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Berlin, 31 May – 2 June 2022

Source:	Institute for Molecular Medicine Finland – FIMM
Title:	Workshop: TG-POC & TG-Histo - When is AI good enough for implementation in diagnostics?
Purpose:	Discussion

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Abstract: This PPT contains a presentation from the TG-POC & TG-Histo workshop on “Validation of annotations for AI models within the scope of point-of-care diagnostics (POC)”

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

When is AI good enough for implementation in diagnostics?

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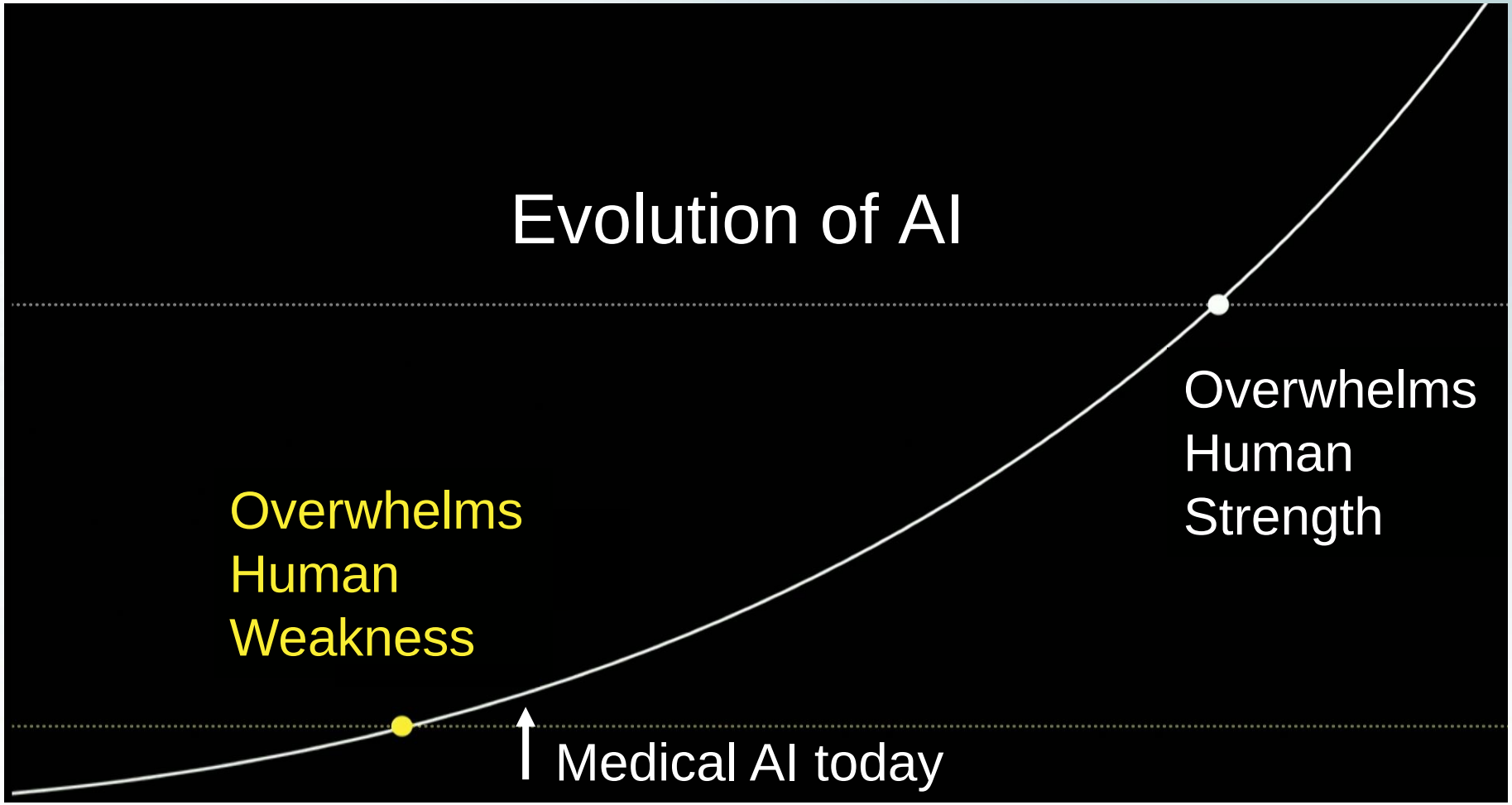
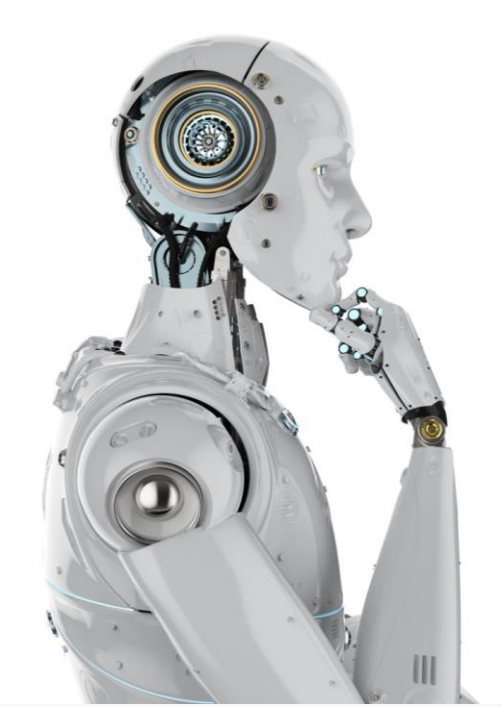
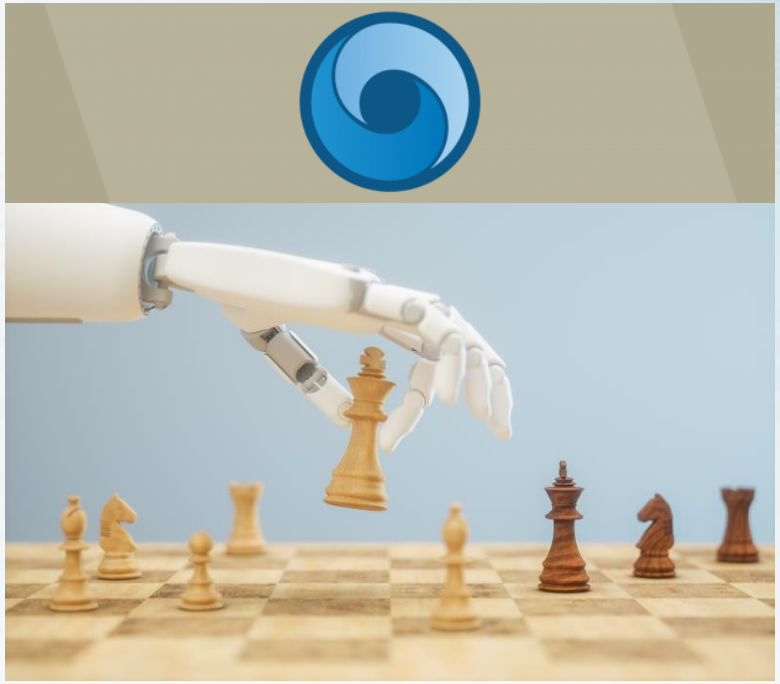


