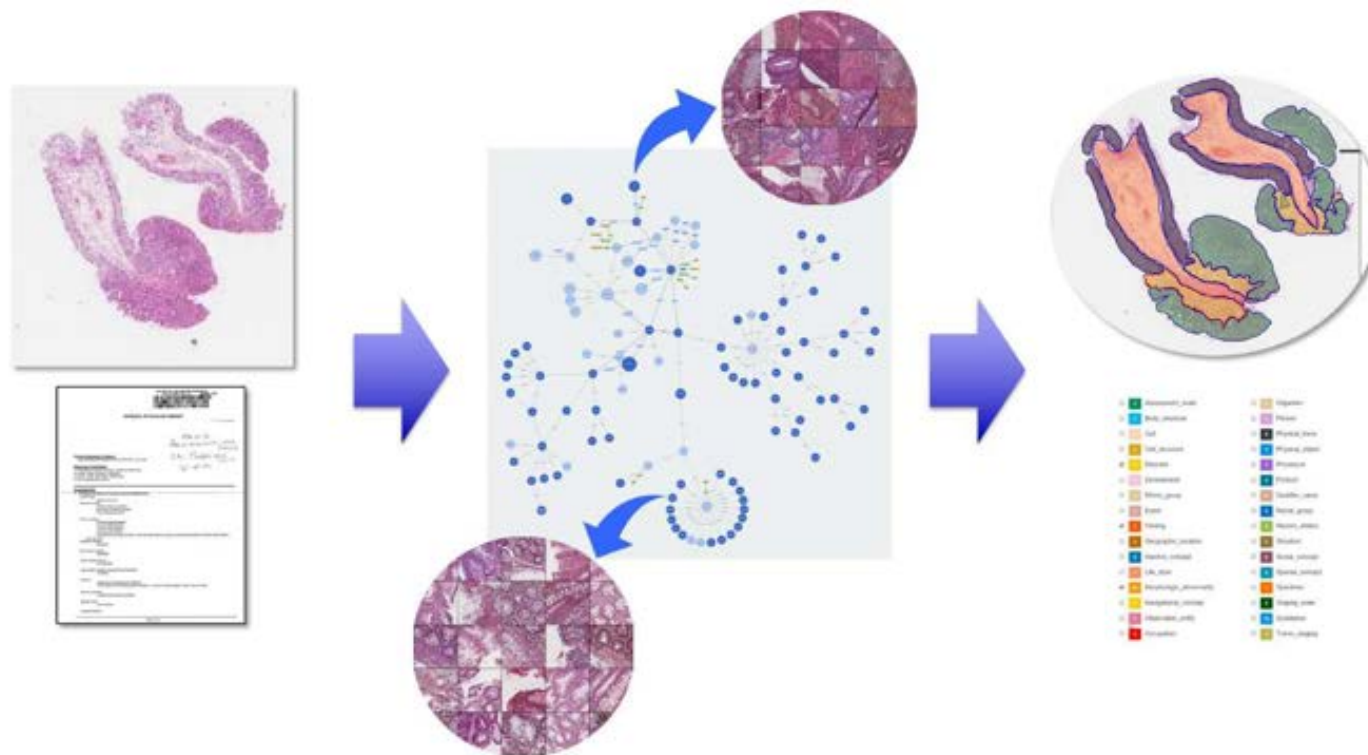


# Challenges for machine learning using medical data



Henning Müller

AIDA lecture

BETA

**AIDA**

ARTIFICIAL INTELLIGENCE  
DOCTORAL ACADEMY

AI4media

ExaMode



# Henning Müller

- **Medical informatics** studies in Heidelberg, Germany



Exchange with Daimler Benz research, USA

- PhD in **CBIR**, computer vision, Geneva, Switzerland (1998-2002)



MONASH University

- Exchange with Monash University, Melbourne, AUS



UNIVERSITÉ  
DE GENÈVE

- Professor in radiology and medical informatics at the University of Geneva (2014-)

- Professor in Computer Science at the HES-SO, Sierre, Switzerland (2007-)



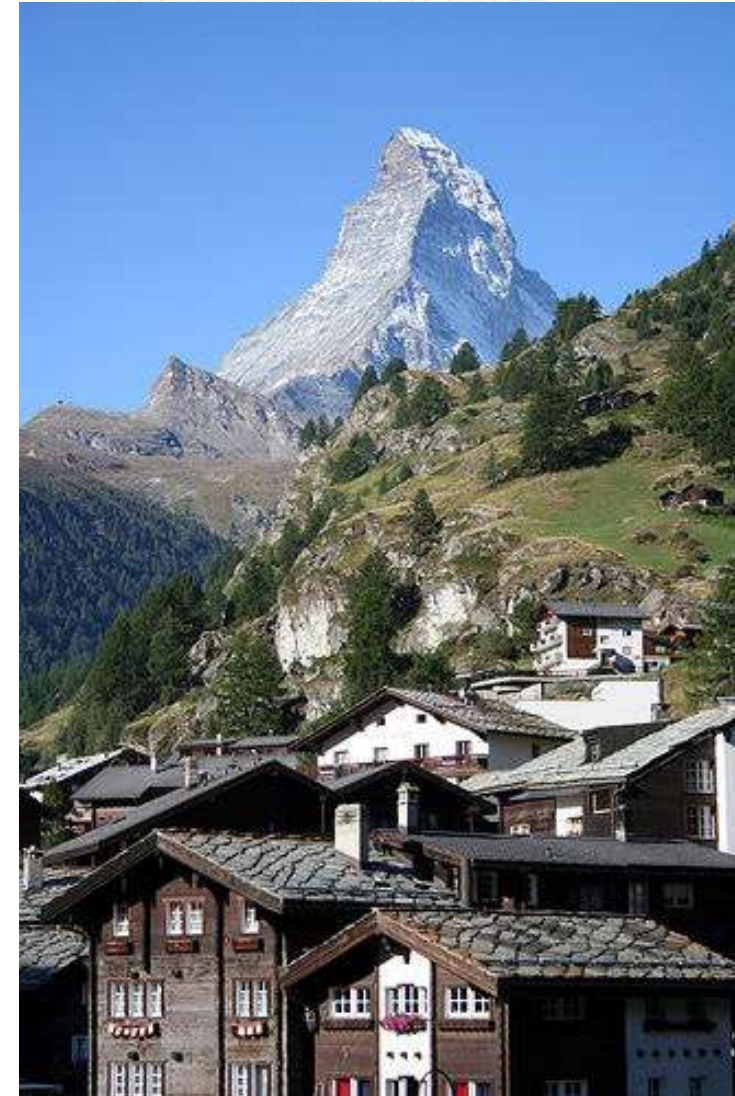
- Visiting faculty at Martinos Center (2015-2016)

- Member of the Swiss National Research Council





# Where we are





# Overview

- Status of medical AI
  - And its **challenges**
- **Projects** addressing the challenges
  - With a bias towards our work
- Open challenges
- Conclusions and **discussion**



# The promise of medical AI

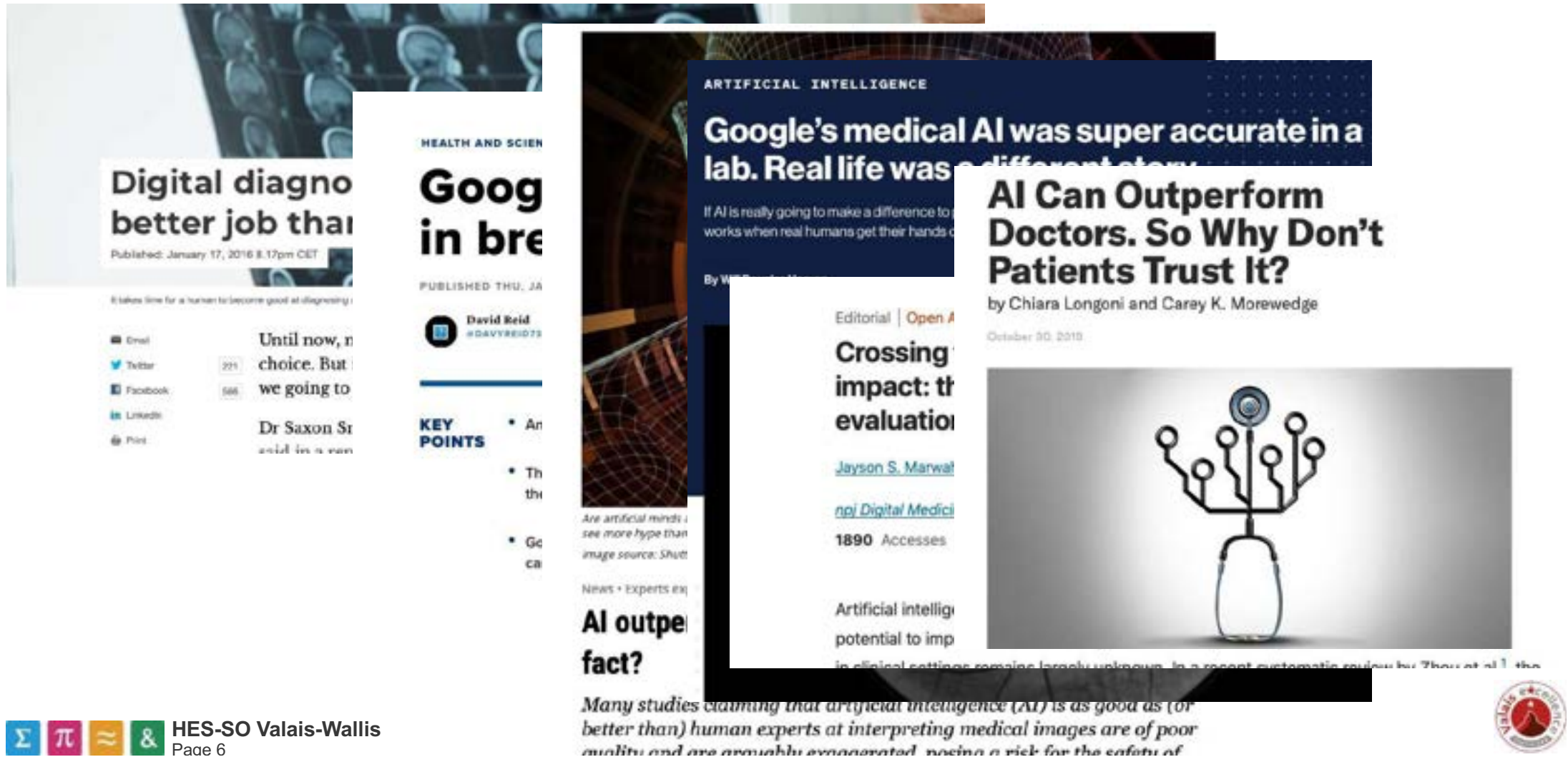


Geoff Hinton: On Radiology

<https://www.youtube.com/watch?v=2HMPRXstSvQ>



# Medical AI in the media



A collage of four news articles about medical AI. The top-left article is titled 'Digital diagnosis better job than human' and mentions 'Until now, no choice. But we are going to...'. The top-right article is titled 'Google's medical AI was super accurate in a lab. Real life was a different story' and includes a sub-headline 'If AI is really going to make a difference to... works when real humans get their hands on...'. The bottom-left article is titled 'AI Can Outperform Doctors. So Why Don't Patients Trust It?' by Chiara Longoni and Carey K. Morewedge, dated October 30, 2018, and features an illustration of a stethoscope with circuit lines. The bottom-right article is titled 'Crossing the impact: the evaluation' by Jayson S. Marwat, dated 1890 Accesses, and includes the text 'Artificial intelligence potential to improve... in clinical settings remains largely unknown...'. The collage also includes a 'KEY POINTS' section with bullet points and a footer with the HES-SO Valais-Wallis logo and page number 6.

**HEALTH AND SCIENCE**

## Digital diagnosis better job than human

Published: January 17, 2016 8:17pm CET

It takes time for a human to become good at diagnosing...

