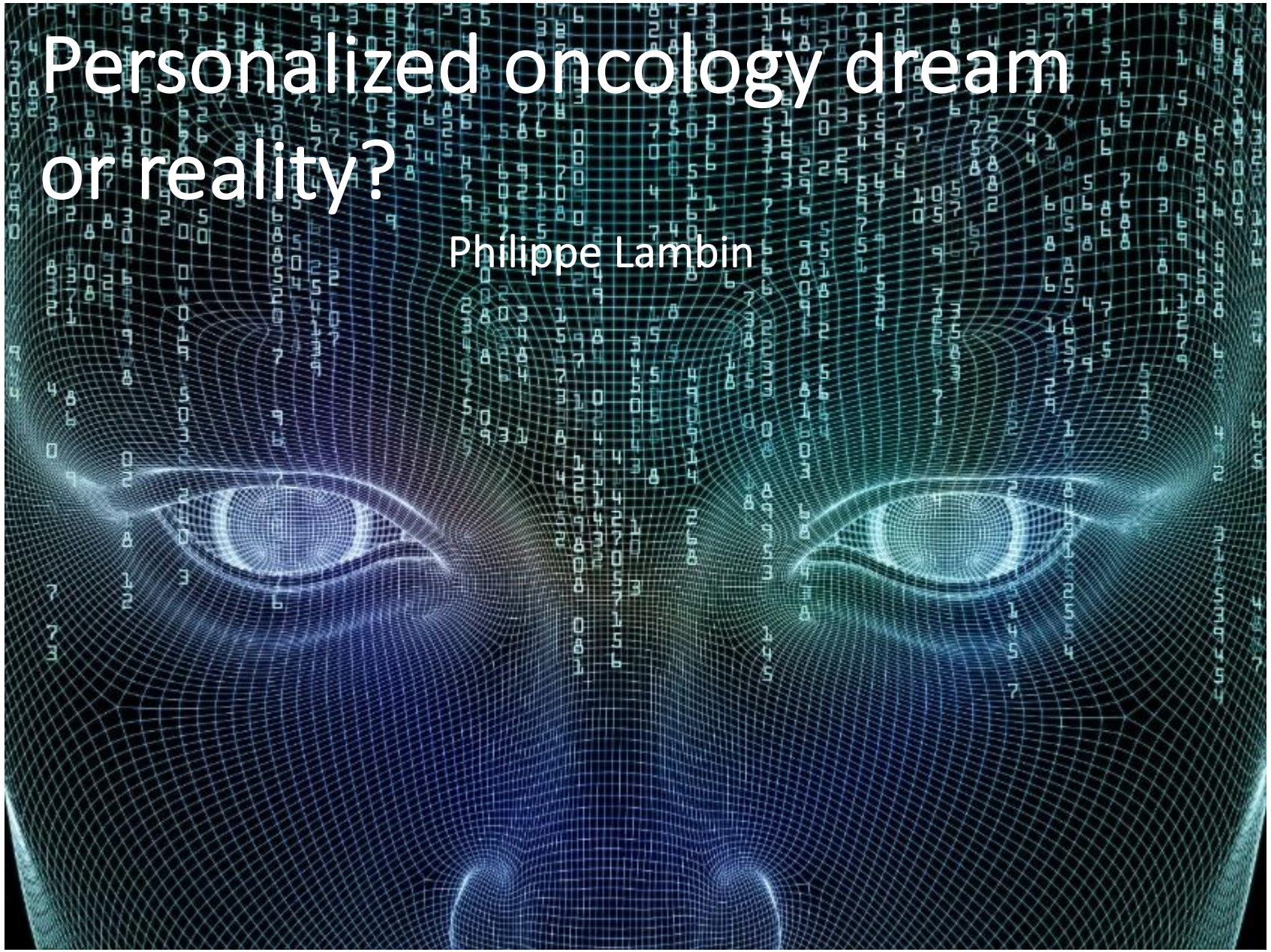
Personalized oncology dream or reality?

Philippe Lambin



precision medicine

Maastricht University

Disclosures

Academic position: 80% - Free lance entrepreneur: 20%

1. **Inventor: Licensed patents**: Two patents on radiomics (PCT/NL2014/050248, PCT/NL2014/050728) licensed to Oncoradiomics, patent on mtDNA (PCT/EP2014/059089) licensed to ptTheragnostic/DNAmito & **non-patentable invention (softwares)** licensed to ptTheragnostic/DNAmito, Oncoradiomics and Health Innovation Ventures.
2. **Share holder & co-founder:** "Radiomics SA" (ex-Oncoradiomics SA), Convert pharmaceuticals SA, LivingMed Biotech and Comunicare
3. **Consulting/Speaker fees - Travel reimbursements**: Merck, Oncoradiomics, BHV, Varian, Elekta

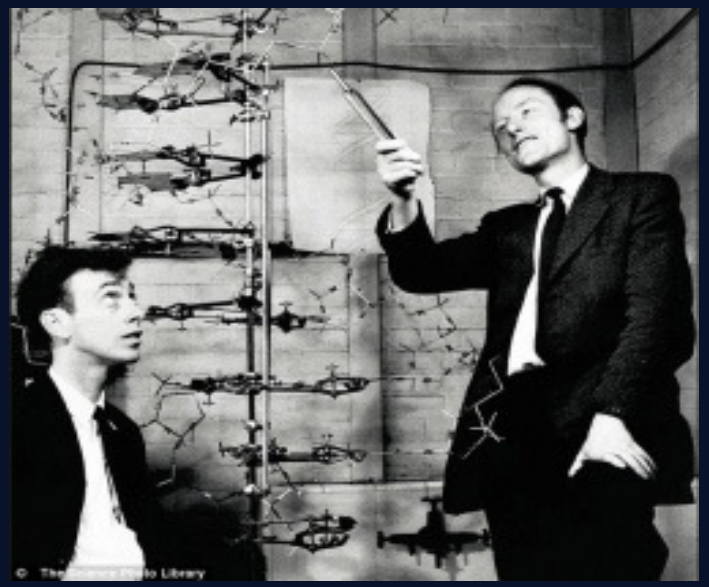
“Progress in science depends on new *techniques*, new *discoveries* and new *ideas*, probably in that order”.

Sidney Brenner, Nobel Laureate 2002

The First Revolution

Molecular and Cellular Biology

DNA Discovered



Nobel Prize

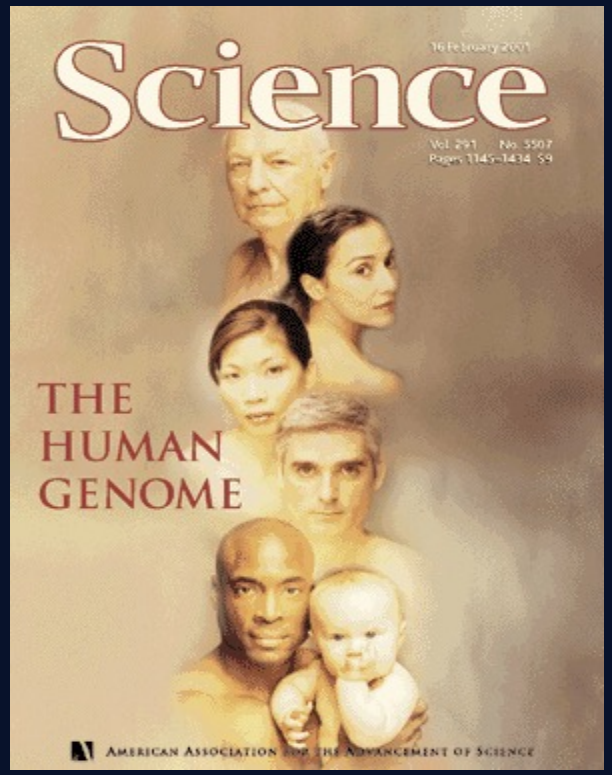
1950 **1953** **1962**

Modified from MIT: The Third Revolution: The Convergence of Life Sciences Physical Sciences and Engineering

The Second Revolution

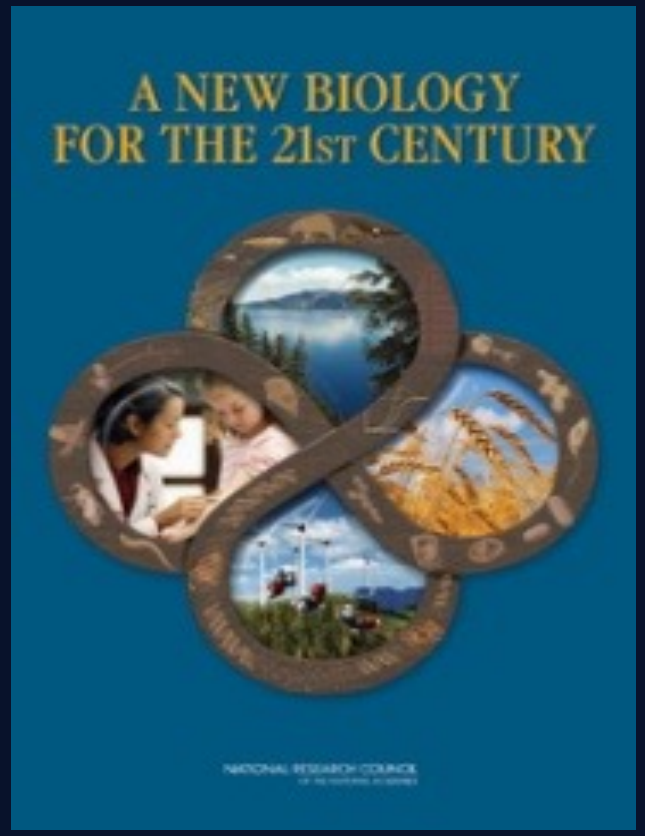
Genomics

Human Genome Project
Working draft of human genome



mid 1970's

2001



The Third Revolution

Convergence

Life Science, Physical Science and Engineering

NAS releases: ‘A New Biology’ report

2003 **2009**

The Fourth Revolution

Digital-Cognitive

Precision Medicine - AI

2005

2015

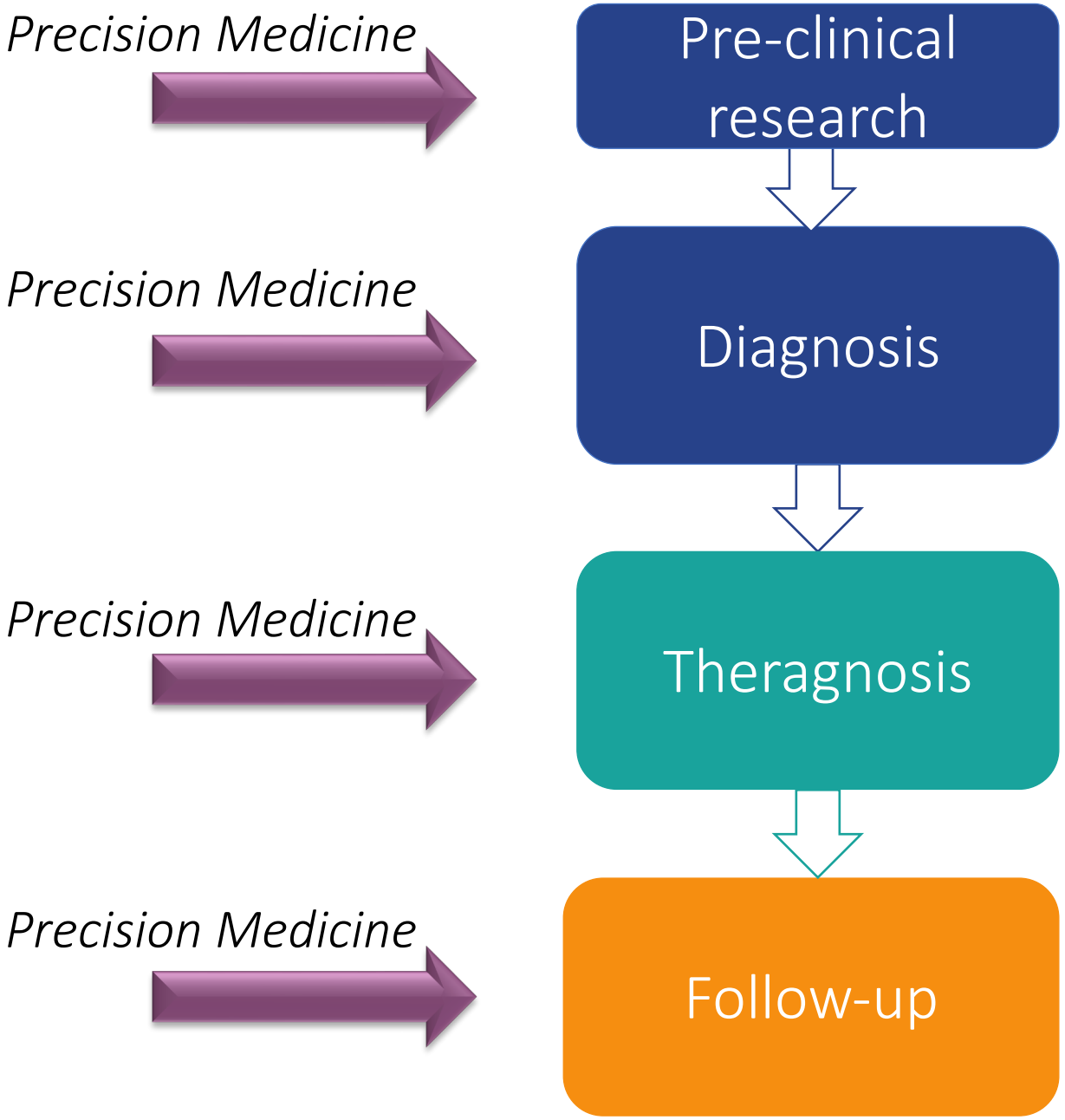
These 4 revolutions prepared the ground for the emergence of precision medicine

Personalized or Precision Medicine?

- There is a lot of overlap between the terms "precision medicine" and "personalized medicine."
- According to the National Research Council, "personalized medicine" is an ***older*** term with a meaning similar to "precision medicine."

What is Precision Medicine?

In precision medicine, the focus is on ***identifying which approaches (preventive, diagnostic, therapeutic, follow-up…) will be effective*** for which patients based on clinical, genetic, environmental, preferences and lifestyle factors.



What is the diagnosis?

Is there a cancer?
Where is the tumour(s)?
Are the nodes positive?

