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Predicting Patient Outcomes from Evidence Based Medicine to Digital Twin

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Modern Radiation Oncology 33rd Residential Course
Rome | October 10, 2023 | 12:30-13:00 (25+5)

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Disclosures

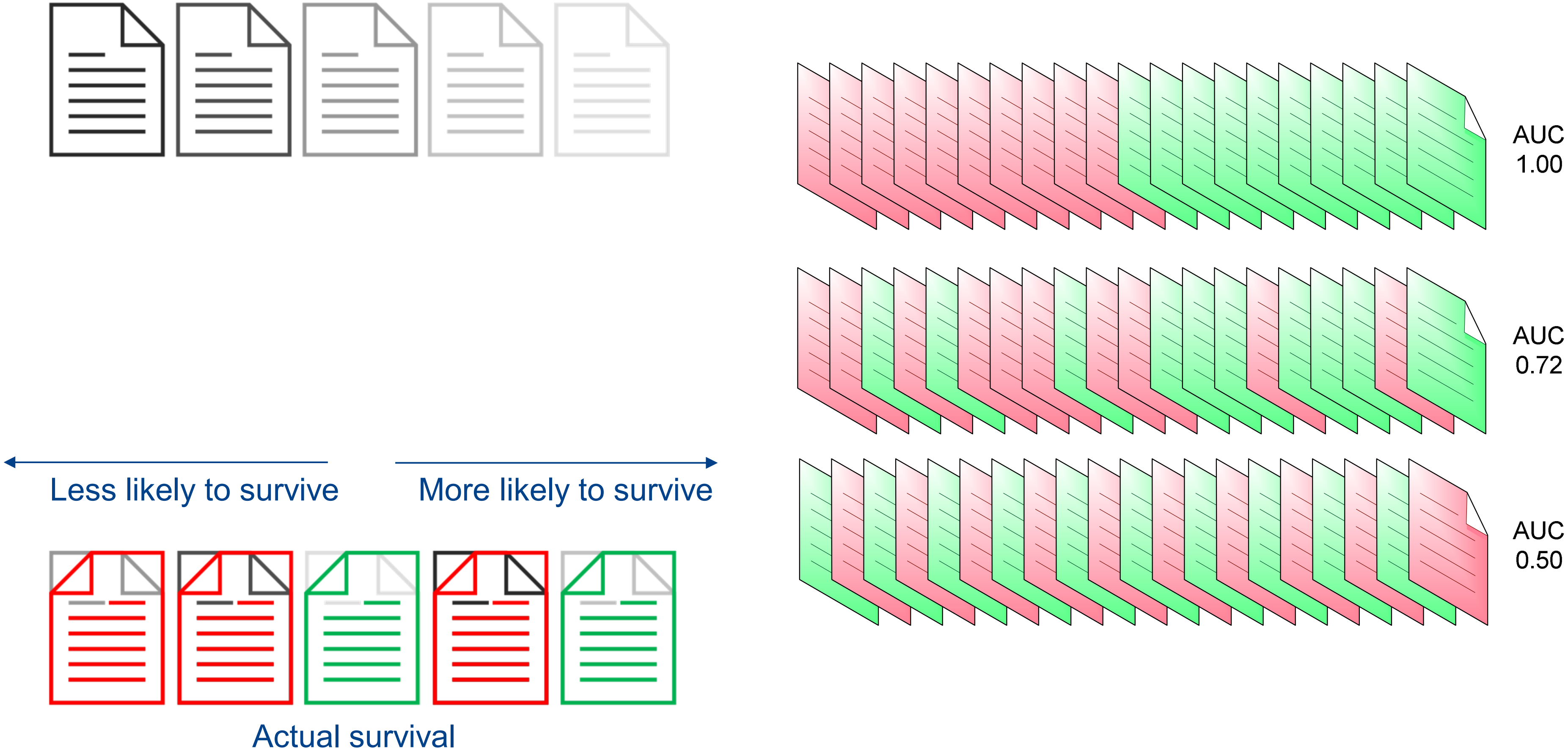
Research collaborations incl. funding, consultancy and speaker honoraria

- Pharma: Roche, Janssen, Bristol-Myers Squibb
- MedTech/Data: Varian - Siemens, Philips, Sohard, Mirada Medical, IQVIA
- Health insurance: CZ Health Insurance

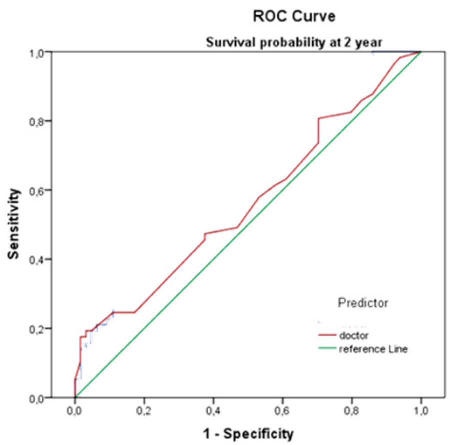
Spin-offs and commercial ventures

- Maastro Innovations B.V.
- Medical Data Works B.V.
- Various patents on medical machine learning & Radiomics

Predicting patient outcome

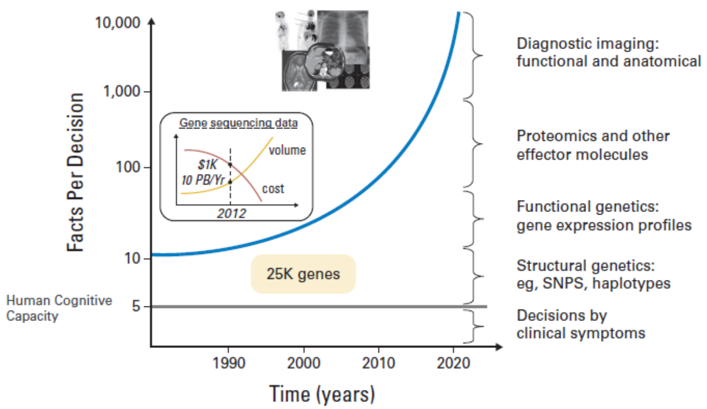


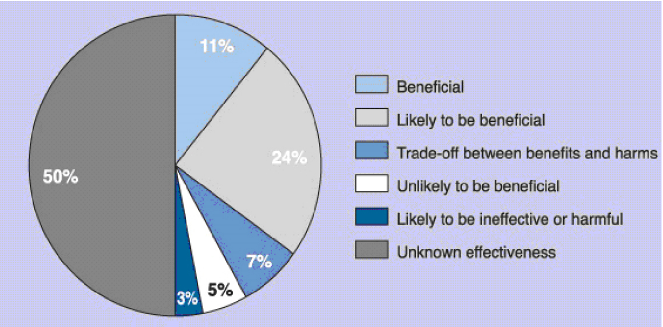
Why predicting patient outcomes is hard



NSCLC (Lung Cancer)
2 year survival
158 patients
5 MDs
Prospective
AUC: 0.56

- Explosion of data
- Explosion of decisions
- Explosion of 'evidence'
  - Too much to read
  - 3 % in trials, bias
  - Sharp knife