Courtesy of Tristan Harris, Center for Humane Technology

Human chess world champion learns from games played by AI





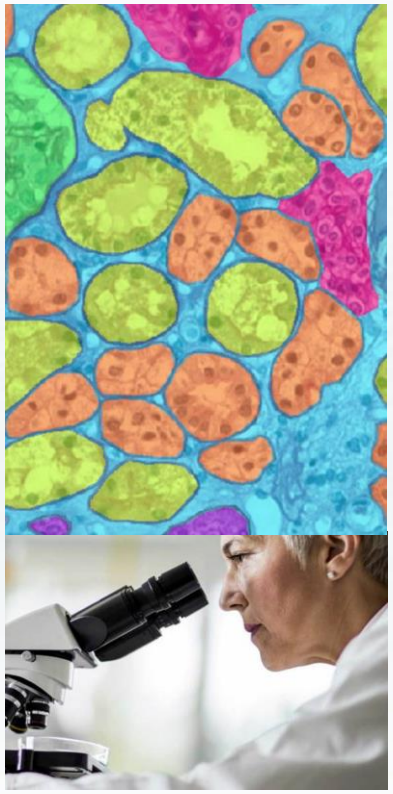
AlphaZero, self-taught AI-based world champion of chess*

Magnus Carlsen, the current human champion of chess

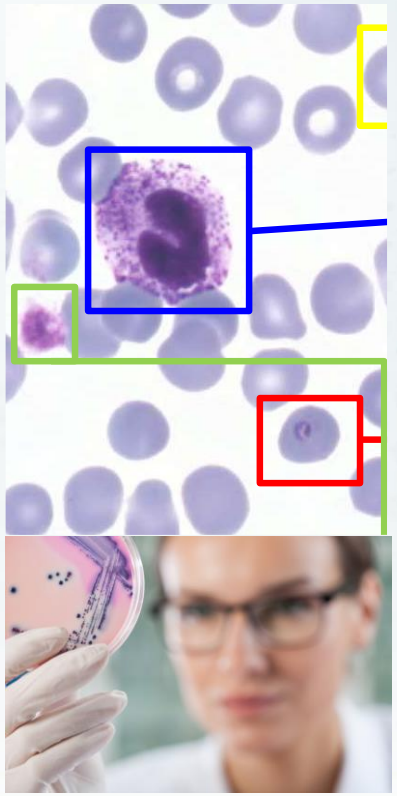
Medical experts are likely to benefit from AI in a similar way

*Silver, D. et al. Science. 362, 1140 (2018).

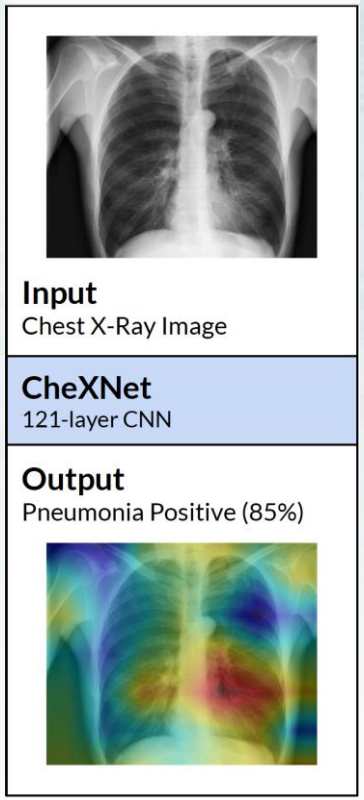
AI will impact all medical fields where an expert makes a visual interpretation



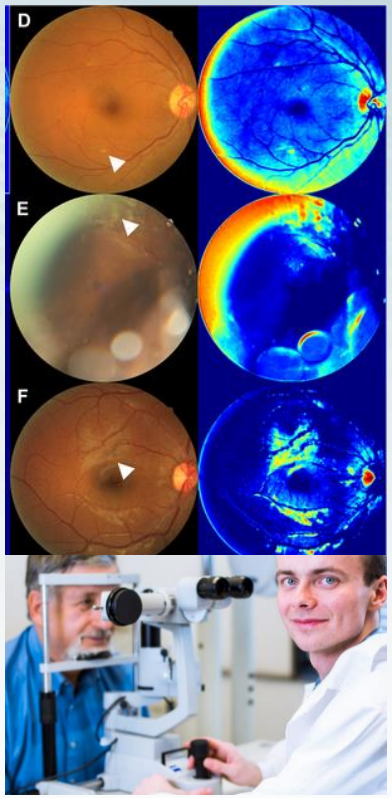
Pathology



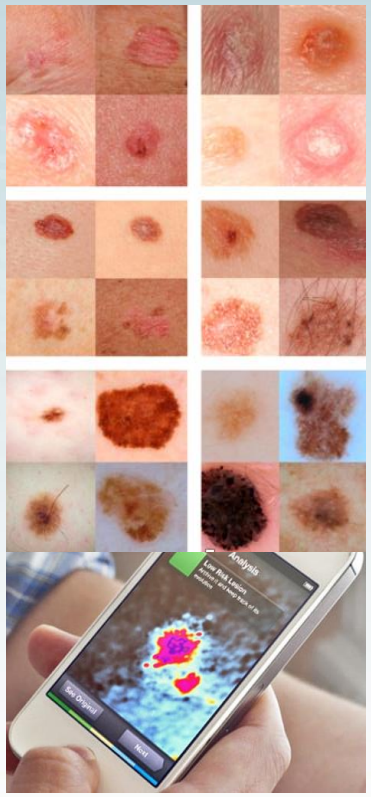
Microbiology



Radiology



Ophthalmology



Dermatology

Crude estimate: minimum >7-8 billion visual diagnostic assessments globally per year

When is AI good enough for implementation in diagnostics?

- When AI achieves the same accuracy or exceeds the current gold standard?
- When AI analyses an order of magnitude more samples than a human expert within a particular time period?
- When AI complements the human expert and finds a significant number of targets that otherwise would have been missed?
- When AI is the only alternative in a setting with shortage of experts?

Ground truth and gold standard tests

- The term ground truth refers to the underlying absolute state of information
- The gold standard strives to represent the ground truth as closely as possible.
- In machine learning and information retrieval, "ground truth" is the preferred term even when classifications may be imperfect
- The gold standard is assumed to be the ground truth

Definition of a gold standard test

In medicine and statistics, a **gold standard test** is usually the diagnostic **test** or benchmark that is the best available under reasonable conditions. Other times, a **gold standard** is the most accurate **test** possible without restrictions.