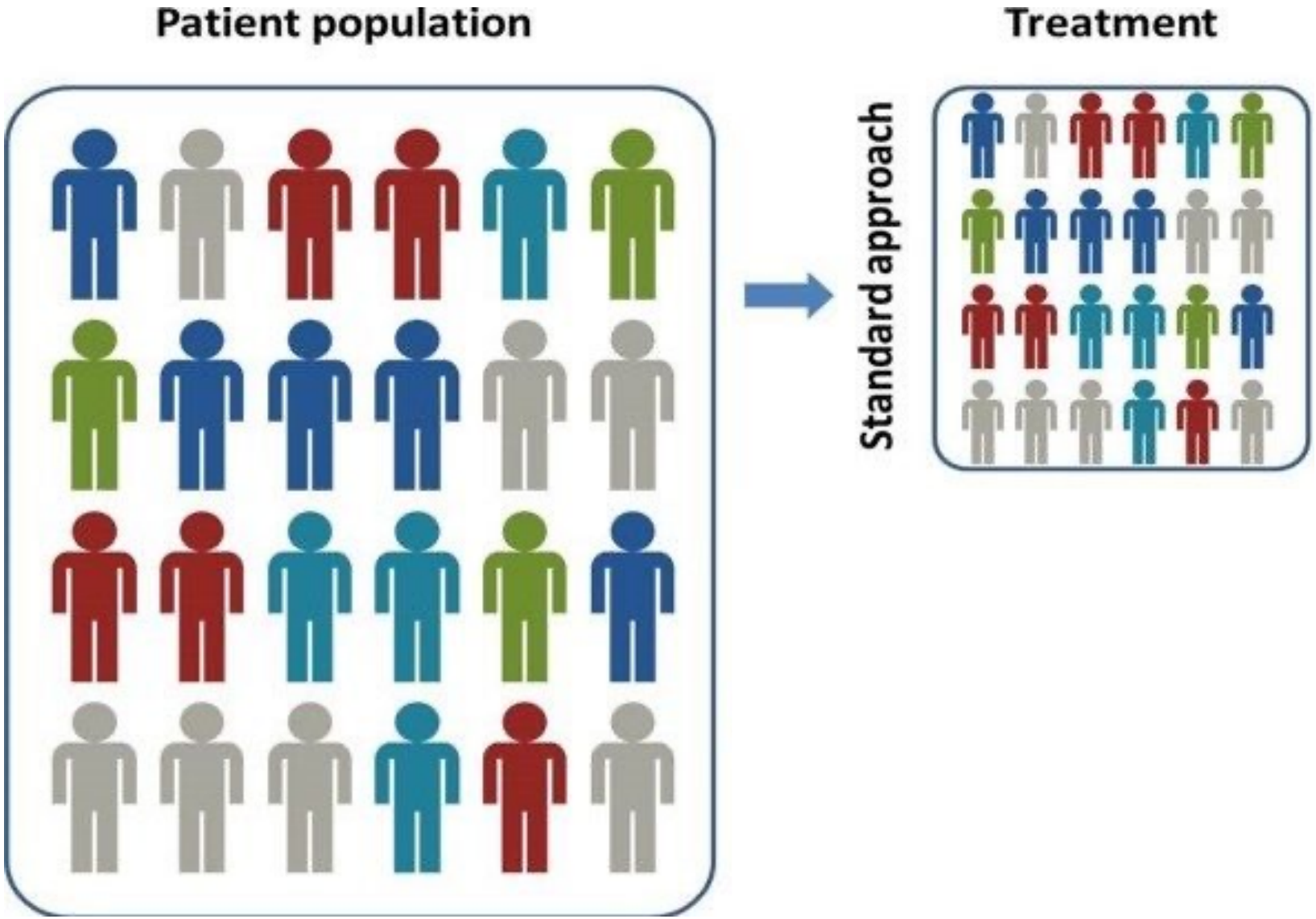
How to treat?

How to target the tumour?
How aggressive is the tumour?
Is the tumour hypoxic?

What is the response?

Is the treatment effecting the tumour?
Is the effect durable?
Is the response complete, partial, stable, or progressive?

Precision medicine

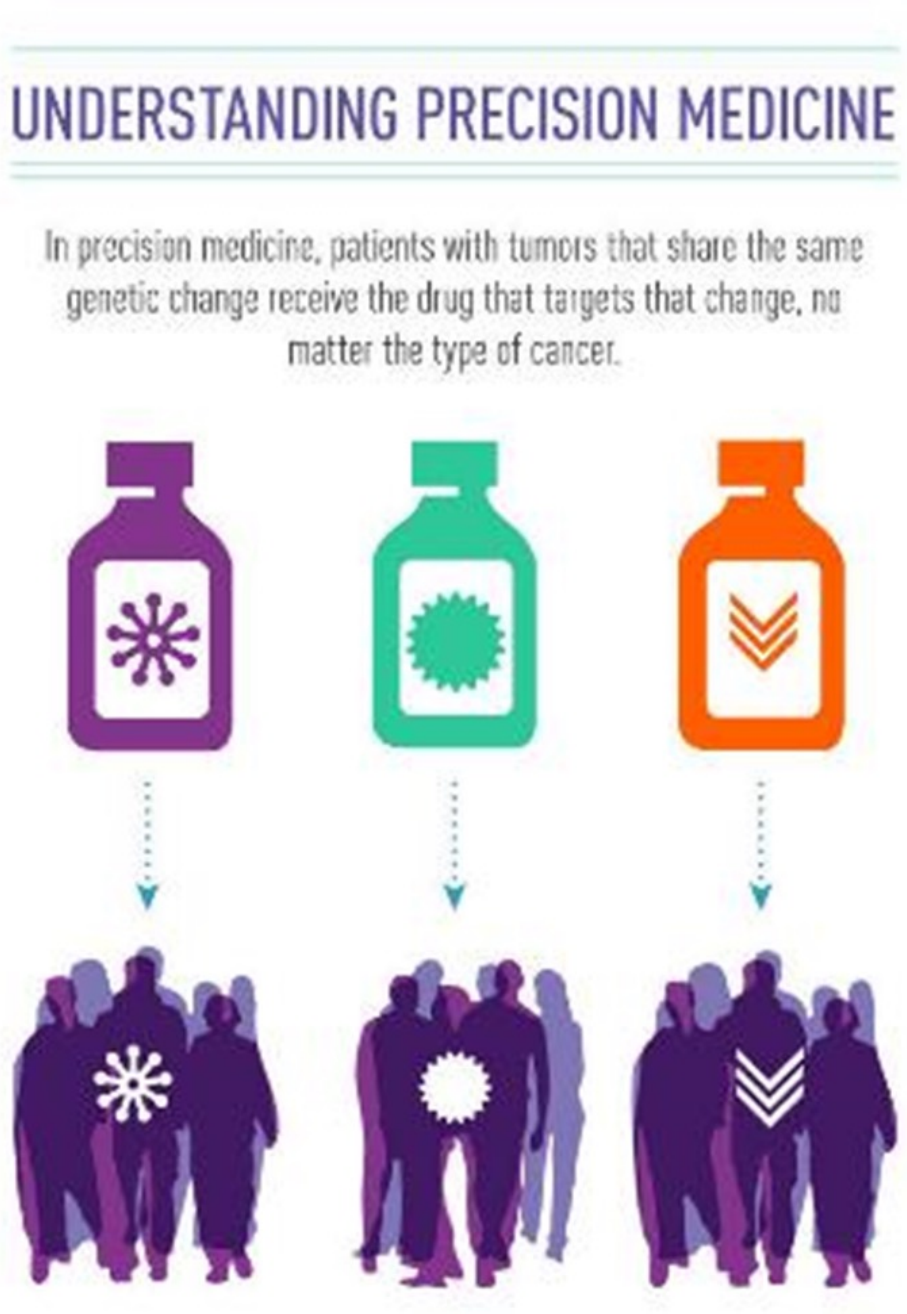


Type of disease

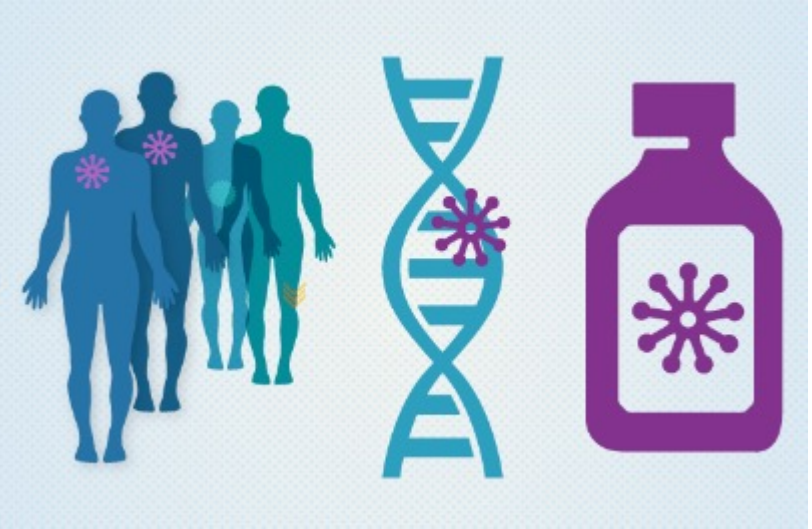
- Breast cancer
- Prostate cancer

A disease-agnostic Approach

Same treatment for different cancer type



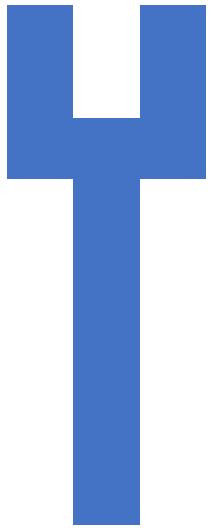
The example of Precision Medicine in Oncology



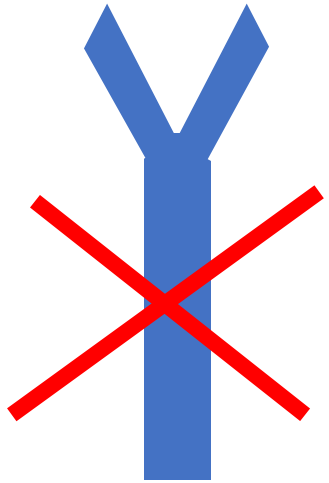
Targeted therapy is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread.

Most targeted therapies are either ***small-molecule drugs*** or ***monoclonal antibodies***.

Drug
x



EGFR receptor “wild-type” (= normal)



EGFR not active

EGFR receptor “mutated”

Biomarkers testing before targeted therapies

Biomarker testing (also called tumor testing, tumor profiling, or tumor genetic testing) finds changes in your cancer that could help you and your doctor choose your cancer treatment.

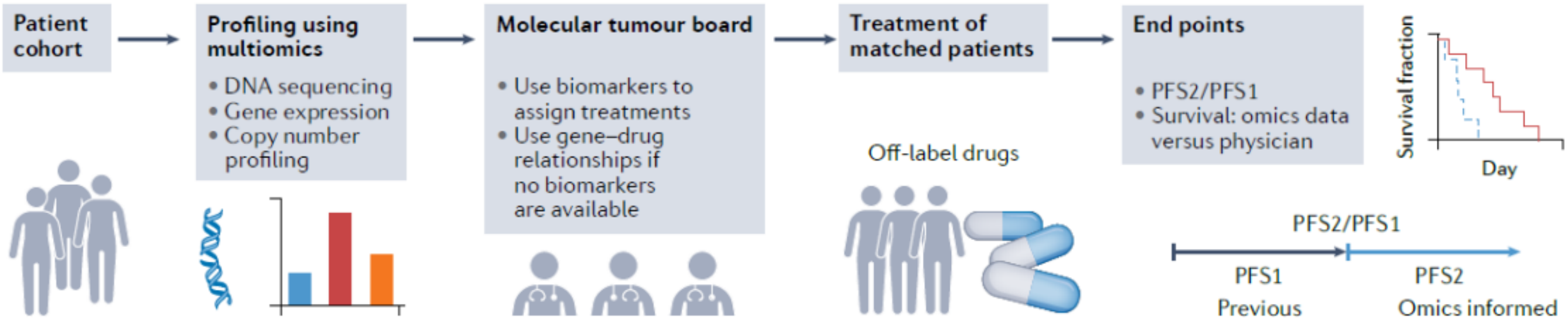
Credit: Darryl Leja, NHGRI

Largest cancer centers: All patients have whole genome sequencing to detect actionable mutations

Example: Targeted therapy approved for lung cancer

- afatinib dimaleate (Gilotrif)
- alectinib (Alecensa)
- amivantamab-vmjw (Rybrevant)
- atezolizumab (Tecentriq)
- bevacizumab (Avastin)
- brigatinib (Alunbrig)
- capmatinib hydrochloride (Tabrecta)
- cemiplimab-rwlc (Libtayo)
- ceritinib (Zykadia)
- crizotinib (Xalkori)
- dabrafenib mesylate (Tafinlar)
- dacomitinib (Vizimpro)
- durvalumab (Imfinzi)
- entrectinib (Rozlytrek)
- erlotinib hydrochloride (Tarceva)
- fam-trastuzumab deruxtecan-nxki (Enhertu)
- gefitinib (Iressa),
- gefitinib (Iressa),
- ipilimumab (Yervoy)
- lorlatinib (Lorbrena)
- mobocertinib succinate (Exkivity)
- necitumumab (Portrazza)
- nivolumab (Opdivo)
- osimertinib mesylate (Tagrisso)
- pembrolizumab (Keytruda)
- pralsetinib (Gavreto)
- ramucirumab (Cyramza)
- selpercatinib (Retevmo)
- sotorasib (Lumakras)
- tepotinib hydrochloride (Tepmetko)
- trametinib dimethyl sulfoxide (Mekinist)

Prospective clinical studies guided by omics data: *Umbrella trials, basket trials, platform trials*



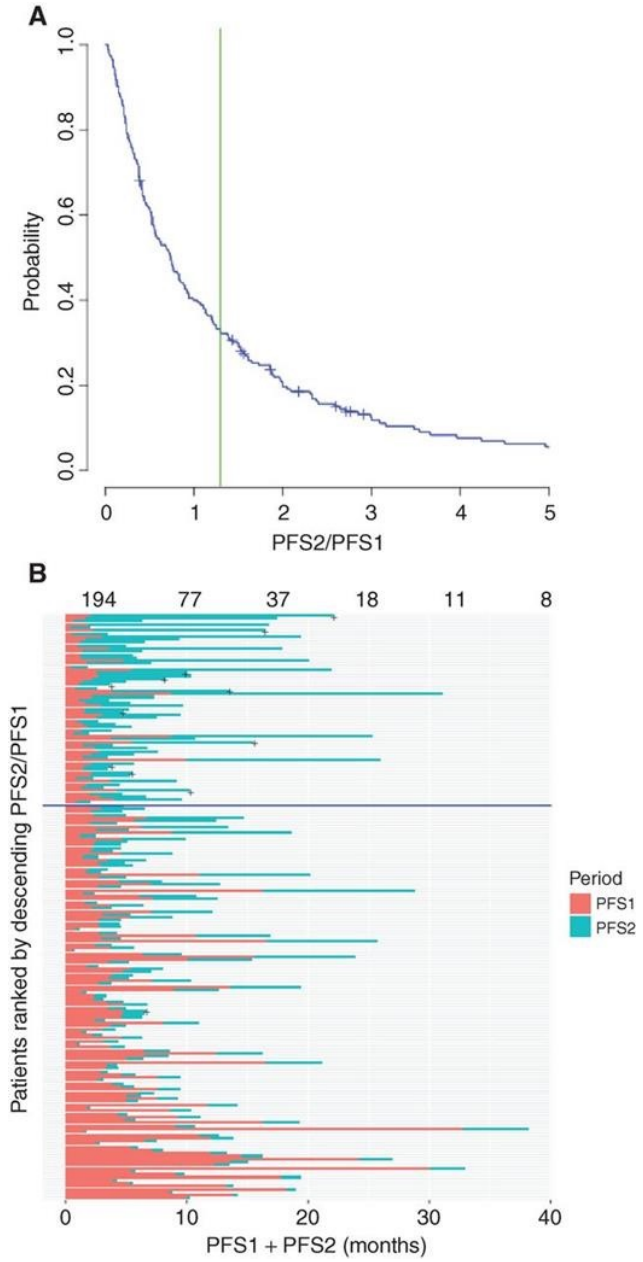
Usually the PFS of the first line treatment is longer then the PFS of the second line treatment

Peng Jiang *et al*. Nat Rev Cancer 2022, Horak et al Cancer Discov 2021; Massard et al Cancer Discov 2017

Ratio PFS2/PFS1

Omics-based

Guidelines-based



Massard et al Cancer Discov 2017

Precision Medicine:
The counter-example

COMMENTARY

The Great Irony of Modern Oncology: Immunotherapy's Imprecision

Bishal Gyawali, MD, PhD

DISCLOSURES | August 30, 2022

Immunotherapy = Imprecision Medicine

However, I think that the paradigms of immunotherapy and precision medicine have become antithetical to each other. We have let our precision medicine principle of "right dose for the right patient at the right time" fly out the window when it comes to immunotherapy.

