

Artificial Intelligence in Medicine

Dennis Bontempi

AIM
Artificial Intelligence
in Medicine Program



HARVARD
MEDICAL SCHOOL



Dana-Farber
Cancer Institute



**BRIGHAM AND
WOMEN'S HOSPITAL**



**MASSACHUSETTS
GENERAL HOSPITAL**



Dennis Bontempi (PhD @ UM & Harvard's AIM)

Hugo Aerts, Director @ AIM

"The Radiomics guy"



HARVARD
MEDICAL SCHOOL

AIM

Artificial Intelligence
in Medicine Program



Maastricht
University



Artificial Intelligence in Medicine: (My Experience Transitioning) from Computer Science to Clinical Studies

Dennis Bontempi

May 27, 2021

Abstract

Over the last decade, there has been a resurgence of interest in artificial intelligence (AI) applications in medicine. Driven by the advent of deep-learning algorithms, AI is poised to become a transformational force in healthcare.

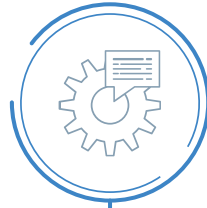
However, most of the deep learning literature published in computer science journals nowadays lacks the depth to be considered helpful to real applications in the medical field. Researchers make dramatic claims that are often not tested in a clinical setting, therefore rendering such publications more proof-of-concept than legitimate scientific studies. More and more experts are pushing back against the AI hype, pointing out that many alleged advances in the field are based on flimsy evidence. Artificial intelligence has become mired in a hype cycle which could lead to a second AI winter.

In this presentation, I will discuss the fundamental differences between AI research in the two aforementioned fields (i.e., computer science and medicine), providing a general overview of all the steps required to develop and validate AI pipelines in the context of medical studies. Furthermore, I will briefly discuss which tools could be borrowed by the computer science (and, more in general, the engineering) community from the medical field to potentially improve the quality of the research in these areas.