Until now, no choice. But we are going to...

Dr Saxon St...

Dr Saxon St...

**Google's medical AI was super accurate in a lab. Real life was a different story**


If AI is really going to make a difference to... works when real humans get their hands on...

By W...

## AI Can Outperform Doctors. So Why Don't Patients Trust It?

by Chiara Longoni and Carey K. Morewedge

October 30, 2018



**Crossing the impact: the evaluation**

Jayson S. Marwat

[npj Digital Medicine](#)

1890 Accesses

Artificial intelligence potential to improve... in clinical settings remains largely unknown... in a recent systematic review by Zhou et al. the

**KEY POINTS**

- An
- Th
- Ge

Are artificial minds... see more hype than... image source: Shutterstock

News • Experts explain

## AI outperforms human experts

Many studies claiming that artificial intelligence (AI) is as good as (or better than) human experts at interpreting medical images are of poor quality and are grossly exaggerated, posing a risk for the safety of

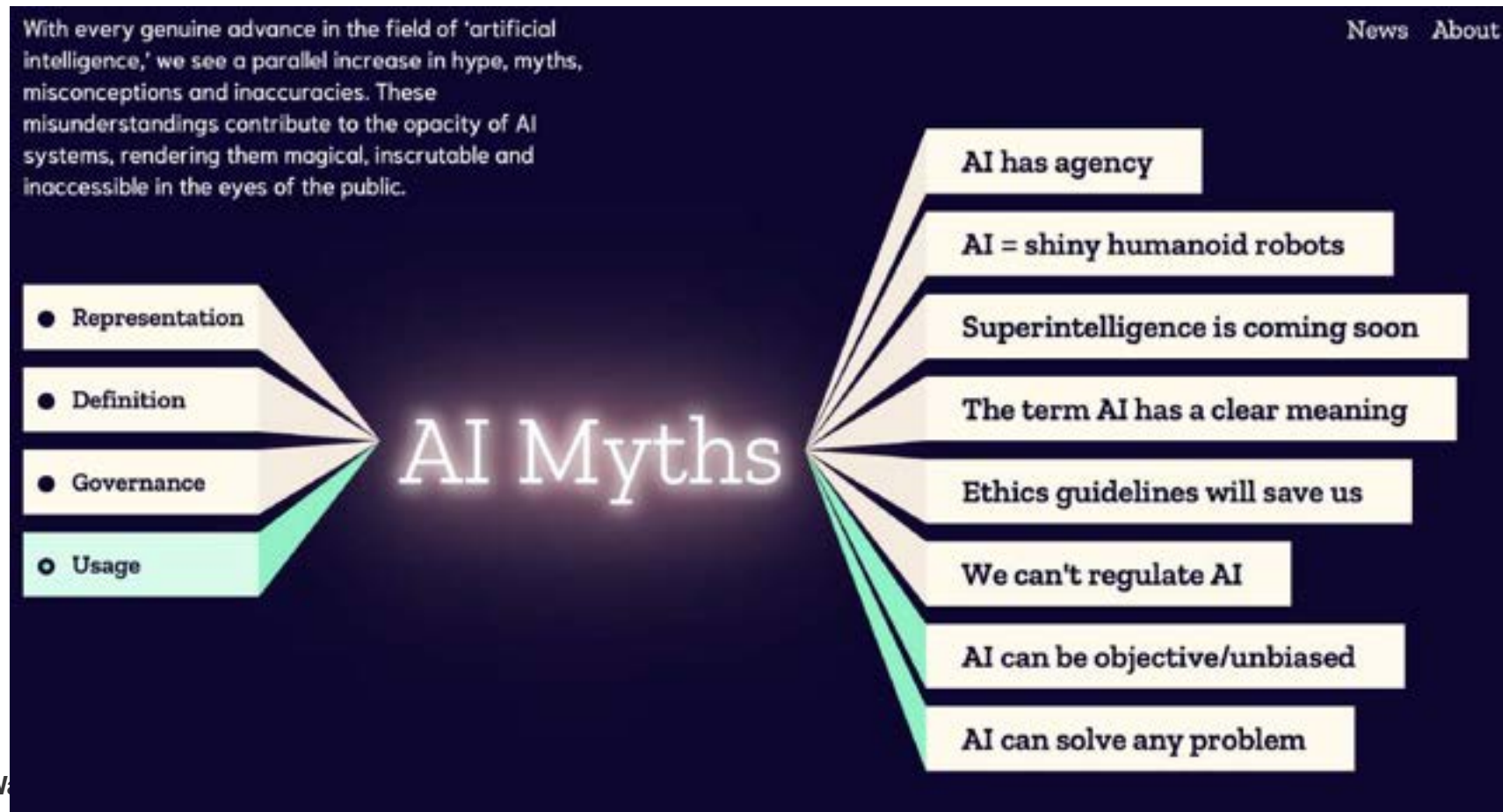
**HES-SO Valais-Wallis**

Page 6



# Realistic expectations

- <https://www.aimyths.org/>





# Advantages of medical data

- Images created under **standardized** conditions
- Images are always attached to a case and a **report** describing it, plus a reason for producing the images
  - **Metadata** exist, and other data on the same patient
    - We know the **context** of the images
- Much medical **knowledge** is available
  - Coded and maintained in ontologies
- Much clinical research is done
  - Medical imaging is estimated to occupy 30% of world storage





# Challenges with medical data

- Data **privacy** and **ethics** can make sharing data hard
- Medical equipment and procedures **vary** across hospitals
  - And equipment changes frequently
- Pixel-level annotations are extremely **expensive**
  - Specialists are needed and often not available (too busy)
- An image is only a very small part in a case with patient history, temporal data, genetics, text, structured data etc.
  - Regions determining a decision are often **extremely small**
    - Needle in a haystack

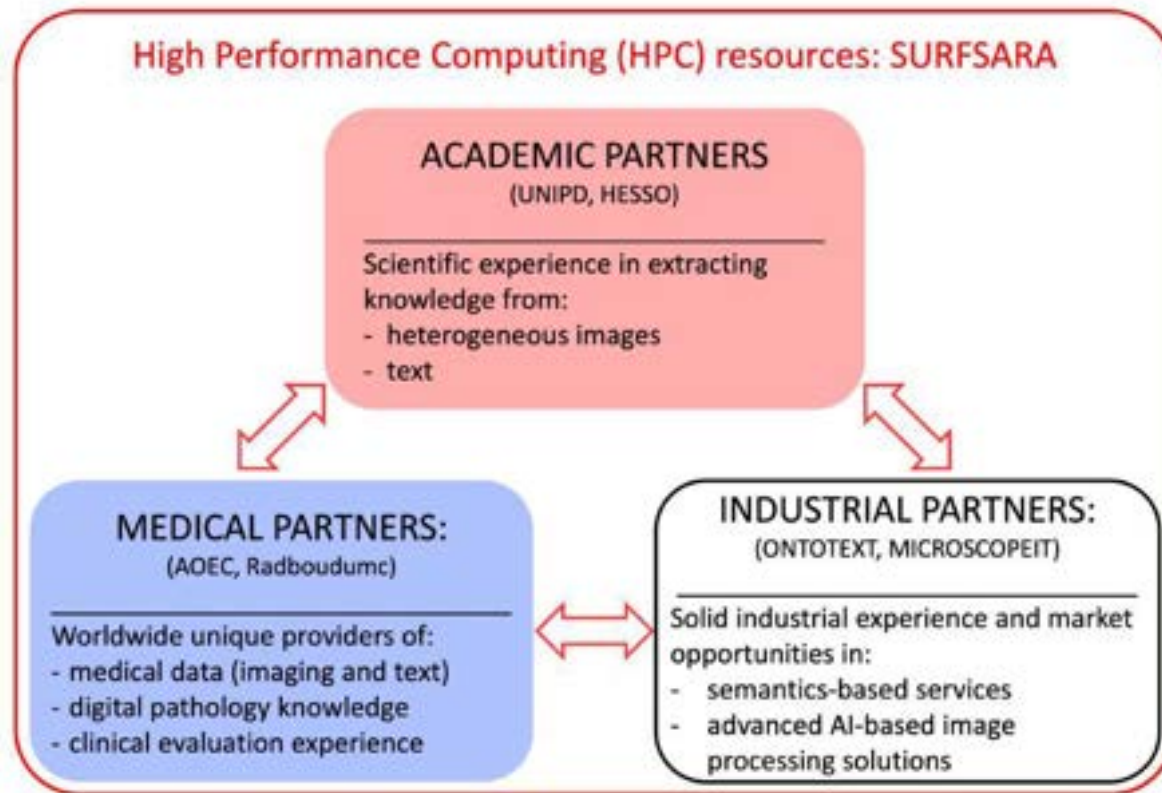


# Challenges for medical AI

- Much data are needed, so solutions need to be **scalable**
  - **Diversity** is required for generalization
  - Data sets are **very unbalanced**
- **Continuous learning** is required due to changing equipment and clinical guidelines (half-life of knowledge)
- Pixel level annotations are not available, as expensive
- Combining **multiple sources** is needed for proper learning
- Results need to be **explainable** for workflow integration
  - Deep learning is a priori a black box



# Examode consortium



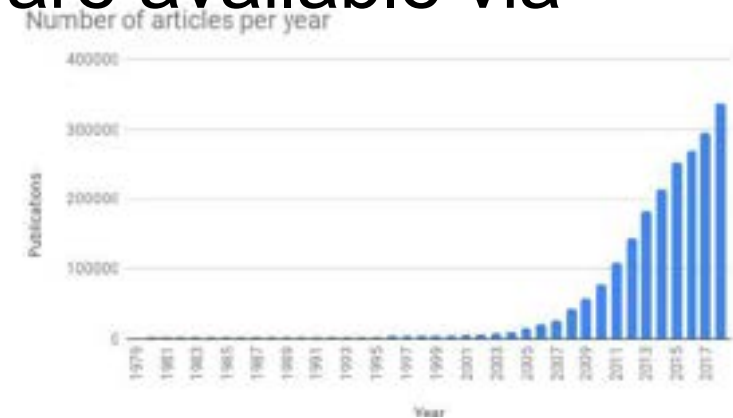
ExaMode





# Image accessibility

- **Open data** policies of funding agencies make large medical data sets available
  - Particularly NIH is pushing towards this
- **TCIA** and **TCGA** are very large repositories
  - There are many scientific challenges
- Images from the Biomedical literature are available via **PubMedCentral**
  - Exponentially increasing
  - Extremely varied, hard to use





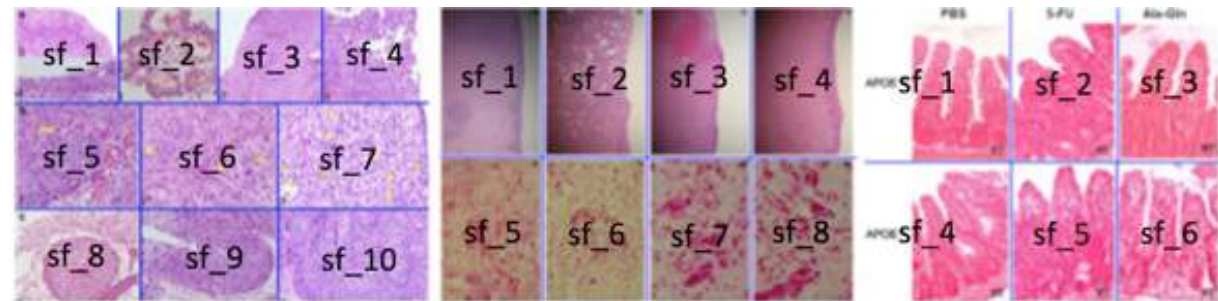
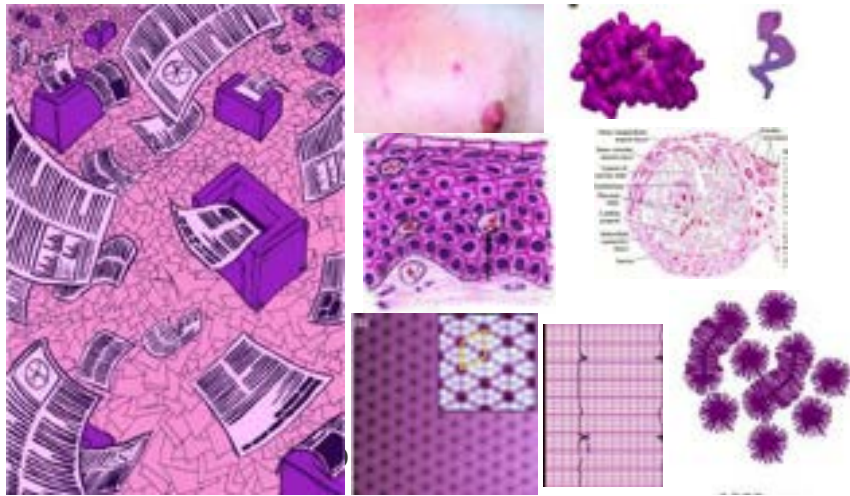
# Unbalanced data sets