Let me explain why. To put it simply, immunotherapy feels anything but precise.

With immunotherapy, we are treating too many patients too long too often, and at too high a dose.

COMMENTARY

The Great Irony of Modern Oncology: Immunotherapy's Imprecision

Bishal Gyawali, MD, PhD

DISCLOSURES | August 30, 2022

IO: No biomarkers for Response or Tox

Contrary to the premise of precision medicine, we don't have good biomarkers to predict a patient's response to immunotherapy nor do we have good biomarkers to predict toxicities. Some patients derive long-term benefit from immunotherapy, whereas others don't benefit at all.

IO = Imprecision Medicine? On exception MMD a tumor agnostic biomarker

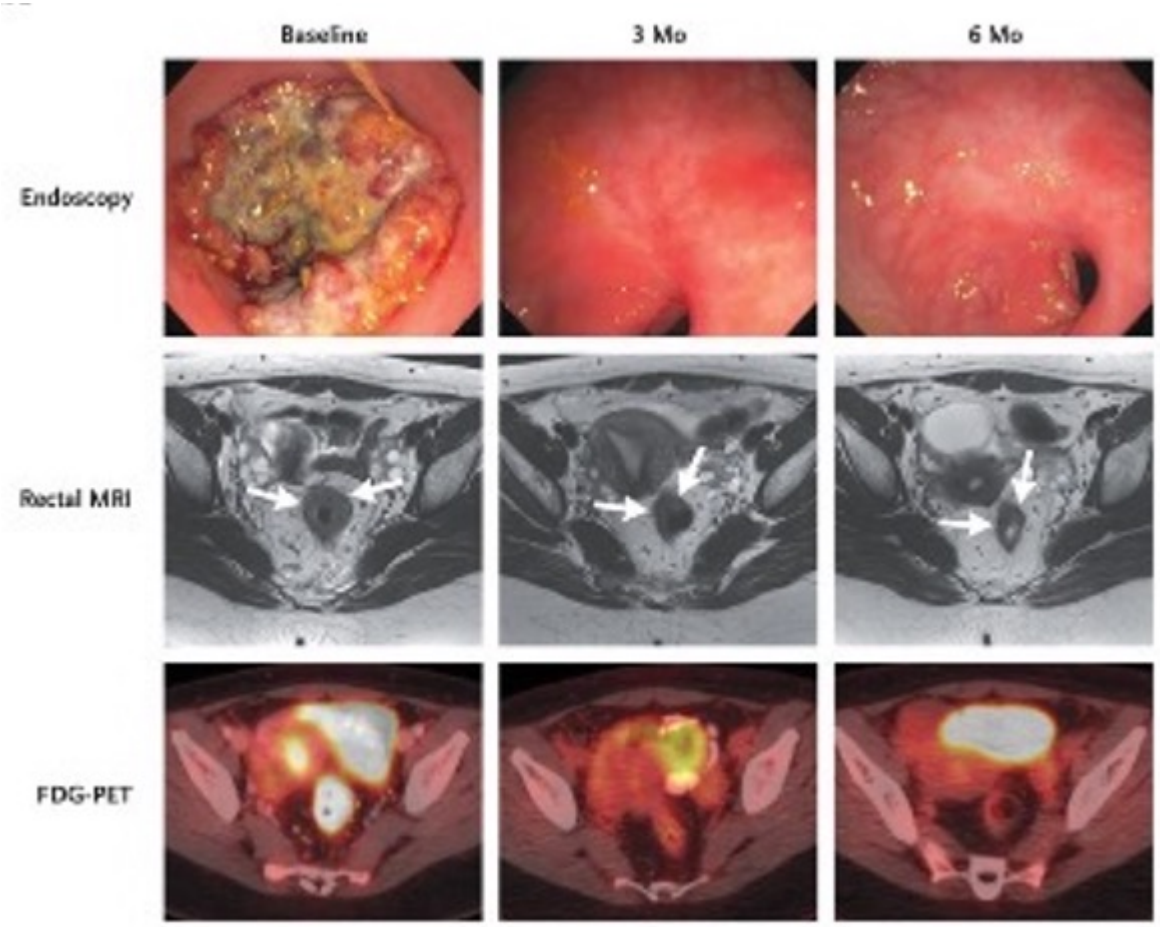
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., et al.

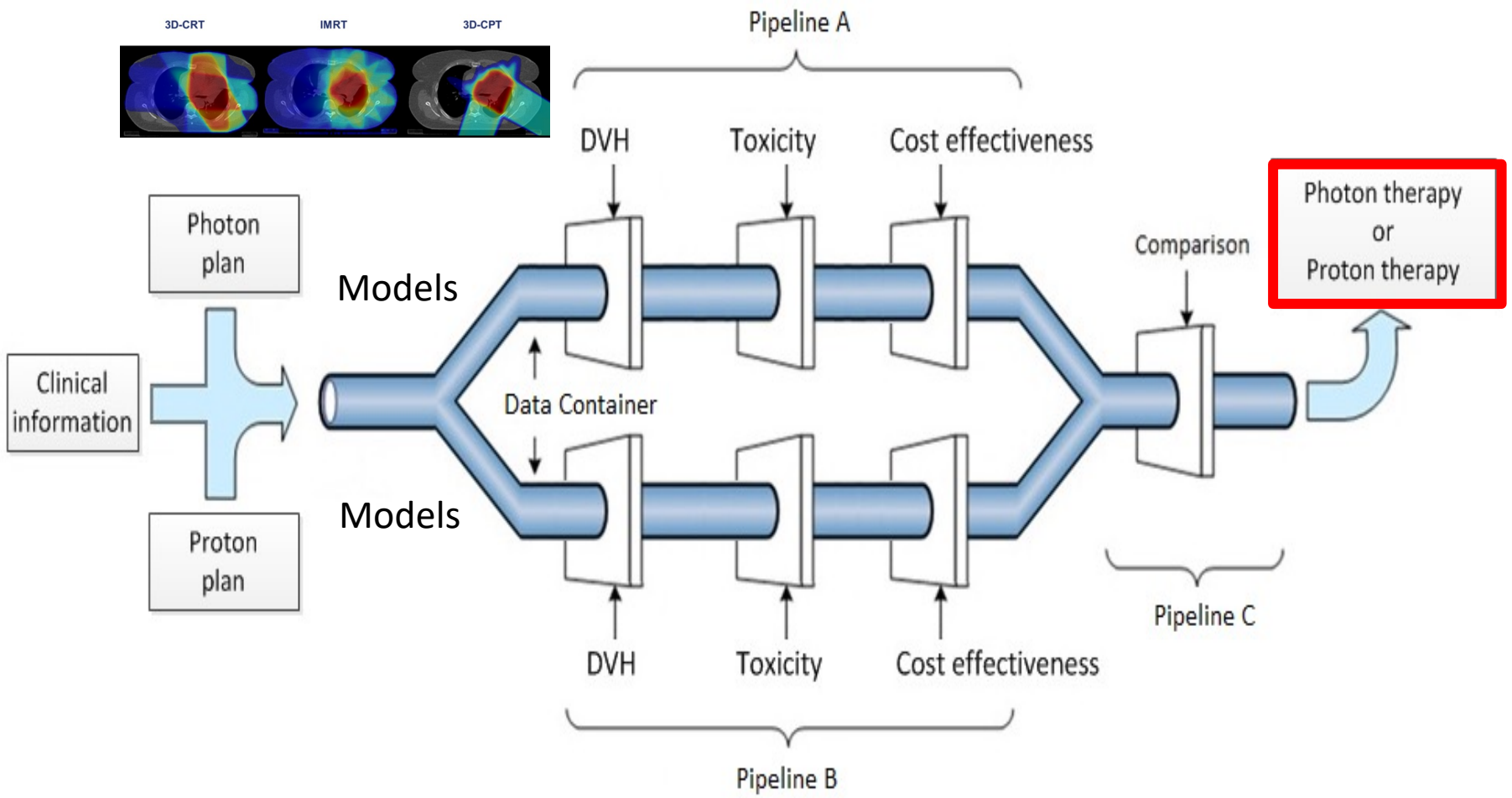
June 23, 2022
N Engl J Med 2022; 386:2363-2376
DOI: 10.1056/NEJMoa2201445



Precision Medicine in Radiotherapy

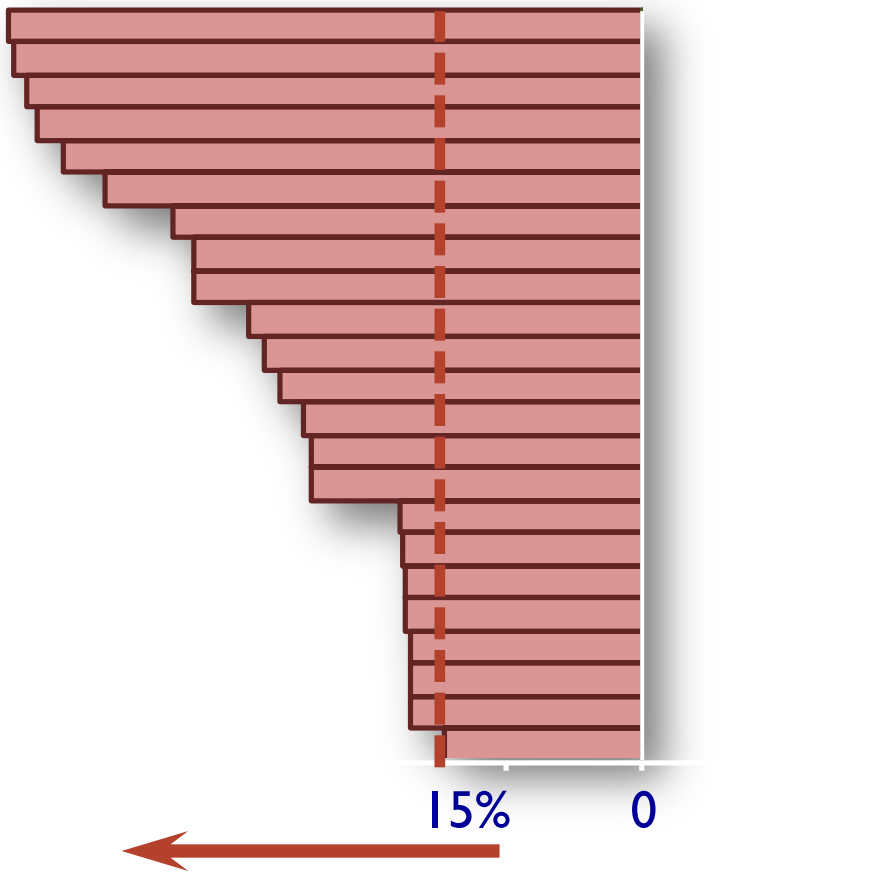
Is simulation & individualized treatment planning enough to be PM?

