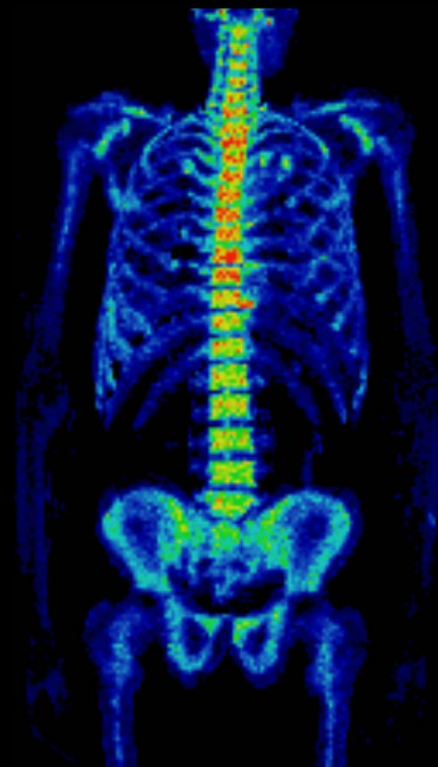


FLT PET

X



CT

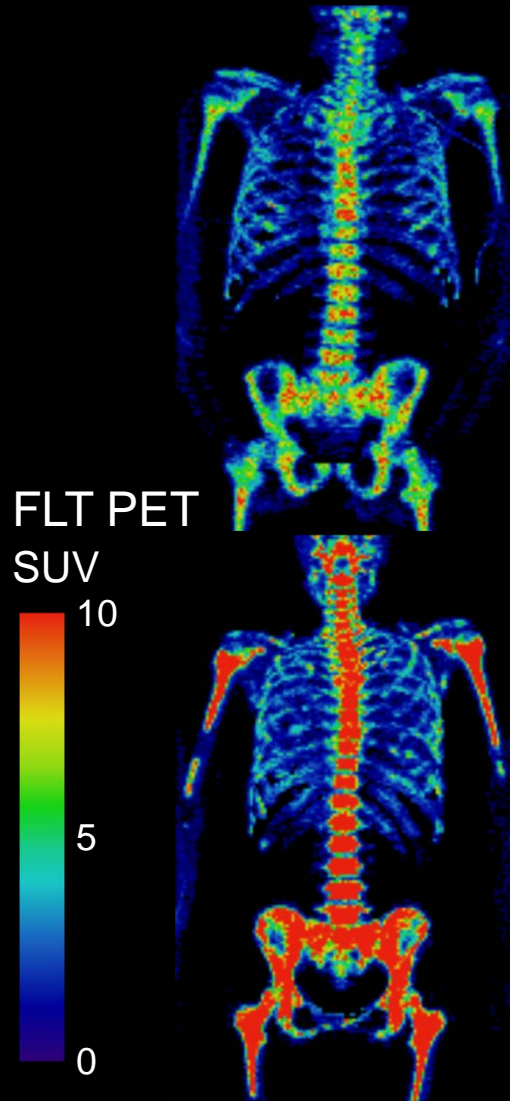


FLT PET
kostnega mozga

FLT PET/CT kot biomarker



Pred terapijo

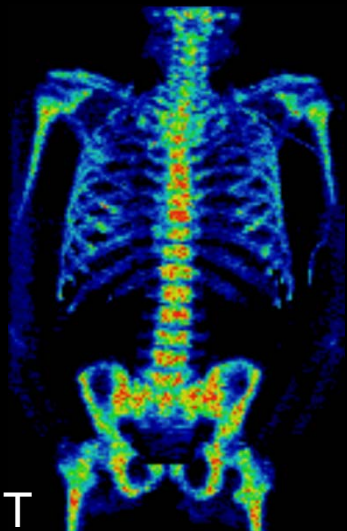


FLT PET/CT kot biomarker

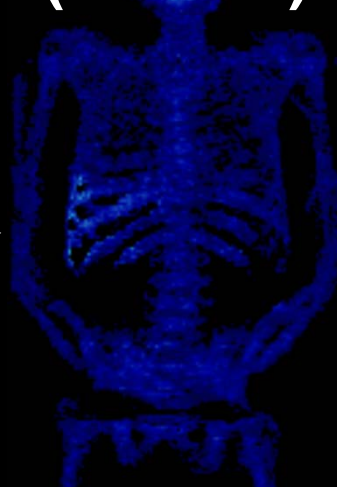


Pred terapijo

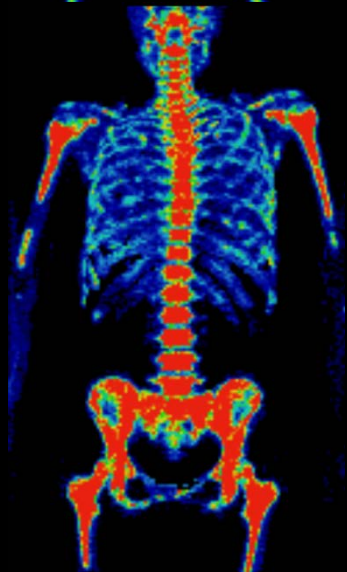
**Po terapiji
(2 tedna)**



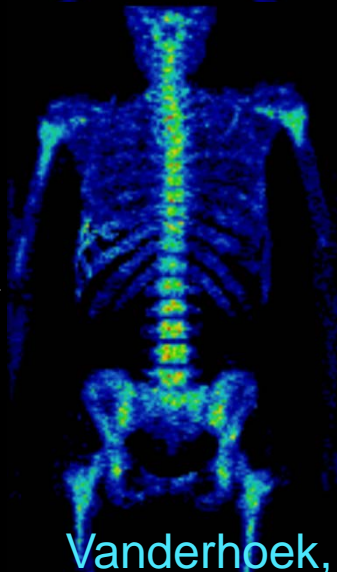
Kemo



FLT PET
SUV



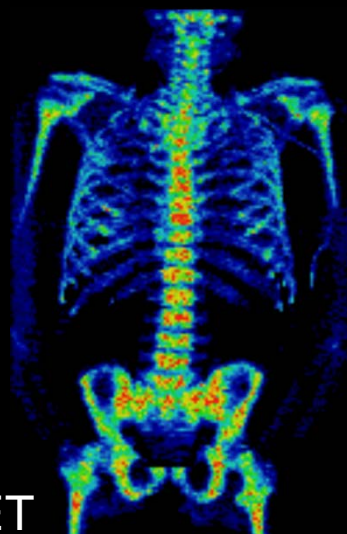
Kemo



FLT PET/CT kot biomarker

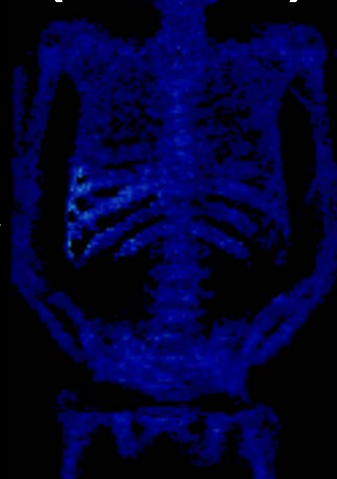


Pred terapijo



Kemo

**Po terapiji
(2 tedna)**



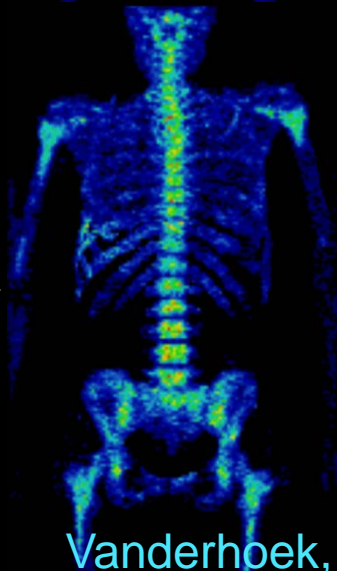
**KLINIČNI
REZULTATI
(6 mo)**

**Kompletna
remisija**

FLT PET
SUV



Kemo



**Rezistenčna
bolezen**

Zgodnje ugotavljanje uspešnosti



Kompletna remisija

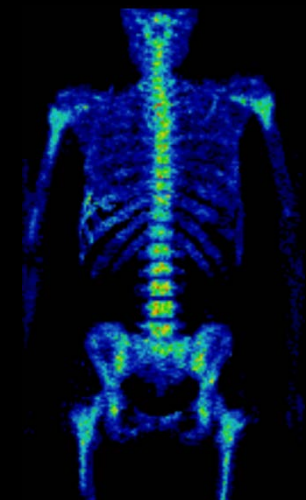
(6 mo)



Pred terapijo

Rezistenčna bolezen

(6 mo)



Po terapiji

SUV
10



5

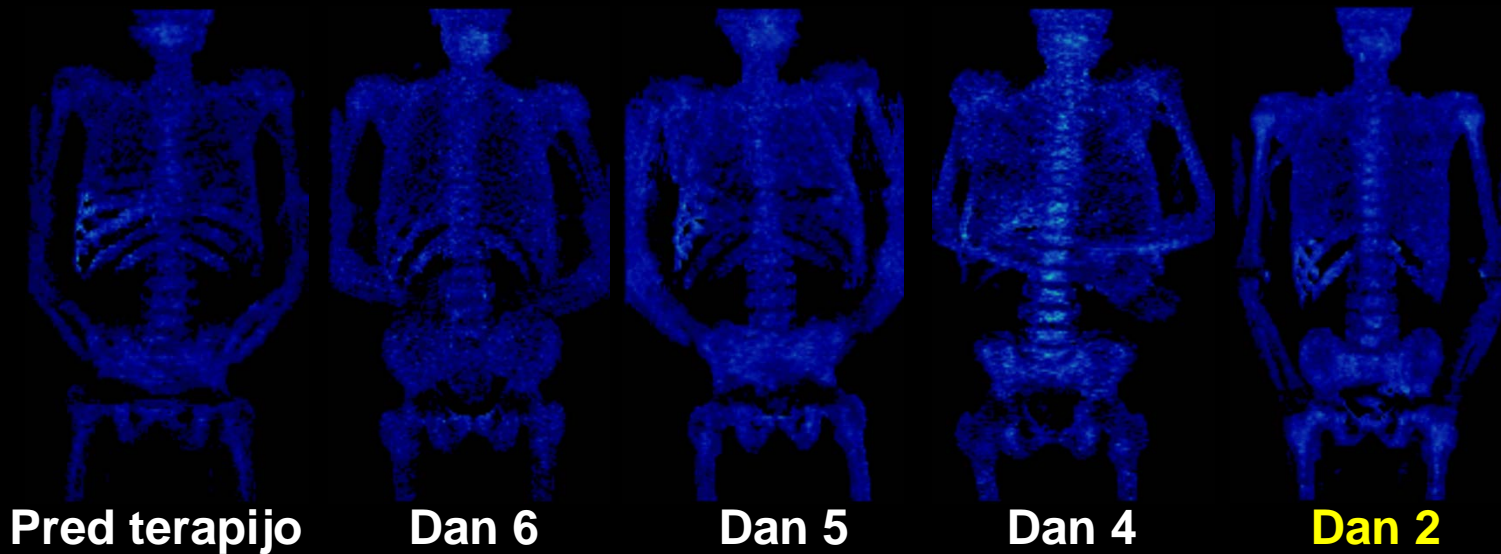
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Zgodnje ugotavljanje uspešnosti