- Differing **frequencies** of the relevant classes need to be taken into account
  - At cancer screen even high-risk people are ~1% positive
  - **Sensitivity** and **specificity** as measures, not accuracy
    - Weight between false positives and false negatives varies
  - Some cases may occur once/twice per year in large hospitals
- **Rare cases** is what is more commonly described in articles
  - Images from articles can thus help (at least in theory)
  - Variety of imaging parameters and laboratories is very high



# Challenges with PubMed

- >20'000'000 images in 2022, many graphs, charts
- **Look-alikes** is a problem, and compound figures
  - Very varied and sometimes strange content needs removal
- **Compound figures** need to be separated
  - Cutting sub figures apart makes content accessible





# Making the images usable

- Removing very small images & strange aspect ratios
- Classify figures into **figure types**
  - Using image data and also text, remove non-relevant images
- Detect and cut **compound figures** into their parts
  - Classify these into figure types again
- Filter **human** vs. animal tissue and specific **organs**
- Check **diseases** or grading/staging images
  - Classes for machine learning



# Advantages of literature images

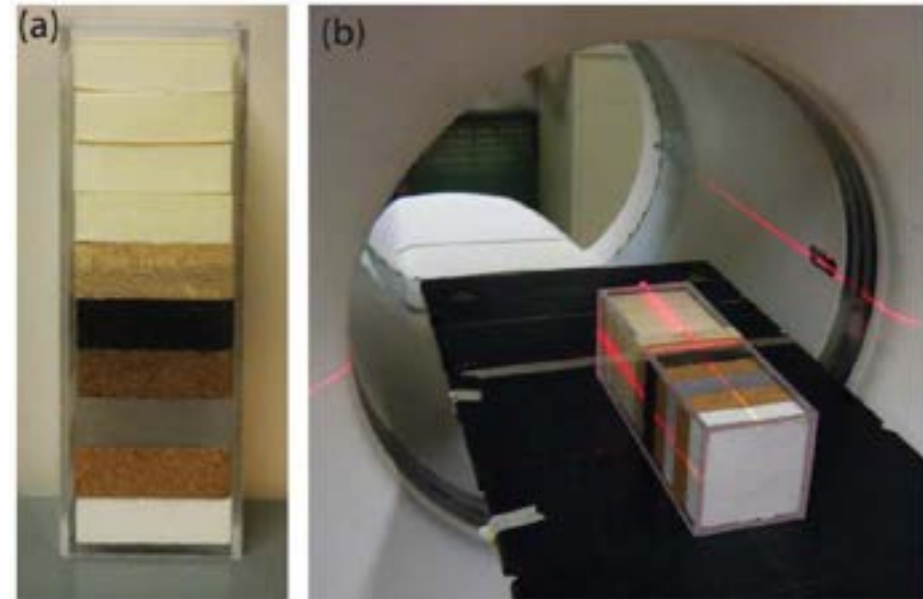
- **Rare images** (unusual, untypical) are generally used for articles and case descriptions
  - A few typical cases but mainly extreme cases
  - Creates critical mass for rare diseases
- Images are from **many laboratories** and thus contain many image variations (staining, scanners)
  - Increase generalizability of learned models thanks to this diversity
- Exponentially **increasing** content



# Image harmonization for radiomics

- Different **scanners produce different images**
  - Many protocols, construction kernels, producers, voxel sizes, ...
    - Strong influence on features extracted
- How can we harmonize this?
  - Deep learning!
- Phantom study with 17 scanners
  - 10 solid textures
  - Features invariant to scanner

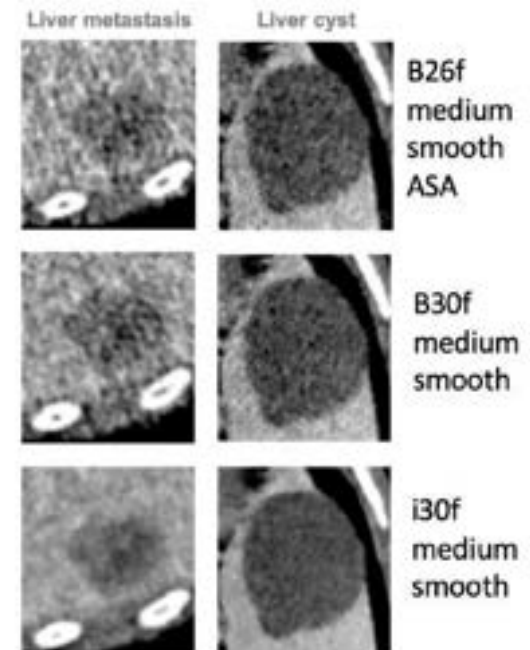
Vincent Andrearczyk, Adrien Depeursinge, and Henning Müller, Neural Network Training for Cross-Protocol Radiomic Feature Standardization in Computed Tomography, Journal of Medical Imaging, 2019.





# Measuring CT variability

- Many CT parameter **variations** stemming from:
  - Acquisition protocols (radiation dose, ...)
  - Image reconstruction parameters
  - Image resolution (slice thickness, overlap, ...)
- Variability has a **strong influence** on the analysis & comparison of radiomics features
- Patient studies evaluating image/feature stability entail ethical concerns with multiple exposures to radiation



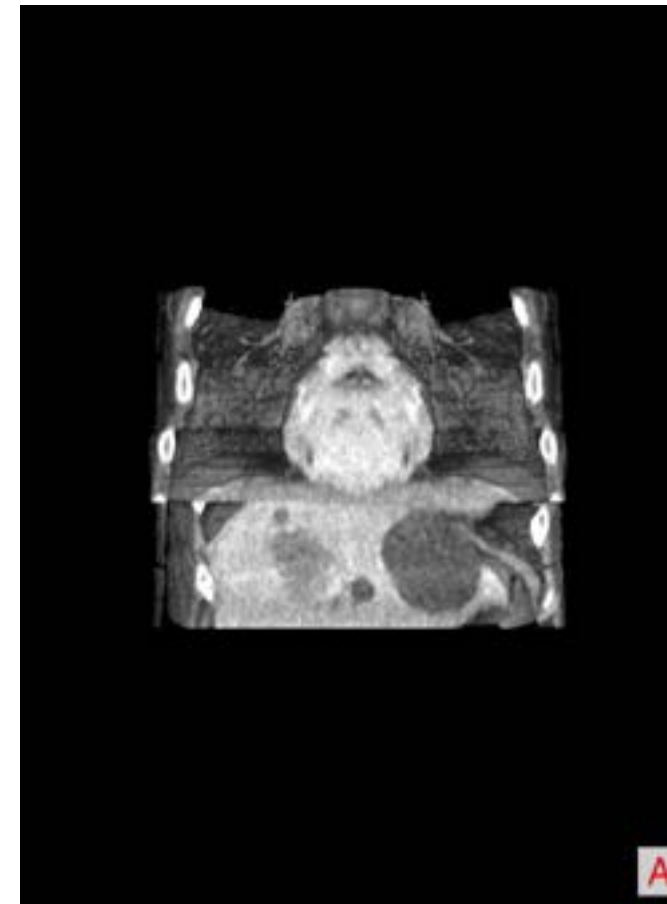
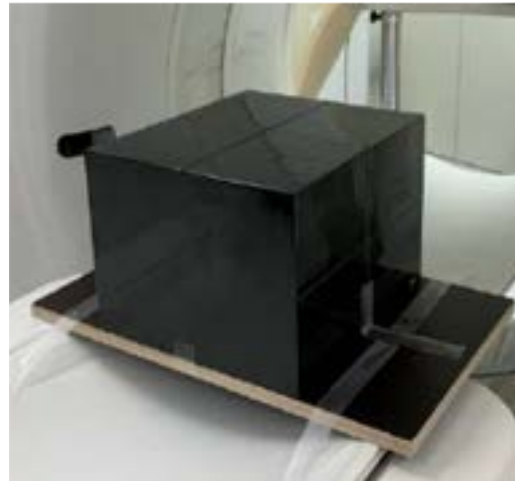
Traverso et al. (2018) *Repeatability and reproducibility of radiomic features: a systematic review*. International Journal of Radiation Oncology Physics **102**.

Solomon et al. (2014) *Quantum noise properties of CT images with anatomical textured backgrounds across reconstruction algorithms: FBP and SAFIRE*. Medical Physics **41**, 091908.