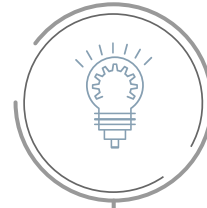
AIM/Introduction

**What does the
group focus on**



Medicine VS Engineering

What's different



Research

**Some of our
research**



Medicine TO Engineering

What translates



AIM/Introduction

**What does the
group focus on**



Medicine VS Engineering

What's different



Research

**Some of our
research**



Medicine TO Engineering

What translates

Artificial Intelligence in Medicine Program





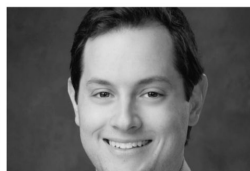
Raymond Mak
Faculty Member



Danielle Bitterman
Faculty Member



Michael Lu
Faculty Member



Benjamin Kann
Faculty Member



Udo Hoffmann
Faculty Member



Roman Zeleznik
Data Scientist



Ahmed Hosny
Data Scientist



Jakob Weiss
Research fellow



Elizabeth Huynh
Medical Physicist



Borek Foldyna
Affiliated Faculty



Zezhong Ye
Postdoctoral Fellow



Osbert Zalay
Research Fellow



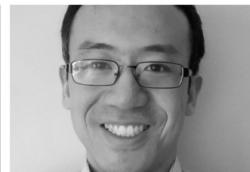
Vineet Raghu
Postdoctoral Fellow



Christian Guthier
Physics Resident



Jack Qian
Resident



Márton Kolossváry
Postdoctoral Fellow



Subha Perni
Resident



Hannah Roberts
Resident



Tafadzwa Chaunzwa
Research Scholar



Yiwen Xu
Physics Resident



Zhongyi Zhang
Research Scholar



Ibrahim Hadžić
Research Scholar



Deborah Plana
Medical Student



Raymond Mak
Faculty Member



Danielle Bitterman
Faculty Member



Michael Lu
Faculty Member



Benjamin Kann
Faculty Member



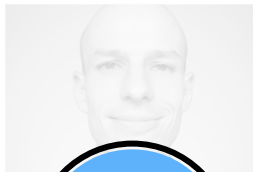
Udo Hoffmann
Faculty Member



Roman Zeleznik
Data Scientist



Ahmed Hosny
Data Scientist



Jake
Resident



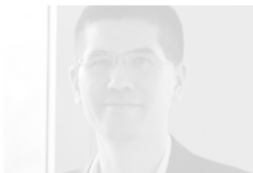
Elizabeth
Medical Student



Borek Foldyna
Affiliated Faculty



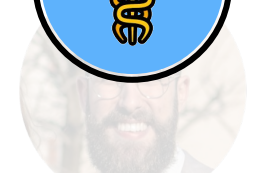
Zezhong Ye
Postdoctoral Fellow



Osbert Zalay
Research Fellow



Vineet Raghu
Postdoctoral Fellow



Christian Guthier
Physics Resident



Jack Qian
Resident