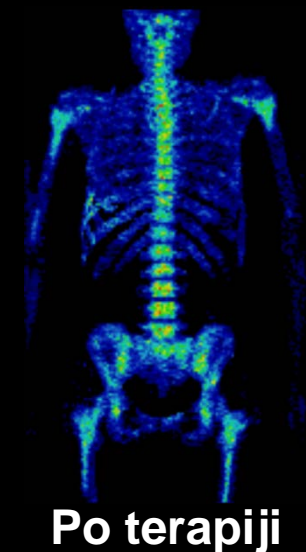
Kompletna remisija

(6 mo)



Rezistenčna bolezen

(6 mo)

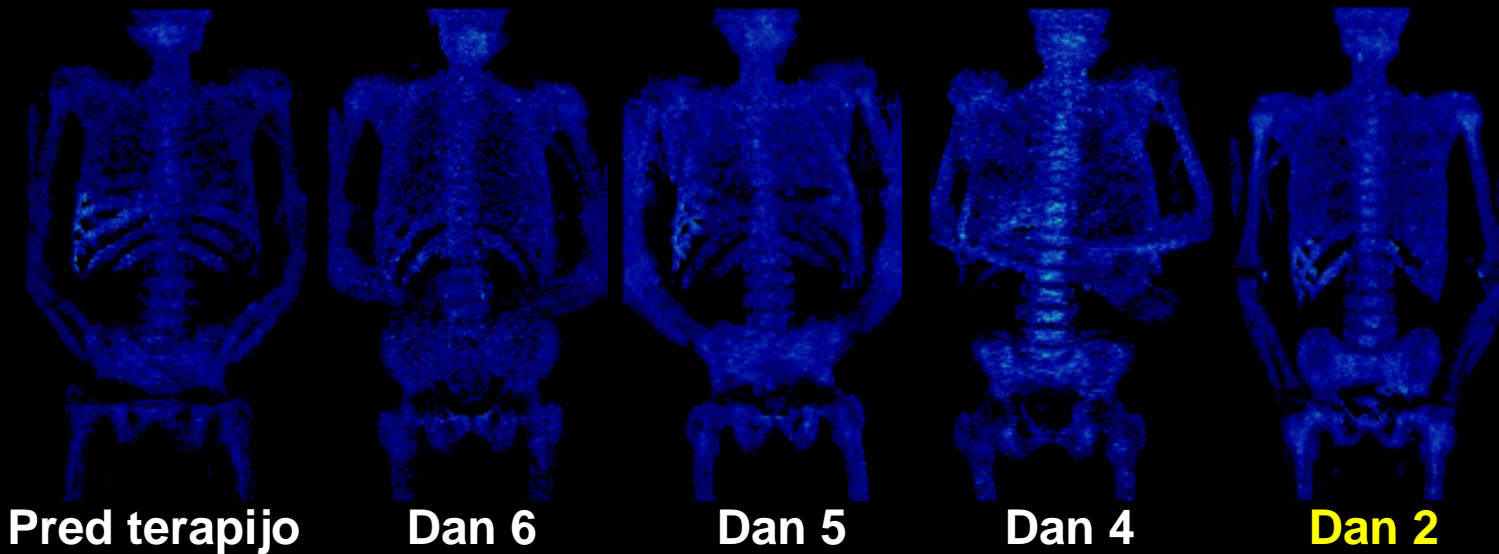


Zgodnje ugotavljanje uspešnosti



Kompletna remisija

(6 mo)

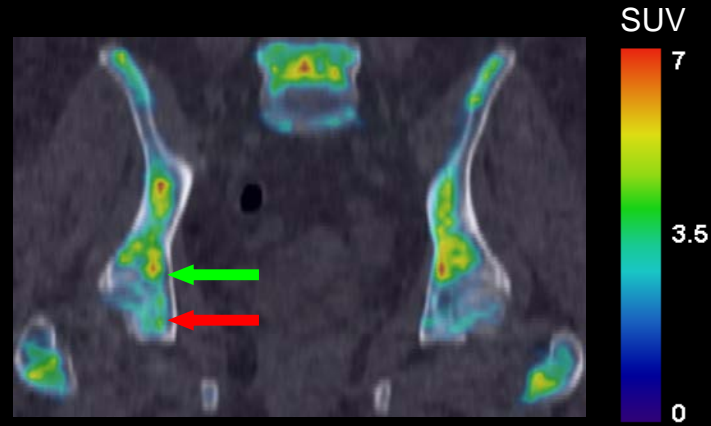
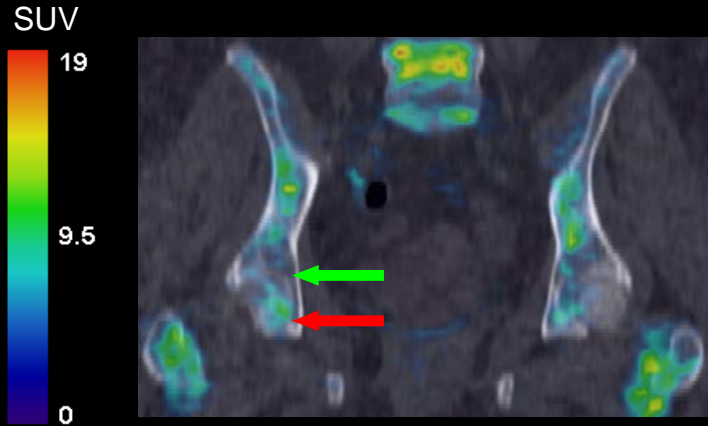


Rezistentna bolezen

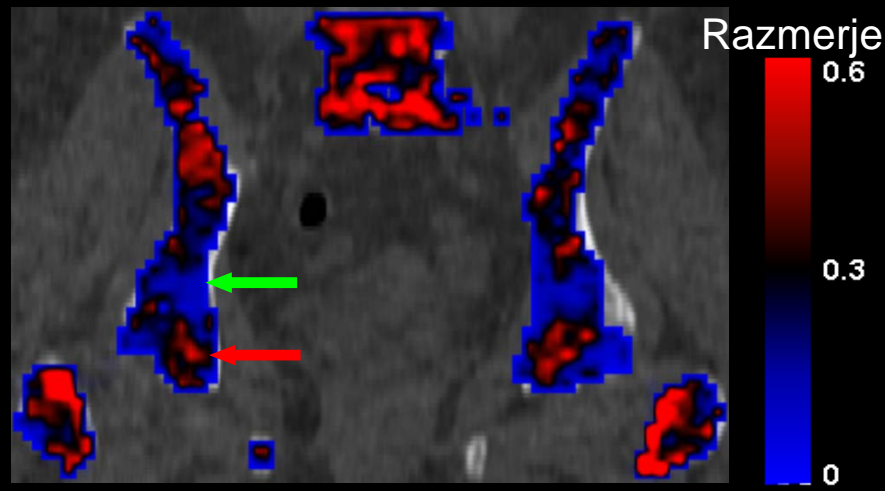
(6 mo)



Heterogenost odziva



Po FLT PET/Pred FLT PET



Povzetek



■

■

■

- Bodočnost medicine je v „**natančni medicini**“:
 - Natačna karakterizacija tumorjev
 - Personalizacija zdravljenja
-
-

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 - Evolucijo tumorjev
- **Kombinacija** omogoča:
 - Napovedovanje uspešnosti zdravljenja
 - Bolj efektiven razvoj novih zdravil