Gold standard (test) - Wikipedia

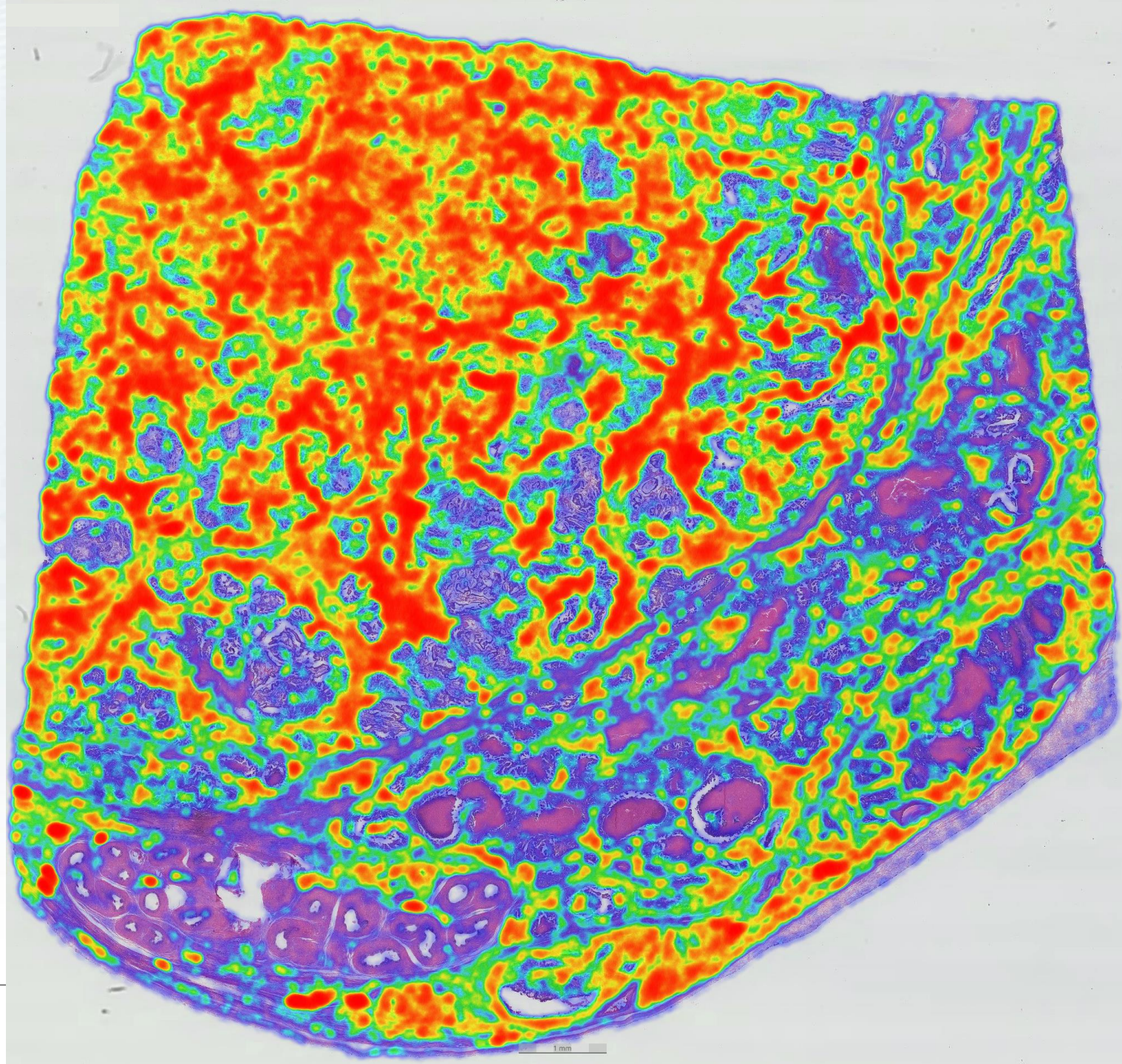
https://en.wikipedia.org › wiki › Gold_standard_(test)

Performance of a gold standard test

- A hypothetical ideal "gold standard" test has a sensitivity of 100% with respect to the presence of the disease and a specificity of 100%.
- In practice, there are sometimes no true gold standard tests.
- Currently, no gold standard tests exist for deep learning applied to pathology or microscopy
- According to the literature, AI-based algorithms typically reach a good to excellent diagnostic accuracy as compared to the ground truth, but the ground truth is rarely a real gold standard

Challenges in the development of gold standard for machine learning in pathology

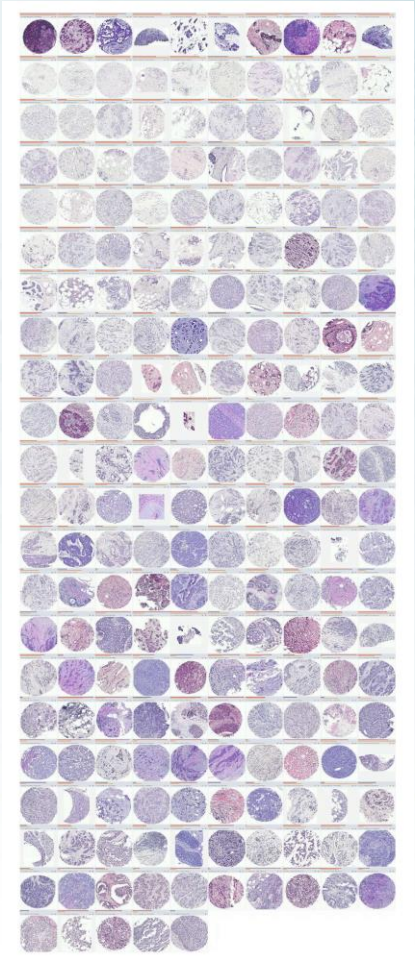
- Samples and data
- Annotations
- Algorithms
- Other challenges