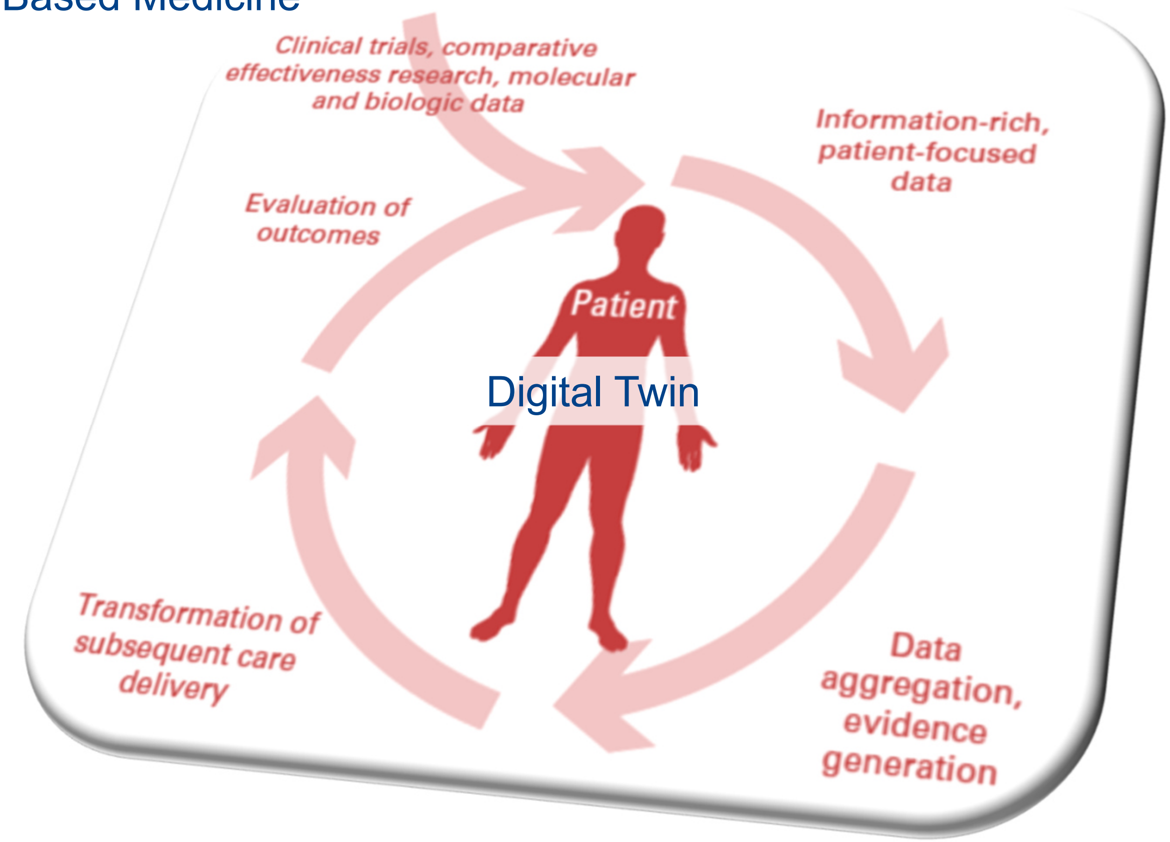


Effectiveness of 3000 treatments as reported in randomised controlled trials selected by Clinical Evidence. This does **not** indicate how oftentreatments are used in healthcare settings or their effectiveness in individual patients.

Oberije et al. , Radiother Oncol. 2014; 112: 37–43 / J Clin Oncol 2010;28:4268 / JMI 2012 Friedman, Rigby / BMJ Clinical Evidence

Learning health care system – From Evidence Based Medicine to Digital Twins

Evidence Based Medicine



J Clin Oncol 2010;28:4268

A Digital Patient Twin

- Patient health simulations
- Data models and AI algorithms
- Lifelong data from diverse sources
- Real-time health information
- Continuous data comparison with:
  - Population studies
  - Data on specific pathologies
  - Typical disease progress
  - Medications and therapies for others
- Informed by evidence, guidelines, economics
- Facilitates holistic, personalized treatments

https://www.siemens-healthineers.com/perspectives/digital-patient-twin

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Data is key for outcome predictions in Digital Twins

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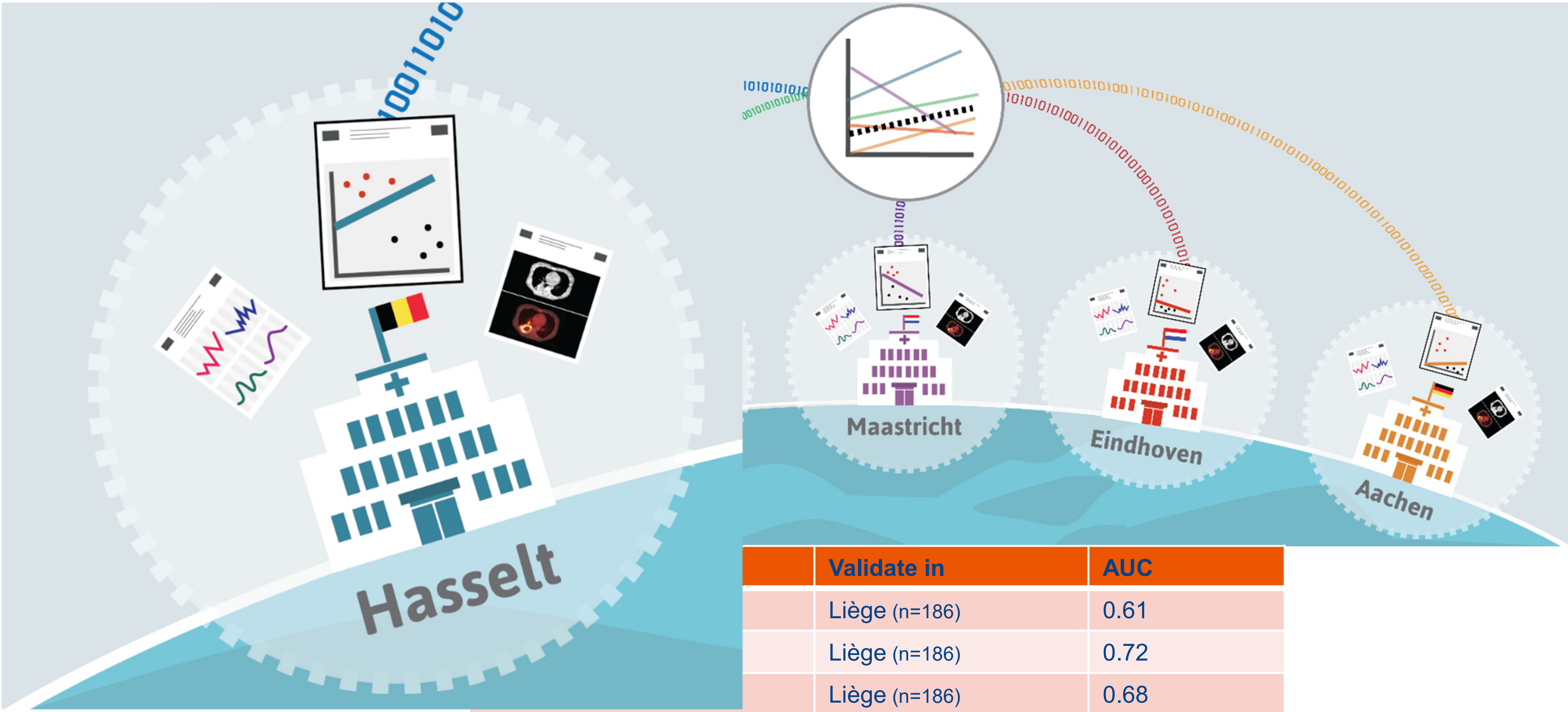
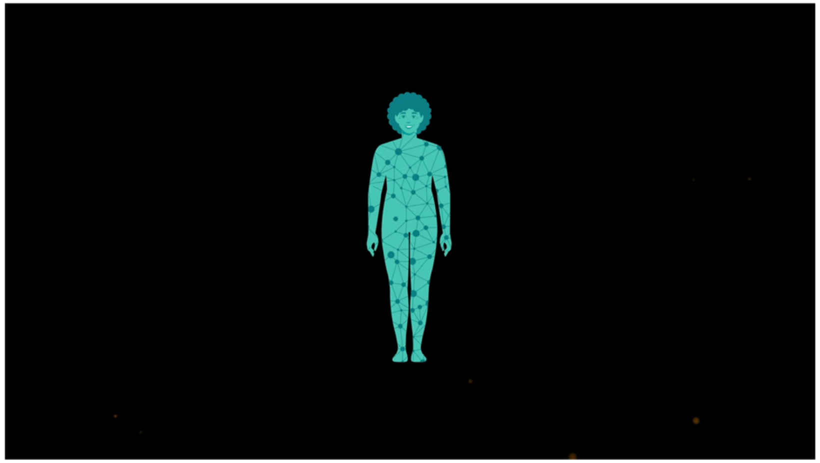
How to learn from data without sharing data