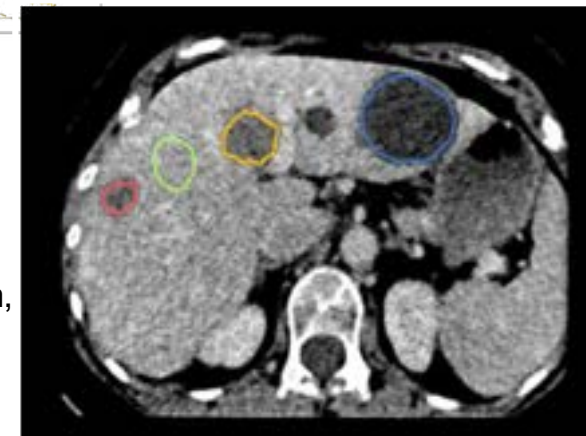
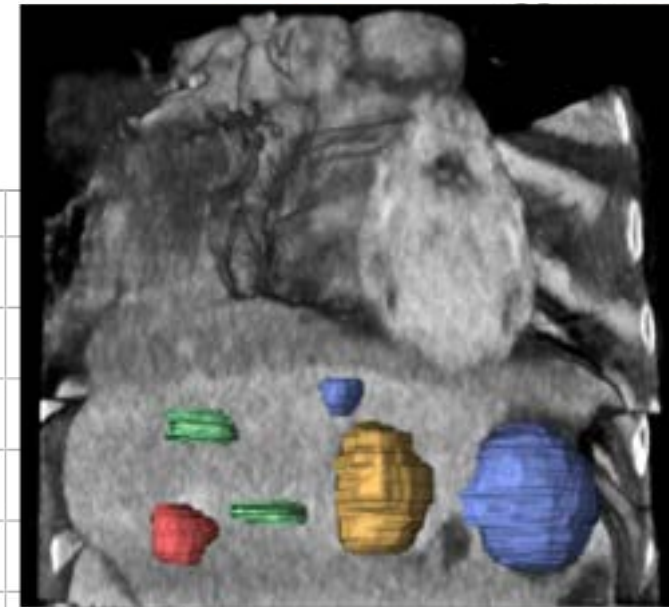
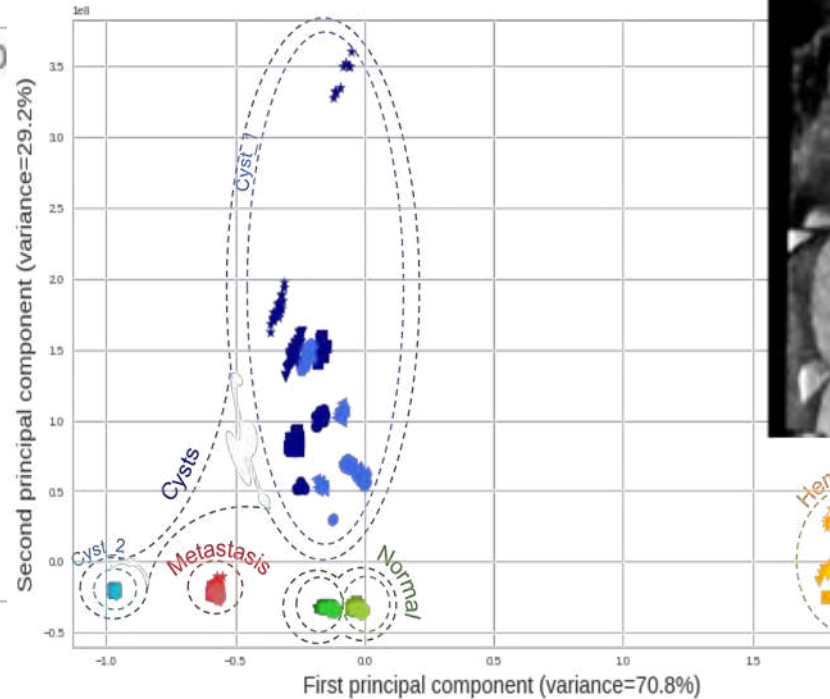
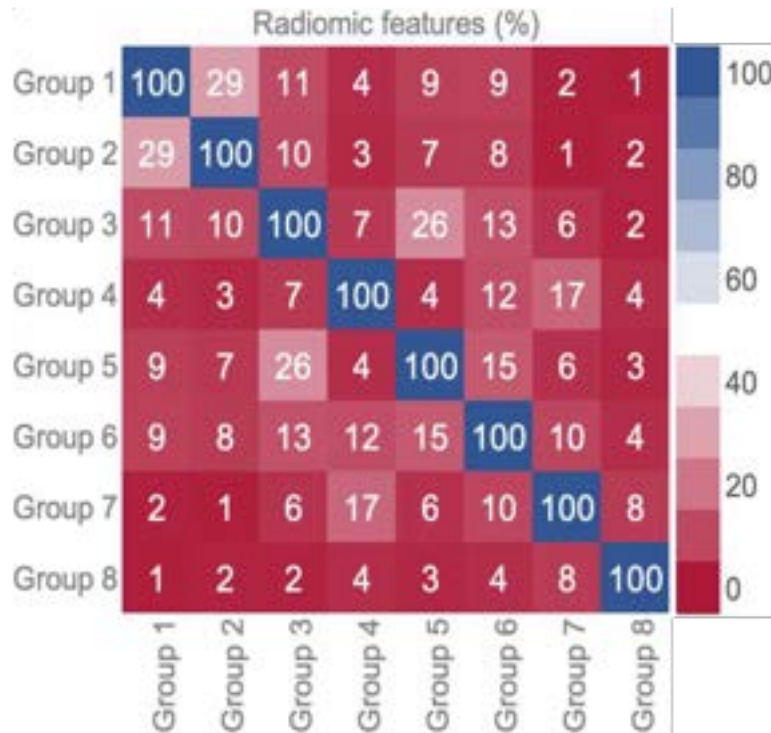
# 3D printed phantom

- Phantoms allow repeated radiation exposure
- Highly controlled acquisitions
  - No patient movement
  - No breathing
  - Precise positioning
- **Limitations**
  - In density (-100 HU to 1000 HU)
  - Small blocks are glued (artifacts)





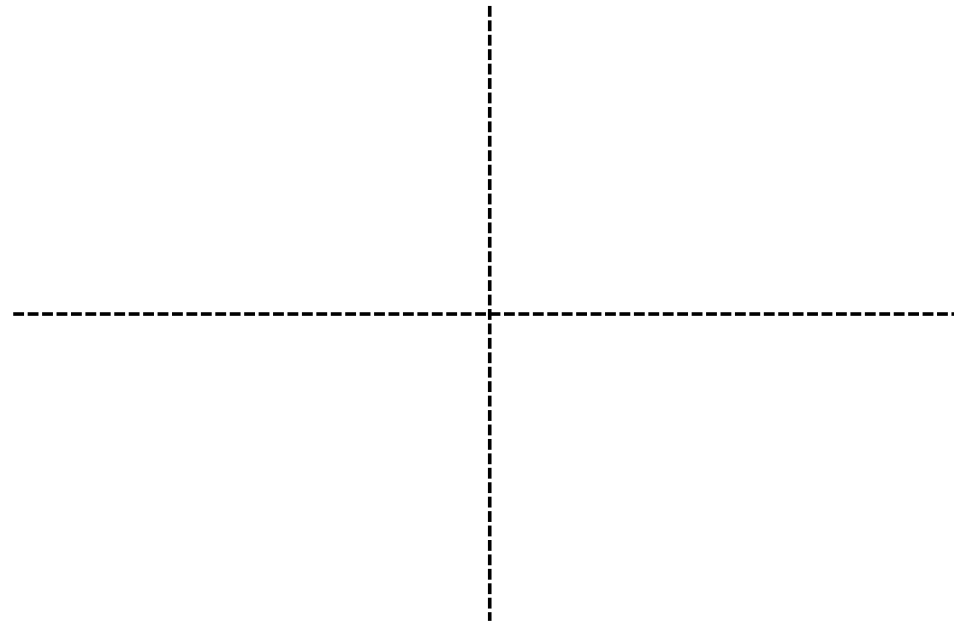
# First results



Oscar Jimenez-del-Toro, Christoph Aberle, Michael Bach, Roger Schaer, Markus Obmann, Kyriakos, Ender Konukoglu, Bram Stieltjes, Henning Müller, Adrien Depeursinge, The discriminative power and reproducibility of radiomics features with CT variations: Task-based analysis in a realistic CT liver phantom, Investigative Radiology, 2021.



# Stability vs. discriminative power



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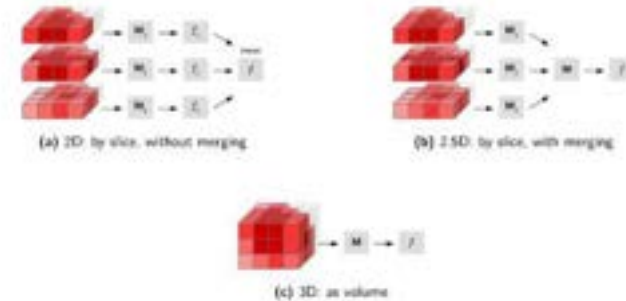
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## ■ Image Biomarker Standardization Initiative

- Define all visual features used in radiomics
  - And compare implementations on the same data
    - Digital phantoms
  - When there are differences then check the implementations
- **Installment 1** is finished,
  - Simple statistical (texture) features
- **Installment 2** is under way
  - Filter banks (Wavelets, Gabor, ...)



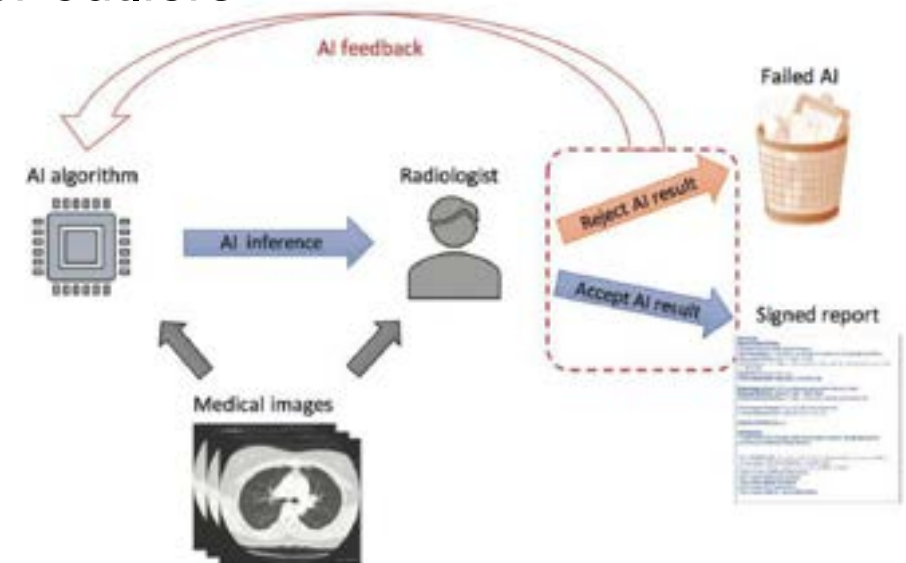
## ■ All information is available at: <https://theibsi.github.io>

Zwanenburg, A., et al. (2020). The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. *Radiology*, 295(2), 328-338.



# Continuous learning

- Add new annotated samples regularly to update algorithms (for example with new machines)
  - Avoid **catastrophic forgetting**
    - By adapting to a few specific cases or outliers
- Regular **feedback** loop
  - With clinicians using AI

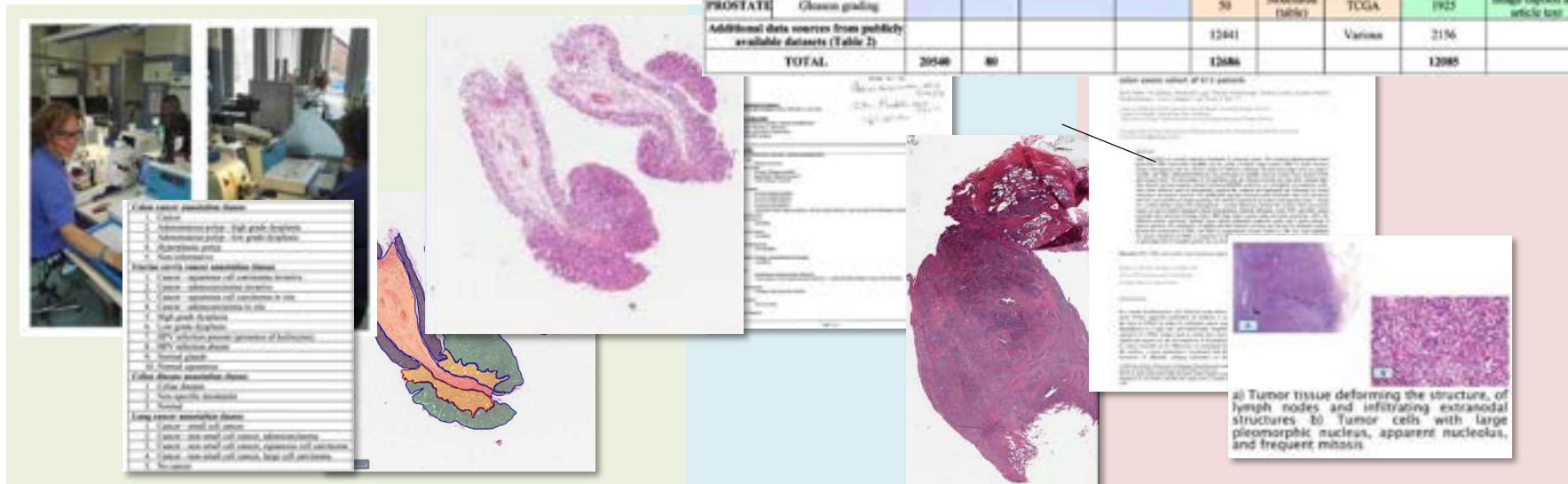


Pianykh, O.S., Langs, G., Dewey, M., Enzmann, D.R., Herold, C.J., Schoenberg, S.O. and Brink, J.A., 2020. Continuous learning AI in radiology: implementation principles and early applications. *Radiology*, 297(1), pp.6-14.