Márton Kolossváry
Postdoctoral Fellow



Subha Perni
Resident



Hannah Roberts
Resident



Tafadzwa Chaunzwa
Research Scholar



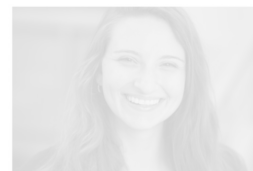
Yiwen Xu
Physics Resident



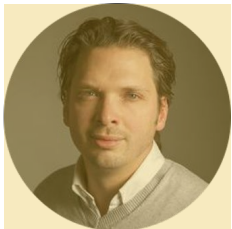
Zhongyi Zhang
Research Scholar



Ibrahim Hadžić
Research Scholar



Deborah Plana
Medical Student



Raymond Mak

Faculty Member



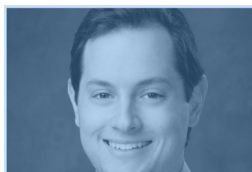
Danielle Bitterman

Faculty Member



Michael Lu

Faculty Member



Benjamin Kann

Faculty Member



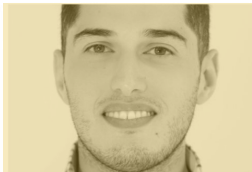
Udo Hoffmann

Faculty Member



Roman Zeleznik

Data Scientist



Ahmed Hosny

Data Scientist



Jakob Weiss

Research fellow



Elizabeth Huynh

Medical Physicist



Borek Foldyna

Affiliated Faculty



Zezhong Ye

Postdoctoral Fellow



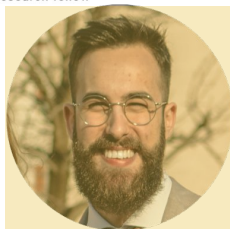
Osbert Zalay

Research Fellow



Vineet Raghu

Postdoctoral Fellow



Christian Guthier

Physics Resident



Jack Qian

Resident



Márton Kolossváry

Postdoctoral Fellow



Subha Perni

Resident



Hannah Roberts

Resident



Tafadzwa Chaunzwa

Research Scholar



Yiwen Xu

Physics Resident



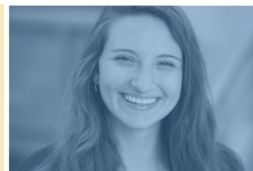
Zhongyi Zhang

Research Scholar



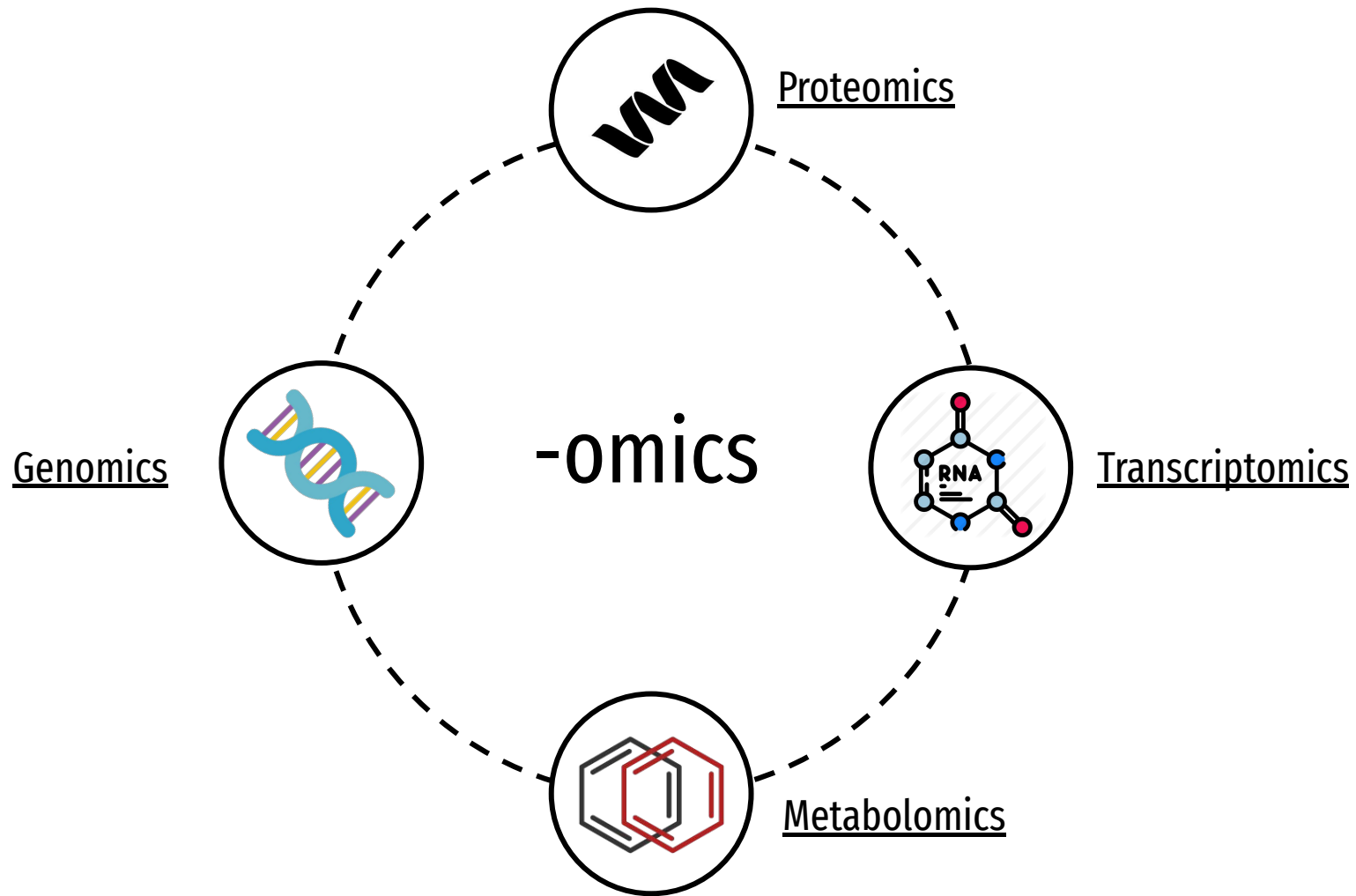
Ibrahim Hadžić

Research Scholar

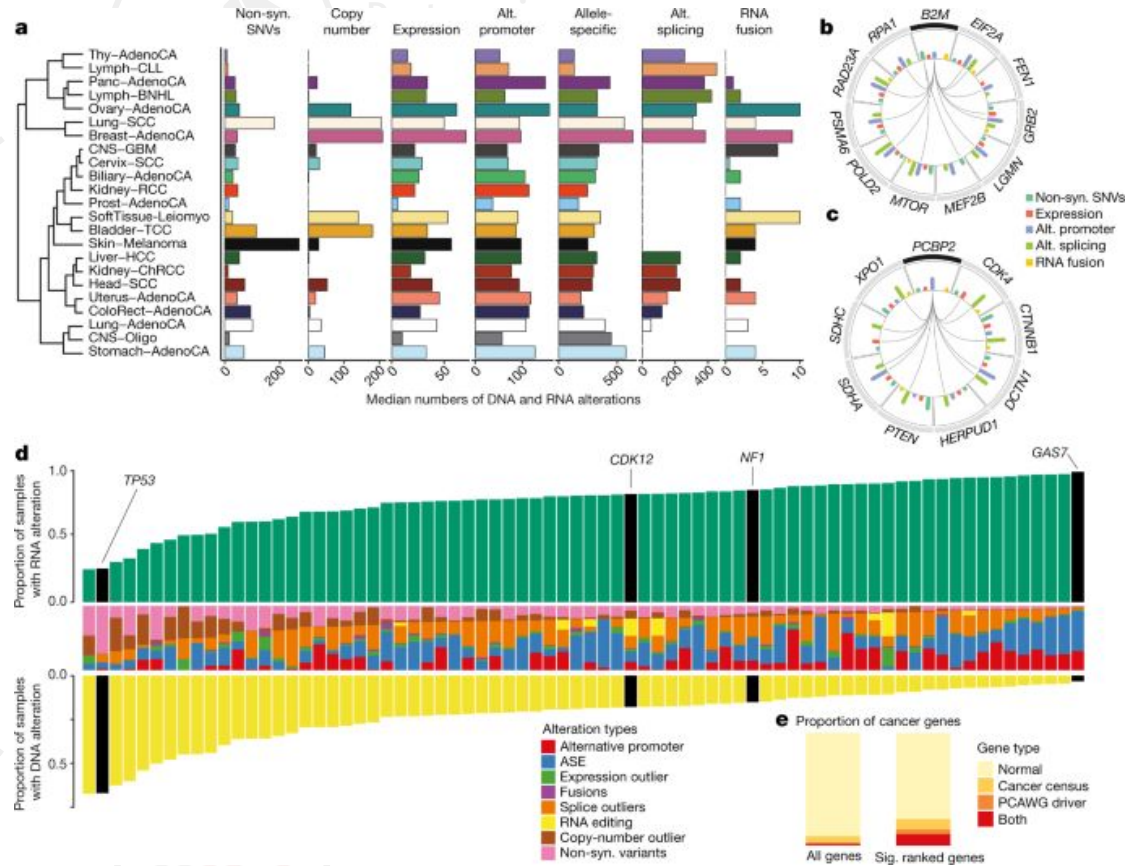


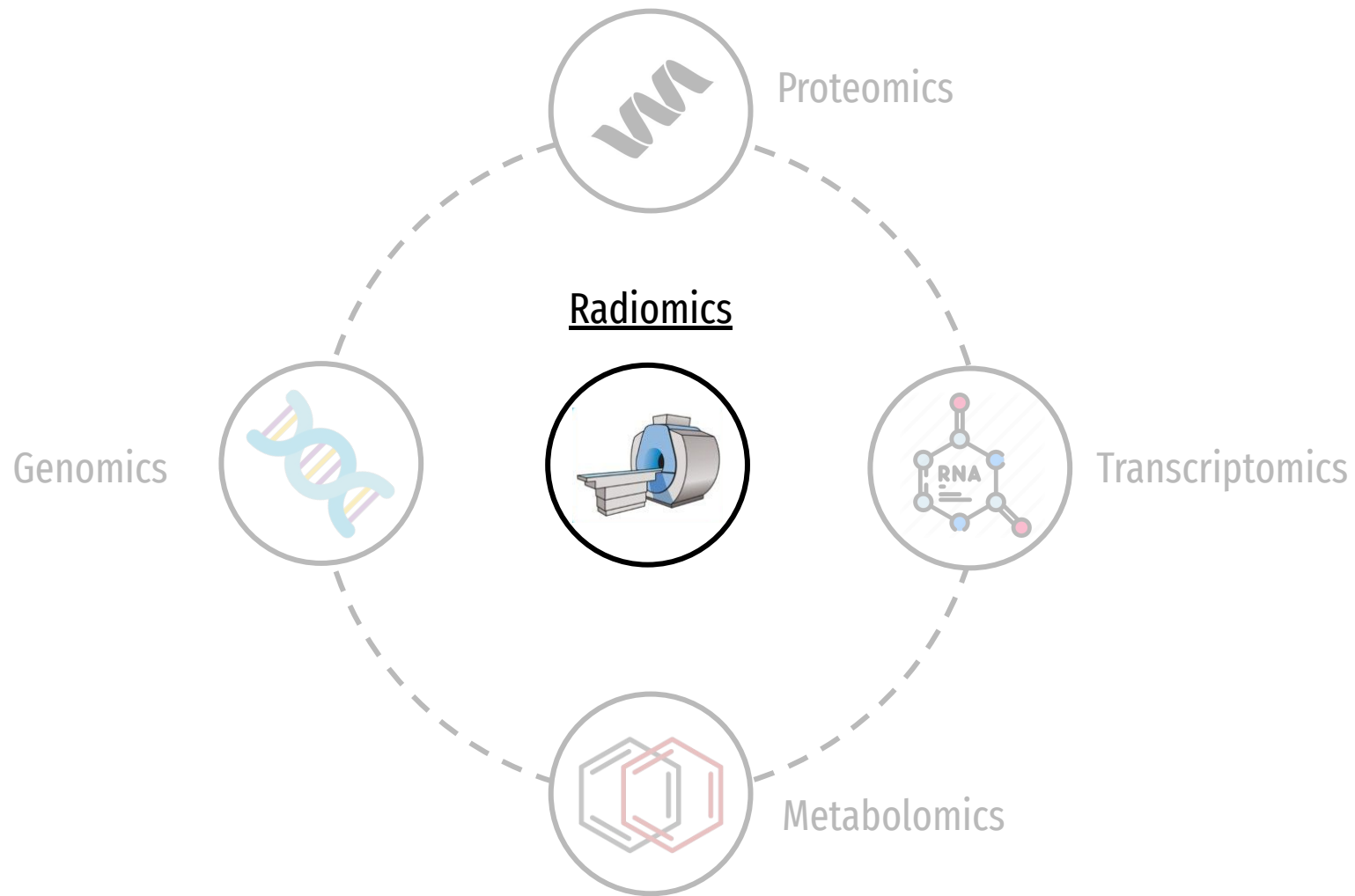
Deborah Plana

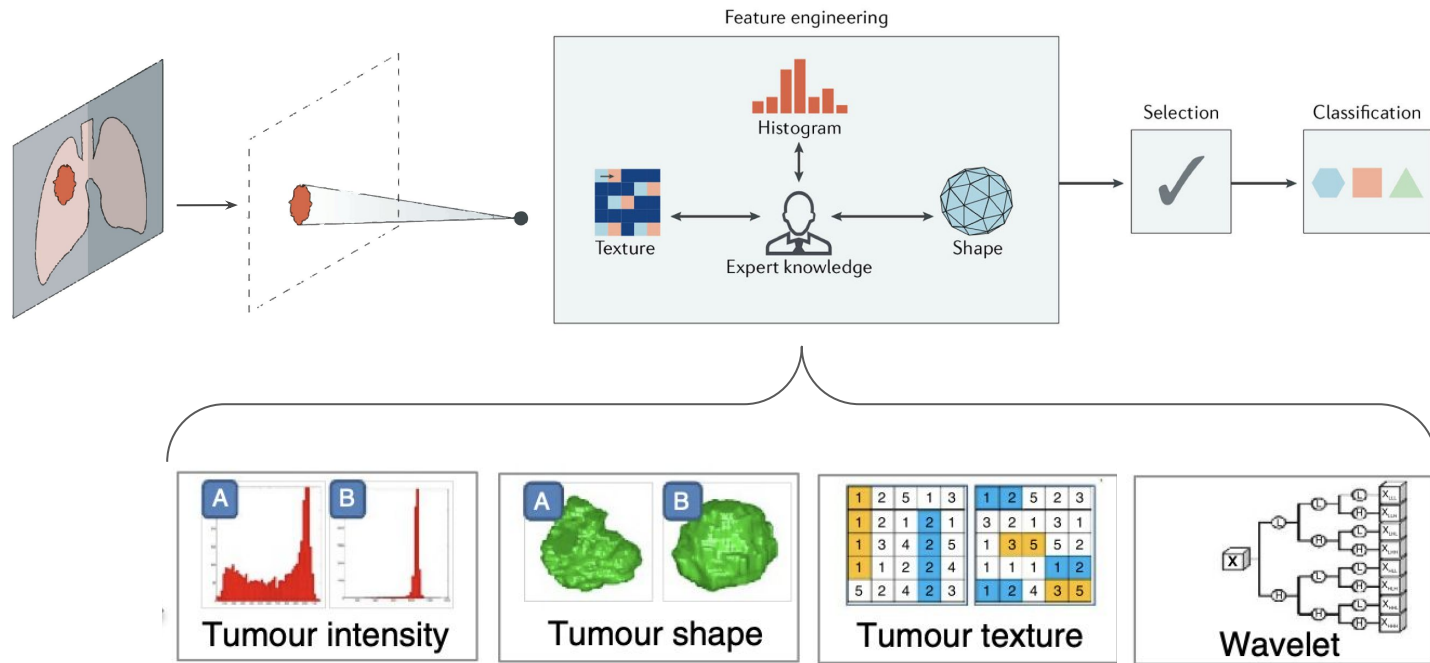
Medical Student



Genomics

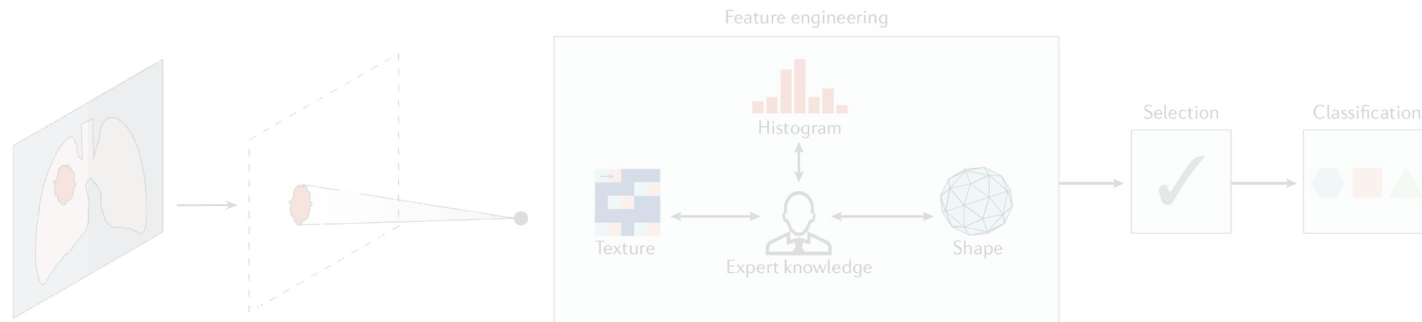




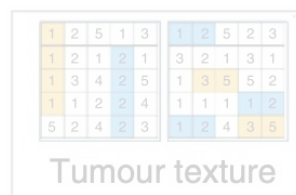
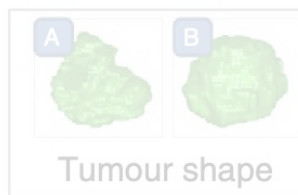
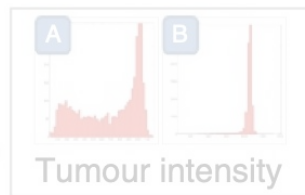


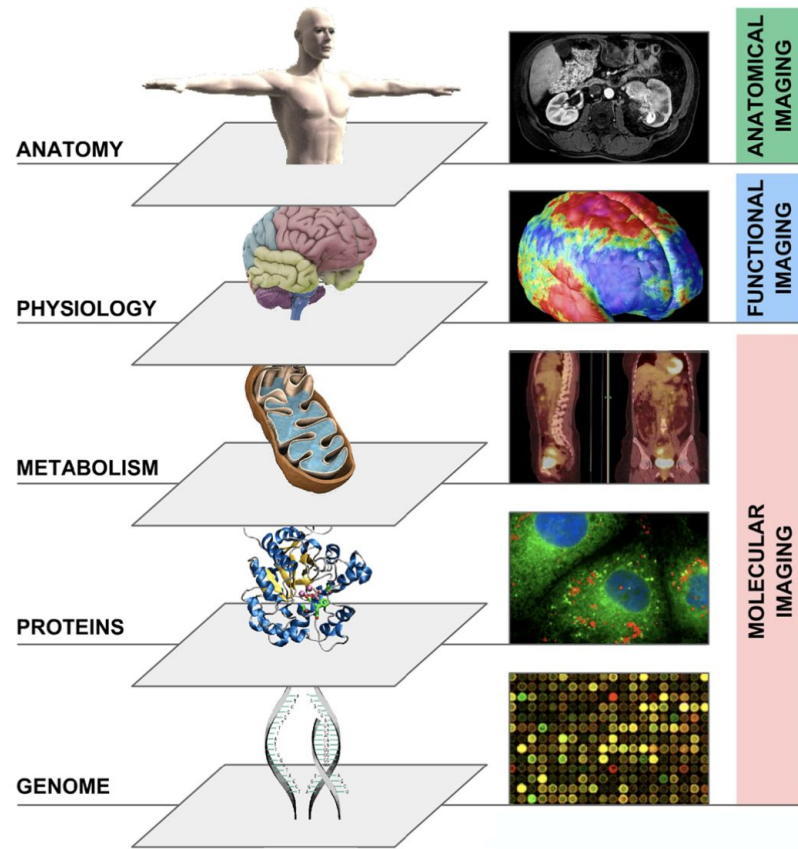
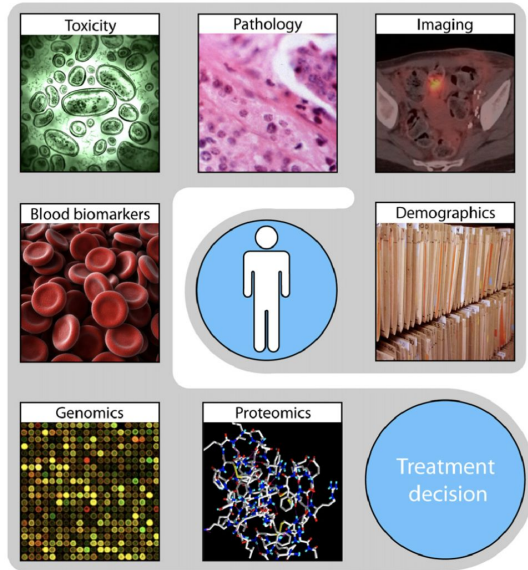
Ahmed Hosny, Chintan Parmar, John Quackenbush, Lawrence H. Schwartz, and Hugo J. W. L. Aerts

Artificial intelligence in radiology (NatRevCancer, 2018)