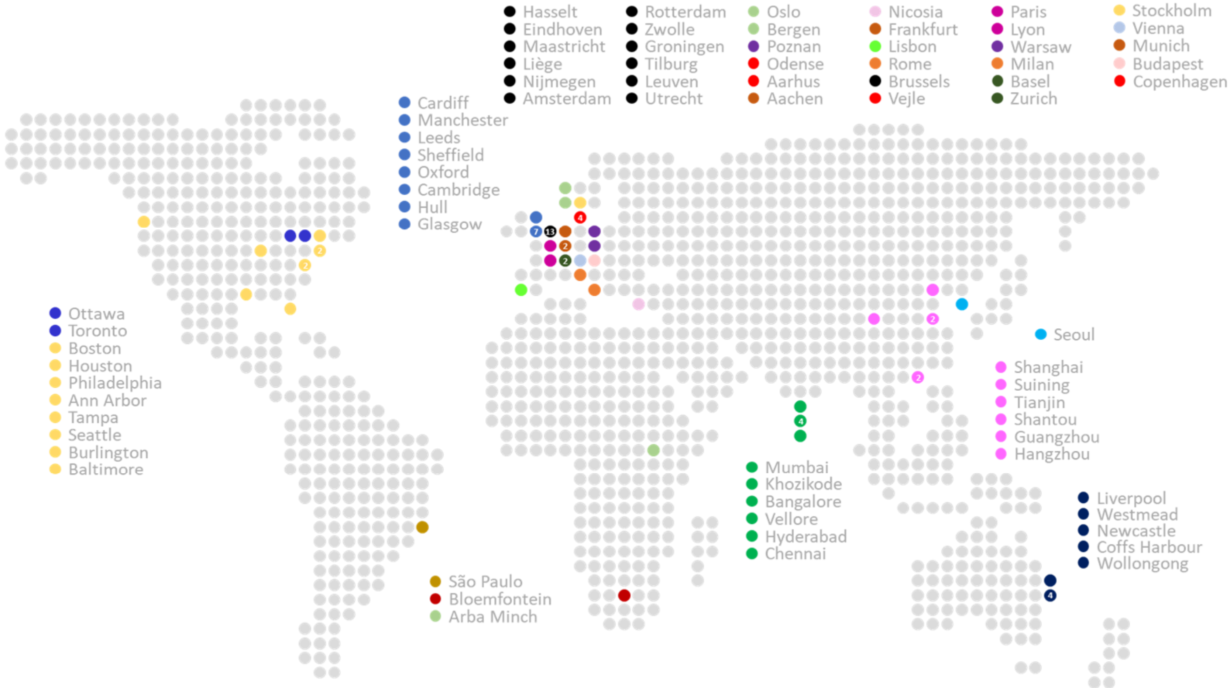


	Validate in	AUC
	Liège (n=186)	0.61
	Liège (n=186)	0.72
	Liège (n=186)	0.68
Maastricht (n=52)	Liège (n=186)	0.75
All 4 together (n=136)	Liège (n=186)	**0.77**
All 5 together (n=322)	World (n=*inf*)	?

Clin Transl Radiat Oncol. 2017;19:24-31.

Building a data community





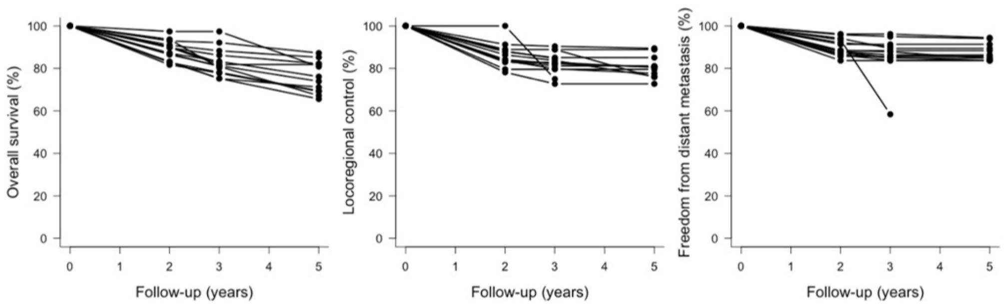
Rare cancers

atomCAT2

14 cancer centers

- Leeds, UK
- Oslo, Norway
- Maastricht, Netherlands
- Hull, UK
- Amsterdam , Netherlands
- Nicosia, Cyprus
- Cardiff, UK
- Lisbon, Portugal
- Rome, Italy
- Poznan, Poland
- Manchester, UK
- Oxford, UK
- Aachen, Germany
- Cambridge, UK

1428 patients



	Overall survival	Locoregional control	Freedom from distant metastasis
Mean global model c-index	0.68	0.71	0.69
Mean leave-one-centre-out validation c-index	0.67	0.69	0.66
	Hazard ratio (95% CI)		
Nodal involvement (N+ relative to N0)	1.45 (1.11-1.89)	1.24 (0.92-1.68)	2.09 (1.42-3.08)
T stage (T3-4 relative to T1-2)	1.42 (1.07-1.89)	1.46 (1.05-2.03)	1.18 (0.80-1.74)
Sex (Female relative to male)	0.65 (0.51-0.83)	0.56 (0.43-0.73)	0.82 (0.58-1.16)
Age at start of radiotherapy (per 10 years)	1.20 (1.07-1.34)	1.08 (0.96-1.22)	1.00 (0.86-1.16)
Gross tumour volume (cm3)	2.02 (1.47-2.76)	2.47 (1.73-3.53)	2.14 (1.40-3.27)
Prescribed dose to primary tumour (log_{10} EQD2, per 10 Gy)	0.96 (0.71-1.29)	1.17 (0.82-1.67)	1.21 (0.79-1.86)
Histology (Basaloid SCC relative to SCC)	0.88 (0.61-1.28)	0.64 (0.39-1.06)	1.04 (0.64-1.69)
Radiotherapy technique (IMRT/VMAT relative to 3D-CRT)	0.96 (0.67-1.39)	1.55 (0.91-2.64)	N/A
Chemotherapy regimen (all relative to no chemotherapy)			
Mitomycin-based	0.35 (0.23-0.53)	0.67 (0.35-1.25)	0.59 (0.28-1.23)
Cisplatin-based	0.32 (0.11-0.92)	0.72 (0.22-2.30)	0.80 (0.21-3.09)
Other chemotherapy	0.81 (0.42-1.56)	0.83 (0.30-2.27)	0.94 (0.31-2.92)