Proton therapy Decision Support System

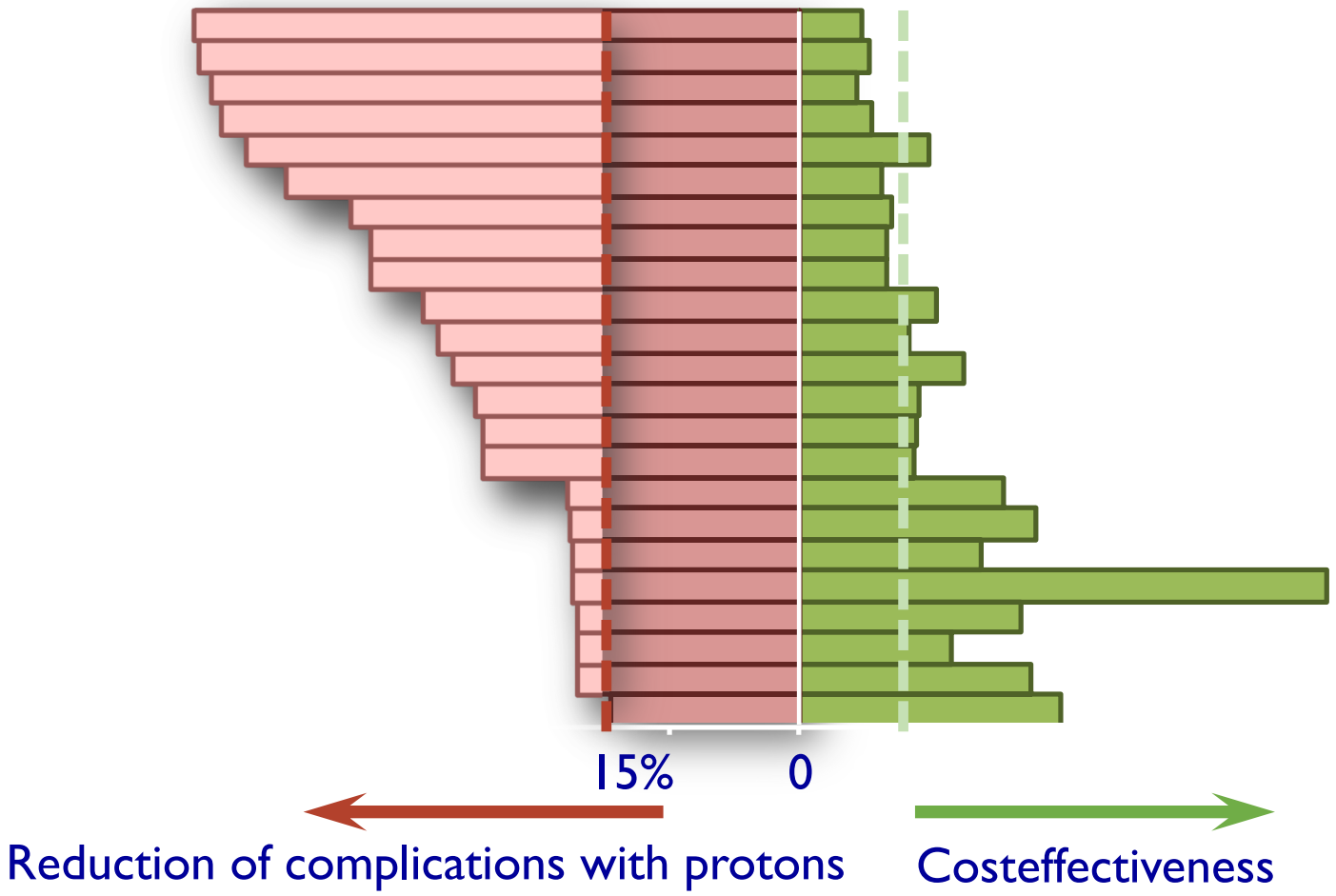


Cheng Q, Roelofs E, Lambin P et al. Radiother Oncol 2016

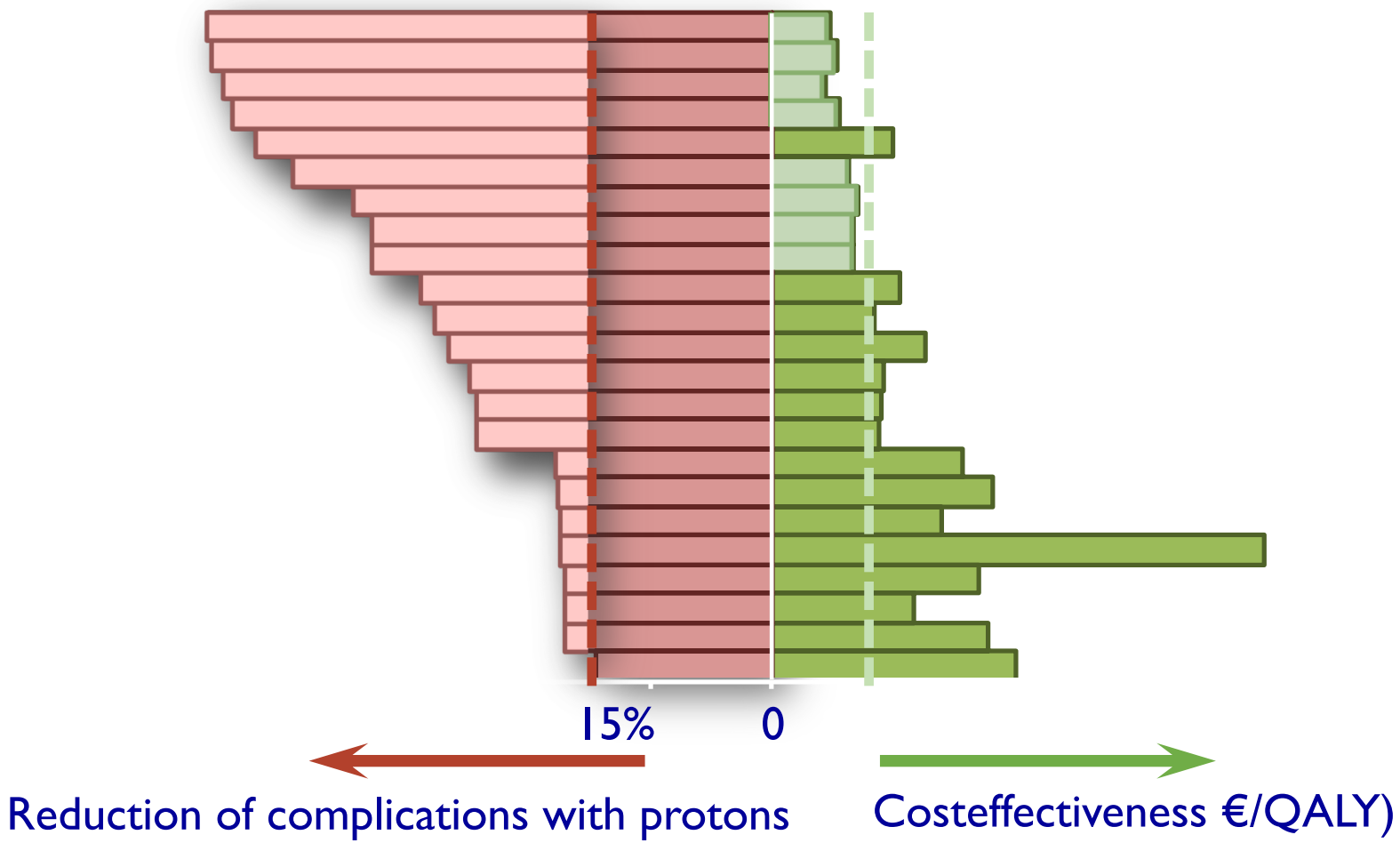
Proton Decision Support for H&N cancer



Proton Decision Support for H&N cancer



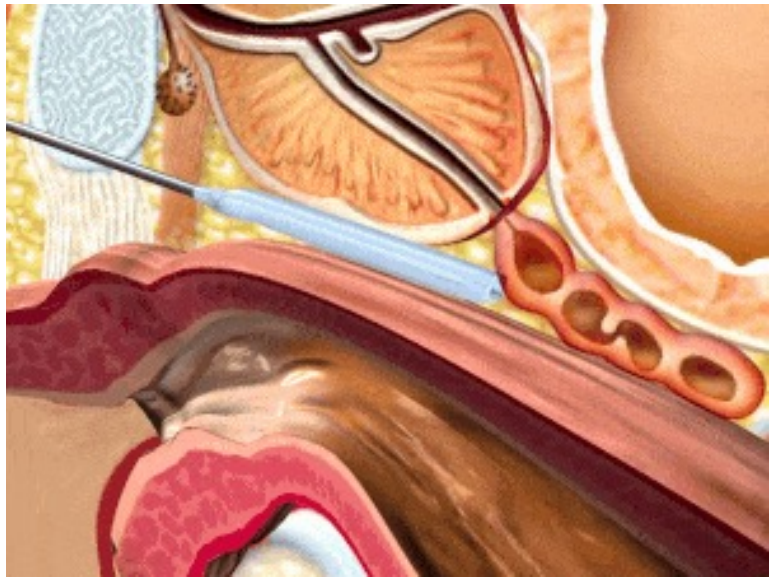
Proton Decision Support for H&N cancer



Example 2: Spacer: only for a fraction of the patients: whom?

- Implantable rectum spacer
- Anterior rectum wall out of high dose region
- Invasive + expensive:

Patient selection?

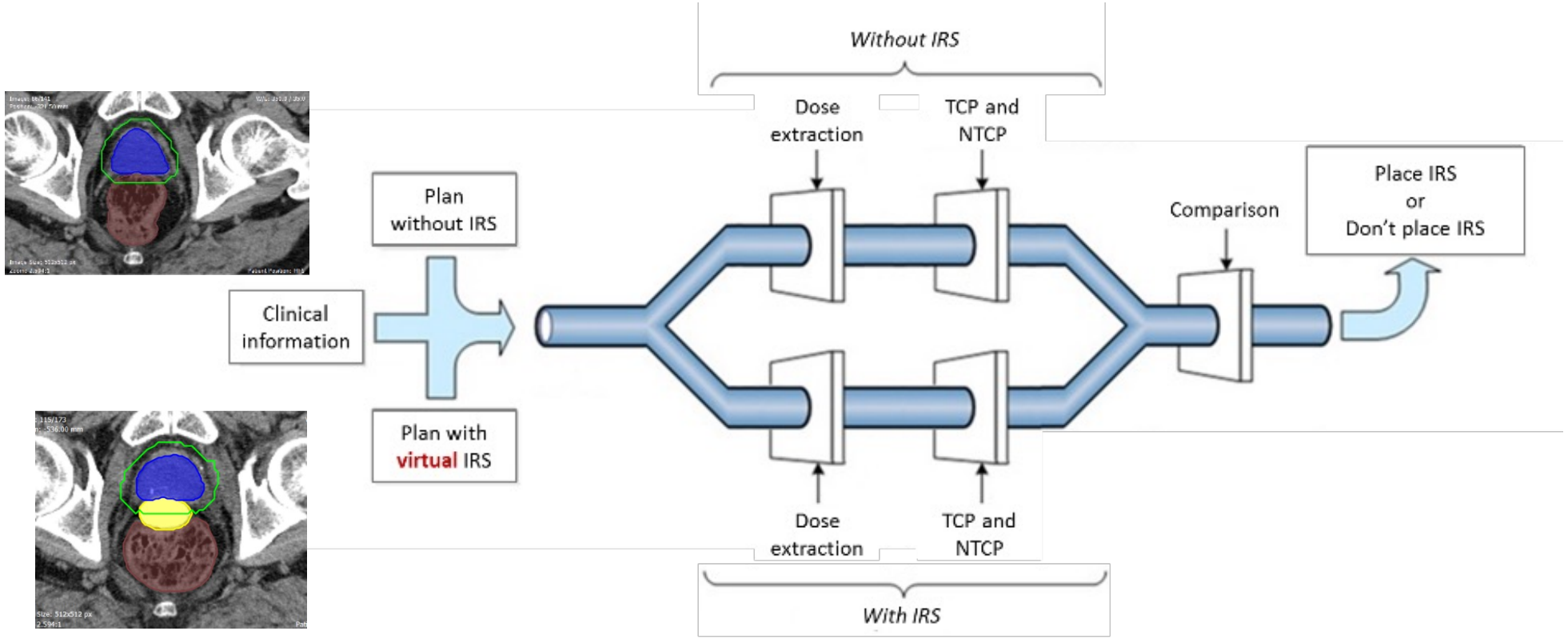


https://youtu.be/4IcrSs_4oiE

Van Wijk, Lambin P *et al.* Radiother Oncol 2017; Acta Oncol 2018

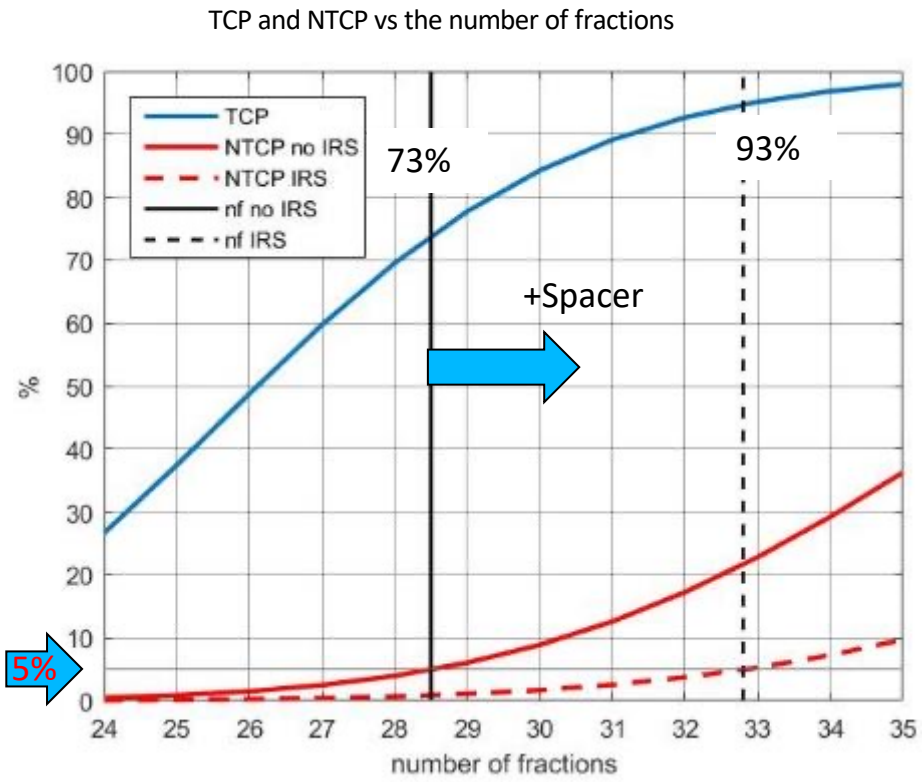
Example 2: Virtual Spacer vs No spacer in prostate cancer

We use a virtual spacer to mimic the real spacer before implantation.



Van Wijk, Lambin P *et al.* Radiother Oncol 2017
Walsh et al. Med Phys 2016

Results: Improving TCP *without* extra side effects



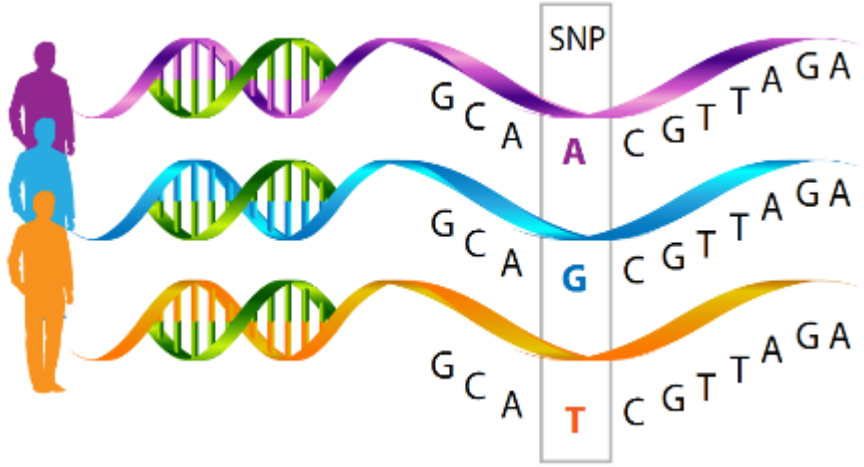
Van Wijk, Lambin P *et al.* Radiother Oncol 2017; Acta Oncol 2018

Are there actionable genetic biomarkers in Radiotherapy?

- Not in routine
- We need to differentiate:
- Gene polymorphisms of germ cells
- Somatic mutations of tumour cells

Adding genetics: SNP's - gene polymorphism of germ cells

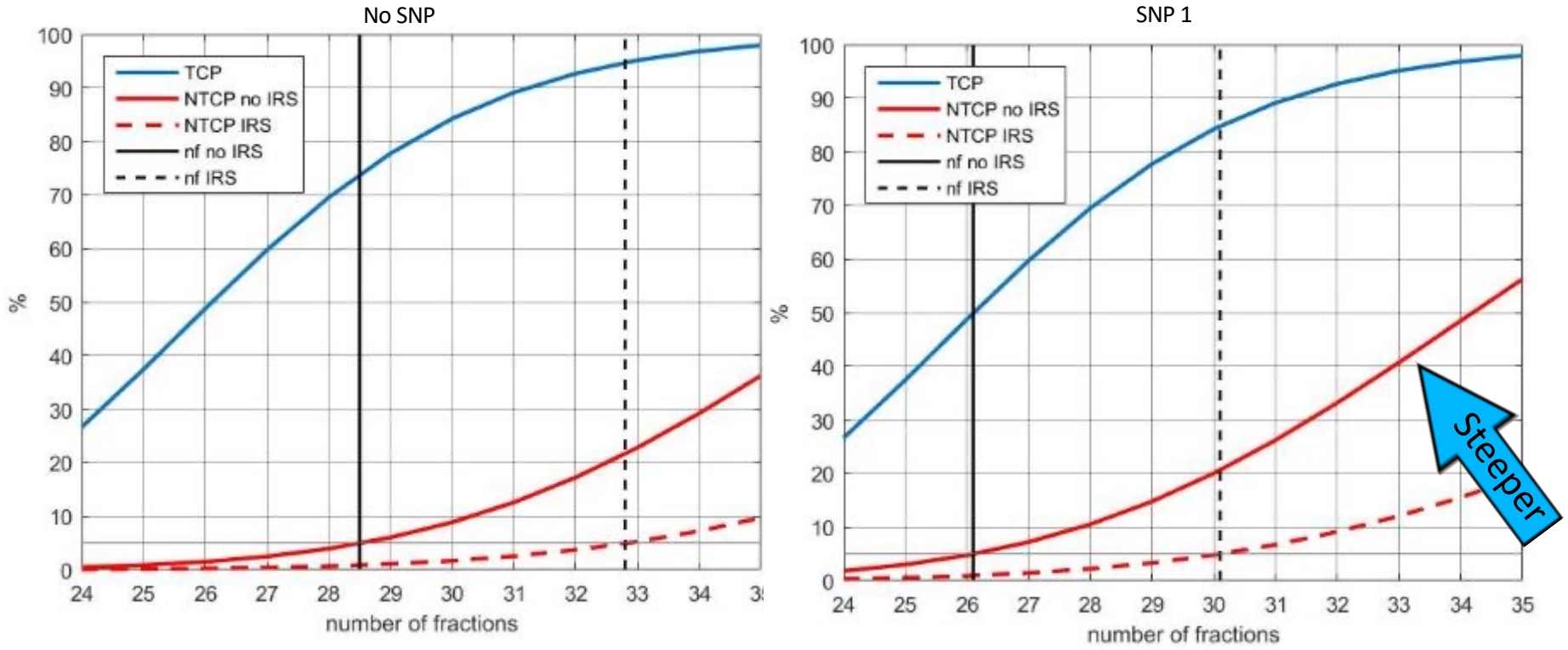
- Single nucleotide polymorphism (SNP)
  - *Common genetic variant*
  - *Heritable radio sensitivity*
- Selected SNP's
  - *rs141044160 (SNP 1)*
  - *rs7432328 (SNP 2)*
  - *~10% of the population*
- Combined with NTCP model
  - *Odds ratio and MAF*



Fachal et al. Nat Genet. 2014; Kerns, S.L. et al. EbioMedicine (2016)

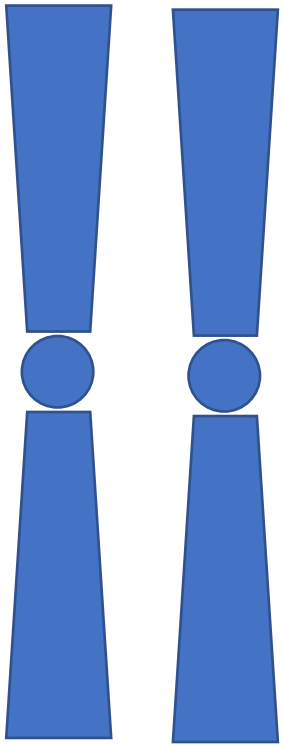
Van Wijk, Lambin P *et al.* Radiother Oncol 2017; Acta Oncol 2018; Kerns SL et al. J Natl Cancer Inst. 2019 May 16. pii: djz075.