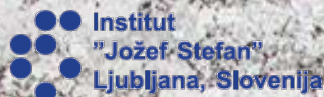
Znanost
na cesti



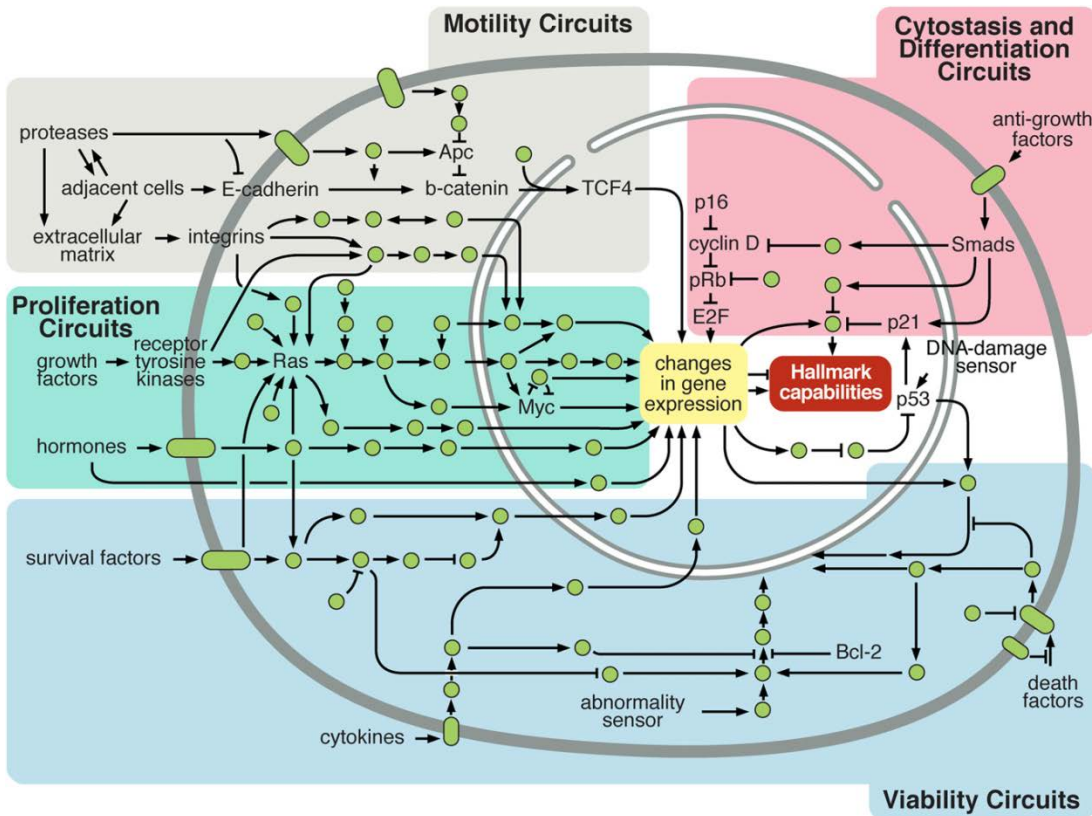
8. april 2015 ob 19h

Varnost in sledljivost živil na slovenskem trgu

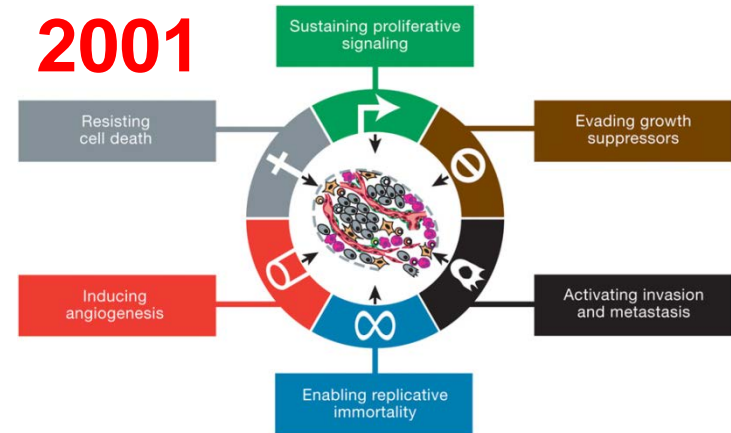
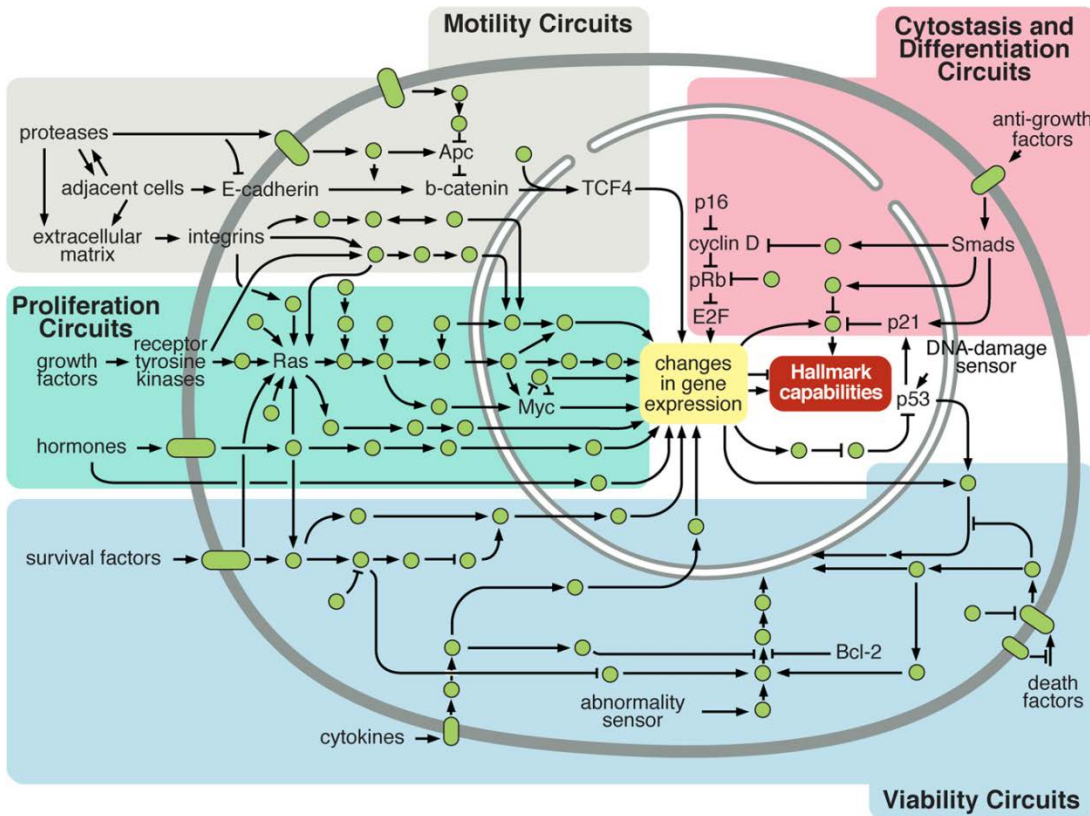
prof. dr. Nives Ogrinc, IJS
Matic Jerman, Radio Slovenija



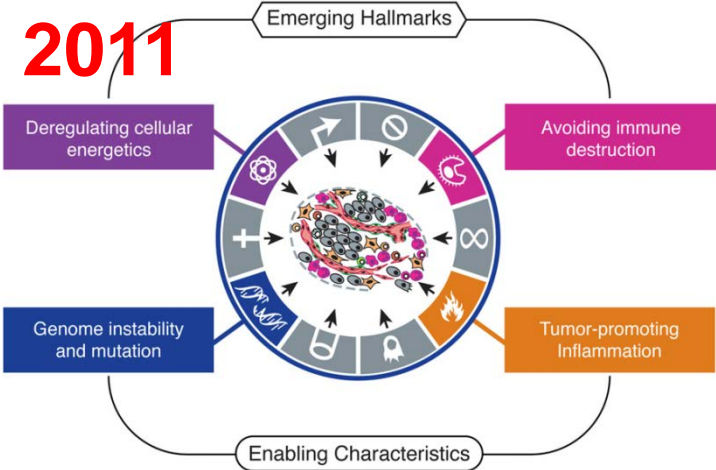
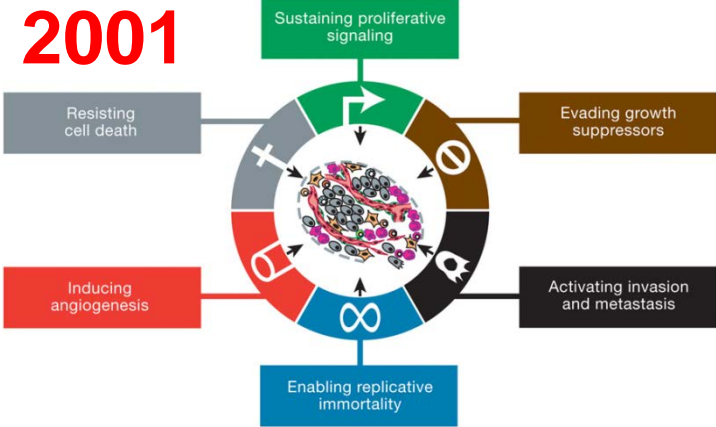
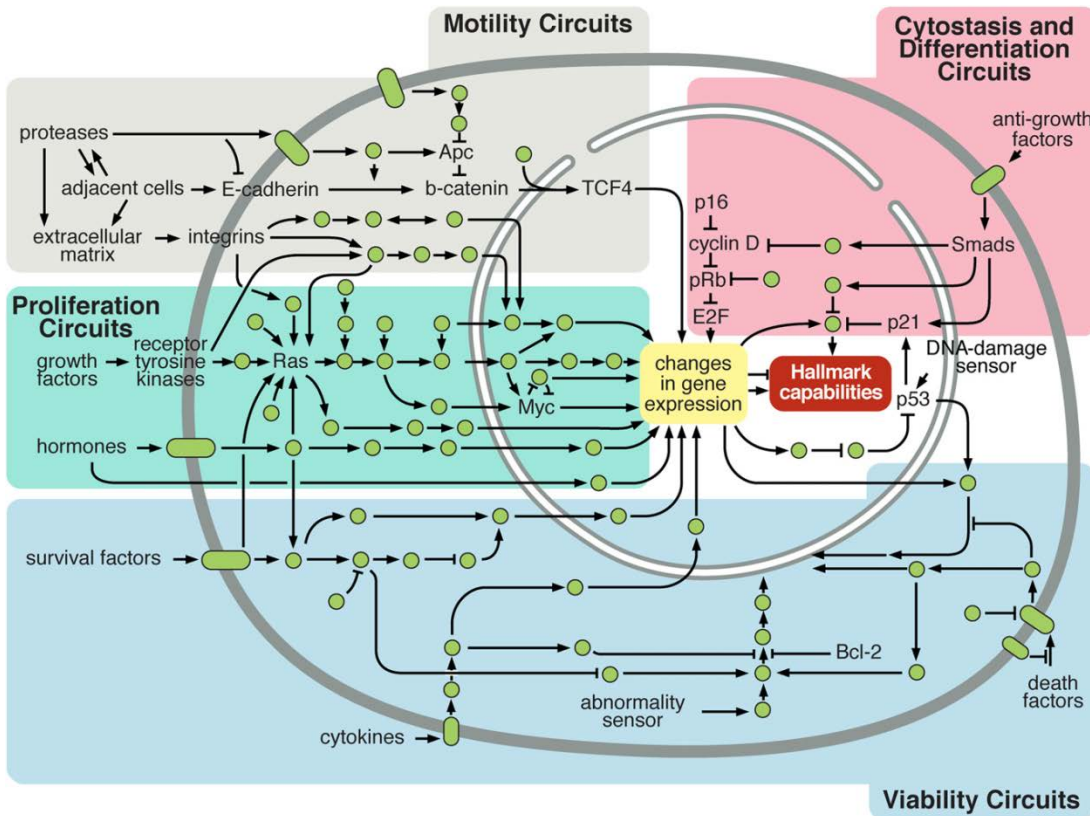
Lastnosti raka