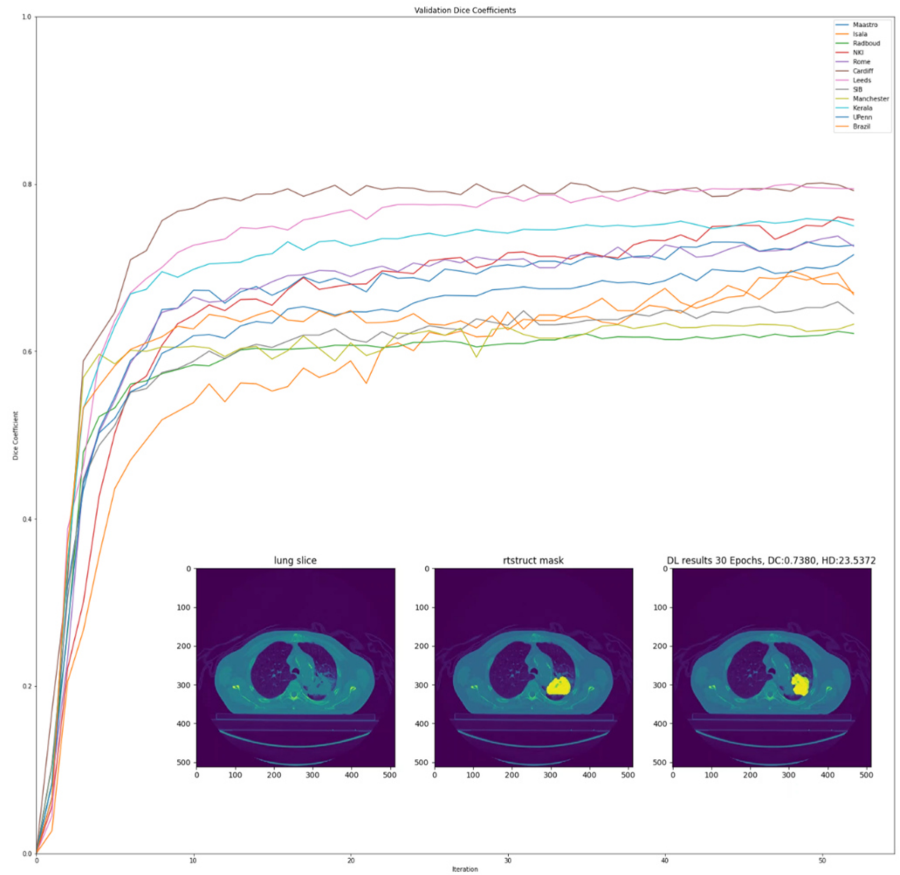
*** Radiotherapy and Oncology (2021) v159 p183-189, https://doi.org/10.1016/j.radonc.2021.03.013**

ARGOS - (AR)tificial intelligence for (G)ross tumour v(O)lume (S)egmentation

- Fully open-sourced code for federated deep learning

- 24 institutional partners across 10 countries
- Executed legal agreements in multiple jurisdictions incl EU, Switzerland, US, China and India

- Inclusivity and diversity – low resource threshold for small clinics and LMICs; each contributes 200+ cases
- In-kind funding from participants



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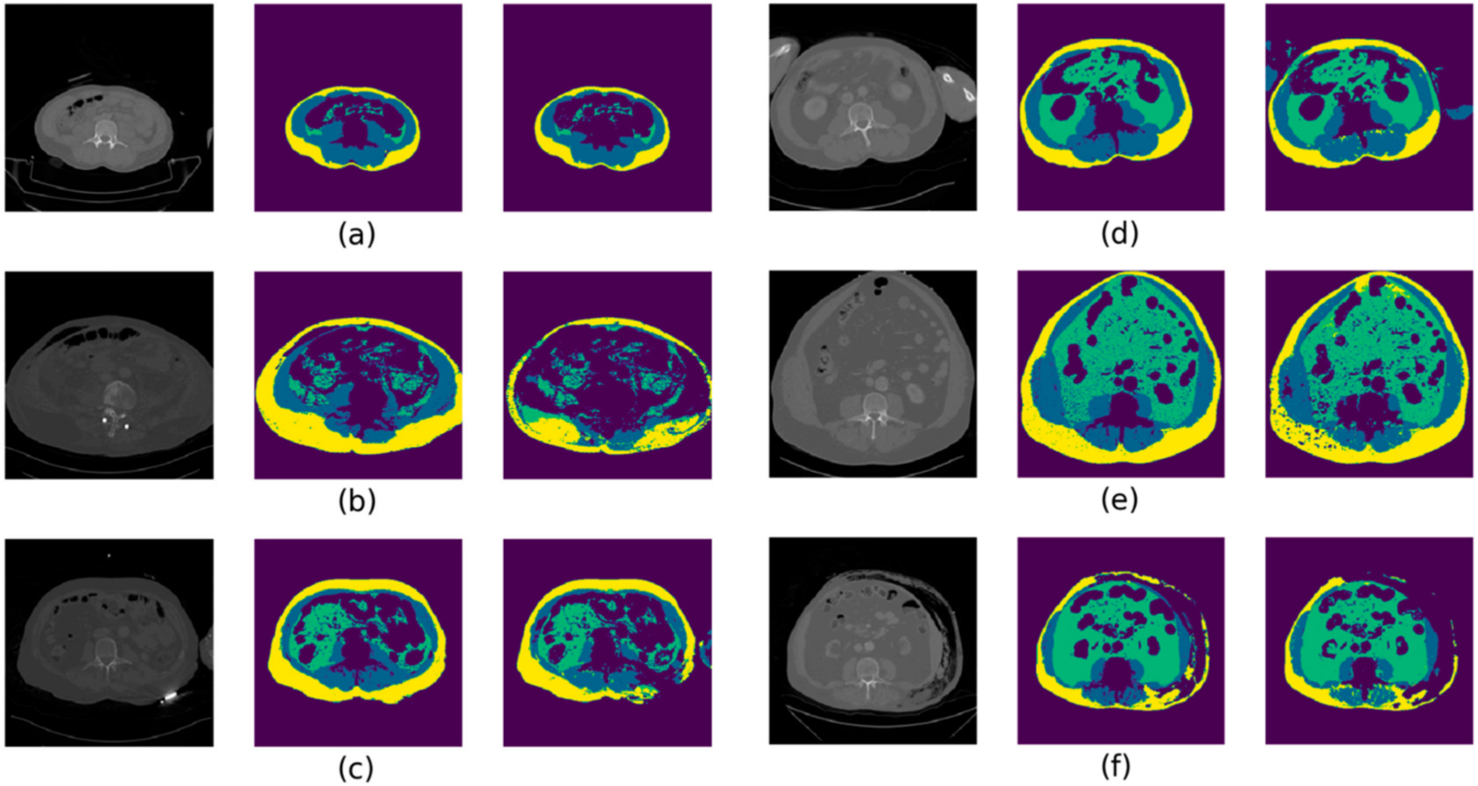
Automated body composition analysis

- 3100 training and cross-validation from multicentre international cancer surgical dataset
- 2500 fully independent external test set
- TRIPOD type 4 generalization study
- 680 independent test cases from polytrauma unit



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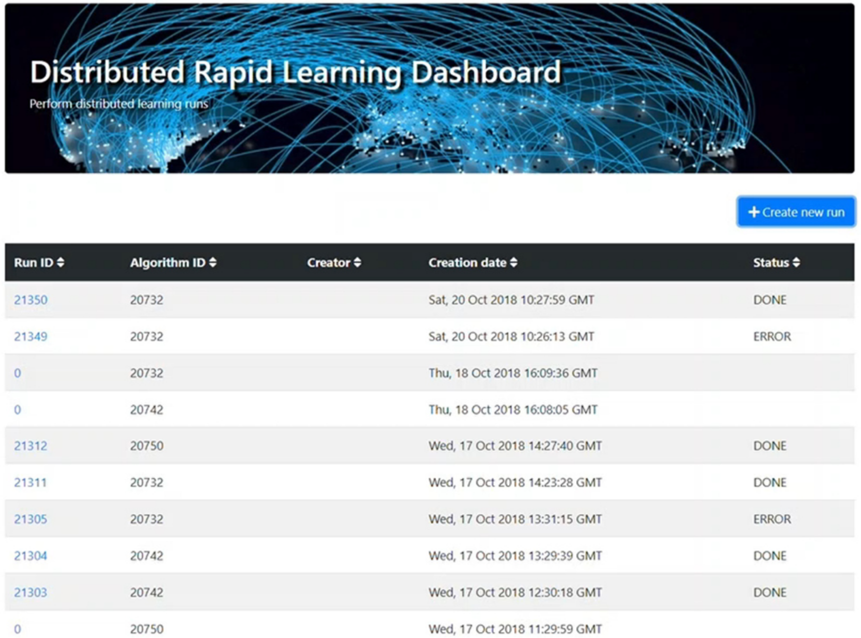
What makes patients similar?