Adding genetics: SNP's - *gene polymorphism of germ cells*

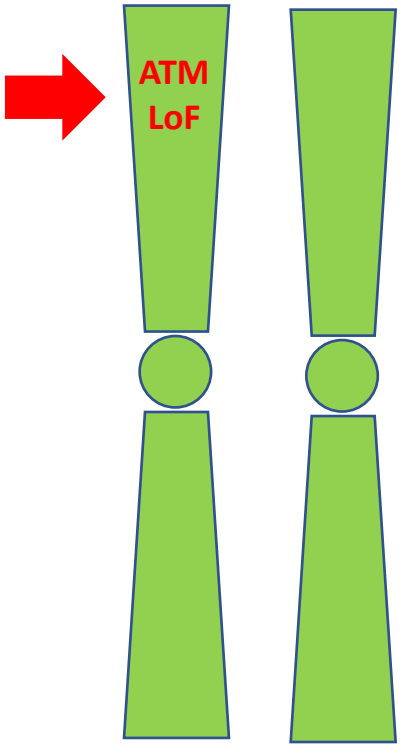


Van Wijk, Lambin P *et al.* Radiother Oncol 2017; Acta Oncol 2018

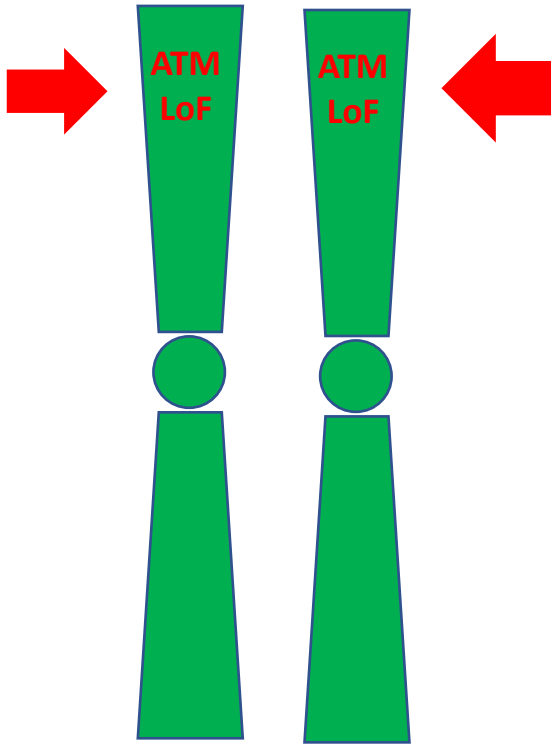
The most important *somatic tumour mutation* for radiotherapy? = ATM mutation – involved in DNA repair



ATM wild-type
(normal)



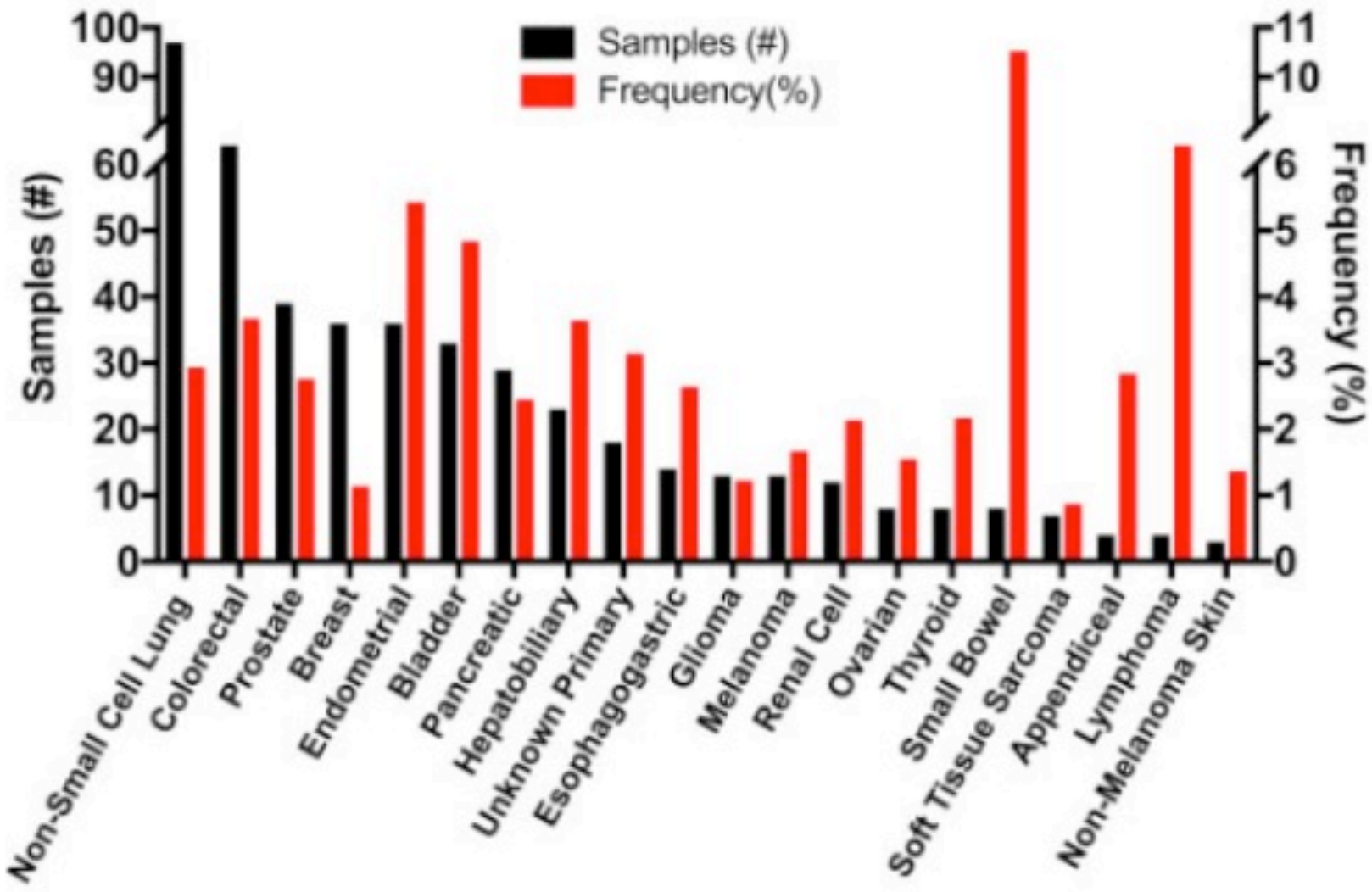
ATM Mono-allelic
Loss of Function



ATM Bi-allelic
Loss of Function

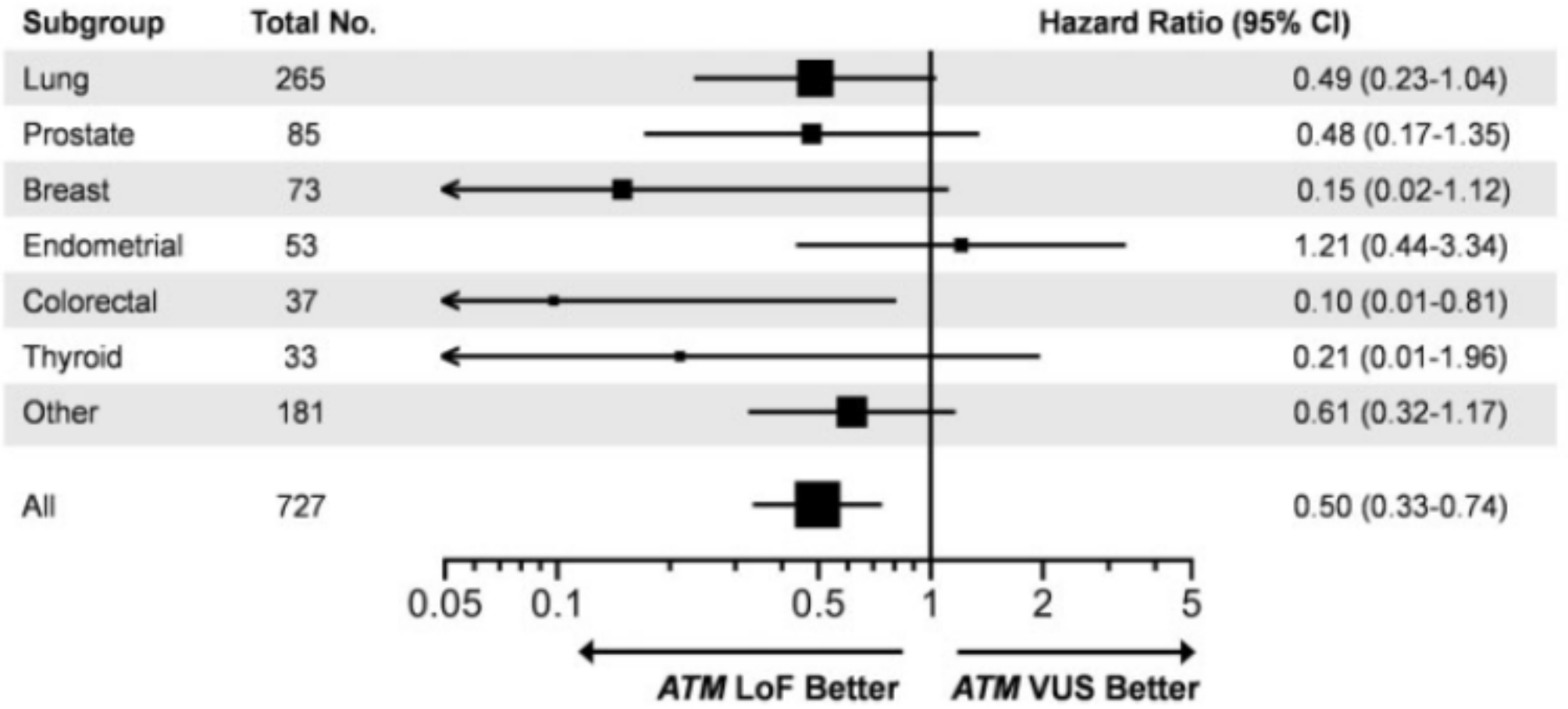
Pitter et al. J Natl Cancer Inst. 2021. doi: 10.1093/jnci/djaa095

ATM somatic mutations



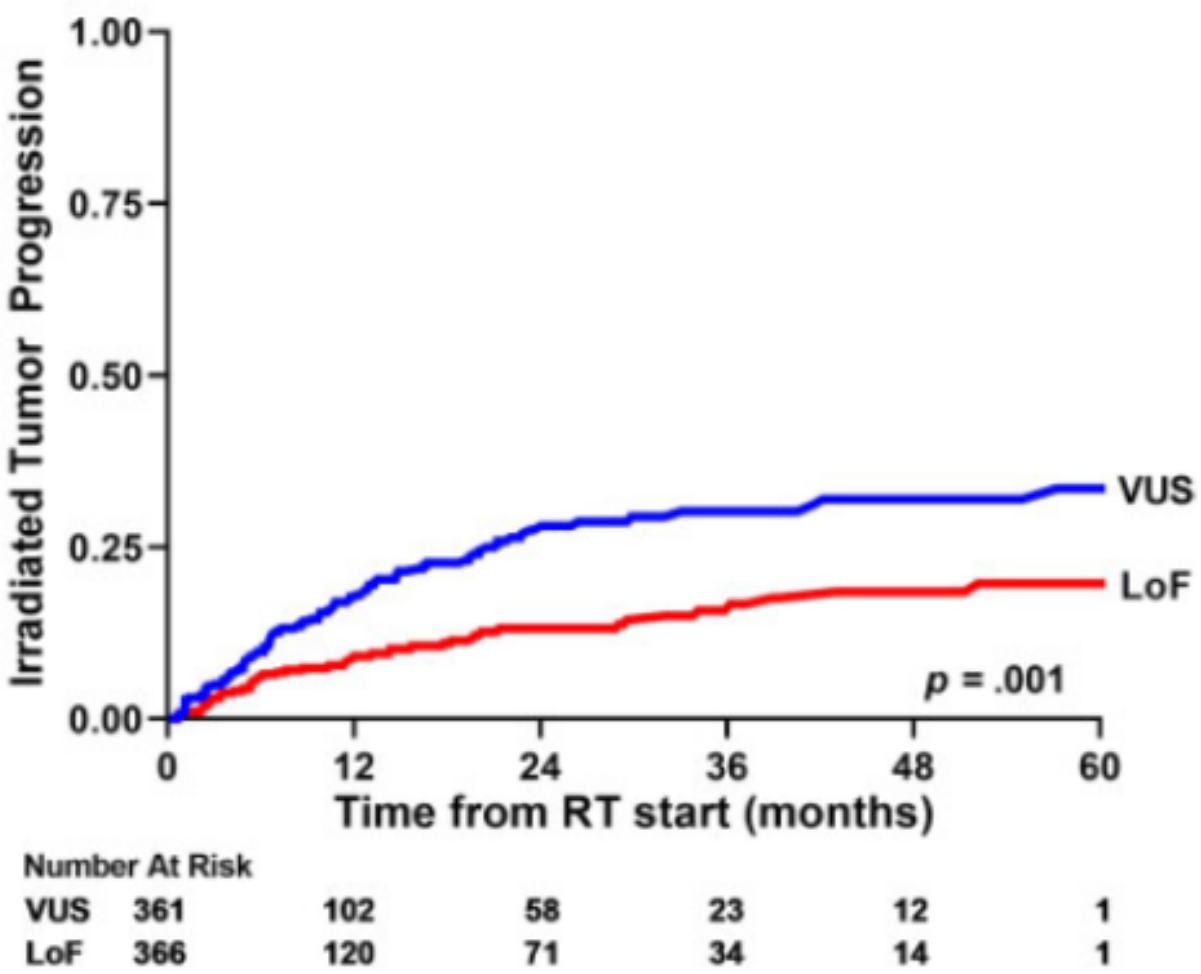
Pitter et al. J Natl Cancer Inst. 2021. doi: 10.1093/jnci/djaa095