Lastnosti raka



Lastnosti raka

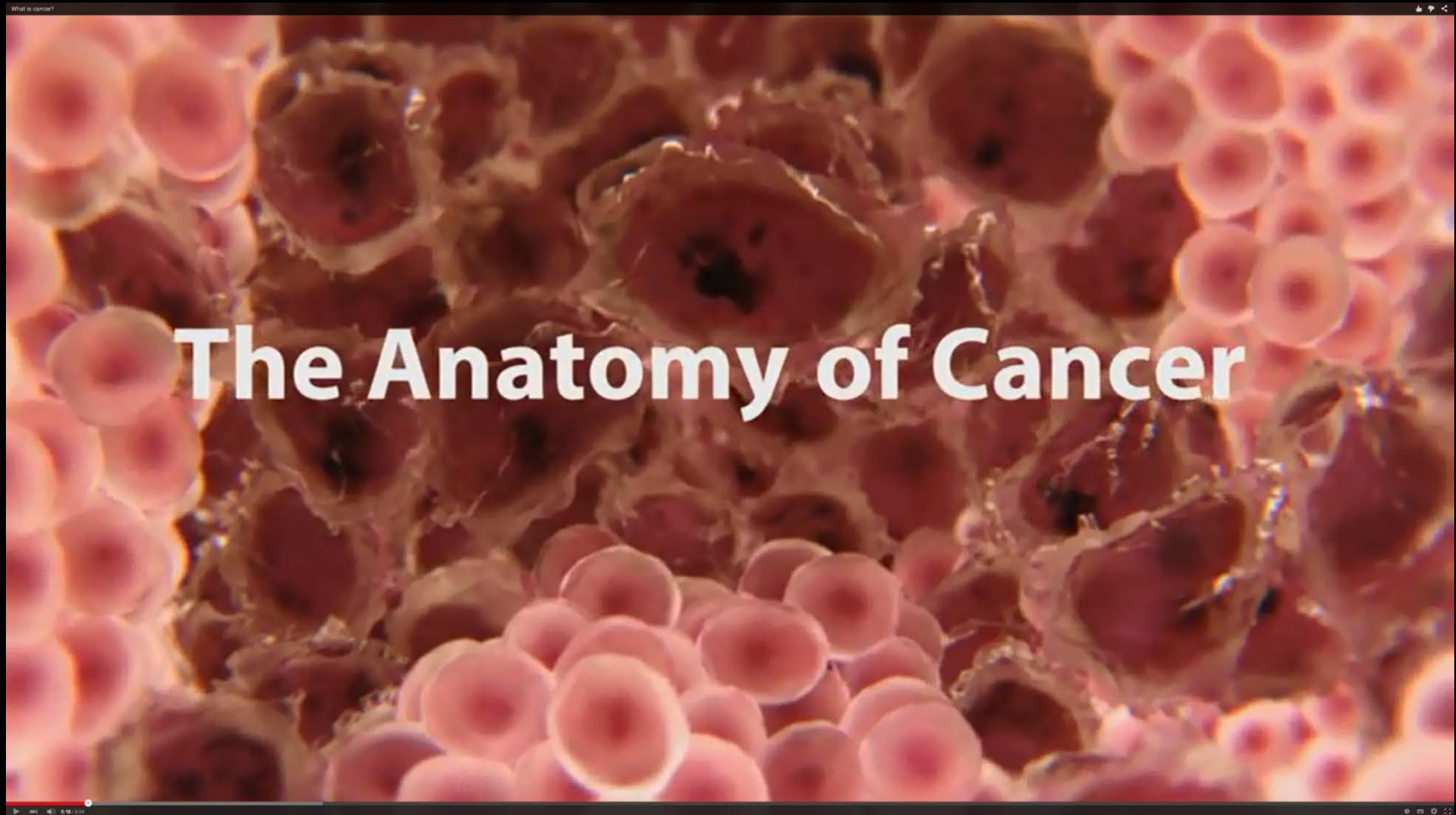


What is cancer?



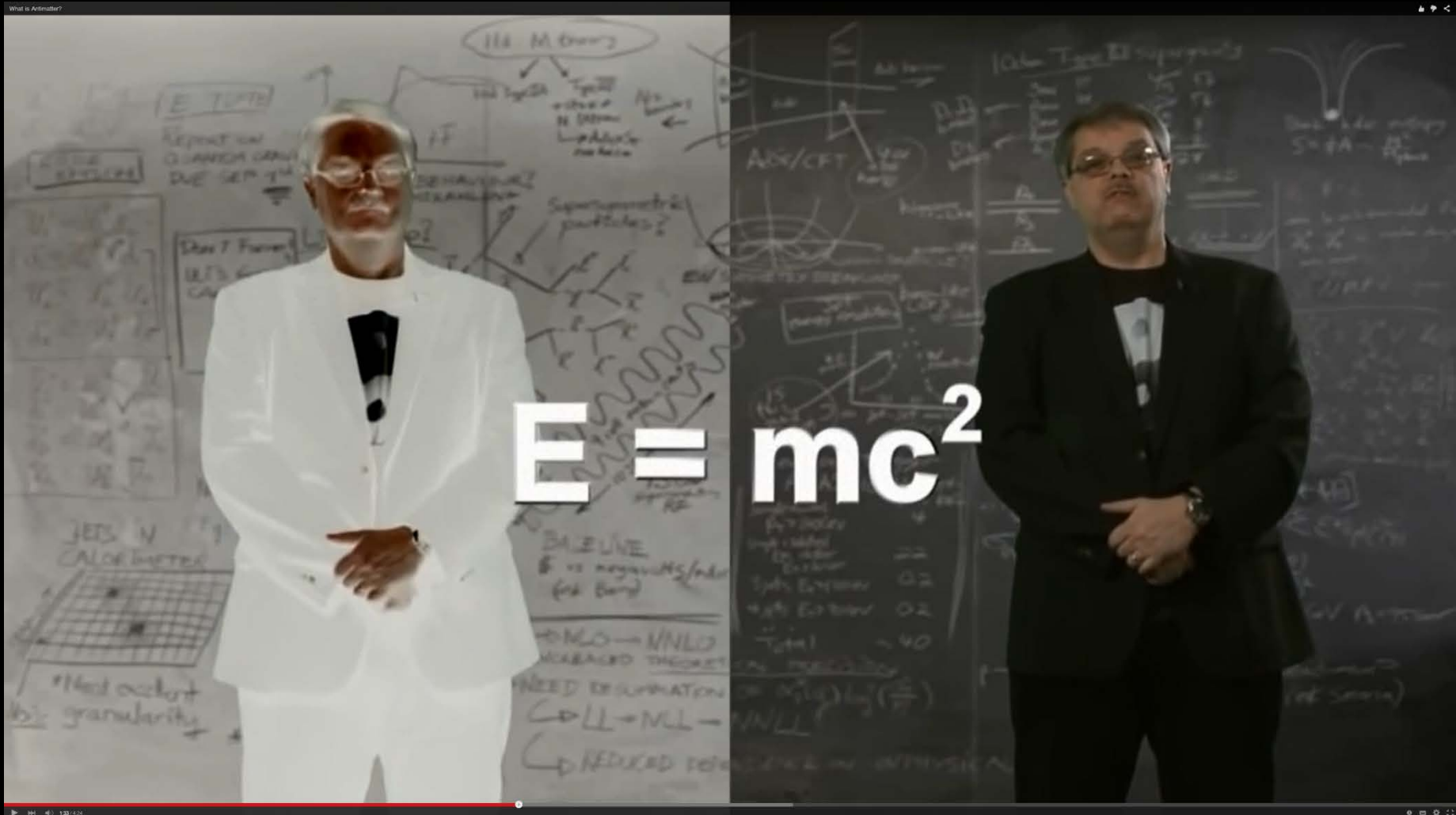
<https://www.youtube.com/watch?v=Qja4z1HGDQo>

What is cancer?