What makes patients similar?

CORAL

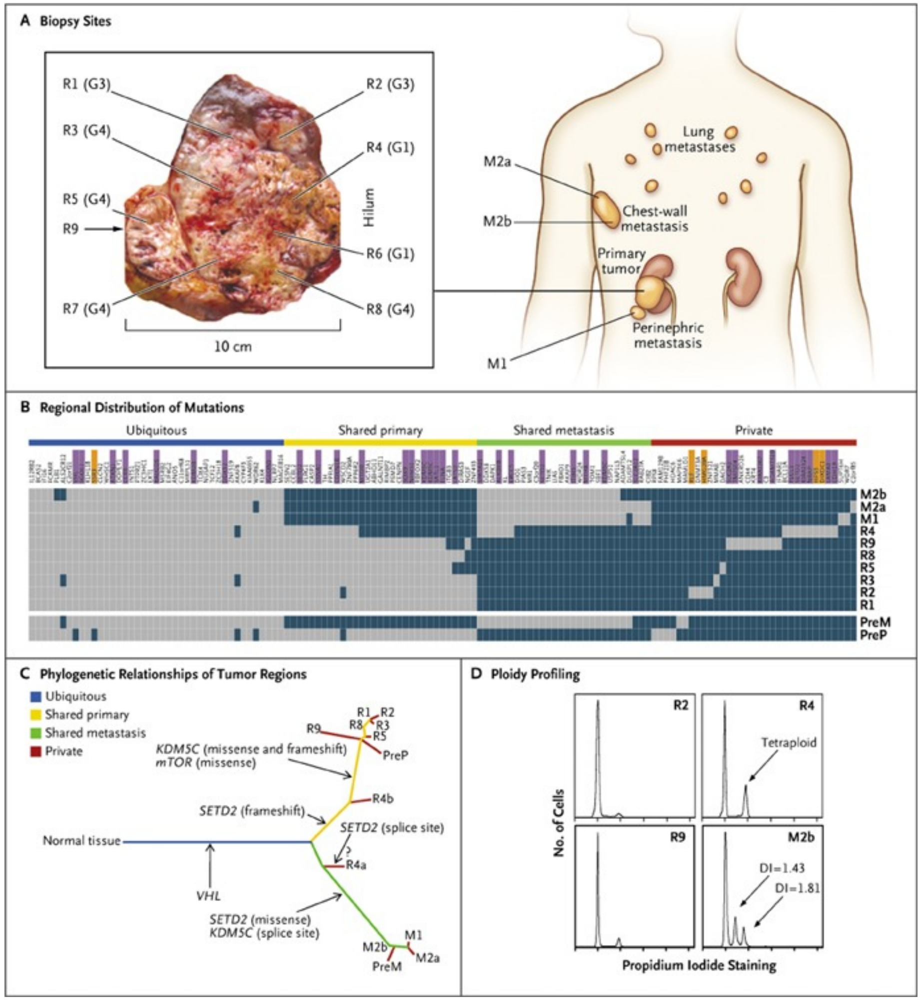


Distributed Rapid Learning Dashboard
Perform distributed learning runs

+ Create new run

Run ID ⬍	Algorithm ID ⬍	Creator ⬍	Creation date ⬍	Status ⬍
21350	20732		Sat, 20 Oct 2018 10:27:59 GMT	DONE
21349	20732		Sat, 20 Oct 2018 10:26:13 GMT	ERROR
0	20732		Thu, 18 Oct 2018 16:09:36 GMT	
0	20742		Thu, 18 Oct 2018 16:08:05 GMT	
21312	20750		Wed, 17 Oct 2018 14:27:40 GMT	DONE
21311	20732		Wed, 17 Oct 2018 14:23:28 GMT	DONE
21305	20732		Wed, 17 Oct 2018 13:31:15 GMT	ERROR
21304	20742		Wed, 17 Oct 2018 13:29:39 GMT	DONE
21303	20742		Wed, 17 Oct 2018 12:30:18 GMT	DONE
0	20750		Wed, 17 Oct 2018 11:29:59 GMT	

What makes patients similar?

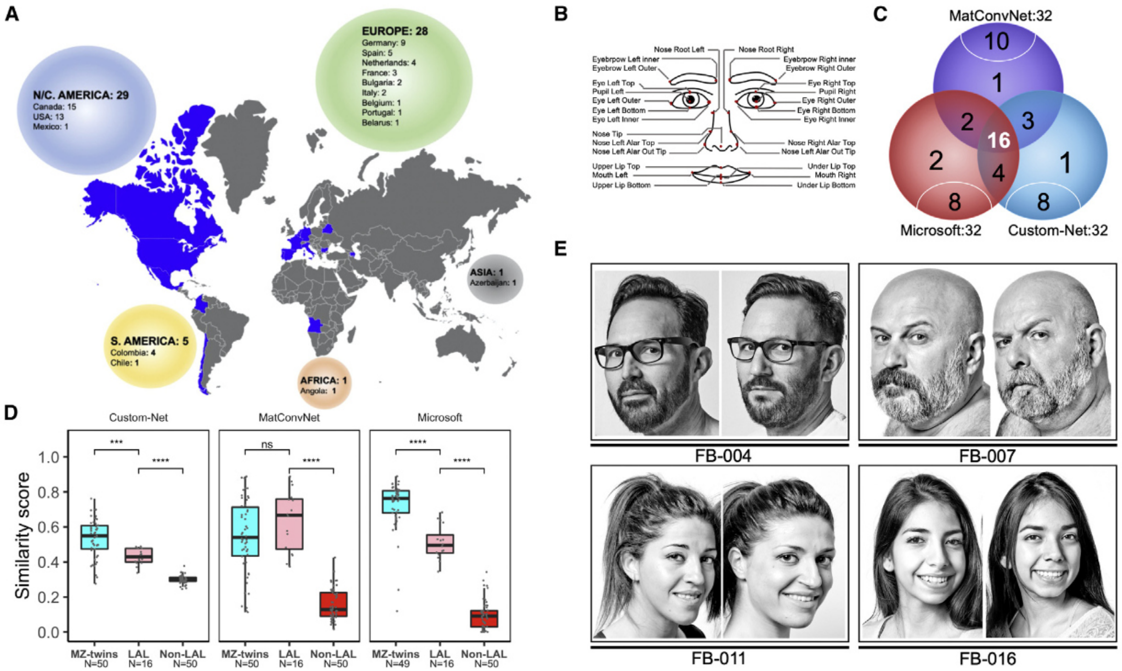


"There were more differences between biopsies from the same tumor at the genetic level than there were similarities"