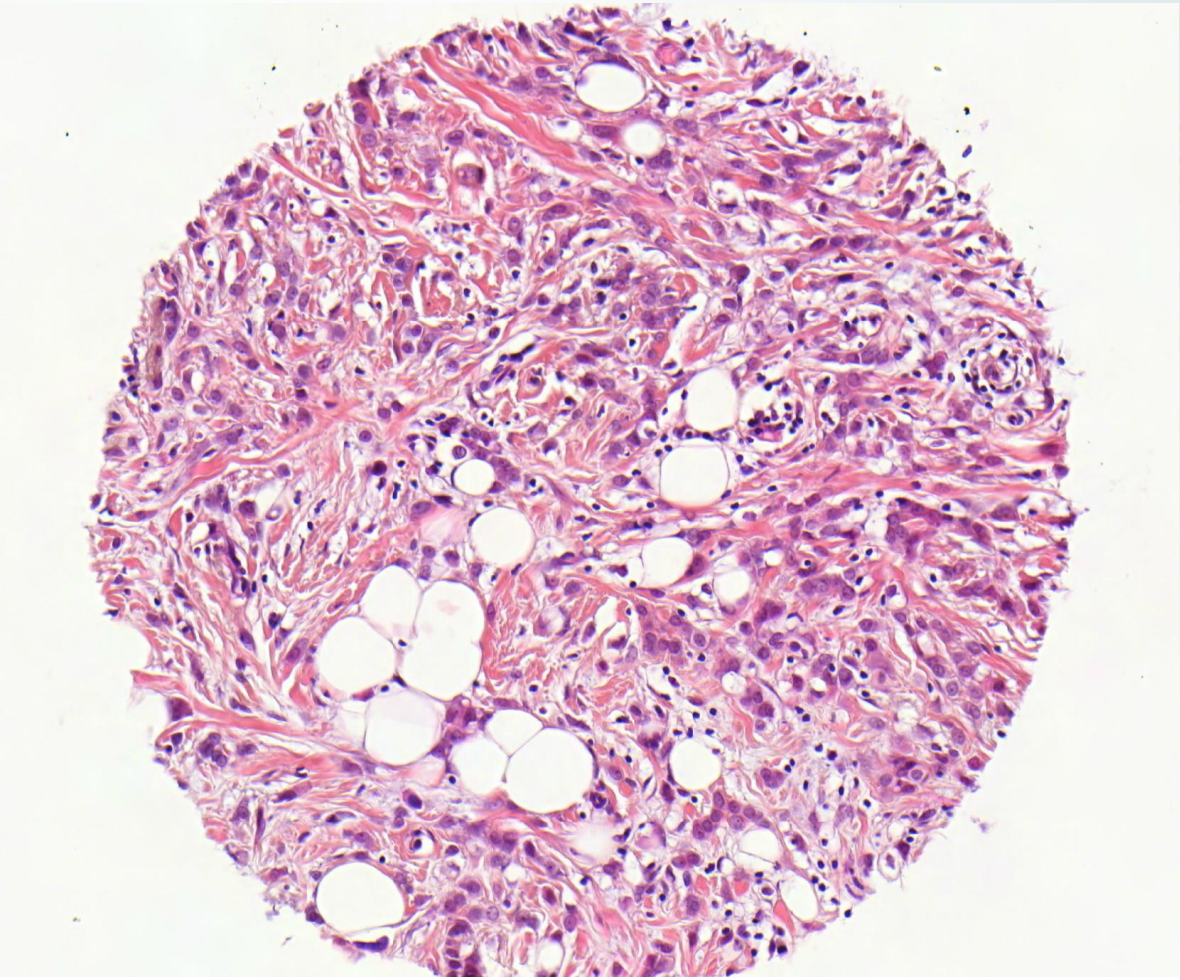
Challenges related to samples, data and annotations

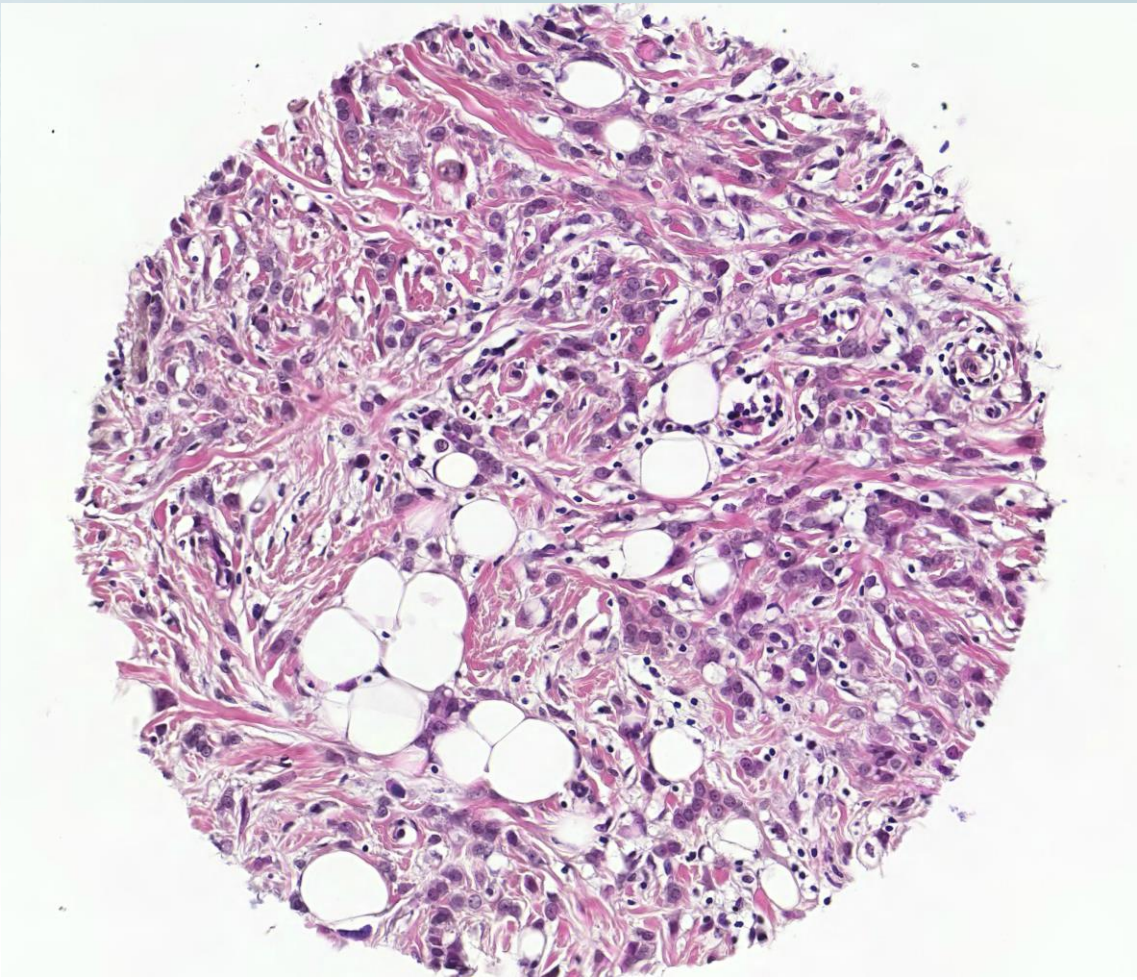
- Limited access to sample images with associated clinical data
  - Share data, form joint projects, use federated or swarm learning
- Lack of annotated images
  - Create public libraries and common repositories of annotated images
- Biased data due to incompleteness or lack of diversity
  - Strive for completeness of data, collect from many centers
- Variable quality, artifacts and heterogeneity of samples
  - Perform quality control (with AI?), re-cut, re-stain, re-scan, color calibrate
  - ..or include all types of artifacts and variabilities in the training set