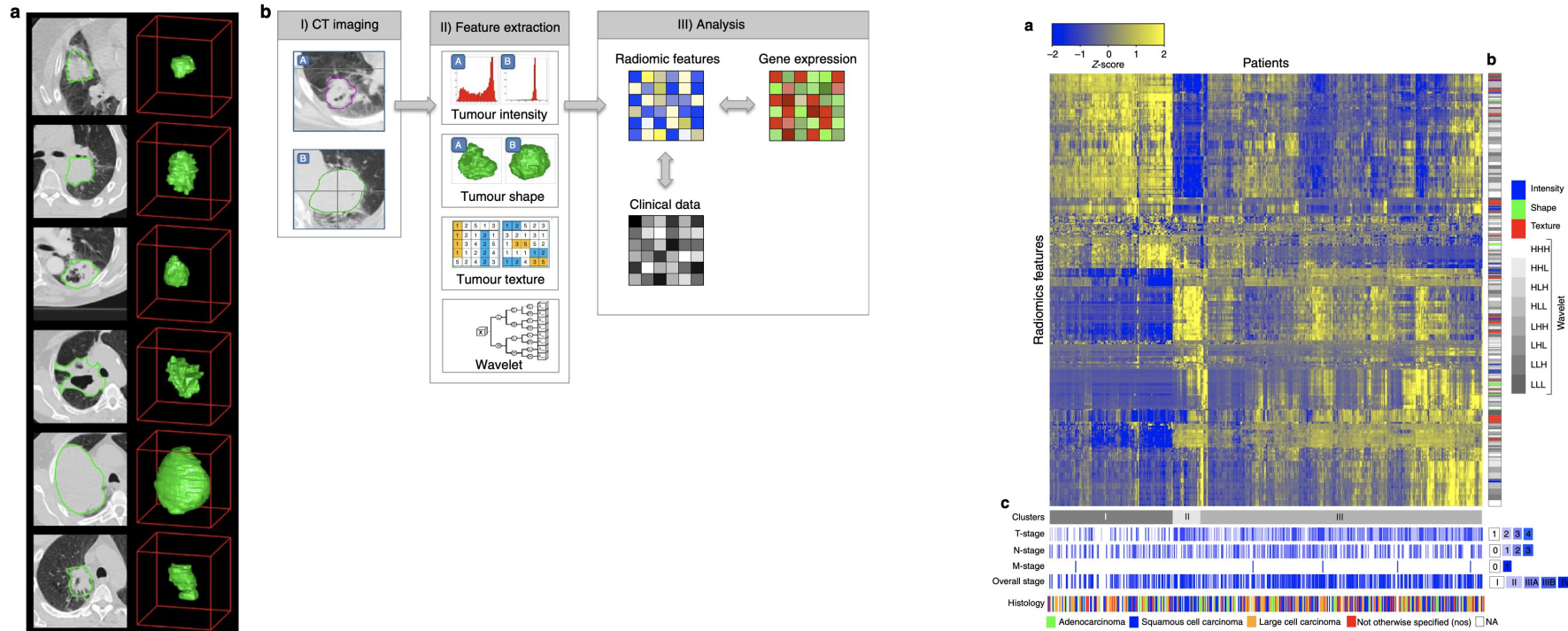
Qualitative → Quantitative





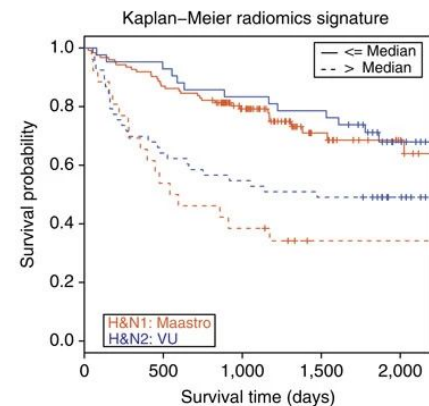
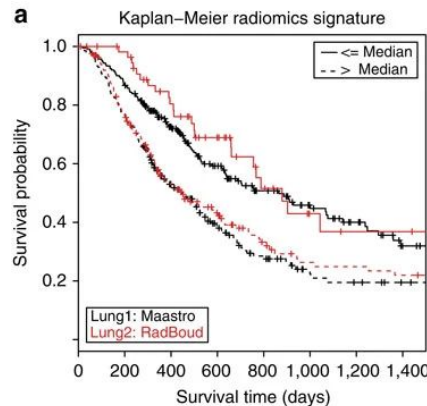
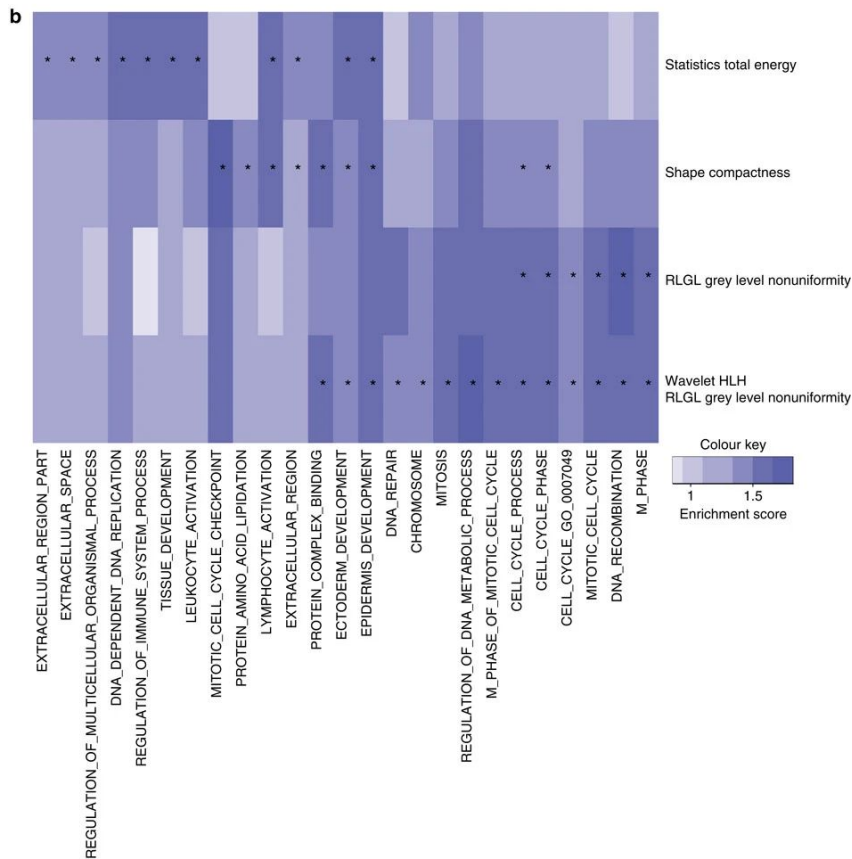
Philippe Lambin, Emmanuel Rios-Velazquez, Ralph Leijenaar, Sara Carvalho, et AL.

Radiomics: Extracting more information from medical image using advanced feature analysis (EU Journal of Cancer, 2012)



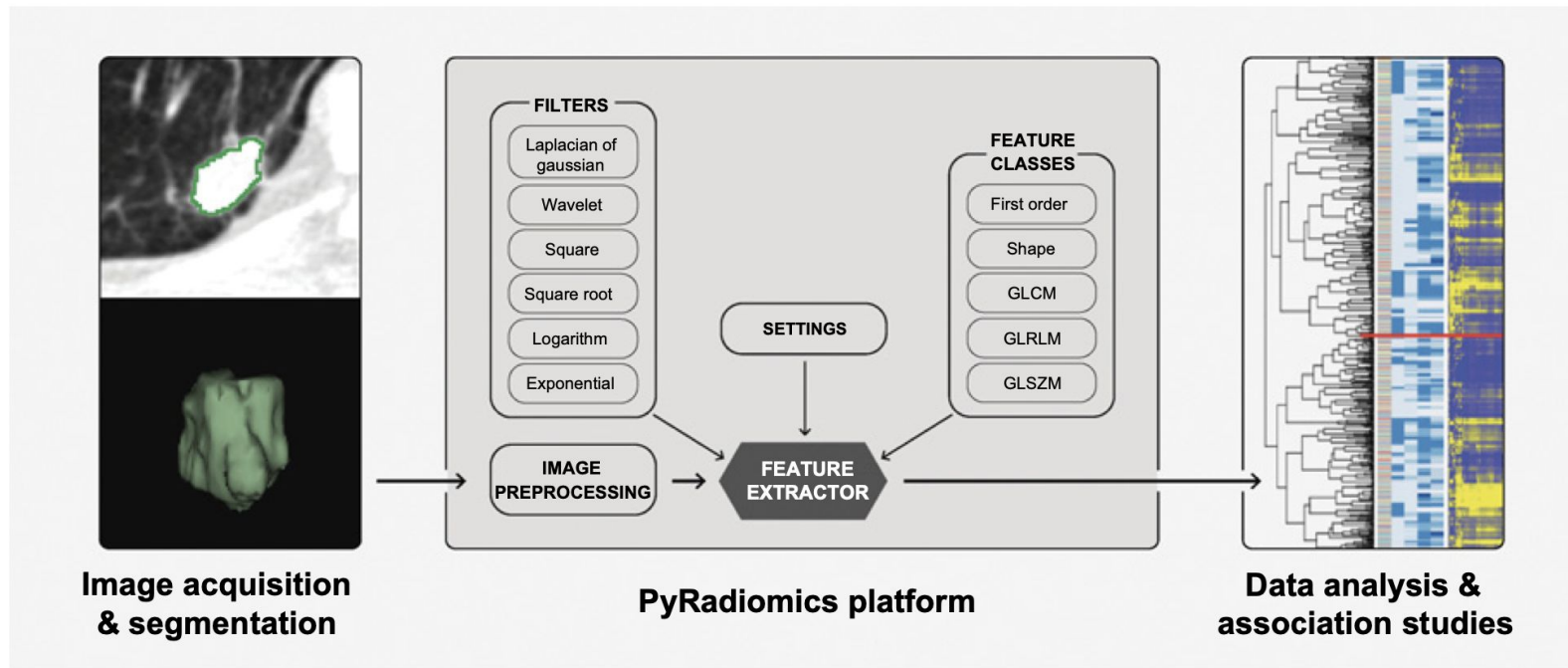
Hugo J. W. L. Aerts, Emmanuel Rios Velazquez, Ralph T. H. Leijenaar, Chintan Parmar, Patrick Grossmann, et al.

Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach (NatCom, 2014)



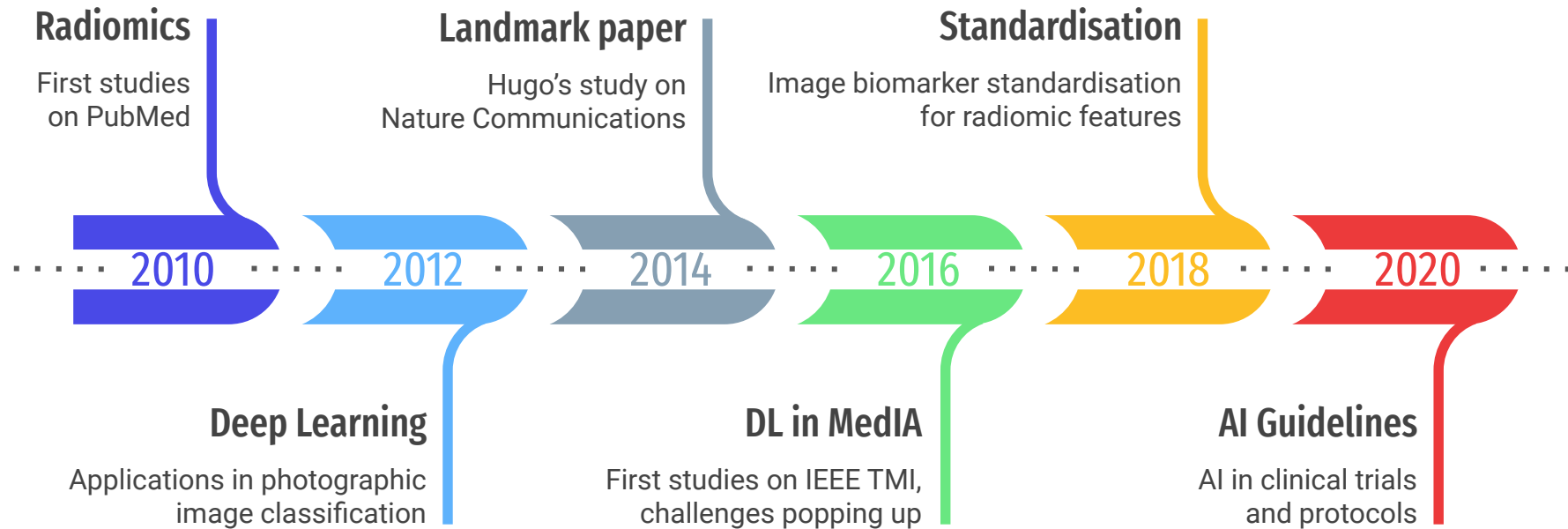
Hugo J. W. L. Aerts, Emmanuel Rios Velazquez, Ralph T. H. Leijenaar, Chintan Parmar, Patrick Grossmann, et Al.

Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach (NatCom, 2014)



Joost J.M. van Griethuysen, Andriy Fedorov, Chintan Parmar, Ahmed Hosny, et AL.

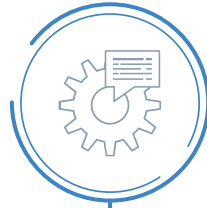
Computational Radiomics System to Decode the Radiographic Phenotype (Cancer Res, 2017)





AIM/Introduction

What does the
group focus on



Medicine VS Engineering

What's different



Research

Some of our
research

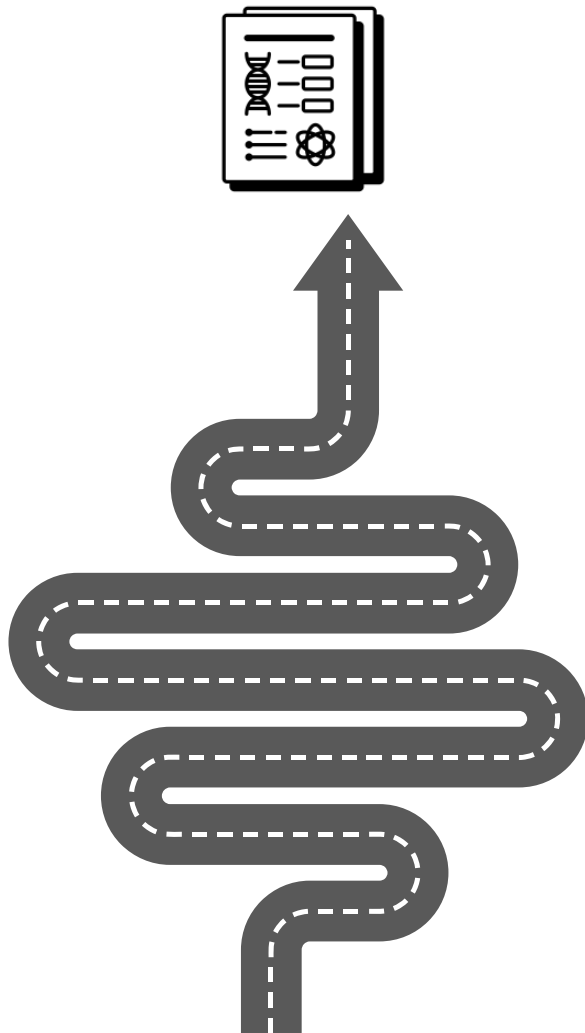


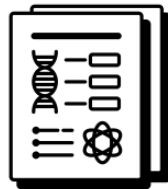
Medicine TO Engineering

What translates



VS





Benchmarking

Against other **methods**
(usually, using **metrics**)



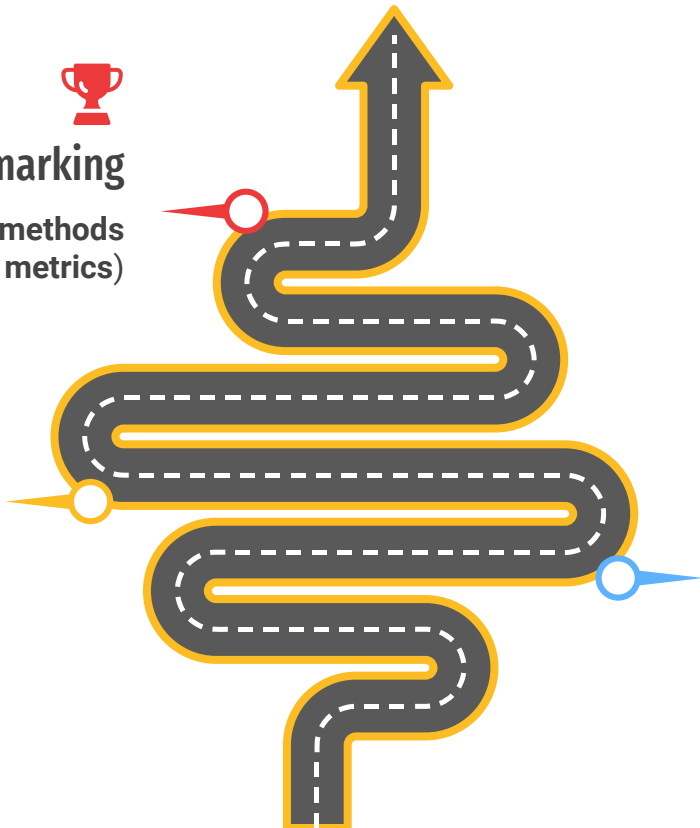
Data Processing

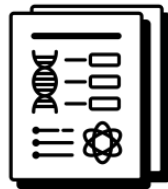
Well, y'all know this already!



Problem to Solve

What are we implementing
(... and why?)





Benchmarking

Against other **biomarkers**
(... more statistics!) 🧐🧐



Hypothesis Testing

Lots of **statistics** 🧐



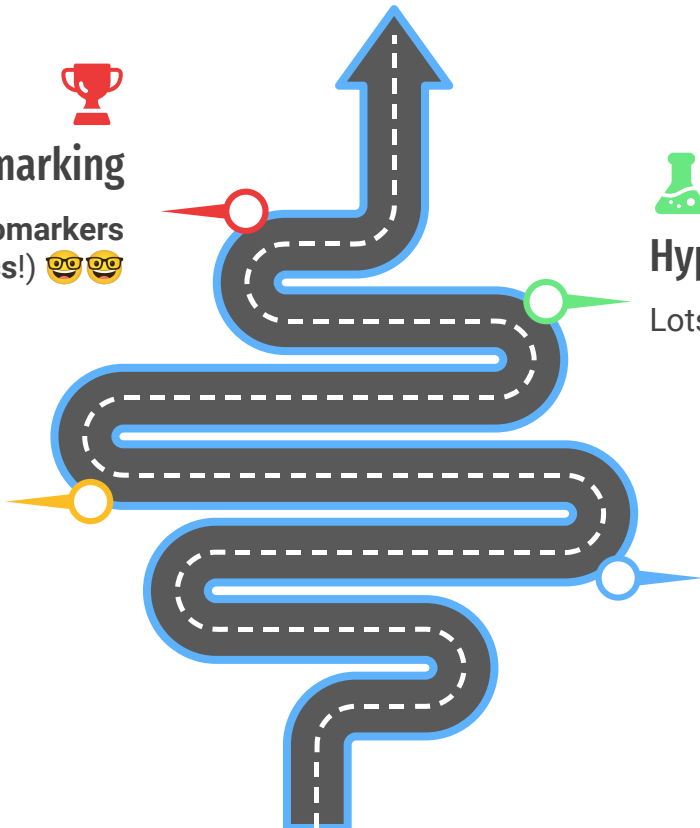
Data Processing

Well, y'all know this already!



Hypothesis (clinical)

What are we looking for
and why (**biomarkers**)





Liver fat from CT
images predicts
overall-survival in
lung-cancer screening
patients

Benchmarking

Against other biomarkers
more statistics



Hypothesis Testing

Lots of statistics 🤖



Data Processing

Well, y'all know this already!



Hypothesis (clinical)

What are we looking for
and why (**biomarkers**)



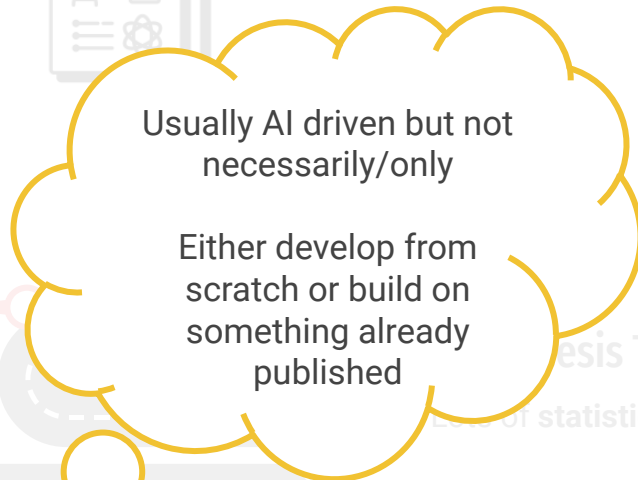
Benchmarking

Against other biomarkers (...
more statistics!) 🧐🧐



Data Processing

Well, y'all know this already!



Usually AI driven but not
necessarily/only

Either develop from
scratch or build on
something already
published

Hypothesis Testing

... of statistics 🧐



Hypothesis (clinical)

What are we looking for
and why (biomarkers)



Benchmarking

Against other biomarkers (...
more statistics!) 🧐🧐



Hypothesis Testing

Lots of **statistics** 🧐

Well, y

Show that the developed
method works adjusting
for **clinical covariates**
(study and dataset
-specific), subgroup
analyses etc.