ATM somatic mutations



Pitter et al. J Natl Cancer Inst. 2021. doi: 10.1093/jnci/djaa095

ATM somatic mutations

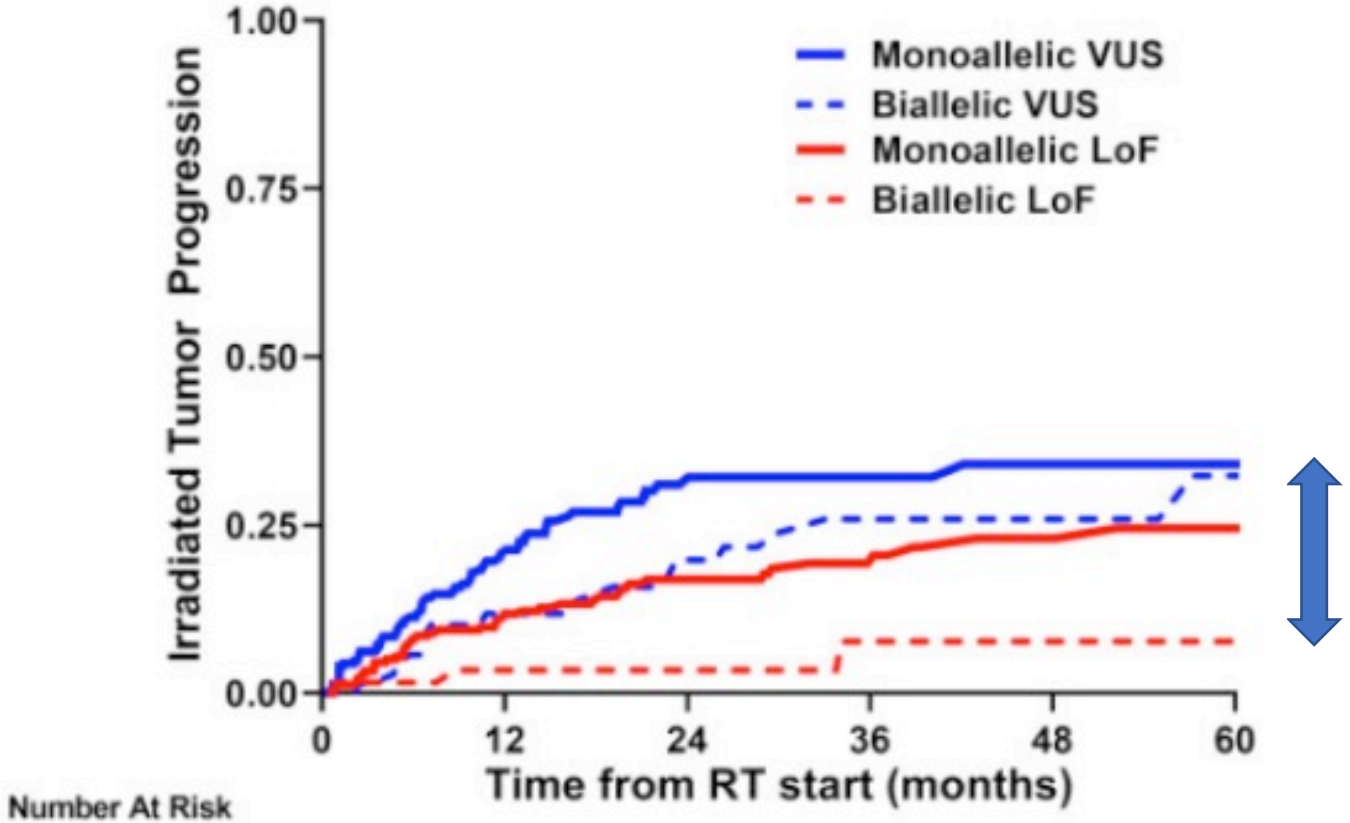


ariants of unknown significance

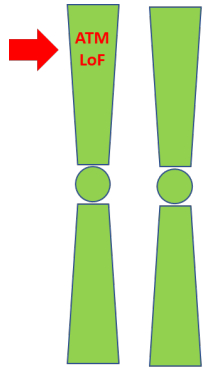
ATM Loss of function

Pitter et al. J Natl Cancer Inst. 2021. doi: 10.1093/jnci/djaa095

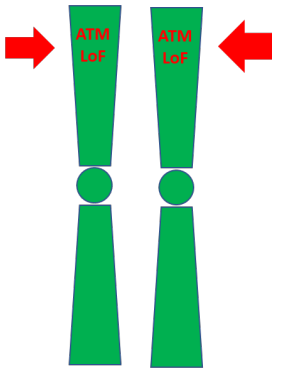
ATM somatic mutations



Number At Risk						
Monoallelic VUS	229	95	36	20	10	10
Biallelic VUS	73	33	16	12	8	5
Monoallelic LoF	243	112	53	28	16	9
Biallelic LoF	63	37	17	10	8	7

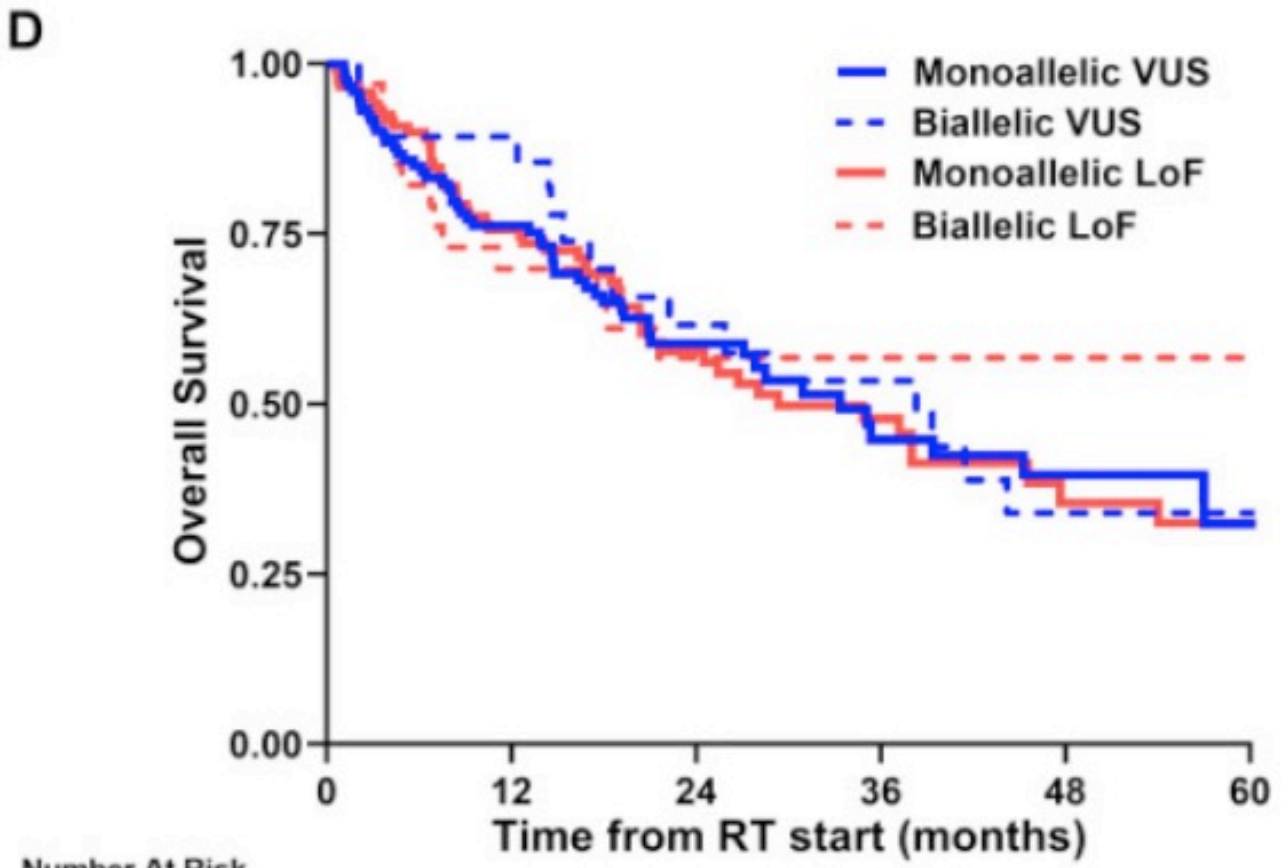


ATM Mono-allelic
Loss of Function



ATM Bi-allelic
Loss of Function

ATM somatic mutations: no effect on survival



Number At Risk						
Monoallelic VUS	123	81	39	21	15	9
Biallelic VUS	29	25	16	12	8	5
Monoallelic LoF	120	79	39	24	13	10
Biallelic LoF	34	31	14	10	8	7

Hypothesis: ATM status of tumour could be an excellent “tumour agnostic” biomarker in the decision Surgery versus Radiotherapy

- Head and neck tumours
- Operable NSCLC
- Pancreatic tumours
- Rectal tumours
- Endometrial tumours
- …

Pitter et al. J Natl Cancer Inst. 2020. doi: 10.1093/jnci/djaa095

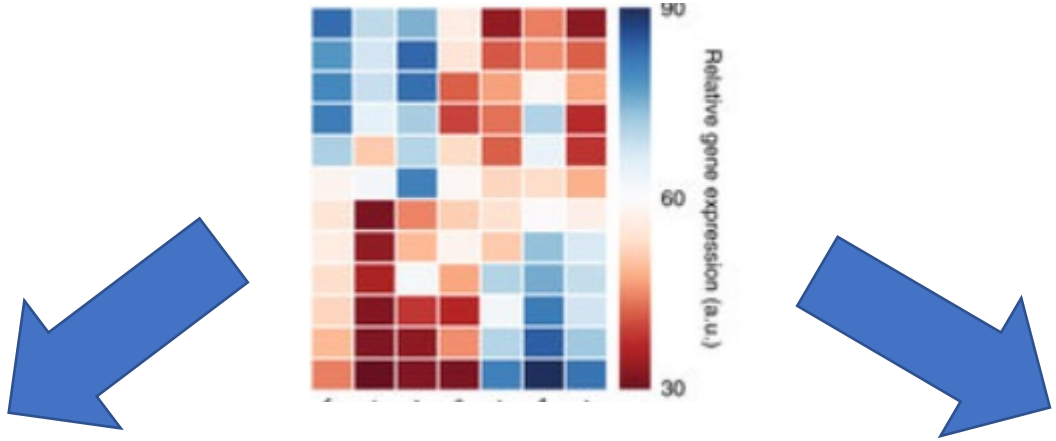
Biomedicines
Multidisciplinary Digital Publishing Institute (MDPI)

Stratification of Oligometastatic Prostate Cancer Patients by Liquid Biopsy: Clinical Insights from a Pilot Study

Antonella Colosini, Simona Bernardi, [...], and Luca Triggiani

Example 3: 15-gene hypoxia classifier in head and neck cancer for prospective use in clinical trials

A Blind Randomized Multicenter Study of Accelerated Fractionated Chemo-radiotherapy With or Without the Hypoxic Cell Radiosensitizer Nimorazole (Nimoral), Using a 15-gene Signature for Hypoxia in the Treatment of Squamous Cell Carcinoma of the Head and Neck.



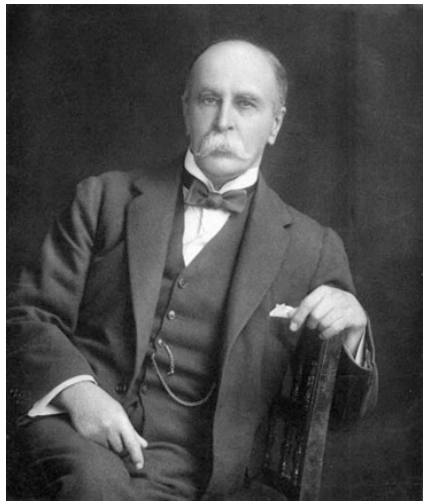
Negative: + Placebo

Positive: + Nimorazole

Is Participative medicine part of Precision Medicine?

Participatory Medicine

"The good physician treats the disease;



the great physician treats the patient who has the disease".

Dr. William Osler, the father of modern medicine

Lambin P *et al.* Adv Drug Deliv Rev. 2017

What is Precision Medicine?

In precision medicine, the focus is on ***identifying which approaches (preventive, diagnostic, therapeutic, follow-up…) will be effective*** for which patients based on clinical, genetic, environmental, preferences and lifestyle factors.

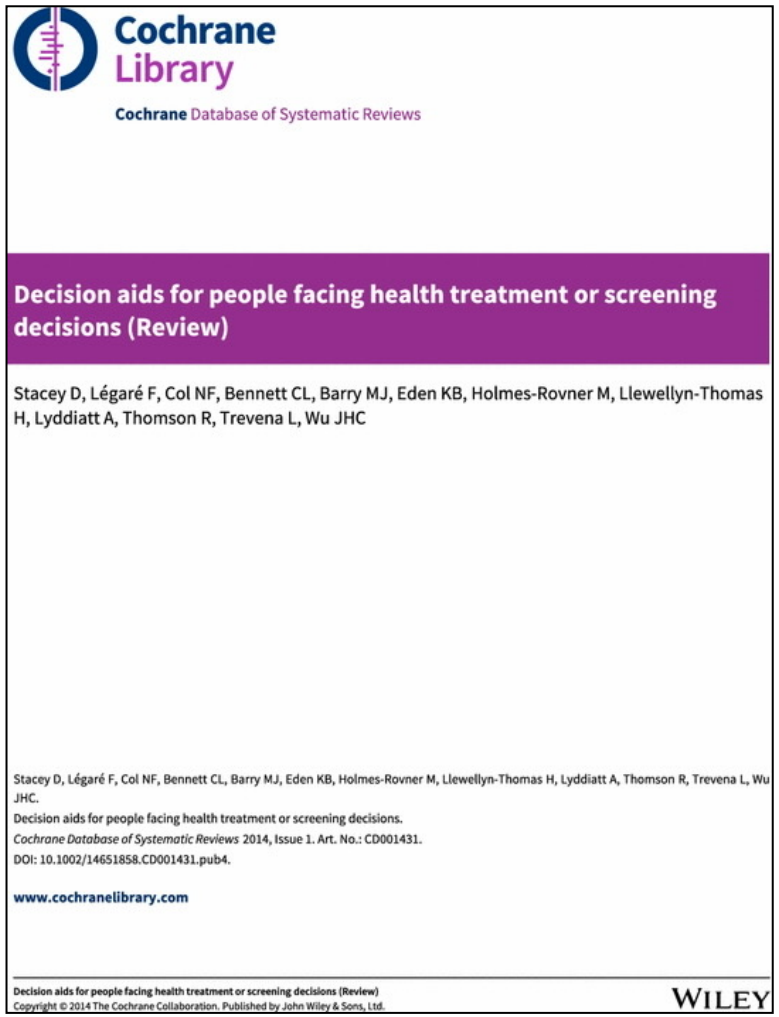
The origins of Shared Decision Making (SDM)

1997

Cathy Charles, Amiram Gafny, Tim Whelan

Shared Decision Making in the medical encounters: What does it mean? *Social Science & Medicine; 44 (5): 682-691*

Shared Decision making: The current evidence



Increase in:

- **Participants' knowledge** (52 studies; N=13.316; ++++)
- **Accuracy** risk of perceptions (17 studies; N=5.096; +++)
- **Congruency** between informed values and care choices (10 studies; N=4.626; ++)

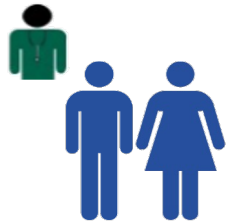
Decrease in:

- **Decisional conflict** (27 studies; N=5.707; +++)
- **Indecision** about personal values (23 studies; N=5.068; +++)
- **Proportion** of passive people in decision making (16 studies; N=3.180; ++)