Sample variability in a breast cancer tissue microarray

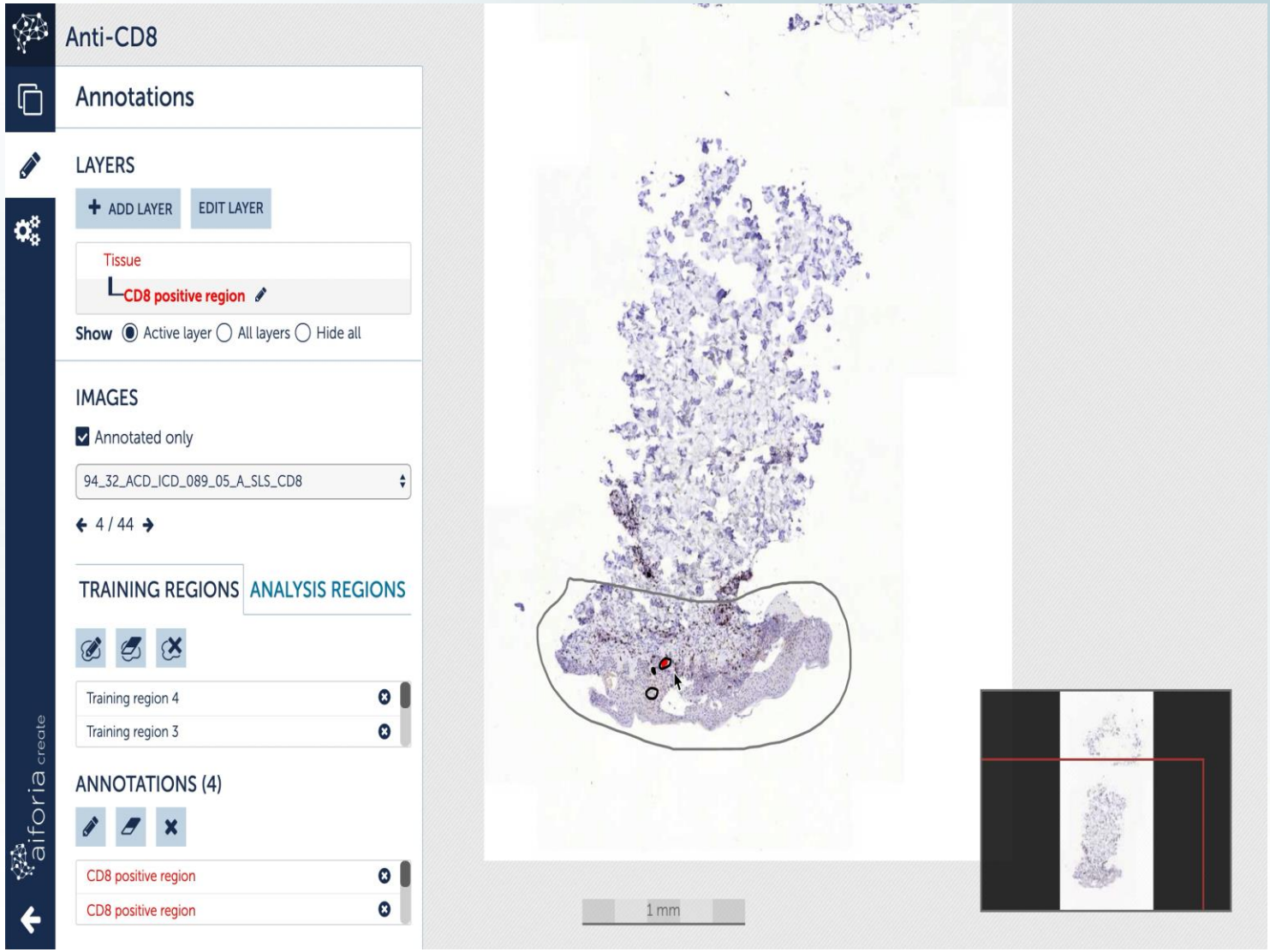


Variability due to the scanner and camera

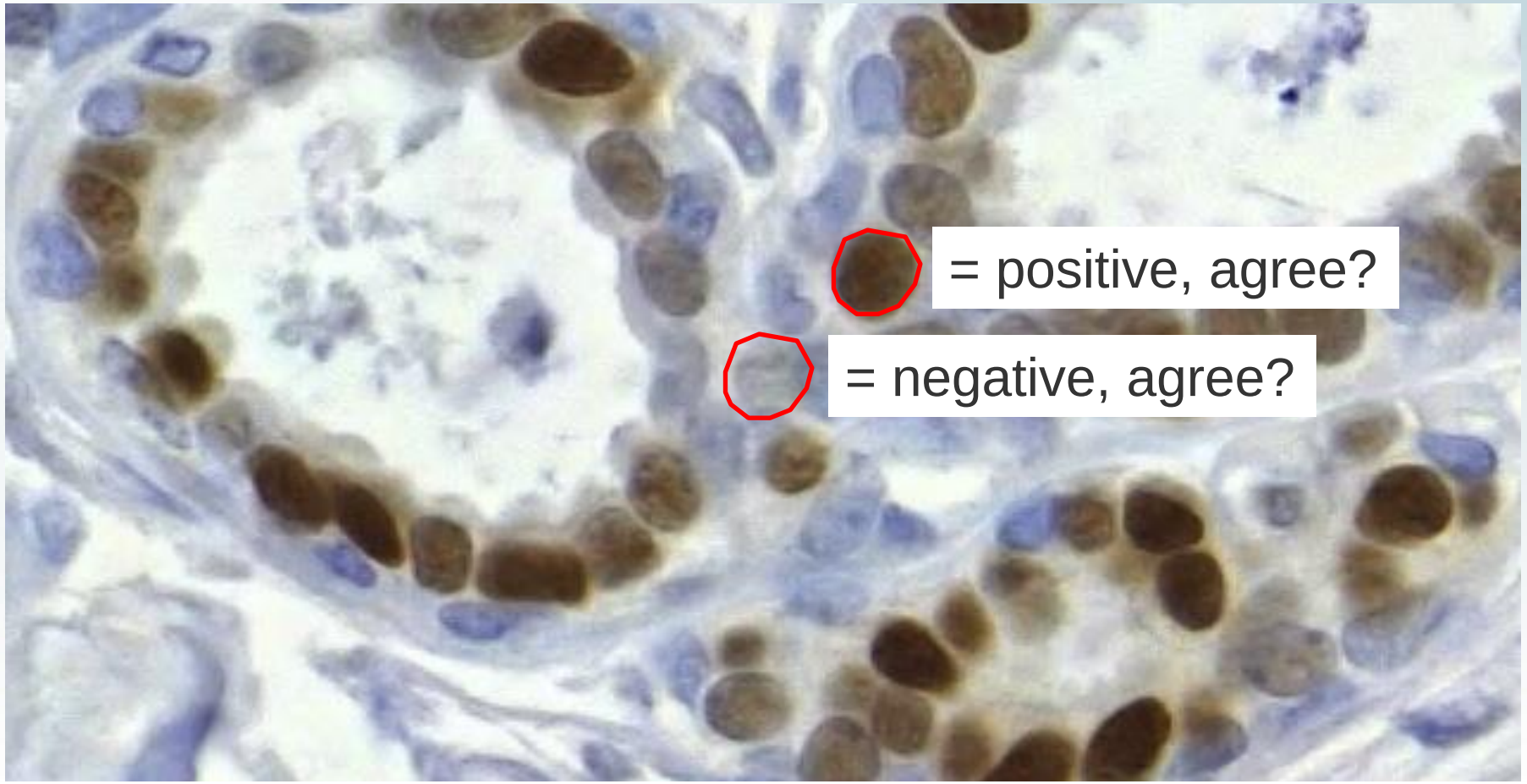




Variable quality of annotations

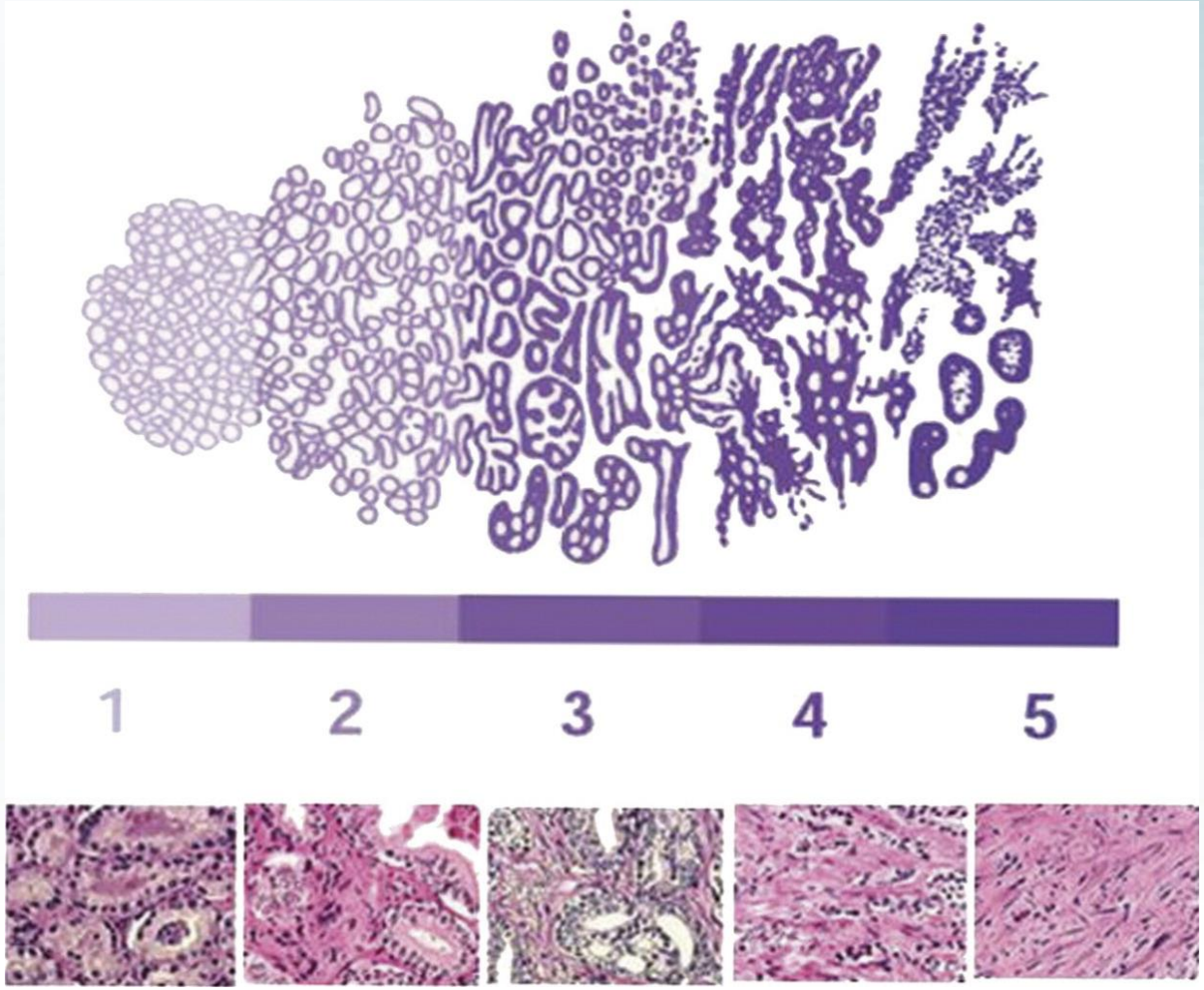


Consistency and representativeness of ground truth -deep learning algorithms just as good as their teacher?