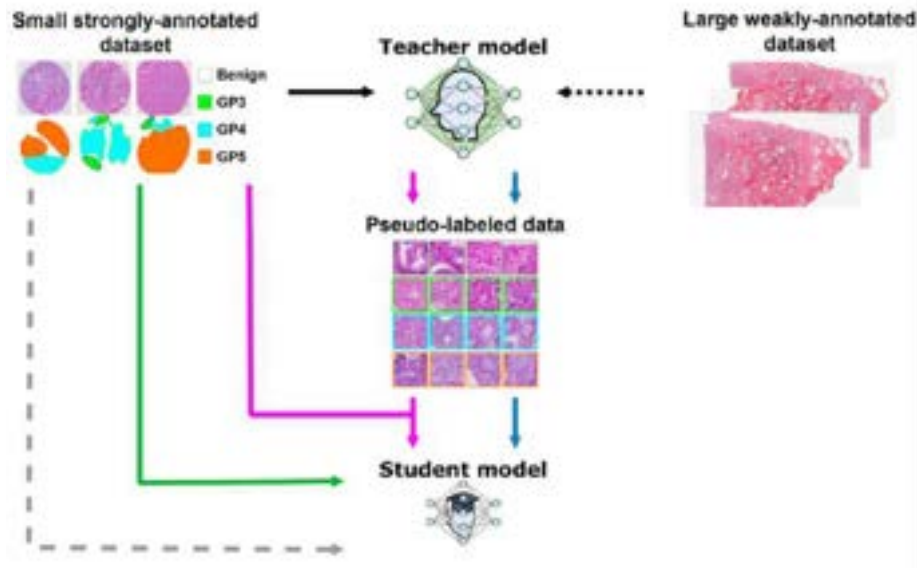
# Data used in ExaMode

TASK		First set of proprietary data				Final set of cured publicly available multimodal and multimedia data					
		WSIs	TMA Images	Text	Source	Publicly available clinical data		Data from scientific literature			Source
						Whole Slide	Text	Images	Text	Source	
COLON	Adenocarcinoma, Detection of cancer in polyps (in screening population)	2000		Diagnostic report, structured (table)	ADEC	50	Structured (table)	TCGAPath	2699	Image caption and article text	PMIC Central
		9000		Synoptic report, structured (table)	Radbound						
		40	80	Structured (table)	Bern University						
UTERINE CERVIX	Squamous cell carcinoma	2000		Diagnostic reports, structured (table)	ADEC	45	Structured (table)	TCGA	962	Image caption and article text	PMIC Central
		2500		Synoptic report	Radbound						
LUNG	Classification/detection of growth patterns related to cancer metastasis, prognosis	2000		Diagnostic report, structured (table)	ADEC	100	Structured (table)	TCGA	4151	Image caption and article text	PMIC Central
CELIAC DISEASE	Celiac disease detection in duodenal biopsies	2000		Diagnostic report, structured (table)	ADEC				165	Image caption and article text	PMIC Central
		1000		Synoptic report	Radbound						
PROSTATE	Gleason grading					50	Structured (table)	TCGA	1925	Image caption and article text	PMIC Central
Additional data sources from publicly available datasets (Table 2)						12441		Various	2156		Various
TOTAL		20540	80			12686		12085			Various





# Weakly supervised learning



Teacher/student paradigm approaches:  
Semi-supervised learning  
Semi-weakly supervised

Student training variants:



## Challenge Report

Semi-supervised training of deep convolutional neural networks with heterogeneous data and few local annotations: An experiment on prostate histopathology image classification

Niccolò Marini<sup>a,b,c,\*</sup>, Sebastian Orlt<sup>a,b</sup>, Henning Müller<sup>a,b</sup>, Manfredo Atzori<sup>a,b</sup>

<sup>a</sup>Department Systems Informatics, University of Applied Sciences Western Switzerland (HES-SO Valais), Rue de l'Industrie 1, Sion 1900, Switzerland

<sup>b</sup>Center Informatics Engineering, University of Geneva, Geneva 1205, Switzerland

<sup>c</sup>Medical Faculty, University of Geneva, Geneva 1205, Switzerland

<sup>d</sup>Department of Pharmacology, University of Pavia, Via Darvino 2, Pavia 27100, Italy

## ARTICLE INFO

Received 1 August 2011  
Received in revised form 24 June 2012  
Accepted 1 July 2012  
Available online 19 July 2012

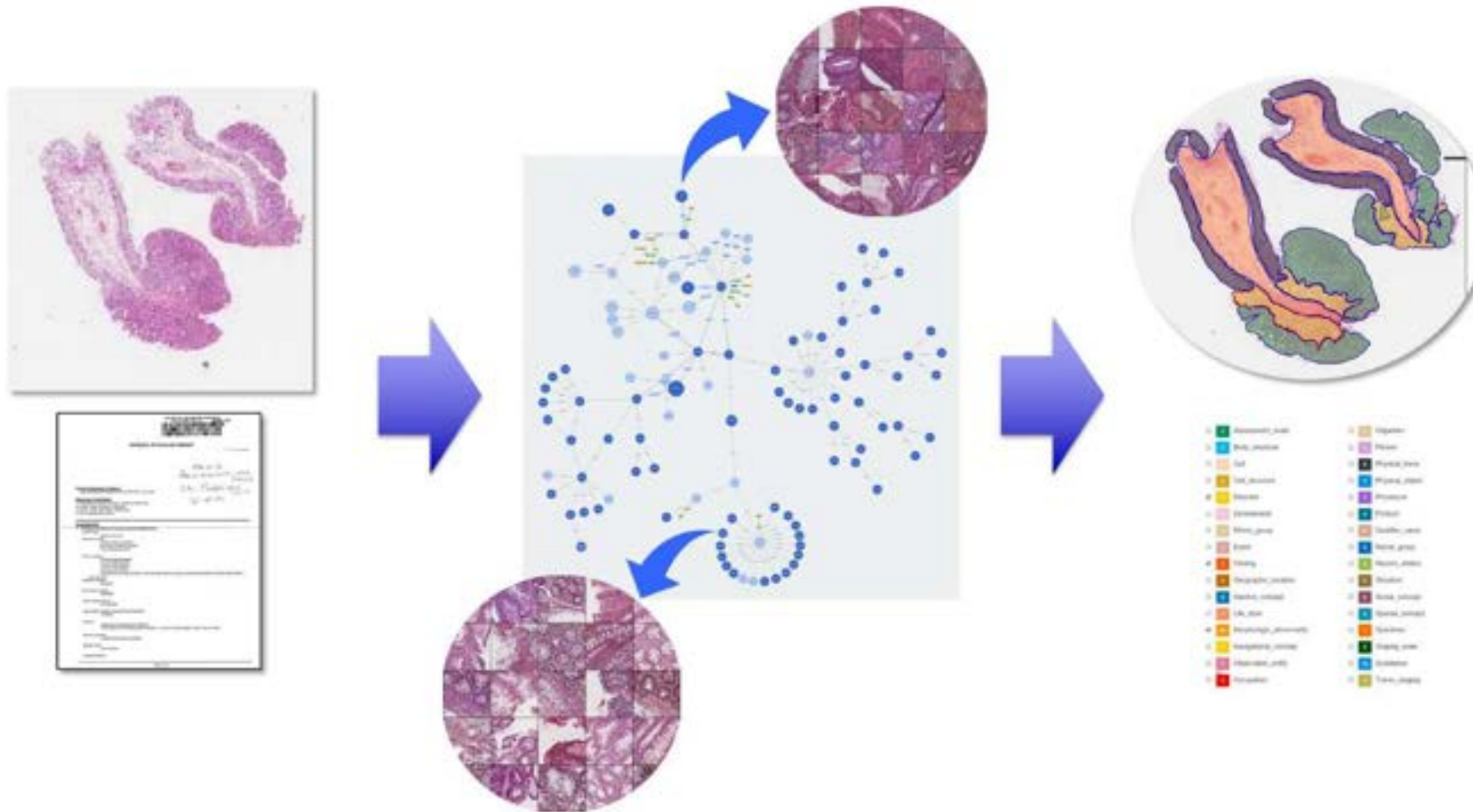
Keywords:  
Convolutional networks  
Deep learning

## ABSTRACT

Convolutional neural networks (CNNs) are state-of-the-art computer vision techniques for various tasks, particularly for image classification. However, there are domains where the training of classification models that generalize to several datasets is still an open challenge because of the highly heterogeneous data and the lack of large datasets with local annotations of the regions of interest, such as histopathology image analysis. Histopathology concerns the microscopic analysis of tissue specimens preserved in glass slides to identify diseases such as cancer. Digital pathology concerns the acquisition, management and automatic analysis of digitized histopathology images that are large, having in the order of 100,000 pixels per image. Digital histopathology images are highly heterogeneous due to the variability of the design acquisition procedures. Creating locally labeled regions (required for the training) is time-consuming and often expensive in the medical field, as physicians usually have to analyze the data. Despite the advances in deep learning increasing rapidly and widely extended towards more classification models, it still an unsolved problem, mainly when data are very heterogeneous. Large amounts of data are needed to clearly decide that generalize well. This paper presents a novel approach to solve CNNs that

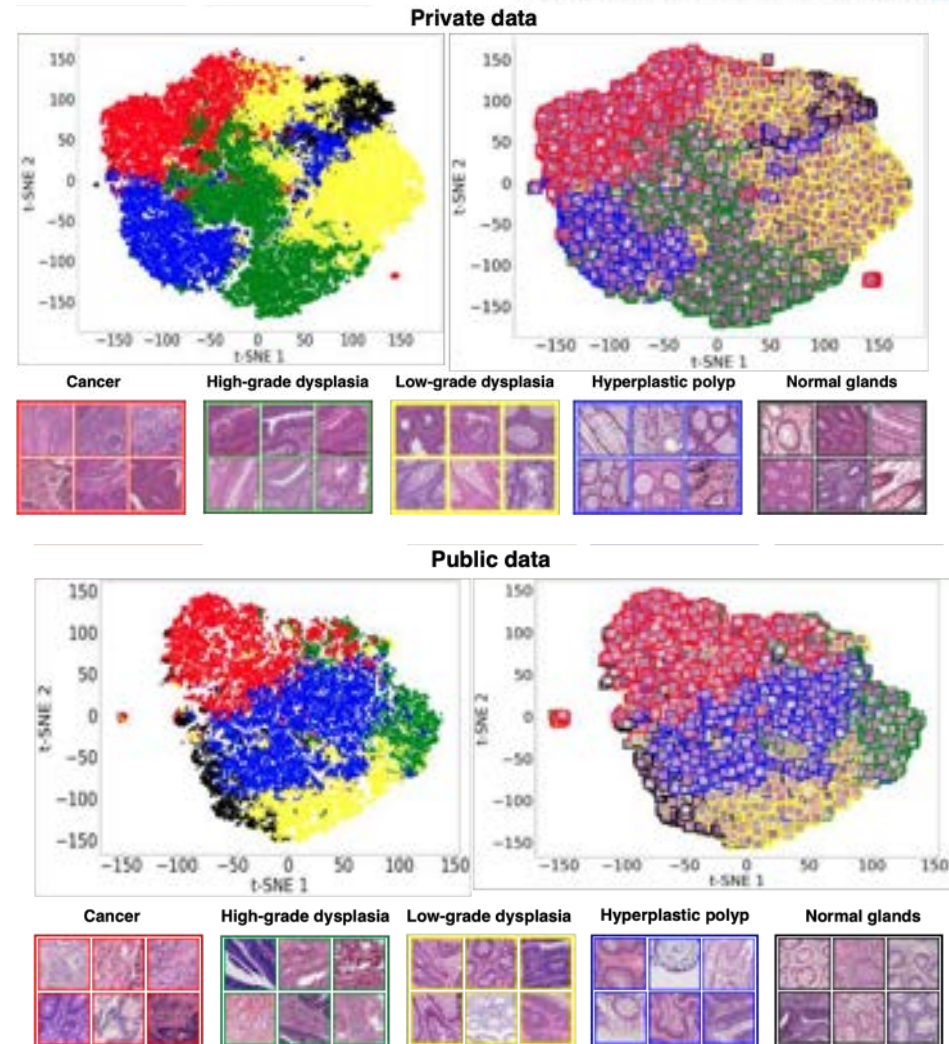
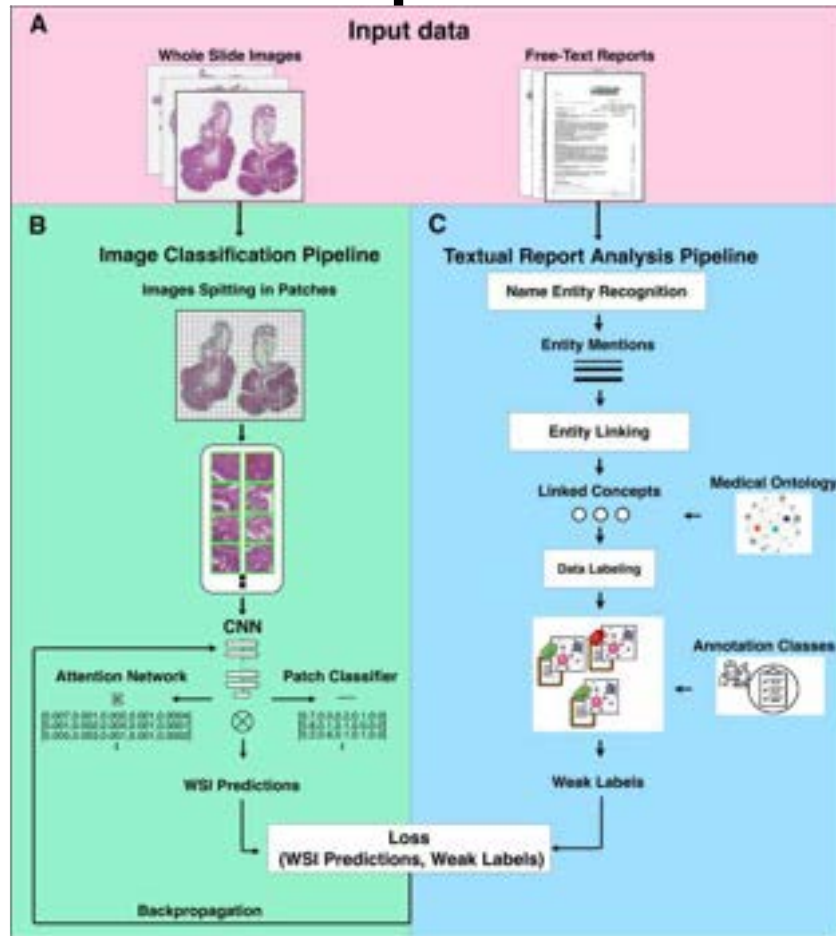