https://www.medscape.com/viewarticle/759877?0=reg=1

N Engl J Med 2012; 366:883-892

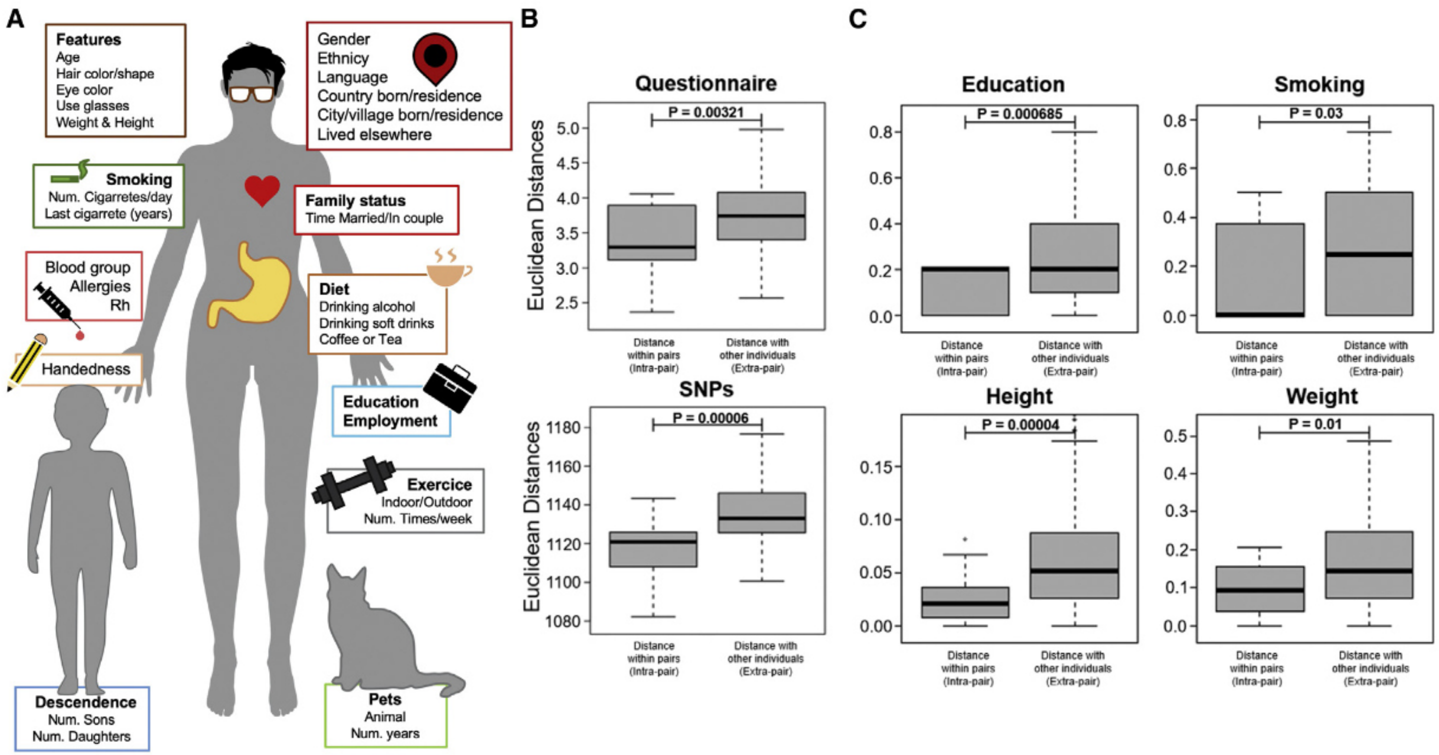
What makes patients similar?



Joshi et al., 2022, Cell Reports 40, 111257

Margot Robbie & Emma Mackey

What makes patients similar?



Nature?

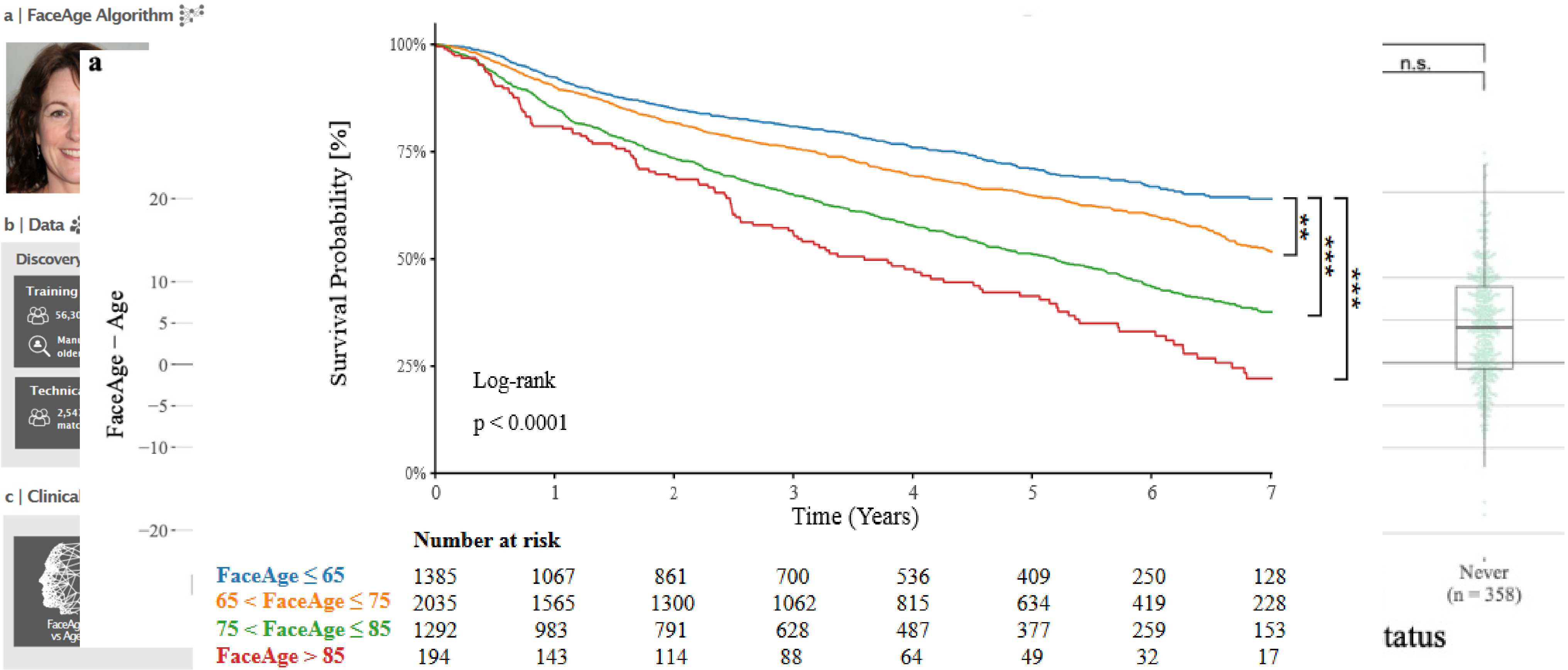
- Similar genetics -> similar facial features?
- Similar genetics -> Similar education, smoking, height, weight?

Nurture?

- Similar facial features -> similar education, smoking, height, weight?
- Similar education, smoking, height, weight -> similar facial features?

Joshi et al., 2022, Cell Reports 40, 111257

What makes patients similar?