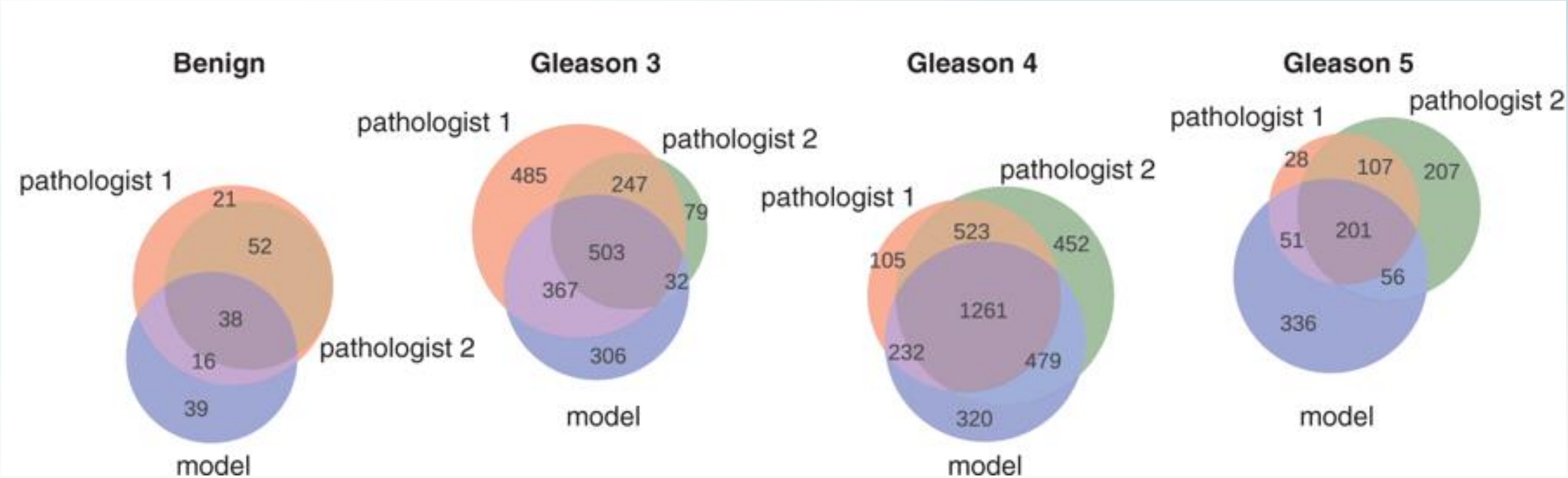


Ground truth digital samples crucial in development of medical AI

More complicated patterns – e.g. Gleason grade in prostate cancer



There is a risk that AI will be just another subjective ”expert” - example of automated grading of Gleason