# Project status



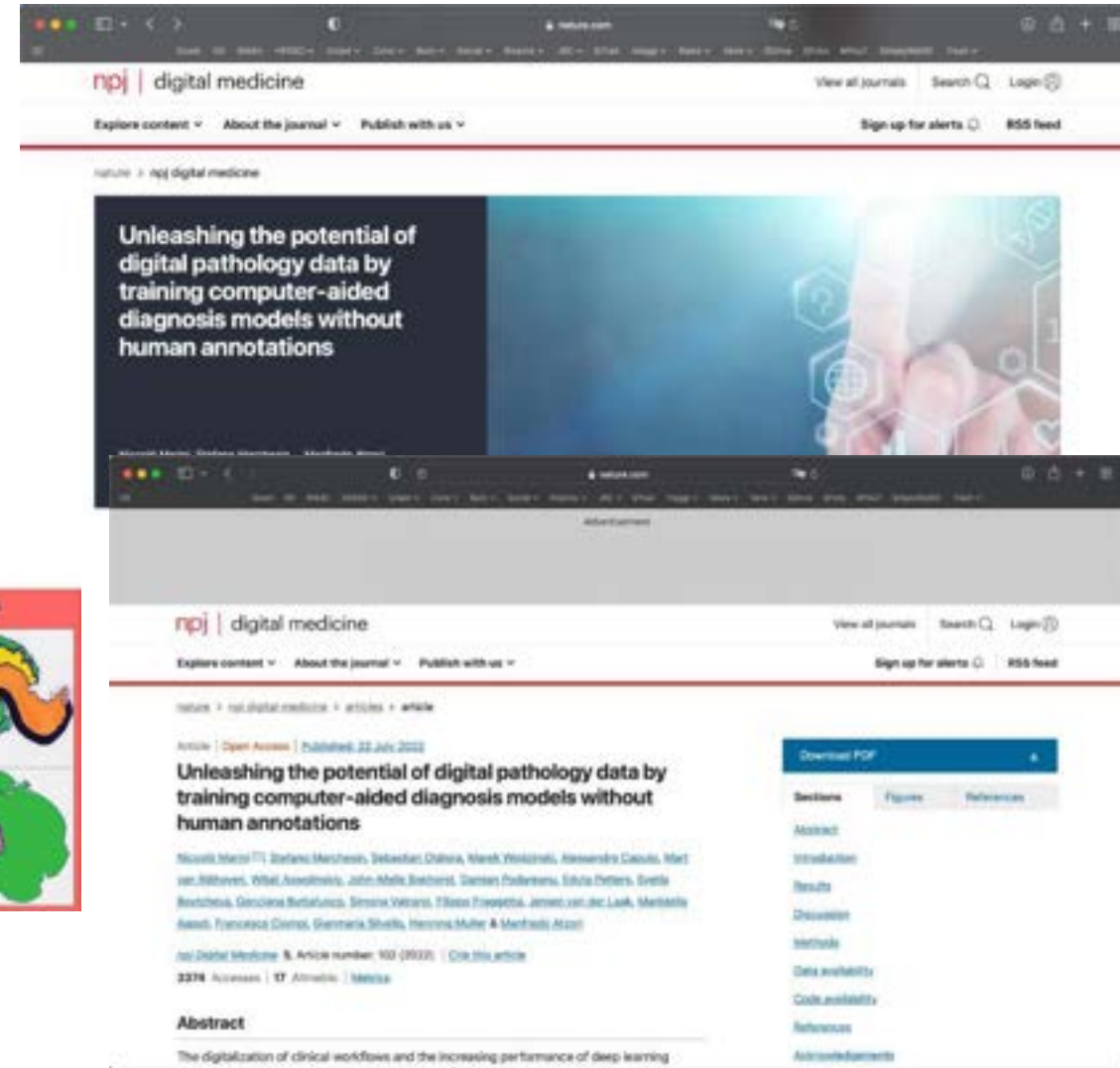
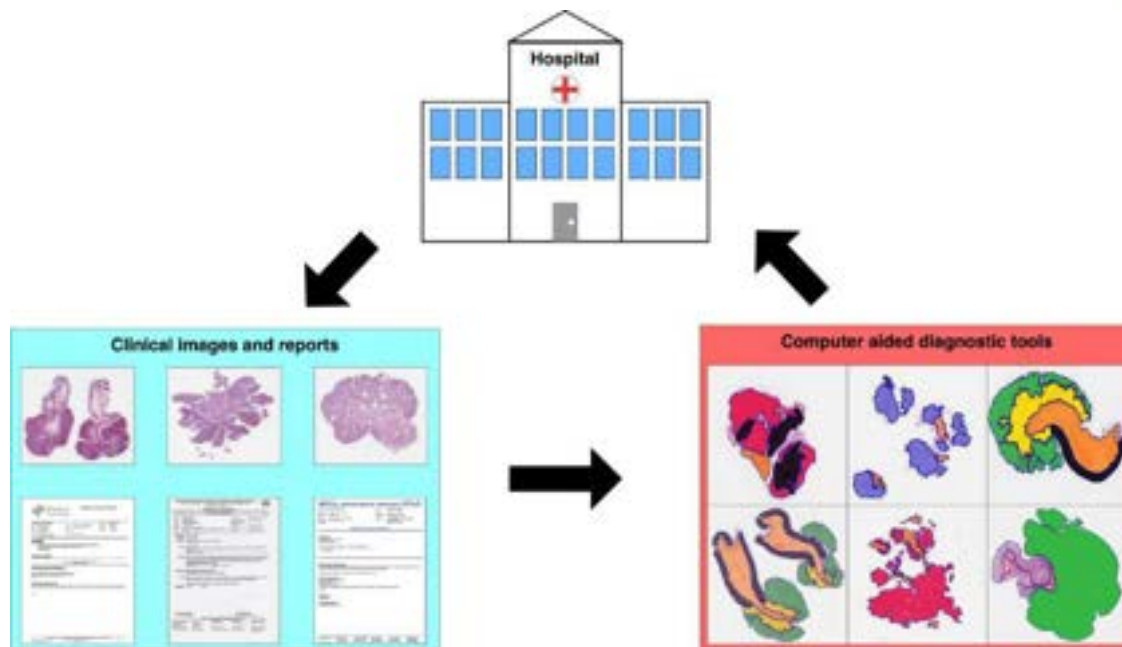


# Weakly supervised learning from reports





# First results on multimodal data





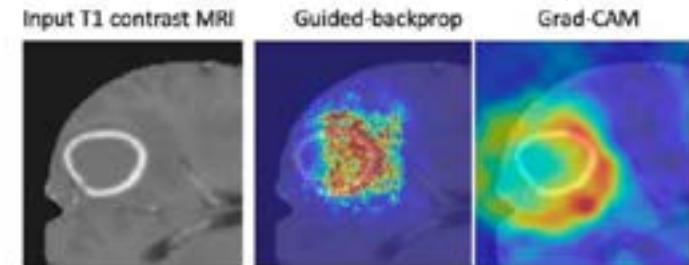
# Clinical workflow and AI

- A clinician **orders** an image
- A radiologist/pathologists produces and views the image and writes a **report** based on the question and anamnesis
  - Much data on the patient (environment, prior diseases, genetics, blood tests, development of a condition, ...)
  - Differential diagnosis, under much **time pressure**
- Any AI needs to be **integrated into the workflow** and tools
  - Adding evidence, identifying bias, uncertainty, ...
    - Explaining the decisions and their context



# Interpretability of Deep Learning

- Make decisions **understandable** & remove black box image
- Make sure that decisions are sound
- Explain why things may not be working
- In medicine it is particularly important to make sure that results can be explained & reproduced
  - High **impact of wrong decisions**
- There are many approaches interpretability
  - 2D projections, PCA, TSNE
  - Class activation maps, saliency, ...