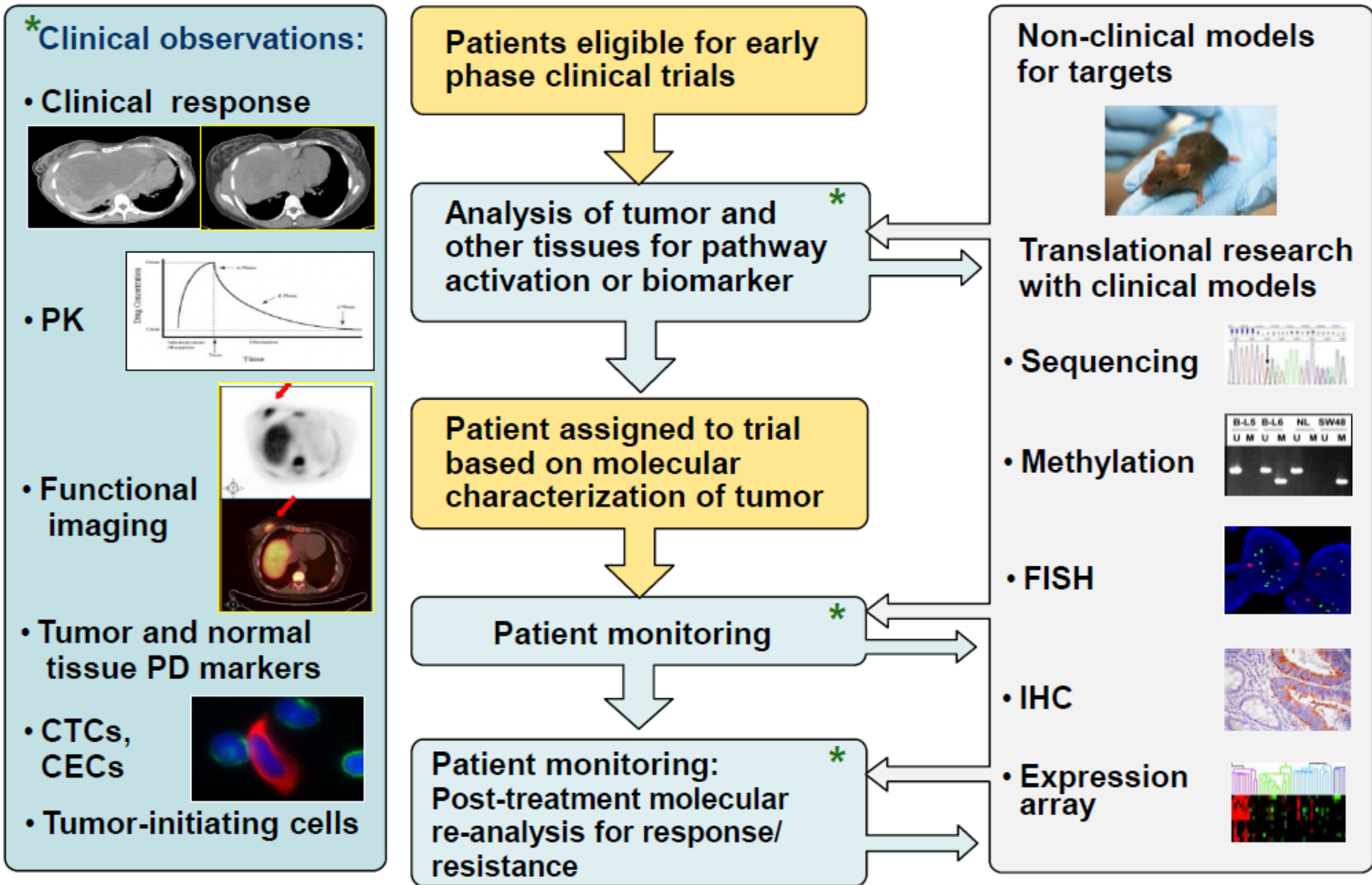


https://www.youtube.com/watch?v=SGaQ0WwZ_0I

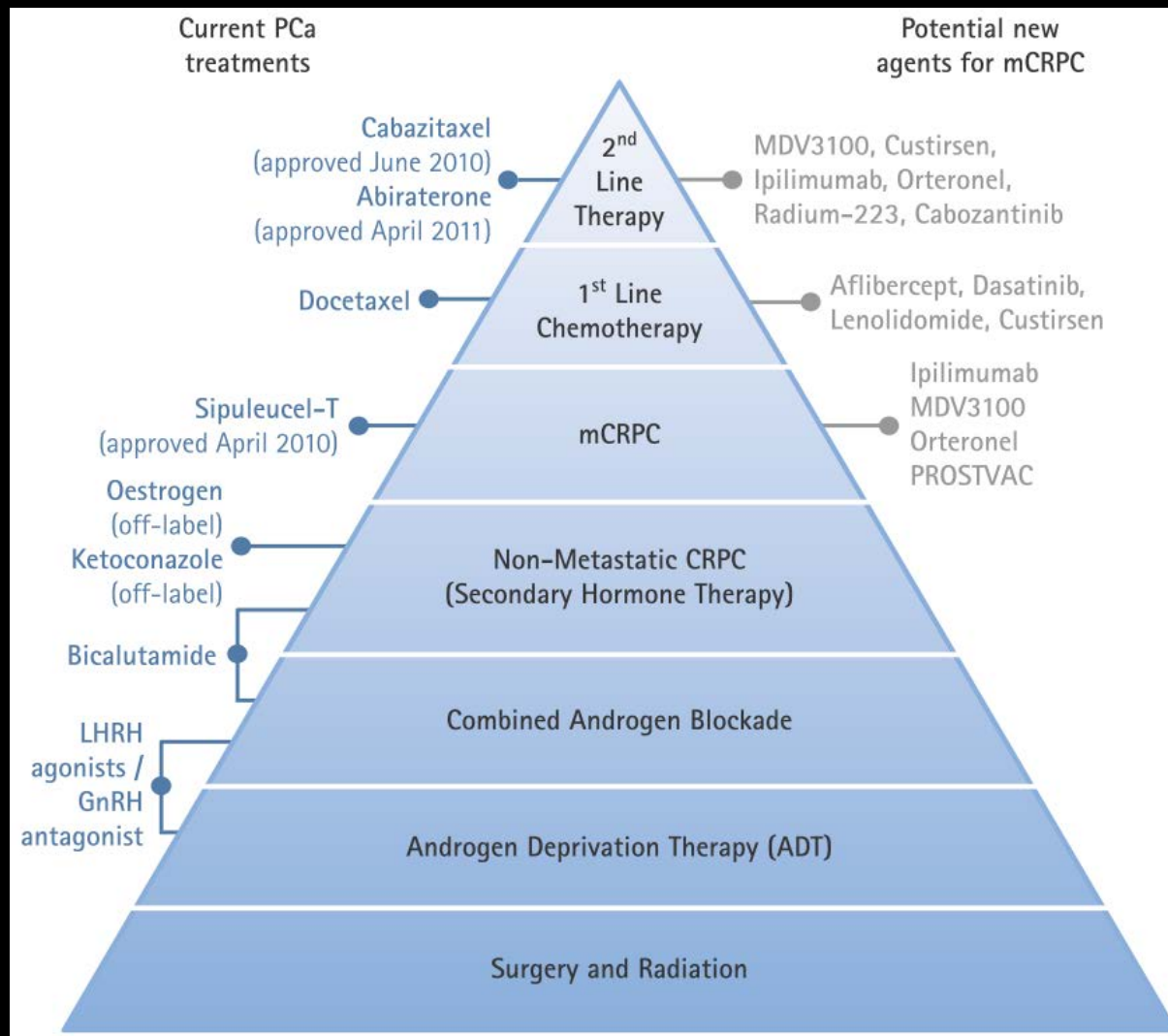
Really cool stuff...



Clinical Translational Research and Cancer Biology: Bedside to Bench and Back



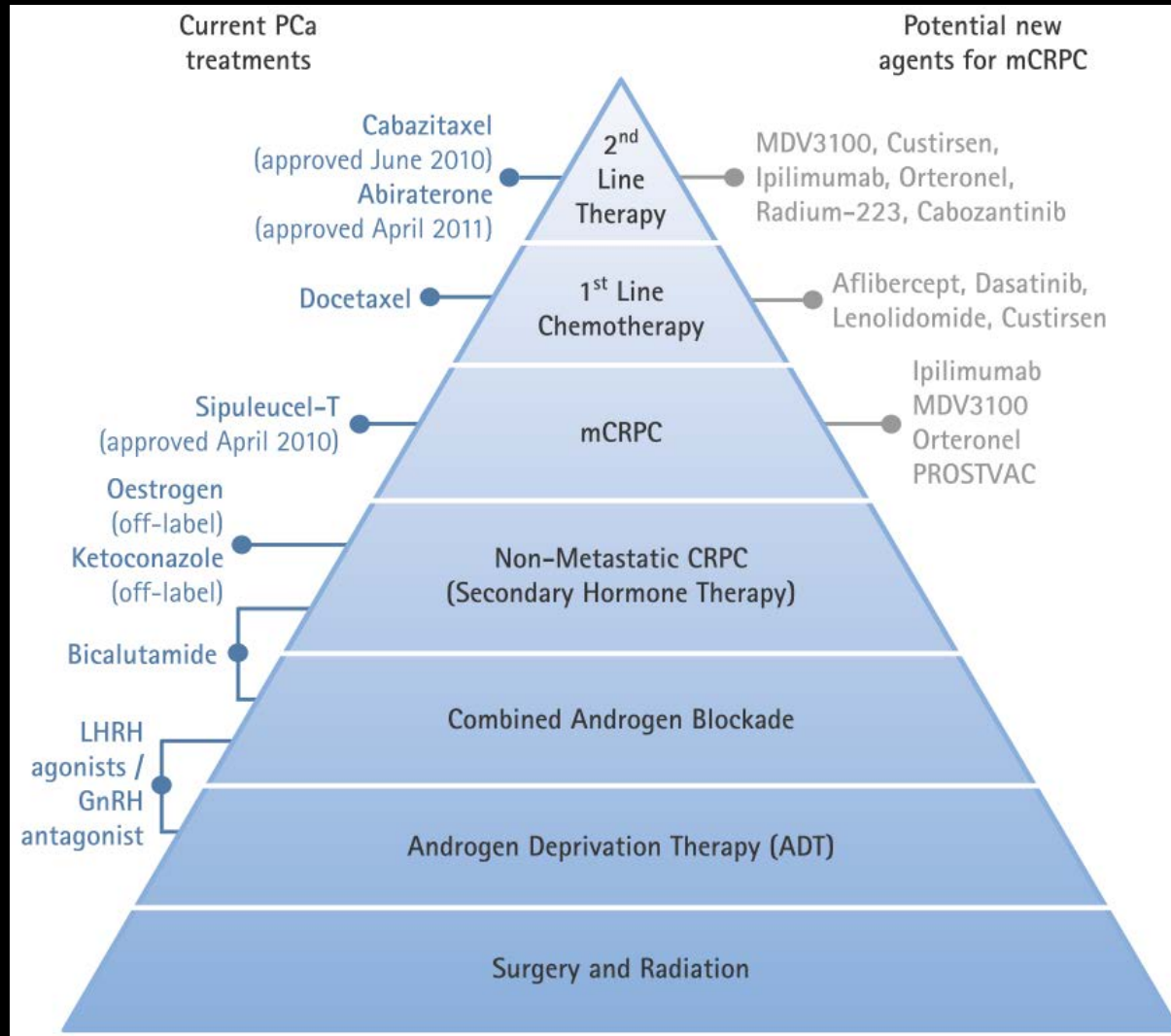
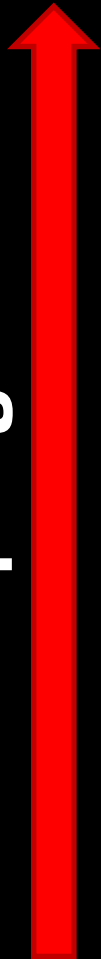
What is the major problem today?



What is the major problem today?



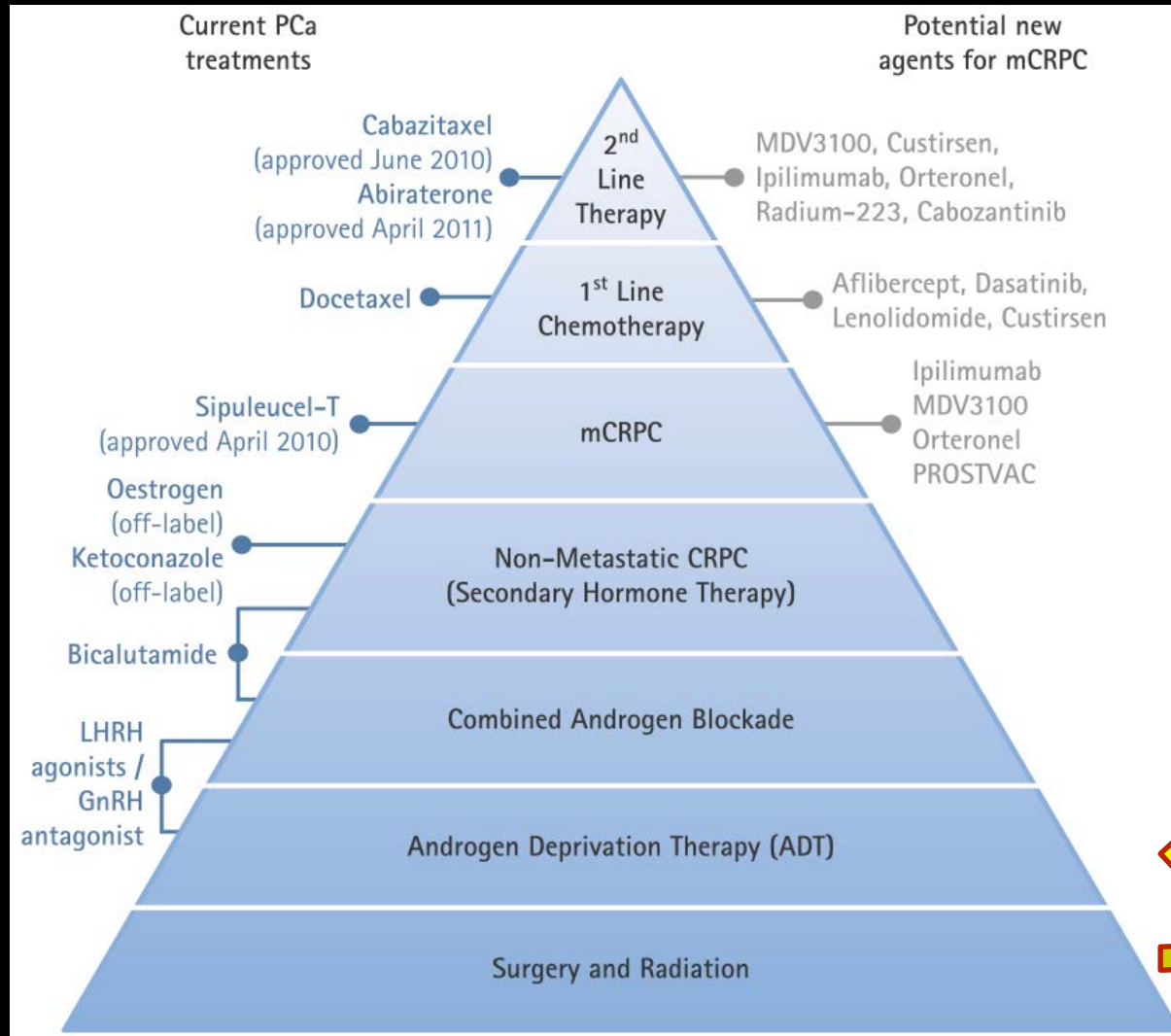
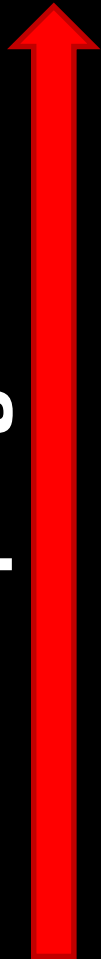
Disease progression



What is the major problem today?