Pathologist 1

Pathologist 2

Model = AI

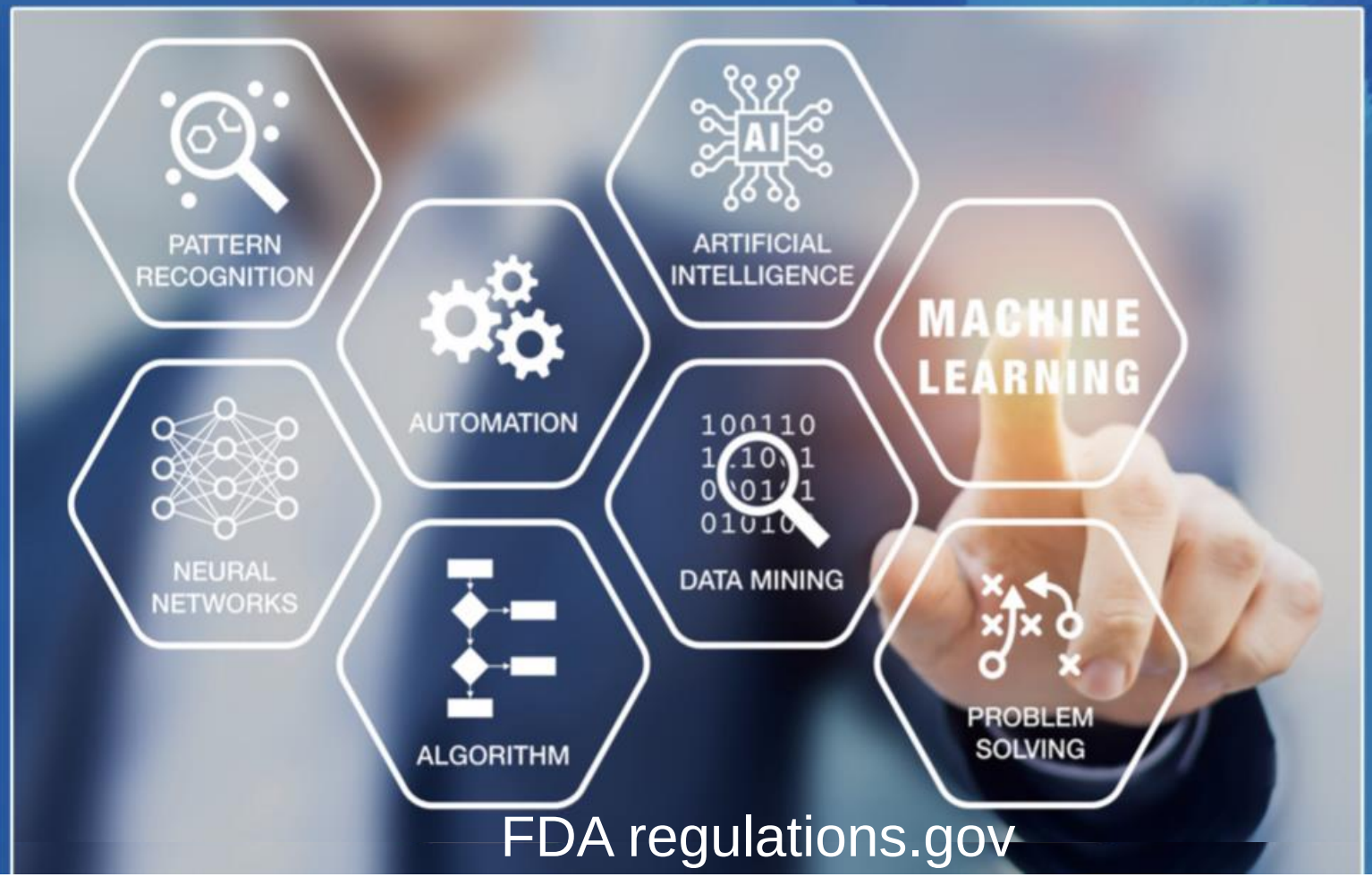
Arvaniti: Scientific Reports 2018; 8: 12054

Other challenges related to AI for diagnostics

- Ownership and access to the images
  - Create public libraries of annotated images for developers
- What to do with rapidly improving and updated algorithms?
  - Allow algorithm performance to be a moving target
  - FDA white paper
- How to handle tens or hundreds of AI:s for the same purpose?
  - Create consensus algorithms? Use swarm learning to adjust parameters?

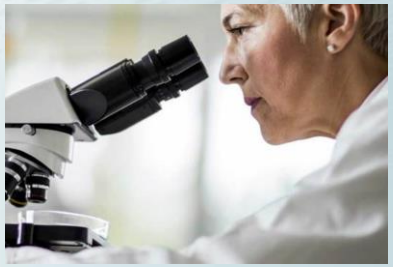
Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)

Discussion Paper and Request for Feedback



FDA regulations.gov

Human vs machine

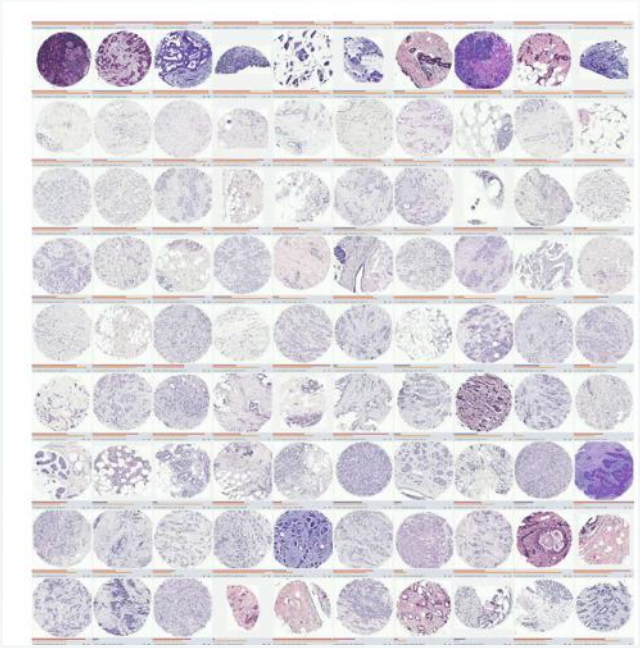


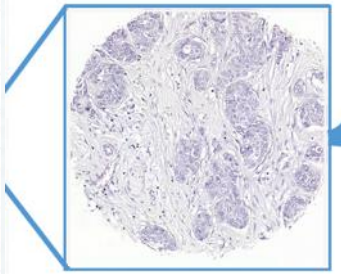
	Human	Machine
› Understand context	1	2
› Reproduce assessment	2	1
› Handle outliers	1	2
› Find rare events	2	1
› Generalize	1	2
› Achieve high throughput	2	1

When is an AI algorithm good enough?