Hypothesis (clinical)

What are we looking for
and why (**biomarkers**)





Benchmarking

Against other **biomarkers**
(... **more statistics!**) 🧐🧐



Data Processing

Well, y'all know this already!



Hypothesis Testing

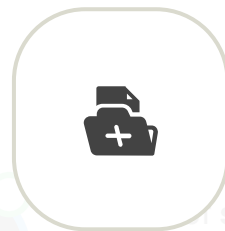
Show that the developed method works adjusting for **known biomarkers** (study and dataset -specific), subgroup analyses etc.



**Large
Datasets**



**Varied
Datasets**



**Real
Datasets**



Imaging Data + Clinical Data

Medical



- Hypothesis testing and generating
- Technical novelty is cool but we don't really care as long as it (really) works
- Really long times at first (basically building on top of the technical, so...), but easier to extend later
- Reviewers will look more at the scientific soundness of the paper
 - Hypotheses (clinical problem)
 - Generalisability
 - Statistics

Engineering



- Problem solving
- Technical novelty is usually very important (if not the only thing that actually matters)!
- Shorter times but harder to extend later (usually more novelty needed)
- Reviewers mostly care about improvements over SOTA
 - Not a lot of statistics (if any)
 - One dataset is usually ok
 - No use-cases are usually ok

Medical



Engineering



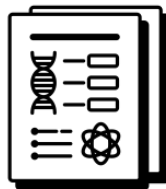
Compare to gold standard (validation)



Segmentation

Downstream task(s):

- Liver segmentation for fat quantification (thresholding)
- Coronary Artery Calcium (CAC) segmentation (and quantification)
- Gamma analysis (RadOnc)
- Simpler biomarkers (e.g., the relative size of heart chambers from contrast CT has prognostic power [...])



- Compare to gold standard (benchmark)
- Compare to (re-implemented) SOTA
- Ablation studies

Medical



Engineering



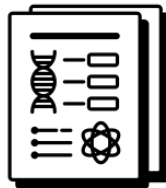
Compute AUROC



Diagnosis/Classification

Downstream task(s):

- Statistical analysis
- Apply the model for eligibility in a trial (retrospective), see how things change
- Task-dependent clinical study
 - Investigate how the AI score correlates with other -omics data



- Compute AUROC
- Ablation studies

Medical



Engineering



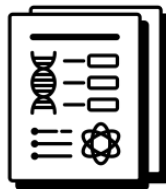
Compute task-specific metrics
(e.g., SSIM, MAE, etc.) + reader test



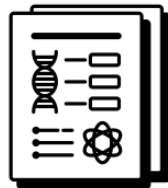
Downstream task(s):

- Re-planning
- Gamma analysis
- HU analysis
 - OOD data
 - Different Phantoms

Image Translation (GANs)



- Compute task-specific metrics
(e.g., SSIM, MAE, etc.) + reader test
- Compare to (re-implemented) SOTA
- Ablation studies



Benchmarking

Against other **biomarkers**
(... **more statistics!**) 🧐🧐



Hypothesis Testing

Lots of **statistics** 🧐



Data Processing

Well, y'all know this already!



Hypothesis (clinical)

What are we looking for
and why (**biomarkers**)

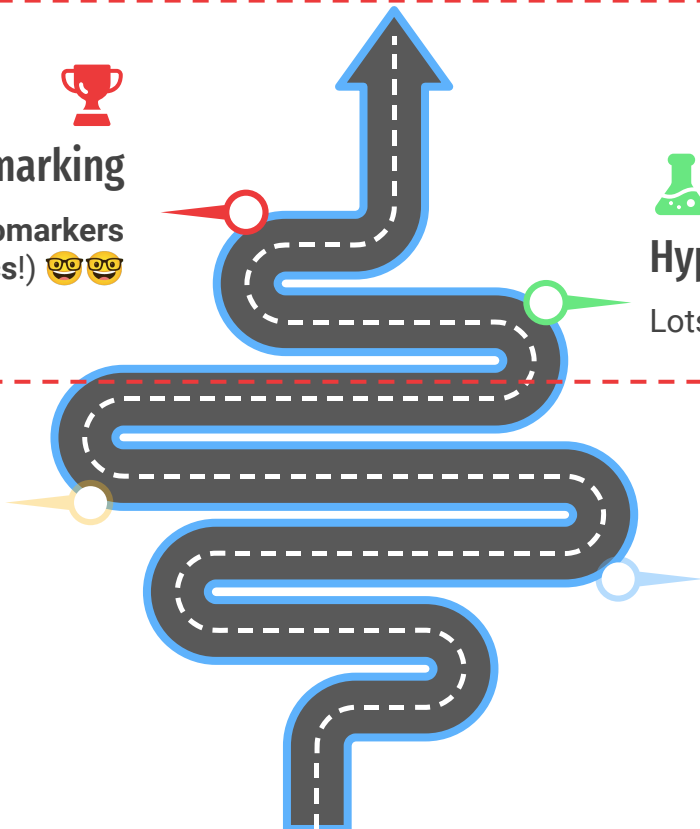
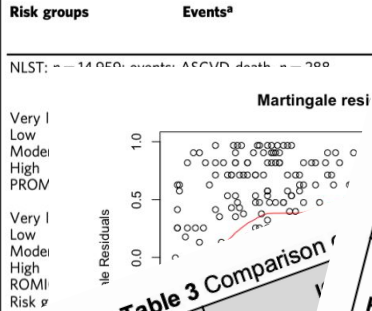


Table 2 Univariate and multivariable survival analyses of the predictive value of deep learning risk scores assessed in the test cohorts.



Supplementary Table 5 AUC comparison for event prediction based on automatically and manually calculated calcium scores.

	P value	Kappa
AI	0.726	
Manual	0.618	

	P value	HR	95% CI	P value
Adjusted for age, sex, diabetes, hypertension, past heart-disease, past stroke				
n/a	Reference	Reference	Reference	Reference
1.57	0.96-2.57	0.069		
2.79	1.70-4.57	<0.001		
3.87	2.45-6.11	<0.001		
Adjusted for Framingham Risk Score				
n/a	Reference	Reference	Reference	Reference
1.57	1.15-3.15	0.012		
2.79	1.47-4.50	0.001		
3.87	2.45-6.11	<0.001		

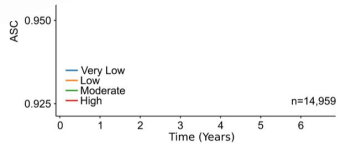
	AI	AUC	SD	SE	95%CI	P-value
NLST: n=396; Events: ASCVD death, n=11	AI	0.69				
	Manual	0.64	0.08	0.08	0.54-0.84	0.0156
PROMISE: n=4,021; Events: ACM, MI, UA, n=130	AI	0.66		0.07	0.50-0.78	0.0552
	Manual	0.68	0.02	0.02	0.62-0.71	3.63 × 10 ⁻¹¹
ROMICAT-II: n=441; Events: ACS, n=38	AI	0.83		0.02	0.63-0.72	9.34 × 10 ⁻¹³
	Manual	0.86	0.03	0.03	0.76-0.90	1.96 × 10 ⁻¹⁴
			0.03	0.03	0.81-0.92	1.94 × 10 ⁻¹⁶

NLST³: National Lung Screening Trial; PROMISE⁴: Prospective Multicenter Imaging Study for Evaluation of Chest Pain; ROMICAT-II⁵: Rule Out Myocardial Infarction using Computer Assisted Tomography II; AUC: Area under the curve, SD: Standard Deviation, SE: Standard Error, CI: Confidence interval. All p-values were calculated using a two-sided Wilcoxon Test.

Supplementary Table 3 Comparison

Cohort	Events
FHS-CT2, n=663	
NLST, n=396	
PROMISE, n=4,021	
ROMICAT-II, n=441	
All test data, n=5521	

FHS-CT2²: Framingham Heart Study, part 2; NLST³: National Lung Screening Trial; PROMISE⁴: Prospective Multicenter Imaging Study for Evaluation of Chest Pain; ROMICAT-II⁵: Rule Out Myocardial Infarction using Computer Assisted Tomography II; ICC: Intraclass Correlation Coefficient, which is the smallest positive floating-point number possible.



Number at risk

	0	1	2	3	4	5	6
Very Low	3613	3596	3577	3532	3496	3451	2961
Low	4730	4706	4665	4614	4552	4492	3820
Moderate	2373	2352	2320	2294	2254	2216	1872
High	4243	4190	4129	4054	3955	3847	3231

Figure 4: Schoenfeld residuals plot for the multivariable (age, sex, diabetes, hypertension, past heart-disease, past stroke) Cox PH model.

Number at risk

	0	1	2	3
Very Low	1615	1498	942	342
Low	1264	1150	713	234
Moderate	557	507	312	96
High	585	530	325	107

CAC group

	Very Low	Low	Moderate	High
ACS=0 (n[%])	256 (98.5)	105 (89.0)	27 (79.4)	15 (51.7)
ACS=1 (n[%])	4 (1.5)	13 (11.0)	7 (20.6)	14 (48.3)
Total	260	118	34	29

cigarettes



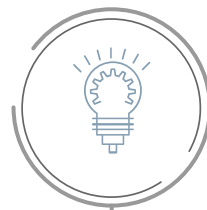
AIM/Introduction

What does the
group focus on



Medicine VS Engineering

What's different



Research

Some of our
research



Medicine TO Engineering

What translates

DL in Medical Imaging



Data Mining

Mine the unknown.

New biomarkers
discovery



Diagnostics

Quantify the known.

From qualitative to
quantitative



Automation

Automate extraction.

Well known biomarkers
extraction automation

DL in Medical Imaging



Data Mining

Mine the unknown.