Cochrane database of systematic reviews 2017, issue 4. Art. No. C0001431

CONVENTIONAL DECISION MAKING

GUIDELINES



TRADITIONAL SHARED DECISION MAKING

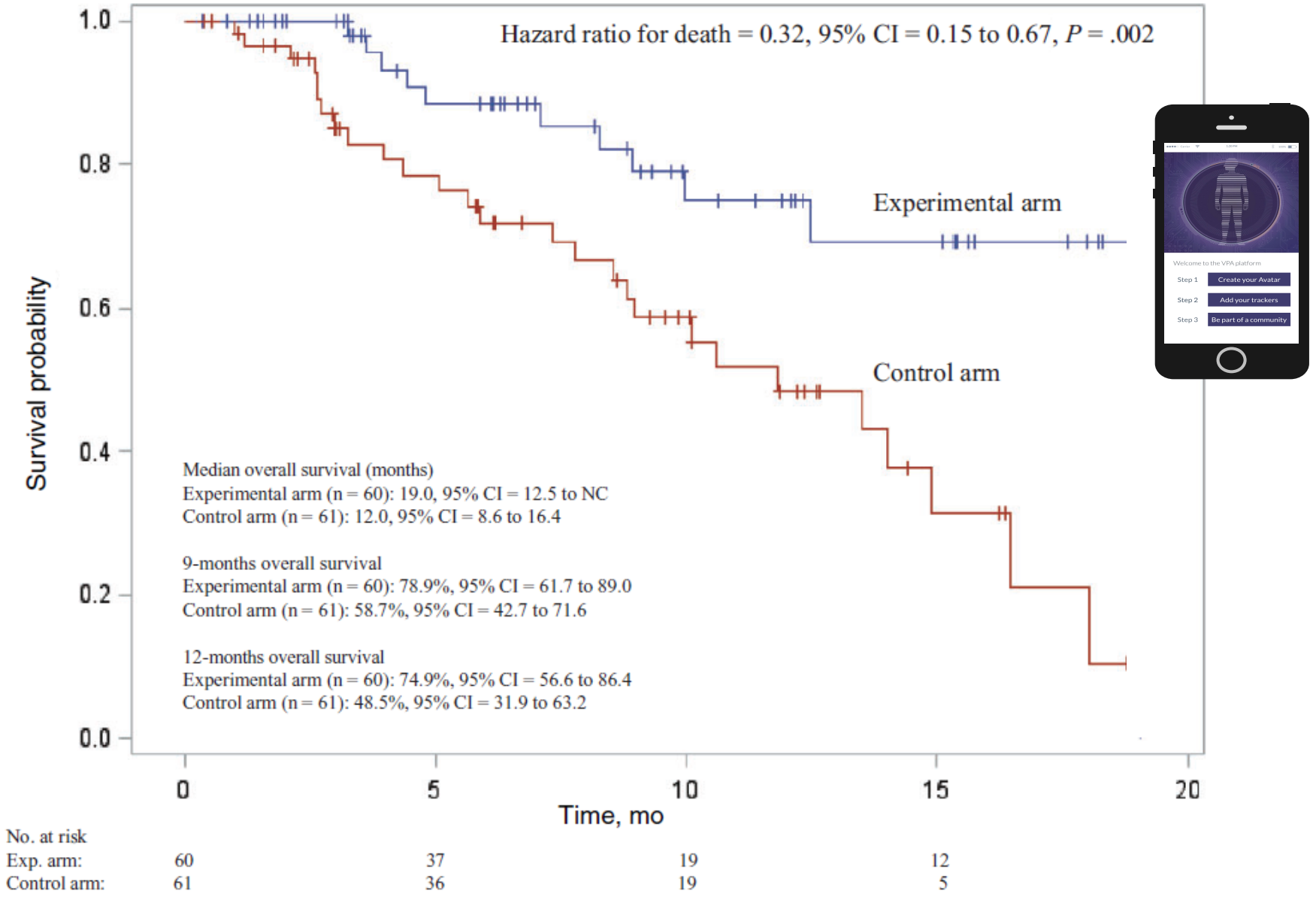
GUIDELINES

PATIENT DECISION AID TOOL

INDIVIDUALIZED SHARED DECISION MAKING

GUIDELINES + **PREDICTION MODELS**

INDIVIDUALIZED PATIENT DECISION AID TOOL

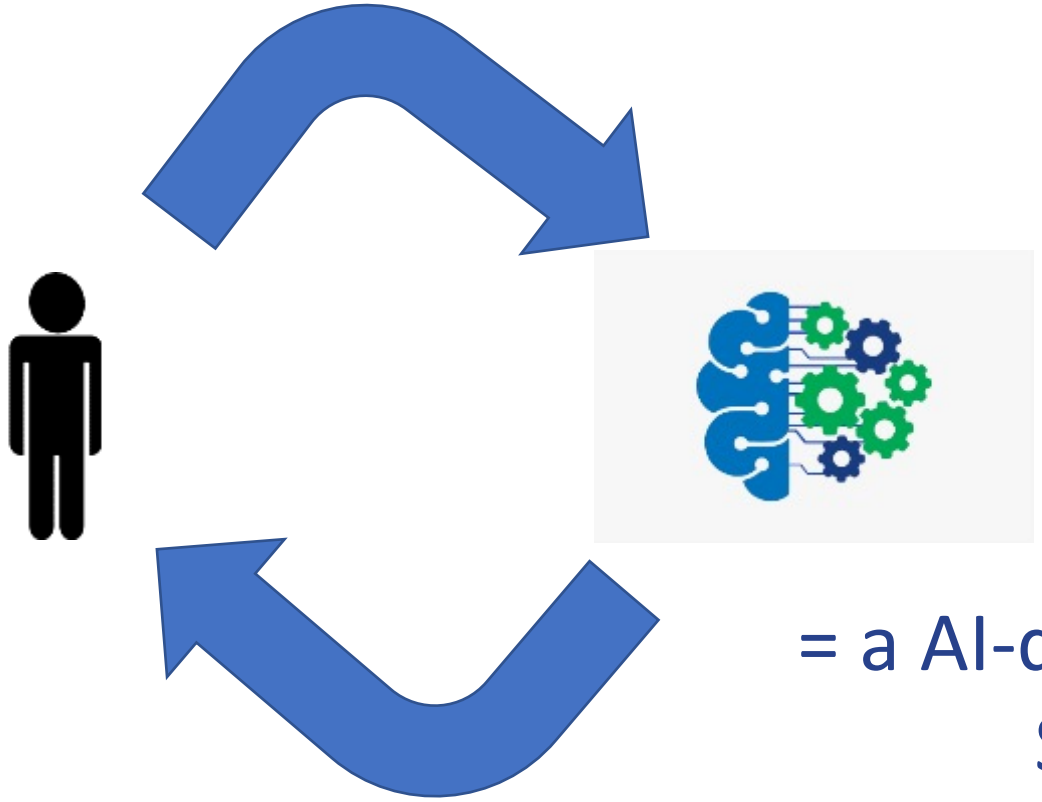


Denis et al. JNCI 2017

Precision Medicine: The next steps

The risk of PM? Increase entropy and error

The Future lies in Human Machine Collaboration



= a AI-driven Decision Support System

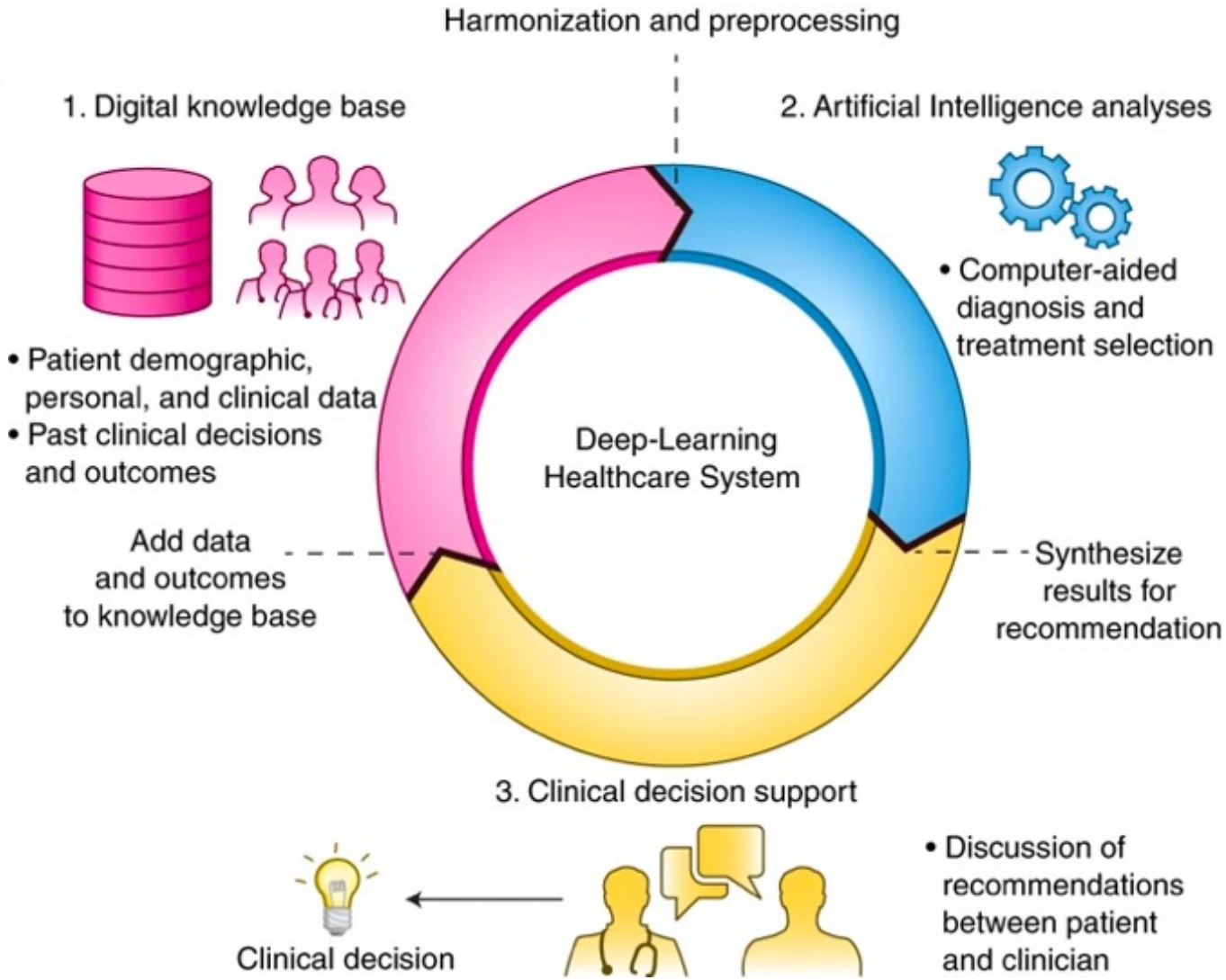
Courtesy of M. Dumontier

nature medicine

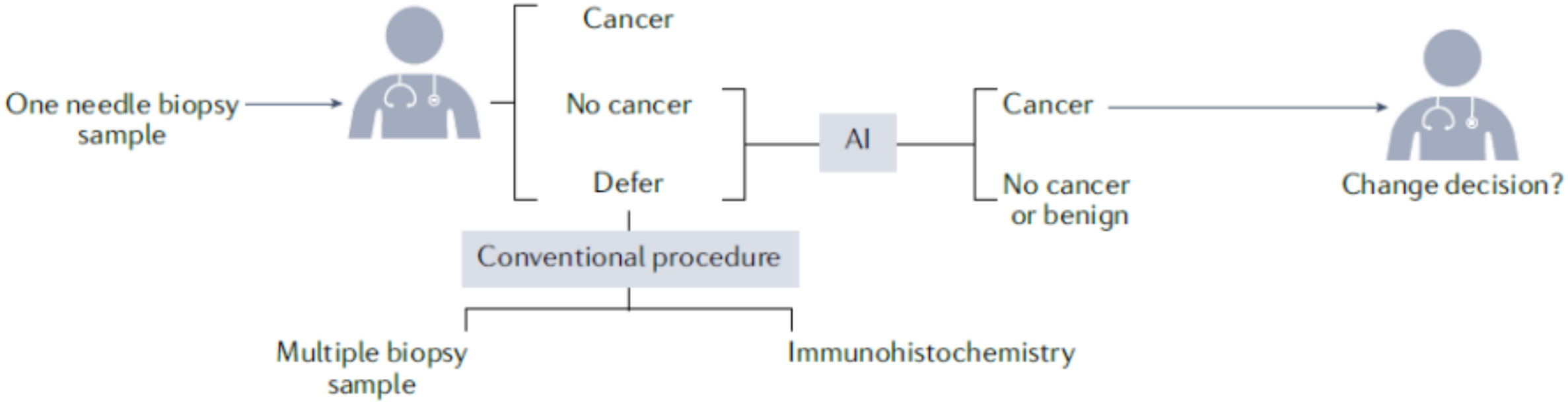
Comment | Published: 07 January 2019

A call for deep-learning healthcare

Beau Norgeot, Benjamin S. Glicksberg & Atul J. Butte



The FDA approved “AI test Paige Prostate”



Peng Jiang *et al*. Nat Rev Cancer 2022 https://doi.org/10.1038/s41568-022-00502-0

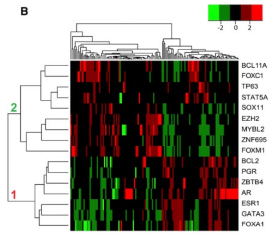
Is AI-multiomic in Oncology the holy grail?

The high dimensionality of cancer

HEALTH

Many clinical trials for new cancer drugs didn't include any data on race

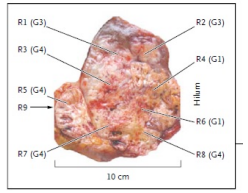
By MEGAN THIELKING @meggophone / AUGUST 19, 2019

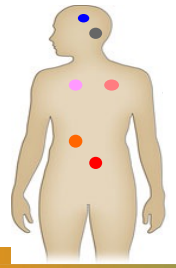


Genetic subtypes

Cancer type

Histology subtypes



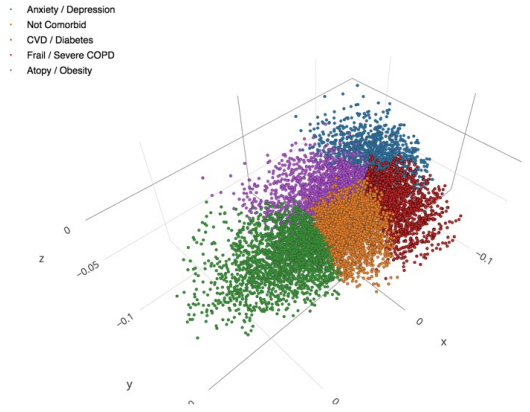


IntraTumor heterogenity

4D - Time

The dimensionality is too high!