- 🤔?
- Needs to outperform or supplement human experts in at least one of the following: Sensitivity, speed, reproducibility
- Generalizability needs to be established
  - robustness to artifacts, outliers and local variations in protocols
- Superiority shown in prediction of clinical endpoints rather the replication of annotations?
  - Outcome and biomarker supervised learning

Outcome supervised learning in colorectal and breast cancer

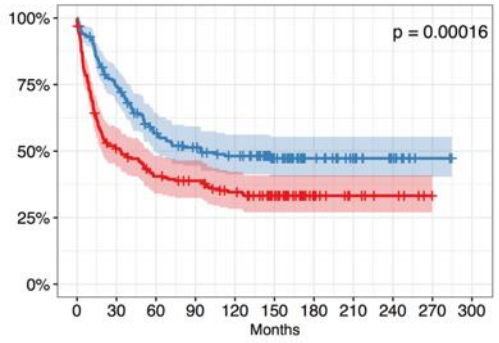




Outcome prediction by pathologists

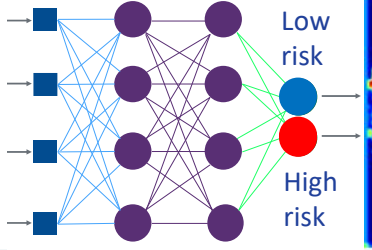
Low risk

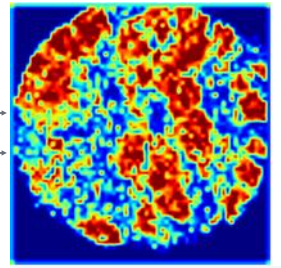
High risk



p-value

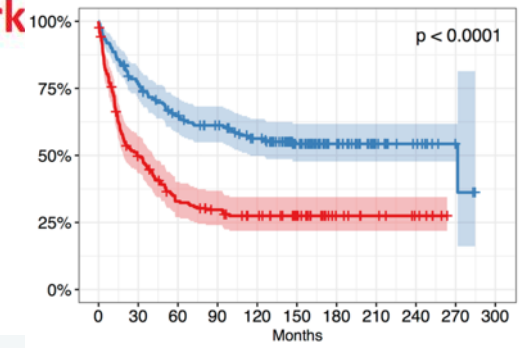
Outcome prediction by deep network





Low risk

High risk



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Digitized tissue samples from cancer patients with known outcome of cancer i.e. survivor or non-survivor

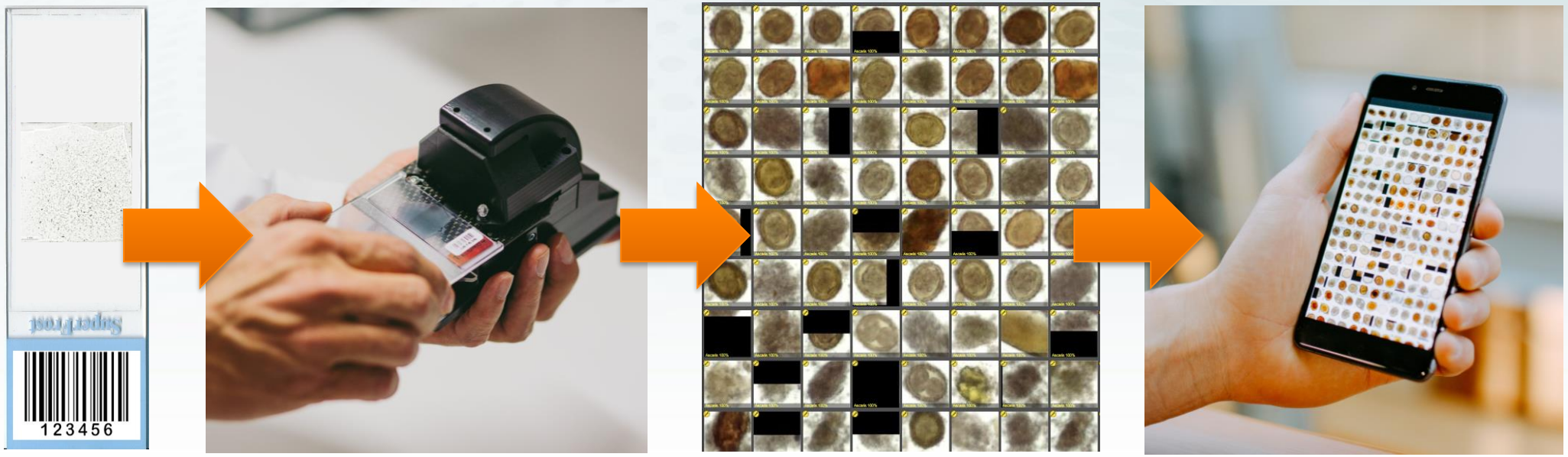
Comparison of human expert-based and AI-based outcome prediction

Deep learning outperformed experienced pathologists in outcome prediction [1-3]

[1]Bychkov et al, Scientific Reports 2018;8:3395 [2]Turkki et al, Breast Can Res Tr 2019;177:41-52 [3]Bychkov et al, J Pathol Informatics 2022;13:9

Human and machine combination:
Sensitive AI algorithm – specific human observer

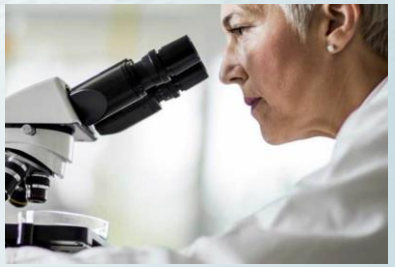
- Example of application to neglected tropical diseases for better access to diagnostics
- Assisted detection of helminth eggs in stool samples and verification by human expert



Stool sample | Scan with mobile microscope | Parasite egg candidates | Human expert reviews results

Global Health Action 2017; 10:1337325.

Human **AND** machine?



	Human	Machine	Human&Machine
› Understand context	1	2	1
› Reproduce assessment	2	1	1
› Handle outliers	1	2	1
› Find rare events	2	1	1
› Generalize	1	2	1
› Achieve high throughput	2	1	1

Some arguments and thoughts as a conclusion

- The quality, selection and annotation of training data for AI is crucial
- How could we get more reliable ground truth?
- There is a risk that we end up with hundreds of AIs for the same purpose but with unclear accuarcy
- Ground truth based on human observation and annotation will always be subjective
- Alternative ground truths, such as sample level diagnosis, patient outcome and response to treatment should be explored

nature reviews cancer

Viewpoint | Published: 17 September 2021

Artificial intelligence in cancer research, diagnosis and therapy

Olivier Elemento ✉, Christina Leslie ✉, Johan Lundin ✉ & Georgia Tourassi ✉

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Building a bridge from discovery to medicine