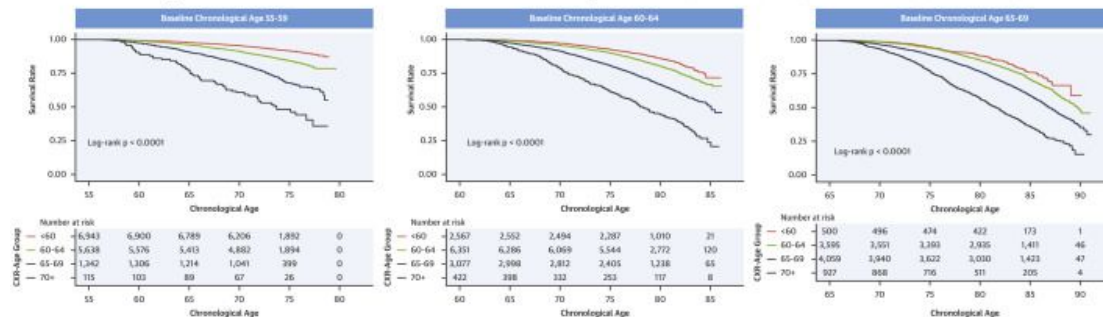
New biomarkers
discovery

Try to extract information doctors don't really know
how to mine (new biomarkers, always based on loose
biological hypotheses anyway)

E.g., from Chest X-Rays:

- Deterioration of a patient with COVID (FB AI)
- Screening eligibility of heavy smokers

→ **hypothesis generating studies**

A**CXR-Age Developed in 116,035 individuals.****Input: Chest X-ray image****CXR-Age
convolutional neural network****Output: Chest x-ray age
of 60 years****Chronological age: 71 years
Observed outcome: Alive at the
end of follow-up at age 94****B****CXR-Age Validated for All-Cause and CV Mortality in PLCO (N = 40,967) and NLST (N = 5,414).****Kaplan-Meier survival by CXR-Age and chronological age in the PLCO test dataset**

Vineet K. Raghu, Jacob Weiss, Udo Hoffmann, Hugo J. W. L. Aerts and Michael T. Lu.

Deep Learning to Estimate Biological Age From Chest Radiographs (JACC, 2021)

DL in Medical Imaging

Try to quantify qualitative information doctors use for clinical decision making (based on strong biological hypotheses)

E.g., from CT scans:

- Predict treatment response
- Predict survival of patients with lung lesions

From Chest X-Rays:

- COVID diagnose/severity



Diagnostics

Quantify the known.

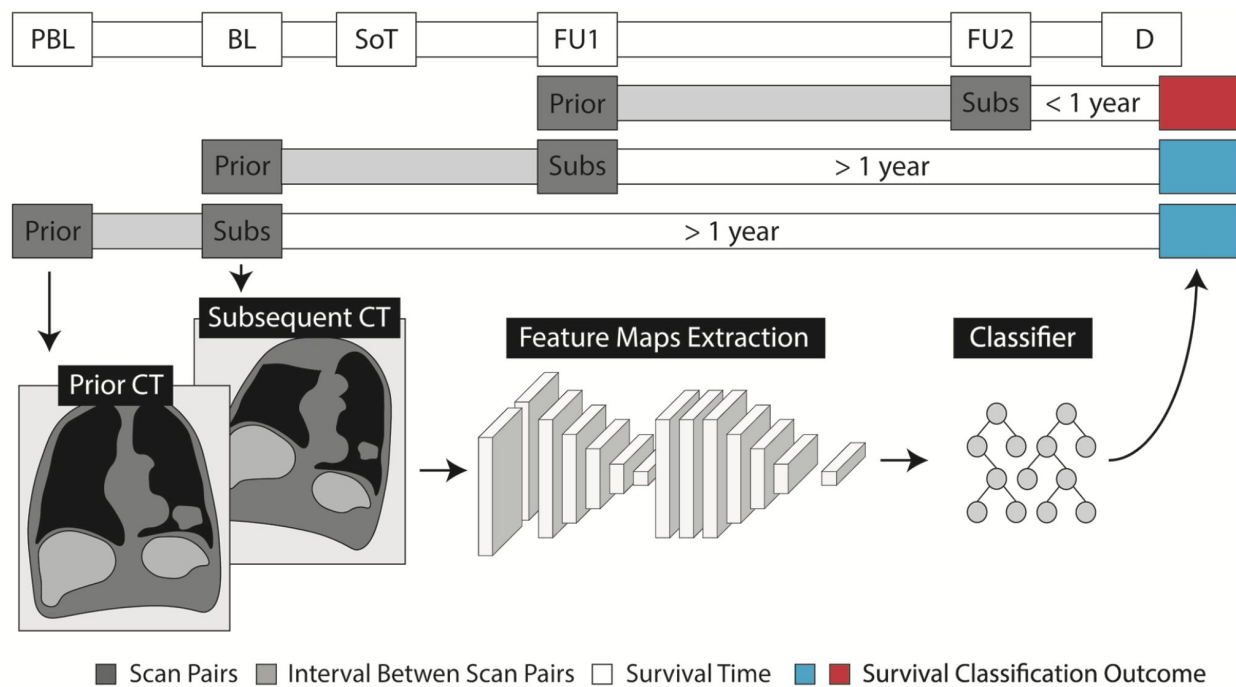
From qualitative to quantitative



→ **hypothesis testing studies**

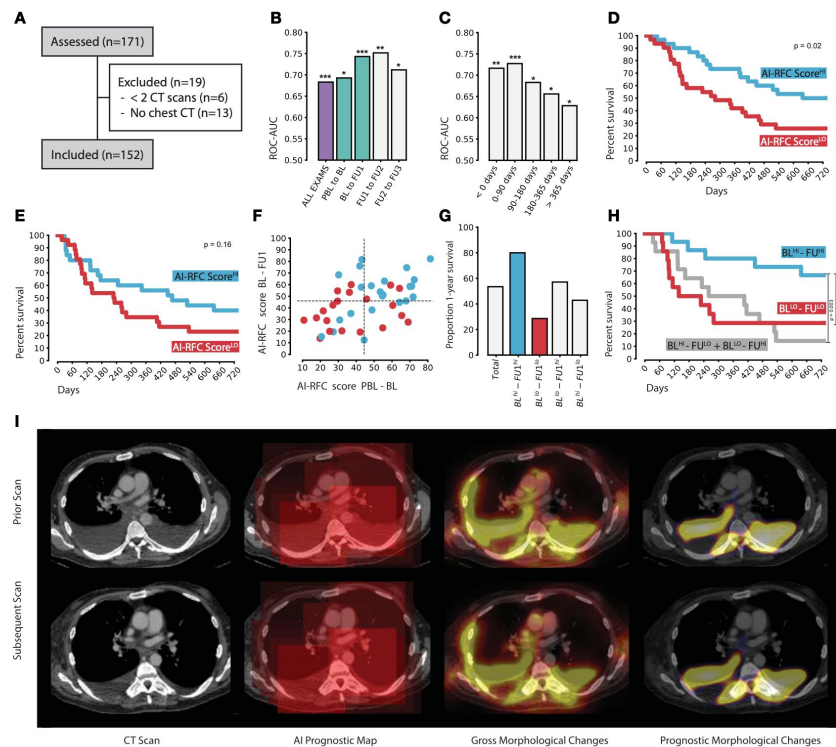
Automate extraction.

Well known biomarkers
extraction automation



Stefano Trebeschi, Zuhir Bodalal, Thierry N. Boellaard, Teresa M. Tareco Bucho, Silvia G. Drago, Ieva Kurilova, et AL.

Prognostic Value of Deep Learning-Mediated Treatment Monitoring in Lung Cancer Patients Receiving Immunotherapy (Front. Oncol, 2021)



Stefano Trebeschi, Zuhir Bodalal, Thierry N. Boellaard, Teresa M. Tareco Bucho, Silvia G. Drago, Ieva Kurilova, et Al.

Prognostic Value of Deep Learning-Mediated Treatment Monitoring in Lung Cancer Patients Receiving Immunotherapy (Front. Oncol, 2021)

DL in Medical Imaging

Automate the extraction of information doctors know how to quantify (well known biomarkers) but often cannot due to time constraints

E.g., from CT scans:

- Liver fat quantification
- Coronary Artery Calcium segmentation

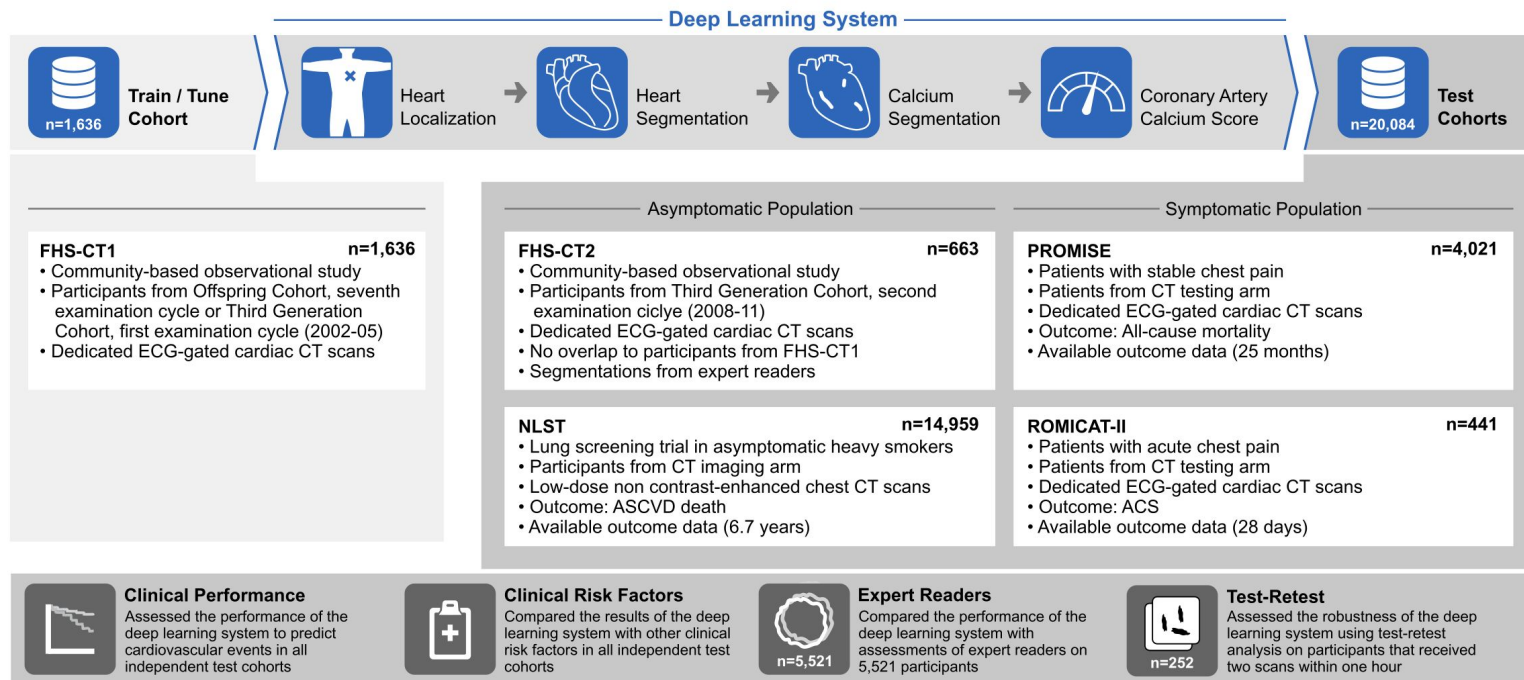
→ **clinical integration, biomarker validation studies**



Automation

Automate extraction.

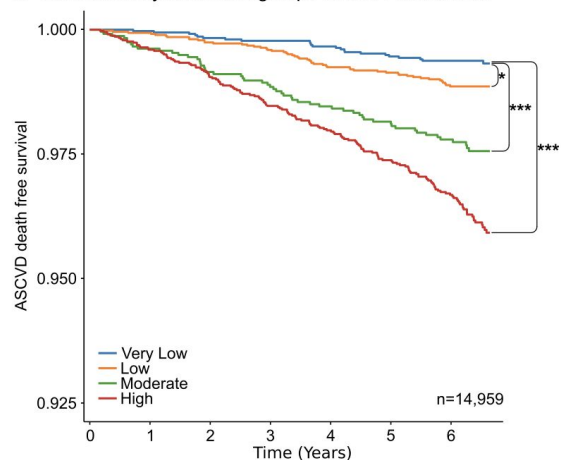
Well known biomarkers
extraction automation



Roman Zeleznik, Borek Foldyna, Parastou Eslami, Jakob Weiss, Ivanov Alexander, Jana Taron, Chintan Parmar, et Al.

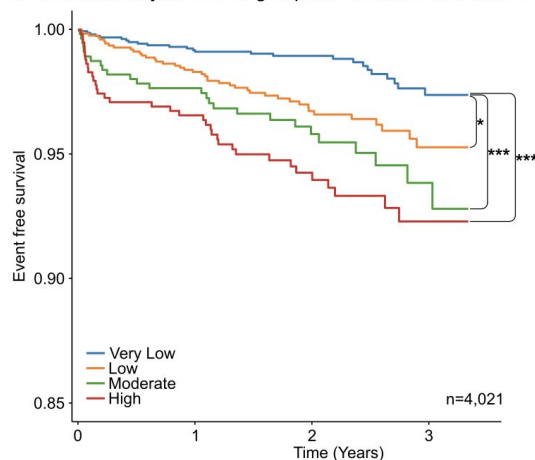
Deep convolutional neural networks to predict cardiovascular risk from computed tomography (NatCom, 2021)

a Survival analysis of CAC groups in NLST test cohort



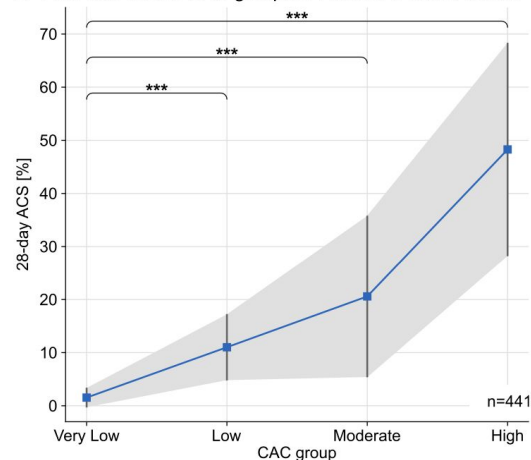
	Number at risk							
Very Low	3613	3596	3577	3532	3496	3451	2961	
Low	4730	4706	4665	4614	4552	4492	3820	
Moderate	2373	2352	2320	2294	2254	2216	1872	
High	4243	4190	4129	4054	3955	3847	3231	

b Survival analysis of CAC groups in PROMISE test cohort



	Number at risk			
Very Low	1615	1498	942	342
Low	1264	1150	713	234
Moderate	557	507	312	96
High	585	530	325	107

c ACS rate across CAC groups in ROMICAT-II test cohort



CAC group	Very Low	Low	Moderate	High
ACS=0 [n(%)]	256 (98.5)	105 (89.0)	27 (79.4)	15 (51.7)
ACS=1 [n(%)]	4 (1.5)	13 (11.0)	7 (20.6)	14 (48.3)
Total	260	118	34	29

Roman Zeleznik, Borek Foldyna, Parastou Eslami, Jakob Weiss, Ivanov Alexander, Jana Taron, Chintan Parmar, et Al.

Deep convolutional neural networks to predict cardiovascular risk from computed tomography (NatCom, 2021)



AIM/Introduction

**What does the
group focus on**



Medicine VS Engineering

What's different



Research

**Some of our
research**



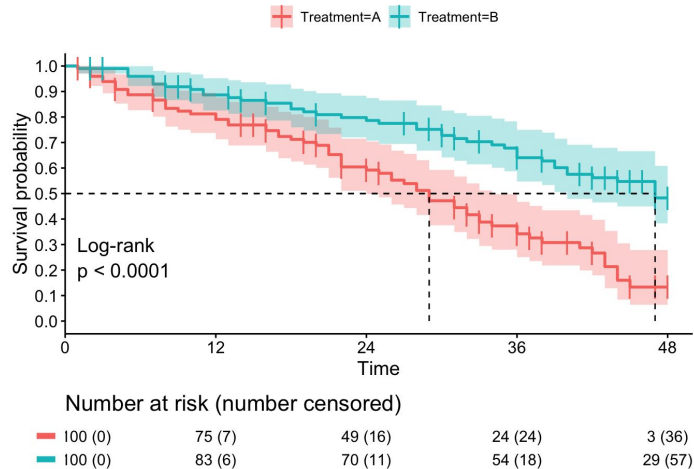
Medicine TO Engineering

What translates

bad
v
“There are three kinds of lies: lies, damned lies, and statistics”

Survival analysis techniques in SP/Network Engineering!

Kaplan-Meier



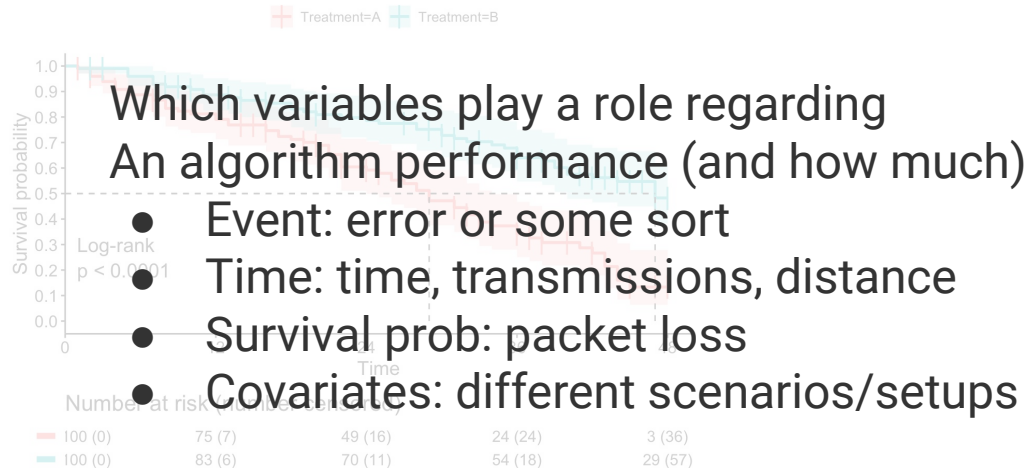
Cox Regression

Algorithm A VS Algorithm B

- Event: error of some sort
- Time: time, transmissions, distance
- Survival prob: packet loss

Survival analysis techniques in SP/Network Engineering!

Kaplan-Meier



Cox Regression

Variable	Recurrence only	
	Hazard ratio (95% CI)	P
Age group, y		
65-69	1.00	
70-74	0.91 (0.87-0.97)	0.001
75-79	0.70 (0.66-0.74)	<0.001
AJCC stage		
I	1.00	
II	1.27 (1.21-1.33)	<0.001
III	2.04 (1.88-2.22)	<0.001
ER/PR status		
Positive ^a	1.00	
Negative	1.17 (1.09-1.25)	<0.001
Unknown	0.91 (0.85-0.96)	0.002
Histologic grade		
Well	1.00	
Moderate	1.22 (1.12-1.31)	<0.001
Poor	1.30 (1.20-1.41)	<0.001
Unknown	1.12 (1.03-1.21)	0.007