Disease progression

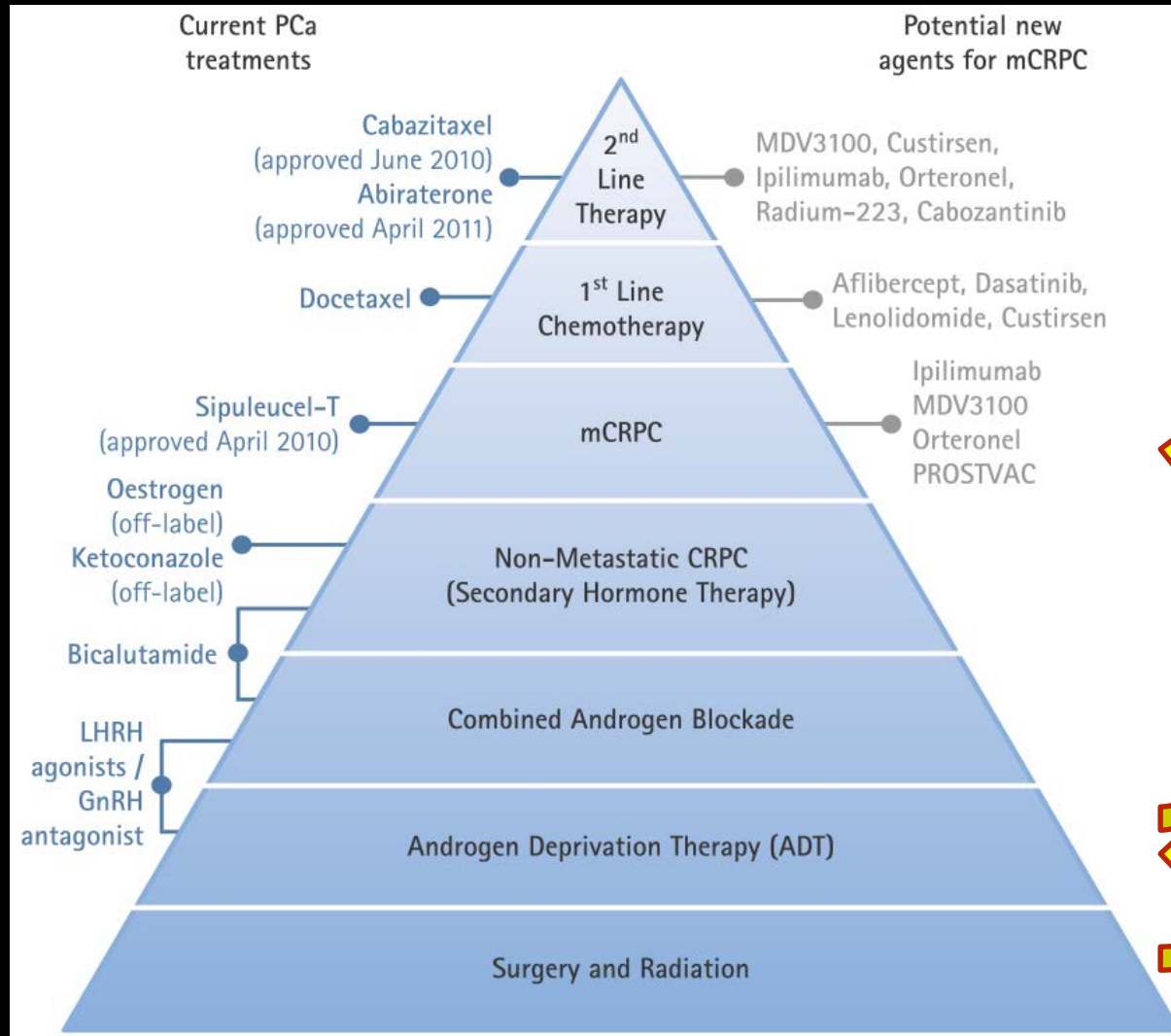
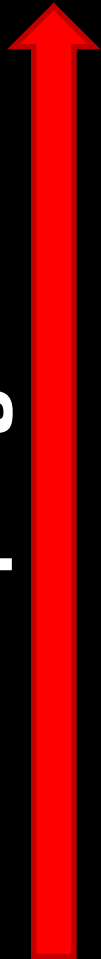


~10 yrs

What is the major problem today?



Disease progression



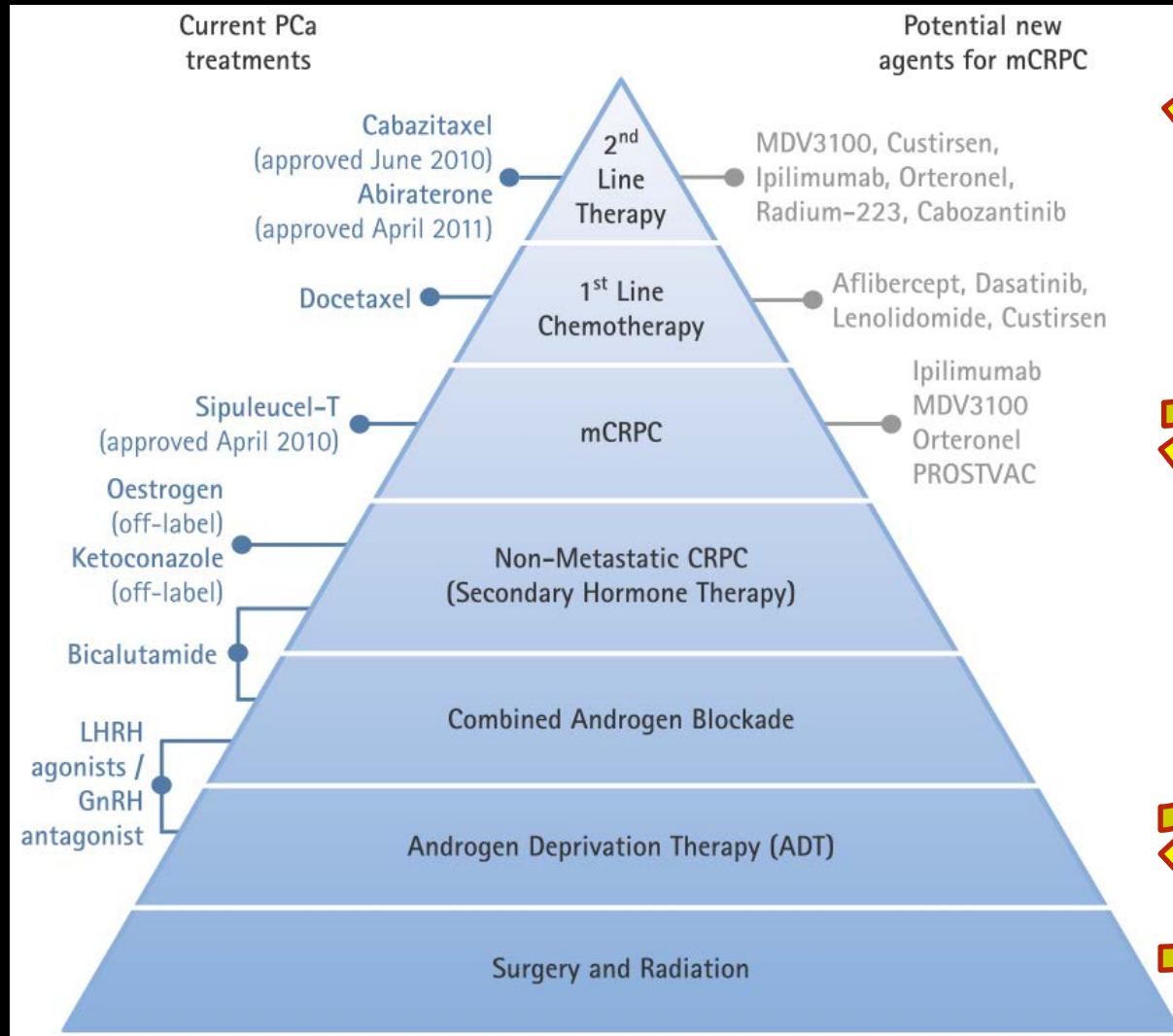
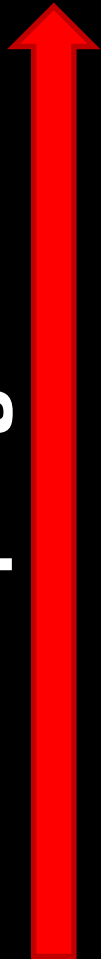
~2-5 yrs

~10 yrs

What is the major problem today?



Disease progression



~1-2 yrs

~2-5 yrs

~10 yrs

Oncology drug development



- For every **1,000 compounds in pre-clinical** development, only **1 compound** may enter **clinical trials**
- For every **10 drugs in clinical trials**, only **1 drug** may lead to **FDA approval**
- Average drug development costs to yield one FDA approved agent is **\$802 million**
 - **Annual cost increase** of **7.4%** above inflation

Where is medicine going?



"4 P's of medicine": Individuals respond differently to environmental conditions, according to their genetic endowment and their own behavior. In the future, research will allow us to **predict** how, when, and in whom a disease will develop. We can envision a time when we will be able to precisely target treatment on a **personalized** basis to those who need it, avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to **preempt** disease before it occurs, utilizing the **participation** of individuals, communities, and healthcare providers in a proactive fashion, as early as possible, and throughout the natural cycle of a disease process.

Elias A. Zerhouni, M.D.

Director, National Institutes of Health (NIH), 2008

Where is medicine going?