# A taxonomy for explainability

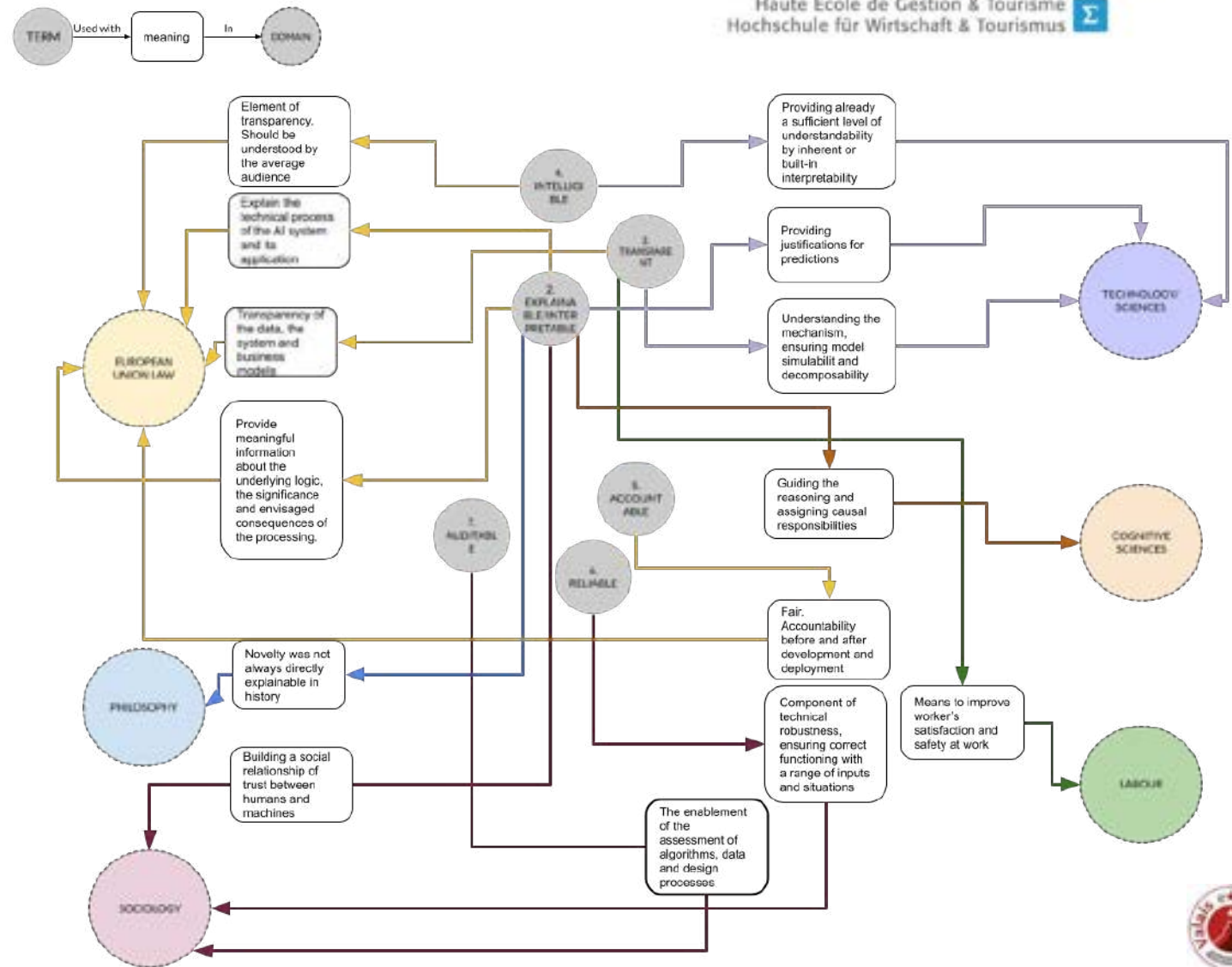
- Many **terms** have been used in slightly different ways for AI: **interpretability**, **explainability**, transparency, accountability, fairness, (opacity) ...
  - Bias, reliability, robustness, uncertainty, confidence
- A workshop was held in the summer of 2021 on this with views from **several domains**: legal, technical, philosophical, social, cognitive, ethical, ...
  - <https://taxonomyinterpretableai.wordpress.com>
- EU is preparing the way
  - **GDPR** on data protection and **AI policy**
    - Limit the strong risks of AI and its use and abuse

M Graziani, L Dutkiewicz, D Calvaresi, J Pereira Amorim, K Yordanova, M Vered, R Nair, P Henriques Abreu, T Blanke, V Pulignano, JO. Prior, L Lauwaert, W Reijers, A Depeursinge, V Andrearczyk, H Müller, A Global Taxonomy of Interpretable AI: Unifying the Terminology for the Technical and the Social Sciences, Artificial Intelligence Reviews, 2022.



# Taxonomy

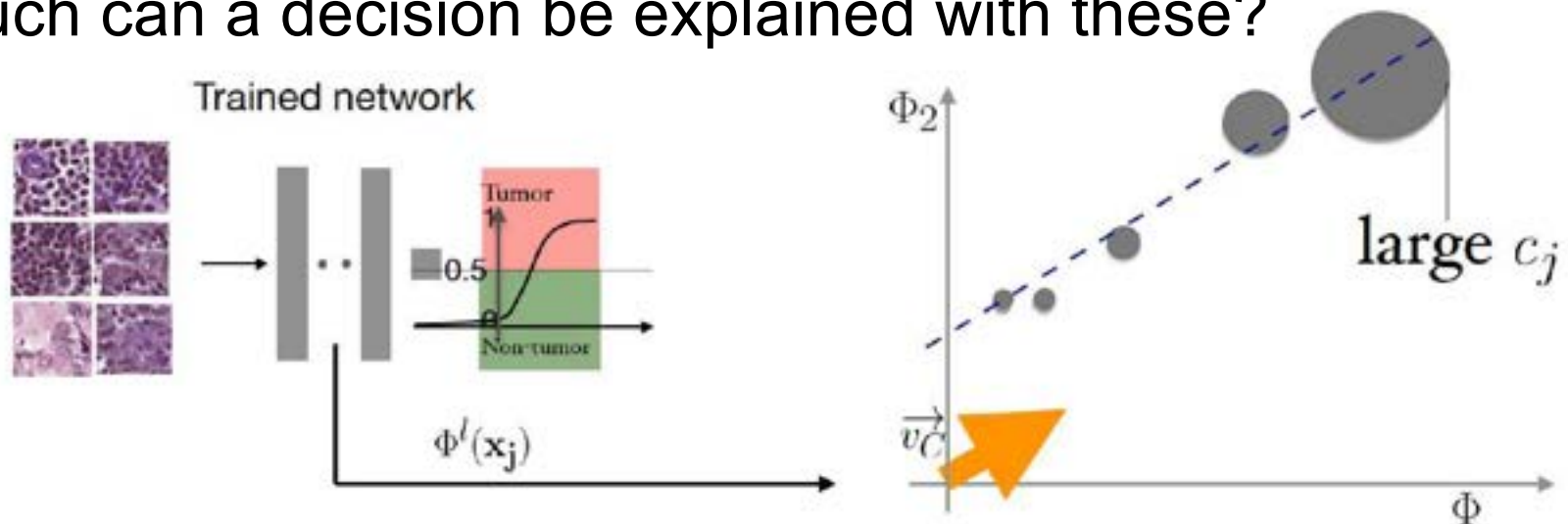
## Interpretable AI terminology Main terms and domains





# Regression concept vectors

- Identify **existing clinical features** and check how the decision layers correlate to these features
  - i.e.: nuclei size, internal heterogeneity, borders, ...
  - How much can a decision be explained with these?

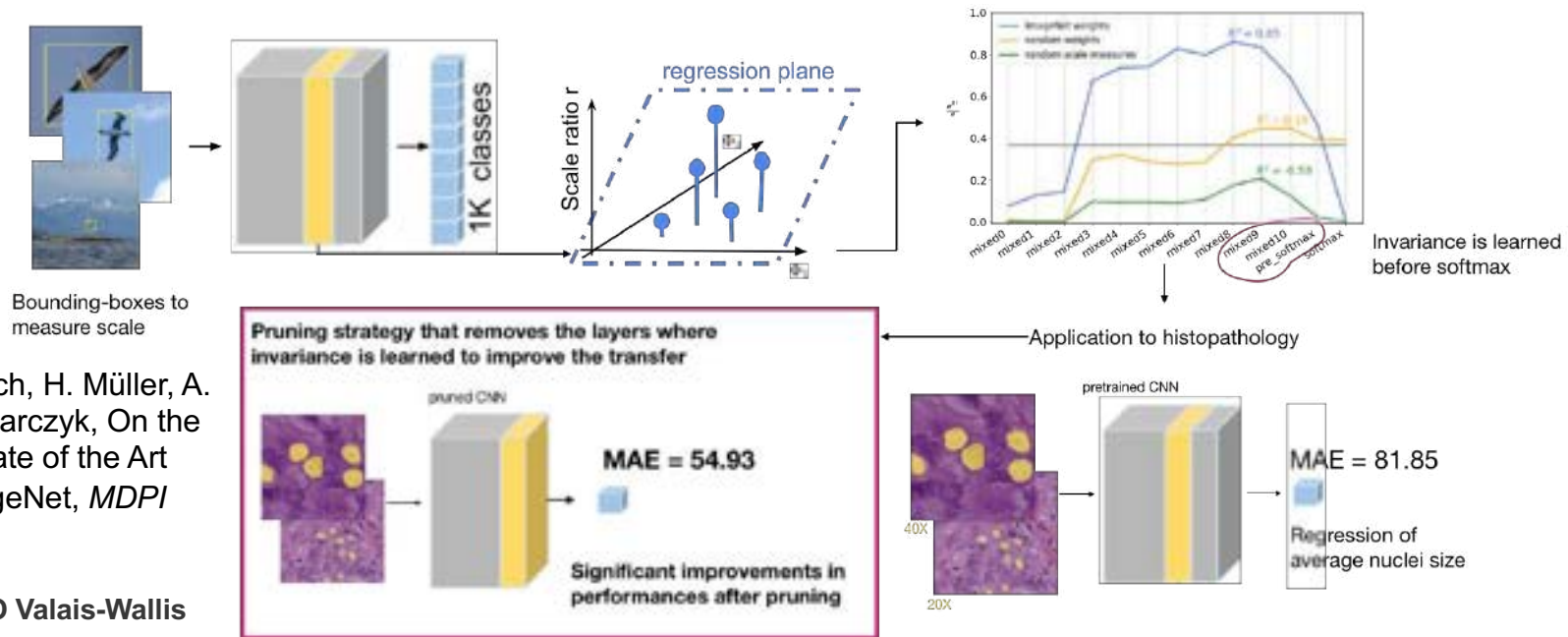


M Graziani, V Andrearczyk, H Müller, Concept attribution: Explaining CNN decisions to physicians, *Computers in Medicine and Biology*, 2020.



# Improve with interpretability

- Pre-trained models often include **scale invariance**
- In medical applications this can be problematic, as scale carries information

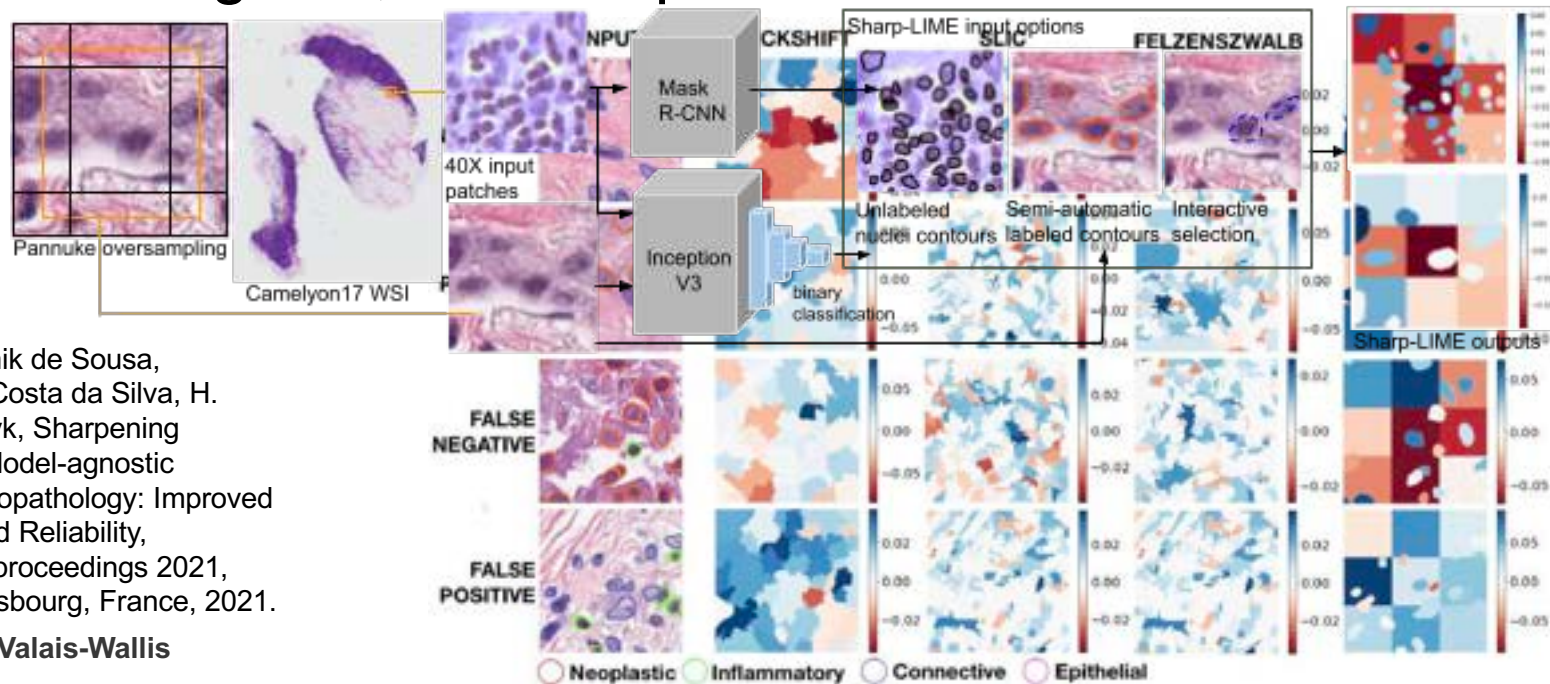


M. Graziani, T. Lompech, H. Müller, A. Depeursinge, V. Andrearczyk, On the Scale Invariance in State of the Art CNNs Trained on ImageNet, *MDPI Make*, 2021.