Number at risk

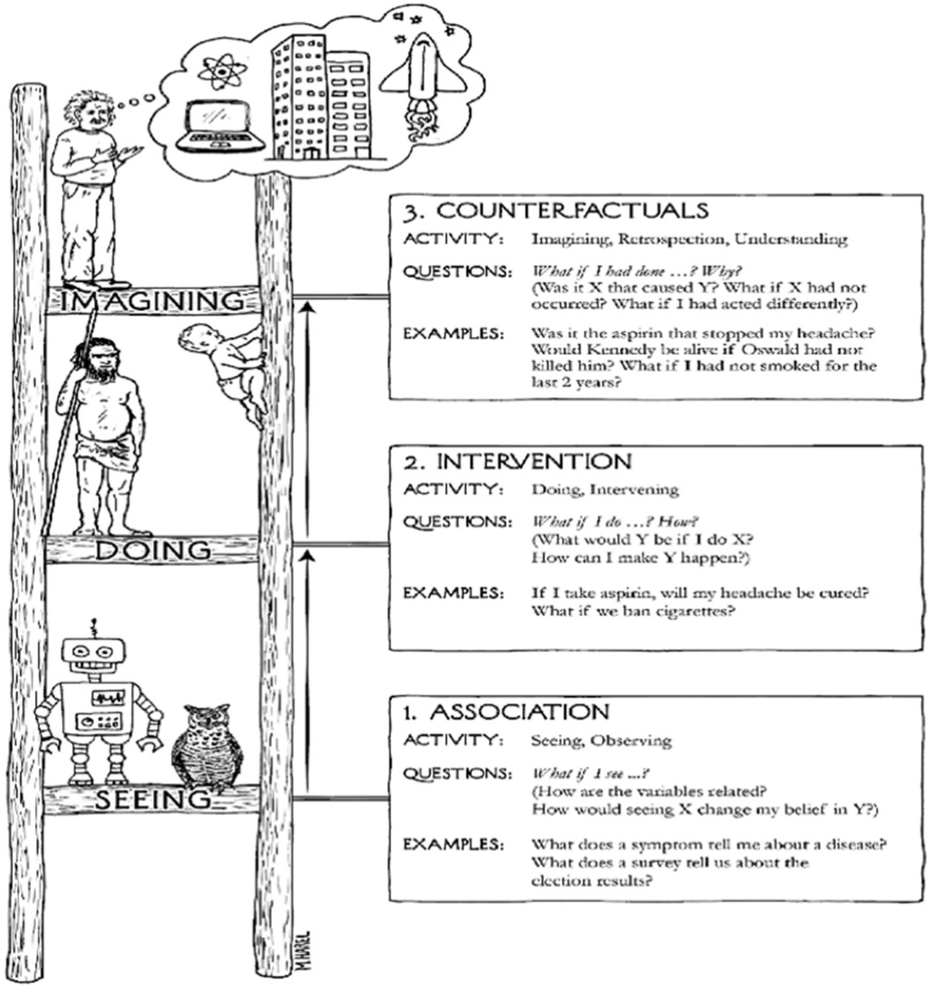
	0	1	2	3	4	5	6	7
FaceAge ≤ 65	1385	1067	861	700	536	409	250	128
65 < FaceAge ≤ 75	2035	1565	1300	1062	815	634	419	228
75 < FaceAge ≤ 85	1292	983	791	628	487	377	259	153
FaceAge > 85	194	143	114	88	64	49	32	17

Zalay et al. medRxiv. 2023 Sep 12;2023.09.12.23295132.

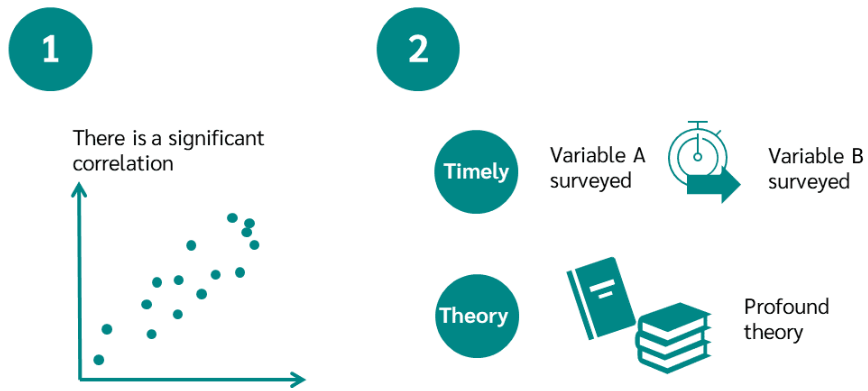
From Digital Twin to Evidence Based Medicine?

Turing Award 2011, Judea Pearl

From Correlation to Causality



Requirements for causality



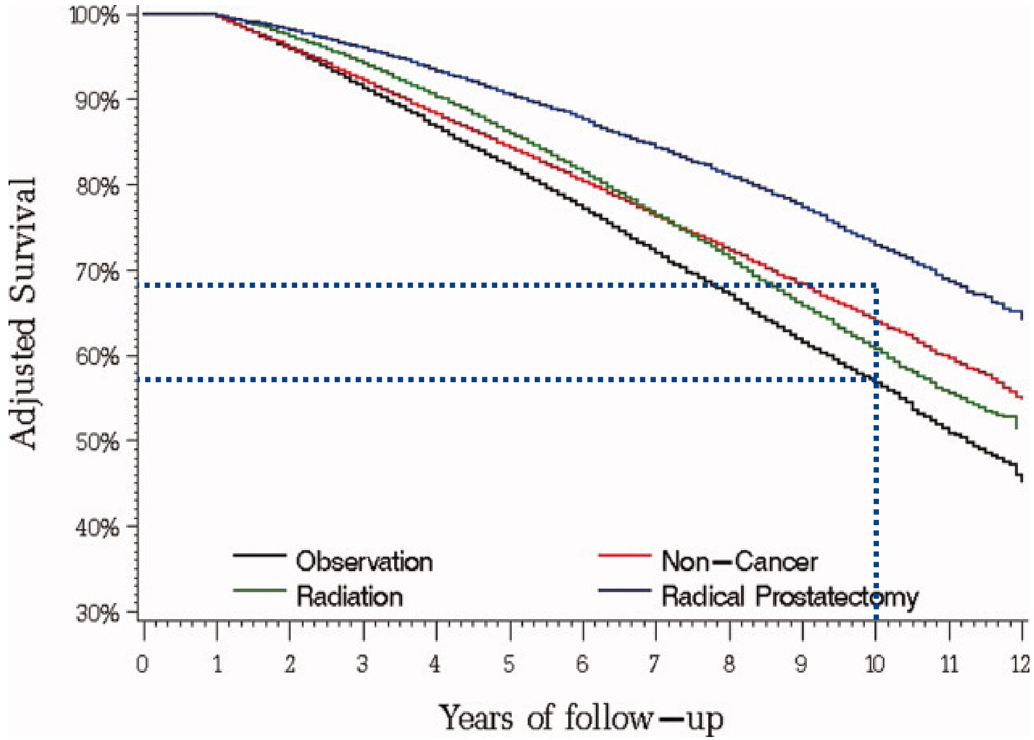
Observational Data, Bayesian Networks & Causality
Active therapy in localized prostate cancer – Dutch Cancer Registry

- RCT1 5%, RCT2 0% 10Y-OS gain
- SEER: ~10% 10Y-OS gain

- Active therapy (n=1.950) vs. observation (n=2.171)
- Causal Blacklist (PSA → age) & whitelist (Tx → 10Y-OS)

- Causal Diagram (Bayesian Network)
- Confounders: Age & year of diagnosis

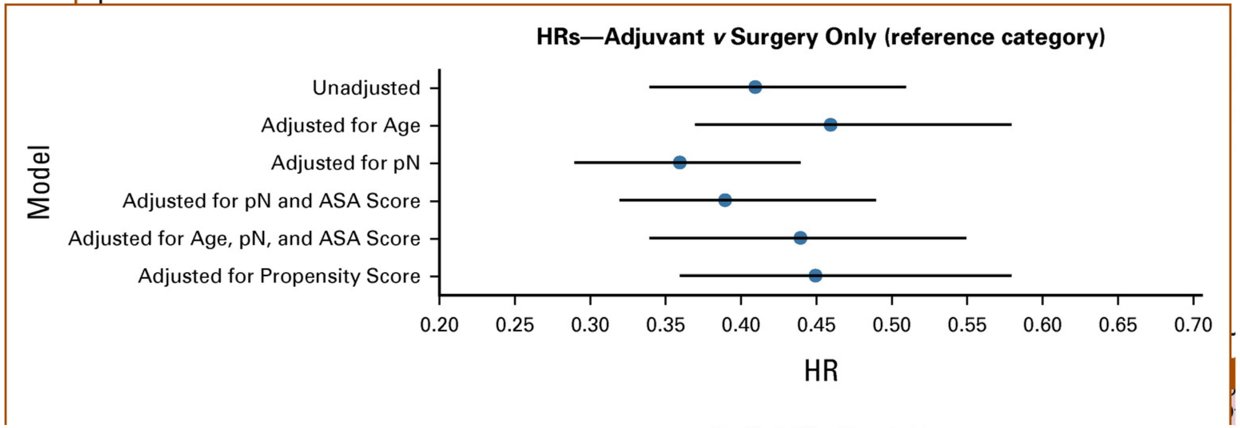
- Bayesian Network: 1% 10Y-OS gain
- Cox corrected for confounders: 3% 10Y-OS gain