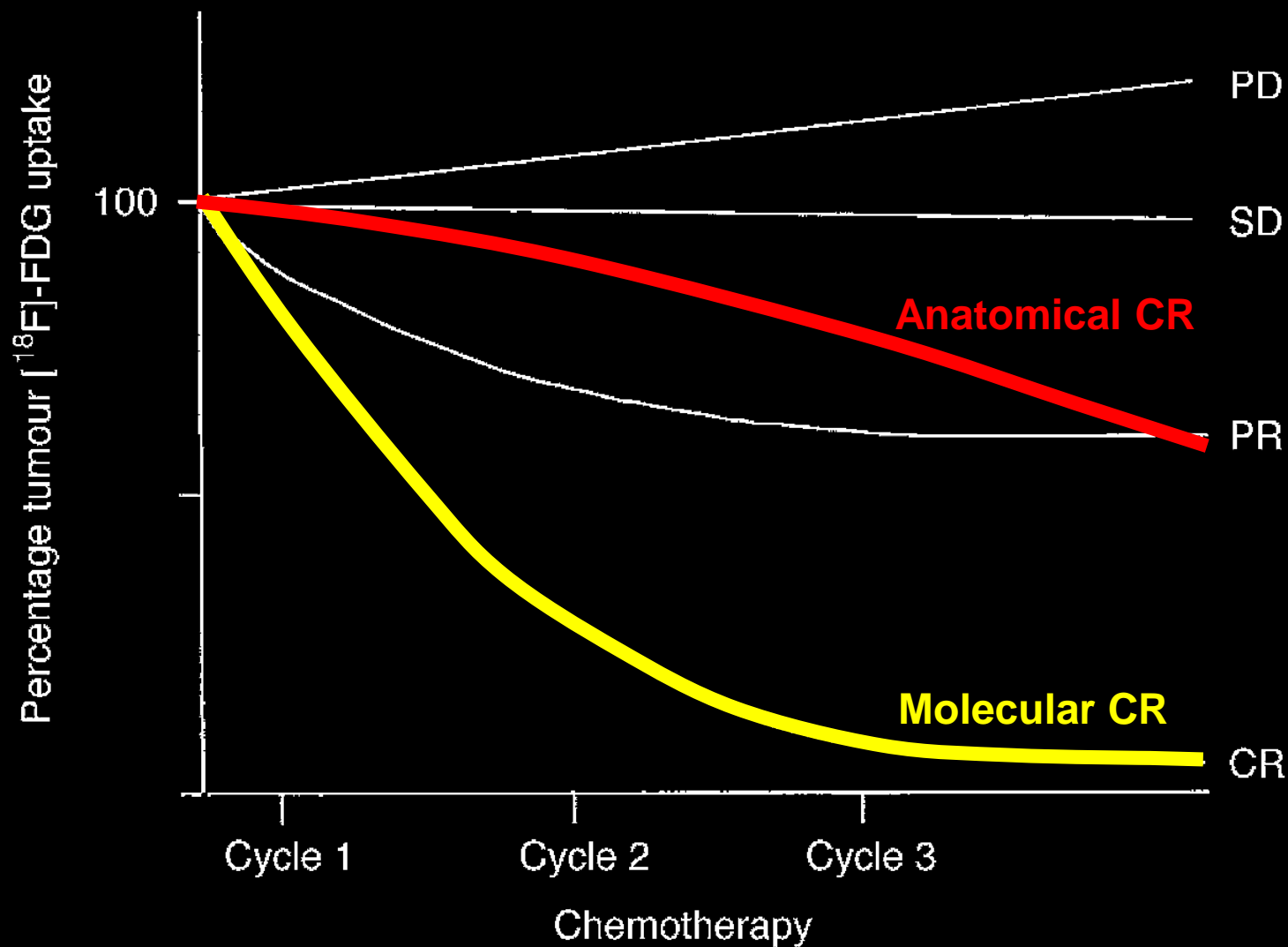


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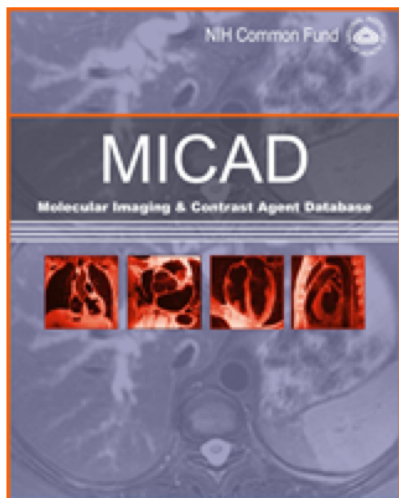
Elias A. Zerhouni, M.D.

Director, National Institutes of Health (NIH), 2008

Anatomsko in molekularno slikanje



Veliko število agentov



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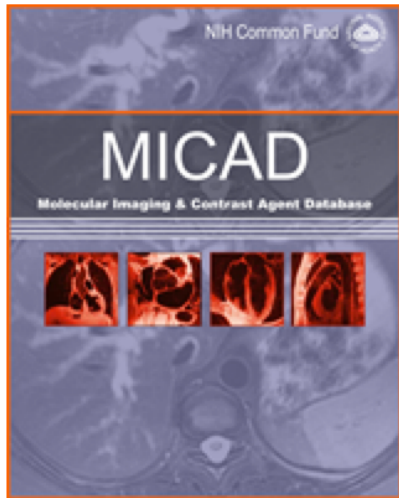
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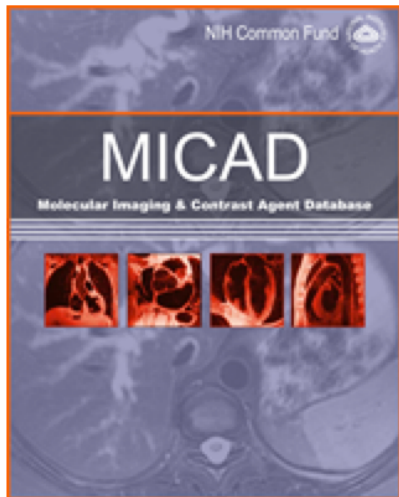
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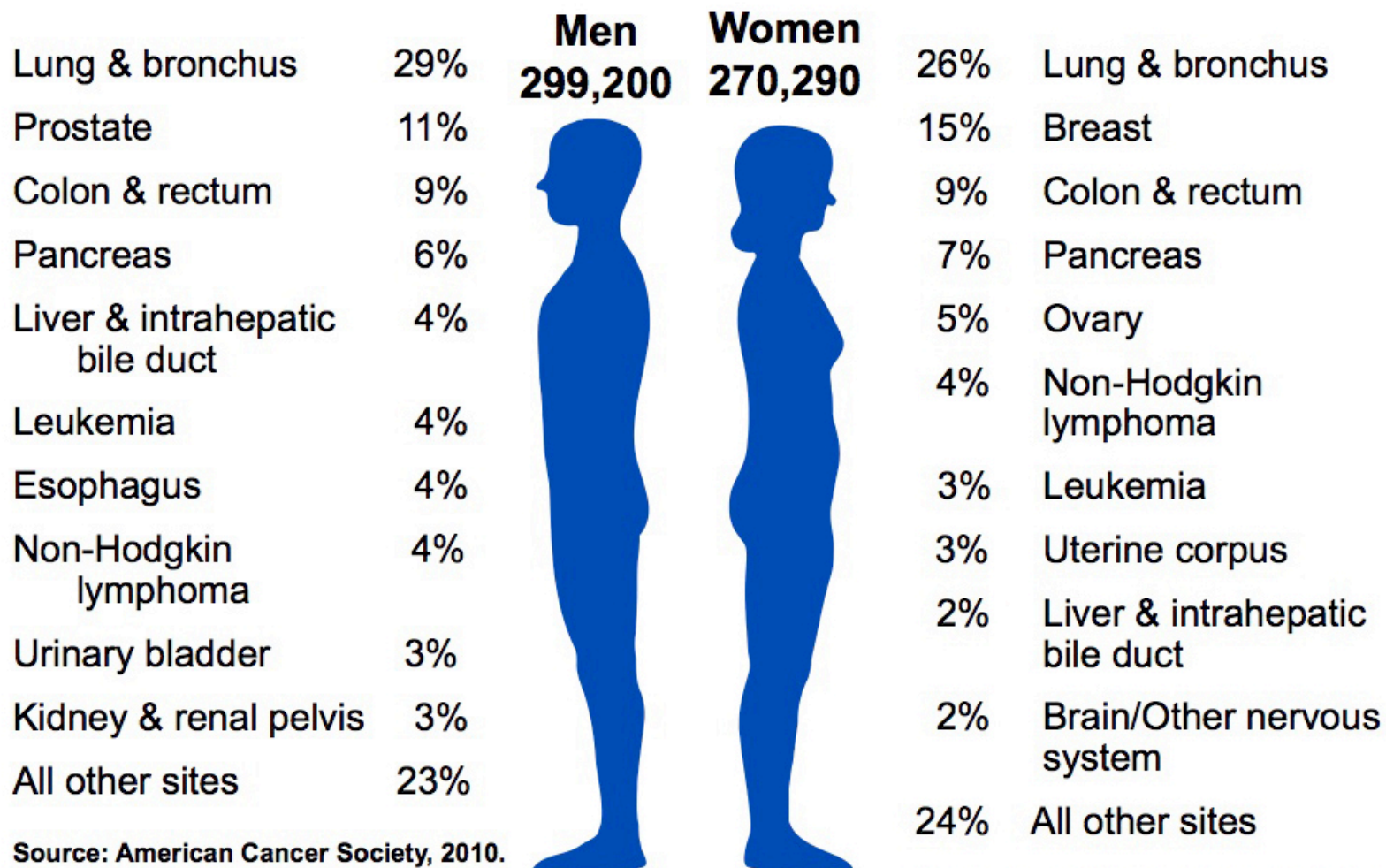
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FDA odobrenih: 241 skupaj, 119 aktivnih