# Visualizations

- Improve visualizations of regions that are relevant for the decision of a DNN
  - LIME is commonly used to highlight regions, but interpretations can be difficult



M. Graziani, I. Palatnik de Sousa,  
M.B.R. Vellasco, E. Costa da Silva, H.  
Müller, V. Andrearczyk, Sharpening  
Local Interpretable Model-agnostic  
Explanations for Histopathology: Improved  
Understandability and Reliability,  
MICCAI conference proceedings 2021,  
Springer LNCS, Strasbourg, France, 2021.



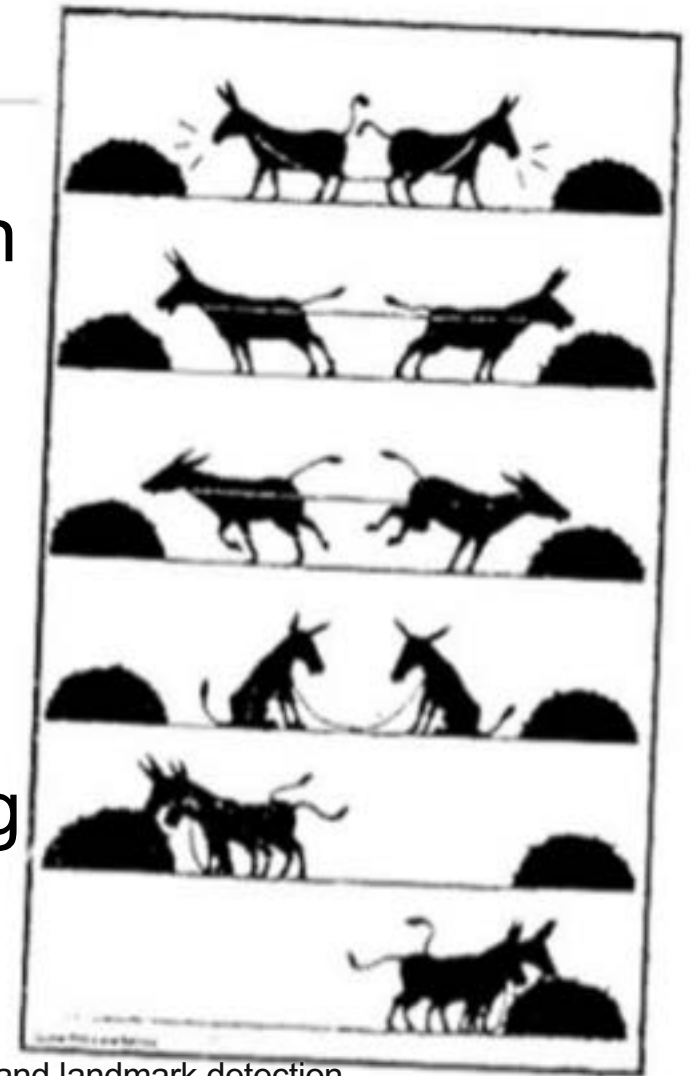
# The importance of user tests!

- Most systems are scripts run under laboratory conditions
  - Does not give many indications of routine use
- **Impact** of the system is hard to measure
  - Better decisions, more confidence, faster, satisfaction?
- What is the **influence** on the patient?
  - Better treatment? Longer survival? Quality of life?
- User tests are more complex to set up but can really help
- AI and users are usually best together



# Scientific challenges

- Cooperation, **Coopetition**, Competition
- Many data sets are now available
  - Also many medical data sets
- **Strong baselines** help to judge quality
  - Not only the results count!
- Challenges can be run without sharing confidential data
  - Provide VMs or Docker containers



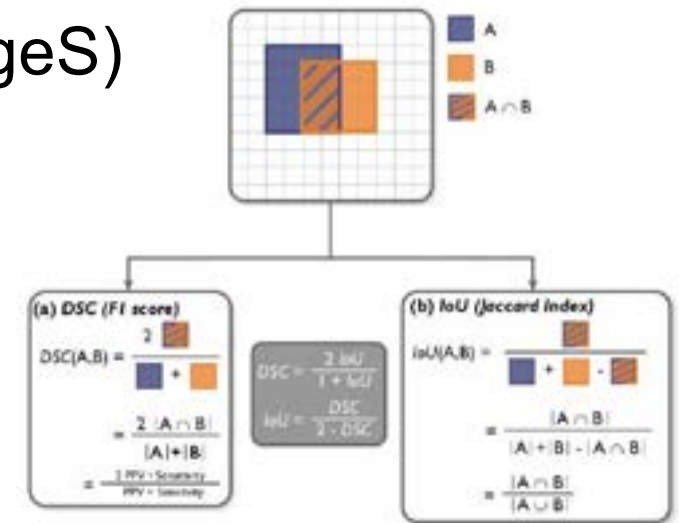
Jimenez-del-Toro, Oscar, et al. "Cloud-based evaluation of anatomical structure segmentation and landmark detection

HES-SO Valais-Wallis algorithms: VISCERAL anatomy benchmarks." *IEEE transactions on medical imaging* 35.11 (2016): 2459-2475.



# Some more best practices

- Reporting for scientific challenges in medical imaging
  - BIAS (Biomedical Image Analysis challengeS)
  - Avoid bias, use the right measures
  - Use meaningful data sets and scenarios
  - How to chose the best evaluation metrics
  - ...



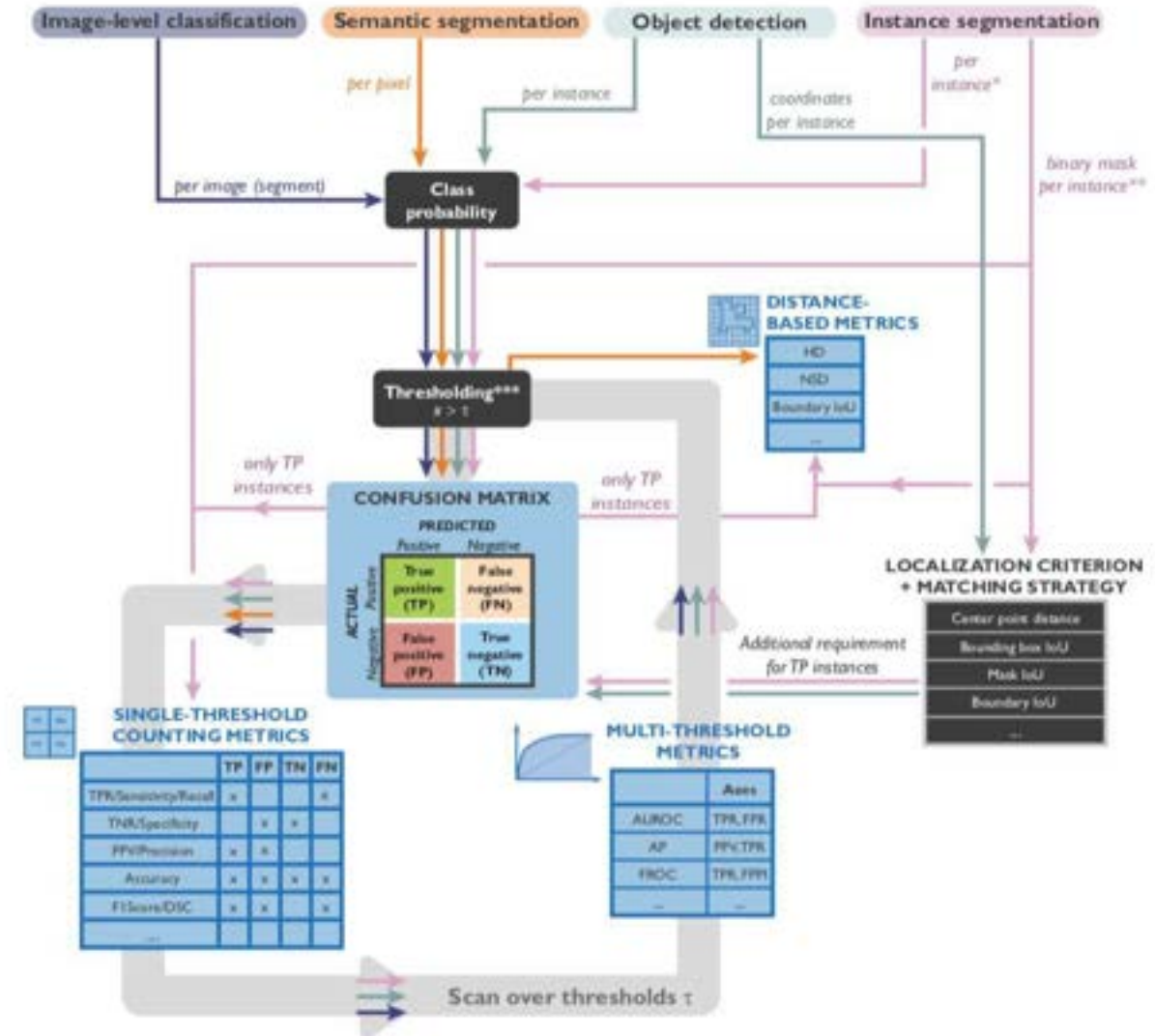
Maier-Hein, L., Eisenmann, M., Reinke, A., Onogur, S., Stankovic, M., Scholz, P., Arbel, T., Bogunovic, H., Bradley, A.P., Carass, A. and Feldmann, C., 2018. Why rankings of biomedical image analysis competitions should be interpreted with care. *Nature communications*, 9(1), pp.1-13.

Maier-Hein, L., Reinke, A., Kozubek, M., Martel, A.L., Arbel, T., Eisenmann, M., Hanbury, A., Jannin, P., Müller, H., Onogur, S. and Saez-Rodriguez, J., 2020. BIAS: Transparent reporting of biomedical image analysis challenges. *Medical image analysis*, 66, p.101796.

Reinke, Annika, et al. "Common limitations of image processing metrics: A picture story." *arXiv preprint arXiv:2104.05642* (2021).



# Tasks and measures





# Certification of medical SW

- Any use of AI in medicine needs to be **certified** (CE, FDA)
  - Software is a “medical device”
  - Unless only for a research study
  - Avoid risks for the patient, tedious process
- **In-vitro diagnostics** is more complex since 2022
  - Transition period for already certified tools
- Expensive to do, so not usable for research tools





# Conclusions

- Medical AI is an extremely **interesting** domain
  - With **high impact** on people's lives!
- AI in medical imaging has many challenges remaining!
  - Some can be addressed relatively easily
  - Many will require much more research
- Consequences of (wrong) decisions are important
- Run user tests (also on prospective data)



# Contact

- More information can be found at
  - <http://medgift.hevs.ch/>
  - <http://publications.hevs.ch/>

- Contact: **Henning.mueller@hevs.ch**