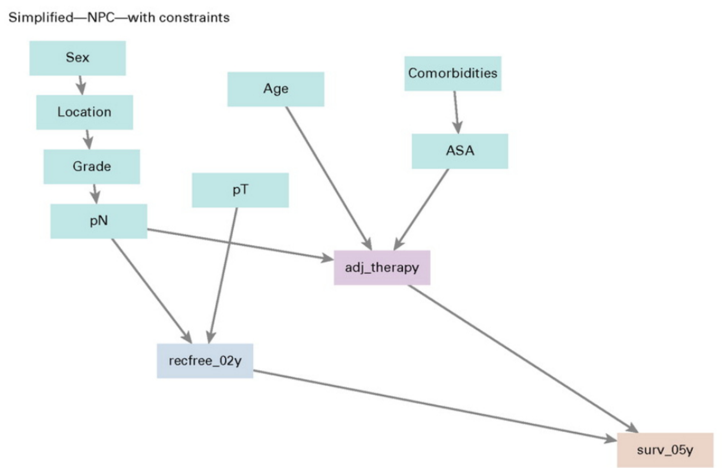


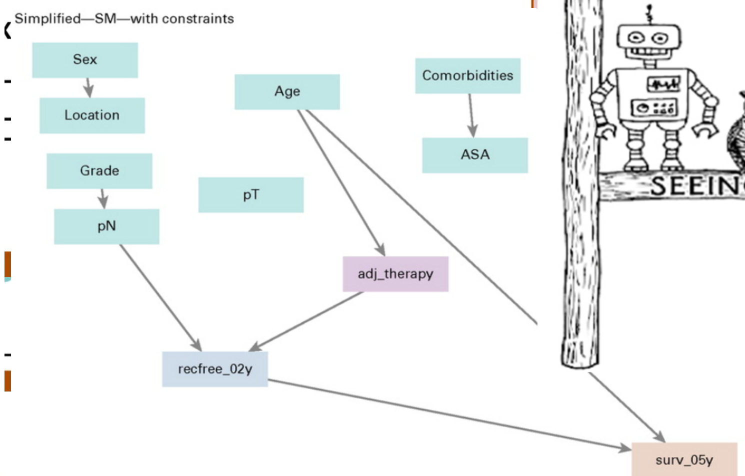
Sieswerda et al. JCO Clin Cancer Inform 7:e220008 | NEJM 352:1977 (2005) | NEJM 375:1415 (2016) | Cancer 112:2456 (2008)

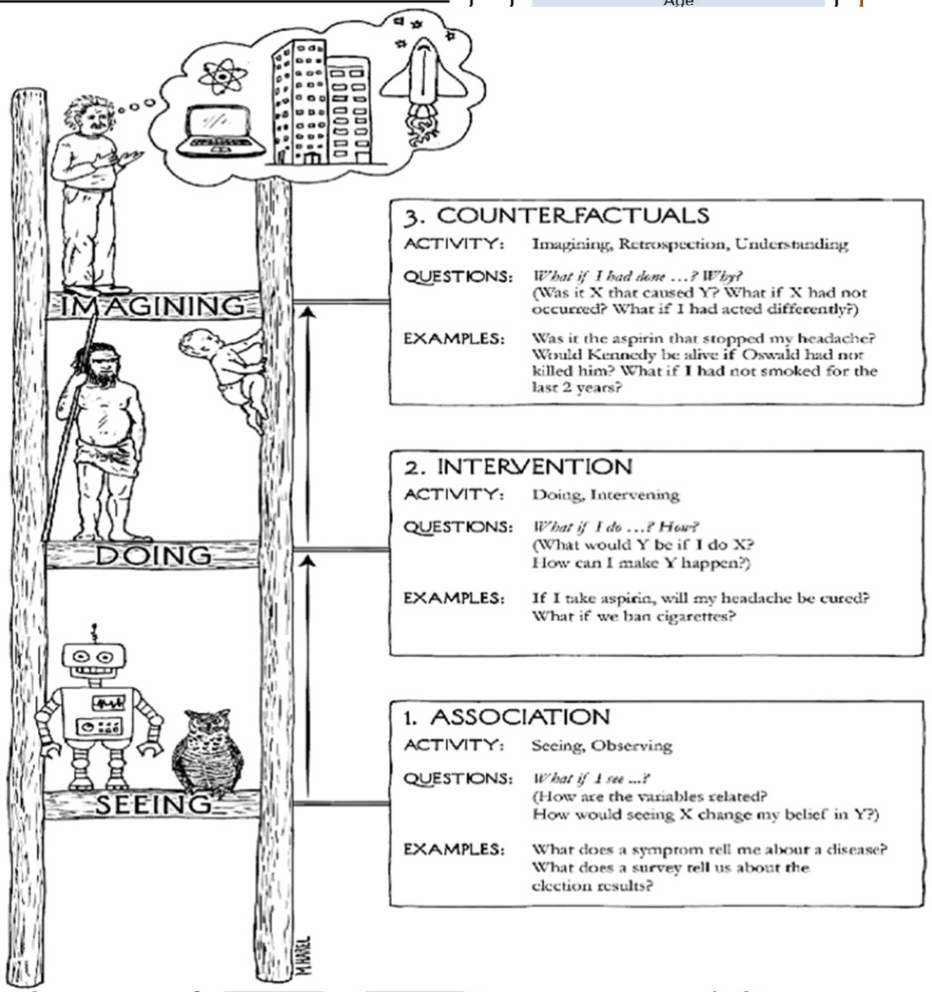
JCO Clin Cancer Inform. 2023 Sep:7:e2300080.

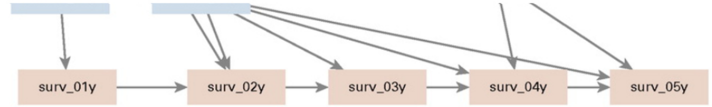
From To	Sex	Age	Grade	Location	pT	pN	Comorbidities	ASA	adj_therapy	recfree_01y	recfree_02y	surv_01y	surv_02y	surv_03y	surv_04y	surv_05y
Sex	-	.	.	X	.	.	.	.	X	X	X					
Age	.	-	.	X	.	.	.	.	X	X	X					
Grade	.	.	-	.	X	X	.	.	.	X	X					
Location	.	.	.	-	.	.	.	.	X	X	X					
pT	.	.	.	.	-	X	.	.	X	X	X					
pN	.	.	.	.	.	-	.	.	X	X	X					











Key Messages

- Only RCT based evidence is not feasible, we need to have complementary evidence
- Digital Twins are a collection of AIs -> to build them we need a lot of diverse data so sharing data effectively on a global scale is mandatory
- Digital Twins complement EBM but might even generate EBM using causal theory

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UZ Leuven, Belgium
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ESTRO 2024

ANNUAL ESTRO CONGRESS

3-7 May 2024
Glasgow, UK

Abstract submission deadline:
25 October 2023

Radiation Oncology:
Bridging the Care Gap