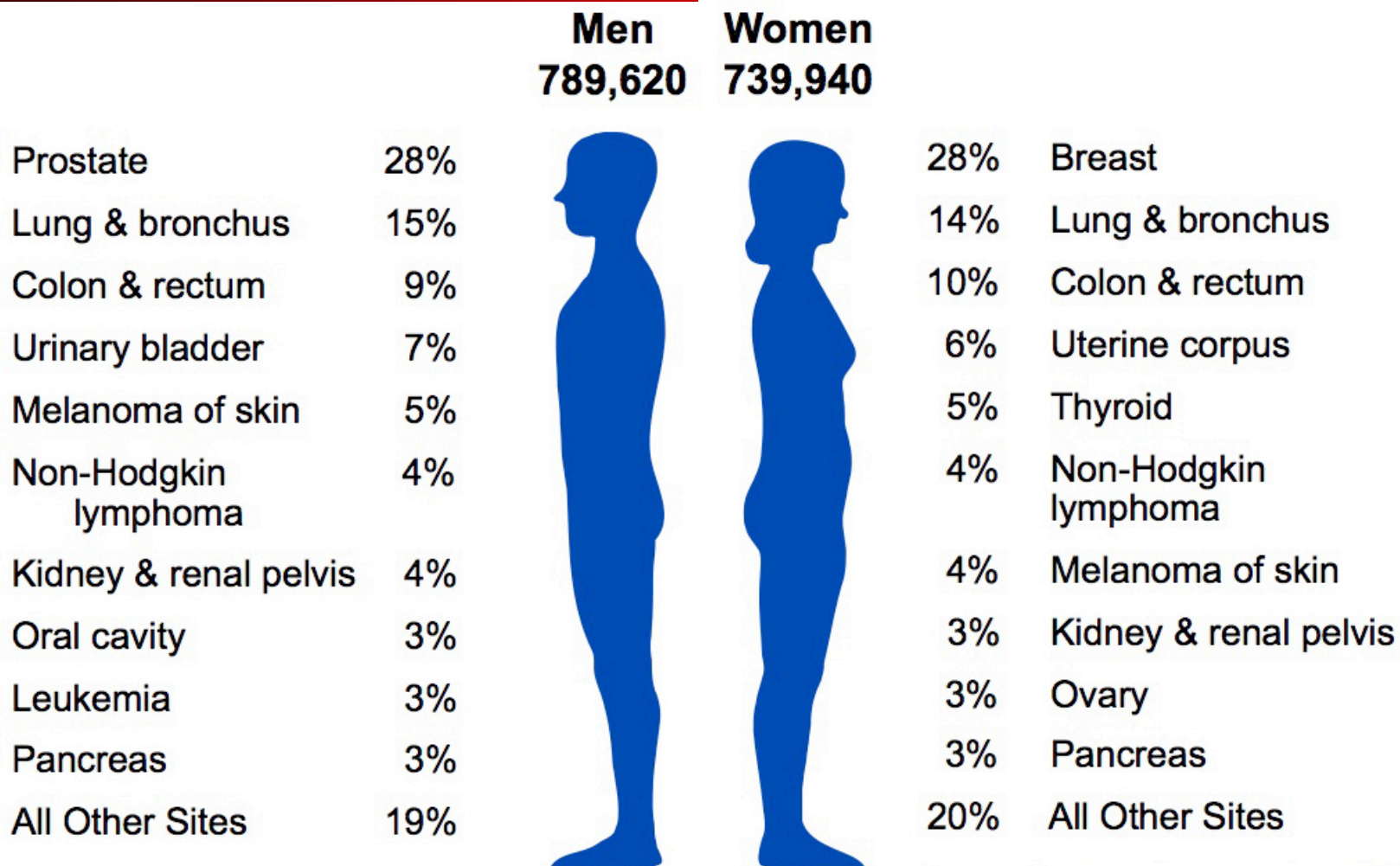
2010 Estimated US Cancer Deaths*



Source: American Cancer Society, 2010.

Source: American Cancer Society, 2010.

2010 Estimated US Cancer Cases*

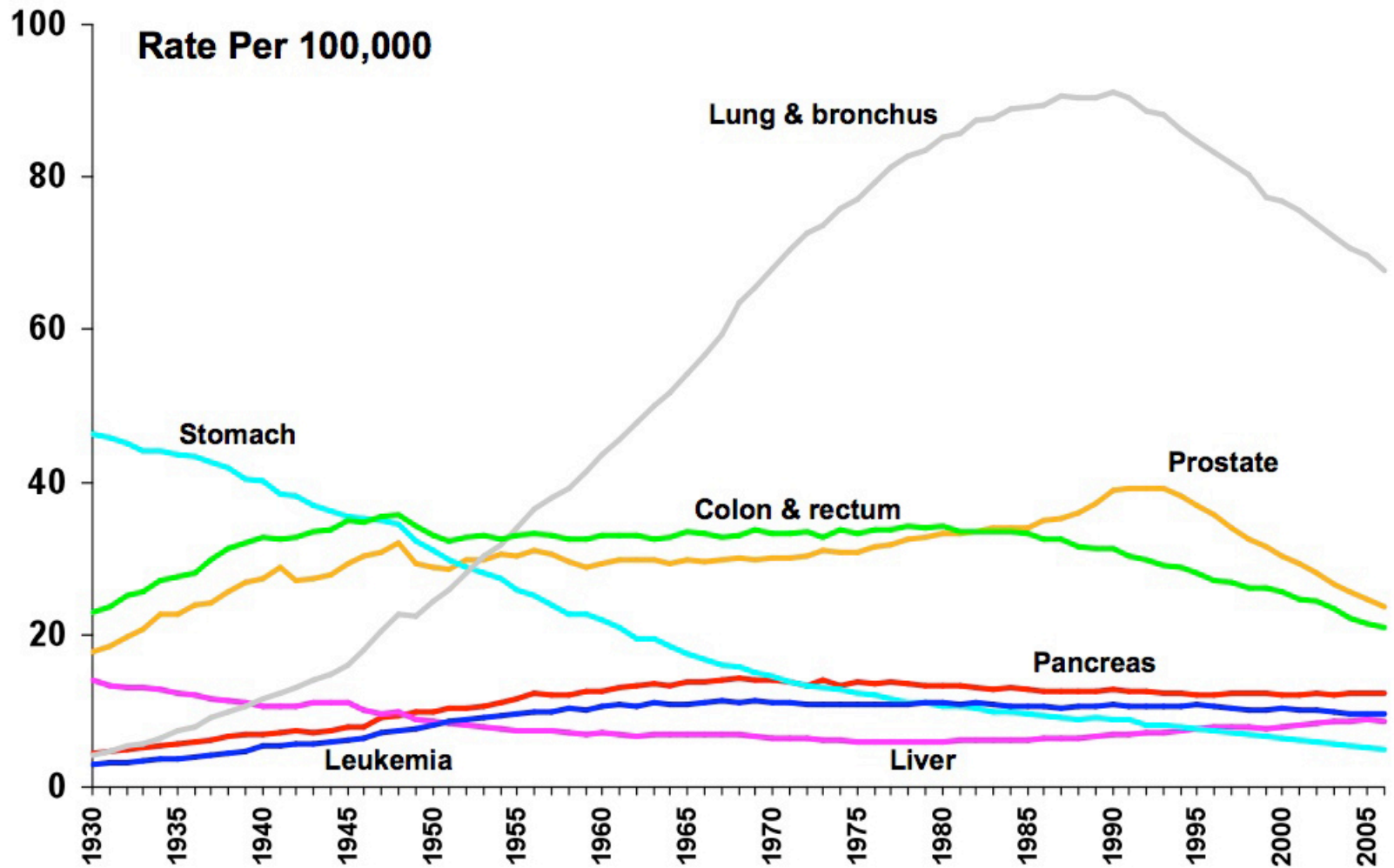


Source: American Cancer Society, 2010.

Source: American Cancer Society, 2010.

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

Cancer Death Rates* Among Men, US, 1930-2006

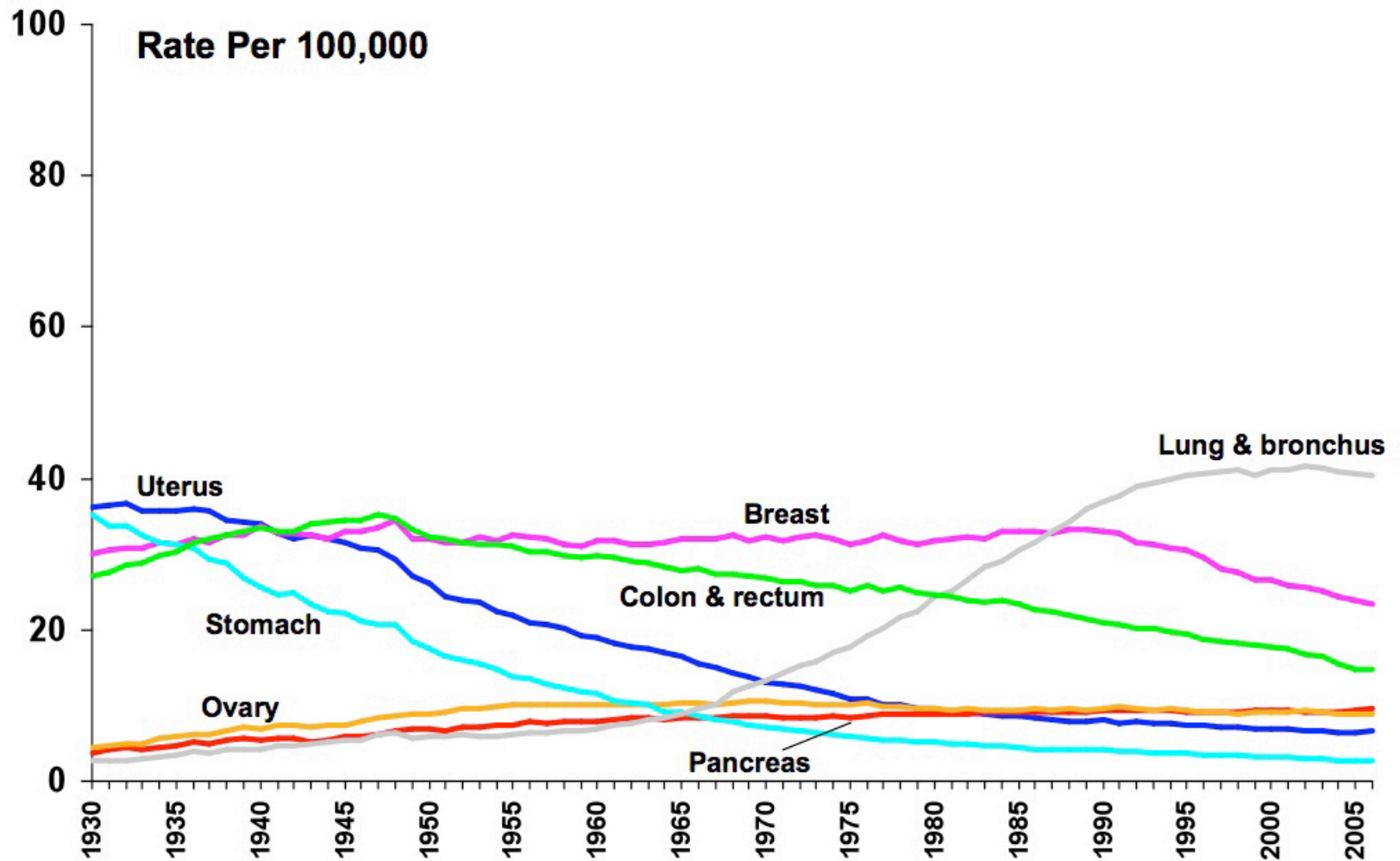


*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,

National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Cancer Death Rates* Among Women, US, 1930-2006



*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,

National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Trends in Five-year Relative Survival (%)* Rates, US, 1975-2005

Site	1975-1977	1984-1986	1999-2005
All sites	50	54	68
Breast (female)	75	79	90
Colon	52	59	66
Leukemia	35	42	54
Lung and bronchus	13	13	16
Melanoma	82	87	93
Non-Hodgkin lymphoma	48	53	69
Ovary	37	40	46
Pancreas	3	3	6
Prostate	69	76	100
Rectum	49	57	69
Urinary bladder	74	78	82

*5-year relative survival rates based on follow up of patients through 2006.

Source: Surveillance, Epidemiology, and End Results Program, 1975-2006, Division of Cancer Control and Population Sciences, National Cancer Institute, 2009.