Co-morbidity



Treatments

Surgery,
Radiotheraphy
Chemo

Targeted agents,
Immunotherapy
Repurposed drugs
…

Different combo

Conclusions

Half dream – Half reality

1. *Use Precision Medicine rather then Personalized medicine*
2. In Precision Medicine, the focus is on identifying which approaches will be effective for which patients based on clinical, genetic, environmental, preferences and lifestyle factors
3. Targeted agents & “umbrella trials” are example of PM
4. Immunotherapy is the counter-example of PM (except MMD)
5. “Patients preferences” are part of the concept of PM
6. Radiotherapy use Decision Support systems without genetic information

Thank you
for your attention

philippe.lambin@maastrichtuniversity.nl

Imaging course: www.ai4imaging.info

Acknowledgments

“The D-Lab team”

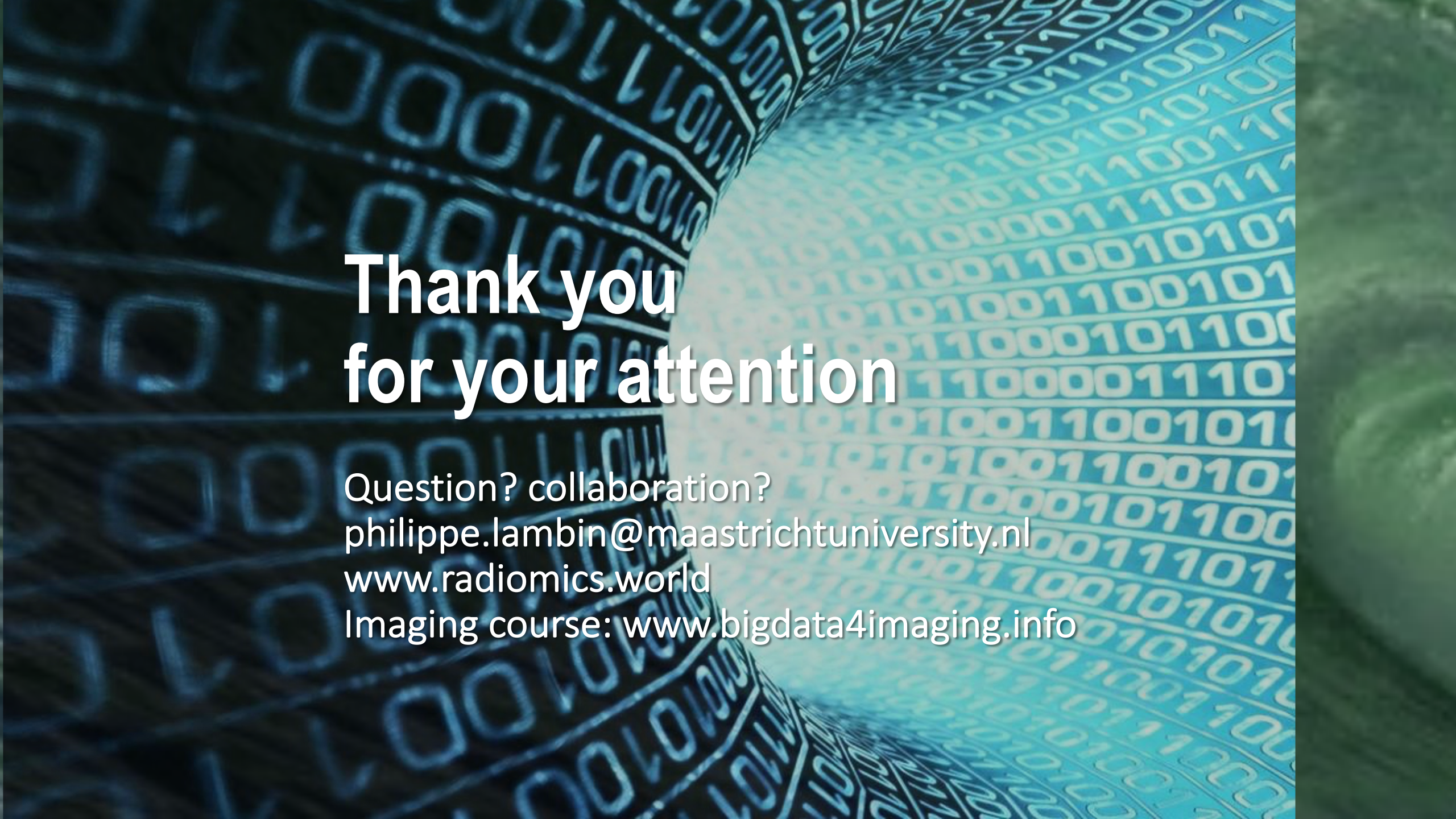
visit: www.thedlab.info

“The M-Lab team”

website under construction

My wife, my seven (step) children

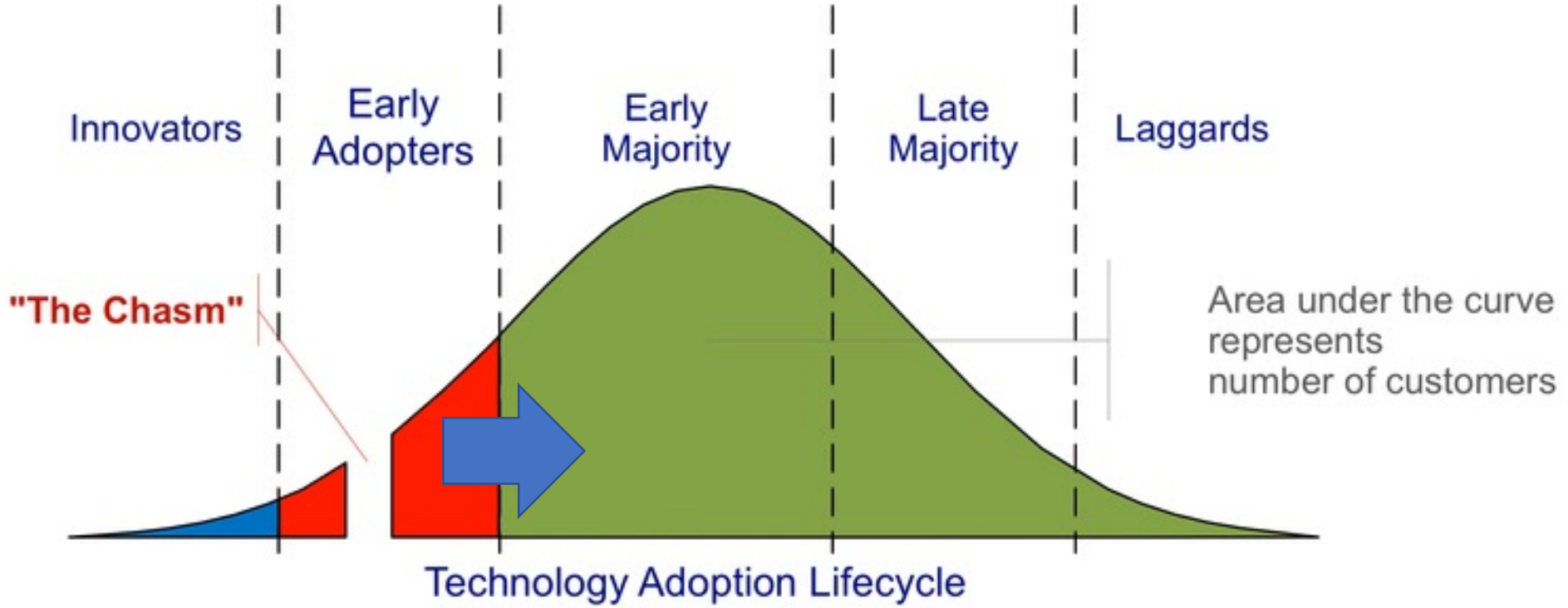
European Research Council
Advanced Grant
erc
NWO
KWF KANKER BESTRIJDING
HORIZON 2020



Thank you for your attention

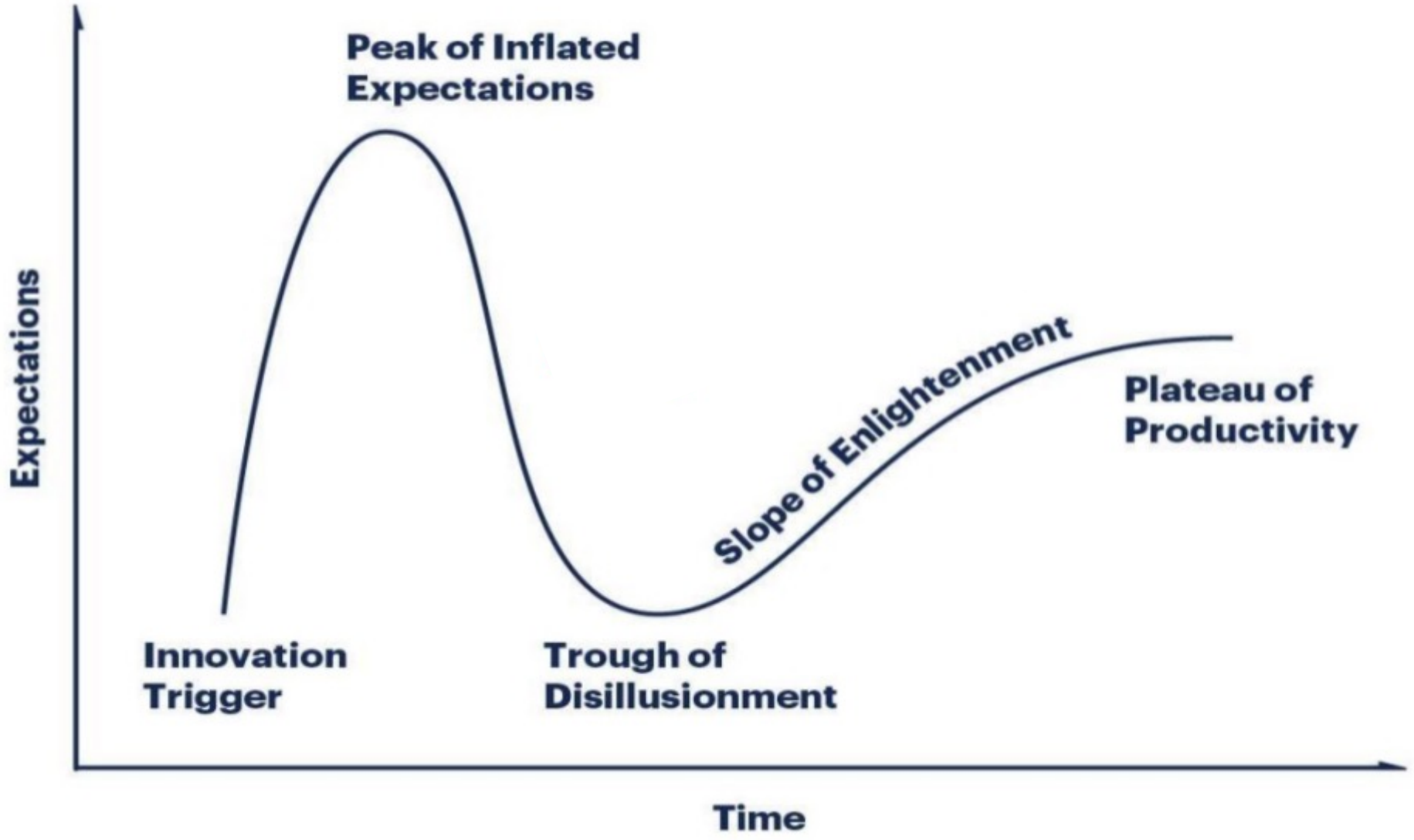
Question? collaboration?
philippe.lambin@maastrichtuniversity.nl
www.radiomics.world
Imaging course: www.bigdata4imaging.info

Technology Adoption Curve: Measurement instrument for determinants of innovations (MIDI)



https://www.tno.nl/en/focus-areas/healthy-living/roadmaps/youth/midi-measurement-instrument-for-determinants-of-innovations/

Hype Curve



Credit: Carole Goble

EU A.I. Act

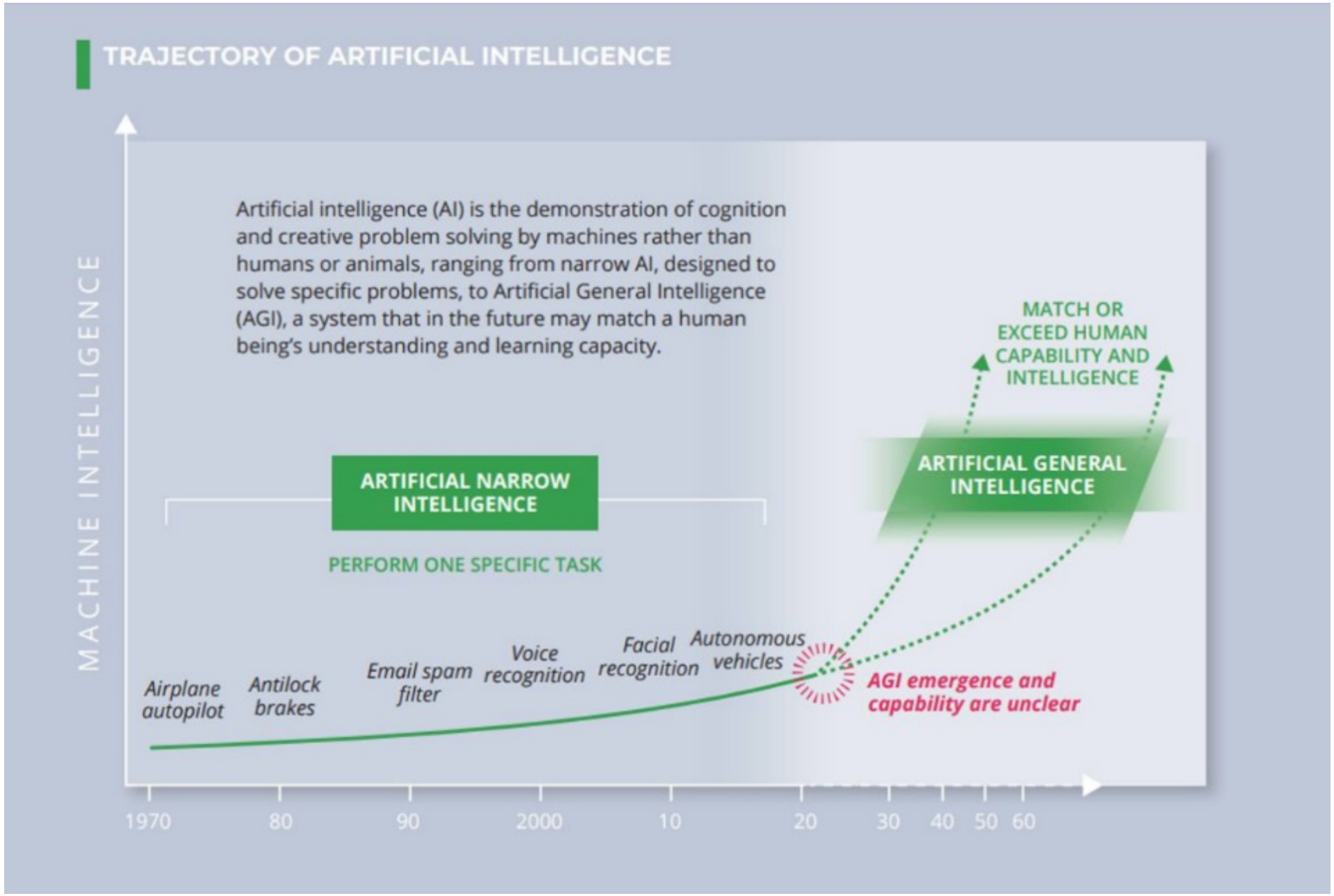
the proposed EU Artificial Intelligence Act. Gianluca Paladini indicated that the proposed regulation will require provenance tracking of data that is used to train AI algorithms, in addition to the test and validation data. This could have implications for distributed or federated learning cases.

https://ec.europa.eu/newsroom/dae/items/709090

Drug
x

EGFR receptor “wild-type” (= normal)

EGFR receptor “mutated”


TRAJECTORY OF ARTIFICIAL INTELLIGENCE
MACHINE INTELLIGENCE
Artificial intelligence (AI) is the demonstration of cognition and creative problem solving by machines rather than humans or animals, ranging from narrow AI, designed to solve specific problems, to Artificial General Intelligence (AGI), a system that in the future may match a human being's understanding and learning capacity.
MATCH OR EXCEED HUMAN CAPABILITY AND INTELLIGENCE
ARTIFICIAL GENERAL INTELLIGENCE
ARTIFICIAL NARROW INTELLIGENCE
PERFORM ONE SPECIFIC TASK
Airplane autopilot
Antilock brakes
Email spam filter
Voice recognition
Facial recognition
Autonomous vehicles
AGI emergence and capability are unclear
1970
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